Aims and scope

Journal of Yeungnam Medical Science is a peer-reviewed and open access journal in the medical field published in English four times a year (January 31, April 30, July 31, and October 31). The journal’s publishers are the Yeungnam University College of Medicine and Yeungnam University Institute of Medical Science. The abbreviated title is J Yeungnam Med Sci (JYMS).

JYMS aims to deliver new medical information to health professionals of various disciplines as well as the general public, and to facilitate the advancement of medicine by publishing high-quality evidence-based articles.

JYMS covers all fields of medical science, including clinical research, basic medical science, and medical education. JYMS is especially interested in medical education for learners of all levels, from residents and fellows to medical students. Its regional scope is primarily Korea but we welcome submissions from researchers all over the world.

JYMS publishes editorials, review articles, original articles, case reports, image vignettes, communications, resident fellow section (RFS; clinical vignette, teaching images), and imagery. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of diseases and for the communication of valuable information about all medical fields.

JYMS was first published in 1984. The original Korean title was "Yeongnam yidae hagsulji" (print ISSN 1225-7737). The Journal was renamed "Yeungnam University Journal of Medicine" (online ISSN 2584-0293) in 2015 and "Journal of Yeungnam Medical Science" (online ISSN 2799-8010) in 2022.


Open access

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher
Yeungnam University College of Medicine, Yeungnam University Institute of Medical Science

Editor-in-chief
So-Young Park, Yeungnam University College of Medicine

Editorial office
Yeungnam University College of Medicine
170 HyoHaeRung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6832 • Fax: +82-53-651-0394 • E-mail: jyms@yu.ac.kr

Printing office
M2PI
8th FL, DreamTower, 66 Seongsu-ro, Seongdong-gu, Seoul 04784, Korea
Tel: +82-2-4866-4930 • Fax: +82-2-4866-4945 • E-mail: support@m2-pl.com

Published on January 31, 2023

Copyright © 2023 Yeungnam University College of Medicine, Yeungnam University Institute of Medical Science

@ This paper meets the requirements of KOS ISO 9706, ISO 19704-1994 and ANSI/NISO 239. 48–1992 (Permanence of paper)
Editorial board

Editor-in-chief
So-Young Park, MD, PhD Yeungnam University, Korea

Deputy editor
Tae Gon Kim, MD Yeungnam University, Korea

Associate editors
Min Cheol Chang, MD Yeungnam University, Korea  Du-Hyong Cho, MD, PhD Yeungnam University, Korea

Editorial board

June Hong Ahn, MD, PhD Yeungnam University, Korea  Ung Kim, MD, PhD Yeungnam University, Koreaa
Kiwon Ban, MD, PhD City University of Hong Kong, Hong Kong  Hideki Koizumi, MD, PhD University of the Ryukyus, Japan
Mathieu Boudier-Revéret, MD Centre Hospitalier de l’Université de Montréal, Canada  Shaw Hua Anthony Kueh, MD Auckland City Hospital, New Zealand
Ramanarayana Boyapati, BDS, MDS Silvra Institute of Dental Sciences, India  Younghoon Kwon, MD University of Washington, USA
Ke-Vin Chang, MD, PhD National Taiwan University, Taiwan  Jae Hee Lee, MD Chungbuk National University, Korea
Joon Hyuk Choi, MD, PhD Yeungnam University, Korea  Jae-Lyun Lee, MD, PhD Ulsan University, Korea
Yoon Seok Choi, MD, PhD Yeungnam University, Korea  Jae Min Lee, MD, PhD Yeungnam University, Korea
Jinmyoung Dan, MD CHA University, Korea  Sufang Liu, MD, PhD Texas A&M University, USA
Jong Ryul Eun, MD Hanyang University, Korea  Yong Su Lim, MD, PhD Gachon University, Korea
Mi Jin Gu, MD, PhD Yeungnam University, Korea  Chul Hyun Park, MD, PhD Yeungnam University, Korea
Ming-Yen Hsiao, MD, PhD National Taiwan University, Taiwan  Eun Young Park, DDS, PhD Yeungnam University, Korea
Insoo Kang, MD Yale University, USA  Jeong Hyun Park, MD, PhD Kangwon National University, Korea
Noriyuki Kanzaki, MD, PhD Kobe University, Japan  Ye Jee Shim, MD, PhD Keimyung University, Korea
Hye-Geum Kim, MD, PhD Yeungnam University, Korea  Young Beom Seo, MD, PhD Yeungnam University, Korea
Hyuckgoo Kim, MD Yeungnam University, Korea  Phil Hyun Song, MD, PhD Yeungnam University, Korea
Jason K. Kim, PhD University of Massachusetts, USA  Hoon-Ki Sung, MD, PhD University of Toronto, Canada
Sang Taek Kim, MD, PhD The University of Texas MD Anderson Cancer Center, USA  Wei-Ting Wu, MD National Taiwan University, Taiwan
Won Jae Kim, MD Yeungnam University, Korea  Wan-Hee Yoo, MD, PhD Chonbuk National University, Korea

Statistical editors

Sang Won Kim, MS Yeungnam University, Korea  Keun Jung Ryu, MD Yonsei Kim & Jung Hospital, Korea

Managing editor

Eun-il Lee Yeungnam University, Korea

Manuscript editors

Hye-Min Cho InfoLumi, Korea  Yoon Joo Seo InfoLumi, Korea
Contents

Vol. 40 · No. 1 · January 2023

Imagery

i  "Lanterns carrying hopes and dreams"
   Man Jin Park

Editorial

1  Appreciation to peer reviewers in 2022
   So-Y oung P ark

Review articles

4  Beneficial effects of intermittent fasting: a narrative review
   Dae-Kyu Song, Yong-Woon Kim

12  Long-term management of Graves disease: a narrative review
    Hyo-Jeong Kim

23  The use of animal models in rheumatoid arthritis research
    Jin-Sun Kong, Gi Heon Jeong, Seung-Ah Yoo

Original articles

30  Incidence of congenital hypothyroidism by gestational age: a retrospective observational study
    Ha Y oung Jo, Eun Hye Yang, Young Mi Kim, Soo-Han Choi, Kyung Hee Park, Hye Won Yoo, Su Jeong Park, Min Jung Kwak

37  Factors associated with the prescription of probiotics in patients with inflammatory bowel disease: a cross-sectional study
    Joo Kyung Kim, Jae Hee Cheon

49  The impact of quality of life measured by WHOQOL-BREF on mortality in maintenance hemodialysis patients: a single center retrospective cross-sectional study
    Seong Gyu Kim, In Hee Lee

58  Satisfaction of industrial health care managers regarding the work of industrial hygiene engineers: a cross-sectional study
    Byung Sik Choi, Min Keun Kim, Joon Sakong
Contents

Vol. 40 · No. 1 · January 2023

65   The effect and therapeutic compliance of adjuvant therapy in patients with cholangiocarcinoma after R0 resection: a retrospective study
     Han Taeuk Jeong, Joonkee Lee, Hyeong Ho Jo, Ho Gak Kim, Jimin Han

78   Auricular acupuncture for sleep quality in participants with mental and behavioral disorders due to prior multiple drug use: a retrospective consecutive case series
     Yuri Gimelfarb, Eran Goldstien

Case reports

86   Scrotal pyocele secondary to gastrointestinal perforation in infants: a case series
     Soo-Hong Kim, Yong-Hoon Cho, Hae-Young Kim, Narae Lee, Young Mi Han, Shin Yun Byun

91   Diagnosis and successful visual biofeedback therapy using fiberoptic endoscopic evaluation of swallowing in a young adult patient with psychogenic dysphagia: a case report
     Youngmo Kim, Sang Hun Han, Yong Beom Shin, Jin A Yoon, Sang Han Kim

96   The endoscopic transnasal approach to the lesions of the craniocervical junction: two case reports
     Baraa Dabboucy, Wissem Lahiani, Damien Bresson, Nouman Aldahak

102  Intra-abdominal hypertension during hip arthroscopy: a case report
     Saeyoung Kim, Hyun-Su Ri, Ji Hyun Kim, Jiyoung Yeom

Image vignette

106  Tarsal tunnel syndrome due to talocalcaneal coalition
     Chul Hyun Park, Mathieu Boudier-Revéret, Min Cheol Chang

Resident fellow section: Teaching images

109  Right arm pain after strength training: ultrasound imaging for pectoralis major tendon strain
     Ting-Yu Lin, Ke-Vin Chang, Wei-Ting Wu, Levent Özçakar
"Lanterns carrying hopes and dreams"

Photograph by Man Jin Park, Daegu, Korea

The “Imagery” section of Journal of Yeungnam Medical Science (JYMS) is devoted to the artistic and imaginative qualities of our readers. JYMS invites you to submit your drawings, illustrations, or photographs, along with appropriate explanatory information, for publication within this section. Please forward electronic images via e-mail to: jyms@yu.ac.kr.
On behalf of the authors, readers, and our editorial board members, I wholeheartedly thank the reviewers for their contribution to publishing the *Journal of Yeungnam Medical Science* (*JYMS*) in 2022. We could not publish *JYMS* without the dedication of the reviewers, who have put considerable time and effort into the meticulous review process. Authors are mainly accountable for the quality of their articles, but they cannot do it alone. Reviewers play tremendous roles in improving the quality of articles by assessing the manuscript and providing helpful suggestions.

After changing the journal title from “Yeungnam University Journal of Medicine” to “Journal of Yeungnam Medical Science” in 2022, *JYMS* has continued to move forward as an academic platform for general medicine in Korea. In addition, the international influence of *JYMS* has dramatically grown. *JYMS* received 136 manuscript submissions in 2022, with 81 (59.6%) from Korea and 55 (40.4%) from foreign countries (Fig. 1).

Bibliometric statistics for the total citations are presented in Fig. 2 and Supplementary Table 1. Authors from 14 countries submitted articles. The submissions from overseas researchers dramatically increased from 13 (10.2%) in 2020 to 55 (40.6%) in 2022. The readership has expanded to 117 countries according to the access statistics in 2022 (Fig. 3). The number of total citations continuously increased. In 2022, *JYMS* was cited 295 times in the CrossRef metadata, 245 times in Scopus, and 230 times in the Web of Science Core Collection. The manually calculated impact factor in Web of Science increased from 0.317 in 2020 to 1.274 in 2022 (135 citations 2020 to 2021/106 documents 2020 to 2021; calculated on January 2, 2023). The CiteScore manually calculated by Scopus increased from 0.25 in 2020 to 1.02 in 2022 (203 citations 2019 to 2022/199 documents 2019 to 2022; calculated on January 2, 2023). The overall acceptance rate decreased from 55.1% in 2020 to 44.6% in 2022 for submitted manuscripts. *JYMS* will steadily grow towards becoming a prestigious journal in general medicine. To achieve this, *JYMS* plans to invite active researchers from all over the world as reviewers in the near future.

Below are the names and affiliations of the reviewers in 2022. The editorial board would like to thank the reviewers again for their contribution and would appreciate their ongoing interest and support in 2023.

Boyapati Ramanarayana, Sibar Institute of Dental Sciences; Hyun-Dong Chae, Hee Kyung Cho, Hyunsuk Choi, Jae-seok Jang, Eon-Ju Jeon, Dong Rak Kwon, Suk-Bong Koh, Geun Woo Lee, Ji-hyun Lee, Jung A Lim, Jung Min Ryu, and Ho Sang Son, Daegu Catholic University; Sung-Hoon Jung, Chonnam National University; Du Hwan Kim, Chung-Ang University; Chae Ha Yang, Daegu Haany University; Young-Eun Lee, Daegu Health College; Seoyon Yang, Ewha Womans University; Sang-Kyu Kim, Se Yun Kwon, Jae Yoon Park, and Jeong Ill Suh, Dongguk University; Mingyo Kim, Young-Ji Lee, and Jung Suk Yeom, Gyeongsang National University; Jay Chol Choi, Jeju University; Ju Yeon Cho, Yong Min Choi,
Mi Hwa Heo, Ilseon Hwang, Ji Hye Jang, Kyung Tae Kang, Keun Tae Kim, Sang Pyo Kim, Yang-Tae Kim, Jung Jeung Lee, Kibeom Park, Sejin Park, Won Kyun Park, Wooyeong Park, Hung Youl Seok, and Ye Jee Shim, Keimyung University; Dong Wook Kim, Hahn Young Kim, and Kee Ho Song, Konkuk University; Kyunghee Chun, Konyang University; Jaechul Koh and Nack Hwan Kim, Korea University; Jung Hee Kim, Meyung Kug Kim, Minjeong Kim, and Young Lim Oh, Kosin University; Jin-Seok Byun, Ji-Rak Kim, Jin-Sung Park, Jae Yun Ahn, Jung Ho Lee, Jae-Kwang Lim, Dong Ja Kim, Jong-Moon Hwang, Sujeong Kim, Yeo Hyang Kim, Yu Kyung Kim, Chul-hyun Kim, Hyun Jung Lee, Inuk Jung, Yong-Gun Kim, and Su-Kyeong Hwang, Kyungpook National University; Wonhee Hur, National Institute of Health; Su Bum Park, Ju-Youn Lee, Hyun-Joo Kim, Yoon Jin Lee, and Sojung Yune, Pusan National University; Ju Sun Oh, Seoul Medical Center; Mi Hae Seo, Hyung Mo Sung, Soonchunhyang University; Eun Jae Go, University of Ulsan; Yoon Mok Chun, Wooridul Spine Hospital; Sangwoon Bae, Young Kyung Bae, Hee Sun Baek, Jong Hyun Baek, Eun Kyung Choi, Joon Hyuk Choi, Kang Un Choi, Yoon Seok Choi, Kyu Jin Chung, Seung Min Chung, Kyung-oh Doh, Jian Hyuk Hur, Byung Ik Jang, Kyung Mi Jang, Hyun Jung Jin, Jiyoon Jung, Sung Mee Jung, Youngjin Jung, Min Kyu Kang, Seok Hui Kang, So Hee Kang, Hyuckgoo Kim, Jae Woon Kim, Jung Ho Kim, Kook Hyun Kim, Kyeong Ok Kim, Min Kyoung Kim, Saeyoon Kim, Sang Won Kim, Seong Ho Kim, Sung Bum Kim, Ung Kim, Yong Woon Kim, Zehwan Kim, Sung Ae Koh, Yu-Jin Koo, So Young Kwak, Doo Hyuk Kwon, Dae Hyung Lee, Dong Gyu Lee, Dong Hyup Lee, Dong Shik Lee, Gun Woo Lee, Jang Hoon Lee, Seok Soo Lee, Soo-Young Lee, You-Jung Lee, Young-Hwan Lee, Sungjun Moon, Youho Mun, Hyung Gyun Na, JongHo Nam, Chan Ho Park, Chul Hyeon Park, Chulyong Park, Donghwi Park, Eun Young Park, Hosun Park, Jong Soo Park, Jong Won Park, Jung Gil Park, Mee Young Park, Sang-Jin Park, So Hee Park, So-Young Park, Min Sagong, Young Beom Seo, Dong Hoon Shin, In-Hwan Song, Phil Hyun Song, Si Youn Song, Ji Sung Yoon, and

Fig. 1. The number of manuscripts submitted by countries to the *Journal of Yeungnam Medical Science* in 2022.

Fig. 2. The number of total citations of the *Journal of Yeungnam Medical Science* articles in Crossref metadata, Scopus, and Web of Science Core Collection from 2018 to 2022 (calculated on January 5, 2023).

https://doi.org/10.12701/jyms.2022.00920
Yu Ra Kim, Yeungnam University; Keun Jung Ryu, Yonsei Kim and Chung Hospital; Geu-Ru Hong and Duk Hwan Moon, Yonsei University.

Supplementary materials

Supplementary Table 1 can be found via https://doi.org/10.12701/jyms.2022.00920.

Fig. 3. Top 10 countries with access to the Journal of Yeungnam Medical Science in 2022 (https://e-jyms.org/metrics/metrics_total_down_ref.php).

<table>
<thead>
<tr>
<th>Country</th>
<th>Total views</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>235,306</td>
</tr>
<tr>
<td>Canada</td>
<td>65,192</td>
</tr>
<tr>
<td>Kuwait</td>
<td>41,767</td>
</tr>
<tr>
<td>Korea</td>
<td>28,676</td>
</tr>
<tr>
<td>Russia</td>
<td>23,553</td>
</tr>
<tr>
<td>Switzerland</td>
<td>12,493</td>
</tr>
<tr>
<td>China</td>
<td>10,823</td>
</tr>
<tr>
<td>Netherlands</td>
<td>8,055</td>
</tr>
<tr>
<td>Indonesia</td>
<td>5,706</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>5,640</td>
</tr>
</tbody>
</table>

Notes

Conflicts of interest
So-Young Park has been the editor-in-chief of Journal of Yeungnam Medical Science since 2021. Otherwise, no potential conflict of interest relevant to this article was reported.
Obesity poses a public health risk worldwide because of its association with metabolic dysregulation such as insulin resistance, hypertension, dyslipidemia, and atherosclerosis [1,2]. Caloric restriction (CR) without malnutrition is the cornerstone for the treatment of obesity and its associated metabolic risk factors. It is well known that prolonged CR reduces body weight and extends life expectancy [3,4]. Moreover, CR in obese subjects improves cardiovascular risk factors, insulin sensitivity, and mitochondrial function [5-10]. However, long-term daily CR is difficult to adhere to in practice [11].

Recently, many studies have reported that intermittent CR (intermittent fasting, IF) may improve dietary adherence; thus, IF has emerged as an alternative intervention for prolonged CR, with similar benefits in body weight reduction and chronic illness control [12-19]. IF originated from religious traditions, such as Ramadan fasting [20]. Muslims fast during the daytime (approximately 15 hours between sunrise and sunset) for a month during the Ramadan period every year. Ramadan fasting has been reported to improve human health [21]. IF involves reduced or no caloric intake in an intermittent pattern, such as short periods of very restricted caloric intake or fasting interspersed with normal caloric intake. Thus, dieter intake is 0 to 500 kcal/day on fasting days. The fasting time varies from several hours per day to a complete day. The most studied IF interventions include 2 days of CR or fasting per week (5:2 diet) and alternate-day fasting (ADF) [22]. One of the most popular variants of IF is time-restricted feeding, in which energy intake is limited to 12 to 16 hours each day and normal caloric intake during the other hours. In this review, we evaluate the results mainly from ADF and 5:2 diet trials.

Weight reduction is the primary mechanism underlying the beneficial effects of IF. As shown in the results from CR, weight reduction per se reduces fasting plasma insulin levels, cardiovascular risk...
factors, and body inflammatory status by regulating metabolic signaling pathways, including those involving forkhead box O (FOXO), mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and autophagy [11]. During the fed state, signaling pathways for nutrient sensing and cellular growth (e.g., mTOR) are activated. Stress-responsive signaling pathways (e.g., FOXO and AMPK) are activated by fasting, resulting in the protection from cell damage and inhibition of cell proliferation [23,24].

An additional mechanism of IF is the metabolic switch between fed and fasting states. Fasting, especially repetitive fasting, induces organisms to shift their metabolic phase, which improves metabolic conditions and extends health expectancy [18]. de Cabo and Mattson [25] reported that fasting optimizes cellular use of fuel sources, favoring ketone bodies and fatty acids over glucose, which ameliorates the blunting of metabolic flexibility observed in obesity and type 2 diabetes mellitus (T2DM) [26] and improves mitochondrial function [27]. Furthermore, fasting activates autophagy and defense mechanisms against oxidative and metabolic stress and suppresses inflammation [28-31]. These effects of IF are similar to those of aerobic exercise [32,33]. Fasting induces glucose and amino acid deprivation, stimulating AMPK activity and suppressing mTOR signaling, which are important nutrient-sensing signaling pathways. These changes inhibit FOXO-dependent gene transcription, resulting in the induction of autophagy and oxidative defense mechanisms [34] (Fig. 1). During IF, the body activates pathways for rejuvenation and repair [19].

Overall, the general effects of IF are beneficial in terms of physiological functions; however, some participants who participated in IF trials experienced reductions in bone density and lean body mass [35-38]. To preserve lean body mass, a protein-rich diet and accompanying resistance training are recommended [39].

**Effects of intermittent fasting on body weight and composition**

The human body has precise regulatory mechanisms to maintain body weight homeostasis [40]. However, chronic caloric excess results in excessive accumulation of fat tissue (obesity) and is associated with various metabolic alterations, such as hypertension, diabetes, dyslipidemia, cardiovascular disease, and even some types of cancer [41,42]; controlling caloric intake may reverse these metabolic alterations. Although the cause of obesity is multifactorial, dietary management is a primary approach to control body weight; thus, optimal dietary treatment should consider safety, efficacy, nutritional balance, cultural acceptance, and economic status [43]. Many studies have indicated that IF is an effective and acceptable intervention in obese subjects, including obese adolescents [2,17,44,45].

As described above, CR has long been applied as a primary treatment modality for obesity; recently, IF has appeared as an alternative dietary intervention to CR because dieters feel that IF is a more tolerable method than CR [4,17-19,46].

According to previous clinical trials [10,47] and reviews [14,48-50], IF (4–24 weeks) induces body weight reductions of 4% to 10% in overweight individuals [51-53]. The varying degree of body weight reduction depends on the dietary pattern, dietary duration, diet composition, sex, and genetic response. Although some studies have shown greater body fat reductions with IF than with CR [14,54], the majority of these studies have shown equivalent effects on reductions in body weight and fat mass following IF or CR in overweight or obese individuals [33,55].

Considering IF patterns, weight reduction effects are more profound in ADF (average weight reduction of 0.75 kg per week) than in 5:2 IF (average weight reduction of 0.25 kg per week) because of different negative energy balances [56,57].

There were mixed results with regard to lean body mass; several systemic reviews suggested that regular IF decreased fat-free mass more than CR [50,58]. However, clinical trials [17,57] and other reviews [47,49,58] indicated that IF and CR produced similar loss of lean body mass. Moreover, Harvie et al. [14] found that IF participants maintained a higher lean mass than CR participants. Stekovic et al. [18] reported that ADF for 6 months did not reduce fat-free mass or bone density in healthy nonobese subjects. However, a recent study showed that IF may be associated with a higher

---

**Fig. 1.** Possible mechanisms of intermittent fasting on health improvement. mTOR, mechanistic target of rapamycin; AMPK, AMP-activated protein kinase; FOXO, forkhead box O; Redox, reduction-oxidation.

---

https://doi.org/10.12701/jyms.2022.00010
rate of weight regain following cessation of the 6-month weight reduction phase than CR in patients with complex obesity [59]. Further studies are needed to assess the ability to lose weight without regaining it.

The basic mechanism of the weight loss by IF involves reduced caloric intake. However, the change in body weight caused by 40% CR and 2-day IF per week was not simply double that caused by 20% CR and 1-day IF per week in mice, suggesting an additional physiological response to fasting [35]. Another mechanism of weight reduction may be associated with the shift from glucose to fatty acid metabolism resulting from the fasting-induced elevation in fat mobilization and utilization [25,31]. The reduction in insulin, an anabolic hormone, by IF may also be responsible for the reduction in body fat mass [60].

**Effects of intermittent fasting on glucose metabolism and insulin sensitivity**

Obesity is currently a leading cause of the development of T2DM, which results from insulin resistance and oxidative stress induced by elevated blood glucose and free fatty acid levels [61]. Weight reduction directly improves insulin resistance and reverses these metabolic alterations [22,62].

Although there are some inconsistent results, most studies indicate that IF decreases insulin concentration and the homeostasis model assessment for insulin resistance [51,63-65].

An IF trial for 12 months in T2DM patients showed that body weights, glycated hemoglobin levels, and fasting levels of glucose and insulin were reduced with IF [47,66] and that the insulin-lowering effect was greater with IF than with CR [67,68]. In the diabetic state, IF reduces the plasma concentrations of glucose and insulin and elevates adiponectin levels [2,69]. Although the primary mechanism of these effects is mediated by weight loss, metabolic switching following repeated feeding and fasting, and reductions in inflammatory cytokines, reactive oxygen species, and cholesterol may be involved [22].

The effect of IF on glucose homeostasis is different in nondiabetic and nonobese subjects. According to a study by Stekovic et al. [18], 4 weeks of ADF treatment did not change insulin sensitivity despite significant body weight reductions in healthy nonobese individuals, suggesting that these participants were already in an insulin-sensitive state. Moreover, Heilbronn and Ravussin [70] showed that 3 weeks of ADF treatment suppressed glucose tolerance in nonobese women, while insulin sensitivity was improved in nonobese men. Clayton et al. [71] also reported that 1 day of severe CR impaired glycemic control in young lean men. This suggests different responses to IF in healthy weight and obese subjects. Overall, IF has benefits on the diabetic state; however, the risks of hypoglycemia, malnutrition of proteins and vitamins, and dehydration have also been reported [22,47,72]. Careful monitoring and adjustment of medication regimens are needed for patients at risk.

In an animal study, IF improved glucose homeostasis by preserving pancreatic β-cell mass through the autophagy-lysosomal pathway in diet-induced obese diabetic mice [73].

**Effects of intermittent fasting on lipid profiles and cardiovascular disease**

A feature of metabolic syndrome is the clustering of metabolic alterations such as abdominal obesity, insulin resistance, dyslipidemia, atherosclerosis, and hypertension, which are associated with the risk of cardiovascular diseases [45,74,75].

Randomized clinical trials have indicated that IF improves lipid profiles related to weight reduction [5-10]. Klempel et al. [8] showed that ADF decreased total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Trepanowski et al. [10] also observed the cardioprotective effects of 6-month ADF in obese adults. These cardioprotective effects of IF have also been observed in obese adolescents [17] and nonobese subjects. Moro et al. [38] observed lipid profile enhancement (increased high-density lipoprotein [HDL] and decreased LDL levels) in a 2-month trial of IF in healthy men. Stekovic et al. [18] observed that a 6-month trial of ADF in healthy nonobese subjects lowered levels of total cholesterol, LDL, very-low-density lipoprotein (VLDL), and triglycerides compared with the corresponding levels in controls. Moreover, the authors observed a decrease in systolic blood pressure, which is consistent with studies conducted on obese subjects [14,48].

The effects of IF on HDL levels have been varied. Meng et al. [76] did not show any change in HDL cholesterol. In contrast, Bhutani et al. [77] observed an elevation in HDL cholesterol.

The mechanisms of improving cardiovascular disease risks by IF may result from obesity control, improved lipid profiles, elevated adiponectin levels [69], and a suppressed inflammatory state [78,79]. Additionally, increased hepatic fatty acid oxidation in the fasting state results in reduced hepatic accumulation of triglycerides, which sequentially decreases the hepatic production of VLDL and plasma levels of VLDL [22,80]. Adiponectin is an adipose tissue-derived adipokine that has anti-atherosclerotic and anti-inflammatory effects [81]. Adiponectin was shown to be elevated by IF intervention in obese subjects [70]. In an animal study, IF protected the heart from oxidative damage via activation of antioxidant defenses [82].
Effects of intermittent fasting on inflammation and redox balance

Macrophages infiltrate hypertrophied adipose tissue and produce proinflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) [83-85], which induce insulin resistance and atherosclerosis and are linked to low-grade systemic inflammation [86,87]. The plasma concentrations of these inflammatory cytokines parallel the degree of obesity and are positively correlated with insulin resistance [85]. Systemic inflammation is linked to the pathogenesis of T2DM, cardiovascular diseases, and some types of cancers [88,89]. Thus, systemic inflammatory markers can predict the development of these metabolic disorders [85].

Body weight reduction decreases adipose tissue macrophages [90], reduces proinflammatory cytokines [83,88,91-95], and improves insulin resistance and systemic inflammatory status [86]. Several clinical trials have shown that IF intervention improves inflammatory status in obese subjects and is associated with reductions in plasma levels of IL-6, TNF-α, C-reactive protein (CRP), and interferon-γ [60,96]. Wang et al. [42] revealed that IF intervention decreased CRP levels without changes in IL-6 and TNF-α compared with the corresponding levels in controls in a systematic review of 18 randomized controlled trials. However, there have been some inconsistent studies. Liu et al. [96] reported that IF increased macrophage infiltration in adipose tissue by fasting in overweight or obese women, which may be associated with elevated adipose tissue lipolysis. Schübel et al. [33] did not observe any changes in IL-6 and TNF-α levels after 12 weeks of IF in randomized controlled trials with obese women.

Conclusion

IF has emerged as an alternative dietary intervention to CR, with equivalent benefits in body weight reduction, improvements in glucose homeostasis and lipid profiles, and anti-inflammatory effects. The beneficial effects of IF are mediated by reductions in body weight. Weight loss per se improves insulin resistance, cardiovascular risks, and systemic inflammatory status because obesity functions as a common pathophysiology of these metabolic alterations, the “common soil hypothesis” [97]. Moreover, the insulin-lowering effect is greater in IF than in CR resulting from fasting physiology, in which repetitive metabolic switching between feeding and fasting states improves the metabolic flexibility that is blunted in obesity and T2DM.

Although the general effects of IF are beneficial in terms of metabolic functions, some participants who participated in IF trials experienced reductions in bone density and lean body mass. Thus, careful monitoring, a protein-rich diet, and accompanying isometric resistance training are recommended to preserve lean body mass and bone density.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization: YWK; Data curation: YWK; Project administration: DKS, YWK; Writing-original draft: DKS, YWK; Writing-review & editing: DKS, YWK.

ORCID
Dae-Kyu Song, https://orcid.org/0000-0002-6749-3538
Yong-Woon Kim, https://orcid.org/0000-0003-2868-9690

References


https://doi.org/10.12701/jyms.2022.00010
27. Abdellatif M, Sedej S. Carbohydrate restriction v. daily energy restriction on weight loss, weight maintenance, and cardioprotection among meta.
59. Antoni R, Johnston KL, Steele C, Carter D, Robertson MD,


85. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflam-
86. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis fac-
87. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin re-
88. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, et al. Chronic inflammation in fat plays a crucial role in the develop-
89. Esser N, Paquot N, Scheen AJ. Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovas-
90. Bruun JM, Helge JW, Richelsen B, Stallknecht B. Diet and exer-
cise reduce low-grade inflammation and macrophage infiltr-
95. Zamarron BF, Mergian TA, Cho KW, Martinez-Santibanez G, Luan D, Singer K, et al. Macrophage proliferation sustains adi-
Long-term management of Graves disease: a narrative review

Hyo-Jeong Kim

Division of Endocrinology and Metabolism, Department of Internal Medicine, Nowon Eulji University Hospital, Eulji University School of Medicine, Seoul, Korea

Graves disease (GD) is the most common cause of hyperthyroidism, accounting for more than 90% of cases in Korea. Patients with GD are treated with any of the following: antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, or thyroidectomy. Most patients begin treatment with ATDs, and clinical guidelines suggest that the appropriate treatment period is 12 to 18 months. While RAI treatment and surgery manage thyrotoxicosis by destroying or removing thyroid tissue, ATDs control thyrotoxicosis by inhibiting thyroid hormone synthesis and preserving the thyroid gland. Although ATDs efficiently control thyrotoxicosis symptoms, they do not correct the main etiology of GD; therefore, frequent relapses can follow. Recently, a large amount of data has been collected on long-term ATDs for GD, and low-dose methimazole (MMZ) is expected to be a good option for remission. For the long-term management of recurrent GD, it is important to induce remission by evaluating the patient’s drug response, stopping ATDs at an appropriate time, and actively switching to surgery or RAI therapy, if indicated. Continuing drug treatment for an extended time is now encouraged in patients with a high possibility of remission with low-dose MMZ. It is also important to pay attention to the quality of life of the patients. This review aimed to summarize the appropriate treatment methods and timing of treatment transition in patients who relapsed several times while receiving treatment for GD.

Keywords: Graves disease; Hyperthyroidism; Long-term care; Recurrence; Review

Introduction

Graves disease (GD) is an autoimmune disease resulting from both genetic and environmental factors. GD is the most common cause of hyperthyroidism, accounting for more than 90% of cases in Korea [1]. Patients with GD are treated with any of the following: antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, or thyroidectomy. In most cases, an ATD is the preferred initial treatment, as in Korea [1]. The remission rate of GD after ATD treatment is approximately 30% to 70% [2]. Thus, approximately half of the patients experience recurrence and eventually find another treatment method despite 12 to 18 months of treatment [3,4]. Several clinical factors, such as male sex, young age, high thyrotropin receptor antibody (TRAb) levels, ophthalmopathy, and smoking, have been proposed as indicators of poor prognosis after ATD therapy [5-8].

This review aimed to summarize the appropriate treatment methods and timing of treatment transition, focusing on cases of patients who relapsed several times while receiving treatment. Furthermore, recent studies on treatment outcomes, adverse events, and quality of life (QoL) will be reviewed and compared among the different treatment modalities.
Etiology

GD is caused by autoantibodies that bind to thyroid-stimulating hormone (TSH) receptors and enhance thyroid hormone function [9,10]. After T cells, which are sensitized to a peptide (antigen) of the TSH receptor, are activated by cytokines that cause inflammation, autoantibodies against the TSH receptor are produced, which subsequently activate B cells [11]. GD is affected by genetics and environmental factors, which cause an immune response in sensitive individuals when stimulated above a threshold. Risk factors for developing GD include genetic susceptibility, female sex, pregnancy, stress, viral infections, iodine overdose, and immunomodulators [12]. TRAb titers, smoking, and RAI treatment are strongly associated with Graves ophthalmopathy (GO) [12].

Diagnosis

If hyperthyroidism is suspected, thyroid hormone levels are first checked. A diagnosis of hyperthyroidism can be established by measurement of TSH levels, which will be suppressed with either elevated or normal free thyroxine (T4) and/or triiodothyronine (T3) levels (overt or subclinical hyperthyroidism). If thyroid hormone levels are elevated and accompanied by characteristic ocular disease and goiter, GD can be diagnosed based on clinical findings alone. If the diagnosis is not apparent based on clinical presentation and initial biochemical evaluation, further diagnostic testing is indicated, as recommended in the 2016 American Thyroid Association (ATA) guidelines [3]. This can include measurement of TRAb, determination of RAI uptake, or measurement of thyroidal blood flow by ultrasonography. TRAb is a sensitive (97%) and specific (98%) tool for the accurate diagnosis of GD [13]. An 123I or 99mTc pertechnetate scan should be obtained when the clinical presentation suggests thyroiditis or toxic adenoma (Fig. 1A-1C). Thyroid ultrasonography can be helpful for diagnosing increased blood flow (Fig. 1D-1F).

Management

All three classic GD treatments began in the 1940s. Surgery was

---

Fig. 1. (A–C) Thyroid scans can assist in the differentiation of patients with thyroid diseases. Typical appearances of 99mTc pertechnetate scans are shown in (A) Graves disease, (B) thyroiditis, and (C) toxic nodular goiter. (D–F) Doppler ultrasonography views of Graves disease show a classic finding of increased blood flow in a 28-year-old man. (D) Transverse view of isthmic area and longitudinal views of the (E) right lobe and (F) left lobe of the thyroid gland.
the only treatment before 1940, after which RAI and ATD treatments were established. Propylthiouracil (PTU) was used as the first ATD in the United States and was approved by the Food and Drug Administration. The ATDs methimazole (MMZ) and carbimazole (CBZ) were also developed. ATDs control hyperthyroidism by inhibiting thyroid hormone synthesis and preserving the thyroid gland. The medical treatment of GD using ATDs requires understanding the various responses of patients and maximizing remission, in addition to standard medical guidelines [3,4]. RAI therapy and surgery treat hyperthyroidism by destroying or removing the thyroid tissue and are considered as definitive therapies. Definitive treatment should be considered in patients with serious side effects from ATDs, poor adherence, obstructive symptoms from a large goiter, or suspicious thyroid nodules. Definitive treatment is also recommended when patients do not achieve remission with prolonged ATD therapy.

Once diagnosed, the physician and patient should discuss each treatment option, including logistics, benefits, expected speed of recovery, drawbacks, potential side effects, and costs [14]. The treatment of GD can be approached using the following steps. First, treatment with an ATD should be initiated upon diagnosis, especially when there is a high possibility of remission. Second, the following special conditions should be considered: (1) starting surgical treatment for thyroid cancer or severe goiter, (2) avoiding RAI therapy when moderate-to-severe ophthalmopathy occurs, and (3) discontinuing the ATD and considering definitive therapy if there are serious side effects, such as agranulocytosis, hepatotoxicity, or vasculitis. Finally, long-term additional low-dose MMZ could be a good option to prevent recurrence after completing 12 to 18 months of standard administration [4,15-17].

1. Antithyroid drugs

There are three types of ATDs. (1) MMZ has the longest half-life, is effective, and is used as the standard treatment. (2) CBZ is a precursor of MMZ developed in Europe, which allows quick switching to MMZ. An MMZ dose of 6 mg is approximately equivalent to 10 mg of CBZ, making it less effective than MMZ at the same dose. (3) PTU blocks the conversion of T4 to T3 in the peripheral tissues and is used in the acute treatment of thyrotoxicosis. As 80% to 90% of PTU binds to albumin in the blood and crosses the placenta less than the other drugs, it is used in the early stages of pregnancy. The starting dose of an ATD depends on the patient’s weight, symptoms, signs, and biochemical severity. Thyroid status should be assessed every 4 weeks for the first 3 months, followed by assessments every 2 or 3 months thereafter. If a patient complains of mild side effects, such as rash, gastric intolerance, or arthralgia, in most cases, they will improve with symptomatic treatment without stopping the medication. However, drugs should be discontinued if they cause serious side effects, such as agranulocytosis, hepatotoxicity, antineutrophilic cytoplasmic antibody-positive vasculitis, or pancreatitis.

The European Thyroid Association (ETA) treatment guidelines recommend that patients diagnosed with GD start with MMZ or CBZ for 18 months in adults and 36 months in children [4,18]. The patient can be consulted from the beginning to decide on RAI therapy or surgery; however, except in special cases, an ATD is preferred. RAI treatment or surgery is recommended if a drug is not available or if patient’s adherence is poor.

According to clinical guidelines, definitive treatment can be considered in cases where TRAb levels are positive despite a period of ATD therapy [4]. However, treatment with ATDs may be continued for an additional 12 months. Definitive therapy is again recommended if TRAb levels remain high after 12 months of additional ATD treatment. Even in patients who have relapsed after the cessation of MMZ, definitive treatment is generally recommended. However, long-term, low-dose MMZ can be an option for patients who do not want definitive treatment [4]. Sequential monitoring of serum TRAb levels can be used to determine the duration of ATD therapy [19].

2. Radioactive iodine therapy

RAI therapy has been used extensively in patients with GD over the past few decades, especially in the United States, because it relieves thyrotoxicosis symptoms within weeks. Sufficient RAI activity is recommended, with a mean dose of 10 to 15 mCi (370–555 MBq) to make the patient hypothyroid [3]. To improve its effectiveness, an ATD can be stopped 3 to 7 days before and after therapy. It may prevent a thyrotoxicosis aggravation from a long-term perspective, especially in elderly people and patients with underlying cardiovascular disease [20,21]. Although RAI is not associated with an increased risk of cancer, it can cause or worsen ophthalmopathy. After RAI therapy, thyroid function must be monitored for life; if present, hypothyroidism should be treated. The risks of hypothyroidism and recurrent hyperthyroidism correlate with the residual thyroid tissue volume. The indications and contraindications for RAI treatment are as follows [3]. Unsurprisingly, pregnancy and breastfeeding are contraindicated, and surgery should be performed if thyroid cancer is confirmed or suspected. In patients planning pregnancy with severe hyperthyroidism who are expected to receive high doses of ATDs, RAI treatment can be attempted 4 to 6 months prior to pregnancy. For safety reasons, conception should be postponed until at least 6 months after RAI in both males and females. Young age (< 5 years), because of a greater long-term theoretical risk of malignancy, and active GO, which
can be exacerbated by RAI, are also contraindicated [18,22]. RAI therapy should be considered in the absence of skilled surgeons. If hyperthyroidism persists for 12 months after RAI, a second course can be considered.

3. Surgery
Thyroidectomy is generally used in patients with a large goiter or suspected thyroid cancer, women who wish to become pregnant, and patients who do not want to receive ATD or RAI therapy. Total thyroidectomy is preferred to subtotal thyroidectomy to reduce the risk of recurrent hyperthyroidism [23]. Thyroid hormone levels should be normal before thyroidectomy to reduce the risk of complications [24]. In addition to ATDs, oral iodine (5–10 drops of Lugol’s solution or 1–4 drops of saturated potassium iodide solution thrice daily) can be helpful in controlling thyrotoxicosis during 1 to 2 weeks before surgery. The indications and contraindications for surgery are summarized in the 2016 ATA guidelines [3]. The indications are as follows: patients with pressure symptoms, a large goiter of ≥ 80 g ( > 50 mL in the ETA guidelines), a nodule suspected to be thyroid cancer, a large nodule, a high TRAb titer, or moderate-to-severe ophthalmopathy with concerns for aggravation with RAI therapy. Surgery is not recommended when GD is accompanied by a disease with a high expected surgical risk. In these cases, there are concerns regarding deterioration and short life expectancy.

Remission rate with antithyroid drugs

Because recurrence is common within 1 year of discontinuing an ATD, remission is defined as normal thyroid function 1 year after discontinuation of treatment. Clinical guidelines for treating GD suggest that the appropriate period of ATD treatment is 12 to 18 months based on previous meta-analyses [25,26]. Patients with severe hyperthyroidism, large goiters, or persistently high titers of TRAb are most likely to relapse when treatment is stopped [5-7]. Male sex, young age, and current smoking are also related to GD relapse [5-7]. In 2016, Vos et al. [8] conducted a prospective study to design a predictive score, called the GREAT (Graves’ Recurrent Events After Therapy) score, by combining the four independent risk factors of age, free T4 level, TRAb titer, and goiter size, particularly in recurrent GD.

The long-term remission rate after ATD treatment in patients with GD is approximately 50%, ranging from 30% to 70% [2]. In the United States, the remission rate was 20% to 30% after ATD treatment for 12 to 18 months, whereas in Europe, it was 50% to 60% after 5 to 6 years of treatment [27]. However, a systematic review and meta-analysis by Azizi et al. [15-17] showed that the duration of ATD treatment was positively associated with remission rate. When comparing the usual treatment group for 1 to 2 years and the long-term administration group for 6 to 10 years, the recurrence rate was 53% and 15%, respectively. A recent Korean study also demonstrated that the duration of ATD therapy was inversely associated with relapse rate in patients with GD and that ATD treatment duration was an independent risk factor for relapse [28].

Cases in which treatment modality was inevitably changed

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Nowon Eulji University Hospital (IRB No: NEUH 2022-10-017) in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the IRB due to the use of anonymized data and the retrospective nature of the study.

In this section, I will present typical cases in our clinic where remission is difficult even with a fairly long ATD period. All of these patients had to change their treatment strategies to prevent frequent relapses and improve their QoL. The four cases described below are patients who had been treated with an ATD for 5 to 10 years.

1. Surgery after antithyroid drug treatment

1) A 56-year-old female who was treated with an antithyroid drug for 8 years

The first case involved a 56-year-old female who underwent surgery after long-term ATD treatment. During the 8 years from 2010 to 2018, her thyrotoxicosis symptoms improved after taking an ATD, but recurred several times despite maintaining a constant dose of 2.5 mg MMZ every other day or 2.5 mg daily. Her body weight fluctuated between 54 and 64 kg. Her TRAb levels did not fall within normal range during the treatment period. She also had a 60 g goiter with multiple thyroid nodules but preferred to continue drug treatment because there were no compressive symptoms. Eight years after the initial diagnosis, a 6 mm highly suspicious nodule was newly detected and found to be atypia of undetermined significance by fine-needle aspiration cytology. Despite long-term ATD treatment, her TRAb titer did not decrease and suspicious nodules were found; therefore, she decided to undergo thyroidectomy. The final diagnosis was nodular hyperplasia after surgery. She had normal thyroid levels while receiving levothyroxine...
and her TRAb titer changed to negative. Most importantly, before the surgery, she visited our hospital four to six times per year and had blood samples drawn every visit, but now, she visits only twice a year and has a blood test once a year. This means that her QoL has improved significantly even though she has gained 4 kg over 2.5 years after the surgery. This is a case of GD where a patient with a 60 g goiter and a suspicious thyroid nodule was finally treated with surgery.

2) Surgical management in patient with a large goiter and a suspicious thyroid nodule
According to clinical guidelines for GD [3,4], patients with persistently high TRAb levels after 12 to 18 months can continue MMZ therapy and repeat the TRAb measurement after an additional 12 months, or undergo definitive therapy such as RAI therapy or thyroidectomy. In this patient, TRAb levels remained high despite long-term ATD treatment. Recurrence occurred even while taking the drug; therefore, definitive therapy was recommended several times. A large goiter was accompanied by multiple thyroid nodules, and a small suspicious nodule was newly detected during follow-up. In a recent meta-analysis by Staniforth et al. [29], the incidence of thyroid carcinoma in GD was reported as roughly 2.5 times that in the overall global population, and a coincidence of GD and thyroid nodules was found in 23% of patients with GD. Furthermore, a previous review and meta-analysis found that the presence of thyroid nodules increased the risk of thyroid cancer [26,30]. Although further research is needed, clinicians should consider screening selected patients with GD for nodules.

2. Radioiodine therapy after antithyroid drug treatment

1) A 30-year-old male who was treated with an antithyroid drug for 10 years
In the second case, RAI treatment was administered after 10 years of MMZ therapy. A 30-year-old man was diagnosed with hyperthyroidism in his early twenties. He had an irregular lifestyle and used to stay up all night playing games. He stopped taking the drug at his own judgement and visited our hospital only when thyrotoxicosis symptoms, such as weight loss, loose stools, and hand tremors, worsened. His body weight fluctuated between 56 and 66 kg. Whenever he arrived, his thyroid hormone levels were high and his TRAb titer was positive, although his goiter was not as large as expected. The patient did not have GO; therefore, RAI treatment was recommended. Initially, the patient and his mother did not want RAI treatment because of a vague sense of anxiety regarding radiotherapy. After the patient graduated from college, he finally decided to receive RAI treatment. Six months after the RAI therapy, his TRAb level normalized, and his MMZ dose was decreased from 25 to 2.5 mg daily. The patient gained 3 kg over 1.5 years. He has also halved the number of hospital visits and blood tests.

2) Radioactive iodine treatment in patient with poor adherence to medication
This patient had poor adherence with the ATD, but only had a mild goiter that did not require surgery. His TRAb titer remained positive despite long-term ATD prescription, and there was recurrence even while taking the drug because of a stressful lifestyle. The success rate of initial RAI therapy was reported to be 73.7% with 370 MBq (10 mCi) and 80.8% with 555 MBq (15 mCi) in a previous randomized controlled study [31]. RAI therapy is less invasive and more cost-effective than surgery. Therefore, many patients who fail to treat GD with an ATD only choose RAI therapy as a second-line treatment. Park et al. [32] reported that the remission rate of RAI therapy as a second-line treatment was 62.8% in Korea.

3. Surgery after antithyroid drug treatment and radioiodine therapy

1) A 22-year-old female who failed to maintain euthyroidism with both antithyroid drug and radioactive iodine treatments
The third case involved a 22-year-old female who had recently undergone surgery after receiving both ATD and RAI therapy. When she was 16 years old, she received high-dose MMZ (30–60 mg) for 9 months, but her thyroid hormone levels did not improve and TRAb was positive. Owing to thyrotoxicosis symptoms such as difficulty breathing, she underwent RAI treatment at 8 mCi. Immediately after 2 months of treatment, her thyroid hormone levels normalized, and her symptoms improved. She did not visit the hospital thereafter. Five years later, she came to the outpatient clinic after her thyrotoxicosis symptoms worsened. At that time, she had lost 20 kg of body weight and had severe thyrotoxicosis symptoms, such as palpitations, heat intolerance, and insomnia. She also had a large goiter (approximately 50 mL), when estimated by ultrasound. The patient was restarted on 30 mg MMZ. On the first day of treatment, she complained of fever and a sore throat. Her white blood cell count started to drop (absolute neutrophil count, 2,238/μL), and MMZ was discontinued to prevent further decreases in neutrophil numbers.

Considering the patient’s QoL, surgery was recommended and she was hospitalized for preoperative thyroid hormone regulation. After 3 weeks of treatment with potassium iodide (starting dose of
180 mg iodine/day, increasing to 480 mg iodine/day), prednisolone, and cholestyramine, her thyroid hormone levels were controlled and total thyroidectomy was performed. In this case, the treatment goal was not achieved with ATD or RAI therapy. The side effects of MMZ were also concerning, and surgery was recommended to reduce the risk of recurrence. After surgery, she had normal thyroid levels while receiving levothyroxine, and her TRAb level decreased to within the normal range. The patient also halved the number of hospital visits and blood tests. She visited our hospital more than 10 times a year before surgery; afterward, she visited the hospital three to four times a year.

2) Graves disease in the young
Graves hyperthyroidism is a relatively rare condition in children. While childhood GD accounts for 5% of all GD cases throughout life [33], its incidence before 15 years old is much lower [34]. Treatment options are similar to those in adults: ATD, RAI, or surgery. However, the risks and benefits of each modality are different from adults. The advantages and disadvantages of RAI and surgery should be carefully considered in young people planning definitive treatment and thyroid hormone replacement.

According to the 2022 ETA guideline for the management of pediatric GD [18], the treatment duration should be at least 3 years, and potentially 5 years or longer, if needed. These guidelines suggest that there are factors associated with an improved likelihood of remission following ATD treatment in children; older age, female sex, ethnicity (e.g., Caucasian), small goiter size, mild biochemical derangement at diagnosis, lower TRAb titer, history of other autoimmune conditions, and duration of ATD treatment [35-37]. The overall remission rate after 2 years of ATD treatment in pediatric patients with GD is 20% to 30% [38]. The remission rate increases with longer treatment durations. Remission rates of 24.1%, 31.0%, and 43.7% were reported after treatment durations of 1.5 to 2.5, 2.5 to 5, and 5 to 6 years, respectively [39]. There is no established role for immunomodulation with new agents, such as biologics, in young patients with GD. In recent studies, young people diagnosed and treated for GD may have a lower QoL than their healthy peers [40]. Long-term MMZ or CBZ should be the mainstay of treatment for children with GD.

4. Long-term low-dose antithyroid drug treatment

1) A 45-year-old male who maintained euthyroidism with long-term low-dose methimazole
The final case was a 45-year-old male who was diagnosed with GD 13 years prior to relapse. He was started on 30 mg MMZ, which was reduced to 5 mg every other day after 3 years of treatment. The patient did not visit the hospital as soon as his symptoms improved. One year after discontinuing treatment, he visited our clinic for thyrotoxicosis symptoms, such as weight loss of 5 kg and dyspnea on exertion. He was diagnosed with GD relapse based on high thyroid function test results and positive TRAb titers. MMZ 30 mg was restarted and the dose was rapidly reduced to 5 mg per day. But each time he overworked, his symptoms worsened despite the administration of 5 mg MMZ. After 18 months of retreatment, his thyroid hormone levels and TRAb titers decreased to normal levels and stabilized. During nine years of low-dose MMZ treatment, he visited the hospital thrice a year without recurrence, and blood tests were performed once a year.

2) Effects and safety of long-term low-dose antithyroid drug treatment
This case was considered to have a high possibility of remission with long-term low-dose ATD treatment; therefore, drug treatment was maintained rather than using definitive treatment. Indications for ATD are simply those cases with a high likelihood of remission and should be considered even if hyperthyroidism persists or relapses. The most important contraindications are the serious side effects of ATD treatment. According to a recent large amount of data on long-term ATD treatment for GD, it is expected that low-dose MMZ maintenance will have few side effects and can reduce the risk of recurrence. Azizi et al. [15-17] reported that 60 to 120 months of MMZ treatment may be safe and effective. Comparing the normal-treatment group (1–2 years) and the long-term administration group (6–10 years), the recurrence rates were 53% and 15%, respectively. There was no significant difference in the frequency of side effects between the two groups. The authors suggested that after administering low-dose MMZ for 12.8 years, when the discontinuation and maintenance groups were observed for 6 years, there was no recurrence in the maintenance group. Meanwhile, recurrence occurred in 19% (6 of 32) of the discontinuation group [41]. A recent Korean study also demonstrated that the duration of ATD therapy was inversely associated with the relapse rate in patients with GD and that ATD treatment duration was an independent risk factor for relapse [28]. The authors showed that the relapse rate according to ATD treatment duration was 42.4% at 1 year, 38.5% at 2 years, 33.8% at 3 years, 31.7% at 4 years, 30.2% at 5 years, 27.8% at 6 years, and 19.1% at > 6 years.

According to a recently published study by Bandai et al. [19], the time for the remission rate to reach a certain level in adults after long-term administration of ATDs was approximately 6.8 years (4.0–10.9 years). When patients were classified based on the pattern of changes in TRAb levels during long-term ATD administration, a positive antibody result after 5 years of treatment reflected a
19.8% remission rate. The remission rate was 88.9% when the antibody titers were reduced and maintained over 5 years of medication but was only 37.2% when the antibody titers fluctuated repeatedly. Therefore, if long-term administration of ATDs is planned, changes in TRAb levels for at least 5 years should be observed.

**Comparison of each treatment modality**

Regarding the choice of treatment, therapeutic guidelines recommend that physicians and patients decide after discussing the mechanism, strengths and weaknesses, duration, side effects, and costs of each choice. More than 90% of patients with GD depend on their doctors when choosing treatment modality, thus requiring extensive consultation.

1. **Treatment outcome**

Surgery is more advantageous because it significantly improves biochemical tests faster than other treatments, and there is little risk of hyperthyroidism recurrence. Meanwhile, the incidence of hypothyroidism is significantly high even when taking levothyroxine. The risk of hypothyroidism during ATD treatment was approximately 9%, which is lower than that with other treatments; however, the risk of hyperthyroidism recurrence was 30% to 70%, even if it was reduced to 15% during long-term treatment [16,42-44]. RAI treatment was at the midpoint between the two treatments; the occurrence of hypothyroidism was 7% to 28% and reported even after 14 years of levothyroxine treatment [42,43, 45,46]. The recurrence of hyperthyroidism after RAI treatment was 10% to 20%, comparable to that of long-term ATD treatment [16,42-44].

2. **Adverse events**

Considering the trend of choosing long-term treatment with ATDs over definitive therapy, it is important to compare the major side effects of ATDs to those of other treatments. Adverse events (AEs) associated with ATDs can be subdivided into major events, such as agranulocytosis, hepatotoxicity, pancreatitis, or vasculitis, and minor events, such as rash, gastric intolerance, and arthralgia.

When comparing ATD treatment and RAI therapy, major AEs were more likely to occur during ATD treatment, particularly at high doses of MMZ. A retrospective analysis found an 8.6-fold increased risk of agranulocytosis with MMZ doses greater than 40 mg/day, but no cases were reported in patients receiving MMZ doses less than 30 mg/day [47]. Azizi and Malboosbaf [15] recently reported 19.1% AEs and 1.5% major AEs in a systematic review of six studies with over 1,500 patients treated with an ATD for a median of 6 years. They reported that major AEs occurred within the first 3 months of treatment and decreased significantly with long-term therapy. These data suggest that long-term ATD treatment is safer than expected if the lowest dose is administered and the patient is monitored well.

Two retrospective studies reported that using low doses of MMZ offers better outcomes and fewer side effects for GO than RAI treatment [48,49]. A systematic review and meta-analysis of two randomized controlled trials involving 425 adults with GD identified that thyroid eye disease developed or worsened in 38% of cases treated with RAI and 19% of those treated with MMZ, giving a relative risk of 1.94 [50].

3. **Quality of life**

The incidence and progression rate of ophthalmopathy are reported to be significantly higher with RAI treatment than with ATD treatment. ThyPRO is a questionnaire on thyroid-related QoL that is responsive to the treatment used for benign thyroid diseases [51]. According to a recent study by Töring et al., [52] regardless of treatment modality, patients with GD had worse thyroid-related QoL over 6 to 10 years after diagnosis than the general population. They also reported that patients receiving RAI therapy had worse thyroid-related QoL than those with 12 to 18 months of ATD therapy or thyroidectomy (ThyPRO score: RAI vs. ATD or thyroidectomy, 27 vs. 21 or 22). Although previous studies have found no significant differences in long-term QoL among the three treatment modalities, these studies were small and did not use thyroid-specific QoL [53,54]. Therefore, further research in Korea is required. In terms of posttreatment weight gain, RAI-treated patients were at a disadvantage compared to long-term ATD-treated patients [55]. This difference could be explained by the higher frequency of hypothyroidism in the RAI-treated group than in the ATD group despite taking levothyroxine after treatment.

**Antithyroid drugs under development**

Although classic treatments control the disease quite well, they are not based on the pathological mechanisms of GD, an immune disorder [9]. Several factors, such as genetics, interactions between endogenous and environmental factors, and immune system dysregulation, have been implicated in the pathogenesis of GD [10]. TRAb is a pathogenesis determinant of GD and its extrathyroidal manifestations.

With this in mind, new treatments are under development. There are ways to prevent the proliferation of T and B cells, which play a central role in the immune response, or to block the connection between T cells and B cells. A treatment may block inflamma-
ory substances that activate T cells, such as tumor necrosis factor-α (TNF-α) or interleukin-6 (IL-6), or inhibit antibody production in B cells. A treatment can also block TSH receptor antibodies or insulin-like growth factor type 1 receptor (IGF-1R) antibodies, which are involved in newly discovered mechanisms of ophthalmopathy development [56,57]. ATX-GD-59, an immunotherapeutic agent specific for the TSH receptor peptide antigen, has been shown to have positive effects against GD in a phase 1 clinical study [58]. A chimeric antibody against CD20 (rituximab) showed some therapeutic effects in GO but not in GD [59,60]. Drugs for treating GO that target cytokines, such as anti-IL-6 (tocilizumab) or anti-TNF-α (etanercept), have been developed [61]. The immunosuppressant (Ki-70), which antagonizes the action of TRAbs, has been shown to be effective in animal experiments [62]. Teprotumumab, a human monoclonal anti-IGF-1R blocking antibody, is very effective in patients with GO [63,64].

**Conclusion**

GD recurs and worsens repeatedly, affecting the patient’s QoL. Current treatments for GD are inadequate for completely restoring thyroid function to a normal state. Based on the cases in the text, there is a significant gap between the current guidelines and the conditions encountered by patients in clinical practice.

In conclusion, to treat GD, it is important to induce remission by appropriately evaluating the patient’s response to the drug, sometimes stopping ATD treatment at an appropriate time, and actively recommending a switch to a definitive therapy, such as RAI or surgery, in addition to standard clinical guidelines. It is sometimes encouraged to continue drug administration for an extended time, because more remission is expected with longer ATD use. If long-term administration of ATD is planned, the lowest possible dose should be used to avoid side effects. The ATD must be finely adjusted to improve the patient’s QoL, reduce a recurrence, and prevent progression to hypothyroidism. As remission rates are predicted by the pattern of changes in TRAb titer, it is necessary to carefully monitor it and to consider RAI or surgery if required.

**Notes**

**Conflicts of interest**

No potential conflict of interest relevant to this article was reported.

**Funding**

None.

**ORCID**

Hyo-Jeong Kim, https://orcid.org/0000-0002-2180-891X

**References**


https://doi.org/10.12701/jyms.2022.00444
38. Wood CL, Cole M, Donaldson M, Dunger DB, Wood R, Morrison N, et al. Randomised trial of block and replace vs dose ti-
62. Furmaniak J, Sanders J, Young S, Kabelis K, Sanders P, Evans M, et al. In vivo effects of a human thyroid-stimulating monoclonal autoantibody (M22) and a human thyroid-blocking autoanti-


The pathological hallmark of rheumatoid arthritis (RA) is a synovial pannus that comprises proliferating and invasive fibroblast-like synoviocytes, infiltrating inflammatory cells, and an associated neoangiogenic response. Animal models have been established to study these pathological features of human RA. Spontaneous and induced animal models of RA primarily reflect inflammatory aspects of the disease. Among various induced animal models, collagen-induced arthritis (CIA) and collagen antibody-induced arthritis (CAIA) models are widely used to study the pathogenesis of RA. Improved transplantation techniques for severe combined immunodeficiency (SCID) mouse models of RA can be used to evaluate the effectiveness of potential therapeutics in human tissues and cells. This review provides basic information on various animal models of RA, including CIA and CAIA. In addition, we describe a SCID mouse coimplantation model that can measure the long-distance migration of human RA synoviocytes and cartilage destruction induced by these cells.

Keywords: Animal models; Cell movement; Rheumatoid arthritis; Severe combined immunodeficient mice; Synoviocytes

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disorder that affects approximately 1% of the global population. It is characterized by tumor-like expansion of the synovium, angiogenesis, and destruction of the articular cartilage and bone [1]. Despite the advent of anticytokine therapies that ameliorate the inflammatory manifestations of RA, there is no curative treatment and the pathogenesis of the disease is not fully understood. In RA joints, various cell populations, including innate immune cells, adaptive immune cells, endothelial cells, and fibroblast-like synoviocytes (FLSs), are activated [1]. Resident synoviocytes participate in the chronic inflammatory response and joint destruction in RA, and in fact, these cells represent the major cell population in the invasive pannus [2]. RA-FLSs have the potential to secrete matrix-degrading enzymes (matrix metalloproteinase 3 [MMP3] and MMP9), pro-inflammatory cytokines (interleukin 1 [IL-1] and IL-6), chemokines (IL-8 and C-C motif chemokine ligand 2), and angiogenic factors (vascular endothelial growth factor and placental growth factor) [2]. Moreover, although RA synoviocytes are primary cells, they proliferate abnormally and display resistance to Fas-mediated apoptosis, similar to cancer cells [2,3]. During RA development, the phenotype of RA-FLSs is altered to an invasive and aggressive behavior, with increased migratory ability and reduced attachment-dependent growth, leading to articular cartilage destruction [2,4]. RA-FLSs can spread by migrating from the af-
fected site to distant unaffected joints in immune-deficient mice [5]. In this regard, antimigratory agents targeting RA synoviocytes may be of therapeutic benefit. Despite the importance of FLSs in RA pathogenesis, no attempt has been made to develop an animal model capable of specifically identifying FLS migration and invasiveness. This review summarizes the immunological properties of mouse models of RA and describes humanized models that are capable of measuring the migration and invasiveness of human synoviocytes.

**Ethical statements:** This study was approved by the Institutional Animal Care and Use Committee (IACUC) of the Catholic University of Korea (IACUC No: CUMC-2020-0182) and the Institutional Review Board (IRB) of the Catholic Medical Center, the Catholic University of Korea (IRB No: KC14TASI0898).

### Murine models of rheumatoid arthritis

As RA is an autoimmune disease characterized by joint destruction, careful consideration is needed when choosing the correct animal model for different *in vivo* experiments. Therefore, careful analysis of specific aspects of the disease and specific knowledge targeted in each study must be considered when choosing an RA animal model. Animal models of RA can be broadly divided into induced and spontaneous models, including mutant and genetically altered strains. The induced models may be polyarthritis (systemic response), which is more likely to be severe, or monoarthritis (local response). Spontaneous models progress naturally and generally involve nonresolving, chronic conditions. In this study, we have summarized the involvement of immune cells and cytokines in these models (Table 1).

<table>
<thead>
<tr>
<th>Model</th>
<th>Immune cell</th>
<th>Cytokine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen-induced arthritis</td>
<td>Monocytes/macrophages, dendritic cells, granulocytes, synoviocytes, T cells, B cells</td>
<td>TNF-α, IL-1β, IL-6, IL-17, IL-23, IL-32, MCP-1, MIP1α</td>
</tr>
<tr>
<td>Antigen-induced arthritis</td>
<td>Monocytes/macrophages, dendritic cells, granulocytes, synoviocytes, T cells, B cells</td>
<td>TNF-α, IL-1β, IL-6, IL-17, IFN-γ</td>
</tr>
<tr>
<td>Proteoglycan-induced arthritis</td>
<td>Monocytes/macrophages, granulocytes, synoviocytes, T cells, B cells</td>
<td>TNF-α, IL-1β, IL-6, IL-12, MCP-1, MIP1α, MIP-2</td>
</tr>
<tr>
<td>Collagen antibody-induced arthritis</td>
<td>Monocytes/macrophages, synoviocytes</td>
<td>IL-1β, IL-6, TNF</td>
</tr>
<tr>
<td>HuTNF transgenic mice</td>
<td>Monocytes/macrophages, granulocytes</td>
<td>TNF-α, IL-1β</td>
</tr>
<tr>
<td>IL-1 receptor antagonist knockout mice</td>
<td>Monocytes/macrophages, synoviocytes</td>
<td>IL-1, IL-17</td>
</tr>
</tbody>
</table>

**1. Induced models of rheumatoid arthritis**

RA in animals is induced by treatment with agents, such as antigens, antibodies, adjuvants, and serum. Examples of induced mouse models of RA include collagen-induced arthritis (CIA), adjuvant-induced arthritis, proteoglycan-induced arthritis (PGIA), and collagen antibody-induced arthritis (CAIA).

1) **Collagen-induced arthritis**

CIA is the most frequently used animal model of RA because it shares both immunological and pathological features with human RA, including symmetric joint involvement, synovitis, and cartilage and bone destruction [2,5]. It is elicited in genetically susceptible mouse strains by immunization with type II collagen (CII) emulsified in complete Freund’s adjuvant (CFA). The requirement of T and B cells in the development of CIA is clear [6]. The autoimmune response to CII is characterized by both the stimulation of CII-specific T cells and secretion of specific immunogens and autoantigens [6]. Moreover, CD4+ T cells are believed to participate in the induction phase of the disease, supporting the activation of collagen-specific B cells [6,7].

Various cytokines have been implicated in the pathogenesis of RA through time-dependent immune system activation [8]. At the time of the clinical onset of arthritis, proinflammatory mediators (tumor necrosis factor alpha [TNF-α], IL-1β, and IL-6) and anti-inflammatory mediators (IL-10, IL-1 receptor antagonist [IL-1Ra], and transforming growth factor-beta isoforms [TGF-β1, TGF-β2, and TGF-β3]) can be detected in CIA joints [8-10]. Because interferon gamma (IFN-γ) inhibits Th17 cell development, IFN-γ receptor-knockout mice develop CIA more readily [11]. IL-23 is also required for the induction of joint inflammation by mediators including IL-17 [12,13].

2) **Antigen-induced arthritis**

Virtually any animal species can be used to generate antigen-in-
duced arthritis (AIA) models. In mice, ovalbumin and bovine serum albumin (BSA) are commonly used, and modified antigens (e.g., methylated antigens) can induce chronic arthritis [14]. Antigens, such as methylated BSA, are cationic substances that bind negatively to cartilage [14,15]. When antigens are injected into one or multiple joints, inflammation progresses quickly and complement is activated locally, resulting in cartilage destruction [14]. AIA is T cell-dependent in hypothymic nu/nu mice [14]. In a recent study, both IL-23p19−/− and IL-17Ra−/− mice displayed significantly milder arthritis than wild-type mice, demonstrating that AIA progression is dependent on IL-23 and IL-17Ra signaling [16,17].

3) Proteoglycan-induced arthritis
PGIA is a progressive polyarthritis characterized by symmetrical synovitis, marginal erosion, pannus formation, and synovial infiltration of immune cells [18]. It is induced by the injection of human cartilage proteoglycans (PGs) into BALB/c (H-2d) mice, which exhibit remission and exacerbation. The first and fourth injections contain PG/CFA, the second and third injections contain PG/incomplete Freund's adjuvant (IFA), and arthritis develops on approximately day 11 and reaches maximum severity 2 to 4 weeks after the last PG injection [19]. Mice with PGIA display CD4+ T cell responses along with an antibody response to PG, and immunoglobulin G (IgG) 2a antibody levels are correlated with disease severity [18]. Although PGIA is a predominantly Th1-type arthritis model, it has been reported that IL-4 deficiency increases the severity of PGIA [20]. In addition, treatment with IL-4 or IFN deficiency suppresses PGIA [21].

4) Collagen antibody-induced arthritis
CAIA can be induced in many susceptible mouse strains, and clinical signs of arthritis generally appear a few days after antibody administration [22]. A cocktail of anti-CII monoclonal antibodies is administered to induce arthritis in the mice. Intrapерitoneal injection of lipopolysaccharide increases disease severity and the incidence of arthritis; however, it is not essential for disease induction [22].

Disease initiation in CAIA models occurs mainly independently of B and T cells; however, immune cells modulate inflammation during the effector phase [23]. The main effector cells appear to be neutrophils and macrophages, which are activated by immune complexes formed in the joints via binding of CII antibodies to cartilage surfaces [23]. Typical pathological changes observed in RA, such as synovitis, pannus formation, and cartilage and bone destruction, are observed in the joints of animals with CAIA [24,25]. Although the cytokines involved in the pathogenesis of CAIA have not been studied in detail, the involvement of IL-1β, IL-6, and TNF is anticipated [24,26].

2. Genetically modified models of rheumatoid arthritis
Genetic manipulations that affect the pathogenesis of arthritis can lead to arthritis in a variety of mice.

1) Human tumor necrosis factor transgenic mice
The first TNF transgenic mouse model was generated by Keffer et al. in 1991 [27]. They generated transgenic mice expressing wild-type and 3′-modified human TNF-α transgenes [27]. In this mouse model, synovial hyperplasia and inflammatory cell infiltration were observed in the joints after 3 to 4 weeks of age, and pannus formation, cartilage destruction, and bone erosion were observed in the mice at approximately 10 weeks of age [28,29]. This model highlights the importance of TNF-α in the pathogenesis of arthritis and can be used for the development of TNF inhibitors.

2) Interleukin-1 receptor antagonist knockout mice
IL-1 is an important inflammatory cytokine produced by a variety of cell types, including activated monocytes, macrophages, fibroblasts, and synovial cells [30]. In contrast, the IL-1 inhibitor IL-1Ra regulates the activity of IL-1 as an anti-inflammatory protein that binds to the IL-1 receptor [31,32]. It has been reported that IL-1Ra knockout mice develop spontaneous arthritis mediated by the amplification of Th17-dependent inflammation [32,33]. In a BALB/c background, polyarthritis develops starting at 5 weeks of age, and by 12 weeks of age, almost all mice are affected [33]. Histopathological analysis revealed marked synovial and periarthritic inflammation, with articular destruction caused by the invasion of granulation tissues, closely resembling RA in humans [32]. Moreover, high levels of antibodies against IgG, CII, and double-stranded DNA were detectable in the sera of these mice [32,33].

3. Collagen-induced versus collagen antibody-induced arthritis
The most commonly used mouse models are CIA and CAIA. CAIA bypasses the host’s generation of autoantibodies to CII; thus, it can be induced in mice that do not possess CIA-susceptible major histocompatibility complex haplotypes (H-2q and H-2r), such as BALB/c and C57BL/6 mice [22,24]. Therefore, CAIA can be induced in most mouse strains, including transgenic and knockout mice, with an arthritis incidence approaching 100% [22]. This model is ideal for screening and evaluating anti-inflammatory agents without the effects of CFA or IFA, which strongly
Table 2 presents the similarities and differences between the CIA and CAIA models, and a time comparison.

Humanized models of rheumatoid arthritis

Mouse models of RA have been used for decades to study the immunopathogenesis of the disease and to explore therapeutic strategies. Nevertheless, differences in the immune systems of humans and mice have limited confidence in the success of disease treatments. To overcome this issue, severe combined immunodeficiency (SCID) mice have been used to investigate human tissues in autoimmune disease [34-37].

The use of SCID mice provides a novel model for studying tissues and cells from patients with RA [5,36]. In this review, we introduce a method that can measure cell migration and the ability to destroy human cartilage by applying synovial cells isolated from patients with RA in SCID mice.

1. Model using synoviocyte migration in severe combined immunodeficiency mice

FLSs, which are components of the synovial membrane, play a critical role in RA pathogenesis through aggressive migration and matrix invasion [2,4]. A model for measuring the migration of synoviocytes to the site of inflammation was established by subcutaneous induction of inflammation with CFA in SCID mice and then injecting synoviocytes from patients with RA around the site of inflammation [38]. One day after the CFA injection, RA-FLSs labeled with fluorescent dyes were implanted intradermally into the mice at a fixed distance (1.2 cm) from the injection site (Fig. 1). Five days after implantation, skin samples were obtained from the FLS-implanted site, CFA-injected site, and a region between these two sites (sites a, c, and b in Fig. 1). The migration of synoviocytes was analyzed according to the presence or absence of human leukocyte antigen class I (+) cells in each tissue site obtained at the end of the experiment [38].

2. Model using synoviocyte migration and invasion in severe combined immunodeficiency mice

RA starts in a few joints; however, as the disease progresses, it can affect all joints [5]. Interestingly, it has been reported that RA synoviocytes in a SCID mouse model can travel long distances through the bloodstream and migrate toward, attach to, and invade the distant cartilage matrix [5]. This model may be useful for elucidating the role and mechanism of an agent targeting activated synoviocytes in RA. In this section, we summarize the protocol for developing a synoviocyte migration and invasion model in SCID mice.

Table 2. Similarities and differences between animal models of CIA and CAIA

<table>
<thead>
<tr>
<th>Variable</th>
<th>CIA</th>
<th>CAIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction method</td>
<td>Type II collagen/CFA</td>
<td>Type II collagen monoclonal antibodies</td>
</tr>
<tr>
<td>Period</td>
<td>7–8 weeks</td>
<td>1–2 weeks</td>
</tr>
<tr>
<td>Mouse strains</td>
<td>Restricted to select mouse strains</td>
<td>Many mouse strains</td>
</tr>
<tr>
<td>Feature of arthritis</td>
<td>Polyarthritis</td>
<td>Polyarthritis</td>
</tr>
<tr>
<td>RF and ACPA</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

CIA, collagen-induced arthritis; CAIA, collagen antibody-induced arthritis; CFA, complete Freund’s adjuvant; RF, rheumatoid factor; ACPA, anticitrullinated protein/peptide antibodies.
1) Implantation experiments
FLSs were prepared from synovial tissues of patients with RA [4,38]. Normal human cartilage was obtained from the nonarthritic knee joints of patients undergoing amputation [5,39]. Cartilage and RA synoviocytes in sponges were coimplanted into SCID mice at the primary site (6–8 weeks), and cartilage without synoviocytes was implanted at the contralateral site [5,35,39]. After 60 days, the implants were removed and either immediately embedded in a snap-frozen medium or fixed in 4% buffered formalin for paraffin embedding [5,37,39]. Using standard hematoxylin and eosin staining, each specimen was evaluated for invasion and perichondrocytic cartilage degradation in the implanted cartilage.

A procedural overview of the current model is shown in Fig. 2.

2) Histological score
The cartilage invasion was evaluated on a 0-to-3-point scale indicating the depth of cell invasion (0, no or minimal invasion; 1, visible invasion [2 cell depths]; 2, invasion [5 cell depths]; and 3, deep invasion [10 cell depths]).

Perichondrocytic cartilage degradation was assessed by scoring the diameter of the chondron (0, no degradation and sharp halo; 1, visible degradation [1 diameter of the chondron]; 2, degradation [1–2 diameters of the chondron]; and 3, intensive degradation [2 diameters of the chondron]) [36,39].

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
This work was supported by grants from the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (2019R1A2C2010897).

Author contributions
Conceptualization, Data curation, Resources, Software: all authors; Formal analysis: SAY, GHJ; Funding acquisition, Validation: SAY, JSK; Methodology, Investigation, Project administration, Visualization, Supervision: SAY; Writing-original draft: SAY; Writing-review & editing: SAY, JSK.

ORCID
Jin-Sun Kong, https://orcid.org/0000-0003-4878-8733
Gi Heon Jeong, https://orcid.org/0000-0003-2935-0293
Seung-Ah Yoo, https://orcid.org/0000-0003-4878-8733

Conclusion
The careful selection, design, and implementation of animal models are important strategies for RA treatment. In this review article, we describe a variety of mouse models that are widely used or that exhibit pathologies similar to those of arthritis in humans. These models were divided into induced and genetically modified groups. This summary of the characteristics of each model will help researchers to select the best animal model for evaluating the effectiveness of experimental treatments for RA. Furthermore, humanized models are extremely important for investigating the role and mechanism of RA-FLSs targeting these cells.

References
2. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effec-


Incidence of congenital hypothyroidism by gestational age: a retrospective observational study

Ha Young Jo, Eun Hye Yang, Young Mi Kim, Soo-Han Choi, Kyung Hee Park, Hye Won Yoo, Su Jeong Park, Min Jung Kwak

Department of Pediatrics, Pusan National University Hospital, Busan, Korea

Background: Congenital hypothyroidism (CH) is the leading cause of preventable physical and intellectual disabilities. This study aimed to assess the incidence and clinical characteristics of CH in newborns.

Methods: We retrospectively reviewed the medical records of all newborns delivered at the Pusan National University Hospital between January 2011 and March 2021. The incidence of CH was compared according to gestational age, birth weight, and small for gestational age (SGA). The patients aged ≥ 3 years who could not maintain normal thyroid function and required levothyroxine treatment were diagnosed with permanent CH. Logistic regression analysis was performed to compare CH risks.

Results: Of 3,722 newborns, 40 were diagnosed with CH (1.07%). Gestational age and birth weight were significantly associated with CH incidence. The odds ratios (ORs) of CH in infants delivered at 32–37, 28–31, and < 28 weeks were 2.568 (95% confidence interval [CI], 1.141–5.778), 5.917 (95% CI, 2.264–15.464), and 7.441 (95% CI, 2.617–21.159) times higher, respectively, than those delivered at term. The ORs of CH in infants weighing 1,500–2,499 g, 1,000–1,499 g, and < 1,000 g were 4.664 (95% CI, 1.928–11.279), 11.076 (95% CI, 4.089–29.999), and 12.544 (95% CI, 4.350–36.176) times greater, respectively, than those in infants weighing ≥ 2,500 g. The OR of CH was 6.795 (95% CI, 3.553–13.692) times greater in SGA than in non-SGA infants.

Conclusion: The CH incidence in South Korea has increased significantly compared with that in the past. Gestational age, birth weight, and SGA were significantly associated with CH incidence.

Keywords: Congenital hypothyroidism; Gestational age; Incidence; Premature infant; Retrospective studies; Small for gestational age infant

Introduction

Congenital hypothyroidism (CH) is the leading cause of preventable physical and intellectual disabilities and is a common endocrine disease in pediatric patients [1,2]. Generally, patients with CH show no symptoms at birth; however, owing to the critical period of thyroid hormone-sensitive neurocognitive development during the first 3 years after birth, rapid diagnosis and treatment are required [3-6]. Newborn screening for CH, first introduced in 1972 in Quebec (Canada) and Pittsburg (United States), has become a routine practice worldwide [7,8]. The global incidence of CH is one in 3,000 to 4,000 newborns and has increased to one in 1,600 to 2,600 newborns in certain regions, such as Quebec and Massachusetts (United States) [1,9-11].

In South Korea, approximately 3,707,773 newborns underwent screening between 1991 and 2005 through the Maternal and...
Child Health Project implemented by the government. Of these, 718 newborns were diagnosed with CH, with an incidence of one in 5,164 [12]. Since 2004, the Korean government has extended the project’s scope to include all newborns. However, to date, no study has reported the incidence of CH in South Korea. Thus, this study aimed to retrospectively analyze the incidence and clinical features of CH in newborns in a South Korean hospital.

Methods

Ethical statements: The Institutional Review Board (IRB) of Pusan National University Hospital (PNUH) approved this study (IRB No: 2106-020-104) and waived the requirement for informed consent as this study analyzed anonymized patient data.

1. Participants
This retrospective study included 3,722 newborns delivered at PNUH between January 2011 and March 2021.

2. Methods
Data on gestational age, birth weight, sex, age, neonatal intensive care unit (NICU) hospitalization, morbidity, and maternal history were collected from the medical records of each patient. According to gestational age, patients were categorized into term (≥ 37 weeks), moderate-to-late preterm (32–37 weeks), very preterm (28–31 weeks), and extremely preterm (< 28 weeks) infants. Patients were also classified by birth weight as follows: normal-birth weight infants (≥ 2,500 g), low birth weight infants (LBWIs; 1,500–2,499 g), very low birth weight infants (VLBWIs; 1,000–1,499 g), and extremely low birth weight infants (ELBWIs; < 1,000 g). An infant with a birth weight less than the third percentile of the corresponding gestational age based on Korean references for birth weight by gestational age and sex was considered small for gestational age (SGA) [13].

As part of the newborn screening, levels of thyroid-stimulating hormone (TSH) and tetraiodothyronine (T4), as well as serum TSH and free thyroxine (FT4), were measured. CH was defined as TSH of ≥ 20 μU/mL or T4 of < 11.0 μg/dL on newborn screening, or TSH of ≥ 10 μU/mL or FT4 of < 0.8 ng/dL in a serum thyroid function test (TFT) analyzed by radioimmunoassay (Shinjin Medic Inc., Goyang, Korea). Newborn screening results at this hospital could only be obtained after 2 weeks; thus, serum TFT was additionally performed for preterm infants and newborns in the NICU 7 days after delivery. A serum TFT was performed prior to treatment for all infants diagnosed with CH via newborn screening.

Imaging included neck ultrasonography and thyroid scans with technetium-99m pertechnetate. The patients with ≥ 3 years of age who were prescribed levothyroxine were diagnosed with permanent CH and those who showed spontaneous recovery were diagnosed with transient hypothyroidism. Among the patients diagnosed with transient hypothyroidism, those who did not require levothyroxine treatment but had TSH levels of 5 to 10 μIU/mL and normal FT4 concentrations were diagnosed with subclinical hypothyroidism.

3. Statistical analysis
Categorical variables are presented as counts and percentages. The chi-square test was used to compare differences in the incidence of CH according to patient groups. Multiple logistic regression analysis was performed to compare the risk of CH according to participant characteristics. Statistical analyses were performed using the IBM SPSS ver. 23 for Windows (IBM Corp., Armonk, NY, USA), and statistical significance was set at p < 0.05.

Results

A total of 3,722 newborns were delivered at PNUH during the study period. Of these, 95 (2.55%) had either an abnormal newborn screening or abnormal serum TFT results; therefore, they underwent an additional serum TFT. Finally, 40 of 3,722 patients (1.07%) diagnosed with CH were included in this study, with an incidence of one in 93 newborns (Fig. 1).

Of the 40 patients with CH, 24 were female (60.0%). There were 31 (77.5%) preterm infants, with predominance of moderate-to-late preterm infants (n = 17, 42.5%). Among the 40 patients, most were LBWIs (n = 17, 42.5%). Fourteen SGA infants (35.0%) and 34 NICU infants (85.0%) were admitted due to premature birth or disease. Regarding comorbidities, bronchopulmonary dysplasia was the most common (n = 8, 20.0%), followed by intraventricular hemorrhage (n = 4, 10.0%) and sepsis (n = 2, 5.0%). Preeclampsia was the most common maternal history (n = 10, 25.0%), followed by diabetes mellitus (n = 7, 17.5%) and thyroid disease (n = 3, 7.5%). Of the mothers with thyroid disease, two had hypothyroidism and one had hyperthyroidism (Table 1).

Logistic regression analysis was performed to identify factors related to the incidence of CH. Compared with those in term infants, the risk of CH was 2.568, 5.917, and 7.441 times higher in moderate-to-late preterm (32–37 weeks), very preterm (28–31 weeks), and extremely preterm (< 28 weeks) infants, respectively (95% confidence interval [CI], 1.141–5.778, p = 0.023; 95% CI, 2.264–15.464, p < 0.001; 95% CI, 2.617–21.159, p < 0.001, respectively).

https://doi.org/10.12701/jyms.2022.00059 31
Normal newborns (n=52)

Patients with transient congenital hypothyroidism (n=20)

Subclinical hypothyroidism (n=9)

Patients lost to follow up (n=4)

All newborns delivered (n=3,722)

Normal newborn screening or serum TFT results (n=3,627)

Abnormal newborn screening or serum TFT results (n=95)

Normal newborns (n=52)

Newborns diagnosed with CH (n=40)

Patients lost to follow up (n=3)

CH patients aged <3 years (n=9)

Patients with transient congenital hypothyroidism (n=20)

Subclinical hypothyroidism (n=9)

CH patients aged ≥3 years (n=31)

Patients with permanent congenital hypothyroidism (n=7)

Patients lost to follow up (n=4)

Fig. 1. Flowchart of patient inclusion and exclusion. Newborns with congenital hypothyroidism (CH) delivered at Pusan National University Hospital between January 2011 and March 2021 are included in this study. TFT, thyroid function test.

Table 1. Characteristics of CH patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>40</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16 (40.0)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (60.0)</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td></td>
</tr>
<tr>
<td>Term, ≥37</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>Preterm</td>
<td></td>
</tr>
<tr>
<td>Moderate-to-late preterm, 32–37</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>Very preterm, 28–31</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td>Extremely preterm, &lt;28</td>
<td>6 (15.0)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td></td>
</tr>
<tr>
<td>Normal, ≥2,500</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>LBWIs, 1,500–2,499</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>VLBWIs, 1,000–1,499</td>
<td>9 (22.5)</td>
</tr>
<tr>
<td>ELBWIs, &lt;1,000</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>SGA</td>
<td>14 (35.0)</td>
</tr>
<tr>
<td>NICU hospitalization</td>
<td>34 (85.0)</td>
</tr>
<tr>
<td>Morbidity</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25 (62.5)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>4 (10.0)</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>8 (20.0)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Othersa)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Maternal history</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>20 (50.0)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>10 (25.0)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (2.5)</td>
</tr>
</tbody>
</table>

Values are presented as number only or number (%). CH, congenital hypothyroidism; LBWIs, low birth weight infants; VLBWIs, very low birth weight infants; ELBWIs, extremely low birth weight infants; SGA, small for gestational age; NICU, neonatal intensive care unit.

aIncludes persistent pulmonary hypertension of the newborn, hypoxic brain damage, and omphalitis.

The incidence of CH was 0.48% (n = 9, one in 208) in term infants and 1.68% (n = 31, one in 60) in preterm infants (p < 0.001) (Table 2).

The risk of CH was significantly higher in LBWIs than in those weighing ≥ 2,500 g. In particular, LBWIs (1,500–2,499 g), VLBWIs (1,000–1,499 g), and ELBWIs (< 1,000 g) were at 4.664, 11.076, and 12.544 times higher risk of developing CH, respectively (95% CI, 1.928–11.279, p = 0.001; 95% CI, 4.089–29.999, p < 0.001; 95% CI, 4.350–36.176, p < 0.001, respectively). Moreover, the risk of CH was 6.975 times higher in SGA infants than in non-SGA infants (95% CI, 3.553–13.692, p < 0.001) (Table 2).

During the follow-up period for infants with ≥ 3 years of age, 27 of the 31 patients diagnosed with CH were reexamined, and thyroid ultrasonography and thyroid scans were performed in 22 of the 27 patients. Based on the ultrasonography results, thyroid hypoplasia was detected in three of the 22 patients. Decreased uptake was observed in three of the 21 patients who underwent thyroid scans; the thyroid scan result of one patient was excluded because it was performed on day 19 of levothyroxine administration. Of the three patients with decreased uptake, one had normal thyroid ultrasonography findings, and thyroid hypoplasia was confirmed in the other two patients. Normal thyroid hormone levels after levothyroxine discontinuation were maintained in 20 patients, nine of whom were diagnosed with subclinical hypothyroidism. Seven patients had permanent CH (Table 3).

Thus, among the 2,658 children who were delivered at PNUH during the study period and were ≥ 3 years old, the incidence of transient CH was one in 215 term infants (six of 1,291, 0.46%) and one in 98 preterm infants (14 of 1,367, 1.02%), whereas the inci-
The incidence of permanent CH was one in 1,291 term infants (one of 1,291, 0.08%) and one in 228 preterm infants (six of 1,367, 0.44%), with a significantly higher incidence of CH in the preterm infants ($p = 0.014$).

### Discussion

This study provides new information on the incidence of CH in Korea based on the latest data. We identified the following factors as being significantly correlated with the incidence of CH: low gestational age, low birth weight, and SGA. According to numerous studies, the high incidence of CH in preterm infants and low birth weight neonates can be attributed to developmental immaturity and various environmental factors [14, 15]. Additionally, the increase in the incidence of premature births and survival of preterm infants due to improved healthcare access may contribute to this, despite the higher incidence of thyroid dysfunction in preterm infants and low birth weight neonates than in term infants [15, 16]. In this study, the risk of CH was 1.675 times higher in female infants than in male infants, albeit not statistically significant. Nonetheless, the risk of CH significantly increases with decreasing gestational age and birth weight.

Waller et al. [17] conducted a cross-sectional study of 5,049,185 infants and reported 1,806 cases of CH. Female infants had a higher incidence of CH than did male infants at all birth weights. Furthermore, infants weighing < 2,000 g had a two-fold higher incidence of CH than those weighing 3,000 to 3,499 g. In a meta-analysis by Zhang and Li [18], low birth weight and preterm birth were identified as risk factors for CH in neonates (odds ratio [OR], 2.674; 95% CI, 1.895–3.772; OR, 2.567; 95% CI, 2.070–3.183, re-
In the present study, we found that the risk of CH was 6.975 times higher in SGA infants than in non-SGA infants. Numerous studies have recommended a second screening for CH in preterm and LBWIs, and our findings indicate that a second screening would also be beneficial for infants who are SGA [4, 15, 19, 20].

Preterm infants and low birth weight neonates have poorer adaptation to the environment and lower levels of thyrotropin-releasing hormone, thyroxine-binding globulin, T4, and triiodothyronine than healthy newborns, which is caused by the premature development of the hypothalamus-pituitary-thyroid axis. These infants are also prone to transient hypothyroidism caused by iodine overload due to the low level of iodine stored in the thyroid [21, 22]. The 2020 to 2021 guidelines of the European Society for Paediatric Endocrinology recommend a second screening between postnatal days 10 and 14 for sick babies, including preterm infants and low birth weight neonates [23].

Ford et al. [24] reported that among 197 CH newborns delivered in Oregon between 2005 and 2011, 29 were diagnosed with CH based on a second screening. Among these patients, 24 were monitored for follow-up, and 17 were term infants. In our hospital, for term infants without any diseases, neither a second screening nor a serum TFT is performed if the newborn screening results are deemed normal. However, a term infant with a normal first screening result may have an abnormal second screening result. Therefore, a mandatory second screening test should be considered for preterm infants and neonates with low birth weights. In full-term infants, a second screening test is generally not necessary. Nevertheless, a second screening test is highly recommended for full-term infants with any disease.

Recent studies have reported an increased incidence of CH in newborns. For example, Mitchell et al. [10] investigated trends in CH incidence rates in Massachusetts. They found that from 2001 to 2004, there was an approximately two-fold increase in incidence (one in 1,660) compared with that from 1991 to 1994 (one in 3,010). They suggested that the increasing incidence of CH in Massachusetts reflected mild and delayed cases and that this increase was attributed to enhanced detection rather than an absolute increase in numbers. In South Korea, a CH incidence of 0.18% (n = 2,133, one in 533) was reported in a single-center study [25]. In contrast, the incidence of CH from 2011 to 2021 in this study was one in 93, a six-fold increase.

An increase in the incidence of transient CH with eutopic glands has been reported in various countries [26-28]. In a retrospective cohort study by Barry et al. [27], the percentages of patients with transient CH at the 3-, 5-, and 10-year follow-ups were 19.8%, 25.3%, and 36.7%, respectively. The authors suggested that preterm birth was statistically related to transient CH. In addition, in a single-center study from 2003 to 2015 in South Korea, Park et al. [28] reported that 65% of patients had transient CH. In the present study, we also found a high proportion of patients (15 of 19, 78.9%) with transient CH and eutopic thyroid glands. These cases may be due to the difference in sample size; however, premature birth may also be a contributing factor.

CH can be classified as transient or permanent. Transient CH is a temporary deficiency of thyroid hormones with spontaneous recovery through normal thyroid hormone production. In contrast, permanent CH requires continuous treatment. The primary causes of permanent CH include abnormal thyroid differentiation, migration, and function [11, 29]. Thyroid dysgenesis accounts for 80% to 85% of overt CH cases, whereas inborn errors in thyroid hormone synthesis (dys hormonogenesis) account for 10% to 15% of cases [29, 30]. Permanent CH includes central hypothyroidism, which was not detected in any patient in our study. Meanwhile, seven of the 27 patients with CH were diagnosed with permanent CH. Of these seven patients, three had abnormal imaging results: one showed bilateral small-sized thyroid lobes on a thyroid ultrasonogram and decreased uptake on a thyroid scan, one had normal ultrasonography results and decreased uptake, and one had thyroid hypoplasia and no thyroid scan data. Notably, more than half of the patients with permanent CH (five of seven) had normal sonographic appearance of the thyroid gland. In addition, one patient with transient CH maintained a state of subclinical hypothyroidism without medication, despite thyroid hypoplasia and decreased uptake. These results indicate that, although imaging studies for CH could assist in identifying the causes of hypothyroidism, they cannot differentiate between transient and permanent CH. Therefore, clinicians should be aware of the various imaging techniques and their purposes, advantages, and limitations.

This study has some limitations. First, a large number of newborns delivered at PNUH, a tertiary medical institution, were preterm infants. Studies have indicated that the number of patients with transient hypo thyroxinemia or transient CH is much higher in preterm infants than in term infants [22, 23]. Similarly, we observed a two-fold higher frequency in preterm infants. Term infants born at tertiary medical institutions are likely to have maternal or perinatal problems. In this study, two term infants with CH (two of nine infants) had a mother diagnosed with disease; both mothers showed hypothyroidism, and one had hypertension as a comorbidity. Second, due to the retrospective study design, there were cases with missing perinatal data. Thus, to better examine the changes in CH incidence rates in South Korea, future prospective studies conducted at multiple centers with larger sample sizes are warranted.
In summary, our findings suggest that the incidence of CH in South Korea has increased significantly compared with that in the past. In addition, as gestational age, birth weight, and SGA were significantly associated with CH incidence, newborns with these conditions are recommended to undergo a second screening test.

**Notes**

**Conflicts of interest**
No potential conflict of interest relevant to this article was reported.

**Funding**
This work was supported by a 2021 clinical research grant from the Pusan National University Hospital.

**Author contributions**
Conceptualization: all authors; Data curation, Investigation: HYJ, MJK, EHY, HWY, SJP; Formal analysis: HYJ, MJK, EHY, YMK, SHC, KHP; Funding acquisition, Validation: MJK; Methodology: HYJ, MJK, SHC, KHP; Project administration: MJK, YMK; Visualization: HYJ, MJK, HWY, SJP; Resources, Software: HYJ, MJK; Supervision: MJK, YMK, SHC, KHP; Writing-original draft: HYJ, MJK, EHY, KHP, HWY, SJP; Writing-review & editing: HYJ, MJK, YMK, SHC.

**ORCID**
Ha Young Jo, https://orcid.org/0000-0001-5934-6733
Eun Hye Yang, https://orcid.org/0000-0003-4866-7333
Young Mi Kim, https://orcid.org/0000-0002-4689-8974
Soo-Han Choi, https://orcid.org/0000-0003-2449-3025
Kyung Hee Park, https://orcid.org/0000-0002-1028-4225
Hye Won Yoo, https://orcid.org/0000-0002-5014-3494
Su Jeong Park, https://orcid.org/0000-0001-7496-7159
Min Jung Kwak, https://orcid.org/0000-0003-1379-6514

**References**

30. Rastogi MV, LaFranchi SH. Congenital hypothyroidism. Orphanet J Rare Dis 2010;5:17.
Factors associated with the prescription of probiotics in patients with inflammatory bowel disease: a cross-sectional study

Joo Kyung Kim, Jae Hee Cheon
Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

**Background:** Commensal bacteria play an important role in the pathogenesis of inflammatory bowel disease (IBD) and probiotics have been used as treatment options. We aimed to explore the current use of probiotics and factors associated with their prescription in patients with IBD.

**Methods:** This cross-sectional study was conducted on a single hospital-based cohort. Patients were eligible if they were ≥ 18 years old, visited the IBD clinic as an outpatient more than twice during the study period, and had a confirmed diagnosis of IBD. Patients were divided into two groups based on the prescription of probiotics. Clinical assessments were compared between the two groups.

**Results:** In total, 217 patients were enrolled in this study. In patients with Crohn disease (CD), moderate or severe abdominal pain; prior use of methotrexate (MTX), iron, thiopurines, or biologics; history of IBD-related surgery; and stool frequency were independently associated with the prescription of probiotics. In patients with ulcerative colitis (UC), moderate or severe abdominal pain, hematochezia, stool frequency, and moderate or severe physician global assessment score were independently associated with the prescription of probiotics.

**Conclusion:** Increased disease activity may be associated with fewer prescriptions of probiotics in patients with IBD. However, physicians prescribed probiotics to control symptoms, such as abdominal pain and increased stool frequency in patients with UC and CD, and hematochezia in patients with UC. Additionally, the use of MTX and iron, and a history of IBD-related surgeries were associated with more frequent probiotic prescriptions in patients with CD.

**Keywords:** Crohn disease; Inflammatory bowel diseases; Prescriptions; Probiotics; Ulcerative colitis
tion regardless of the strain, genetic background, or method used to induce inflammation [4]. In patients with IBD, serum antibodies against microorganisms have been used as parameters to diagnose or differentiate between CD and UC [5]. In patients with CD, high-level immune responses to microbial antigens are associated with severe disease activity or the occurrence of disease-related complications [6]. These findings highlight that commensal bacteria are essential for the initiation of intestinal inflammatory conditions and are closely associated with IBD pathogenesis.

Based on this evidence, many attempts have been made to use probiotics as a treatment option for IBD. Most studies have focused on the role of probiotics in the induction or maintenance of remission. Although results regarding the effectiveness of probiotics are controversial, most studies have not indicated that probiotics are harmful [7]. According to the Korean guidelines for CD and UC, probiotics are considered to play a minor role in the management of IBD. In the UC guideline, *Escherichia coli* Nissle 1917 is considered an alternative therapy when a patient is intolerant to 5-aminosalicylic acids during induction therapy [8]. In contrast, the use of probiotics was not mentioned in the CD guideline [9]. However, in real-life practice, probiotics are frequently prescribed to patients with IBD. However, few studies have evaluated the patterns, factors, or outcomes of probiotics prescribed by physicians. This study aimed to explore the current use of probiotics and factors associated with the prescription of probiotics in patients with IBD.

**Methods**

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Yonsei University Health Systems, Severance Hospital (IRB No: 4-2021-0539). There was no requirement for consent because this study involved only a retrospective medical chart review of anonymous patient data.

**1. Study participants**

This study was a cross-sectional, single hospital-based cohort study. Patients with CD and UC were recruited from outpatients at the IBD clinic in Severance Hospital in Seoul, Korea. The inclusion criteria were as follows: (1) age of ≥ 18 years; (2) attended the IBD clinic as an outpatient more than twice between December 2019 and November 2020; and (3) confirmed diagnosis established by clinical, radiological, endoscopic, and histopathologic criteria [10]. We excluded patients who procured probiotics without a prescription. The patients were divided into two groups according to the timing of the probiotic prescription. The probiotics group comprised patients who were prescribed probiotics for the first time during the study period after the diagnosis of IBD. The control group included patients with IBD who were not prescribed probiotics during the study period.

**2. Probiotic formulation**

The four probiotics reviewed in this study were as follows: (1) Lacidofil (Pharmbio Korea Co, Seoul, Korea), a powder of a mixed bacterial culture of *Lactobacillus rhamnosus* R0011 and *Lactobacillus helveticus* R0052 20 mg; (2) Medilac (Hanmi Pharma Co, Seoul, Korea), *Enterococcus faecium* and *Bacillus subtilis* culture 250 mg; (3) Ramnos (Hanwha Pharma Co, Seoul, Korea), freeze-dried *Lactobacillus casei* variety *rhamnosus* culture 250 mg; and (4) Bioflor (Kuhnil Pharma Co, Seoul, Korea), *Saccharomyces boulardii* 250 mg.

**3. Clinical assessments**

All patients visited the IBD clinic regularly based on a physician's medical judgment. At each visit, the patients underwent clinical examinations, including the determination of physician global assessment (PGA), Crohn disease activity index (CDAI), partial Mayo score, drug compliance, gastrointestinal symptoms, extraintestinal manifestations, systemic symptoms, and laboratory findings. PGA and drug compliance were assessed by a physician based on his/her subjective judgment. PGA is one of the items comprising the UC disease activity index [11]. In this study, in addition to the CDAI and partial Mayo score, PGA was used to assess the disease activity of both CD and UC and was assessed based on a 4-point scale as follows: 0, remission; 1, mild; 2, moderate; and 3, severe. Laboratory tests included complete blood count, blood chemistry, C-reactive protein level, and erythrocyte sedimentation rate (ESR). In addition, we counted the number of days that patients consumed probiotics in the probiotics group. We reviewed the clinical assessments mentioned above at the initiation of probiotics in the probiotics group and at the first visit during the study period in the control group. The history of previous medications was defined as the history of medication use before the prescription of probiotics in the probiotics group and before the end of the study period in the control group. Biologic or small-molecule agents included infliximab, vedolizumab, adalimumab, ustekinumab, tofacitinib, and golimumab. Immunomodulators included methotrexate (MTX) and thiopurines, such as azathioprine (AZA) and 6-mercaptopurine (6-MP).

**4. Statistical analysis**

Descriptive analyses were performed to assess the differences in baseline characteristics between the probiotics and control groups.
Quantitative data are expressed as arithmetic means ± standard deviation, where appropriate. Categorical data are presented as total percentages. The chi-square test, Fisher exact test, and linear-by-linear association are used for categorical variables. The Student t-tests were used to compare continuous variables. In addition, we performed a binary logistic regression test to determine factors associated with the prescription of probiotics. Kaplan-Meier analysis was used to assess the proportion of patients prescribed probiotics, and the log-rank test was used to compare the Kaplan-Meier curves for CD and UC. All p-values are two-sided, and the results were considered statistically significant if the p-value was < 0.05. Statistical analyses were conducted using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA).

Results

During the 1-year study period, 217 patients were enrolled in this study, of which 52 (24.0%) were included in the probiotics group. The baseline characteristics of the enrolled patients according to probiotic prescriptions are shown in Table 1. Lacidofil was the most frequently prescribed probiotic (40.4%), followed by Medilac (28.8%), Bioflor (25.0%), and Ramnos (5.8%). The probiotics group had a longer disease duration (p = 0.020) and higher stool frequency (p = 0.014) than the control group did. The proportion of patients who were diagnosed with CD (p < 0.001), moderate or severe abdominal pain (p < 0.001), and a history of IBD-related surgeries (p = 0.002) was higher in the probiotics group than in the control group.

1. Comparison of clinical characteristics between the probiotics and control groups in each IBD type

As each IBD type can have different clinical characteristics and treatment options, we analyzed these variables individually for each IBD type. Of the 217 enrolled patients, 87 (40.1%) were patients with CD, of whom 33 (37.9% of the total patients with CD) were prescribed probiotics (Table 2). The most frequently prescribed probiotics in patients with CD were Lacidofil (36.4%), followed by Ramnos (30.3%), Medilac (24.2%), and Bioflor (9.1%). In the univariate analysis, the patients with CD in the probiotics group showed greater stool frequency (p = 0.002) and moderate or severe abdominal pain (p = 0.001) than those in the control group. In terms of medications, the proportion of patients who had previously used thiopurines (p = 0.010), MTX (p = 0.018), or iron (p = 0.027) was higher in the probiotics group than in the control group. There were 130 patients with UC (59.9%), and 19 of them (14.6% of the total patients with UC) were administered probiotics (Table 3). Similar to that observed in the patients with CD, Lacidofil (47.4%) was the most often prescribed probiotic in the patients with UC. Abdominal pain (p = 0.002) was the only variable that showed a significant difference between the probiotics and control groups among the patients with UC.

2. Factors associated with probiotic prescriptions in patients with IBD

Multivariate analysis using a binary logistic regression model was performed to determine the factors associated with probiotic prescriptions. We included all variables that demonstrated either a statistically significant difference in the univariate analysis or were clinically related to probiotic prescriptions.

In patients with CD, logistic regression revealed that a moderate or severe abdominal pain (odds ratio [OR], 81.846; 95% confidence interval [CI], 5.707–1173.788; p = 0.001), prior MTX use (OR, 31.702; 95% CI, 2.016–498.540; p = 0.014), prior iron use (OR, 15.054; 95% CI, 2.963–76.475; p = 0.001), history of IBD-related surgeries (OR, 4.588; 95% CI, 1.233–17.068; p = 0.023), stool frequency (OR, 2.458; 95% CI, 1.381–4.374; p = 0.002), prior thiopurine use (OR, 0.206; 95% CI, 0.048–0.891; p = 0.035), and prior biologics use (OR, 0.158; 95% CI, 0.030–0.825; p = 0.029) were independently associated with prescribing probiotics (Table 2).

Moderate or severe abdominal pain (OR, 44.705; 95% CI, 3.683–542.598; p = 0.003), hematochezia (OR, 10.479; 95% CI, 1.042–105.376; p = 0.046), stool frequency (OR, 2.069; 95% CI, 1.256–3.409; p = 0.004), and moderate or severe PGA (OR, 0.006; 95% CI, 0.000–0.291; p = 0.010) were independently associated with prescribing probiotics in patients with UC (Table 3).

3. Proportion of patients who were prescribed probiotics

After plotting Kaplan-Meier curves, we compared the proportion of patients who continued probiotic use, among those who were prescribed probiotics, between the different IBD types by log-rank test. There was no significant difference (p = 0.474) between the two curves (Fig. 1).

Discussion

Few studies have reported the factors associated with the prescription of probiotics to patients with IBD by physicians in clinical practice. Most previous studies have focused on either the effects of probiotics on disease activity or the evaluation of their efficacy in inducing or maintaining remission. Although some studies have demonstrated beneficial effects, others have not shown any positive effects of probiotics in reducing disease activity [7]. Because of these inconsistent results, the Korean guidelines for UC recommend only a certain probiotic strain for maintaining, but not in-

https://doi.org/10.12701/jyms.2022.00031
Table 1. Comparison of baseline clinical characteristics between the probiotics and control groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Probiotics group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>52</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>34.5 ± 15.7</td>
<td>38.5 ± 13.1</td>
<td>0.069</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (63.5)</td>
<td>108 (65.5)</td>
<td>0.793</td>
</tr>
<tr>
<td>Female</td>
<td>19 (36.5)</td>
<td>57 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>22.3 ± 40.3</td>
<td>8.7 ± 13.5</td>
<td>0.020</td>
</tr>
<tr>
<td>Body mass index (kg/m^2)</td>
<td>22.2 ± 3.9</td>
<td>22.6 ± 3.6</td>
<td>0.492</td>
</tr>
<tr>
<td>Duration of probiotics prescription (day)</td>
<td>180.2 ± 127.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of probiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacidofil</td>
<td>21 (40.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medilac</td>
<td>15 (28.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioflor</td>
<td>13 (25.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramnos</td>
<td>3 (5.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of IBD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crohn disease</td>
<td>33 (63.5)</td>
<td>54 (32.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>19 (36.5)</td>
<td>111 (67.3)</td>
<td></td>
</tr>
<tr>
<td>Physician global assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission or mild</td>
<td>46 (88.5)</td>
<td>153 (92.7)</td>
<td>0.331</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>6 (11.5)</td>
<td>12 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Stool frequency (/day)</td>
<td>2.93 ± 2.15</td>
<td>2.13 ± 1.48</td>
<td>0.014</td>
</tr>
<tr>
<td>Stool consistency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>31 (59.6)</td>
<td>117 (70.9)</td>
<td>0.127</td>
</tr>
<tr>
<td>Loose stool or diarrhea</td>
<td>21 (40.4)</td>
<td>48 (29.1)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence or mild</td>
<td>38 (73.1)</td>
<td>157 (95.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>14 (26.9)</td>
<td>8 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Hematochezia(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>43 (84.3)</td>
<td>127 (77.0)</td>
<td>0.263</td>
</tr>
<tr>
<td>Presence</td>
<td>8 (15.7)</td>
<td>38 (23.0)</td>
<td></td>
</tr>
<tr>
<td>History of IBD-related surgeries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>18 (34.6)</td>
<td>25 (15.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Absence</td>
<td>34 (65.4)</td>
<td>140 (84.8)</td>
<td></td>
</tr>
<tr>
<td>Drug compliance(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>45 (90.0)</td>
<td>146 (89.0)</td>
<td>0.845</td>
</tr>
<tr>
<td>Poor</td>
<td>5 (10.0)</td>
<td>18 (11.0)</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>10.5 ± 17.3</td>
<td>4.17 ± 12.3</td>
<td>0.027</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>18.7 ± 22.4</td>
<td>15.8 ± 16.7</td>
<td>0.451</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.7 ± 2.3</td>
<td>13.8 ± 1.6</td>
<td>0.788</td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>7.2 ± 0.6</td>
<td>11.6 ± 5.55</td>
<td>0.599</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%). IBD, inflammatory bowel disease; ESR, erythrocyte sedimentation rate.


\(^b\) One case was not reported in the probiotics group. Two cases and one case were not reported in the probiotics group and control group, respectively.

Reducing, remission in patients intolerant to 5-aminosalicylic acid [8]. However, the Korean guidelines for CD do not mention the role of probiotics in this disease [9]. However, probiotics are frequently consumed by patients with IBD [12]. Thus, we evaluated the current status of the use of probiotics and the factors associated with their prescription in clinical practice.

In this study, probiotics were more frequently prescribed to patients with CD than to those with UC. Although some studies
Table 2. Comparison of baseline clinical characteristics between the probiotics and control groups in patients with Crohn disease

<table>
<thead>
<tr>
<th></th>
<th>Probiotics group (n = 33)</th>
<th>Control group (n = 54)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>31.5 ± 12.6</td>
<td>33.5 ± 11.2</td>
<td>0.461</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (72.7)</td>
<td>42 (77.8)</td>
<td>0.593</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9 (27.3)</td>
<td>12 (22.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease duration (yr)</strong></td>
<td>22.6 ± 40.1</td>
<td>9.1 ± 15.8</td>
<td>0.074</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>22.0 ± 4.1</td>
<td>21.8 ± 3.1</td>
<td>0.804</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>16 (48.5)</td>
<td>14 (25.9)</td>
<td>0.034</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>1 (3.0)</td>
<td>2 (3.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel and colon</td>
<td>16 (48.5)</td>
<td>38 (70.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disease behavior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>18 (54.5)</td>
<td>33 (61.1)</td>
<td>0.810</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistulating</td>
<td>11 (33.3)</td>
<td>13 (24.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis</td>
<td>4 (12.1)</td>
<td>8 (14.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of probiotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription (day)</td>
<td>196.1 ± 134.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Types of probiotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacidofil</td>
<td>12 (36.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medilac</td>
<td>8 (24.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioflor</td>
<td>3 (9.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramnos</td>
<td>10 (30.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fistula</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>18 (54.5)</td>
<td>29 (53.7)</td>
<td>0.939</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>15 (45.5)</td>
<td>25 (46.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physician global assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission or mild</td>
<td>29 (87.9)</td>
<td>52 (96.3)</td>
<td>0.133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>4 (12.1)</td>
<td>2 (3.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CDAI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 150</td>
<td>29 (87.9)</td>
<td>52 (96.3)</td>
<td>0.133</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild‡</td>
<td>4 (12.1)</td>
<td>2 (3.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stool frequency (/day)</strong></td>
<td>2.8 ± 1.8</td>
<td>1.7 ± 1.0</td>
<td>0.002</td>
<td>2.458 (1.381–4.374)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Stool consistency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>21 (63.6)</td>
<td>39 (72.2)</td>
<td>0.401</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loose stool or diarrhea</td>
<td>12 (36.4)</td>
<td>15 (27.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence or mild</td>
<td>24 (72.7)</td>
<td>52 (96.3)</td>
<td>0.001</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>9 (27.3)</td>
<td>2 (3.7)</td>
<td></td>
<td>81.846 (5.707–173.788)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>History of IBD-related surgeries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>18 (54.5)</td>
<td>19 (35.2)</td>
<td>0.076</td>
<td>4.588 (1.233–7.068)</td>
<td>0.023</td>
</tr>
<tr>
<td>Absence</td>
<td>15 (45.5)</td>
<td>35 (64.8)</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Drug compliance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>28 (87.5)</td>
<td>48 (88.9)</td>
<td>0.846</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>4 (12.5)</td>
<td>6 (11.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior biologics use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>12 (36.4)</td>
<td>20 (37.0)</td>
<td>0.950</td>
<td>0.158 (0.030–0.825)</td>
<td>0.029</td>
</tr>
<tr>
<td>Absence</td>
<td>21 (63.6)</td>
<td>34 (63.0)</td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

(Continued to the next page)
showed contrasting results, anxiety episodes were more prevalent [13], and the proportion of complementary and alternative medicine users was higher among patients with CD than among those with UC [14]. The differences in probiotic prescriptions according to disease type may reflect the characteristics of patients with CD. However, the proportion of patients who maintained probiotic use among those who were prescribed probiotics did not differ between the patients with CD and those with UC.

Both moderate or severe abdominal pain and stool frequency were associated with a high likelihood of probiotic prescription in patients with CD and in those with UC. In addition, hematochezia was associated with a high likelihood of probiotic prescription in patients with UC. Some studies have demonstrated the positive effects of probiotics on such gastrointestinal symptoms in UC. Patients receiving *Bifidobacterium longum* 536 or VSL#3 as an adjunct to standard treatment showed a significant decrease in rectal bleeding [15,16]. Probiotic users who were administered a multispecies probiotic including *Bifidobacterium* and *Lactobacillus* were more likely to experience a reduction in stool frequency and abdominal pain as well as an improvement in stool texture [17]. When combined with mesalazine (i.e., 5-aminosalicylic acid), probiotics also led to a significant improvement in rectal bleeding and stool frequency compared with that of mesalazine alone [18]. Although data on the role of probiotics in CD are scarce, some studies have shown improvements in gastrointestinal symptoms in patients with CD who consume probiotics. A yeast preparation of *S. boulardii* was shown to reduce the frequency of bowel movements [19].

Probiotic and prebiotic combined therapy, consisting of *Bifidobacterium breve*, *L. casei*, *B. longum*, and psyllium (*Plantago ovata*), significantly reduced the daily incidence of diarrhea and the abdominal pain index [20]. In contrast, *Bifidobacterium* in the form of fermented milk products did not show any effects on abdominal

| Table 2. Continued |
|-------------------|----------------|----------------|----------|----------------|----------|
| Prior oral 5-ASA use | Probiotics group (n = 33) | Control group (n = 54) | p-value | OR (95% CI) | p-value |
| Presence | 33 (100) | 50 (92.6) | 0.109 | | |
| Absence | 0 (0) | 4 (7.4) | | | |
| Prior topical 5-ASA use | Probiotics group (n = 33) | Control group (n = 54) | p-value | OR (95% CI) | p-value |
| Presence | 3 (9.1) | 2 (3.7) | 0.295 | | |
| Absence | 30 (90.9) | 52 (96.3) | | | |
| Prior thiopurine use | Probiotics group (n = 33) | Control group (n = 54) | p-value | OR (95% CI) | p-value |
| Presence | 21 (63.6) | 47 (87.0) | 0.010 | 0.206 (0.048–0.891) | 0.035 |
| Absence | 12 (36.4) | 7 (13.0) | 1 | |
| Prior corticosteroid use | Probiotics group (n = 33) | Control group (n = 54) | p-value | OR (95% CI) | p-value |
| Presence | 15 (45.5) | 31 (57.4) | 0.278 | | |
| Absence | 18 (54.5) | 23 (42.6) | | | |
| Prior methotrexate use | Probiotics group (n = 33) | Control group (n = 54) | p-value | OR (95% CI) | p-value |
| Presence | 5 (15.2) | 1 (1.9) | 0.018 | 31.702 (2.016–498.540) | 0.014 |
| Absence | 28 (84.8) | 53 (98.1) | 1 | |
| Prior iron use | Probiotics group (n = 33) | Control group (n = 54) | p-value | OR (95% CI) | p-value |
| Presence | 14 (42.4) | 11 (20.4) | 0.027 | 15.054 (2.963–76.475) | 0.001 |
| Absence | 19 (57.6) | 43 (79.6) | 1 | |
| Prior psychotropic drug use | Probiotics group (n = 33) | Control group (n = 54) | p-value | OR (95% CI) | p-value |
| Presence | 3 (9.1) | 1 (1.9) | 0.118 | | |
| Absence | 30 (90.9) | 53 (98.1) | | | |
| C-reactive protein (mg/L) | | | | | |
| Mean ± SD | 11.9 ± 18.3 | 7.7 ± 19.4 | 0.319 | | |
| ESR (mm/hr) | | | | | |
| Mean ± SD | 17.3 ± 22.7 | 18.1 ± 21.1 | 0.870 | | |
| Hemoglobin (g/dL) | | | | | |
| Mean ± SD | 13.7 ± 2.5 | 13.7 ± 1.8 | 0.938 | | |
| Total protein (g/dL) | | | | | |
| Mean ± SD | 7.0 ± 0.6 | 7.1 ± 0.5 | 0.683 | | |

Values are presented as mean ± standard deviation or number (%) unless otherwise specified.

OR, odds ratio; CI, confidence interval; CDAI, Crohn disease activity index; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid; ESR, erythrocyte sedimentation rate.


a) Chi-square test. b) Logistic regression. c) Mild CDAI was defined as CDAI of 150-220. d) One case was not reported in probiotics group of Crohn disease.
Table 3. Comparison of baseline clinical characteristics between the probiotics and control groups in patients with ulcerative colitis

<table>
<thead>
<tr>
<th></th>
<th>Probiotics group (n = 19)</th>
<th>Control group (n = 111)</th>
<th>p-value$^a$</th>
<th>OR (95% CI)</th>
<th>p-value$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>39.6 ± 19.2</td>
<td>40.9 ± 13.3</td>
<td>0.778</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (47.4)</td>
<td>66 (59.5)</td>
<td>0.324</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (52.6)</td>
<td>45 (40.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>21.8 ± 41.7</td>
<td>8.5 ± 12.4</td>
<td>0.183</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>22.6 ± 3.6</td>
<td>23.0 ± 3.7</td>
<td>0.685</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctosigmoiditis</td>
<td>11 (57.9)</td>
<td>51 (45.9)</td>
<td>0.328</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left-sided</td>
<td>1 (5.3)</td>
<td>16 (14.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive</td>
<td>7 (36.8)</td>
<td>44 (39.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of probiotics prescription (day)</td>
<td>152.6 ± 111.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of probiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacidofil</td>
<td>9 (47.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medilac</td>
<td>7 (36.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioflor</td>
<td>3 (15.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramnos</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician global assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission or mild</td>
<td>17 (89.5)</td>
<td>101 (91.0)</td>
<td>0.688</td>
<td>1</td>
<td>0.010</td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>2 (10.5)</td>
<td>10 (9.0)</td>
<td>0.006 (0.000–0.291)</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Partial Mayo score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>8 (42.1)</td>
<td>75 (67.6)</td>
<td>0.156</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>9 (47.4)</td>
<td>26 (23.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (5.3)</td>
<td>6 (5.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (5.3)</td>
<td>4 (3.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stool frequency (/day)</td>
<td>3.2 ± 2.7</td>
<td>2.3 ± 1.6</td>
<td>0.180</td>
<td>2.069 (1.256–3.409)</td>
<td>0.004</td>
</tr>
<tr>
<td>Stool consistency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>10 (52.6)</td>
<td>78 (70.3)</td>
<td>0.129</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Loose stool or diarrhea</td>
<td>9 (47.4)</td>
<td>33 (29.7)</td>
<td>0.088 (0.007–1.137)</td>
<td>0.063</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence or mild</td>
<td>14 (73.7)</td>
<td>105 (94.6)</td>
<td>0.002</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Moderate or severe</td>
<td>5 (26.3)</td>
<td>6 (5.4)</td>
<td>44.705 (3.683–542.598)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Hematochezia$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>11 (61.1)</td>
<td>83 (74.8)</td>
<td>0.227</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>7 (38.9)</td>
<td>28 (25.2)</td>
<td>10.479 (1.042–105.376)</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>History of IBD-related surgeries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>0 (0)</td>
<td>6 (5.4)</td>
<td>0.299</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>19 (100)</td>
<td>105 (94.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug compliance$^d$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>17 (94.4)</td>
<td>98 (89.1)</td>
<td>0.486</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>1 (5.6)</td>
<td>12 (10.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior biologics use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>3 (15.8)</td>
<td>18 (16.2)</td>
<td>0.963</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>16 (84.2)</td>
<td>93 (83.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior oral 5-ASA use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>18 (94.7)</td>
<td>106 (95.5)</td>
<td>0.884</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>1 (5.3)</td>
<td>5 (4.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Continued to the next page)
Table 3. Continued

<table>
<thead>
<tr>
<th></th>
<th>Probiotics group (n = 19)</th>
<th>Control group (n = 111)</th>
<th>p-value (^a)</th>
<th>OR (95% CI)</th>
<th>p-value (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior topical 5-ASA use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>15 (78.9)</td>
<td>90 (81.1)</td>
<td>0.827</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>4 (21.1)</td>
<td>21 (18.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior thiopurine use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>3 (15.8)</td>
<td>33 (29.7)</td>
<td>0.210</td>
<td>0.214 (0.035–1.301)</td>
<td>0.094</td>
</tr>
<tr>
<td>Absence</td>
<td>16 (84.2)</td>
<td>78 (70.3)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior corticosteroid use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>11 (57.9)</td>
<td>51 (45.9)</td>
<td>0.335</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>8 (42.1)</td>
<td>60 (54.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior iron use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>1 (5.3)</td>
<td>9 (8.1)</td>
<td>0.667</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>18 (94.7)</td>
<td>102 (91.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior psychotropic drug use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>2 (10.5)</td>
<td>5 (4.5)</td>
<td>0.283</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>17 (89.5)</td>
<td>106 (95.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>6.2 ± 13.8</td>
<td>2.2 ± 4.6</td>
<td>0.367</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>22.8 ± 22.0</td>
<td>14.5 ± 13.6</td>
<td>0.088</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.8 ± 1.9</td>
<td>13.9 ± 1.5</td>
<td>0.810</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total protein (g/dL)</td>
<td>7.5 ± 0.7</td>
<td>13.9 ± 68.0</td>
<td>0.756</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%) unless otherwise specified.
OR, odds ratio; CI, confidence interval; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid; ESR, erythrocyte sedimentation rate.

\(^a\)Chi-square test. \(^b\)Logistic regression. \(^c\)One case was not reported in probiotics group of ulcerative colitis. \(^d\)One case was not reported in both probiotics and control group.

Fig. 1. Proportion of patients who maintained use of probiotics among those prescribed probiotics stratified by the type of inflammatory bowel disease. CD, Crohn disease; UC, ulcerative colitis.

Symptoms, stool frequency, or rectal bleeding [21]. Some studies have reported side effects of probiotics, such as abdominal pain, in patients with IBD [22]. Although probiotics may not be effective for some gastrointestinal symptoms or they may show side effects, physicians can expect some positive effects of probiotics and prescribe them to improve symptoms.

A high PGA score did not lead to increased prescription of probiotics by physicians. Moderate or high PGA scores were negatively associated with prescribing probiotics to patients with UC. PGA is an important component in evaluating disease activity, such as the UC disease activity index, and correlates well with disease activity [23]. Physicians may prescribe probiotics to patients with UC to relieve gastrointestinal symptoms, such as abdominal pain, hematochezia, or increased stool frequency, but not to control disease activity. Abdominal pain, increased stool frequency, and hematochezia are related to disease activity; however, they can occur even if disease activity does not increase. For example, the disease activity of IBD can remain unchanged, but the above symptoms may occur with gastroenteritis, infectious colitis, or irritable bowel syndrome. Therefore, it can be inferred that probiotics tend to be used when symptoms, which are not related to increased disease...
activity, worsen. In addition, even if objective indicators such as endoscopic findings are useful for assessing disease activity, patients with IBD often complain of subjective gastrointestinal or irritable bowel syndrome symptoms. Controlling these subjective symptoms as well as disease activity is important. Physicians tend to take this into account when prescribing probiotics.

Surgical treatment is often considered in patients with IBD. In patients with CD, the 10-year surgery risk was 46.6% [24], and surgery was indicated in cases of bowel perforation, abscesses, massive hemorrhage, cancer development, or bowel obstruction not alleviated by medical therapies [25]. In the present study, a history of IBD-related surgery was associated with probiotic prescriptions in patients with CD. Previous studies have focused on the role of probiotics in the prophylaxis of postoperative CD recurrence with contradictory results. Treatment with VSL#3 within 30 days after ileal resection and reanastomosis resulted in a reduction in severe endoscopic recurrence by day 90 [26]. In addition, when combined with antibiotics, probiotics could be efficacious in the prophylaxis of postoperative recurrence of CD [27]. In contrast, some studies showed the ineffectiveness of probiotics in preventing recurrence after surgery for CD [28,29]. Although there was no information on the temporal relationship between the administration of probiotics, surgery, and concomitant medications in this study, probiotics were used to prevent recurrence after surgery. From a psychiatric point of view, patients with CD who underwent IBD-related surgery had a risk of anxiety [30,31]. Physicians may prescribe probiotics to reduce such neurotic symptoms.

The past use of certain medications was associated with the prescription of probiotics in patients with CD. Patients with prior MTX or iron prescriptions were prescribed a significantly higher number of probiotics than patients without these prior medications. MTX is an anti-metabolite known to induce intestinal mucositis. MTX can induce or maintain remission in moderate-to-severe CD. These findings reveal that probiotics are not generally prescribed to patients with moderate-to-severe CD. This tendency can be consistent with UC, in which moderate or severe PGA had a negative relationship with probiotic prescriptions in the present study. The use of biologics could also eliminate the need for probiotics. Patients receiving biologics reported a high degree of satisfaction with their therapy and appeared physically and emotionally healthier than their counterparts who did not receive biologics [40].

This study had some limitations. First, regarding the medication data, previously used medications were considered and not concomitant prescriptions. Thus, it is unclear whether these medications were associated with the prescription of probiotics in the probiotics group. Second, over-the-counter use of probiotics was not considered in this study. Probiotics are often considered over-the-counter drugs and do not require prescriptions. Thus, physicians may not have prescribed probiotics to patients who were already consuming them. Third, the factors associated with probiotic pre-

plays an important role in IBD [35]. Another study that used an animal model indicated the possibility of a protective effect of probiotic administered in combination with iron supplementation in IBD. Specifically, the probiotic E. coli Nissle 1917 outcompeted pathogenic bacteria in a dextran sodium sulfate-induced colitis model [35]. The absorption of iron can also be increased in combination with probiotics. In a previous study, freeze-dried Lactobacillus plantarum 299v was shown to enhance iron absorption when administered with a meal catered to ensure high iron bioavailability [36]. In this context, physicians may prescribe probiotics in combination with iron supplementation. The development of iron-deficiency anemia is related to disease activity, as blood loss is triggered by intestinal inflammation [37]. MTX may be used in patients with moderate-to-severe CD [9]. In other words, iron and MTX were used more often in patients with severe inflammation. Physicians should consider prescribing probiotics to reduce inflammation in patients with severe symptoms.

A history of biologics and thiopurine use, including AZA or 6-MP, was associated with lower probiotic prescriptions in patients with CD. Infliximab and adalimumab are generally used to induce and maintain remission in moderate-to-severe CD [9]. Vedolizumab and ustekinumab also induce response and remission in patients with moderately to severely active CD who are unresponsive to either tumor necrosis factor antagonists or conventional therapy [38,39]. Thiopurine alone is not recommended as an induction therapy but can be used with infliximab in moderate-to-severe CD for induction [9]. It can also be used as a maintenance therapy when induction is achieved with systemic steroids [9]. In other words, biologic drugs and thiopurines are indicated for moderate-to-severe CD. These findings reveal that probiotics are not generally prescribed to patients with moderate-to-severe CD. This tendency can be consistent with UC, in which moderate or severe PGA had a negative relationship with probiotic prescriptions in the present study. The use of biologics could also eliminate the need for probiotics. Patients receiving biologics reported a high degree of satisfaction with their therapy and appeared physically and emotionally healthier than their counterparts who did not receive biologics [40].

This study had some limitations. First, regarding the medication data, previously used medications were considered and not concomitant prescriptions. Thus, it is unclear whether these medications were associated with the prescription of probiotics in the probiotics group. Second, over-the-counter use of probiotics was not considered in this study. Probiotics are often considered over-the-counter drugs and do not require prescriptions. Thus, physicians may not have prescribed probiotics to patients who were already consuming them. Third, the factors associated with probiotic pre-
criptions were assessed retrospectively based on medical charts. Since this study was retrospectively designed, we were not able to follow up on changes in gastrointestinal symptoms after using probiotics. Fourth, the probiotics were prescribed based on the subjective symptoms of the patients and at the discretion of the physician, which might have affected the results.

In conclusion, increased disease activity might be associated with lower probiotic prescriptions in both patients with UC and those with CD. In contrast, physicians prescribe probiotics more frequently in patients who complain of abdominal pain and increased stool frequency in both UC and CD, as well as in UC patients experiencing hematochezia. Some medications, such as MTX and iron supplements, and a history of IBD-related surgeries were also associated with more probiotic prescriptions in patients with CD. Although there have been studies that have shown the usefulness of probiotics in patients with IBD, there is still a lack of consistent opinions concerning their effectiveness. Thus, rather than determining the effectiveness of probiotics in patients with IBD, we believe that it is important to identify the factors for which patients are more likely to be prescribed probiotics. In particular, the results of this study are meaningful considering that probiotics are prescribed when patients have subjective symptoms, even though the disease activity of IBD is well controlled.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization, Validation, Supervision: JHC; Methodology, Formal analysis, Investigation: JHC, JKK; Software, Data curation: JKK; Writing-original draft: JKK; Writing-review & editing: JHC; Approval of final manuscript: all authors.

ORCID
Joo Kyung Kim, https://orcid.org/0000-0003-0080-9785
Jae Hee Cheon, https://orcid.org/0000-0002-2282-8904

References

2012;6:345–53.


The impact of quality of life measured by WHOQOL-BREF on mortality in maintenance hemodialysis patients: a single center retrospective cross-sectional study

Seong Gyu Kim, In Hee Lee
Division of Nephrology, Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, Korea

**Background:** Several previous studies have reported that quality of life (QoL) in hemodialysis patients affects mortality. However, the 36-item Short Form Health Survey, which has been used mainly in previous studies, is complicated in terms of questionnaire composition and interpretation. This study aimed to identify the impact of QoL on mortality in hemodialysis patients using an easier and simpler diagnostic tool.

**Methods:** This retrospective study included 160 hemodialysis patients. QoL was evaluated using the World Health Organization Quality of Life Questionnaire-Brief version (WHOQOL-BREF). Psychosocial factors were evaluated using the Hospital Anxiety and Depression Scale, Multidimensional Scale of Perceived Social Support, Montreal Cognitive Assessment, and Pittsburgh Sleep Quality Index. We also evaluated medical factors, such as dialysis adequacy and laboratory results.

**Results:** The mean hemodialysis vintage was 70.7 ± 38.0 months. The proportion of patients who were elderly was higher in the mortality group than in the surviving group, and the Charlson Comorbidity Index score was also higher in the former group. Of the four domains of the WHOQOL-BREF, the physical health and psychological scores of the mortality group were significantly lower than those of the survival group. When the score in the physical health domain or psychological domain was ≤ 10, the 10-year mortality rate after hemodialysis initiation increased by approximately 2.3- and 2-fold, respectively.

**Conclusion:** QoL may have a significant effect on mortality in patients undergoing hemodialysis. The WHOQOL-BREF is an instrument that can measure QoL relatively easily and can be used to improve the long-term prognosis of patients undergoing hemodialysis.

**Keywords:** Hemodialysis; Mortality; Quality of life; WHOQOL-BREF

**Introduction**

Advances in hemodialysis technology have led to a significant reduction in mortality rates and complication risks directly related to hemodialysis since the early 2000s [1]. However, mortality among hemodialysis patients still exceeds 20% annually [2,3]. Robinson et al. [4] analyzed patients from 11 countries who participated in the Dialysis Outcomes and Practice Patterns Study (DOPPS) and reported that the highest mortality occurred in the first 120 days of hemodialysis.

Based on data from the End-stage Renal Disease Registry Committee of the Korean Society of Nephrology, 87,993 patients were...
on hemodialysis, and the 10-year mortality rates on hemodialysis were 38.1% and 62.8%, respectively, in 2017 [5]. Since then, the incidence of hemodialysis has been rapidly increasing by 7% to 10% every year [5].

Hemodialysis patients are more likely to have psychological problems, limited economic activities, and a reduced quality of life (QoL) due to the impact of end-stage renal disease, comorbidities, and hemodialysis on daily life [6-9]. Numerous studies have reported an association between a lower QoL and mortality in hemodialysis patients [10,11]. Most previous studies have assessed QoL using the 36-item Short Form Health Survey (SF-36) containing 36 questions. However, the SF-36 assesses physical and mental health domains using the same questions and can yield complicated results. Recently, Lee et al. [12] reported that the mortality rate of hemodialysis patients in Korea may increase if the QoL measured using the Kidney Disease Quality of Life Short Form version 1.3 (KDQOL-SF 1.3) is low. However, although the KDQOL-SF 1.3 is a well-validated test tool, it consists of 80 items and has limitations in simplicity and convenience. Furthermore, there have been relatively few reports of QoL-related mortality in hemodialysis patients in Korea, and the sample size is not large.

Thus, in this study, we used the World Health Organization Quality of Life Questionnaire-Brief version (WHOQOL-BREF), which is relatively simple and easy to interpret, as a diagnostic tool for QoL. Psychosocial and medical factors as well as QoL were investigated and used to analyze the mortality rate in hemodialysis patients. This study aimed to investigate the impact of QoL measured by the WHOQOL-BREF on the mortality rate of hemodialysis patients using these factors.

Methods

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University Hospital (IRB No: CR-13-076). Informed consent was obtained from all subjects when they were enrolled.

1. Study design
This single center retrospective cross-sectional study analyzed 160 patients undergoing hemodialysis at the Daegu Catholic University Hospital in Daegu, Korea. Data from September 2013 to October 2013 were used, and a questionnaire survey was conducted during the same period. Patients who could understand, speak, and read Korean were included in this study. Patients with vision problems completed the questionnaire with the examiner’s assistance. Patients who received treatment for acute disease completed the questionnaire after recovery. Patients who were on hemodialysis at Daegu Catholic University Hospital for < 1 month (n = 4), were < 20 years or ≥ 80 years old (n = 4), had a history of psychological disorders (n = 3), or refused to participate (n = 8) were excluded from the study at the time of recruitment. All participants received hemodialysis three times per week for 4 hours per session.

We investigated hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular accident, cancer, and liver disease as underlying diseases. The investigation of these underlying diseases was conducted based on electronic medical records within 6 months of the same period during which the subjects were included in the study, and tests for QoL and psychosocial indicators were performed. Individuals with hypertension, diabetes, cardiovascular disease, and cerebrovascular accidents were defined as those who had been diagnosed or were already taking therapeutic medications prior to inclusion in this study. Cardiovascular disease included myocardial infarction, other ischemic heart diseases, congestive heart failure with or without preserved systolic function, arrhythmias, and valvular disease. As the underlying disease, cancer was defined as a non-overt disease with a history of diagnosis and treatment prior to participation in this study. Liver disease was defined as chronic hepatitis or cirrhosis. The Charlson Comorbidity Index (CCI) is widely used to assess the risk of comorbidities that affect patient mortality and was determined for each patient in this study [13]. The CCI was calculated based on each patient’s status at baseline.

The WHOQOL-BREF was used to assess QoL. The WHOQOL-BREF contains 24 questions across four domains (physical health, psychological, social relationships, and environmental domains) and two questions on overall QoL and general health awareness [14]. The total score for each domain ranges from 4 to 20 points. Although there is no official cutoff value, higher scores indicate a higher QoL. In this study, the cutoff value for each domain of the WHOQOL-BREF was set to 10 points, which is half of the maximum. The Korean version of the WHOQOL-BREF with verified validity and reliability was used in this study [15].

The Hospital Anxiety and Depression Scale (HADS), Multidimensional Scale of Perceived Social Support (MSPSS), Montreal Cognitive Assessment (MoCA), and Pittsburgh Sleep Quality Index (PSQI) were used to assess psychosocial factors. All these instruments are self-reported questionnaires with verified validity and reliability [16-23]. The HADS has 14 questions, with the odd-numbered questions assessing anxiety (HADS-A) and even-numbered questions assessing depression (HADS-D). The score for each question ranges from 0 to 3 points. The cutoff value for the total score for depression and anxiety is 14 points [16,17]. The MSPSS consists of 12 questions evenly spread across three
Results

1. Baseline characteristics

A comparison of the basic characteristics of the survival and mortality groups is summarized in Table 1. Of the 160 patients, 41 were in the mortality group and 119 were in the survival group. The mean hemodialysis vintage was 72.0 and 66.9 months for the respective groups, with no significant difference \( (p = 0.465) \). The mean age and proportion of patients aged > 60 years were significantly higher in the mortality group than in the survival group \( (\text{mean age}, p < 0.001; \text{proportion } > 60 \text{ years}, \text{mortality group} \ [73.2\%] \text{ vs. survival group} \ [41.2\%], p < 0.001) \). Significantly higher rates of underlying cardiovascular disease and cancer were found in the mortality group compared to that in the survival group \( \text{cardiovascular disease, } p = 0.024; \text{cancer, } p = 0.004) \). A significant difference was found in the mean CCI score between the mortality and survival groups \( (p = 0.006) \). However, no significant difference in the proportion of patients with CCI scores of ≥ 4, which indicates severe comorbidities, was found between the two groups \( (p = 0.114) \).

Among the medical factors, the mean diastolic blood pressure after hemodialysis was lower in the mortality group than in the survival group \( (p = 0.006) \). The mean serum calcium concentration was lower in the mortality group than in the survival group \( (p = 0.014) \). The proportion of patients with serum calcium concentrations of < 8.7 mg/dL was 67.5% and 48.7% in the mortality and survival groups, respectively; thus, more patients had hypercalcemia in the mortality group than in the survival group \( (p = 0.040) \).

2. Comparisons of indicators between survival and mortality groups

A comparison of the indicators between the survival and mortality groups is summarized in Table 2. Among the four domains of the WHOQOL-BREF, the mean scores in the physical health, psycho-
Table 1. Comparisons of basic characteristics and medical parameters between survival and mortality groups in maintenance hemodialysis patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival</th>
<th>Mortality</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>119</td>
<td>41</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.7 ± 11.7</td>
<td>65.3 ± 9.5</td>
<td>58.2 ± 11.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>66 (55.5)</td>
<td>25 (61.0)</td>
<td>91 (56.9)</td>
<td>0.539</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.1 ± 2.9</td>
<td>21.0 ± 2.8</td>
<td>21.9 ± 2.9</td>
<td>0.038</td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>63 (52.9)</td>
<td>26 (63.4)</td>
<td>89 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (20.1)</td>
<td>8 (19.5)</td>
<td>32 (20.0)</td>
<td></td>
</tr>
<tr>
<td>CGN</td>
<td>16 (13.5)</td>
<td>2 (4.9)</td>
<td>18 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>16 (13.5)</td>
<td>4 (9.8)</td>
<td>20 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Cause of mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>66 (55.5)</td>
<td>29 (70.7)</td>
<td>95 (59.4)</td>
<td>0.057</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88 (74.0)</td>
<td>35 (85.4)</td>
<td>123 (76.9)</td>
<td>0.076</td>
</tr>
<tr>
<td>CVD</td>
<td>26 (21.9)</td>
<td>16 (39.0)</td>
<td>42 (26.3)</td>
<td>0.024</td>
</tr>
<tr>
<td>CVA</td>
<td>17 (14.3)</td>
<td>8 (19.5)</td>
<td>25 (15.6)</td>
<td>0.390</td>
</tr>
<tr>
<td>Liver disease</td>
<td>10 (8.4)</td>
<td>1 (2.4)</td>
<td>11 (6.9)</td>
<td>0.023</td>
</tr>
<tr>
<td>Cancer</td>
<td>2 (1.7)</td>
<td>5 (12.2)</td>
<td>7 (4.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>CCI</td>
<td>3.7 ± 1.3</td>
<td>4.4 ± 1.4</td>
<td>3.9 ± 1.4</td>
<td>0.006</td>
</tr>
<tr>
<td>HD vintage (mo)</td>
<td>72.0 ± 37.2</td>
<td>66.9 ± 40.3</td>
<td>70.7 ± 38.0</td>
<td>0.465</td>
</tr>
<tr>
<td>BP, post HD (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>136.6 ± 21.4</td>
<td>136.8 ± 22.9</td>
<td>136.7 ± 21.7</td>
<td>0.978</td>
</tr>
<tr>
<td>DBP</td>
<td>77.8 ± 11.9</td>
<td>71.8 ± 12.2</td>
<td>76.3 ± 12.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.4 ± 0.5</td>
<td>1.4 ± 0.3</td>
<td>1.4 ± 0.5</td>
<td>0.925</td>
</tr>
<tr>
<td>nPCR</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.2</td>
<td>0.736</td>
</tr>
<tr>
<td>White blood cell (fL/μL)</td>
<td>5,954 ± 1,850</td>
<td>6,230 ± 1,475</td>
<td>6,023 ± 1,763</td>
<td>0.393</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.1 ± 1.1</td>
<td>10.2 ± 1.1</td>
<td>10.1 ± 1.1</td>
<td>0.731</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>30.7 ± 3.4</td>
<td>30.9 ± 3.4</td>
<td>30.8 ± 3.4</td>
<td>0.769</td>
</tr>
<tr>
<td>Platelet (10³/μL)</td>
<td>176.7 ± 63.2</td>
<td>168.1 ± 47.6</td>
<td>174.5 ± 59.6</td>
<td>0.433</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>137.4 ± 31.2</td>
<td>145.2 ± 39.0</td>
<td>139.3 ± 33.4</td>
<td>0.203</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>42.5 ± 14.1</td>
<td>41.4 ± 10.8</td>
<td>42.2 ± 13.3</td>
<td>0.644</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>83.8 ± 28.1</td>
<td>86.2 ± 27.9</td>
<td>84.5 ± 28.0</td>
<td>0.651</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>121.6 ± 66.9</td>
<td>127.3 ± 84.9</td>
<td>123.0 ± 71.6</td>
<td>0.665</td>
</tr>
<tr>
<td>Protein (g/dL)</td>
<td>6.8 ± 0.6</td>
<td>6.8 ± 0.6</td>
<td>6.8 ± 0.6</td>
<td>0.502</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.0 ± 0.4</td>
<td>3.8 ± 0.3</td>
<td>3.9 ± 0.3</td>
<td>0.045</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.9 ± 0.8</td>
<td>8.5 ± 0.6</td>
<td>8.8 ± 0.8</td>
<td>0.014</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.6 ± 1.9</td>
<td>5.1 ± 2.0</td>
<td>5.4 ± 1.9</td>
<td>0.159</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.7 ± 1.6</td>
<td>6.9 ± 1.7</td>
<td>6.7 ± 1.6</td>
<td>0.509</td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td>136.2 ± 3.1</td>
<td>135.9 ± 3.0</td>
<td>136.1 ± 3.1</td>
<td>0.531</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>5.0 ± 0.9</td>
<td>4.9 ± 0.7</td>
<td>5.0 ± 0.8</td>
<td>0.390</td>
</tr>
<tr>
<td>Cl (mmol/L)</td>
<td>95.3 ± 4.2</td>
<td>94.7 ± 2.8</td>
<td>95.1 ± 3.9</td>
<td>0.429</td>
</tr>
<tr>
<td>tCO₂ (mmol/L)</td>
<td>21.0 ± 3.3</td>
<td>20.5 ± 3.1</td>
<td>20.9 ± 3.3</td>
<td>0.436</td>
</tr>
<tr>
<td>Ferritin (ng/mL)</td>
<td>261.8 ± 231.1</td>
<td>293.8 ± 255.3</td>
<td>269.9 ± 237.0</td>
<td>0.463</td>
</tr>
<tr>
<td>iPTH (pg/mL)</td>
<td>334.0 ± 314.4</td>
<td>274.3 ± 176.4</td>
<td>318.9 ± 302.9</td>
<td>0.283</td>
</tr>
<tr>
<td>25-Vitamin D (ng/mL)</td>
<td>15.8 ± 8.5</td>
<td>13.0 ± 7.2</td>
<td>15.2 ± 8.3</td>
<td>0.082</td>
</tr>
<tr>
<td>1,25-Vitamin D (ng/mL)</td>
<td>8.5 ± 4.0</td>
<td>7.9 ± 3.1</td>
<td>8.4 ± 3.8</td>
<td>0.380</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>7.1 ± 1.8</td>
<td>7.1 ± 1.7</td>
<td>7.1 ± 1.8</td>
<td>0.968</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>4.1 ± 10.4</td>
<td>7.7 ± 14.3</td>
<td>5.0 ± 11.6</td>
<td>0.151</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%). ESRD, end-stage renal disease; CGN, chronic glomerulonephritis; CVD, cardiovascular disease; CVA, cerebrovascular accident; CCI, Charlson Comorbidity Index; HD, hemodialysis; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; Kt/V, urea clearance × time/volume; nPCR, normalized protein catabolic rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Na, sodium; K, potassium; Cl, chloride; tCO₂, total carbon dioxide; iPTH, intact parathyroid hormone; HbA1c, glycated hemoglobin.
logical, and environmental domains were significantly lower in the mortality group than in the survival group (physical health domain, \( p = 0.009 \); psychological domain, \( p = 0.013 \); environmental domain, \( p = 0.038 \)). We compared the proportions using a cutoff value of 10 points, which is half of the total score of 20 points for each domain of the WHOQOL-BREF. The results showed that the proportion of scores \( \leq 10 \) in the physical health and psychological domains was higher in the mortality group than in the survival group (physical health domain, 74.3\% vs. 52.2\%, \( p = 0.021 \); psychological domain, 45.7\% vs. 26.5\%, \( p = 0.032 \)). However, the proportion of environmental domain scores \( \leq 10 \) did not differ significantly between the mortality (42.5\%) and survival (57.1\%) groups (\( p = 0.128 \)).

No significant differences in the mean scores of the total HADS, HADS-A, and HADS-D were found between the two groups. No significant differences in the total MSPSS score and scores for family, friends, and significant others were found between the two groups. The mean MoCA score showed that cognitive ability decreased significantly more in the mortality group than in the survival group (\( p = 0.045 \)). However, no significant difference was found in the proportion of patients with moderate-to-severe cognitive impairment between the mortality group (61.0\%) and the survival group (51.3\%) (\( p = 0.084 \)). No significant differences were found in the mean PSQI scores between the two groups.

### Table 2. Comparison of WHOQOL-BREF domain and psychosocial indicators between survival and mortality groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survival (n = 119)</th>
<th>Mortality (n = 41)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHOQOL-BREF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health domain</td>
<td>10.5 ± 2.8</td>
<td>9.0 ± 3.1</td>
<td>0.009</td>
</tr>
<tr>
<td>Psychological domain</td>
<td>10.7 ± 2.8</td>
<td>9.3 ± 3.0</td>
<td>0.013</td>
</tr>
<tr>
<td>Social relationship domain</td>
<td>10.8 ± 3.1</td>
<td>10.1 ± 3.3</td>
<td>0.254</td>
</tr>
<tr>
<td>Environmental domain</td>
<td>11.0 ± 2.5</td>
<td>10.0 ± 2.2</td>
<td>0.038</td>
</tr>
<tr>
<td>HADS, total</td>
<td>14.2 ± 7.2</td>
<td>14.6 ± 8.6</td>
<td>0.273</td>
</tr>
<tr>
<td>HADS-A</td>
<td>5.6 ± 4.0</td>
<td>4.7 ± 4.4</td>
<td>0.201</td>
</tr>
<tr>
<td>HADS-D</td>
<td>8.6 ± 4.2</td>
<td>9.9 ± 5.4</td>
<td>0.781</td>
</tr>
<tr>
<td>MSPSS, total</td>
<td>36.5 ± 10.8</td>
<td>35.7 ± 10.9</td>
<td>0.523</td>
</tr>
<tr>
<td>Family</td>
<td>14.8 ± 4.3</td>
<td>15.3 ± 4.2</td>
<td>0.433</td>
</tr>
<tr>
<td>Friends</td>
<td>10.6 ± 4.6</td>
<td>9.9 ± 5.3</td>
<td>0.462</td>
</tr>
<tr>
<td>Significant other</td>
<td>11.1 ± 4.4</td>
<td>10.5 ± 4.7</td>
<td>0.696</td>
</tr>
<tr>
<td>MoCA</td>
<td>19.9 ± 7.1</td>
<td>17.0 ± 8.5</td>
<td>0.046</td>
</tr>
<tr>
<td>PSQI</td>
<td>7.9 ± 4.5</td>
<td>7.8 ± 4.9</td>
<td>0.981</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation. WHOQOL-BREF, World Health Organization Quality of Life Questionnaire-Brief version; HADS, Hospital Anxiety and Depression Scale; HADS-A, HADS-Anxiety; HADS-D, HADS-Depression; MSPSS, Multidimensional Scale of Perceived Social Support; MoCA, Montreal Cognitive Assessment; PSQI, Pittsburgh Sleep Quality Index.

### 3. Association between quality of life scales and mortality

The results of the Cox regression analysis of the QoL-related 10-year mortality rate after hemodialysis initiation are summarized in Table 3. In the univariate analysis, among the domains of the WHOQOL-BREF, only the physical health and psychological domains were significantly associated with a score of \( \leq 10 \) in each domain and 10-year mortality after hemodialysis initiation. In the univariate analysis, if the score in the physical health or psychological domains was \( \leq 10 \), the 10-year mortality rate after hemodialysis initiation was significantly higher in the mortality group (51.3\%) vs. the survival group (42.5\%). However, no significant differences were found in the proportion of patients with moderate-to-severe cognitive impairment between the mortality group (61.0\%) and the survival group (51.3\%) (\( p = 0.084 \)). No significant differences were found in the mean PSQI scores between the two groups.

### Table 3. Univariate and multivariate analysis for patient mortality using Cox proportional hazard regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate regression model</th>
<th>Multivariate regression model</th>
<th>Multivariate regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHOQOL-BREF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical health domain score, ( \leq 10 )</td>
<td>1.95 (1.02–3.91)</td>
<td>2.27 (1.02–5.05)</td>
<td>2.04 (1.02–4.09)</td>
</tr>
<tr>
<td>Psychological domain score, ( \leq 10 )</td>
<td>2.28 (1.14–4.57)</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>Social relationship domain score, ( \leq 10 )</td>
<td>1.49 (0.74–2.98)</td>
<td>0.262</td>
<td></td>
</tr>
<tr>
<td>Environmental domain score, ( \leq 10 )</td>
<td>1.34 (0.66–2.69)</td>
<td>0.418</td>
<td></td>
</tr>
<tr>
<td>Elderly, ( \geq 60 ) yr</td>
<td>3.15 (1.48–6.69)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>0.99 (0.51–1.91)</td>
<td>0.980</td>
<td></td>
</tr>
<tr>
<td>CCI, ( \geq 4 )</td>
<td>1.52 (0.72–3.24)</td>
<td>0.276</td>
<td></td>
</tr>
<tr>
<td>Calcium, &lt; 8.7 mg/dL</td>
<td>2.60 (1.31–5.16)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Moderate-to-severe cognitive impairment</td>
<td>1.67 (0.79–3.54)</td>
<td>0.276</td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio; CI, confidence interval; WHOQOL-BREF, World Health Organization Quality of Life Questionnaire-Brief version; CCI, Charlson Comorbidity Index.

The result of multiple regression analysis of the patient mortality rate for the physical health domain score of the WHOQOL-BREF. These results were adjusted by male sex, age of \( \geq 60 \) years, CCI scores of \( \geq 4 \) points, moderate-to-severe cognitive impairment by Montreal Cognitive Assessment, and serum calcium of < 8.7 mg/dL.
was increased by approximately 2.0 and 2.3 times, respectively, and it was statistically significant (physical health domain, \( p = 0.038 \); psychological domain, \( p = 0.020 \)). In addition, in the multivariate analysis adjusted for variables such as male sex, age of \( \geq 60 \) years, CCI of \( \geq 4 \), moderate-to-severe cognitive impairment by MoCA, and serum calcium concentrations of \( < 8.7 \) mg/dL, when the score in the physical health or psychological domains was \( \leq 10 \), the 10-year mortality rate after initiation of hemodialysis was significantly increased by approximately 2.3 and 2.0 times, respectively (physical health domain, \( p = 0.036 \); psychological domain, \( p = 0.036 \)).

Among the adjusted factors in the multivariate analysis, the significant risk factors for 10-year mortality after hemodialysis initiation were age of \( \geq 60 \) years and hypocalcemia in both the physical and psychological domains. Even when these two factors were analyzed univariately, the mortality rate at 10 years after starting dialysis significantly increased. The 10-year cumulative death curves of the physical health and psychological domains of the WHOQOL-BREF as determined through the multivariate regression analysis are presented in Fig. 1.

**Discussion**

Several previous studies have reported an association between reduced QoL and increased mortality in patients receiving hemodialysis [10-12,26-28]. Most studies have assessed QoL using the SF-36. The SF-36 consists of 36 items and assesses two domains; physical health and mental health [29]. However, in the SF-36, five questions corresponding to general health and four questions corresponding to vitality out of the 36 questions are duplicated in these two domains. Therefore, there might be some limitations in the interpretation of the SF-36 results. To overcome this SF-36 limitation, we assessed QoL in this study using the WHOQOL-BREF, which has four independent domains as well as questions and results that are relatively easy to understand. The WHOQOL-BREF is an abbreviated version of the 100-question WHOQOL-100. The latter also consists of four domains, and it was confirmed that the score of each domain of the WHOQOL-BREF was highly correlated with the score of each domain of the WHOQOL-100 [14]. The WHOQOL-BREF demonstrated cross-cultural validity and reproducibility in a study of 11,830 adults in 23 countries [30]. In the present study, the mortality group scored lower in the physical and psychological domains of the WHOQOL-BREF than the survival group did. The multivariate Cox proportional regression analysis showed a 2.3- and 2-fold increase in 10-year mortality after initiation of hemodialysis in maintenance hemodialysis patients whose scores in the physical health domain or psychological domain were \( \leq 10 \) points, respectively. In previous studies using DOPPS cohort data, Mapes et al. [11] reported that the hazard ratio increased 1.25- and 1.13-fold for every 10-point decrease in

![Fig. 1. Cumulative death rate curves using Cox proportional regression hazard model according to (A) physical health domain and (B) psychological domain of World Health Organization Quality of Life Questionnaire-Brief version adjusted by male sex, age of \( \geq 60 \) years, Charlson Comorbidity Index of \( \geq 4 \) points, moderate-to-severe cognitive impairment by Montreal Cognitive Assessment, and serum calcium of \( < 8.7 \) mg/dL, HD, hemodialysis.](https://doi.org/10.12701/jyms.2022.00080)
the scores for the physical and psychological domains of the SF-36, and Perl et al. [10] reported that the hazard ratio for death increased 1.09- and 1.05-fold for every 5-point decrease in the scores for the respective domains of the SF-36. Liebman et al. [28] measured SF-36 scores twice at 6-month intervals and reported that the mortality rate 1 year after the second test increased 1.33-fold when the score for the psychological domain decreased by at least five points. Unlike the two previous studies, although Liebman et al. [28] did not show a significant difference in the mortality rate in the physical health domain, lower scores in the physical health domain tended to have a higher mortality rate. In addition, Liebman et al. [28] showed that the mean score in the physical health domain decreased in the follow-up surveys at 6-month intervals. This suggests that lower scores in the physical health and psychological domains are important for the patient mortality rate in the QoL measured by the SF-36. Although our study used different diagnostic tools, lower physical health and psychological domains showed increased patient mortality, which may be consistent with these other studies. However, one difference is that our study assessed the long-term mortality rate that affects QoL, whereas the other studies analyzed a short-term mortality rate of 6 months to 1 year.

Studies on the impact of QoL measured using the WHOQOL-BREF on the mortality rate in hemodialysis patients are few, but relatively small-scale studies have been reported in Taiwan [31]. Wang et al. [31] reported that the lowest QoL tertile measured by the WHOQOL-BREF for 151 hemodialysis patients had a significantly higher 3-year mortality rate. In this study by Wang et al. [31], the mean score of all four domains of the WHOQOL-BREF was significantly lower in the mortality group. Among the four domains of the WHOQOL-BREF, those where the lowest tertile had a significantly higher 3-year mortality rate were the physical health, social, and environmental domains [31]. In particular, the finding that the physical health domain had the greatest effect on mortality in hemodialysis patients was consistent with our results; however, the other domains that affected mortality in hemodialysis patients were different. These differences might be due to the possibility that social or environmental domains could be affected by national, regional, and economic conditions. Moreover, in our study, there was no significant difference between the mortality and survival groups in the social support level measured by MSPSS or the average score of the social domain of the WHOQOL-BREF, which could be different from the results of Wang et al. [31]. Interestingly, in that study by Wang et al. [31], although depression and poor sleep quality were associated with an increase in the mortality rate of hemodialysis patients, the psychological domain of the WHOQOL-BREF did not show a statistically significant relationship with the mortality rate of hemodialysis patients. In contrast, in the present study, a low psychological domain score of the WHOQOL-BREF increased the mortality rate of hemodialysis patients, but there was no difference in depression or sleep quality, as assessed by the HADS or PSQI, between the mortality and survival groups. However, it should be considered that the cutoff values for each domain in the WHOQOL-BREF were different in each study and that both studies had small sample sizes. Therefore, large-scale, well-designed studies and a consensus on the appropriate cutoff values for the application of WHOQOL-BREF to hemodialysis patients are needed in the future.

Recently, a nationwide multicenter study was conducted on the effect of QoL in hemodialysis patients in Korea using the Clinical Research Center for End-Stage Renal Disease (CRC for ESRD) cohort [12]. Lee et al. [12] reported that among the final 568 hemodialysis patients, a lower score in the physical health domain was associated with an increase in the mortality rate among the QoL measures of the KDQOL-SF 1.3, but the psychological domain was not related to the mortality rate. Lee et al. [12] also hypothesized that the reason for the different QoL domains related to mortality in previous studies was a difference in the basic characteristics of the study populations. Although it is not possible to compare the differences in basic characteristics directly between the studies, when compared with that of Lee et al. [12], our study population had a higher rate of cardiovascular disease, while the mean CCI tended to be lower. However, as mentioned in the Introduction, the KDQOL-SF 1.3 consists of 100 questions; thus, it may be difficult to use this questionnaire repeatedly for hemodialysis patients.

This study had several limitations. First, there may have been selection bias. In Korea, after hemodialysis is initiated at a tertiary general hospital, only some patients continue on outpatient maintenance dialysis at tertiary general hospitals; most are transferred to other hemodialysis centers. Because this process is not carried out consistently for medical judgment or research purposes, differences in basic characteristics may occur between the transferred and non-transferred groups or between tertiary hospitals. Second, this study comprised a small sample size and involved a single institution. Third, this cross-sectional study did not account for changes in various indicators that occur over time. Despite these limitations, this study had several strengths. First, it elucidated the impact of QoL on mortality in patients undergoing hemodialysis. Second, the WHOQOL-BREF, used to assess QoL in this study, has been translated into various languages and is widely used worldwide. It is a simple questionnaire with four clearly defined domains that patients can complete while undergoing hemodialysis, and its results are easy to interpret. Third, this study collected a
relatively wide range of laboratory data, including data on various factors affecting mortality in hemodialysis patients, and used various instruments to assess the QoL and psychological health of hemodialysis patients.

In summary, QoL can significantly affect mortality in patients undergoing maintenance hemodialysis. It may be useful not only to obtain laboratory data such as age, comorbidities, and blood calcium concentrations, but also to assess QoL and the long-term prognosis of patients on maintenance hemodialysis. The WHO-QOL-BREF is a tool that allows for a relatively simple QoL assessment and may be considered when trying to predict the long-term outcome of patients on maintenance hemodialysis.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization, Formal analysis, Methodology, Investigation: SGK, IHL; Data curation, Project administration, Visualization, Software, Validation: SGK; Supervision: IH Lee; Writing-original draft: SGK; Writing-review & editing: SGK, IHL.

ORCID
Seong Gyu Kim, https://orcid.org/0000-0001-7900-7560
In Hee Lee, https://orcid.org/0000-0003-3562-7586

References

18. Zimet GD, Powell SS, Farley GK, Werkman S, Berkoﬀ KA. Psy-
Satisfaction of industrial health care managers regarding the work of industrial hygiene engineers: a cross-sectional study

Byung Sik Choi¹, Min Keun Kim², Joon Sakong³

¹Korean Industrial Health Association, Gyeongsan, Korea
²Department of Occupational and Environmental Medicine, Yeungnam University Hospital, Daegu, Korea
³Department of Preventive Medicine and Public Health, Yeungnam University College of Medicine, Daegu, Korea

**Background:** A group health service is a system that delegates workplace health management to an entrusted institution. There have been various studies on group health services to date, but recent changes, such as an increase in foreign workers, are rapidly changing industry characteristics.

**Methods:** Satisfaction was assessed using a 27-question survey distributed among 203 workplaces employing health professionals. The survey items consisted of general characteristics, comprehensive satisfaction, requirements for health professionals’ work, and satisfaction with work environment management, ergonomic management, and healthcare management. Multiple regression and frequency analyses were performed.

**Results:** The comprehensive satisfaction was 4.08 points on average, out of 5. The comprehensive satisfaction of health professionals in the industry was positively correlated with each factor. Hazardous materials and chemical management (material safety data sheets, MSDSs) were the most common requirements.

**Conclusion:** A low level of satisfaction with work environment management indicates high demand for healthcare management. The working environment should be improved by identifying characteristics of the workplace, examining harmful substances, inspecting equipment, and enhancing worker methods. The shorter the work experience of health professionals, the more dependent they are on group health services. The variables affecting comprehensive satisfaction were the period of work, healthcare management satisfaction, and work environment management satisfaction. Most of the requirements of health professionals in the workplace were practical improvement case presentations, MSDSs, and legal document management.

**Keywords:** Consumer health information; Occupational health services; Public health practice

**Introduction**

Occupational health practices require experience, technology, and professional expertise. Small businesses find it difficult to provide occupational health care on their own, so health management in small workplaces is commonly entrusted to health management institutions, called group health services.

The Enforcement Decree of the Industrial Safety and Health Act was promulgated in July 1990, and a system of small-sized businesses (50–300 workers), entrusting comprehensive health man-
agement to specialized institutions was created [1]. Occupational health programs are conducted by doctors, nurses, and health management institutions to provide health counseling, health education, work environment management, ergonomic management, healthcare management, and health promotion [2,3]. Research on group health services is also increasing [4-6]. Recently, the demand for industrial health services has increased rapidly, leading to abrupt changes in the general characteristics of the industry. Therefore, new studies on the needs of and satisfaction with industrial health services are required to correctly assess the satisfaction of healthcare workers in the field. Therefore, it is important to clarify the impact of individual satisfaction factors on comprehensive satisfaction.

This study aimed to identify comprehensive satisfaction with services provided by professional healthcare institutions, including work environment management satisfaction, ergonomic management satisfaction, healthcare management satisfaction, and the practical needs for services by industry and scale.

Methods

Ethical statements: The protocol of this study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No. 2017-003-005). Written informed consent was obtained from all participants for publication.

1. Study design
This study examined satisfaction with services provided by health management institutions in Daegu (region) and Gyeongsangbuk-do (including Yeongcheon, Gyeongsan, Gyeongju, and Pohang) in Korea. Excluding the businesses of which the researchers were in charge, 203 health professionals in the workplace were targeted. The survey was conducted from March 2, 2018 to March 30, 2018.

The survey items consisted of general characteristics (10 items), comprehensive satisfaction (one item), work environment management satisfaction (six items), ergonomic management satisfaction (three items), healthcare management satisfaction (six items), and requirements for health professionals’ work (one item). The range of satisfaction was very satisfied (5 points), generally satisfied (4 points), usually satisfied (3 points), dissatisfied (2 points), and very dissatisfied (1 point). In this study, work environment management comprised providing assistance, advice, and guidance when purchasing health-related protective equipment, maintaining material safety data, and engineering improvements in workplace ventilation systems (e.g., full ventilation and local exhaust systems); conducting inspections of the workplace and facilities; changing work processes and procedures; and conducting inspections of the general environment (e.g., shower rooms, hallway stairs, toilets, lounges, and restaurants). Ergonomic management tasks comprised identifying and advising 11 items of musculoskeletal system burden work, investigating harmful factors in the workplace due to musculoskeletal burden work, and establishing appropriate preventive measures for weight-handling work. Healthcare management tasks consisted of the investigation and analysis of the causes of industrial accidents, prevention of recurrence, maintenance and analysis of statistics on industrial accidents, implementation of health matters under the Industrial Safety and Health Act, risk assessment, and health education plans. The general characteristics of a workplace included the number of workers and the industry. The general characteristics of health professionals included sex, age, work period, health service duration, department, and academic background. The practical needs for services included (1) practical improvement case presentations, (2) material safety data sheets (MSDSs), and (3) legal document management.

2. Statistical analyses
A frequency analysis was conducted to identify the general characteristics of the participants, and a reliability index, Cronbach α, was calculated. To identify differences in satisfaction with health service personnel by industry, t-tests were conducted. Independent t-tests, one-way analysis of variance, and Scheffe post-hoc tests were conducted to identify the difference in satisfaction with health service personnel in manufacturing and nonmanufacturing industries. Correlation analysis was conducted to understand the relationship between the sub-factors of satisfaction and health professionals.

Results

Cronbach alpha values for the overall satisfaction survey, work environment management satisfaction, and healthcare management satisfaction were found to be highly reliable (0.887, 0.867, and 0.900, respectively) (Table 1). The study included 151 men (74.4%) and 52 women (25.6%) among the participants. The most common types of participants were aged between 30 and 39 years (44.8%), had 1 to 4 years of service (46.8%), and worked as assistant managers (22.2%). The most common workplace size was between 50 and 99 workers (50.7%), followed by between 100 and 199 workers (20.7%), less than 50 workers (17.7%), and 200 or more workers (10.8%) (Table 2).

https://doi.org/10.12701/jyms.2022.00073
Out of a maximum score of 5, the average comprehensive satisfaction was 4.08, the average healthcare management satisfaction was 3.90, the average work environment management satisfaction was 3.81, and the average ergonomic management satisfaction was 3.86. The comprehensive satisfaction of the health service group did not differ according to the characteristics of the manufacturing and nonmanufacturing sectors (Table 3). The satisfaction level with ergonomic management did not vary with the characteristics of the health professional in the workplace (Table 4). The satisfaction level of healthcare management at the manufacturing sites showed no statistically significant differences (Table 5).

### Table 1. Reliability of satisfaction survey questions

<table>
<thead>
<tr>
<th>Subregion</th>
<th>Questionnaire items</th>
<th>Cronbach alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive satisfaction</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Work environment management</td>
<td>6</td>
<td>0.887</td>
</tr>
<tr>
<td>Ergonomic management satisfaction</td>
<td>3</td>
<td>0.867</td>
</tr>
<tr>
<td>Health care management satisfaction</td>
<td>6</td>
<td>0.900</td>
</tr>
</tbody>
</table>

Frequency analysis, Cronbach alpha calculated as reliability index.

### Table 2. Common characteristics of business and health professionals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Manufacturing</th>
<th>Nonmanufacturing</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Business</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of workers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>29 (18.6)</td>
<td>7 (14.9)</td>
<td>36 (17.7)</td>
</tr>
<tr>
<td>50–99</td>
<td>77 (49.4)</td>
<td>26 (55.3)</td>
<td>103 (50.7)</td>
</tr>
<tr>
<td>100–199</td>
<td>35 (22.4)</td>
<td>7 (14.9)</td>
<td>42 (20.7)</td>
</tr>
<tr>
<td>≥ 200</td>
<td>15 (9.6)</td>
<td>7 (14.9)</td>
<td>22 (10.8)</td>
</tr>
<tr>
<td><strong>Health professionals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>118 (75.6)</td>
<td>33 (70.2)</td>
<td>151 (74.4)</td>
</tr>
<tr>
<td>Female</td>
<td>38 (24.4)</td>
<td>14 (29.8)</td>
<td>52 (25.6)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>20 (12.8)</td>
<td>6 (12.8)</td>
<td>26 (12.8)</td>
</tr>
<tr>
<td>30–39</td>
<td>70 (44.9)</td>
<td>21 (44.7)</td>
<td>91 (44.8)</td>
</tr>
<tr>
<td>40–49</td>
<td>45 (28.8)</td>
<td>10 (21.3)</td>
<td>55 (27.1)</td>
</tr>
<tr>
<td>≥ 50</td>
<td>21 (13.5)</td>
<td>10 (21.3)</td>
<td>31 (15.3)</td>
</tr>
<tr>
<td>Overall period of work (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>70 (44.9)</td>
<td>25 (53.2)</td>
<td>95 (46.8)</td>
</tr>
<tr>
<td>5–9</td>
<td>42 (26.9)</td>
<td>6 (12.8)</td>
<td>48 (23.6)</td>
</tr>
<tr>
<td>≥ 10</td>
<td>44 (28.2)</td>
<td>16 (34.0)</td>
<td>60 (29.6)</td>
</tr>
<tr>
<td>Position of work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staff</td>
<td>31 (19.9)</td>
<td>11 (23.4)</td>
<td>42 (20.7)</td>
</tr>
<tr>
<td>Administrative manager</td>
<td>18 (11.5)</td>
<td>12 (25.5)</td>
<td>30 (14.8)</td>
</tr>
<tr>
<td>Assistant manager</td>
<td>34 (21.8)</td>
<td>11 (23.4)</td>
<td>45 (22.2)</td>
</tr>
<tr>
<td>Manager</td>
<td>33 (21.2)</td>
<td>5 (10.6)</td>
<td>38 (18.7)</td>
</tr>
<tr>
<td>Deputy general manager</td>
<td>12 (7.7)</td>
<td>0 (0.0)</td>
<td>12 (5.9)</td>
</tr>
<tr>
<td>Department manager</td>
<td>21 (13.5)</td>
<td>6 (12.8)</td>
<td>27 (13.3)</td>
</tr>
<tr>
<td>Others (workplace safety manager, etc.)</td>
<td>7 (4.5)</td>
<td>2 (4.3)</td>
<td>9 (4.4)</td>
</tr>
<tr>
<td>Period of work as health professional (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>23 (14.7)</td>
<td>10 (21.3)</td>
<td>33 (16.3)</td>
</tr>
<tr>
<td>1–2</td>
<td>29 (18.6)</td>
<td>10 (21.3)</td>
<td>39 (19.2)</td>
</tr>
<tr>
<td>3–4</td>
<td>29 (18.6)</td>
<td>11 (23.4)</td>
<td>40 (19.7)</td>
</tr>
<tr>
<td>4–5</td>
<td>29 (18.6)</td>
<td>4 (8.5)</td>
<td>33 (16.3)</td>
</tr>
<tr>
<td>6–10</td>
<td>27 (17.3)</td>
<td>6 (12.8)</td>
<td>33 (16.3)</td>
</tr>
<tr>
<td>&gt; 11</td>
<td>19 (12.2)</td>
<td>6 (12.8)</td>
<td>25 (12.3)</td>
</tr>
<tr>
<td>Workplace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>137 (87.8)</td>
<td>37 (78.7)</td>
<td>174 (85.7)</td>
</tr>
<tr>
<td>Other than office</td>
<td>14 (9.0)</td>
<td>8 (17.0)</td>
<td>22 (10.8)</td>
</tr>
<tr>
<td>Production</td>
<td>5 (3.2)</td>
<td>2 (4.3)</td>
<td>7 (3.4)</td>
</tr>
<tr>
<td>Total</td>
<td>156 (100)</td>
<td>47 (100)</td>
<td>203 (100)</td>
</tr>
</tbody>
</table>

Values are presented as number of workers (%).
Table 3. Satisfaction of health care management affairs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Manufacturing (n = 156)</th>
<th>Nonmanufacturing (n = 47)</th>
<th>Sum</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Comprehensive satisfaction of health care entrustment</td>
<td>4.08 ± 0.62</td>
<td>4.09 ± 0.75</td>
<td>4.08 ± 0.65</td>
<td>0.987</td>
</tr>
<tr>
<td>Work environment management satisfaction</td>
<td>3.79 ± 0.61</td>
<td>3.89 ± 0.62</td>
<td>3.81 ± 0.61</td>
<td>0.323</td>
</tr>
<tr>
<td>Ergonomic management satisfaction</td>
<td>3.87 ± 0.68</td>
<td>3.83 ± 0.75</td>
<td>3.86 ± 0.69</td>
<td>0.731</td>
</tr>
<tr>
<td>Healthcare management satisfaction</td>
<td>3.89 ± 0.61</td>
<td>3.96 ± 0.67</td>
<td>3.90 ± 0.63</td>
<td>0.513</td>
</tr>
</tbody>
</table>

Independent t-test, Scheffe post-hoc tests, and analysis of variance were conducted.
SD, standard deviation.

Table 4. Satisfaction of ergonomic management guidance according to the characteristics of business and health professionals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Manufacturing (n = 156)</th>
<th>Nonmanufacturing (n = 47)</th>
<th>Sum</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>No. of workers</td>
<td>0.784</td>
<td>0.287</td>
<td>0.638</td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>3.78 ± 0.67</td>
<td>3.87 ± 0.78</td>
<td>3.86 ± 0.68</td>
<td></td>
</tr>
<tr>
<td>50–99</td>
<td>3.88 ± 0.67</td>
<td>3.71 ± 0.76</td>
<td>3.88 ± 0.70</td>
<td></td>
</tr>
<tr>
<td>100–199</td>
<td>3.94 ± 0.66</td>
<td>3.43 ± 0.71</td>
<td>3.90 ± 0.68</td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
<td>3.80 ± 0.79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.166</td>
<td>0.766</td>
<td>0.309</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.91 ± 0.68</td>
<td>3.81 ± 0.70</td>
<td>3.89 ± 0.68</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3.74 ± 0.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.473</td>
<td>0.723</td>
<td>0.718</td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>4.07 ± 0.66</td>
<td>3.67 ± 0.37</td>
<td>3.97 ± 0.62</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>3.81 ± 0.71</td>
<td>3.78 ± 0.84</td>
<td>3.81 ± 0.73</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>3.90 ± 0.61</td>
<td>3.80 ± 0.77</td>
<td>3.88 ± 0.64</td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>3.79 ± 0.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period of work overall (yr)</td>
<td>0.340</td>
<td>0.478</td>
<td>0.707</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>3.91 ± 0.66</td>
<td>3.71 ± 0.68</td>
<td>3.86 ± 0.66</td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>3.93 ± 0.72</td>
<td>3.89 ± 0.72</td>
<td>3.92 ± 0.71</td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>3.74 ± 0.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Position of work</td>
<td>0.787</td>
<td>0.356</td>
<td>0.590</td>
<td></td>
</tr>
<tr>
<td>Staff</td>
<td>3.88 ± 0.65</td>
<td>3.88 ± 0.67</td>
<td>3.88 ± 0.65</td>
<td></td>
</tr>
<tr>
<td>Administrative manager</td>
<td>3.91 ± 0.62</td>
<td>3.78 ± 0.66</td>
<td>3.86 ± 0.63</td>
<td></td>
</tr>
<tr>
<td>Assistant manager</td>
<td>3.90 ± 0.69</td>
<td>3.58 ± 0.97</td>
<td>3.82 ± 0.77</td>
<td></td>
</tr>
<tr>
<td>Manager</td>
<td>3.85 ± 0.77</td>
<td>3.93 ± 0.80</td>
<td>3.86 ± 0.77</td>
<td></td>
</tr>
<tr>
<td>Deputy general manager</td>
<td>4.03 ± 0.59</td>
<td>4.39 ± 0.57</td>
<td>4.03 ± 0.59</td>
<td></td>
</tr>
<tr>
<td>Department manager</td>
<td>3.84 ± 0.68</td>
<td>3.33 ± 0.47</td>
<td>3.96 ± 0.69</td>
<td></td>
</tr>
<tr>
<td>Others (workplace safety manager, etc.)</td>
<td>3.48 ± 0.63</td>
<td></td>
<td>3.44 ± 0.58</td>
<td></td>
</tr>
<tr>
<td>Period of work as health professional (yr)</td>
<td>0.594</td>
<td>0.333</td>
<td>0.498</td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>3.96 ± 0.68</td>
<td>4.00 ± 0.50</td>
<td>3.82 ± 0.80</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>3.87 ± 0.63</td>
<td>3.94 ± 0.66</td>
<td>3.91 ± 0.59</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.91 ± 0.67</td>
<td>3.50 ± 0.43</td>
<td>3.92 ± 0.66</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.92 ± 0.77</td>
<td>4.28 ± 0.68</td>
<td>3.87 ± 0.75</td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>3.89 ± 0.57</td>
<td>3.67 ± 0.97</td>
<td>3.96 ± 0.60</td>
<td></td>
</tr>
<tr>
<td>≥ 10</td>
<td>3.60 ± 0.77</td>
<td></td>
<td>3.61 ± 0.80</td>
<td></td>
</tr>
<tr>
<td>Workplace</td>
<td>0.369</td>
<td>0.634</td>
<td>0.569</td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>3.90 ± 0.67</td>
<td>3.83 ± 0.62</td>
<td>3.88 ± 0.70</td>
<td></td>
</tr>
<tr>
<td>Other than office</td>
<td>3.64 ± 0.73</td>
<td>4.33 ± 0.47</td>
<td>3.71 ± 0.68</td>
<td></td>
</tr>
<tr>
<td>Production</td>
<td>3.73 ± 0.68</td>
<td></td>
<td>3.90 ± 0.66</td>
<td></td>
</tr>
</tbody>
</table>

Correlation analysis was conducted.
SD, standard deviation.
A survey was conducted with health professionals at 203 workplaces to understand comprehensive satisfaction, work environment management satisfaction, ergonomic management satisfaction, healthcare management satisfaction, and the requirements of health professionals.

The overall satisfaction of health professionals averaged 4.08 out of 5, 3.90 for health care management satisfaction, 3.86 for work environment management satisfaction, and 3.81 for ergonomic management satisfaction. A reason for this result may be that regular visits by doctors, nurses, and industrial hygiene engineers maintain continuity in group health services. The working environment should be improved by identifying characteris-

Table 5. Satisfaction of guidance on industrial health information management according to the characteristics of business health professionals and industrial hygiene management engineers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Manufacturing</th>
<th>Nonmanufacturing</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>p-value</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>No. of workers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>3.87 ± 0.51</td>
<td>0.989</td>
<td>4.03 ± 0.64</td>
</tr>
<tr>
<td>50–99</td>
<td>3.89 ± 0.62</td>
<td></td>
<td>3.64 ± 0.78</td>
</tr>
<tr>
<td>100–199</td>
<td>3.91 ± 0.67</td>
<td></td>
<td>3.81 ± 0.82</td>
</tr>
<tr>
<td>≥ 200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3.93 ± 0.59</td>
<td>0.109</td>
<td>3.92 ± 0.72</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>4.13 ± 0.58</td>
<td>0.258</td>
<td>3.78 ± 0.55</td>
</tr>
<tr>
<td>30–39</td>
<td>3.85 ± 0.64</td>
<td></td>
<td>3.98 ± 0.62</td>
</tr>
<tr>
<td>40–49</td>
<td>3.83 ± 0.55</td>
<td></td>
<td>3.82 ± 0.83</td>
</tr>
<tr>
<td>≥ 50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period of work overall (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>3.95 ± 0.62</td>
<td>0.146</td>
<td>3.93 ± 0.64</td>
</tr>
<tr>
<td>5–9</td>
<td>3.95 ± 0.63</td>
<td></td>
<td>3.94 ± 0.62</td>
</tr>
<tr>
<td>≥ 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Position of work</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staff</td>
<td>3.97 ± 0.59</td>
<td>0.737</td>
<td>4.06 ± 0.66</td>
</tr>
<tr>
<td>Administrative manager</td>
<td></td>
<td></td>
<td>3.89 ± 0.65</td>
</tr>
<tr>
<td>Assistant manager</td>
<td></td>
<td></td>
<td>3.71 ± 0.74</td>
</tr>
<tr>
<td>Manager</td>
<td>3.79 ± 0.58</td>
<td></td>
<td>4.03 ± 0.48</td>
</tr>
<tr>
<td>Deputy general manager</td>
<td></td>
<td></td>
<td>4.39 ± 0.69</td>
</tr>
<tr>
<td>Department manager</td>
<td></td>
<td></td>
<td>3.67 ± 0.94</td>
</tr>
<tr>
<td>Others (workplace safety manager, etc.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period of work as health professional (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>4.00 ± 0.56</td>
<td>0.130</td>
<td>4.08 ± 0.53</td>
</tr>
<tr>
<td>1–2</td>
<td>3.91 ± 0.61</td>
<td></td>
<td>4.00 ± 0.52</td>
</tr>
<tr>
<td>3</td>
<td>3.95 ± 0.66</td>
<td></td>
<td>3.79 ± 0.37</td>
</tr>
<tr>
<td>4</td>
<td>3.97 ± 0.63</td>
<td></td>
<td>4.25 ± 0.76</td>
</tr>
<tr>
<td>5–9</td>
<td>3.88 ± 0.59</td>
<td></td>
<td>3.89 ± 0.89</td>
</tr>
<tr>
<td>≥ 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workplace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office</td>
<td>3.90 ± 0.63</td>
<td>0.718</td>
<td>3.96 ± 0.63</td>
</tr>
<tr>
<td>Other than office</td>
<td></td>
<td></td>
<td>3.76 ± 0.61</td>
</tr>
<tr>
<td>Production</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Correlation analysis was conducted.
SD, standard deviation.

Discussion

A survey was conducted with health professionals at 203 workplaces to understand comprehensive satisfaction, work environment management satisfaction, ergonomic management satisfaction, healthcare management satisfaction, and the requirements of health professionals.

The overall satisfaction of health professionals averaged 4.08 out of 5, 3.90 for health care management satisfaction, 3.86 for work environment management satisfaction, and 3.81 for ergonomic management satisfaction. A reason for this result may be that regular visits by doctors, nurses, and industrial hygiene engineers maintain continuity in group health services. The working environment should be improved by identifying characteris-
tics of the workplace, examining harmful substances, inspecting equipment, and reviewing procedures before workshop tour inspections to provide realistic guidance suitable for the characteristics of the workplace [7]. The level of work environment management satisfaction was found to be high in the production and office groups of manufacturing industries. Healthcare management satisfaction differed significantly according to the duration of work experience. Workers with less than 1 year of experience had the highest satisfaction, and those with more than 10 years of experience had the lowest satisfaction. This means that the shorter the experience of a health professional at the workplace, the more dependent he or she is on group health services. The higher the work environment and health care management satisfaction, the higher the comprehensive satisfaction. In the manufacturing industry, a health professional work period of 2 to 3 years, work period of 3 to 5 years, work environment management satisfaction, and healthcare management satisfaction had significant effects on comprehensive satisfaction. In the non-manufacturing industry, healthcare management satisfaction had a significant impact on comprehensive satisfaction. Multiple regression analysis revealed that the work period of health professionals, health care management satisfaction, and work environment management satisfaction were variables that affected comprehensive satisfaction.

Three items accounted for most requirements of healthcare professionals in the workplace: (1) practical improvement case presentations, (2) MSDSSs, and (3) legal document management. The reason these requirements were so high is that, first, improvement measures presented by occupational health program institutes can be difficult to apply practically; therefore, specific and realistic guidance is likely required. Second, acute poisoning accidents caused by chemicals frequently occur because of the lack of information about chemicals in the workplace. Data are needed for the rights of workers to know about chemicals and prevent occupational diseases and industrial accidents; therefore, the demand is high for health professionals and workers to have access to health education and MSDSSs, and how to use them [8]. Third, most health professionals in the field perform other tasks (such as those related to worker safety, environment, water quality, fire safety, and the environment); hence, it is difficult to manage the legally required documents. Regarding the need for improvement, groups with 2 to 3, 3 to 5, and more than 10 years of work experience required the most management of hazardous materials and chemicals.

The study was conducted through a health management agency in Daegu and North Gyeongsangbuk-do Province using a satisfaction survey of health professionals in the workplace.

Notes

Conflicts of interest
Joon Sakong has been editorial board member of Journal of Yeungnam Medical Science since 2010. He was not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

Funding
This work was supported by a grant from the Chunma Medical Research Foundation, Korea, 2021.

Author contributions
Conceptualization, Formal analysis, Supervision: JS; Funding acquisition: JS; Writing-original draft: BSC; Writing-review & editing: MKK.

ORCID
Min Keun Kim, https://orcid.org/0000-0002-2857-6277
Joon Sakong, https://orcid.org/0000-0003-3623-7619

References

3. Ministry of Employment and Labor. Enforcement Regulations of the Occupational Safety and Health Act: Ordinance of the Ministry of Employment and Labor of 2017, No. 197 [Internet]. Sejong: Ministry of Employment and Labor; 2017 [cited 2022 Mar 22]. https://www.law.go.kr/%EB%B2%95%EB%A0%B9/%EC%82%B0%EC%97%85%EC%95%88%EC%A0%84%EB%B3%B4%EA%B1%B4%EB%B2%95%EC%88%B9%ED%96%89%EA%B7%9C%EC%B9%99.
5. Park HM. The survey on opinions for workplace visiting health care by group health care agency [dissertation]. Seoul: Yonsei


The effect and therapeutic compliance of adjuvant therapy in patients with cholangiocarcinoma after R0 resection: a retrospective study

Han Taek Jeong, Joonkee Lee, Hyeong Ho Jo, Ho Gak Kim, Jimin Han

Department of Internal Medicine, Daegu Catholic University School of Medicine, Daegu, Korea

Background: This study aimed to compare clinical outcomes between surveillance and adjuvant therapy (AT) groups after R0 resection for cholangiocarcinoma (CCA).

Methods: A total of 154 patients who underwent R0 resection for CCA at the Daegu Catholic University Medical Center between January 2010 and December 2019 were included. Overall survival (OS) and progression-free survival (PFS) were analyzed.

Results: The median follow-up duration was 899 days. There were 109 patients in the AT group and 45 patients in the surveillance group. The patients in the AT group were younger (67 years vs. 74 years, \( p < 0.001 \)) and included more males (64.2% vs. 46.7%, \( p = 0.044 \)). The proportion of patients with stage III CCA was larger in the AT group than in the surveillance group (13.8% vs. 2.2%, \( p = 0.005 \)). In addition, AT did not improve OS (5-year OS rate, 69.3% in the AT group vs. 64.2% in the surveillance group, \( p = 0.806 \)) or PFS (5-year PFS rate, 42.6% in the AT group vs. 48.9% in the surveillance group, \( p = 0.113 \)). In multivariate analysis using the Cox proportional hazards model, stage III CCA (hazard ratio [HR], 10.81; 95% confidence interval [CI], 2.92–40.00; \( p < 0.001 \)) was a significant predictor of OS. American Society of Anesthesiologists classification II (HR, 0.50; 95% CI, 0.31–0.81; \( p = 0.005 \)), and American Joint Committee on Cancer stages II (HR, 3.14; 95% CI, 1.25–7.89; \( p = 0.015 \)) and III (HR, 8.08; 95% CI, 2.80–23.32; \( p < 0.001 \)) were independent predictors of PFS.

Conclusion: AT after R0 resection for CCA did not improve OS or PFS.

Keywords: Adjuvant chemotherapy; Biliary tract surgical procedures; Cholangiocarcinoma; Survival analysis; Watchful waiting
30% of cases are resectable at diagnosis [3,4]. Moreover, more than two-thirds of patients relapse within 5 years after surgery [3]. Therefore, various studies on adjuvant therapy (AT) for CCA have investigated many chemotherapeutic agents, radiotherapy, or both, which had previously been demonstrated to be effective for locally advanced and metastatic CCA [3]. However, the few large prospective studies on AT conducted to date have produced disappointing results [6-10]. The effect of AT on CCA has been inconsistent among several recent retrospective studies [11-20]. In particular, if patients have undergone R0 resection, the National Comprehensive Cancer Network guidelines recommend all possible options: observation, systemic therapy, or clinical trial [21].

Therefore, this study aimed to retrospectively investigate the effect of AT on CCA after R0 resection. We also analyzed prognostic factors associated with overall survival (OS) and progression-free survival (PFS). Furthermore, the therapeutic compliance of AT was evaluated.

Methods

Ethical statements: This study was performed in compliance with the ethical guidelines of the revised Helsinki Declaration of 2013. This study was reviewed and approved by the Institutional Review Board (IRB) of the Daegu Catholic University Medical Center (IRB No: CR-21-107-L). Since this study was retrospective, the need for informed consent was waived.

1. Study population
A total of 210 patients who underwent curative surgery for CCA at Daegu Catholic University Medical Center between January 2010 and December 2019 were eligible for this study (Fig. 1). Cases were collected using diagnostic codes (C221, C240, C248, and C249) based on the 8th revision of the Korean Standard Classification of Diseases. The following were exclusion criteria: (1) positive resection margins, (2) death due to surgical complications, (3) follow-up at another hospital after surgery, (4) distant metastasis at the time of surgery, and (5) neuroendocrine tumors.

2. Study design
This was a retrospective single-center study. The following data were collected from medical records: demographics, preoperative serum carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) levels, tumor location, AT regimen, radiologic findings, and pathologic findings such as perineural invasion, differentiation, lymphovascular invasion, and extent of resection. Survival data were also obtained from the medical records. Disease stage was reclassified based on the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (8th edition). Patients were then divided into surveillance and AT groups to investigate the effects of AT. We also investigated the therapeutic adherence to AT.

3. Definitions
Patients who received planned chemotherapy or chemoradiotherapy after R0 resection were assigned to the AT group. Patients who continued follow-up without adjuvant chemotherapy or chemoradiotherapy after surgery were assigned to the surveillance group. OS was defined as the time from the date of surgery to the date of death from any cause. PFS was defined as the time from the date of surgery to the date of recurrence. The American Society of Anes-
theresiologists (ASA) classification was used to evaluate patient performance status. The cut-off level for serum CA 19-9 was 37 U/mL, and that for serum CEA was 5.2 ng/mL.

4. Treatment strategy and follow-up
The AT regimen for each patient was decided at the discretion of the clinician. In the AT group, an abdominal computed tomography (CT) scan was performed every 2 or 3 months during the AT and every 6 or 12 months thereafter. In the surveillance group, a CT scan was performed every 6 or 12 months. In both groups, a CT scan was also performed regardless of the follow-up schedule if the clinician determined that it was necessary because of symptoms or signs such as abdominal pain, fever, and jaundice. Follow-up continued until December 31, 2021, or until death.

5. Statistical analysis
Statistical analysis was performed using IBM SPSS ver. 19.0 for Windows (IBM Corp., Armonk, NY, USA). The chi-square or Fisher exact tests were used to compare categorical variables. Since the continuous variables were not normally distributed, they were described as medians with interquartile ranges, and the Mann-Whitney U-test was used to compare them. OS and PFS were analyzed using Kaplan-Meier survival analysis. The OS and PFS of the AT group and surveillance group were compared with the log-rank test. Subgroup analysis of the following variables was performed: lymphovascular invasion, perineural invasion, AJCC stage, and AT regimens. Univariate analysis was used to identify the prognostic factors associated with OS and PFS in patients with R0-resected CCA. Multivariate analysis was performed using the Cox proportional hazards model with backward elimination for the factors that were significant in the univariate analysis or those considered clinically meaningful in previous studies. The results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical significance was defined as a p-value of <0.05 (two-tailed).

Results

1. Baseline characteristics of patients
A total of 154 patients with CCA who underwent R0 resection during the study period were investigated. Of these, 109 patients (70.8%) received AT (AT group) and 45 patients (29.2%) were only followed up (surveillance group). The baseline patient characteristics are shown in Table 1. The patients in the AT group were younger than those in the surveillance group (67 years vs. 74 years, p < 0.001). There was also a higher proportion of males and patients with AJCC stage III disease in the AT group than in the surveillance group (64.2% vs. 46.7%, p = 0.044 and 13.8% vs. 2.2%, p = 0.005, respectively). However, other characteristics, including ASA classification, tumor marker levels, tumor location, and pathologic findings, were not significantly different between the two groups. There were 29 intrahepatic CCA (18.8%), 43 perihilar CCA (27.9%), and 82 distal CCA cases (53.2%). Most cases were adenocarcinomas (96.8%). The most common histologic differentiation was moderately differentiated cancer (56.5%), followed by poorly differentiated (25.3%) and well-differentiated (14.3%) cancer. Lymphovascular invasion and perineural invasion were observed in 53 (34.4%) and 91 patients (48.9%), respectively. The most common AJCC stage was stage II (73.4%), followed by stage I (16.2%) and stage III (10.4%). With regard to the AT regimen, tegafur/uracil (37.6%) was the most commonly used, followed by gemcitabine (25.7%) and gemcitabine/cisplatin (20.2%). Twelve patients in the AT group (11.0%) received chemoradiotherapy.

2. Survival analysis
The survival analysis of the patients is shown in Table 2. The median follow-up duration was 899 days. There was no statistically significant difference between the two groups (924 days in the AT group vs. 788 days in the surveillance group, p = 0.404). The 1-year, 3-year, and 5-year OSRs for all patients were 94.5%, 75.6%, and 68.0%, respectively. There were no significant differences between the two groups (95.2%, 75.8%, and 69.3% in the AT group vs. 92.8%, 75.9%, and 64.2% in the surveillance group, respectively, p = 0.806). In contrast, the PFS rate (PFSR) was higher in the surveillance group, although the difference was not statistically significant (p = 0.113). The 1-year, 3-year, and 5-year PFSRs for the surveillance group were 88.2%, 67.3%, and 48.9%, respectively, and those for the AT group were 70.3%, 45.4%, and 42.6%, respectively.

A comparison of the OS and PFS for all patients is shown in Fig. 2. The comparisons of OS and PFS in the subgroups including lymphovascular invasion, perineural invasion, and AJCC stage are shown in Figs. 3, 4, respectively. AT did not demonstrate a survival benefit in any of the analyses. The comparison of OS according to AT regimens is shown in Fig. 5. The 1-year, 3-year, and 5-year OSRs were 100%, 92.8%, and 69.3% in the gemcitabine/cisplatin group; 90.7%, 67.0%, and 55.8% in the gemcitabine group; and 100%, 86.3%, and 81.5% in the tegafur/uracil group, respectively. The tegafur/uracil group showed the highest OSR among the regimens, although the difference was not statistically significant (p = 0.358). However, tegafur/uracil did not demonstrate a survival benefit compared with the surveillance group (p = 0.268). A
Table 1. Baseline characteristics of patients with R0-resected cholangiocarcinoma

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Surveillance</th>
<th>Adjuvant therapy</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>154</td>
<td>45 (29.2)</td>
<td>109 (70.8)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>70 (61–74)</td>
<td>74 (68–77)</td>
<td>67 (60–73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>91 (59.1)</td>
<td>21 (46.7)</td>
<td>70 (64.2)</td>
<td>0.044</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
<td></td>
<td>0.740</td>
</tr>
<tr>
<td>I</td>
<td>45 (29.2)</td>
<td>14 (31.1)</td>
<td>31 (28.4)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>109 (70.8)</td>
<td>31 (68.9)</td>
<td>78 (71.6)</td>
<td></td>
</tr>
<tr>
<td>Tumor marker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA 19-9 (U/mL)</td>
<td>40 (15–139)</td>
<td>50 (17–109)</td>
<td>35 (14–172)</td>
<td>0.725</td>
</tr>
<tr>
<td>CEA (ng/mL)</td>
<td>2.8 (2.0–4.8)</td>
<td>2.9 (2.0–5.1)</td>
<td>2.7 (2.0–4.5)</td>
<td>0.526</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrahepatic</td>
<td>29 (18.8)</td>
<td>9 (20.0)</td>
<td>20 (18.3)</td>
<td>0.187</td>
</tr>
<tr>
<td>Perihilar</td>
<td>43 (27.9)</td>
<td>8 (17.8)</td>
<td>35 (32.1)</td>
<td></td>
</tr>
<tr>
<td>Distal</td>
<td>82 (53.2)</td>
<td>28 (62.2)</td>
<td>54 (49.5)</td>
<td></td>
</tr>
<tr>
<td>Pathologic classification</td>
<td></td>
<td></td>
<td></td>
<td>0.969</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>149 (96.8)</td>
<td>43 (95.6)</td>
<td>106 (97.2)</td>
<td></td>
</tr>
<tr>
<td>Others&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (3.2)</td>
<td>2 (4.4)</td>
<td>3 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Histologic differentiation</td>
<td></td>
<td></td>
<td></td>
<td>0.526</td>
</tr>
<tr>
<td>Well</td>
<td>22 (14.3)</td>
<td>6 (13.3)</td>
<td>16 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Moderately</td>
<td>87 (56.5)</td>
<td>29 (64.4)</td>
<td>58 (53.2)</td>
<td></td>
</tr>
<tr>
<td>Poorly</td>
<td>39 (25.3)</td>
<td>8 (17.8)</td>
<td>31 (28.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (3.9)</td>
<td>2 (4.4)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>AJCC stage</td>
<td></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>I</td>
<td>25 (16.2)</td>
<td>13 (28.9)</td>
<td>12 (11.0)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>113 (73.4)</td>
<td>31 (68.9)</td>
<td>82 (75.2)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>16 (10.4)</td>
<td>1 (2.2)</td>
<td>15 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
<td></td>
<td>0.904</td>
</tr>
<tr>
<td>Negative</td>
<td>81 (52.6)</td>
<td>24 (53.3)</td>
<td>57 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>53 (34.4)</td>
<td>16 (35.6)</td>
<td>37 (33.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>20 (13.0)</td>
<td>5 (11.1)</td>
<td>15 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Perineural invasion</td>
<td></td>
<td></td>
<td></td>
<td>0.254</td>
</tr>
<tr>
<td>Negative</td>
<td>30 (19.5)</td>
<td>11 (24.4)</td>
<td>19 (17.4)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>91 (59.1)</td>
<td>22 (48.9)</td>
<td>69 (63.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>33 (21.4)</td>
<td>12 (26.7)</td>
<td>21 (19.3)</td>
<td></td>
</tr>
<tr>
<td>Regimen</td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Tegafur/uracil</td>
<td>41 (26.6)</td>
<td>0 (0)</td>
<td>41 (37.6)</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine/cisplatin</td>
<td>22 (14.3)</td>
<td>0 (0)</td>
<td>22 (20.2)</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine only</td>
<td>28 (18.2)</td>
<td>0 (0)</td>
<td>28 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Others&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18 (11.7)</td>
<td>0 (0)</td>
<td>18 (16.5)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (interquartile range).
ASA, American Society of Anesthesiologists; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; AJCC, American Joint Committee on Cancer; N/A, not applicable.

<sup>a</sup>Others include three adenosquamous carcinomas, one mixed adenoneuroendocrine carcinoma, and one undifferentiated carcinoma.
<sup>b</sup>Others include 12 fluorouracil/radiotherapy and six fluorouracil/cisplatin.

Comparison of PFS according to the AT regimens is shown in Fig. 6. Similar to the OSR analysis, the tegafur/uracil group showed the highest PFSR among the regimens, although it was not statistically significant (p = 0.138). However, no survival benefit was observed with tegafur/uracil compared with the surveillance group (p = 0.891).
Table 2. Clinical outcomes of patients with R0-resected cholangiocarcinoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 154)</th>
<th>Surveillance (n = 45)</th>
<th>Adjuvant therapy (n = 109)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival rate, yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>94.5</td>
<td>92.8</td>
<td>95.2</td>
<td>0.806</td>
</tr>
<tr>
<td>3</td>
<td>75.6</td>
<td>75.9</td>
<td>75.8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>68.0</td>
<td>64.2</td>
<td>69.3</td>
<td></td>
</tr>
<tr>
<td>Progression-free survival rate, yr</td>
<td></td>
<td></td>
<td></td>
<td>0.113</td>
</tr>
<tr>
<td>1</td>
<td>75.2</td>
<td>88.2</td>
<td>70.3</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50.9</td>
<td>67.3</td>
<td>45.4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>45.0</td>
<td>48.9</td>
<td>42.6</td>
<td></td>
</tr>
<tr>
<td>Follow-up (day)</td>
<td>899 (461–1,372)</td>
<td>788 (389–1,237)</td>
<td>924 (487–1,436)</td>
<td>0.404</td>
</tr>
</tbody>
</table>

Values are presented as percentage or median (interquartile range). Log-rank test and Mann-Whitney U-test were used.

Fig. 2. Comparison of survival curves for patients with R0-resected cholangiocarcinoma. (A) Overall survival. (B) Progression-free survival.

3. Prognostic factors associated with overall survival and progression-free survival

In the univariate analysis, CEA elevation (HR, 3.38; 95% CI, 1.30–8.74; \( p = 0.012 \)), lymphovascular invasion (HR, 2.11; 95% CI, 1.10–4.03; \( p = 0.023 \)), and AJCC stage III (HR, 9.81; 95% CI, 2.67–36.10; \( p < 0.001 \)) were useful prognostic factors for OS (Table 3). However, AT was not a statistically significant factor (HR, 0.92; 95% CI, 0.45–1.86; \( p = 0.806 \)). In the multivariate analysis, only AJCC stage III (HR, 10.81; 95% CI, 2.92–40.00; \( p < 0.001 \)) was a statistically significant prognostic factor associated with OS (Table 3). CA 19-9 elevation (HR, 1.80; 95% CI, 0.93–3.52; \( p = 0.083 \)) was useful but not statistically significant. Prognostic factors associated with PFS were analyzed and are shown in Table 4. In the multivariate analysis, ASA classification II (HR, 0.50; 95% CI, 0.31–0.81; \( p = 0.005 \)), AJCC stage II (HR, 3.14; 95% CI, 1.25–7.89; \( p = 0.015 \)), and AJCC stage III (HR, 8.08; 95% CI, 2.80–23.32; \( p < 0.001 \)) were significant prognostic factors for PFS (Table 4). Poorly differentiated cancer was statistically significant in the univariate analysis (HR, 1.92; 95% CI, 1.17–3.16; \( p = 0.010 \)), but not in the multivariate analysis (HR, 1.64; 95% CI, 0.98–2.75; \( p = 0.060 \)). As in the OS analysis, AT was not a statistically significant factor associated with PFS (HR, 1.57; 95% CI, 0.89–2.78; \( p = 0.117 \)).

4. Therapeutic adherence to adjuvant therapy according to regimen

Therapeutic adherence in the AT group according to the regimen is summarized in Table 5. Of the 109 patients who received AT, 72
No. at risk | Surveillance | Adjuvant therapy | Surveillance | Adjuvant therapy | Surveillance | Adjuvant therapy | Surveillance | Adjuvant therapy |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>16 8 5 1 0 0 0</td>
<td>37 25 16 9 3 1 0</td>
<td>22 13 6 2 2 0 0</td>
<td>69 46 28 12 3 2 1</td>
<td>22 13 6 2 2 0 0</td>
<td>69 46 28 12 3 2 1</td>
<td>31 20 11 4 4 0 0</td>
<td>113 60 40 2 5 3 1</td>
</tr>
</tbody>
</table>

**Fig. 3.** Comparison of overall survival for patients with R0-resected cholangiocarcinoma. (A) Patients with lymphovascular invasion. (B) Patients with perineural invasion. (C) Patients with American Joint Committee on Cancer (AJCC) stage I disease. (D) Patients with AJCC stage II disease.

(66.1%) completed the therapeutic schedule, and 37 (33.9%) did not finish the cycle. The reasons for cessation included recurrence (37.8%), patient refusal (24.3%), neutropenia (8.1%), and loss to follow-up (5.4%). Of the 109 patients who received AT, 36 (33.0%) received second-line therapy.

**Discussion**

To our knowledge, there have been only five large prospective studies on adjuvant chemotherapy for CCA [6-10]. Only two of these studies showed positive results in patients who underwent surgery with curative intent, and these results were only marginally positive. In the ESPAC-3 trial, adjuvant chemotherapy was associated with increased OS in multivariate analysis (HR, 0.75; 95% CI, 0.57–0.98; \( p = 0.03 \)) [7], and in the BILCAP study, the median OS was 53 months in the capecitabine group and 17.5 months in the observation group (HR, 0.75; 95% CI, 0.58–0.97; \( p = 0.028 \)) in per-protocol analysis [8]. In contrast, retrospective studies of AT for CCA showed more positive results [11-18]. However, the subgroups that showed survival benefits differed among studies and included AJCC stage II and III biliary tract cancer [11], R1 resection or lymph node involvement [12], perineural invasion [13], and intrahepatic and AJCC stage III cancer [16]. There are two explanations for the inconsistent results among these studies. First,
Fig. 4. Comparison of progression-free survival for patients with R0-resected cholangiocarcinoma. (A) Patients with lymphovascular invasion. (B) Patients with perineural invasion. (C) Patients with American Joint Committee on Cancer (AJCC) stage I disease. (D) Patients with AJCC stage II disease.

the CCA subtypes varied in each study. CCA is divided into three subtypes according to location, and each subtype has different characteristics, including risk factors and genetic aberrations [1].

Second, selection bias exists in retrospective studies. In the real world, patients considered to be at high risk of recurrence are likely to receive AT [13].

In this single-center analysis, AT did not demonstrate survival benefits. There are several possible explanations for this finding. First, all the patients included in this study underwent R0 resection. Previous studies on the effect of AT on R0-resected CCA are summarized in Table 6. Of these studies, four investigated R0 resection only [11,16-18], and the other two addressed it by subgroup analysis [9,20]. This shows that a survival benefit of AT in patients with R0-resected CCA has not been clearly demonstrated. Second, the CCA subtypes included in each study were different. For example, in previous studies in which AT showed positive results, the proportion of gallbladder cancer ranged from 13.6% to 48.3% [11-13,15]. However, patients with gallbladder cancer were not included in the present study. Third, differences in the AT regimen could be an important factor. Among several prospective studies, the only drug that showed an increase in OS was capecitabine [8]. However, none of the patients in the present study received capecitabine. Instead, patients who received tegafur/uracil, which is similar to capecitabine, showed the highest

https://doi.org/10.12701/jyms.2022.00213
OSR and PFSR among the regimens, although the difference was not statistically significant. Furthermore, patients in the AT group had a more advanced AJCC stage, which was a significant prognostic factor for OS and PFS in this study.

Another possible explanation for the failure to demonstrate survival benefits is the low AT completion rate. In this study, one-third of the patients who received AT did not complete their planned schedule. This result is similar to that reported in recent studies (26.0%–53.7%) [8,10,15]. The goal of adjuvant chemotherapy is the eradication of micrometastasis, and it is important to achieve complete remission to increase survival [22]. From this perspective, completion of the therapeutic schedule is important. In this study, the second most common cause of cessation was patient refusal (21.7%). Toxicity, including cytopenia and skin eruptions, was also an important cause. These factors can be corrected with meticulous intervention. One example of this is individualized chemotherapy. The standard method for determining the dose of chemotherapy is based on the body surface area calculated using the patient’s weight and height [23]. However, several studies have reported improved clinical outcomes and reduced toxicity with individualized chemotherapy based on pharmacokinetic monitoring of the colorectal cancer [24,25].

Fig. 5. Comparison of overall survival for patients with R0-resected cholangiocarcinoma according to regimens. (A) Comparison between gemcitabine group and surveillance group. (B) Comparison between gemcitabine/cisplatin group and surveillance group. (C) Comparison between tegafur/uracil group and surveillance group. (D) Comparison of overall survival among regimens.
In this study, PFSR tended to be lower in the AT group, although the difference was not statistically significant. This could be explained by two factors. First, the time interval of follow-up CT was shorter in the AT group, which might have allowed for the early detection of disease progression. Second, as noted previously, patients considered to be at high risk of recurrence are likely to receive AT [13]. To overcome this bias, a Cox proportional hazards model was used. In the multivariate analysis, AJCC stage III was a significant factor associated with OS. ASA classification II, AJCC stage II, and AJCC stage III were independent prognostic factors associated with PFS. Advanced AJCC stage was also identified as significant prognostic factor in previous studies [17,19]. In contrast, perineural and lymphovascular invasion were not statistically significant factors in this study. However, it should be taken into consideration that lymphovascular invasion and perineural invasion were unknown in 12.8% and 21.2% of the patients, respectively.

Interestingly, ASA classification was a favorable prognostic factor for PFS in this study. Chauhan et al. [26] reported that a high preoperative Charlson comorbidity index was an independent
A risk factor associated with significantly worse PFS (HR, 7.36; 95% CI, 2.68–12.12; p < 0.001) in patients with R0-resected perihepatic CCA. However, the patients included in the present study were either ASA classification I (normal healthy patients) or ASA classification II (patients with mild systemic disease, such as current smokers or those with obesity, well-controlled diabetes, hypertension, or mild lung disease) [27]. Therefore, additional research on the relationship between mild systemic diseases and PFS is required.

This study has several limitations. First, this was a retrospective study; thus, quality of life and adverse events were not investigated. The characteristics of both the AT and surveillance groups, including sex, age, and disease stage, were different owing to selection bias. Furthermore, the Eastern Cooperative Oncology Group per-
Table 4. Prognostic factors associated with progression-free survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.78 (0.49–1.24)</td>
<td>0.296</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 70</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>&gt; 70</td>
<td>0.95 (0.60–1.51)</td>
<td>0.830</td>
</tr>
<tr>
<td>CA 19-9 (U/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 37</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>≥ 37</td>
<td>1.09 (0.69–1.73)</td>
<td>0.702</td>
</tr>
<tr>
<td>CEA (ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 5.2</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>≥ 5.2</td>
<td>1.99 (0.86–4.60)</td>
<td>0.110</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrahepatic</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Perihilar</td>
<td>0.85 (0.44–1.67)</td>
<td>0.638</td>
</tr>
<tr>
<td>Distal</td>
<td>0.91 (0.50–1.66)</td>
<td>0.768</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative or unknown</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.28 (0.80–2.07)</td>
<td>0.303</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative or unknown</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1.58 (0.98–2.56)</td>
<td>0.061</td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well and moderately differentiated</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>1.92 (1.17–3.16)</td>
<td>0.010</td>
</tr>
<tr>
<td>0.010</td>
<td>1.64 (0.98–2.75)</td>
<td>0.060</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0.60 (0.38–0.97)</td>
<td>0.036</td>
</tr>
<tr>
<td>AJCC stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2.88 (1.15–7.20)</td>
<td>0.024</td>
</tr>
<tr>
<td>III</td>
<td>8.38 (3.00–23.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.57 (0.89–2.78)</td>
<td>0.117</td>
</tr>
</tbody>
</table>

Cox regression analysis was used.

HR, hazard ratio; CI, confidence interval; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ASA, American Society of Anesthesiologists; AJCC, American Joint Committee on Cancer.

Table 5. Clinical course of the adjuvant therapy group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 109)</th>
<th>Gemcitabine based (n = 50)</th>
<th>Others(^a) (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation</td>
<td>37 (33.9)</td>
<td>12 (24.0)</td>
<td>25 (42.4)</td>
</tr>
<tr>
<td>Cause for cessation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>14 (37.8)</td>
<td>2 (16.7)</td>
<td>12 (48.0)</td>
</tr>
<tr>
<td>Refusal</td>
<td>9 (24.3)</td>
<td>5 (41.7)</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3 (8.1)</td>
<td>3 (25.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Follow-up loss</td>
<td>2 (5.4)</td>
<td>0 (0)</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Skin eruption</td>
<td>2 (5.4)</td>
<td>1 (8.3)</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Others(^b)</td>
<td>7 (18.9)</td>
<td>1 (8.3)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Second-line therapy</td>
<td>36 (33.0)</td>
<td>24 (48.0)</td>
<td>12 (20.3)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

\(^a\)Others included 41 tegafur/uracil, 12 fluorouracil/radiotherapy, and six fluorouracil/cisplatin.

\(^b\)Others included three severe infection, one hepatic failure, one pancytopenia, one cerebrovascular accident, and one pancreatic cancer.

Performance status was not evaluated in most patients; therefore, ASA classification was used in this study instead. Second, it is difficult to generalize the results of this study because it was a single-center study. Third, capcitabine was not administered to the patients in this study. This is because capcitabine was approved by Korean Health Insurance in 2019. Fourth, patients with gallbladder cancer were excluded from the study. Finally, treatment and follow-up were performed at the discretion of the clinician. However, this study is meaningful because we analyzed adherence and the effect of AT in a real-world scenario with a large number of patients.

In conclusion, AT did not improve OS or PFS in patients with CCA who underwent R0 resection. AJCC stage III was a signifi-
Table 6. Studies about AT for R0-resected cholangiocarcinoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Location</th>
<th>Regimen</th>
<th>No. of patients</th>
<th>Median (mo)</th>
<th>5-Yr OSR (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebata et al. [9]</td>
<td>Prospective</td>
<td>BD</td>
<td>AT</td>
<td>106</td>
<td>NA</td>
<td>60</td>
<td>0.965</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al. [11]</td>
<td>Retrospective</td>
<td>GB, BD</td>
<td>AT</td>
<td>94</td>
<td>NA</td>
<td>60</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamanaka et al. [16]</td>
<td>Retrospective</td>
<td>GB, BD, AoV</td>
<td>AT</td>
<td>186</td>
<td>NA</td>
<td>68.0(^{\text{a}})</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al. [17]</td>
<td>Retrospective</td>
<td>BD(^{c})</td>
<td>AT, CRT, RT</td>
<td>56</td>
<td>72.9</td>
<td>NA</td>
<td>0.172</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al. [18]</td>
<td>Retrospective</td>
<td>BD(^{d})</td>
<td>AT, CRT, RT</td>
<td>73</td>
<td>24.7</td>
<td>NA</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yin et al. [20]</td>
<td>Retrospective</td>
<td>GB, BD, AoV</td>
<td>AT</td>
<td>40</td>
<td>33.7</td>
<td>37.9(^{\text{b}})</td>
<td>0.114</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This study</td>
<td>Retrospective</td>
<td>BD</td>
<td>AT, CRT, RT</td>
<td>111</td>
<td>21.1</td>
<td>21.1(^{\text{d}})</td>
<td>0.878</td>
</tr>
</tbody>
</table>

OSR, overall survival rate; BD, bile duct; AT, adjuvant therapy; N/A, not applicable; GB, gallbladder; AoV, ampulla of Vater; CRT, chemoradiotherapy; RT, radiotherapy.

\(^{a}\)This is an approximate number obtained from the graph. \(^{b}\)This is a 3-year OSR. \(^{c}\)This includes distal cholangiocarcinoma. \(^{d}\)This includes intrahepatic and perihilar cholangiocarcinoma.

cant prognostic factor for OS. The prognostic factors associated with PFS were ASA classification II, AJCC stage II, and AJCC stage III. After adjusting for confounding variables using the Cox proportional hazards model, AT did not show any survival benefit. However, we found that AT was not completed in one-third of patients. Therefore, additional efforts are required to increase adherence to AT.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization: all authors; Data curation: JL; Formal analysis: all authors; Methodology, Supervision: HGK, JH; Investigation: HTJ, JL, HHJ; Writing-original draft: HTJ; Writing-review & editing: HTJ, HHJ, HGK, JH.

ORCID
Han Taek Jeong, https://orcid.org/0000-0001-9246-3819
Joonkee Lee, https://orcid.org/0000-0002-8961-8063

Hyeong Ho Jo, https://orcid.org/0000-0002-4950-5435
Ho Gak Kim, https://orcid.org/0000-0003-3365-1662
Jimin Han, https://orcid.org/0000-0001-8674-370X

References

Auricular acupuncture for sleep quality in participants with mental and behavioral disorders due to prior multiple drug use: a retrospective consecutive case series

Yuri Gimelfarb, Eran Goldstien

AMHC administration, affiliated with the Sackler Faculty of Medicine of Tel Aviv University, Bat Yam, Israel

Background: Poor sleep quality is associated with psychoactive substance abuse/addiction/withdrawal. Auricular acupuncture (AA) is a nonpharmacological method used for the treatment of sleep disturbances. This study aimed to examine the quality of sleep before and after AA in participants with mental and behavioral disorders due to prior multiple drug use in the therapeutic community.

Methods: This was a consecutive case series of 27 participants (25 male [92.6%]). The median age was 35.0 years (interquartile range [IQR], 29.0–37.2 years), methadone/buprenorphine were not used, and the participants were treated with AA (median number of treatments, 15.0 [IQR, 12.0–18.0]) during a median period of 51.0 days (IQR, 49.0–51.0 days) according to the National Acupuncture Detoxification Association (NADA)-Acudetox protocol. Sleep quality was determined using the Pittsburgh Sleep Quality Index (PSQI), a self-rated questionnaire that assesses sleep quality and disturbances over a 1-month interval.

Results: The global PSQI score dropped (indicating better sleep quality) by a median of 3.0 points (IQR, 0.0–8.0 points) after treatment. In the multivariate logistic regression analysis, with an increase in global PSQI score during AA by 1 point, there was a 0.73-fold reduction in the risk of poor sleep quality post-AA (adjusted odds ratio, 0.73; 95% confidence interval, 0.52–1.01; \( p < 0.055 \); Nagelkerke’s \( R^2 = 0.66 \)).

Conclusion: The results revealed a positive effect of AA (by the NADA-Acudetox protocol) on sleep quality (as measured by PSQI) among participants in a treatment center with mental and behavioral disorders due to multiple drug use.

Keywords: Ear acupuncture; Logistic models; Sleep quality; Therapeutic community

Introduction

Sleep is an active phenomenon, cyclical from a biological point of view and essential for the survival of the human race. Sleep disorders are commonly found among substance abusers, including alcohol [1], stimulants (amphetamines, cocaine, and caffeine), and opiates. Sleep disorders are common during both active substance use and detoxification [2]. In addition, there are no differences in sleep quality among mildly, moderately, and severely dependent drinkers [1].
Both sleep disturbance and substance use disorders have been associated with negative outcomes, including decreased health-related quality of life [3], motor vehicle accidents [4], and suicide [6].

Therefore, promoting clinical care for patients with sleep disturbances and substance use disorders has the hypothetical effect of having a cascading positive impact on recovery from substance use disorders [6,7].

Nonpharmacological therapies to improve sleep in substance use disorders are attractive because they avoid adverse effects and the need for long-term pharmacological therapies. One nonpharmacological intervention for patients with substance use disorders is auricular acupuncture (AA). AA is an important component of traditional Chinese medicine. It has been accepted in China for thousands of years and is now used as an alternative and complementary medical therapy in Western countries. AA is one method by which specific points on the auricle are stimulated to treat various conditions [6,8,9].

Chen et al. [10] published a systematic review of six randomized controlled trials (RCTs) and papers written in Chinese or English. They concluded that AA intervention for insomnia produces better index rates of improvement and recovery than alternative interventions. AA also produces better rates of insomnia improvement and recovery than diazepam. Compared to control interventions, AA treatment is favored by increasing nocturnal sleep up to 6 hours, with subjects feeling sufficiently refreshed upon waking [10].

Lee et al. [11] published a systematic review of 10 RCTs performed in China, Korea, and the USA. The results suggested beneficial effects of AA on sleep efficiency compared with placebo [11]. Therefore, AA is often recommended as a treatment option for a wide spectrum of chronic conditions, such as sleep disturbances.

Very few studies have investigated sleep quality due to AA among patients with psychoactive substance use (Table 1). This imbalance was addressed in this study.

The objective of this study was to examine the quality of sleep before and after AA in participants with mental and behavioral disorders due to multiple drug use. The research hypothesis is that treatment with AA is associated with an improvement in the quality of sleep in this population.

### Methods

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of AMHC (IRB No: 43Z), without requirement for informed consent because of the retrospective analysis of prospectively collected data.

#### 1. Patients

To participate in the current study, male or female patients had to meet the following inclusion criteria: (1) age 18 years and older; (2) experienced mental and behavioral disorders due to psychoac-

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study and duration</th>
<th>Participant</th>
<th>Intervention</th>
<th>Control</th>
<th>PSQI outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang et al. [33]</td>
<td>2010</td>
<td>Single-blinded, RCT, 4 weeks</td>
<td>People with insomnia</td>
<td>AA (n = 63)</td>
<td>AA on sham points (n = 62)</td>
<td>As compared to control population, AA improved the quantity and quality of sleep</td>
</tr>
<tr>
<td>Jiao et al. [34]</td>
<td>2015</td>
<td>A three-factor (3 needling protocols) and three-level experimental scheme, based on orthogonal method</td>
<td>Patients of insomnia differentiated as internal harassment of phlegm-heat syndrome (n = 64)</td>
<td>AA</td>
<td>Body acupuncture and abdominal acupuncture</td>
<td>AA, after body acupuncture, is the second best choice for insomnia</td>
</tr>
<tr>
<td>King et al. [35]</td>
<td>2015</td>
<td>A feasibility 3-week study</td>
<td>Veterans with post-traumatic stress disorder and sleep disturbance</td>
<td>Multimodal treatment +9 AA treatments (n = 12)</td>
<td>Multimodal treatment without AA (n = 8)</td>
<td>Differences between groups were found on sleep quality (p&lt;0.003) and daytime dysfunction (p&lt;0.004) components</td>
</tr>
<tr>
<td>Current study</td>
<td>2022</td>
<td>Consecutive case series study, median period of 7.3 weeks</td>
<td>Patients with mental and behavioral disorders due to multiple drug use in therapeutic community</td>
<td>AA according to NADA-Acudetox protocol (n = 27)</td>
<td>No</td>
<td>PSQI global score declined by median of 3.0 points (p&lt;0.0001)</td>
</tr>
</tbody>
</table>

AA, auricular acupuncture; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized controlled trial; NADA, National Acupuncture Detoxification Association.
tive substance use (codes F10–F19) according to the International Classification of Diseases and Related Health Problems, 10th edition; (3) were in the therapeutic community Ramot Yehuda-Zoharim, Israel; (4) received AA as an integrated part of the comprehensive treatment in the community; and (5) were not treated with buprenorphine or methadone at that time. The exclusion criteria were severe metabolic or systemic disease and female participants who were pregnant or lactating.

We analyzed prospectively collected data [12,13] in a consecutive case series (level IV evidence).

2. Setting
This study was conducted in the therapeutic community Ramot Yehuda-Zoharim, Israel, which was established to treat and rehabilitate users and addicts in all areas of life, based on a broad range of different theories, treatment strategies, and methods, as well as various approaches to rehabilitation.

Each participant was interviewed by the center’s admission committee. Each potential participant was interviewed by a doctor, social worker, and the director of admissions. The admissions committee consisted of the staff of the therapeutic community. The admissions interviews consisted of three parts. In the medical section, the medical files of the patients, illnesses, and medications were reviewed by the physician. In the social part, a psychosocial interview was conducted by the social worker to gauge the level of personal psychosocial ability of each candidate, and the mental and social support factors that generally exist in his/her life. In the final administrative part, the laws that govern life in the community were explained.

The participants underwent extensive medical examinations and tests. Tests were performed to detect acquired immunodeficiency syndrome and tuberculosis, and a dental examination was performed to treat acute conditions as soon as possible.

The center’s principles are based on obtaining a maximum level of independence, as well as progress in changing behaviors and previous drug-based lifestyles. The center is a laboratory of preparation for return to life that is normative in the drug-free sense. The staff has a varied background from many professions and includes previous drug users. To prevent drug use, the use of drug substitutes or any other pharmacological substances is prohibited.

3. Outcome measure
The Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire that examines sleep quality retrospectively over a period of 1 month. Nineteen items are included in seven “component” scores: C1, subjective sleep quality; C2, sleep latency; C3, sleep duration; C4, habitual sleep efficiency; C5, sleep disturbances; C6, use of sleeping medication; and C7, daytime dysfunction. The questionnaire is easy to manage and can be completed within 5 minutes [14].

Each component score is weighted equally on a scale from 0 (no difficulty) to 3 (severe difficulty), with higher scores representing poorer sleep quality. The seven component scores are then summed to yield a global PSQI score, which has a range of 0 to 21; higher scores indicate worse sleep quality [14]. In previous studies, the internal consistency coefficient (as measured by Cronbach alpha) ranged from 0.72 [15-17] to 0.85 [14,16,18,19], indicating a high degree of internal consistency. Cronbach alpha was used to assess the consistency of results across items in the current test.

The internal consistency of the PSQI has not yet been investigated in populations with substance use. Nonetheless, for the Hebrew version of the PSQI, internal consistency was supported with Cronbach alpha scores from 0.52 to 0.70 in one study [17] and 0.63 in another [20].

Poor sleep quality was defined as a global score of > 5 on the PSQI [21-23], which has been determined to yield a diagnostic sensitivity of 89.6% [14] to 98.7% [19] and a specificity of 84.4% [19] to 86.5% [14] in identifying poor sleep quality vs. good sleep quality (PSQI of < 5).

4. Interventions
Participants were treated by acupuncturists (E.G.) according to the National Acupuncture Detoxification Association (NADA)-Acu-detox protocol [6-8,24]. The protocol included the insertion of acupuncture needles into two auricles (after wiping them with alcohol). The needles were inserted at five points (sympathetic, kidney, Shen Men, liver, and lung), four to five times per week. They were left in place for 20 to 40 minutes during each treatment session. The sessions were conducted in a quiet place. Needle stimulation was performed by inserting sterilized ear acupuncture needles (type DB2, stainless steel, 15 × 0.18 mm; Dong Bang Acupuncture, Inc., Boryeong, Korea) to a depth of 1 to 3 mm at the appropriate points [9]. AA was the only treatment performed during the study period.

5. Measurement
The Hebrew version of the PSQI [17,20-22,25] was administered before the beginning of the AA process and within 72 hours after finishing the treatment process. A clinically significant effect was defined as a decrease of at least 1.93 for a beneficial effect and an increase of 2.9 or more for a negative effect [26].

6. Statistical analysis
Data were analyzed using IBM SPSS ver. 20.0 for Windows (IBM
Categorical variables are presented as frequency tables and continuous variables as medians with interquartile ranges (IQRs). Nonparametric analysis was conducted.

Internal consistency analysis of the seven-component PSQI score items was conducted using Cronbach alpha [27]. The pre-post comparison of the total PSQI and all components was performed using the Wilcoxon signed-rank test.

Univariate and multivariate (while controlling for confounding variables) logistic regression analysis was performed (with odds ratios [ORs] and 95% confidence intervals [CIs]) to establish predictors of post-AA poor sleep quality (PSQI of > 5) vs. good sleep quality (PSQI of < 5). Variables that were significant at the \( p < 0.10 \) level in the univariate logistic regression analysis were included in the multivariate logistic regression model with post-AA sleep quality as the dependent dichotomous variable (PSQI of > 5, and others) to enable evaluation of predictive performance after controlling for other variables [28, 29].

The predictive performance of these parameters was also examined using receiver operating characteristic (ROC) curves. Differences between ROC curves were identified using nonparametric comparisons of the area under the curve (AUC) [30-32]. A \( p \)-value of < 0.05 was considered to be statistically significant.

## Results

### 1. Participants

The sample was comprised of 27 participants. Of these participants, 25 (92.6%) were male and 14 (51.8%) were single. At the beginning of the study, the median age of the participants was 35.0 years (IQR, 29.0–37.2 years). The median length of stay (LOS) in the therapeutic community was 78.5 days (IQR, 22.0–142.0 days).

### 2. Descriptive data

1) Characteristics of substance use

All participants had mental and behavioral disorders due to multiple drug use. All reported drug use, while only eight participants (30.8%) reported alcohol use. The median age when they began drug use was 16.0 years (IQR, 14.0–19.0 years). The median number of previous withdrawal attempts was 2 (IQR, 1.0–4.8). In the past, participants had received treatment in one to three other residential facilities and were free from psychoactive substance use during a median period of 12 months (IQR, 1.0–30.0 months).

2) Auricular acupuncture treatment

Participants received a median of 15 treatment sessions (IQR, 12.0–18.0 sessions) in the current study. The median period of time for treatments was 51.0 days (IQR, 49.0–51.0 days). After the AA treatments, 16 participants (59.3%) reported a positive change in how they felt, and 11 participants (40.7%) reported that they felt no change.

### 3. Outcome data

1) Global Pittsburgh Sleep Quality Index at the beginning of follow-up

Cronbach alpha for the global PSQI at the beginning of the follow-up period was 0.53. The median global PSQI score was 9.0 (IQR, 7.0–13.0).

2) Global Pittsburgh Sleep Quality Index at the end of follow-up

Cronbach alpha for the global PSQI at the end of the follow-up period was 0.71. The median global PSQI score was 6.0 points (IQR, 2.0–7.0 points). At the end of the follow-up period, 14 participants (51.9%) reported poor post-AA sleep quality (PSQI of > 5).

3) Comparison between Pittsburgh Sleep Quality Index components and global scores pre- and post-auricular acupuncture

Comparisons between PSQI components and global scores during AA treatment are presented in Table 2 and Fig. 1. From the data presented in Table 2 and Fig. 1, it can be seen that there were statistically significant reductions in subjective sleep quality (\( p < 0.002 \)), sleep latency (\( p < 0.011 \)), habitual sleep efficiency (\( p < 0.023 \)), sleep disturbances (\( p < 0.007 \)), and daytime dysfunction (\( p < 0.015 \)) components, as well as in global score (\( p < 0.0001 \)). The global score dropped (indicating better sleep quality) by a median of 3.0 points (IQR, 0.0–8.0 points) post-AA treatment.

### 4. Other analyses

1) Univariate analysis of post-auricular acupuncture poor sleep-quality prediction

The results of the univariate logistic regression analysis are shown in Table 3. As shown in Table 3, younger age at first use (\( p < 0.05 \)), fewer withdrawal attempts (\( p < 0.03 \)), and little change in global PSQI score (\( p < 0.02 \)) were found to be significant predictors of poor post-AA sleep quality. The number of AA treatments was not found to be a predictor of poor sleep quality (OR, 0.85; 95% CI, 0.68–1.06; \( p < 0.15 \)).
2) Multivariate analysis of post-auricular acupuncture poor sleep-quality prediction
The results of the multivariate logistic regression model are presented in Table 4. Only variables that significantly predicted poor sleep quality in the univariate models were chosen for multivariate analysis. With an increase in the global PSQI score during AA by 1 point, there was a 0.73-fold reduction in the risk of poor sleep quality post-AA (OR, 0.73; 95% CI, 0.52–1.01; p < 0.055).

3) Feasibility of multivariate model for post-auricular acupuncture poor sleep-quality prediction
Statistical analysis of the multivariate logistic regression model (Table 4) revealed a statistically significant change from the basic

---

Table 2. Comparison between Pittsburgh Sleep Quality Index components and global scores by Wilcoxon signed-rank test (n=27)

<table>
<thead>
<tr>
<th>Component</th>
<th>Pre-AA Median (IQR)</th>
<th>Post-AA Median (IQR)</th>
<th>Z</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-Subjective sleep quality</td>
<td>1.0 (1.0–2.0)</td>
<td>1.0 (0.0–1.0)</td>
<td>−3.1</td>
<td>0.002</td>
</tr>
<tr>
<td>C2-Sleep latency</td>
<td>2.0 (1.0–3.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>−2.5</td>
<td>0.011</td>
</tr>
<tr>
<td>C3-Sleep duration</td>
<td>1.0 (1.0–2.0)</td>
<td>1.0 (0.0–1.0)</td>
<td>−1.7</td>
<td>0.090</td>
</tr>
<tr>
<td>C4-Habitual sleep efficiency</td>
<td>0.0 (0.0–2.0)</td>
<td>0.0 (0.0–0.25)</td>
<td>−2.3</td>
<td>0.023</td>
</tr>
<tr>
<td>C5-Sleep disturbances</td>
<td>1.0 (1.0–2.0)</td>
<td>1.0 (1.0–2.0)</td>
<td>−2.7</td>
<td>0.007</td>
</tr>
<tr>
<td>C6-Use of sleeping medication</td>
<td>0.0 (0.0–0.0)</td>
<td>0.0 (0.0–0.0)</td>
<td>−2.7</td>
<td>0.785</td>
</tr>
<tr>
<td>C7-Daytime dysfunction</td>
<td>2.0 (1.0–3.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>−2.4</td>
<td>0.015</td>
</tr>
<tr>
<td>Global score</td>
<td>9.0 (7.0–13.0)</td>
<td>6.0 (2.0–7.0)</td>
<td>−3.5</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Table 3. Summary of univariate logistic regression analysis revealing the possible factors predicting post-AA poor sleep quality (n=27)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>0.92 (0.81–1.03)</td>
<td>0.15</td>
</tr>
<tr>
<td>Sex, males vs. females</td>
<td>1.08 (0.06–19.3)</td>
<td>0.96</td>
</tr>
<tr>
<td>LOS in Zoharim pre-AA (day)</td>
<td>1.01 (0.99–1.02)</td>
<td>0.17</td>
</tr>
<tr>
<td>Previous treatments in therapeutic communities</td>
<td>1.34 (0.40–4.56)</td>
<td>0.63</td>
</tr>
<tr>
<td>Previous treatments in Zoharim</td>
<td>2.20 (0.33–14.73)</td>
<td>0.42</td>
</tr>
<tr>
<td>Substance use, drugs with alcohol vs. drugs</td>
<td>1.67 (0.30–9.16)</td>
<td>0.56</td>
</tr>
<tr>
<td>Age at first substance use (yr)</td>
<td>0.76 (0.58–1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Withdrawal attempts</td>
<td>0.61 (0.39–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Duration of being free from psychoactive substances</td>
<td>0.99 (0.96–1.02)</td>
<td>0.35</td>
</tr>
<tr>
<td>Global PSQI score pre-AA (point)</td>
<td>1.04 (0.87–1.25)</td>
<td>0.67</td>
</tr>
<tr>
<td>AA treatment sessions</td>
<td>0.85 (0.68–1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Length of AA treatments (day)</td>
<td>0.98 (0.92–1.05)</td>
<td>0.56</td>
</tr>
<tr>
<td>Global PSQI score change (point)</td>
<td>0.76 (0.60–0.96)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

AA, auricular acupuncture; OR, odds ratio; CI, confidence interval; LOS, length of stay; PSQI, Pittsburgh Sleep Quality Index.

Table 4. Summary of multivariate analysis revealing possible factors predicting post-auricular acupuncture poor sleep quality (n=27)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first use (yr)</td>
<td>0.76 (0.48–1.20)</td>
<td>0.240</td>
</tr>
<tr>
<td>Withdrawal attempts</td>
<td>0.59 (0.30–1.15)</td>
<td>0.120</td>
</tr>
<tr>
<td>Global PSQI score change (point)</td>
<td>0.73 (0.52–1.01)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; PSQI, Pittsburgh Sleep Quality Index.

For the multivariate logistic regression model, Nagelkerke $R^2 = 0.66$; sensitivity = 92.3%; specificity = 81.8%; likelihood-ratio test = 16.35; degree of freedom (df) = 3; p = 0.001; Hosmer–Lemeshow test, $X^2$ = 5.84; df = 8; p < 0.67; area under the receiver operating characteristic curve = 0.90 (95% CI, 0.77–1.00), p < 0.001.

---

Fig. 1. Box-and-whisker plots (n=27) for change in components and global Pittsburgh Sleep Quality Index (PSQI) scores during auricular acupuncture. C1, subjective sleep quality; C2, sleep latency; C3, sleep duration; C4, habitual sleep efficiency; C5, sleep disturbances; C6, use of sleeping medication; C7, daytime dysfunction; O, outliers.

---

https://doi.org/10.12701/jyms.2022.00542
model (likelihood-ratio test, 16.35; degree of freedom [df] = 3; $p < 0.001$). The explained variation in the model was high at approximately 66% (Nagelkerke $R^2 = 0.66$). The Hosmer-Lemeshow goodness of fit test was not significant ($\chi^2 = 5.84; df = 8; p < 0.67$). The sensitivity and specificity of predicting post-AA poor sleep quality were 92.3% and 81.8%, respectively. The AUC-ROC of the model was 0.90 (95% CI, 0.77–1.00; $p < 0.001$), which was considered high discrimination.

4) Adverse events
No adverse events were observed during the follow-up period.

**Discussion**

This study examined changes in sleep quality due to AA among participants with mental and behavioral disorders due to multiple drug use treated in a therapeutic community. The findings point to a beneficial effect of AA on sleep quality, as measured by global PSQI scores, and allowed us to accept the study hypothesis that AA treatment is associated with an improvement in the quality of sleep in psychoactive substance users. The global score pre- and post-AA treatment dropped by a median of 3.0 points, indicating that AA was clinically effective in improving sleep quality [26]. Our findings are consistent with those of previous studies, not only of pre-post cohort studies [24] but also of RCTs [6,33] and other types of studies with control subpopulations [34,35].

In the meta-analysis, the effectiveness of AA was expressed using recovery from insomnia and improvement proportions, and the efficiency of AA ($n = 338$) was better than that of the alternative treatments (oral estazolam [$n = 65$], oral diazepam [$n = 60$], barbiturates [$n = 60$], and sham AA [$n = 30$]) in the control population (relative risk, 1.93; 95% CI, 1.40–2.66). When the effectiveness of AA was expressed using sleep time for more than 6 hours, the effectiveness of AA ($n = 158$) was better than that of the alternative interventions (oral estazolam [$n = 65$], oral diazepam [$n = 30$]) in the control population (relative risk, 2.64; 95% CI, 1.22–7.22) [10]. Another meta-analysis indicated that acupuncture and acupuncture pressure may help improve sleep-quality scores when compared to placebo ($p < 0.006$) or no treatment ($p < 0.002$) [36].

A variety of possible biophysiological explanations have been proposed to understand the effect of AA on sleep quality. In traditional Chinese medicine, the insertion of needles into points on the body or ears releases *qi* (“life energy”) blockage. Each of the five ear points in the NADA-Acudetox protocol has a specific role. The Shen Men (“Spirit Gate”, in Chinese) point calms the emotions, and the sympathetic point balances activity in the parasympathetic and sympathetic nervous systems and relaxes muscle tension. The lung, liver, and kidney points balance the functions of these organs. NADA-Acudetox treatment also affects the balance between *yang* and *yin*, two opposing factors that regulate functioning in living organisms in nature. NADA-Acudetox “tonifies *yin*,” meaning that *yin* elements such as softness, humidity, and darkness become stronger. This occurs at the expense of *yang* elements such as hardness, dryness, and lightness. Moreover, “empty fire” syndrome is treated, indicating that the feeling of inner emptiness typical of psychoactive substance misusers is replaced, during a period of treatment sessions, with a psychophysiological feeling of solidity and fullness [8].

The western approach to acupuncture effects on the human body originates from studies (on humans and animals) focusing on the release of neurotransmitters and inhibition of pain, as well as the identification of activated areas in the human brain. AA treatment evidently affects the parasympathetic component of the autonomic nervous system and its influence on reflexes in the cerebral cortex, hypothalamus, brainstem, and spine [8].

Moreover, previous studies have demonstrated that acupuncture increases endogenous opioid and nocturnal melatonin levels. The opioidergic system is theorized to have a somnogenic effect and may interact with melatonin to normalize the circadian cycle and promote sleep. These findings provide a possible physiological basis for how acupuncture affects sleep [11,29,37,38].

An additional possible explanation for the positive effect of AA treatment on sleep quality is staying in the therapeutic community after the withdrawal process and, as a result, being free from the influence of multiple substances. Another rationale is the acquired personal skills of participants to adopt a new life without multiple substances in the therapeutic community.

Participants with minimal changes in global PSQI scores were more likely to suffer from poor sleep quality than those with substantial changes. Analysis of this finding was not the aim of the current study, and there is currently no way to establish a cause-and-effect relationship between these variables.

This study has several limitations. First, this was a consecutive case series study, as has been published in previous studies, but not in controlled trials [12,13]. Therefore, one cannot exclude that the improvement in sleep quality was due to indwelling in the therapeutic community and not specifically because of the AA treatment process. To overcome this possible uncertainty, the expected effect of time spent in the therapeutic community on sleep quality was examined. The LOS in the therapeutic community was not found to be a predictor of sleep quality. Thus, it can be concluded that staying in a therapeutic community is unlikely to improve sleep quality among subjects with mental and behavioral disorders.
due to multiple drug use.

Second, the effect of AA on sleep quality was not examined after an equal number of AA treatments. To overcome this bias, we examined the expected effect of the number of AA treatments on sleep quality. The number of AA treatments was not found to be a predictor of sleep quality. From this, it can be concluded that cumulative exposure to AA-treatment processes only likely does not improve sleep quality in this subpopulation.

Third, middle- and/or long-term outcomes may be more meaningful and helpful in providing patients with mental and behavioral disorders due to multiple drug use.

Fourth, logistic regression models, based on small study populations, may have limited power. However, each of the parameters mentioned above in the multivariate model, alone and together, indicated that the multivariate logistic regression model was accurate for post-AA poor sleep quality prediction.

Finally, the participants in our study had mental and behavioral disorders due to multiple drug use. Because of the retrospective design of the study, there was no way to determine the different types of substances used pre-AA and, therefore, to establish the influence of each substance on changes in sleep quality.

With minimal utilization of high-cost equipment, AA can be included in integrated care for sleep-quality improvement. In our study, the results revealed a positive effect of AA (by the NADA-Acudetox protocol) on sleep quality (as measured by PSQI) among participants, who are in a therapeutic community, with mental and behavioral disorders due to multiple drug use. Future prospective designs need to be more specific in methodology, such as implementation, protocol selection, extension, and time of AA stimulation in participants exposed to different substances. We expect that this study will raise attention to this low-cost, safe interventional method and produce scientific evidence to support its application in populations with mental and behavioral disorders due to multiple drug use.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization, Data curation: YG, EG; Formal analysis, Project administration, Supervision: EG; Methodology, Investigation, Software: YG; Writing-original draft: YG; Writing-review & editing: YG, EG.

ORCID
Yuri Gimelfarb, https://orcid.org/0000-0002-5059-7648
Eran Goldstien, https://orcid.org/0000-0002-9499-7205

References
12. Wu Y, Zou C, Liu X, Wu X, Lin Q. Auricular acupressure helps improve sleep quality for severe insomnia in maintenance he-
Introduction

Scrotal swelling is common among neonates and infants; however, its etiology varies. Most of these diseases, such as hydroceles, do not require prompt treatment [1]. One rare cause of scrotal swelling is scrotal pyocele, which is also very rare in neonates and infants. Scrotal pyocele should be treated immediately, and when treatments fail, orchiectomy may be required [2].

There are various etiologies of scrotal pyocele in infants. In patients with peritonitis due to gastrointestinal perforation, the spread of infection or inflammatory material from the intraperitoneal cavity through a patent processus vaginalis could be causative [3]. Herein, we report three cases of scrotal pyocele related to peritonitis due to gastrointestinal perforation in neonates and present a brief literature review.

Cases

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Pusan National University Yangsan Hospital (IRB No: 05-5021-198), and the requirement for informed consent from the patients was waived by the IRB.

The patients’ characteristics are summarized in Table 1.
1. Case 1
A 5-day-old male neonate was transferred to our neonatal intensive care unit due to necrotizing enterocolitis. He was born at 38 weeks and 5 days of gestation via normal vaginal delivery, weighing 3,360 g. Before the transfer, his oral intake was poor, he was vomiting bile-colored contents, and his abdomen was distended. An emergent exploratory laparotomy was performed after an infantogram revealed pneumoperitoneum. A gastric perforation from the fundus to the mid-body along the lesser curvature was observed, and primary closure was performed. Right scrotal swelling and fever (up to 37.4°C) were noted 4 days after the surgery. Serum C-reactive protein (CRP) level was high at 5.08 mg/dL (range, < 0.5 mg/dL); other laboratory findings were within normal limits. Ultrasonography revealed complex fluid collection in the right scrotum, accompanied by multiple amorphous calcifications (Fig. 1). Vascular flow between the right testis and spermatic cord was preserved. With an inguinal incision, high ligation of the patent processus vaginalis, and irrigation and drainage of the abscess were performed. Intravenous cefotaxime was injected. Because the swelling and redness of the scrotum persisted, we recognized a remnant abscess. Thus, 2 weeks later, we performed an additional scrotal incision and drainage due to the remnant abscess. After the second operation, intravenous cefotaxime was administered for 2 more weeks. Three weeks after the second incision and drainage, the patient was discharged without any other problems. Follow-up ultrasound examination after 6 months revealed no abnormal findings in the testes and scrotum.

2. Case 2
A male neonate, born at 37 weeks and 1 day of gestation via normal vaginal delivery, weighing 3,290 g, was referred due to abdominal distension and scrotal swelling (Fig. 2). On prenatal ultrasonography, fetal ascites was found, and fetal bowel perforation was suspected. The next day, an exploratory laparotomy was performed. Operative findings revealed ileal atresia and generalized peritonitis due to small bowel perforation. Small bowel segmental resection and anastomosis were performed. After the surgery, feeding intolerance did not improve and the scrotum, which collapsed immediately after surgery, gradually swelled the next day, leading to redness and a heating sensation. Vital signs, whole blood cell counts, and serum CRP levels were within normal limits. An upper gastrointestinal series and colon studies showed delayed contrast passage in the small bowel. Because passage disturbance at the

---

**Table 1. Summary of patients**

<table>
<thead>
<tr>
<th>Case</th>
<th>Gestational age (wk)</th>
<th>Sex</th>
<th>Birth weight (g)</th>
<th>Age at diagnosis (day)</th>
<th>Leukocyte (10^9/L)</th>
<th>CRP (mg/dL)</th>
<th>Cultured organism</th>
<th>Antibiotics</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>38.5</td>
<td>Male</td>
<td>3,360</td>
<td>9</td>
<td>5.37 (N)</td>
<td>5.08 (E)</td>
<td>-</td>
<td>Cefotaxime</td>
<td>Surgical drainage</td>
</tr>
<tr>
<td>Case 2</td>
<td>37+1</td>
<td>Male</td>
<td>3,290</td>
<td>15</td>
<td>11.08 (N)</td>
<td>0.37 (N)</td>
<td>MRSE, Enterococcus faecium</td>
<td>Vancomycin</td>
<td>Surgical drainage</td>
</tr>
<tr>
<td>Case 3</td>
<td>27+5</td>
<td>Male</td>
<td>1,151</td>
<td>28</td>
<td>14.01 (N)</td>
<td>4.11 (E)</td>
<td>Escherichia coli (ESBL+)</td>
<td>Meropenem</td>
<td>Aspiration</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; MRSE, methicillin-resistant *Staphylococcus epidermidis*; N, within normal range; E, elevated; ESBL+, extended-spectrum beta-lactamase positive.

---

**Fig. 1.** Doppler ultrasonography reveals high attenuation fluid collection at the right scrotum accompanied by multiple clustered and curvilinear calcifications.

**Fig. 2.** Severe scrotal swelling due to scrotal hydrocele found at birth.
anastomosis site or intestinal motility disorder was considered based on the contrast studies, loop ileostomy was planned. Ultrasoundography revealed a complex right scrotal hydrocele with a patent processus vaginalis (Fig. 3). Scrotal exploration was performed with loop ileostomy. The patent processus vaginalis was closed on the peritoneal side. The complex fluid was removed using a scrotal incision, and a drainage tube was inserted. Methicillin-resistant Staphylococcus epidermidis and Enterococcus faecium were cultured from a pyocele. Intravenous vancomycin was administered. Two days after the surgery, the drainage tube was removed, and the pyocele had healed. Six months later, the patient underwent ileostomy repair and was discharged. He is scheduled to undergo surgery for a buried penis when he is 2 years old.

3. Case 3
A 7-day-old boy presented with abdominal distension. He was born by cesarean section due to premature rupture of the membranes at 27 weeks and 5 days of gestation, weighing 1,151 g. After birth, respiratory distress syndrome and persistent pulmonary hypertension were diagnosed, and surfactant and nitrogen oxides were administered and tapered. After transfer, pneumoperitoneum was found on an infantogram; thus, an exploratory laparotomy was performed immediately. A perforation site in the stomach along the greater curvature from the gastroesophageal junction to the mid-body was found, and the perforation was repaired. Two weeks after the surgery, desaturation occurred. Serum CRP level was elevated to 4.11 mg/dL and Escherichia coli was cultured from the peripheral blood. Physical examination revealed left inguinal swelling. Ultrasonography revealed bilateral small patent processus vaginalis and a left inguinal abscess connected to the left patent processus vaginalis (Fig. 4). The abscess was aspirated (Fig. 5), and intravenous meropenem was administered. E. coli was also cultured from the abscesses. After 10 weeks, the patient was discharged without any complications, and an intact testis was confirmed on follow-up sonography.

**Discussion**

Pyocele is also known as an infected hydrocele and scrotal abscess [4,5]. To date, only approximately 30 cases have been reported in patients younger than 18 months of age, and few of these are neonatal cases [2,6].

Pyocele has various etiologies, including hematogenous spread, secondary infection from neighboring structures such as the testis or epididymitis, and spread through a patent processus vaginalis [3]. Cases associated with maternal sepsis or idiopathic cases have also been reported [6]. In particular, the proportion of preterm cases (e.g., case 3 in this report) with a patent processus vaginalis, which is connected to the peritoneal cavity, is relatively high. With neonates or infants, especially premature infants who have undergone surgery for peritonitis due to gastrointestinal perforation, the incidence might be relatively high due to the presence of the processus vaginalis. Careful observation of scrotal swelling is necessary.

Fig. 3. Doppler ultrasonography shows septated fluid collection (arrow) of multiple echogenic foci in the right scrotal sac.

Fig. 4. Doppler ultrasonography shows septated fluid collection of multiple echogenic foci in the left scrotal sac.

Fig. 5. Aspirated pus.
Because patent processus vaginalis is prevalent in males, most cases of infantile pyocele are male patients. However, in girls, hydroceles could also develop through a patent processus vaginalis, also called the canal of Nuck [7]. A female infant with a pyocele in the inguinal area through a patent processus vaginalis has also been reported [8].

The symptoms of pyocele are not significantly different from those of other disorders with scrotal swelling. Tense scrotal edema and overlying skin erythema are common symptoms [3]. In particular, this erythema was helpful in identifying pyocele rather than simple hydrocele in this study. The silk gloves sign, for a patent processus vaginalis, was difficult to interpret in all three cases in this study due to swelling of neighboring tissues.

Doppler ultrasonography was accurate in diagnosing pyocele in patients with scrotal swelling [6]. Doppler ultrasonography is useful in differentiating other diseases that produce acute scrotum, such as testicular torsion, epididymitis, and orchitis [9]. Ultrasonography revealed fine multiple septations, a fluid-fluid level with a dependent area of increased echogenicity, thickening of the scrotal layers, and layering debris [1,3]. When pyocele is suspected, it is recommended to perform Doppler ultrasonography quickly for differential diagnosis and immediate treatment.

Various organisms have been reported to cause pyoceles. The majority of reported cases of spreading through a patent processus vaginalis have revealed infection with *E. coli*, and other idiopathic cases have revealed the involvement of *Staphylococcus aureus*, *S. epidermidis*, enterococci, *Citrobacter freundii*, and *Staphylococcus hominis* [2,3]. Sometimes, the culture results would be negative due to the effects of immediate antibiotic administration [3,10].

Surgical exploration and drainage with intravenous antibiotic administration are the most commonly used treatment options. Scrotal incisions are more commonly used than inguinal incisions [3,5,6,8,11]. When surgeries are performed, the patent processus vaginalis should be repaired, if possible, to prevent ascending infection into the peritoneum and potential inguinal hernia [11]. However, the tissue of the patent processus vaginalis could be very fragile due to infection and inflammation; therefore, repair could be very difficult [3]. Some studies have shown favorable outcomes with percutaneous aspiration of abscesses and intravenous antibiotic administration. This method has the advantage of avoiding general anesthesia and is applicable to patients in poor general health [2,3]. Because various microorganisms, including antibiotic-resistant bacteria, should be considered causative organisms, the administration of broad-spectrum antibiotics should be performed first, followed by antibiotic adjustment according to culture results, regardless of whether surgical drainage or aspiration is performed.

Appropriate treatment options should be selected according to the severity of the disease or the condition of the patient.

There are no clear criteria or recommendations for which cases require surgical drainage or aspiration only. In cases 1 and 2, the abscesses were organized and seemed to be difficult to aspirate. The abscesses were larger in cases 1 and 2 than in case 3. In case 3, the abscess was also in a liquefied state and nearly complete aspiration was performed. Therefore, in our experience, for large and organized abscesses, surgical drainage is preferred; in contrast, for small and liquefied abscesses, aspiration should be attempted first.

There are few reports on the long-term condition of the testis after treatment; therefore, it is difficult to determine prognosis. In our experience, when properly treated, the testes are well preserved. However, there was a report of orchiectomy due to severe inflammation and the risk of overwhelming sepsis [5].

In summary, when scrotal swelling is encountered in infants or neonates, pyoceles should be included in the list of differential diagnoses. Careful attention is needed for infants, especially preterm infants who previously had peritonitis due to gastrointestinal perforation. If a pyocele is suspected, Doppler ultrasonography should be performed quickly and appropriate treatment initiated so that favorable results can be obtained without losing the testis.

**Notes**

**Conflicts of interest**

No potential conflict of interest relevant to this article was report-ed.

**Funding**

This work was supported by a clinical research grant from Pusan National University Yangsan Hospital in 2021.

**Author contributions**

Conceptualization: SHK, YHC; Data curation: NL, YMH, SYB; Formal analysis: SHK, HYK; Investigation: YHC; Funding acquisition: SHK; Writing-original draft: SHK; Writing-review & editing: YHC, HYK.

**ORCID**

Soo-Hong Kim, https://orcid.org/0000-0001-7085-5969
Yong-Hoon Cho, https://orcid.org/0000-0003-0170-9997
Hae-Young Kim, https://orcid.org/0000-0002-2316-5815
Narae Lee, https://orcid.org/0000-0002-8281-6550
Young Mi Han, https://orcid.org/0000-0002-6120-0490
Shin Yun Byun, https://orcid.org/0000-0002-9034-5533

https://doi.org/10.12701/yujm.2021.01508
References

Diagnosis and successful visual biofeedback therapy using fiberoptic endoscopic evaluation of swallowing in a young adult patient with psychogenic dysphagia: a case report

Youngmo Kim¹, Sang Hun Han¹, Yong Beom Shin¹,², Jin A Yoon¹,², Sang Hun Kim¹

¹Department of Rehabilitation Medicine, Biomedical Research Institute, Pusan National University Hospital, Busan, Korea ²Department of Rehabilitation Medicine, Pusan National University School of Medicine, Busan, Korea

Case report
Psychogenic dysphagia is a deglutition disorder characterized by a fear of swallowing, with no structural or functional causes. This report presents the case of a young male patient who had severe malnutrition due to psychogenic dysphagia and was provided visual biofeedback using fiberoptic endoscopic evaluation of swallowing (FEES). A healthy 25-year-old man presented to our clinic with a complaint of throat discomfort when swallowing that had started 6 months prior. As the symptoms worsened, he became fearful of food spreading to his lungs after swallowing and the development of respiratory difficulties. His food intake gradually decreased, resulting in a weight loss of 20 kg within 2 months. Evaluation of organic and other functional causes of dysphagia was performed, but no abnormalities were detected. The sensation of a lump in his throat, fear of swallowing, and anxiety were transformed into somatic symptoms. The patient was diagnosed with psychogenic dysphagia. After visual biofeedback by a physician who performed FEES, the patient resumed eating normally and increased his food intake. If routine tests do not reveal structural or functional causes of dysphagia, assessment of a psychogenic swallowing disorder should be considered. FEES can help in the diagnosis and management of psychogenic dysphagia.

Keywords: Deglutition disorders; Globus sensation; Laryngoscopy; Somatoform disorders

Introduction

Psychogenic dysphagia is a swallowing disorder with no structural or organic cause. The etiology of psychogenic dysphagia is not well understood. The most common symptoms of the disorder include fear of swallowing, feeling lumps or fullness in the throat, and complaints of difficulty breathing when swallowing. These symptoms may be accompanied by somatic symptoms such as depression, anxiety, restlessness, insomnia, and anorexia [1,2]. Weight loss, avoidance of eating, and malnutrition can also occur, lowering the quality of life. Psychogenic dysphagia has been described using several terms, including choking phobia [3,4], globus hystericus [5], hysterical dysphagia [6], and phagophobia [7].

Although the prevalence of psychogenic dysphagia has not been well studied, one study indicated that 20% of patients with globus hystericus had psychogenic dysphagia [8], while another videoflu-
oroscopic swallowing study (VFSS) showed that 22 out of 1,844 patients suffering from this condition [9]. Based on these cases, we can deduce that psychogenic dysphagia is often overlooked and is relatively common.

In this report, we present the details of a case of diagnosis and visual biofeedback intervention using fiberoptic endoscopic evaluation of swallowing (FEES) in a young male patient who suffered severe malnutrition and weight loss due to psychogenic dysphagia.

**Case**

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Pusan National University Hospital (IRB No: 2111-022-109). Written informed consent from the patient was waived by the IRB.

A 25-year-old man visited our clinic with complaints of dysphagia that had started 6 months earlier. At that time, the patient was suspected of having respiratory symptoms related to coronavirus disease. To treat these symptoms, he was administered a single pill of the antimalarial drug combination pyronaridine-artesunate. Following treatment, the patient felt discomfort on the left side of his throat when swallowing. As time passed, the discomfort spread to the right side of his throat and was accompanied by pain. The symptoms worsened, causing breathing difficulties and a sensation of food spreading to his lungs. This caused the patient to become terrified of food intake. He had never experienced these symptoms previously and did not consult a psychiatrist.

He visited the Department of Pulmonology and Cardiology for assessment of dyspnea and chest discomfort. Blood tests, chest computed tomography, pulmonary function tests, and electrocardiography were performed, but no abnormalities were detected. His body weight markedly decreased from 85 kg (body mass index [BMI], 25.6 kg/m$^2$) to 66 kg (BMI, 19.9 kg/m$^2$) in 2 months. He was referred to the Department of Rehabilitation Medicine and was admitted for evaluation of dysphagia and nutritional management.

Physical and cranial nerve examinations did not reveal any abnormalities related to dysphagia. Laboratory findings were normal other than the presence of urine ketone 3+, which is common in cases of starvation. Thyroid function tests and assessments for the levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were performed to detect thyroid diseases or tumors. The results of the tests were within normal ranges. The patient’s serum creatine kinase (CK) level was 114 U/L (range, 5–217 U/L), and his lysosomal acid α-glucosidase activity was normal. A nerve conduc-

Fig. 1. Esophagography shows no structural abnormality or dysmotility from (A) the upper and middle thoracic esophagus to (B) the lower thoracic esophagus and esophagogastric junction.
problems and that the patient's fear of swallowing and abnormal sensations were consistent with the pattern of psychogenic dysphagia, in which anxiety is transformed into somatic symptoms. He had previously taken numerous nutritional supplements owing to excessive health concerns. His family history revealed a younger sister with a diagnosis of schizophrenia. The patient was referred to the Department of Psychiatry where he was diagnosed with somatoform disorder. However, he did not want to undergo further psychiatric evaluations. After 1 week, a follow-up FEES was performed in a comfortable environment with a minimum number of observers. The test materials included an ionized beverage and porridge eaten at home instead of the hospital-provided diet of liquid and puree. No abnormalities related to symptoms were observed after the study. With guidance from a physician and with the help of images, the patient reconfirmed that tracheal aspiration in the airway did not occur. After the swallowing test, the patient was able to eat half of his meals and consume two cans of commercial enteral formulas twice a day (Harmonilan; Youngjin Pharm, Seoul, Korea). The patient gradually gained weight; after 3 months in the outpatient clinic, his body weight was 81 kg (BMI, 24.4 kg/m²).

**Discussion**

In this report, we described a case of psychogenic dysphagia in a healthy young man. It is important to differentiate psychogenic dysphagia from organic or other types of functional dysphagia. In psychogenic dysphagia, the fear of swallowing occurs due to experiencing or witnessing a choking event or feeling a lump or fullness in the throat when swallowing [1,3-5]. Therefore, obtaining a detailed and accurate medical history is important. The medical history should include when and under what circumstances dysphagia occurs and what symptoms are present. In this case, the patient complained of a lump and pain during swallowing and feared that food would spread to his lungs. The patient started experiencing dysphagia after taking a single antimalarial pill. Therefore, we considered the possibility of dysphagia and myopathy induced by the antimalarial drug. There have been reports of induced myopathy after taking antimalarial drugs (chloroquine and hydroxychloroquine) for at least 6 months [10,11]. However, there have been no reports of myopathy in people taking antimalarial drugs containing pyronaridine-artesunate.

We evaluated the patient for neuromuscular diseases that may cause swallowing disorders in healthy young men [12]. His serum CK levels were normal [13], and assessment of lysosomal acid a-glucosidase activity for possible late-onset Pompe disease showed normal values [14].

The results of the nerve conduction study excluded neuromuscular disease. The patient’s poor performance in the handgrip strength and 6-minute walk tests were believed to be due to transient general weakness caused by low food intake. As his nutritional intake increased, his physical performance gradually improved to 554 m in a follow-up 6-minute walk test. Brain lesions were excluded because there were no other neurological problems, apart from deterioration of physical function due to his poor general condition, and a cranial nerve examination was normal.

FEES and a VFSS were performed to determine the patient's swallowing ability. During the first swallowing test, unpleasant fa-
cial expressions were noted, and effortful swallowing was observed at the start of the oral phase. There were no abnormal findings, and VFSS images confirmed that the food was not aspirated. Floppy epiglottis was observed in the patient’s FEES. There was a reported case involving a patient with amyotrophic lateral sclerosis with floppy epiglottis [15]. Therefore, motor neuron disease was evaluated, but no related abnormalities were found. The patient attempted to eat after the swallowing test, but the feeling of aspiration persisted and he could not increase the amount of food he ate due to fear. Although he was initially diagnosed in the Department of Psychiatry, he refused further evaluation and intervention.

FEES is a treatment method that uses visual feedback and has several advantages. Anatomical structures are presented on a video screen, making it easy for patients to understand their swallowing physiology. Since there is no radiation exposure, patients can try swallowing training using visual feedback without time limitations. In addition, barium contrast agent is not required during the examination, allowing the patient to eat a usual meal with familiar tastes and flavors. Therefore, based on these advantages and the results of a previous study [16], visual biofeedback therapy using FEES was attempted. The follow-up FEES environment was made as comfortable as possible to minimize the psychological anxiety felt by the patient. The physician provided repeated explanations and reassurance, and the patient could see on the monitor that no aspiration was occurring during swallowing. The patient gradually overcame the fear of swallowing and began to eat. After observation at the outpatient clinic for more than 3 months, his food intake and body weight increased. A combination of psychological treatment and dysphagia therapy is the most effective treatment for psychogenic dysphagia [1]. The psychological treatment includes behavior therapy, insight-oriented therapy, and family therapy. The dysphagia therapy includes a swallowing exercise program and education on normal swallowing physiology. Reportedly, pharmacological treatment is also effective in treating psychogenic dysphagia [3]. However, if psychiatric evaluation and treatment are not possible for various reasons, visual biofeedback by the physician who performs FEES helps to improve the symptoms of psychogenic dysphagia. FEES visualizes the oropharyngeal phase of swallowing and reassures the patient. Therefore, FEES should be considered one of the best options for the diagnosis and management of psychogenic dysphagia. FEES has the advantage of providing visual biofeedback therapy and diagnosis simultaneously. Thus, it could be used as a treatment strategy for various swallowing disorders in the future.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

Funding

This work was supported by a clinical research grant from Pusan National University Hospital in 2021.

Author contributions

Conceptualization: YK, SHK, YBS, JAY; Data curation: SHK, SHH; Formal analysis: YK, SHK, SHH, YBS, JAY; Funding acquisition: SHK, YBS, JAY; Methodology, Project administration, Visualization, Investigation, Resources: YK, SHK; Supervision, Validation: SHK, YBS, JAY; Writing—original draft: YK; Writing—review & editing: YK, SHK, YBS, JAY.

ORCID

Youngmo Kim, https://orcid.org/0000-0002-2518-530X
Sang Hun Han, https://orcid.org/0000-0002-0558-1399
Yong Beom Shin, https://orcid.org/0000-0001-5026-1696
Jin A Yoon, https://orcid.org/0000-0001-5762-0559
Sang Hun Kim, https://orcid.org/0000-0003-4849-5228

References

The endoscopic transnasal approach to the lesions of the craniocervical junction: two case reports

Baraa Dabboucy¹, Wissem Lahiani², Damien Bresson², Nouman Aldahak²

¹Department of Neurosurgery, Faculty of Medicine, Lebanese University, Beirut, Lebanon
²Department of Neurosurgery, AP-HP, Henri Mondor Hospital, Créteil, France

Introduction

Surgical planning to manage a craniovertebral junction (CVJ) deformity is difficult, mainly because of a variety of anatomical reasons, including bony, ligamentous, and adjacent neurovascular structures that render access to this region relatively challenging [1]. Anterior access to the CVJ has traditionally been performed using the transoral approach for many pathologies, including rheumatoid pannus, os odontoideum, fracture of the upper cervical vertebrae, suspected tumor with compression of the spinal cord, and basilar invagination (BI) [2-4]. This approach is associated with multiple morbidities, mainly tongue swelling due to a long retraction time, wound healing complications, and velopharyngeal insufficiency. Recently, the endoscopic endonasal approach (EEA) has been considered an alternative, safer approach with less morbidity [5-7]. We present two challenging cases for the management of CVJ pathology. In the first case, we used the EEA followed by C0-C1-C2 fusion using a posterior approach to decompress the CVJ, which was complicated by rhinorrhea and Candida albicans meningitis. The second case involved basilar invagination with syringomyelia previously treated using a posterior approach, where aggravation of neuropathic symptoms required combined treatment with EEA and occipitocervical fusion of C0-C2-C3-C4, with the postoperative course challenged by operative site infection requiring drainage with debridement and antibiotic therapy. The EEA is an alternative approach for accessing the CVJ in well-selected patients. Knowledge of EEA complications is crucial for the optimal care of patients.

Keywords: Candida albicans; Endoscopy; Meningitis; Odontoid process; Postoperative complications
ing drainage with debridement and antibiotic therapy.

Cases

**Ethical statements:** Our institution does not require Institutional Review Board approval for case reports. Informed consent was obtained from the patients.

1. Case 1

A 51-year-old previously healthy man presented to the emergency department with an episode of abrupt transitory tetraplegia that started after an episode of sneezing and lasted for only 2 minutes. He reported numbness and the sensation of electrical discharge in his four extremities over the last 6 months. On clinical examination, his vital signs were within normal ranges. The neurological examination was nonfocal. There was no evidence of motor or sensory deficits and proprioception was intact; ataxia and pyramidal signs were not observed. Computed tomography (CT) and magnetic resonance imaging (MRI) of the cervical spine revealed an os odontoideum associated with anterior displacement of the occipitocervical junction, resulting in compression of the spinal cord at the level of the odontoid process (Fig. 1).

The case was discussed in a spine board meeting, and the decision was made to proceed with two-stage surgery, resection by EEA of the anterior arch of C1 and odontoid tip in the first surgery, and occipitocervical fusion of C0-C1-C2 by the Harms technique in the second surgery 5 days later. Orotracheal intubation was performed. Rigid fixation was applied to the head, which was flexed and rotated ipsilaterally to the right side. The nostril cavity was prepared with betadine solution. Antibiotic prophylaxis was administered 30 minutes prior to incision. We used the binostril approach without turbinectomy or sphenoidectomy but with removal of the posterior 1 to 2 cm of the nasal septum to enlarge the choana and facilitate the binostril application of instruments. A 0° endoscope was introduced into the nostril. The free end of the middle turbinate led to the superior lateral aspect of the choana. The posterior and caudal portions of the nasal septum were then resected. Once at the choana, the endoscope was directed to the base of the odontoid. Using monopolar electrocautery, an inverted U-shaped incision was then made in the posterior oral pharynx, and the overlying longus colli and longus capitis muscles were reflected laterally. Subperiosteal exposure of the anterior arch of C1 and base of the odontoid process was then performed. The C1 arch was drilled first, followed by the dens. The ligamentous attachments were released at the apex of the dens. A high-speed drill and Kerrison Rongeur were used to remove residual posterior cortical bone. No evidence of cerebrospinal fluid (CSF) leakage was observed during the first operation (i.e., the EEA).

A CT scan of the cervical spine performed after the first surgery showed the extent of bony resection of the C1 anterior arch and odontoid process and a persistent, although reduced, C1 spinal stenosis of 7 mm in anteroposterior diameter. A CT scan of the cervical spine performed after the second surgery showed the extent of decompression and reduction in displacement with occipitocervical fusion of C0-C1-C2 by the posterior approach (Fig. 2).

In the postoperative period, the patient complained of severe occipital headaches. He also developed a fever of 38.8°C on postop-

![Fig. 1. (A) Sagittal, (B) axial T2 magnetic resonance imaging, and (C) sagittal computed tomography scan of the cervical spine show an os odontoideum associated with anterior displacement of the occipitocervical junction resulting in compression of the spinal cord at the level of the odontoid process tip marked by arrows.](https://doi.org/10.12701/jyms.2022.00234)
operative day (POD) 3. A CT scan of the brain and cervical spine showed pneumocephalus at the prepontic cistern without obvious collection. An infection was suspected in the CSF from lumbar punctures that were performed on PODs 3 and 5, but we failed to identify the microorganism by Gram stain and culture. The patient was started on an empirical antibiotic treatment (cefotaxime, linezolid, and metronidazole). The patient improved progressively during empirical treatment, with regression of fever until POD 10, when he developed rhinorrhea. A third lumbar puncture was performed, and *C. albicans* was identified. The patient's antimicrobial medication was switched to amphotericin B and flucytosine, and he underwent surgery for insertion of an external lumbar drain and endoscopic endonasal closure of a dural tear using a nasoseptal flap. The patient was maintained on amoxicillin to prevent pneumococcal meningitis. The patient started to improve progressively with resolution of his rhinorrhea and fever.

Endoscopic transnasal control under general anesthesia was performed after 8 days to visualize any leakage sites, and a Valsalva maneuver was performed, which confirmed no evidence of CSF leak. Fluorescein dye was not used, as there was no evidence of leakage or persistent CSF fistula. The external lumbar drain was removed on day 8. The patient was switched to oral fluconazole for a total of 4 weeks. The last examination of the patient after 6 months confirmed normal neurological and laboratory findings.

2. Case 2

A 70 year-old-gentleman was diagnosed in September 2017 with BI associated with syringomyelia from C4 to T1, with the main symptoms being C5 and C6 bilateral cervicobrachialgia with paresthesia of both upper limbs. He subsequently underwent surgery at another hospital for occipital craniectomy with resection of the posterior C2 arch and duroplasty. The syringomyelic cavity and previously described neuropathic pain persisted after the surgery. The patient presented to the neurosurgery clinic for posttraumatic aggravation of the neuropathic pain that now extended from the cervicodorsolumbar spine to the four extremities. There was no dysphagia or other associated symptoms on interrogation. Neurological examination showed alterations in coordination and precise movements in both hands, with the absence of pyramidal signs and obvious motor deficits. CT and MRI of the craniocervical junction were performed in February 2020, confirming stability of the residual syringomyelic cavity from C4 to T1, compression of the brainstem by the BI, and pseudomeningocele at the operative site (Fig. 3A, 3B).

The case was discussed in a spine board meeting, and the decision was made to proceed with two-stage surgery, using EEA for resection of the anterior C1 arch and odontoid tip in the first surgery, followed 72 hours later by occipitocervical fusion of C0-C2-C3-C4 (Fig. 3C, 3D; Fig. 4).

The postoperative course was complicated after 3 weeks by a purulent secretion from the posterior cervical wound. Because of suspicions of deep surgical-site infection, he underwent surgery immediately for drainage of the collection and debridement of the surgical site. Intraoperative culture was used to determine the appropriate antibiotic treatment. The patient was treated with empirical antibiotics (cefepime and vancomycin). The intraoperative cultures yielded two multisensitive bacteria: *Enterobacter cloacae* and *Enterococcus faecalis*. The patient improved progressively with resolution of fever and surgical site pain, and normalization of inflammatory markers. After 2 weeks, the patient was switched to...
oral ciprofloxacin and amoxicillin for a total duration of 6 weeks. The last neurological, clinical, and biological examination of the patient after 6 months was normal.

Discussion

A variety of congenital, developmental, and acquired pathologies can affect the CVJ, leading to bulbomedullary compression. Surgical treatment remains challenging owing to the complex anatomical characteristics of the region. For many years, the microsurgical transoral approach has been considered the “gold standard” for anterior decompression [8]. This approach is often associated with multiple complications such as infection, bleeding, severe postoperative swelling, and upper airway obstruction [9].

A complete EEA is feasible based on anatomical studies. In recent years, anatomical studies and surgical experience using this approach have been reported. In 2002, Alfieri et al. [10] published a cadaveric study to develop an EEA for the ventral craniocervical junction and odontoid process. They demonstrated that this approach was a valid alternative to the transoral approach. It allows access from the anterior cranial fossa to the whole clivus and the upper cervical spine up to the C2 body. In addition, because the surgical trajectory of this endonasal approach is relatively inclined in a rostral-to-caudal direction, the stability of C1-2 can be maintained, eliminating the necessity of spinal fusion [10].

Kassam et al. [11] were the first to report the feasibility of this approach for odontoid process resection. They mentioned that the defect created by the transnasal approach is above the level of the soft palate and should not be exposed to the same degree as other approaches to bacterial contamination from the oral cavity and oropharynx. Nayak et al. [12] demonstrated the feasibility of pure EEA for the resection of the odontoid process. Potential advantages that were noted included improved visualization, limited morbidity, decreased pain, and faster recovery compared to traditional approaches.

In addition to being a more comfortable and safer approach, extended transnasal access to the CVJ facilitates radical treatment of lesions in this location. A combination of transnasal resection and occipital-cervical stabilization demonstrated excellent preliminary results for brainstem compression resulting from C2 odontoid pro-
cess invagination. Compared to the transoral procedure, this method offers direct access to CVJ lesions and allows for more complex combined procedures [13]. This approach, as described by Yu et al. [14], provides a wider view of the surgical field and improves visualization in deep surgical corridors. Because the use of mouth retractors is no longer necessary with this approach, the risk of tongue swelling and tooth damage is eliminated. Additionally, the lower risk of tongue and posterior oropharyngeal wall swelling decreases the need for nasogastric tube feeding and prolonged extubation or tracheostomy. Soft palate splitting or hard palate resection is not required, which minimizes the risk of postoperative dysphonia or velopharyngeal insufficiency [14].

More than 119 patients with CVJ disease treated with EEA have been reported in the literature. Among 107 of these patients, CSF leak (intraoperative and/or postoperative) was reported in 13 (12.1%), transient velopharyngeal incompetence, variably associated with nasal speech and swallowing impairment, was reported in 6 (5.6%), postoperative epistaxis was reported in 2 (1.9%), and respiratory dysfunction requiring tracheostomy was reported in 2 of them (1.9%) [15]. In a recent meta-analysis, neurologic outcomes improved by 94.0% after transnasal odontoidectomy, whereas none of the patients experienced worsening of neurologic outcomes after the procedure [16]. Study results from a systematic review by Shriver et al. [16] of complications related to transoral and transnasal endoscopic odontoidectomy across a heterogeneous group of surgeons and patients showed that surgical procedures involving transoral odontoidectomy were more commonly associated with medical complications, while transnasal endoscopic procedures commonly resulted in intraoperative and postoperative CSF leaks. Compared to the findings of studies in which transnasal procedures were performed, those in which transoral procedures were performed had significantly higher rates of postoperative tracheostomy, but there was no statistically significant difference in complication rates [16].

A major risk of this approach is secondary craniocervical dislocation of the C1 lateral masses caused by the vertical pressure exerted by the weight of the head and loss of continuity of the C1 arch. The C1-C2 fusion is essential following transection of the anterior arch or laminectomy of C1 to limit the risk of lateral expulsion of the C1 lateral masses. C1 anterior arch preservation with angulated instrumentation and minimal resection of the odontoid apex can limit the risk of craniocervical destabilization [14].

This case series highlights the potential benefits of EEA for CVJ. Although EEA has been shown to be safe and effective in selected patients, one of our patients developed severe candidal meningitis, which opens a discussion on the safety of such a procedure combined with instrumentation. Knowledge of this atypical infection in patients with spinal instrumentation following this type of surgery will reduce diagnostic delays and allow appropriate, timely treatments.

The EEA approach should only be considered in carefully selected cases in which the anterior CVJ needs to be accessed. Although EEA does not replace the transoral approach, it is a viable alternative that may result in less morbidity when performed in centers that are experienced in the procedure. There is still a learning curve, and only time will provide a clearer picture of how it compares to traditional methods. The pitfall of this approach is the difficulty in repairing dural defects and subsequent CSF leakage, where the nasoseptal flap and external lumbar drain are effective treatments. A patient’s prognosis can still be compromised by serious postoperative complications such as fungal meningitis, especially in cases involving instrumentation.

Notes

Conflicts of interest
No potential conflicts of interest relevant to this article were reported.

Funding
None.

Author contributions
Conceptualization, Formal analysis, Resources, Supervision, Validation: all authors; Investigation, Methodology: BD; Data curation: BD, NA; Project administration: BD, DB, NA; Visualization: WL, DB, NA; Writing-original draft: BD, NA; Writing-review & editing: BD, NA.

ORCID
Baraa Dabboucy, https://orcid.org/0000-0002-3534-7229
Wissem Lahiani, https://orcid.org/0000-0003-3447-4960
Damien Bresson, https://orcid.org/0000-0001-6250-8932
Nouman Aldahak, https://orcid.org/0000-0002-7611-400X

References

3. Mummaneni PV, Haid RW. Transoral odontoidectomy. Neuro-
Intra-abdominal hypertension during hip arthroscopy: a case report

Saeyoung Kim, Hyun-Su Ri, Ji Hyun Kim, Jiyong Yeom

Department of Anesthesiology and Pain Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea

Symptomatic extravasation of irrigation fluid is a rare complication of hip arthroscopy. However, depending on the amount of fluid, intra-abdominal hypertension (IAH) may occur and even develop into abdominal compartment syndrome, which can seriously alter hemodynamic circulation. Therefore, it is important for anesthesiologists to promptly recognize the abnormal signs of IAH for early diagnosis and better clinical outcomes. Nevertheless, these signs are difficult to detect because they are usually obscured when the patient is under anesthesia and masked by surgical drapes. We report a case of IAH under general anesthesia during hip arthroscopy to highlight possible symptoms and signs.

Keywords: Arthroscopy; Compartment syndromes; Hypothermia; Intra-abdominal hypertension

Introduction

Hip arthroscopy has recently become popular because it is a minimally invasive technique with a short recovery time. It is considered a relatively safe procedure because the complication rate is less than 1.5% [1]. Among the complications, the incidence of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) caused by extravasation of irrigation fluid is only 0.16% [2]. Despite their extremely low frequency, these complications can be catastrophic and lead to hemodynamic collapse. In most cases, the physiological signs are difficult to distinguish from those of other conditions, although a clinical diagnosis must be made. We report a rare case of IAH that occurred during hip arthroscopy under general anesthesia.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: 2022-06-004). Patient consent was obtained for the publication of this case report.

A 56-year-old woman (height, 155 cm; weight, 45 kg) with chronic osteoarthritis was scheduled to undergo arthroscopy of the right hip joint and labral repair for excision of a right ganglion cyst under general anesthesia. The patient was otherwise healthy and had no other disease. Additionally, laboratory test results were normal. Standard monitoring was performed in the operating room, including noninvasive blood pressure (BP), electrocardiography,
bispectral index, body temperature, and pulse oximetry monitoring. General anesthesia was induced and maintained with lidocaine, propofol, remifentanil, rocuronium, and desflurane. Arthroscopy was performed with the patient in the supine position. Subsequently, anterior, anterolateral, and posterior ports were inserted. The irrigation fluid was prepared by mixing 3 L of 0.9% sodium chloride solution with 2 mg of epinephrine. A total of 25 L of irrigation fluid was applied, and the patient’s vital signs remained stable throughout the surgery.

However, 3 hours after commencing the surgery, when suturing was almost complete, her systolic BP suddenly decreased from 130 to 80 mmHg, with an increase in peak inspiratory pressure (PIP) from 15 to 24 mmHg. We initially suspected bronchial spasm or embolism. However, auscultation was unremarkable, and the end-tidal CO\textsubscript{2} curves did not show any significant changes, including signs of spontaneous breathing recovery. Her BP returned to baseline after phenylephrine administration. However, her increased PIP level did not normalize even after endotracheal tube suction, albuterol application, and lung recruitment. Additionally, a sudden decrease in body temperature, which had been maintained at approximately 36.5°C during the surgery, was detected. However, we initially overlooked this sign because the decrease was not large, from 36.7°C to 35.0°C, and body temperature tends to drop gradually during arthroscopy. Moreover, we assumed that the position of the esophageal temperature probe tip might have changed during surgery. Despite the abrupt changes in PIP and body temperature, we decided to awaken the patient because all other vital signs seemed stable. When the surgical drapes were removed, abdominal distention was observed, indicating IAH. Arterial blood gas was analyzed to differentiate between hemorrhage and irrigation fluid. The hematocrit (34.8%) and electrolyte (sodium, 135 mmol/L; potassium, 3.5 mmol/L) values were unremarkable. However, metabolic acidosis was confirmed (pH, 7.295; HCO\textsubscript{3}–, 16.8; base excess, −8.5). Based on these findings, an accumulation of irrigation fluid was highly suspected to be causing the abdominal distention rather than bleeding. After discussion with the orthopedic surgeons, we decided to consult general surgeons postoperatively because the latter were not immediately available. Subsequently, sugammadex was administered to reverse muscle relaxation. Approximately 5 to 8 minutes later, extubation was performed upon complete recovery of spontaneous breathing, and the patient seemed to recover from sedation. No remarkable events occurred during the emergence period.

However, as the patient regained consciousness, although her vital signs were stable and she could breathe without discomfort, she experienced abdominal pain. Ketorolac was administered for pain control, and intravenous fluid administration was restricted in the postoperative care unit. The patient was transferred for confirmation using abdominal computed tomography (CT), which revealed a large amount of fluid in the abdominal cavity, particularly around the right perihepatic space (Fig. 1). According to the general surgeon, emergent surgical decompression was not indicated in this case. Percutaneous catheter drainage was performed in the right perihepatic space. After approximately 1.5 L of fluid was drained from the catheter, the patient’s symptoms improved. On the second postoperative day, a follow-up CT scan showed no residual fluid. She was discharged 6 days later without any further

---

**Fig. 1.** Postoperative abdominal computed tomography reveals a large amount of fluid accumulating in the (A) abdominal cavity and (B) right perihepatic space.
symptoms or complications. Patient consent was obtained for publication of this case report.

Discussion

Although hip arthroscopy is considered to be a relatively safe procedure, more complications have been reported as its popularity has increased. Haskins et al. [3] recently reported extravasation of irrigation fluid in 16% of patients who underwent hip arthroscopy. Among them, the incidence of symptomatic intraperitoneal accumulation of irrigation fluid was only 0.16% [2]. In most cases, this can result in increased postoperative pain [3]. However, careful attention must be paid to this complication because, depending on the amount of fluid accumulated, it can be fatal, and even a case of cardiac arrest has been reported [4].

IAH is defined as a sustained increase in intra-abdominal pressure of ≥ 12 mmHg; if the pressure exceeds 20 mmHg, ACS can develop with organ dysfunction [5]. However, the mechanism by which irrigation fluid accumulates in the intraperitoneal space remains unclear. Once the tendon sheath of the iliopsoas muscle is opened, irrigation fluid can flow into the retroperitoneal space. Verma and Sekiya [6] hypothesized that occasional congenital communication between the retroperitoneum and peritoneal space may be present, which functions as an entrance gate. In addition, there is always a possible risk of the anchor perforating the anteromedial cortex of the acetabular dome and iliopsoas muscle during hip arthroscopy, allowing irrigation fluid to flow into the psoas tunnel [7,8]. High perfusion pressure is also a known risk factor for IAH [8]. The amount or pressure of irrigation fluids should be checked, and if baseline values are exceeded, hemodynamic variations should be carefully monitored. According to Papavasiliou and Bardakos [9], an inflow pressure of 40 to 50 mmHg for hip arthroscopy minimizes the risk of fluid extravasation. Every other condition related to diminished abdominal wall compliance and increased intra-abdominal contents, such as a history of abdominal surgery and obesity, can be considered a tentative risk [10]. Therefore, anesthesiologists should be vigilant in checking if excessive irrigation fluid pressure is used, especially when the patient has risk factors for IAH.

Similar to other compartment syndromes of the extremities, ACS is also a clinical diagnosis [11]. However, many institutions, including our institution, do not perform real-time abdominal pressure monitoring. Therefore, an awareness of the physiological signs of IAH is important. Abdominal extension and discomfort are the most common symptoms. However, these are usually hidden during surgery, as the patient is under anesthesia and the surgical drapes cover the abdominal area. Increased PIP and decreased oxygen saturation, BP, urine output, and body temperature have been commonly reported in similar cases [3,6]. As the pressure in the abdominal cavity increases, the diaphragm may be pushed upward, while the renal parenchyma and vessels are compressed. Additionally, as abdominal vessels are compressed, stroke volume can be affected by reduced venous return and increased peripheral vascular resistance. In our case, although saturation and urine output were unremarkable, sudden changes in PIP and BP were detected. However, these findings were not sufficiently specific to immediately suspect IAH. Thromboembolism and other hemorrhagic or respiratory events also share these features. Therefore, the differential diagnoses included hypovolemia, respiratory spasm, and embolic events. The accuracy could have improved if bronchoscopy had been applied to evaluate other respiratory conditions. However, the procedure was not available during this period at our center. With the help of end-tidal CO₂ monitoring and arterial blood gas analysis, we were able to exclude other differential diagnoses.

However, it was difficult to suspect IAH until the surgical cover was removed and abdominal distention was detected, as in many other reported cases [1,12]. Therefore, anesthesiologists must be aware of all IAH features. Sudden hypothermia should be considered as an important diagnostic sign. Although some degree of hypothermia is commonly observed during hip arthroscopy, there is only a slight difference. Typically, the patient’s temperature during surgery tends to decrease gradually and linearly [13,14]. However, in the case of IAH, a sudden and dramatic decrease in the temperature has been observed. Several studies have highlighted the importance of this sign. Bartlett et al. [4] and Sharma et al. [15] reported a sudden decrease in temperature to 33.3°C. However, our patient showed a decrease of 1.7°C, which was not large. However, we believe that the magnitude of decrease can differ depending on the severity of extravasation; therefore, attention should be paid to a sudden change within several minutes. Early observation of this change can be an important additional clue to other findings and differential diagnosis.

Several management strategies have been suggested to reduce intra-abdominal pressure. For anesthesiologists, improved abdominal wall compliance can be expected by appropriate sedation with analgesia and neuromuscular blockade [10]. In our case, we maintained lower intra-abdominal pressure by maintaining sedation and muscle relaxation until the completion of drainage. However, the consulting general surgeon was not available immediately; therefore, CT was performed to determine further treatment. Surgical decompression for IAH should be considered when intra-abdominal pressure is > 20 mmHg and new organ dysfunction is present [10]. CT is an accurate method to confirm the possibility of damage to other organs. However, we assume that if vital signs
are stable, such as in our case, perioperative ultrasonography can be a useful tool for the early and reliable diagnosis of fluid accumulation. With early application of ultrasonography and drainage, the patient would have experienced less pain, even if she had needed further CT evaluation.

In summary, hip arthroscopy has progressed over the decades and has recently become a more common procedure. Therefore, anesthesiologists must be aware of the complications that may occur. Despite its rare incidence, when physiological alterations that are highly suggestive of IAH occur, prompt inspection should be performed to prevent ACS from occurring with devastating results. Early diagnosis of IAH is essential to prevent this event; however, its detection remains challenging. Herein, we report a case of IAH during hip arthroscopy to highlight the physiological signs that contributed to earlier diagnosis and improved clinical outcomes.

Notes

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

Funding
None.

Author contributions
Conceptualization: all authors; Investigation: JY; Resources: JY; Writing-original draft: SK, JHK, JY; Writing-review & editing: HSR.

ORCID
Saeyoung Kim, https://orcid.org/0000-0003-1650-3385
Hyun-Su Ri, https://orcid.org/0000-0002-7305-4144
Ji Hyun Kim, https://orcid.org/0000-0003-0352-4929
Jiyong Yeom, https://orcid.org/0000-0001-9386-792X

References

Tarsal tunnel syndrome due to talocalcaneal coalition

Chul Hyun Park¹, Mathieu Boudier-Revéret², Min Cheol Chang³

¹Department of Orthopedic Surgery, Yeungnam University College of Medicine, Daegu, Korea
²Department of Physical Medicine and Rehabilitation, Centre hospitalier de l’Université de Montréal, Montréal, Canada
³Department of Physical Medicine and Rehabilitation, Yeungnam University College of Medicine, Daegu, Korea

A 26-year-old man visited the orthopedic department of our university hospital due to recently aggravated right medial ankle pain and tingling sensation over the plantar side of the foot that had started 8 years ago without trauma. Symptoms were aggravated by walking on uneven surfaces. On physical examination, the range of motion of the subtalar joint was limited. Tinel sign was positive along the tibial nerve at the tarsal tunnel. Also, a double medial malleolus sign was observed, which represents the enlarged fused middle facet (Fig. 1A). On lateral ankle standing radiograph, the C-sign, formed by the medial outline of the talar dome and posteroinferior aspect of the sustentaculum tali [1], was observed, and the bony prominence over the sustentaculum tali and medial process of talus was revealed (Fig. 1B). On computed tomography of the right ankle, talocalcaneal coalition was observed in the middle and posterior facets of the subtalar joint and involved about 40% of the joint on semicoronal image (Fig. 1C–1E). Magnetic resonance imaging showed the talocalcaneal coalition, and the tibial nerve was observed just adjacent to the talocalcaneal coalition, with the medial plantar nerve component compressed by it (Fig. 1F–1H). Coalition resection and subtalar joint arthrodesis were conducted. Intraoperatively, the tibial nerve was directly compressed and stretched over the talocalcaneal coalition (Fig. 1I). At 3-month follow-up, the patient’s symptoms had nearly disappeared.

Tarsal tunnel syndrome (TTS) is a compressive neuropathy of the tibial nerve or one of its branches in the tarsal tunnel [2], which is a fibro-osseous channel located posterior to the medial malleolus of the ankle, and delineated by the talus, sustentaculum tali, medial calcaneal wall and the flexor retinaculum on the outside. Within the tarsal tunnel, the tibial nerve splits into three branches including calcaneal nerve (innervating the heel) and medial and lateral plantar nerves (innervating the bottom of the foot). TTS presents with paresthesias over the heel and plantar area of the foot [2]. Because the flexor retinaculum acts as a roof over an osseous tunnel, increment of pressure within the tunnel frequently causes compression of the nerves. There are several etiologies of TTS, including trauma, malalignment of the ankle joint, and space-occupying lesions such as ganglion or synovial cyst, and pigmented villonodular synovitis [3]. In our case, the talocalcaneal coalition increased the pressure on tibial nerve within tarsal tunnel causing TTS.

Talocalcaneal coalition is one of the common types of tarsal coalition. It is a fibrous, cartilaginous, or osseous union of ≥ 2 of the tarsal bones [1] and develops because of disturbance or failure of mesenchymal segmentation [4]. In the general population, its incidence is reported to be approximately 1% to 6% [1]. Most symptomatic cases present during adolescence when the ossification of talocalcaneal bridge occurs.

If a patient complains of medial ankle pain with neurological symptoms on the plantar side of the foot, especially if symptoms began at adolescence, clinicians should consider the possibility of TTS due to talocalcaneal coalition.
Fig. 1. (A) The prominence on the posterior inferior aspect of the right medial malleolus (red arrow) called the “double medial malleolus sign” (yellow arrow, medial malleolus). (B) Lateral radiograph of the right ankle reveals a continuous C-shaped arc (yellow arrows), which is formed by the medial outline of the talar dome and posteroinferior aspect of the sustentaculum tali due to their bridging, and the bony prominence (red arrow) over the right sustentaculum tali and medial process of talus were observed. (C) Axial, (D) semicoronal, and (E) sagittal right ankle computed tomography show talocalcaneal coalition (asterisks) in the posterior subtalar joint. (F) Axial, (G) coronal, and (H) sagittal T2-weighted magnetic resonance imaging of the right ankle reveal the talocalcaneal coalition (asterisks) and tibial nerve adjacent to the coalition. The medial plantar nerve (red arrow) was compressed by the coalition (yellow arrows, lateral plantar nerve). (I) Intraoperative finding of talocalcaneal coalition.
Notes

Ethical statements
This study was approved by the Institutional Review Board of the Yeungnam University Hospital (IRB No: 2021-06-061). Written informed consent was obtained for publication of this report and accompanying images.

Conflicts of interest
Chul Hyun Park and Mathieu Boudier-Revéret have been editorial board member of Journal of Yeungnam Medical Science (JYMS) since 2021. Min Cheol Chang has been Associate editor of JYMS since 2021. They were not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

Funding
This study was supported by the National Research Foundation of Korea Grant funded by the Korean Government (No. NRF2021R1A2C1013073).

Author contributions
Conceptualization: all authors; Investigation, Data curation: CHP, MCC; Formal analysis, Funding acquisition, Supervision: MCC; Methodology: CHP; Visualization: MB, MCC; Writing-original draft: all authors; Writing-review & editing: all authors.

References
Right arm pain after strength training: ultrasound imaging for pectoralis major tendon strain

Ting-Yu Lin, Ke-Vin Chang, Wei-Ting Wu, Levent Özçakar

1Department of Physical Medicine and Rehabilitation, Lo-Hsu Medical Foundation, Inc., Lotung Poh Ai Hospital, Yilan, Taiwan
2Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
3Department of Physical Medicine and Rehabilitation, Bei-Hu Branch of National Taiwan University Hospital, Taipei, Taiwan
4Center for Regional Anesthesia and Pain Medicine, Wang-Feng Hospital, Taipei Medical University, Taipei, Taiwan
5Department of Physical and Rehabilitation Medicine, Hacettepe University Medical School, Ankara, Turkey

A 29-year-old man presented to the clinic with severe right proximal arm pain for 3 days. He described the pain as having suddenly appeared while performing a dumbbell fly on a bench. He had been weight training regularly for 3 years and had no known systemic disease or prior surgical history. Physical examination revealed mild swelling and marked tenderness in his right proximal arm, the range of motion of the right shoulder was not limited, and the muscle strength of the right upper limb was normal, except for shoulder adduction and internal rotation. Plain shoulder radiography revealed normal bone alignment without fractures. Ultrasound was performed with a high-frequency linear transducer positioned over the bicipital groove and then moved downward. The pectoralis major tendon was scanned anterior to the biceps brachii and coracobrachialis muscle bellies. A side-to-side comparison noted a loss of fibrillar pattern and increased thickness just before its attachment to the greater tubercle (Fig. 1). No muscle tears or hematomas were observed. Furthermore, the latissimus dorsi and teres major were examined with the shoulder fully abducted; both muscles as well as their conjoint tendons were normal [1]. Analgesics were prescribed. We advised the patient to maintain mobilization without resistance and to refrain from strength training. At a control visit 1 month later, the patient was asymptomatic and a comparative ultrasound examination was unremarkable.

The pectoralis major is a triangular, multipennate muscle, whose main actions are flexion, adduction, and internal rotation of the humerus. In addition to functioning as a dynamic shoulder stabilizer, it contributes to the superficial contour of the anterior chest wall and axillary fold. Its broad origin comprises the clavicular (arising from the medial half of the clavicle), the largest sternal head (arising from the second to sixth ribs and the costal margin of the sternum), and the abdominal head (arising from the aponeurosis of the external oblique muscle) [2]. The muscle fibers of the three heads run laterally to form the superficial and deep laminae of the pectoralis major tendon, and eventually fuse in front of the muscle insertion at the lateral edge of the intertubercular sulcus [3].

Pectoralis major tendon injuries predominantly result from indirect trauma, particularly during forceful eccentric contraction with the shoulder abducted and externally rotated [4]. Bench press exercises are the most commonly reported mechanisms of injury. The frequency of pectoralis major injuries has been increasing, and the majority of patients are active young men [4]. This trend is likely related to the growing popularity of weight training. A stiff, atrophic pectoralis major muscle can also be harmed while attempting a rather strenuous activity. Less commonly, pectoralis muscle ruptures can occur in cases of direct impact to the axillary region [5]. Based on the anatomical location, pectoralis major injuries can be classified into one of the following catego-
Pectoralis major injuries: (1) muscle origin or belly, (2) at or between the musculotendinous junction and tendinous insertion, and (3) bony avulsion at the humerus. The decision to operate depends on patient characteristics (young and athletic vs. immobile and elderly), timing (acute vs. chronic), and the extent and location of the tear.

Conservative treatments are reserved for proximal tears, partial tears, and patients with low activity levels.

A pectoralis major tear can be easily diagnosed in patients with a typical clinical history and manifestations. Physical examination often reveals bruising and swelling of the anterolateral chest wall. The axillary fold may appear different between sides if there is medial retraction of the muscle. However, further assessments are warranted if the diagnosis is uncertain. For our patient, ultrasound was an efficient tool for evaluating the musculotendinous architecture of the pectoralis major. The ultrasound probe should be navigated through the broad, fan-shaped muscle, paying special attention to the distal part of the muscle. Abduction and external rotation of the arm can maintain muscle tautness for high-quality imaging. Positive ultrasound findings for this injury include disruption of muscle striations, hematoma formation, change in tendon echotexture, and retraction of the muscle. Tendon avulsions are frequently accompanied by fluid collection at the musculotendinous junction.

In this case, we demonstrated the utility of ultrasound in uncovering an unusual sports injury. Physicians should consider the possibility of pectoralis major tendon lesions in susceptible populations to ensure timely evaluation and management.

**Learning points**

- Pectoralis major injuries mostly occur during strength training when forceful eccentric contraction is performed with shoulder abduction and external rotation.
- Ultrasound examination for pectoralis major injuries should encompass the entire muscle, but especially focusing on the musculotendinous junction and humeral insertion.

---

**Fig. 1.** (A) Ultrasound imaging of the right proximal region shows loss of fibrillar pattern and increased thickness of the pectoralis major tendon (arrow) near its insertion on the humerus. (B) The pectoralis major tendon (arrowhead) on the unaffected side has normal thickness and fibrillar pattern. CRB, coracobrachialis muscle; DEL, deltoid muscle; GT, greater tubercle; LHB, long head of the biceps muscle; SHB, short head of the biceps muscle; TM, teres major muscle; PMA, pectoralis major muscle.
• Conservative treatment is indicated when the tear is partial, located inside the muscle belly, or observed in a sedentary patient who is elderly. Otherwise, surgical referral is suggested.

Notes

Ethical statements
Written patient consent was obtained for the publication of this report.

Conflicts of interest
Ke-Vin Chang and Wei-Ting Wu have been editorial board member of Journal of Yeungnam Medical Science (JYMS) since 2021. He was not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

Funding
This work was funded by National Taiwan University Hospital, Bei-Hu Branch; Ministry of Science and Technology (MOST 106-2314-B-002-180-MY3 and 109-2314-B-002-114-MY3); and the Taiwan Society of Ultrasound in Medicine.

Author contributions
Conceptualization, Funding acquisition: KVC, WTW, LÖ; Investigation: KVC; Validation: WTW, LÖ; Writing-original draft: TYL; Writing-review & editing: KVC, LÖ.

References
Instructions to authors

Table of Contents

General information
Copyrights and creative commons attribution license
Types of publication
Research and publication ethics
Author qualifications, language requirement, and reporting guideline
Submission and peer review process
Manuscript preparation
Final preparation for publication
Article processing charge

General information

*Journal of Yeungnam Medical Science (JYMS)* is the official journal of the Yeungnam University College of Medicine and Yeungnam University Institute of Medical Science. Anyone who would like to submit a manuscript is advised to carefully read the aims and scope section of this journal. Manuscripts should be prepared for submission to *JYMS* according to the following instructions. For issues not addressed in these instructions, the author is referred to the International Committee of Medical Journal Editors (ICMJE) “Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals” (http://www.icmje.org). It also adheres completely to the Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by COPE, DOAJ, WAME, and OASPA; https://doaj.org/apply/transparency/) if otherwise not described below.

Copyrights and creative commons attribution license

A submitted manuscript, when published, will become the property of the journal. Copyrights of all published materials are owned by the Yeungnam University College of Medicine and Yeungnam University Institute of Medical Science. The Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/4.0/) is also in effect.

Types of publication

*JYMS* publishes editorials, review articles, original articles, case reports, image vignettes, communications, RFS (clinical vignette, teaching images), and imagery.

Editorials are invited perspectives on an area of medical science, dealing with very active fields of research, current medical interests, fresh insights and debates.

Review articles provide a concise review of a subject of importance to medical researchers written by an invited expert in medical science.

Original articles are papers reporting the results of basic and clinical investigations that are sufficiently well documented to be acceptable to critical readers.

Case reports deal with clinical cases of medical interest or innovation.

Image vignettes present state-of-the-art imaging that can be used in the evaluation of unusual clinical cases.

Communications are interesting and instructive information for readers.

RFS: clinical vignette is interesting clinical cases focused on developing clinical reasoning skills of resident or fellow trainees.

RFS: teaching images are previously unpublished magnetic resonance images, computed tomography scans, ultrasound images, X-rays, patient photographs/videos, or other pictorial/video-graphic material.

Imagery is drawings, illustrations, or photographs of artistic and imaginative qualities of the readers.

Research and publication ethics


Authorship

Authorship credit should be based on (1) substantial contributions to the conception and design, acquisition of data, and/or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Every author should meet all of these four conditions. After the initial submission of a manuscript,
any changes whatsoever in authorship (adding author(s), deleting author(s), or re-arranging the order of authors) must be explained by a letter to the editor from the authors concerned. This letter must be signed by all authors of the paper. A copyright assignment must also be completed by every author.

- Corresponding author and first author: JYMS does not allow multiple corresponding authors for one article. Only one author should correspond with the editorial office and readers for one article. JYMS accepts notice of equal contribution for the first author when the study is clearly performed by co-first authors.
- Correction of authorship after publication: JYMS does not correct authorship after publication unless the editorial staff has erred. Authorship may be changed before publication but after submission when an authorship correction is requested by all of the authors involved with the manuscript.

Originality, plagiarism, and duplicate publication
Submitted manuscripts must not have been previously published or be under consideration for publication elsewhere. No part of the accepted manuscript should be duplicated in any other scientific journal without permission from the Editorial Board. Submitted manuscripts are screened for possible plagiarism or duplicate publication by Similarity Check using the ‘Turnitin’ program (iParadigms, LLC, Oakland, CA, USA). If plagiarism or duplicate publication is detected, the manuscript may be rejected, the authors will be announced in the journal, and their institutions will be informed. There will also be penalties for the authors. A letter of permission is required for any and all materials that have been published previously. It is the responsibility of the author to request permission from the publisher for any material that is being reproduced. This requirement applies to the text, figures, and tables.

Secondary publication
Manuscripts can be republished if they satisfy the conditions of secondary publication in the ICMJE Recommendations (https://www.icmje.org/urm_main.html).

Conflicts of interest
The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors’ interpretation of the data. Examples of potential conflicts of interest are financial support from or connections to companies, political pressure from interest groups, and academically related issues. In particular, all sources of funding applicable to the study should be explicitly stated.

Statement of human and animal rights
Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Declaration of Helsinki of 1975 (revised 2013) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Clinical studies that do not meet the Declaration of Helsinki will not be considered for publication. Human subjects should not be identifiable, such that patients’ names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

Statement of informed consent and Institutional Review Board approval
Copies of written informed consent documents should be kept for studies on human subjects, which includes identifiable information or sensitive information. For clinical studies of human subjects, a certificate, agreement, or approval by the Institutional Review Board (IRB) of the author’s institution is required. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

Process for managing research and publication misconduct
When the journal faces suspected cases of research and publication misconduct, such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, an undisclosed conflict of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author’s idea or data, complaints against editors, and so on, the resolution process will follow the flowchart provided by the Committee on Publication Ethics (COPE, https://publicationethics.org/resources/flowcharts). The discussion and decision on the suspected cases are carried out by the Editorial Board.

Process for handling cases requiring corrections, retractions, and editorial expressions of concern
Cases that require editorial expressions of concern or retraction shall follow the COPE flowcharts (https://publicationethics.org/guidance/flowcharts). If correction needs, it will follow the ICMJE Recommendation for Corrections, Retractions, Reproductions, and Version Control (https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html) as follows:
Honest errors are a part of science and publishing and require the publication of a correction when they are detected. Corrections are needed for errors of fact. The minimum standards are as follows: (1) it shall publish a correction notice as soon as possible detailing changes from and citing the original publication on both an electronic and numbered print page that is included in an electronic or a printed Table of Contents to ensure proper indexing; (2) it shall post a new article version with details of the changes from the original version and the date(s) on which the changes were made through CrossMark; (3) it shall archive all prior versions of the article. This archive can be directly accessible to readers; (4) previous electronic versions shall prominently note that there are more recent versions of the article via CrossMark.

Editorial responsibilities
The Editorial Board will continuously work to monitor and safeguard publication ethics: guidelines for retracting articles; maintenance of the integrity of the academic record; preclusion of business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and excluding plagiarism and fraudulent data. The editors maintain the following responsibilities: responsibility and authority to reject and accept articles; avoiding any conflict of interest with respect to articles they reject or accept; promoting the publication of corrections or retractions when errors are found; and preservation of the anonymity of reviewers.

Author qualifications, language requirement, and reporting guideline

Author qualifications
Any researcher throughout the world can submit a manuscript if the scope of the manuscript is appropriate.

Language
Manuscripts should be submitted in good scientific English.

Reporting guidelines for specific study designs
For specific study designs, such as randomized controlled trials, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, we strongly recommend that authors follow and adhere to the reporting guidelines relevant to their specific research design. For case reports, authors should follow the CARE guidelines (https://www.care-statement.org). Authors should upload a completed CARE checklist (https://www.care-statement.org/checklist) for the appropriate reporting guidelines during original submission. Some reliable sources of reporting guidelines are EQUATOR Network (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

Submission and peer review process

Submission
All manuscripts should be submitted via e-submission system (https://submit.e-jyms.org). If any authors have difficulty in submitting via e-submission system, please send a manuscript to jyms@yu.ac.kr.

Peer review process
JYMS reviews all manuscripts received. A manuscript is first reviewed for its format and adherence to the aims and scope of the journal. If the manuscript meets these two criteria, it is checked for plagiarism or duplicate publication with Similarity Check. After confirming its result, it is sent to two (or more) relevant investigators available for review of the contents. The editor selects peer referees by recommendation of editorial board members or from the board's specialist database. JYMS adopts a double-blind review, which means that the reviewers and authors cannot identify each other's information. The authors' names and affiliations are removed during peer review. Assuming the manuscript is sent to reviewers, JYMS waits to receive opinions from at least two reviewers. In addition, if deemed necessary, a review of statistics may be required. The acceptance criteria for all papers are based on the quality and originality of the research and its scientific significance. Acceptance of a manuscript is decided based on the critiques and recommended decisions of the reviewers.

An initial decision is normally made within 4 weeks of receipt of a manuscript, and the reviewers’ comments are sent to the corresponding author by e-mail. The corresponding author must indicate the alterations that have been made in response to the reviewers’ comments item by item. Failure to resubmit the revised manuscript within 12 weeks of the editorial decision is regarded as a withdrawal. A final decision on acceptance/rejection for publication is forwarded to the corresponding author from the editor.

We neither guarantee acceptance without review nor very short peer review times for unsolicited manuscripts. Solicited manuscripts are also reviewed before publication.

Peer review process for handling submissions from editors, employees, or members of the editorial board
All manuscripts from editors, employees, or members of the editorial board are processed the same way as the other unsolicited
Manuscripts. During the review process, submitters do not engage in the decision process. Editors will not handle their own manuscripts, although they are commissioned ones.

**Manuscript preparation**

**General requirements**

The main document with manuscript text and tables should be prepared in an MS Word (docx) format.

The manuscript should be double spaced on 21.6 × 27.9 cm (letter size) or 21.0 × 29.7 cm (A4) paper with 3.0 cm margins at the top, bottom, right, and left margin.

All manuscript pages are to be numbered at the bottom consecutively, beginning with the Title as page 1. Neither the author's names nor their affiliations should appear on the manuscript pages.

We recommend using the manuscript template provided by JYMS (https://e-jyms.org/authors/authors.php).

The authors should express all measurements according to International System (SI) units with some exceptions such as seconds, mmHg, or °C.

Only standard abbreviations should be used. Abbreviations should be avoided in the title of the manuscript. Abbreviations should be spelled out when first used in the text—for example, extensible markup language (XML)—and the use of abbreviations should be kept to a minimum.

The names and locations (city, state, and country only) of manufacturers should be given.

When quoting from other sources, a reference number should be cited after the author's name or at the end of the quotation.

Manuscript preparation is different according to the publication type, including editorials, review articles, original articles, case reports, image vignettes, communications, resident fellow section (RFS; clinical vignette, teaching images), and imagery.

**Review article**

All review articles will undergo peer review. An abstract is required whereas Methods section and a Results section are not required (no more than 250 words). The length of review articles is limited to 6,000 words with a maximum of 100 references.

**Original article**

Original articles should begin with the title page followed by an abstract; a list of key words; an Introduction, Methods, Results, Discussion, References (up to 40 references), and tables and/or illustrations.

1) **Title page**

The title page should contain the following information: (1) title (less than 150 characters, including spaces); (2) author list (first name, middle name, and last name); (3) name of the institutions at which the work was performed; (4) acknowledgement of research support; (5) name, address, telephone, fax number, and e-mail address of the corresponding author; (6) running title (less than 50 characters, including spaces).

2) **Abstract**

Abstract must be organized and formatted according to the following headings: Background, Methods, Results, and Conclusion. The abstract length is typically no more than 250 words.

3) **Keywords**

List 3-6 keywords from the list provided in Index Medicus under "Medical Subject Heading (MeSH)."

4) **Text**

The text of manuscripts must have the following sections: Introduction, Methods, Results, and Discussion. The body of the manuscript should be written as concisely as possible. All pages of the manuscript should be numbered.

**Introduction**

This should provide a context or background for the study and states the specific purpose or research objective of or hypothesis tested by the study. This may include mention of papers most closely related to the article, and of the problem.

**Methods**

Explanation of the experimental methods should be concise but sufficient to allow other workers to reproduce the results. This provides the technical information, apparatus (the manufacturer’s name and brief address) and procedures. Give references and brief descriptions for the methods that have been published. Describe statistical methods with enough detail to enable a reader with access to the original data to verify the reported results. Define statistical terms, abbreviations, and most symbols.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases.
(e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

Results
This should include a concise textual description of the data presented in tables and figures.

Discussion
This section includes the new and important aspects of the study and the conclusions. The data should be interpreted concisely. Speculation is permitted, but it must be supported by the data presented by the authors.

References
References should be numbered consecutively in the order in which they are first mentioned in the text, with numbers in square brackets before any closing punctuation. They should be listed on a separate document under the heading “References,” and double-spaced. Reference format should conform to that set forth in “Uniform Requirements for Manuscripts Submitted to Biomedical Journals. 5th ed.” (JAMA 1997;277:927-34). Titles of journals should be abbreviated according to the Index Medicus style.

Reference style:

Journal articles
• List all authors when six or less; when seven or more, list the first six and add et al. Vega KJ, Pina I. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.

Book

Book chapter

Web resources

5) Tables
Tables should fit within a single page. The Table’s legend may include any pertinent notes and must include definitions of all abbreviations and acronyms that have been used in the Table. For footnotes, the following symbols should be used in this sequence: a), b), c), d), e), f), g), h), etc. Authors are obligated to indicate the significance of their observations by appropriate statistical analysis.

6) Illustrations
Authors must submit illustrations as electronic files. Acceptable figure file formats are JPEG, TIFF, and PPT/PPTX. Each figure needs to be prepared in a resolution higher than 300 dpi with good contrast and sharpness. The file size of each submitted figure should not exceed 10 MB per figure. If the patient’s photograph is presented in a paper, it should be manipulated to make it difficult to recognize. Patients introduced in the manuscripts should be informed and aware that their photographs, videotapes, and other images (imaging records) will be released by the authors, and the authors should attach the Authorization and Release Form available at the JYMS website (https://e-jyms.org/authors/ethics.php) including each patient’s signature. If the patient is a minor, a written consent of the guardian must be submitted.

7) Legends for tables and illustrations
Typed legends that use double-spacing should start on a separate page with Arabic numerals corresponding to the Tables or Illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the Tables or Illustrations, they should be individually identified and explained clearly in the legend.

8) Abbreviations
Authors should limit the use of abbreviations to an absolute
minimum. Abbreviations are not to be used in titles. Abstracts may contain abbreviations for terms mentioned many times in the abstract section, but each term must be identified the first time it is mentioned.

9) Unit of measurement
Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperature should be in degrees Celsius. Authors must consult the information for authors for the particular journal and should report laboratory information in both the local and International System of Units (SI).

Case report
Case reports should consist of an Abstract (no more than 250 words), Keywords, Introduction, Case, Discussion, and References (no more than 20). Case reports should have fewer than nine authors and follow the CARE guidelines.

Image vignette
Image vignette should be organized in the following sequence: a summary of the presentation, imaging features and discussion. No abstract is required for this manuscript. There should be no more than five references and no more than two figures. Total length should be no longer than 500 words (excluding figure legends, ethical statements, conflicts of interest, author contributions, ORCID, and references).

Communications
Although communication articles are not limited in the format, they should contain a self-standing abstract and references. The abstract should be concisely written and not exceed 250 words.

Resident fellow section
RFS is designed to provide clinical cases and images that are informative for resident or fellow trainees. We encourage article submissions where the primary author(s) are prepared by trainees under the supervision of their attending physicians. We require a statement to be provided within the cover letter of any article submitted to this section that confirms the primary author(s) are residents or fellows. The following categories of articles will be included in the RFS:

1) Clinical vignette
Interesting clinical cases focused on developing clinical reasoning skills of resident or fellow trainees. Authors should follow the CARE guidelines.

Cases may focus on either diagnosis or management. Vignettes should progress logically and be divided into the following sections:
- Brief history and physical exam. Include pertinent history of present illness, medical history, and physical exam findings.
- Differential diagnosis or potential approaches to management. Include discussion regarding reasons for selected differential or potential management approaches.
- Diagnostic results including lab results/imaging (if relevant).
- Diagnosis and discussion of management and outcomes. Include a discussion of the relevant literature related to the vignette.

Clinical vignette should be maximum of 1,500 words, 1-2 tables or 1-2 figures and maximum of 10 references.

2) Teaching images
Previously unpublished magnetic resonance images, computed tomography scans, ultrasound images, X-rays, patient photographs/videos, or other pictorial/videographic material. These pictorials should clearly demonstrate distinct examples of either rare, conventionally common, or uniquely pathognomonic observations, techniques, or findings intended to further the education of the trainee audience. The title of the article should be brief and include the patient’s age and sex, accompanied by a succinct 5-10 words description of the patient’s presentation. Up to two labeled images or figures should be provided with a short description and/or legend. The case description should be written in 500 words or less and directly address the image provided while detailing the clinical significance of the presented findings and correlation with the patient’s symptoms. Intended for trainees, teaching images should progress through a patient’s history and physical exam while focusing on differential diagnoses, the clinical reasoning for selecting the particular diagnostic study, and the appropriate interpretation, subsequent treatment strategies, and achieved outcome. Finally, 2-3 bulleted learning points should accompany the submission to advance trainee knowledge (will not count toward word limit).

Imagery
This is a regular section of JYMS, featured at the beginning of issue and devoted to the artistic and imaginative qualities of the readers. JYMS invites your drawings, illustrations, or photographs with a brief explanation. Please send electronic images via e-mail to: jyms@yu.ac.kr. These contributions will not be returned.
Final preparation for publication

Final version
After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher resolution image files should be submitted at this time. Color images must be created as CMYK files. The electronic original should be sent with appropriate labeling and arrows. The JPEG, TIFF, and PPT/PPTX formats are preferred for submission of digital files of photographic images. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal’s column widths. All of the symbols must be defined in the figure caption. If the symbols are too complex to appear in the caption, they should appear on the illustration itself, within the area of the graph or diagram, not to the side. If references, tables, or figures are moved, added, or deleted during the revision process, they should be renumbered to reflect such changes so that all tables, references, and figures are cited in numeric order.

Manuscript corrections
Before publication, the manuscript editor may correct the manuscript such that it meets the standard publication format. The author(s) must respond within 2 days when the manuscript editor contacts the author for revisions. If the response is delayed, the manuscript’s publication may be postponed to the next issue.

Galley proof
The author(s) will receive the final version of the manuscript as a PDF file. Upon receipt, within 2 days, the editorial office (or printing office) must be notified of any errors found in the file. Any errors found after this time are the responsibility of the author(s) and will have to be corrected as an erratum.

Article processing charge
No page charge or article processing charge applies. There is also no submission fee.

Enactment December 30, 1984
First revision April 20, 2011
Second revision May 22, 2012
Third revision July 17, 2013
Fourth revision April 22, 2014
Fifth revised December 23, 2014
Sixth revised April 30, 2018
Seventh revised July 7, 2021
Eighth revised December 10, 2021
Recently revised May 24, 2022
Research ethics


Authorship

Authorship credit should be based on (1) substantial contributions to the conception and design, acquisition of data, and/or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Every author should meet all of these four conditions. After the initial submission of a manuscript, any changes whatsoever in authorship (adding author(s), deleting author(s), or re-arranging the order of authors) must be explained by a letter to the editor from the authors concerned. This letter must be signed by all authors of the paper. A copyright assignment must also be completed by every author.

- Corresponding author and first author: The Journal of Yeungnam Medical Science (JYMS) does not allow multiple corresponding authors for one article. Only one author should correspond with the editorial office and readers for one article. JYMS accepts notice of equal contribution for the first author when the study is clearly performed by co-first authors.
- Correction of authorship after publication: JYMS does not correct authorship after publication unless the editorial staff has erred. Authorship may be changed before publication but after submission when an authorship correction is requested by all of the authors involved with the manuscript.

Originality, plagiarism, and duplicate publication

Submitted manuscripts must not have been previously published or be under consideration for publication elsewhere. No part of the accepted manuscript should be duplicated in any other scientific journal without permission from the Editorial Board. Submitted manuscripts are screened for possible plagiarism or duplicate publication by Similarity Check using the ‘Turnitin’ program (iParadigms, LLC, Oakland, CA, USA). If plagiarism or duplicate publication is detected, the manuscript may be rejected, the authors will be announced in the journal, and their institutions will be informed. There will also be penalties for the authors. A letter of permission is required for any and all materials that have been published previously. It is the responsibility of the author to request permission from the publisher for any material that is being reproduced. This requirement applies to the text, figures, and tables.

Secondary publication

Manuscripts can be republished if they satisfy the conditions of secondary publication in the ICMJE Recommendations (https://www.icmje.org/urn_main.html).

Conflicts of interest

The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors’ interpretation of the data. Examples of potential conflicts of interest are financial support from or connections to companies, political pressure from interest groups, and academically related issues. In particular, all sources of funding applicable to the study should be explicitly stated.

Statement of human and animal rights

Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Declaration of Helsinki of 1975 (revised 2013) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Clinical studies that do not meet the Declaration of Helsinki will not be considered for publication. Human subjects should not be identifiable, such that patients’ names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, research should be performed based on the National or Institutional Guide
for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

**Statement of informed consent and Institutional Review Board approval**

Copies of written informed consent documents should be kept for studies on human subjects, which includes identifiable information or sensitive information. For clinical studies of human subjects, a certificate, agreement, or approval by the Institutional Review Board (IRB) of the author’s institution is required. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

**Process for managing research and publication misconduct**

When the journal faces suspected cases of research and publication misconduct, such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, an undisclosed conflict of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author’s idea or data, complaints against editors, and so on, the resolution process will follow the flowchart provided by the Committee on Publication Ethics (COPE, https://publicationethics.org/resources/flowcharts). The discussion and decision on the suspected cases are carried out by the Editorial Board.

**Process for handling cases requiring corrections, retractions, and editorial expressions of concern**

Cases that require editorial expressions of concern or retraction shall follow the COPE flowcharts (https://publicationethics.org/guidance/Flowcharts). If correction needs, it will follow the ICMJE Recommendation for Corrections, Retractions, Replications, and Version Control (https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html) as follows:

- Honest errors are a part of science and publishing and require the publication of a correction when they are detected. Corrections are needed for errors of fact. The minimum standards are as follows: (1) it shall publish a correction notice as soon as possible detailing changes from and citing the original publication on both an electronic and numbered print page that is included in an electronic or a printed Table of Contents to ensure proper indexing; (2) it shall post a new article version with details of the changes from the original version and the date(s) on which the changes were made through CrossMark; (3) it shall archive all prior versions of the article. This archive can be directly accessible to readers; (4) previous electronic versions shall prominently note that there are more recent versions of the article via CrossMark.

**Editorial responsibilities**

The Editorial Board will continuously work to monitor and safeguard publication ethics: guidelines for retracting articles; maintenance of the integrity of the academic record; preclusion of business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and excluding plagiarism and fraudulent data. The editors maintain the following responsibilities: responsibility and authority to reject and accept articles; avoiding any conflict of interest with respect to articles they reject or accept; promoting the publication of corrections or retractions when errors are found; and preservation of the anonymity of reviewers.
All authors pledges that we follow the basic standards of research and publication ethics in the submission process to *Journal of Yeungnam Medical Science*

<table>
<thead>
<tr>
<th>Check Yes if</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Research subject, research object and size, setting of controls, and the methods of data collection are suitable for the research ethics.</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Authors should ensure that their submitted manuscripts are not against publication ethics such as fabrication, falsification or plagiarism.</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>In clinical research involving human, informed consent from patient should be conducted and written in the method section of the manuscript.</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>All clinical research involving human and animal subjects to be approved by the author’s Institutional Review Board (IRB) or equivalent committees.</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>This study is conducted in compliance with the Declaration of Helsinki and this comment is written in the method section of the manuscript.</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>All Authors must disclose all relationships that could be viewed as potential conflicts of interest. This relationship also includes any potential conflicts of interest with all material, products, and companies in the manuscript.</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Authors should confirm that the submitted work is not under consideration or accepted for publications elsewhere, and would not be submitted in any other journals after acceptance.</td>
<td>□ Yes □ No</td>
</tr>
<tr>
<td>Duplicate publication, which includes ‘imalas publication’, ‘plagiarism’, and ‘salami publication’, is strictly not conducted.</td>
<td>□ Yes □ No</td>
</tr>
</tbody>
</table>

If the rationale provided by the authors remains unsatisfactory in the judgment of the editors, the manuscript will be rejected or retracted. The authors will not be allowed to subsequently submit their research to *Journal of Yeungnam Medical Science*. The authors should keep the above mentioned disadvantages in mind.

**Date:** ________________________________

**Corresponding author’s name:** ________________________________
In consideration of editors and publisher's effort in reviewing and editing our/my Article, the undersigned authors hereby transfer, convey, and assign all copyrights in the Article to the Editorial Board of the Journal of Yeungnam Medical Science (JYMS). The copyright transfer covers the right to print, publish, distribute and sell throughout the world the said contribution and parts thereof, including all revisions or versions and future editions, in all forms and media.

The authors certify that I have participated in the intellectual content, the analysis of data, and the writing of the Article, to take public responsibility for it. The authors reviewed the final version of the Article, believe it represents valid work and approve it for publication. The authors certify that none of the material in the manuscript has been published previously, is included in another manuscript. The authors also certify that the Article has not been accepted for publication elsewhere, nor have they assigned any right or interest in the Article to any third party. The authors will obtain and include with the manuscript written permission from any respective copyright owners for the use of any text, figures, and tables that have been previously published. The authors agree that it is their responsibility to pay fees charged for permissions.

Author’s name  |  Signature
----------------|------------------
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
I am informed and aware of photographs, videotapes and other images (imaging records) taken by Dr. _______________ or his designee(s) of myself or any parts of my body regarding surgical procedures carried out by Dr. _______________. I understand and consent that such imaging records may and will be used by Dr. _______________ as reference in diagnosing and treating other patients in the future. I further consent to the release and transfer of copyright ownership by Dr. to Journal of Yeungnam Medical Science of such imaging records.

I understand that by consenting on release of my imaging records, these may and will be used in upcoming issue or issues of the journal, as well as on the journal website, or any other print or electronic media for the purpose of informing medical professionals or other readers about surgical methods. I understand that when these imaging records are included in any articles, medical information regarding sex, age, operative date and treatment results may and will be included together. (In case of facial photographs, the photo is cropped to only necessary parts in order to make individual identification impossible.) I understand that whether I consent on this form or not, it bears no consequences whatsoever on any future actions, and that there will be no effect on the medical treatment I receive from Dr. _______________ or any subordinates.

I grant this consent as a voluntary contribution in the interest of public education, and certify that I have read the above Consent, Authorization and Release form and fully understand its terms. I understand that, if I do not revoke this authorization, it will expire 10 years from the date written below.

I hereby transfer in above-mentioned terms, the copyright of my imaging records to

Dr. ____________________________________________

Name: ____________________________________________  Signature: ________________________________
Hospital: __________________________________________  Department: _______________________________
Designated Doctor: _________________________________  Signature: ________________________________

20 . . . .