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Aims and scope

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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.

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Hypertension and cognitive dysfunction: a narrative review

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Cognitive dysfunction is relatively less considered a complication of hypertension. However, there is sufficient evidence to show that high blood pressure in middle age increases the risk of cognitive decline and dementia in old age. The greatest impact on cognitive function in those with hypertension is on executive or frontal lobe function, similar to the area most damaged in vascular dementia. Possible cognitive disorders associated with hypertension are vascular dementia, Alzheimer disease, and Lewy body dementia, listed in decreasing strength of association. The pathophysiology of cognitive dysfunction in individuals with hypertension includes brain atrophy, microinfarcts, microbleeds, neuronal loss, white matter lesions, network disruption, neurovascular unit damage, reduced cerebral blood flow, blood-brain barrier damage, enlarged perivascular damage, and proteinopathy. Antihypertensive drugs may reduce the risk of cognitive decline and dementia. Given the high prevalence of dementia and its impact on quality of life, treatment of hypertension to reduce cognitive decline may be a clinically relevant intervention.

Keywords: Cognition; Dementia; Hypertension; Review

Introduction

Hypertension is a serious medical condition that significantly increases the risk of cardiovascular, cerebral, renal, and other organ dysfunction [1]. Cognitive impairment is comparatively less considered to be an adverse effect of hypertension. However, accumulating evidence supports the causal role of hypertension in cognitive decline beyond its relationship with stroke [2]. Cognitive decline in old age is regarded as an irreversible condition due to degenerative changes, and in many cases, it reduces quality of life and is difficult to treat in diagnosed patients [3]. However, this cognitive decline is affected by many other factors in addition to normal age-related degenerative changes, and hypertension is one of the most important risk factors because it can be controlled and modified and has a high prevalence [4]. Therefore, useful research evidence should be obtained to review and summarize the cognitive dysfunction in patients with hypertension. The purpose of this study is to examine the characteristics of cognitive dysfunction in patients with hypertension and to summarize studies showing the association of hypertension with cognitive disorders and how hypertension causes pathophysiological changes in the brain that lead to cognitive dysfunction.

Epidemiological evidence

Epidemiological data from the Framingham study [5] suggest that
there is no association between blood pressure (BP) and co-measured cognitive ability. However, a longitudinal reanalysis of the data showed that the 20-year mean BP was inversely related to cognitive ability [5]. A midlife hypertension and 20-year cognitive cohort study demonstrated that only high systolic BP in midlife, not increased systolic BP in late life was associated with more cognitive decline during the 20-year study [6]. Other cohort studies have also shown that midlife hypertension is a significant predictor of both cognitive dysfunction and morphological changes in the brain [7,8]. A retrospective cohort study including 721 individuals also found that midlife hypertension was associated with late-life dementia [9,10]. The Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) study, including 1,449 participants aged 65 to 79 years with an average follow-up of over 21 years, suggested that midlife hypertension was associated with an increased risk of dementia in late life [11]. Another study indicated that hypertension in middle age increases the risk of mild cognitive impairment (MCI). A population-based study, using the same cohort of CAIDE study, suggested that midlife hypertension is associated with the development of MCI in late life [12]. The Atherosclerosis Risk in Communities (ARIC) cohort study showed that hypertension and prehypertension in midlife are associated with an increased risk of dementia in late life [9]. The association between midlife hypertension and dementia was also suggested by the Honolulu-Asia Aging Study of 3,703 participants, which showed a consistent association between Alzheimer disease (AD) and vascular dementia [13]. A recent meta-analysis that included 209 prospective studies also showed that midlife hypertension has a stronger association than late-life hypertension. In that meta-analysis, midlife hypertension was associated with an excess risk of 1.19 to 1.55 times that of cognitive impairment. The dose-response relationship was also analyzed, and a midlife systolic BP greater than 130 mmHg was associated with an increased risk of cognitive disorders [14]. The follow-up Honolulu-Asia Aging Study, including 2,505 male participants aged 71 to 93 years, showed that pulsatile pressure was not associated with the incidence of dementia; however, midlife systolic BP was the strongest predictor of dementia incidence [15]. Another study investigated the interactive effects of apolipoprotein E ε4 (APOE-ε4) and hypertension on cognitive decline and brain atrophy. In that study, hypertension was associated with early cognitive decline and brain atrophy in mid-to-late life, particularly in APOE-ε4 carriers [16].

In addition, an U-shaped relationship between hypertension and dementia incidence was reported in a longitudinal population-based study [17]. Low diastolic BP in late life is also associated with an increased risk of AD [18].

**Characteristic cognitive dysfunction domains in hypertension**

Cognitive impairments in hypertension can occur across multiple neuropsychological domains, including learning and memory, attention, abstract reasoning, mental flexibility, psychomotor skills, and visuospatial functioning [19]. Although cognitive impairment associated with hypertension may be global, when a more detailed neuropsychological battery is implemented and hypertension-specific effects are considered and compared, the greatest impact of hypertension is on executive function [6], motor speed, and attention [20]. Other studies have reported that hypertensive cerebrovascular disease generally causes damage to the prefrontal subcortex, making it difficult to form goals, abstract, initiate, plan, organize, and sequence [19,21,22]. These characteristic cognitive domains are thought to be involved in subcortical diseases such as classical vascular disease and pure vascular dementia [23]. Although these impairments in executive or prefrontal lobe function usually mask the memory impairment characteristic of AD, impairments in these two cognitive functions often co-occur. Memory impairments in hypertension often tend to be characterized by impairments in recall, but relatively intact recognition, benefit from cues and mild forgetfulness [13].

In a cross-sectional cohort study of 67 patients aged 60 years and older who were hypertensive with MCI or subjective cognitive problems, markers of beta-amyloid retention were associated with worsening episodic memory. In contrast, high white matter intensity, a marker of subcortical ischemic injury, was not associated with performance in any cognitive domain [24]. Because the function of the prefrontal cortex is dependent on the integrity of the cortical-striatal loop through the prefrontal white matter, this type of lesion is very likely to cause a decline in working memory, executive function, and other cognitive abilities assisted by the prefrontal cortex [25]. Therefore, it can be hypothesized that subcortical cerebrovascular disease is more likely to cause cognitive symptoms that are distinguishable from those of AD [26]. Neuropsychological studies of clinically diagnosed patients have reported that compared to patients with AD, patients with vascular dementia performed better on memory tests and poorer on executive function tests. This observation suggests that predominant executive dysfunction may serve as a useful diagnostic marker of vascular dementia. However, a study of 62 autopsy cases showed that major memory impairment was present in 71% of AD cases and predominant executive dysfunction accounted for only 45% of cerebrovascular diseases [26]. In contrast, within large groups that are likely to overlap with the pathology of AD, distinguishing subtypes of dementia based on patterns in impaired cognitive domains is diffi-
difficult in individuals with mixed MCI and dementia conditions. Finally, a recent meta-analysis showed an association between midlife hypertension and overall cognitive and executive function but not memory [14].

Possible cognitive disorder associated with hypertension

Hypertension has been implicated in various neurocognitive disorders ranging from mild to major [27]. A clear pathophysiological process of vascular dementia in hypertension has been reported [28]. However, hypertension has also been considered a risk factor for AD, although this relationship has not been as clearly elucidated as that between hypertension and vascular dementia [29,30]. In one study, 1,385 participants with a diagnosis of MCI were analyzed to determine whether the degree of high BP was associated with a faster decline in certain cognitive function domains. There were significant main effects of high BP (systolic BP of ≥ 140 mmHg or diastolic BP of ≥ 90 mmHg) on neuropsychological measures of visuomotor sequencing, set shifting, and naming. It showed that high BP is associated with a faster decline in cognitive function in people at risk of dementia [31]. Another prospective community-based cohort study also showed that hypertension was related to an increased risk of MCI, and this relationship was stronger in patients with non-amnestic MCI [32].

A significant association was found between frontotemporal dementia and type 2 diabetes [33]. However, in a cohort study, hypertension and other cerebrovascular risk factors were not identified as risk factors for frontotemporal dementia [34]. In a population-based study, hypertension significantly increased the risk of both AD and diffuse dementia with Lewy body (DLB). However, the relationship between hypertension and DLB has been less studied [35]. Finally, a retrospective study investigating BP difference among individuals with different dementia disorders, found that for those patients over 80 years of age, BP did not differ as a function of various dementia disorders [27,34].

In summary, there is strong evidence of an association between vascular dementia and hypertension. However, high BP may contribute to other neurocognitive disorders, such as AD and DLB. Hypertension can negatively affect MCI and shorten the transition to major neurocognitive impairment (Table 1).

Pathophysiology

Chronic hypertension is associated with adaptive and degenerative structural changes in the cerebral vessels. These structural changes initially reflect an adaptive response to protect the downstream microvessels from increased transwall pressure. However, this process becomes maladaptive over time. The mechanism of pathological changes associated with hypertension includes vascular remodeling and stiffening, cerebral autoregulation impairment, microbleeding and microinfarction, white matter lesions, lacunar infarction, amyloid angiopathy, and cerebral atrophy [23,36-43]. Brain atrophy, microinfarction, and microhemorrhage can cause nerve cell loss and impaired brain function. In addition, microinfarction and microhemorrhage disrupt brain connectivity and reduce efficiency of the network. Damage to white matter specifically reduces network connectivity, particularly in the thalamic cortical circuit [23,44]. Alterations in the perivascular space can impair brain clearance and promote the accumulation of proteins in the brain and blood vessels. Dysfunction of the neurovascular unit is linked to vascular dysfunction and blood-brain barrier damage [23,45]. Oxidative stress, hypoxic ischemia, inflammation, and blood-brain barrier dysfunction are important vascular factors that threaten the integrity and function of the subcortical white matter. There are possible regional differences in the effects of hypertension on white matter, and white matter in the frontal lobe may be more affected [46,47].

Epidemiological studies have shown that hypertension is a risk factor for vascular cognitive impairment and AD. The effects of hypertension on vascular pathologies have been quite clearly established; however, its impact on AD pathologies is unclear and controversial. In a prospective cohort study of 346 subjects, a cumulative number of midlife vascular risk factors were associated with elevated brain amyloid deposition in late life [48]. However, hyper-

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**Table 1.** Cognitive domains and disorders associated with hypertension

<table>
<thead>
<tr>
<th>Characteristic cognitive dysfunction domains</th>
<th>Greater impact on frontal lobe executive function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal formation</td>
<td>Abstract thinking</td>
</tr>
<tr>
<td>Initiating</td>
<td>Planning</td>
</tr>
<tr>
<td>Organizing</td>
<td>Sequencing</td>
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<tr>
<td>Performed better on memory tests</td>
<td>Impairments in recall</td>
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<tr>
<td></td>
<td>Relatively intact recognition</td>
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<td></td>
<td>Benefit from cues</td>
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<tr>
<td></td>
<td>Mild forgetfulness</td>
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<tr>
<td>Cognitive disorders (the strength of the association is in the order listed)</td>
<td>Vascular dementia</td>
</tr>
<tr>
<td></td>
<td>Alzheimer disease</td>
</tr>
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<td></td>
<td>Dementia with Lewy body</td>
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https://doi.org/10.12701/jyms.2022.00605
tension itself was not significantly associated with elevated amyloid deposition. Another study evaluating the effect of vascular health on AD imaging biomarkers showed that vascular health had a significantly larger effect on neurodegeneration than on amyloid deposition [49]. In a study of 1,300 deceased participants, some associations were found between systolic BP and neurofibrillary tangles [49,50]. A cerebrospinal fluid biomarker study also found that hypertension was not associated with amyloid-beta 1–42, and that APOE did not have a modifying effect. However, hypertension was directly related to tau, and ptau-181 was modified by the APOE genotype [51]. These findings suggest that hypertension is associated with AD but affects the disease through a pathway different from that involved in amyloid pathology. Unlike clinical studies, experimental studies have suggested that hypertension can contribute to both amyloid and tau pathology in AD, although whether hypertension is a contributor or pathological factor needs to be determined [52-55].

In a longitudinal, prospective, population-based study, men with hypertension who were middle-aged and did not receive antihypertensive treatment had a higher risk of hippocampal atrophy than age-matched men with normal BP. Treatment with antihypertensives reduced the risk associated with these high BPs [56]. These findings suggest that the management of hypertension to lower the risk of AD is important, although the magnitude of the effect of hypertension on AD could be smaller than that on vascular dementia (Fig. 1).

Antihypertensive effects on cognitive function

Data from randomized controlled clinical trials on the efficacy of antihypertensive therapy for the prevention of dementia are contradictory [57-63]. A meta-analysis, including nine randomized controlled trials with 34,994 participants (> 60 years) treated for at least 12 months, showed that antihypertensive treatment could reduce cognitive decline with modest effect sizes and did not worsen cognitive dysfunction [64]. Another meta-analysis demonstrated the benefits of antihypertensives. Compared to controls, a drop in

Fig. 1. Pathophysiology of cognitive dysfunction associated with hypertension.

Cheon. Hypertension and cognitive dysfunction
BP was significantly associated with a reduced risk of dementia or cognitive impairment (12 trials, 92,135 participants) [65]. A recent review argued that the correlation between BP and cognitive decline was U-shaped and varied according to age. That is, high BP in middle age may be related to cognitive decline in old age, while hypertension in old age may be less related to cognitive decline. In addition, excessively low BP may be associated with cognitive decline; therefore, these U-shaped associations may neutralize the outcomes [18,66]. Subdivided age-specific studies and studies that removed these confounding factors more consistently showed the effects of hypertension on cognitive dysfunction and the ability of antihypertensive drugs to lessen cognitive decline. There is evidence that all effective BP-lowering drugs, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, and aldosterone antagonists, can be used to prevent cognitive decline in patients with hypertension and there is no evidence for a difference in effectiveness between these antihypertensives [58,60,67-74]. In addition, a meta-analysis of AD risk factors investigated the relationship between antihypertensive drugs and the risk of cognitive decline. This meta-analysis found that antihypertensive treatment was one of the protective factors for AD with grade I evidence (pooled population of > 5,000 individuals) [75].

Conclusion

In this review, we discussed previous studies on hypertension-related cognitive dysfunction. Epidemiological data have shown that midlife hypertension is associated with late-life cognitive impairment. These cognitive disorders encompass both mild and major neurocognitive disorders. Hypertension showed the strongest association with vascular dementia, followed by AD and DLB. Frontotemporal dementia showed no evidence of an association. Hypertension was found to be the most consistent risk factor for dementia only at a certain age; that is, middle-aged hypertension was a risk factor for late-life dementia. In addition, hyptension in old age can be a risk factor for cognitive decline along with hypertension; therefore, BP and cognitive decline have an U-shape relationship. Considering these two characteristics will enable a more consistent interpretation of the mixed research results. Cognitive decline related to hypertension is possible in all areas, however, the decline in executive function related to the frontal lobe is particularly noticeable. This is consistent with the characteristics of vascular dementia, but there are many cases in which AD and vascular dementia coexist in clinical practice, making it difficult to diagnose patients with only these cognitive function characteristics. Many studies have been conducted on the mechanisms by which hypertension causes cognitive decline, including brain atrophy, microinfarcts, microbleeds, neuronal loss, white matter lesions, network disruption, neurovascular unit damage, reduced cerebral blood flow, blood-brain barrier damage, enlarged perivascular damage, and proteinopathy. Medications, lifestyle, and comorbidities, such as diabetes and hyperlipidemia, may have indirect effects in addition to the direct pathophysiology of high BP causing cognitive dysfunction. Hypertension is also a risk factor for other diseases that cause cognitive decline, such as chronic kidney disease or heart failure. Although these factors were identified as confounding factors in the studies included in this review and corrections were made, a more detailed study and review are required in the future. Recent meta-analyses have demonstrated that antihypertensive drugs can reduce the risk of cognitive decline and dementia. Therefore, hypertension is an important risk factor for cognitive decline and dementia and is clinically meaningful because it can be controlled and treated. Considering the high prevalence of both conditions and the serious impact of cognitive function on quality of life, active and timely management of hypertension is required. Additional research is needed, such as a study to determine the optimal BP according to age, which would be helpful for cognitive function, and a therapeutic alternative to address the pathophysiological changes in the brain caused by hypertension.

Notes

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

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The purpose of this study aims to analyze research trends related to ‘evaluation’ in Korean medical education through a systematic review. This study used a systematic review method, which is a research methodology for research trends and ‘literature analysis.’ Researchers searched the Korean journal literature published until the end of December 2020 in the Korean research database with keywords related to medicine and evaluation. Thus, 5,205 cases were identified. Based on these data, 143 papers were selected through a logical screening process, requiring 1 month to complete the data search and analysis process. In terms of publications, medical journals overwhelmingly outnumbered nonmedical journals until 2015; however, after 2016, the number of papers published in nonmedical journals increased, and the number of published papers was similar to that of medical journals. In terms of evaluation-related research, research on student and program evaluations has been very active compared to that on accreditation. As the number of evaluation studies has gradually decreased over the past 10 years, preparing a plan to revitalize them in Korean medical education is necessary. Considering that the role of evaluation in education has been emphasized in recent years, research on reestablishing the concept of evaluation; developing evaluation indicators; analyzing the status of student evaluation, program evaluation, and accreditation; and deriving measures to improve medical education through evaluation is required.

Keywords: Accreditation; Educational measurement; Medical education; Systematic review

Introduction

In Korean education, evaluation was mainly used to describe a test for students in schools [1]. However, the meaning and role of evaluation has been expanding recently because of increased interest in evaluation for academic characteristics. Thus, institutions in charge of the professional evaluation of educational programs have been established, and the purpose of these institutions is the quality management and certification of educational programs [1,2]. Because Korean medical education focuses on the transfer of knowledge and student academic achievement is judged only by intellectual abilities [3], evaluation targets are often limited to students. However, interest in the role or meaning of evaluation in medical education increased as the Korean Institute of Medical Education and Evaluation (KIMEE) played a role in managing the quality of medical education and accrediting medical schools. According to the development history of education evaluation outlined by Lee [4], education evaluation began to be known as an independent discipline in the early 20th century, and the meaning of education evaluation expanded and changed as follows. While...
early educational evaluation focused on measuring characteristics of the subject being evaluated, second-generation educational assessment focused on comparisons between the actual data obtained and the description of the behavior a student exhibits when successfully completing a curriculum or program. Third-generation educational evaluation focused on experts making professional judgments on the evaluation target. Fourth-generation educational evaluation focused on the role of the evaluator in responding to the needs of stakeholders, gathering agendas to be managed in the negotiation process from a phenomenological perspective, providing information needed by the stakeholders, and guiding the adjustment of opinions. With the introduction of performance-based education aimed at complete learning and norm-oriented evaluation in medical education [5], it is inevitable that educational evaluation activities take place throughout the course of medical education. (1) Before class: are the process outcome establishment and class design suitable? (2) In class: are students achieving the learning objectives? If not, what improvements can be undertaken? If objectives are being achieved, how can further improvements be implemented? (3) After class: students, subject, curriculum, and overall evaluations of medical school education are implemented. Evaluation studies of Korean medical education are ongoing; therefore, researchers in the field intend to analyze how evaluation studies are being conducted in Korean medical education.

The purpose of this study was to collect basic data for research on the improvement in medical education through evaluation because the meaning and role of evaluation has expanded in Korea after the introduction of the performance-based paradigm, evaluation, and certification system in medical education. In this regard, this study aimed to identify research trends in the evaluation of Korean medical education in the 21st century.

**Design**

1. **Study design and literature search**

This study analyzed research trends in the evaluation of Korean medical education by searching papers on subject words related to medical education and evaluation in January 2021. The research databases were the Korea Education and Research Information Service (www.riss.kr/index.do), National Assembly Library (www.nanet.go.kr), Koreanstudies Information Service System (https://kiss.kstudy.com/), and Academic Education Center (www.earticle.net). The search keywords were “medical education” & “evaluation,” “medical school” & “evaluation,” and “me-di-school” & “evaluation.”

2. **Selection and exclusion criteria**

The selection criteria for the publications extracted in this study were as follows. First, the keywords were limited to Korea, medical education, and evaluation, and the presentation period was not limited. Second, this study was aimed at academic journals (except for candidate papers, research reports, posters, conference presentations, books, internet materials, and other types of research) of Korea Citation Index (KCI)-registered (candidate) journals or higher. Third, only subjects that were confirmed to be originally written in Korean were included. Fourth, the subjects of the evaluation study were limited to students associated with basic medical education (BME) and medical schools, and data from major doctors and patients were excluded.

The research problem of this study was the analysis of research trends, subjects, and results regarding the evaluation of Korean BME. To answer this research question, two analysts reviewed and discussed the collection and selection of literature, derivation of analysis criteria, and coding and analysis of results. This study was conducted in the following manner according to the standards of systematic review suggested by Cook et al. [6].

First, the bias and subjectivity of the study were removed based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [7]. Second, the research issues were clarified by analyzing the trends, subjects, and results of evaluation research in Korean BME. Third, the literature search, literature selection, analysis results, and discussion were conducted to draw a comprehensive conclusion by selecting appropriate literature and analyzing its research content.

As a result of searching the database according to the scope and criteria of our analysis, 5,205 papers were identified, 3,199 papers were selected through the first screening process, 242 papers were selected through the second screening process, and 143 papers were selected through the final selection process (Fig. 1, Supplementary material 1).

3. **Measured outcomes**

In this study, three variables were derived: student evaluation, program evaluation, and accreditation. As there was no previous study with the same purpose, two Doctors of Education with more than 3 years of medical education participated as analysts. The researchers reviewed and discussed the literature collection and selection, analysis standards derivation, coding, and analysis results through online and offline meetings.

**Literature related to evaluation**

The research team reviewed 143 papers that were extracted based
on evaluation of Korean medical education and classified them into three categories according to the subject of evaluation: student evaluation, program evaluation, and accreditation (Table 1). The literature was classified as follows. (1) Student evaluation: literature that evaluated or researched student-learning abilities. (2) Program evaluation: literature that evaluated or researched educational programs, including subjects or curricula. (3) Accreditation: studies on BME accreditation or KIMEE, an institution for the accreditation of medical education evaluation.

The 143 papers extracted were classified into 67 papers related to student evaluation (46.9%), 62 related to program evaluation (43.4%), and 14 related to accreditation (9.8%). According to the distribution of journals in which the 143 extracted papers were published, 73 papers (51.0%) were published in the Korean Journal of Medical Education (KJME), followed by 28 papers (19.6%) in the Korean Medical Education Review (KMER) (Table 2).

Literature related to student evaluation

Among the 143 papers, 67 (46.9%) were related to student evaluation. Among them, publications from 2001 to 2005 were the most common, followed by those from 2006 to 2010 (Table 1). The 67 student evaluation-related papers were classified into seven categories according to research content: knowledge evaluation, skill evaluation, attitude evaluation, development of teaching methods and evaluation tools, information and communication technology (IT), item analysis, and other evaluations. Papers included in each category were as follows: (1) knowledge evaluation: a study on ‘interstation works’ among academic achievement, clinical comprehensive, and clinical performance evaluations; (2) skill evaluation: research on clinical performance evaluation and clinical practice; (3) attitude evaluation: studies on relationships between patients and doctors in medical professionalism, self-directed learning, and

Fig. 1. Strategy of the scoping review. KCI, Korea Citation Index.
clinical performance evaluation; (4) development of teaching methods and evaluation tools: research on standards, scales, and new teaching methods; (5) IT: research on computer-based tests, e-portfolio evaluation, and video evaluation; (6) item analysis: studies on item quality, psychometric analysis, and ability parameters; and (7) other evaluations: papers that did not correspond to the previously classified categories, such as how to use peer evaluation in problem-based learning (PBL). Most papers analyzed the validity of the evaluation tool rather than the evaluation content. As a result of the classification, skill evaluation was the most common, with 18 papers (26.9%), followed by other evaluations, with 12 papers (17.9%) (Table 3). According to the distribution of the 67 papers by journal, there were 38 papers (56.7%) in KJME, followed by 10 papers (14.9%) in KMER (Table 4).

## Literature related to program evaluation

Among the 143 total papers, 62 (43.4%) were related to program evaluation, and among them, publications from 2006 to 2010 (n = 22) were the most common, followed by those from 2001 to 2005 (n = 20) (Table 1). The research team reviewed 61 program evaluation-related studies and reclassified them into the following nine categories: (1) evaluation for curriculum; (2) evaluation for clinical practice education (evaluation for clinical practice); (3) evaluation for medical humanity education (evaluation for medical humanities); (4) evaluation for other single education subjects/courses excluding clinical practice and medical humanity education programs (evaluation for other single education subjects/courses); (5) clinical performance assessment-applied evaluation (evaluation for clinical performance assessment); (6) PBL-applied

### Table 1. Analysis of literature related to evaluation in medical education by year

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<td>Accreditation</td>
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<td>4 (2.8)</td>
<td>14 (9.8)</td>
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<tr>
<td>Total</td>
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<td>45 (31.5)</td>
<td>42 (29.4)</td>
<td>23 (16.1)</td>
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</table>

Values are presented as number (%).

### Table 2. Analysis of literature related to evaluation in medical education by published journal

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<td>10 (7.0)</td>
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<tr>
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<td>42 (29.4)</td>
<td>23 (16.1)</td>
<td>26 (18.2)</td>
<td>143 (100)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

program evaluation (evaluation for PBL programs); (7) evaluation for lecture assessment; (8) indicator/conformance development and validation; and (9) others. The categories with the most papers were clinical practice program evaluation, medical humanities program evaluation, and lecture evaluation, each of which contained 10 papers (16.1% each) (Table 5). According to the distribution of the 62 papers by journal, there were 30 publications (48.4%) in KJME, followed by 10 publications (16.1%) in KMER (Table 6).

### Literature related to accreditation

Fourteen out of 143 papers (9.8%) were related to accreditation. The literature related to accreditation was reviewed and reclassified into the following three categories: (1) utilization and development direction of accreditation; (2) accreditation of medical education by KIMEE; and (3) development/validation of accreditation standards. As a result, the category with the highest number of accreditation-related publications was use and development direction of accreditation at nine (64.3%), and there were three publications (21.4%) in development/validation of accreditation standards (Table 7). According to the distribution of accreditation-related papers published by the journal, KMER accounted for the majority, with eight (57.1%), followed by five (35.7%) in KJME, and one (7.1%) in the Journal of the Korean Medical Association (Table 8).

### Conclusion

This study aimed to identify research trends in the evaluation of Korean medical education. For this purpose, 143 papers were found by searching for publications related to evaluation in the medical field among papers published in domestic certified academic journals from 1995 to 2020. These papers were analyzed in relation to the publication year, journal, and research topic.

The results related to the publication year of the study were as follows. Among the 143 searched papers, 95% were published after 2000, and 62% were published during the first decade of the 21st century (2001–2010). In other words, interest in evaluation-related research in Korean medical education emerged at the beginning of the 21st century. As a result of dividing the papers into three areas (student evaluation, program evaluation, and accreditation) according to the evaluation target, there were few published papers in the 20th century, but there were relatively many papers on accredi-
### Table 5. Literature analysis related to program evaluation by year

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<td>1 (1.6)</td>
<td>10 (16.1)</td>
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<td>10 (16.1)</td>
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<td>3 (4.8)</td>
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<td>7 (11.3)</td>
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<td>5 (8.1)</td>
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<td>3 (4.8)</td>
<td>5 (8.1)</td>
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<tr>
<td><strong>Total</strong></td>
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<td>22 (35.5)</td>
<td>5 (8.1)</td>
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Values are presented as number (%).

PBL, problem-based learning.

### Table 6. Analysis of literature related to program evaluation by published journal

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<td>4 (6.5)</td>
<td>6 (9.5)</td>
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<tr>
<td><strong>Total</strong></td>
<td>2 (3.2)</td>
<td>20 (32.3)</td>
<td>22 (35.5)</td>
<td>5 (8.1)</td>
<td>13 (21)</td>
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</table>

Values are presented as number (%).


### Table 7. Analysis of literature related to evaluation and certification by year

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<td>4 (28.6)</td>
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<td>1 (7.1)</td>
<td>4 (28.6)</td>
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</table>

Values are presented as number (%).

KIMEE, Korean Institute of Medical Education and Evaluation.

### Table 8. Analysis of literature related to evaluation certification by published journal

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<td>1 (7.1)</td>
<td>4 (28.6)</td>
<td>14 (100)</td>
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Values are presented as number (%).


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https://doi.org/10.12701/jyms.2022.00563
tation. In 2000, as we entered the 21st century, research on student and program evaluations increased explosively in the first 10 years. While the number of papers related to program evaluations has continued to increase in the past 5 years, the number of studies related to student evaluations has decreased.

The results related to journals were as follows. Most of the 143 papers (83.2%) were published in medical journals, including KJME (51.0%) and KMER (19.6%). However, recently, the number of papers published in KJME has gradually decreased, and no papers have been published in KJME in the last 5 years. Conversely, the number of papers published in KMER in the last 5 years has increased, and most evaluation-related papers in medical journals in the last 5 years have been published in medical journals. There were no papers published in nonmedical journals before 2000; however, in the 21st century, the number of papers published in nonmedical journals has gradually increased, and in the last 5 years, the number of papers similar to those published in medical journals has been increasing. Thus, it can be seen that researchers wanting to publish evaluation-related papers are more interested in nonmedical journals than in medical journals.

The results related to research topic analysis were as follows. Papers related to student evaluation were classified into seven categories according to their content: knowledge evaluation, skill evaluation, attitude evaluation, teaching method and evaluation tool development, IT, item analysis, and other evaluations. As a result, papers on skill evaluation accounted for the greatest number at 26.9%, and there were no other research topics that were particularly interested in research. The skill evaluation category includes research related to clinical performance and clinical practice evaluations. Student-evaluation-related papers were published the most frequently in KJME, followed by KMER.

However, looking at the trend over the past 5 years, the number of published papers related to student evaluations has sharply decreased. In addition, while no papers were published in KJME, most were published in KMER and nonmedical journals. Papers related to program evaluation were classified into the following nine categories: (1) evaluation for curriculum; (2) evaluation for clinical practice education (evaluation for clinical practice); (3) evaluation for medical humanity education (evaluation for medical humanities); (4) evaluation for other single education subjects/courses excluding clinical practice and medical humanities education programs (evaluation for other single education subjects/courses); (5) clinical performance assessment-applied evaluation (evaluation for clinical performance assessment); (6) PBL-applied program evaluation (evaluation for PBL programs); (7) evaluation for lecture assessment; (8) indicator/conformance development and validation; and (9) others. As a result, it was found that most papers were published in evaluation for clinical performance assessment, evaluation for medical humanities, lecture evaluation, and program evaluation; program evaluation was conducted in various other fields. The distribution by journal of the 62 publications related to program evaluation was found to be the highest for KJME, followed by KMER. However, over the past 5 years, the number of papers related to program evaluation has sharply declined, with no published papers in KJME and two papers published in KMER; papers published in nonmedical journals accounted for the majority during this time period.

The 14 papers related to accreditation were divided into three periods: before 2000, 2001 to 2005, and 2016 to 2020. Before 2000, all of these publications focused on the use of accreditation and direction of development. From 2001 to 2005, all papers were related to KIMEE medical education accreditation. From 2016 to 2020, all published papers were related to the use of accreditation and direction of development. Looking at the 14 papers related to accreditation by published journals, it can be seen that KMER published more papers than KJME. In particular, papers published before 2000 and between 2016 and 2020 were published in KMER, and all papers published between 2001 and 2010 were published in KJME.

Supplementary materials

Supplementary material 1 can be found via https://doi.org/10.12701/jyms.2022.00563.

Notes

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

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Author contributions
Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Validation, HJP, YRK; Project administration, Visualization: YRK; Writing-original draft: HJP, Writing-review & editing: HJP, YRK.
References

Advances in management of pediatric chronic immune thrombocytopenia: a narrative review

Jae Min Lee
Department of Pediatrics, Yeungnam University College of Medicine, Daegu, Korea

Immune thrombocytopenia (ITP) is a disease in which thrombocytopenia occurs because of immune-mediated platelet destruction and decreased platelet production. Although many pediatric patients with ITP experience spontaneous remission or reach remission within 12 months of first-line therapy, approximately 20% progress to chronic ITP. Patients who do not respond to first-line treatment or experience frequent relapses are of great concern to physicians. This review summarizes recent treatments for second-line treatment of pediatric chronic ITP.

Keywords: Dapsone; Idiopathic thrombocytopenic purpura; Rituximab; Splenectomy; Thrombopoietin

Introduction

Immune thrombocytopenia (ITP) is a disease in which thrombocytopenia occurs because of immune-mediated platelet destruction and decreased platelet production. The overall pediatric ITP incidence in Korea is 18.1 per 100,000 person-years [1].

The generation of antiplatelet autoantibodies is thought to be a fundamental event in ITP, although the pathophysiology of this condition is not fully understood [2]. Through the activation of Fc receptors, these autoantibodies target platelets for destruction by macrophages in the spleen, liver, or both. Spleen tyrosine kinase regulates this process. The ability of megakaryocytes to produce platelets may be inhibited by the autoantibodies, which can kill platelets in other ways. Major histocompatibility complex class II delivers antigens from phagocytosed platelets to T-cell receptors, activating autoreactive T cells. T helper (Th) cells in ITP are skewed toward type 1 (Th1) and type 17 (Th17) phenotypes, and regulatory T cell activity is decreased. These T-cell alterations are thought to be pathologic.

Bleeding that requires treatment occurs in 30% to 56% of patients with newly diagnosed pediatric ITP [3-5], and bleeding that requires immediate management is reported in up to 4% of all patients with ITP. Fatal intracranial hemorrhage is reported in up to 3% of all patients with ITP [6-13]. It is known that approximately 2/3 of adult ITP cases progress to chronic ITP, but 20% to 25% of pediatric ITP cases persist to chronic ITP [14]. This review summarizes recent treatments for pediatric chronic ITP.

Definition of chronic immune thrombocytopenia

According to the definition of an international working group, ITP is categorized as newly diagnosed, persistent, or chronic according to disease duration. Newly diagnosed ITP is diagnosed within 3
months of onset, persistent ITP has lasted between 3 and 12 months, and chronic ITP is defined as ITP lasting more than 12 months [15].

**Natural course of immune thrombocytopenia**

Three percent to 10% of cases are children with one or more comorbidities, and ITP in children is often acute and resolves spontaneously [16,17]. According to data from the Pediatric and Adult Registry on Chronic ITP, 70% of patients had spontaneous remission within 6 months, and the mean age of patients with late remission at 12 and 24 months was higher than that of children with early remission at 6 months. Twenty-eight percent of pediatric patients with chronic ITP achieved remission within 24 months.

ITP often has a benign course in pediatric patients, and 86% of these patients fully recover within 1 year of diagnosis. After extensive follow-up, children with chronic ITP display a high rate of remission [18].

At 2 and 5 years after diagnosis, the chances of complete remission of chronic ITP were 50% and 76%, respectively [19]. Three to 4 years after diagnosis, approximately 45% of children with chronic ITP spontaneously improve, while 2/3 of patients continue to have a platelet count below 50 × 10^9/L [20].

**Diagnostic approach for patients with chronic immune thrombocytopenia**

Bone marrow aspiration and biopsy are not required in children with newly diagnosed ITP who show isolated thrombocytopenia on complete blood count and no abnormalities other than evidence of thrombocytopenia on blood smear or physical examination. Bone marrow examination is not necessary, even when considering second-line therapy [21,22]. According to the recent American Society of Hematology (ASH) guidelines, if spontaneous platelet increase is not observed for 3 to 6 months or more or does not respond to treatment, bone marrow aspiration, biopsy, and cytogenetics should be performed. Next-generation sequencing or targeted sequencing should be considered [23]. Tests for autoimmune diseases such as lupus (antinuclear antibody, antcardiolipin antibody, and lupus anticoagulant) that require immunosuppressive treatment and tests for chronic infections caused by, for example, hepatitis virus, cytomegalovirus, human immunodeficiency virus, and Helicobacter pylori are also required.

**Management of chronic immune thrombocytopenia**

1. **Thrombopoietin receptor agonists**

   Thrombopoietin is a major factor that regulates megakaryocyte production. The main mechanism of action of thrombopoietin receptor agonists (TPO-RAs) is to stimulate bone marrow megakaryocytes [24,25]. Eltrombopag and romiplostim are TPO-RA drugs approved by the U.S. Food and Drug Administration for use in children. Both drugs showed efficacy and safety compared with placebo in children, but no clinical trials comparing the two drugs have been conducted. The ASH 2019 guidelines recommend the use of TPO-RA rather than rituximab in children with ITP who do not respond to first-line treatment [26].

2. **Eltrombopag**

   Eltrombopag is a once-daily, oral TPO-RA requiring some dietary restrictions. Peak levels are obtained 2 to 6 hours after oral ingestion. After a single oral dose of 75 mg, the bioavailability was > 52%. When taking eltrombopag with a high-fat, high-calcium diet versus on an empty stomach, the area under the curve decreased by 59%, the maximum serum concentration (C_{max}) decreased by 65%, and the time to reach C_{max} was delayed by 1 hour [27]. Additionally, eltrombopag is metabolized in the liver, and its half-life ranges from 21 to 32 hours [28]. The dose of eltrombopag depends on the patient’s age, ethnicity, and hepatic function. In addition, the dose should be adjusted according to platelet response (maximum dose, 75 mg/day).

   The efficacy and safety of eltrombopag in children were verified in two multicenter randomized trials, PETIT and PETIT2 [29,30]. Eltrombopag showed response rates of 62% in PETIT and 75% in PETIT2. It also showed a reduction in bleeding events and the requirement for additional treatments. The median time to response was 12 to 20 days depending on the patient’s age.

   In a recent retrospective multicenter study conducted in 17 centers affiliated with the Italian Association of Pediatric Hematology and Oncology, 68% and 44% of patients achieved platelet counts of 30 × 10^9/L and 100 × 10^9/L, respectively [31].

3. **Romiplostim**

   In a phase 1/2 trial with children, romiplostim showed an improvement in platelet counts compared with that of placebo [32]. In that study, 88% of patients in the romiplostim group had platelet counts ≥ 50 × 10^9/L and 20 × 10^9/L above baseline for 2 consecutive weeks. In contrast, none of the patients in the placebo group showed improvement. In the open label extension study after the
phase 1/2 trial, the median average weekly dose was 5.4 μg/kg [33]. In a phase 3 trial, romiplostim showed a high rate of platelet response and reduced rate of bleeding events in pediatric patients with chronic ITP [34]. A durable platelet response was achieved in 52% of patients in the romiplostim group compared with 10% in the placebo group.

The starting dose is 1 μg/kg/week and is increased by 1 μg/kg/week according to the platelet count to a maximum of 10 μg/kg/week. The goal is to determine the minimum dose that maintains a platelet count of at least 50 × 10^9/L. If there is no response after 4 weeks of maximum weekly dosing, other treatments should be considered.

Unlike eltrombopag, romiplostim is not affected by diet. It is known that the serum concentration of the drug is the same in adults and in children over 1 year of age. Platelet production peaks on days 8 to 15 after romiplostim injection and returns to baseline on days 22 to 28 [35]. In an adult study, 32% of patients maintained a platelet count of > 50 × 10^9/L after discontinuing romiplostim following 12 months of treatment [36]. Romiplostim was also effective in patients with an ITP duration of ≤ 1 year who failed first-line treatment [37]. In the pediatric study, there were no treatment-related serious adverse events. Headache and epistaxis are the most common side effects in both pediatric and adult patients [32-34]. Bone marrow examination was not routinely performed in pediatric studies despite the controversial issue of bone marrow fibrosis in adults. However, no bone marrow reticulin or fibrosis was observed in five bone marrow biopsies performed in the pediatric extension study [33].

4. Rituximab

Rituximab is a monoclonal antibody against CD20+ B cells that produce autoantibodies to platelets [38]. Rituximab is infused at 375 mg/m² once weekly over 4 weeks [39-42]. Rituximab produced a complete response in 22% to 79% of pediatric patients with ITP. The 58% of patients who responded to rituximab maintained platelet counts of > 50 × 10^9/L for at least 1 year after rituximab treatment, and 25% to 30% maintained a response for more than 5 years. Most patient relapse occurred within 2 years [43,44]. Rituximab, when administered in combination with dexamethasone in adults, showed superior effects compared to dexamethasone alone [45-47]. In a study in which rituximab and dexamethasone were combined in children, 30% of patients showed prolonged remission after treatment with a standard dose of rituximab and 4 days of dexamethasone [48]. Reported toxicities of rituximab, including neutropenia, infection, hypogammaglobulinemia, and infusion-related reactions, were minimized with steroid premedication.

5. Dapsone

Dapsone is an inexpensive and effective therapeutic option for the treatment of chronic ITP. Since it was first known to be effective against chronic ITP in 1988, dapsone has been one of the oldest and safest agents in the management of chronic ITP [49]. The mechanism of action of dapsone is not well understood. Hemolysis caused by dapsone is known to interfere with platelet destruction in the reticuloendothelial system and suppress antiplatelet antibodies.

Dapsone has a response rate of 50% to 72%, a complete response of 20% to 48%, and a partial response of 17% to 48% [50-52]. The duration to response is approximately 1 to 3 months, and the relapse rate is approximately 10% to 20%. As well-known hematologic adverse effects, methemoglobinemia and hemolysis occur in 10% to 20% of cases. Rarely, agranulocytosis and aplastic anemia may also occur, and characteristic hypersensitivity reactions such as fever, eosinophilia, and skin rash may occur with dapsone [50-52].

There are few reports on the use of dapsone in children. However, because it is a drug whose safety has been verified for a long time, it is worth considering as an alternative if the disease is refractory to other treatments.

6. Splenectomy

Splenectomy is an effective therapeutic option for children with chronic ITP. Recently, TPO-RAs and rituximab have been preferred, and splenectomy is performed less frequently today. Owing to the development of new treatments, approximately 90% of patients now show complete remission, and less than 5% of patients show refractoriness.

The splenectomy registry of the Intercontinental Cooperative ITP Study Group collected the splenectomy data of pediatric patients with ITP. The overall response rate was 93%, and 81% of patients showed complete response. Of the latter patients, 76% showed a sustained complete response and 24% showed fluctuation of platelet counts to < 100 × 10^9/L [53].

Although there is a low risk of perioperative adverse events, the long-term outcomes and quality of life should be considered. Fatal sepsis and lifelong susceptibility to bacterial infection are of concern. The incidence of sepsis and venous thromboembolism in adults with ITP is approximately 10%, and age and comorbidities are important factors [54]. Prognostic factors that can be expected for remission after splenectomy are older patient age and good response to intravenous immunoglobulin and steroids in children [55-59].
**Conclusion**

The clinical course and treatment of chronic ITP were reviewed. Due to the recent introduction of TPO-RAs in the treatment of pediatric chronic ITP, the health-related quality of life of pediatric patients with chronic ITP has improved compared to that of patients receiving conventional treatment [60-62]. However, further studies on the treatment effects of drugs and prognostic factors should be conducted. Pediatric chronic ITP treatment should be individualized and based on the risks and benefits of treatment.

**Notes**

**Conflicts of interest**

Jae Min Lee has been an editorial board member of *Journal of Yeungnam Medical Science* since 2021. He was not involved in the review process of this manuscript. There is no conflicts of interest to declare.

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**Effects of propofol-remifentanil versus sevoflurane-remifentanil on acute postoperative pain after total shoulder arthroplasty: a randomized trial**

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| **Background:** | While some evidence indicates that propofol-based anesthesia has less postoperative pain than sevoflurane-based anesthesia, these results are controversial. We compared acute postoperative pain intensity and opioid consumption after total shoulder arthroplasty between propofol-remifentanil (PR) and sevoflurane-remifentanil (SR) anesthesia. |
| **Methods:** | Among 48 patients undergoing shoulder arthroscopic surgery anesthetized with PR or SR, postoperative pain intensity was assessed at 30 minutes and at 2, 6, 12, and 24 hours. The total patient-controlled analgesia volume and number of patients requiring rescue analgesics were assessed. |
| **Results:** | No significant difference in postoperative pain intensity was observed between the two groups. Postoperative opioid consumption and analgesic requirements were also comparable in the first 24 hours after surgery. |
| **Conclusion:** | PR and SR anesthesia for shoulder arthroscopic surgery provide comparable postoperative analgesia results. |

**Keywords:** Anesthesia; Propofol; Sevoflurane; Total shoulder arthroplasty

**Introduction**

Postoperative pain management is the main challenge for anesthetiologists and surgeons in patients undergoing shoulder arthroscopic surgery. Inadequate control of postoperative pain is associated with prolonged recovery, increased healthcare costs, and increased risks of undesirable surgical outcomes [1]. Various pharmacotherapeutics, including opioids, nonsteroidal anti-inflammatory drugs, gabapentinoids, and regional nerve blocks, have been used alone or in combination to prevent postoperative pain.

Previous studies have shown that an anesthetic regimen may activate peripheral nociceptive neurons or suppress nociceptive signal propagation. Recent studies have demonstrated that the effect on postoperative pain of propofol-based anesthesia is superior to that of sevoflurane-based anesthesia [2,3]; however, other studies have not corroborated the superiority of propofol for treating postoperative pain [4,5].

This study aimed to compare acute postoperative pain intensity and opioid consumption after total shoulder arthroplasty (TSA) between patients receiving propofol-remifentanil (PR) and sevoflurane-remifentanil (SR) anesthesia.
Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: KNUH 2016-12-009-001). Informed consent was obtained from all patients.

1. Study design
This prospective, randomized, double-blind study enrolled 48 patients aged 18 to 65 years with American Society of Anesthesiologists (ASA) physical status (PS) classification I or II undergoing TSA. The exclusion criteria were routine use of analgesics, history of neurologic or psychological disease, body mass index of > 35 kg/m², and intake of any sedatives or analgesics within 24 hours before surgery. This study was registered at ClinicalTrials.gov ([https://clinicaltrials.gov/ct2/show/NCT04333992](https://clinicaltrials.gov/ct2/show/NCT04333992)).

The patients were assigned to either the PR or SR group using computer-generated randomization. Standardized monitoring was performed in the operating room. In the PR group, anesthetic induction was achieved with initial propofol and remifentanil target concentrations of 4 μg/mL and 3 to 4 ng/mL, respectively, using target-controlled infusion (TCI) devices (Orchestra Base Primea, Fresenius Vial, Brézins, France) and rocuronium 0.8 mg/kg. After intubation, anesthesia was maintained with a fixed target concentration of propofol 2 to 4 μg/mL and remifentanil 2 to 3 ng/mL to maintain an acceptable hemodynamic response and bispectral index (BIS) values of 40 to 60. In the SR group, anesthesia was induced with thiopental 5 mg/kg and an initial target remifentanil concentration of 3 to 4 ng/mL using TCI and rocuronium 0.8 mg/kg. Anesthesia was maintained with 1.5% to 2.5% end-tidal concentration of sevoflurane in 50% oxygen with air, and remifentanil 2 to 3 ng/mL was continuously infused to maintain acceptable hemodynamics and BIS values of 40 to 60. Propofol or sevoflurane with remifentanil administration was stopped at the end of surgery. Ketorolac 30 mg was administered intravenously (IV) for postoperative pain control and ramosetron 0.3 mg was administered IV for antiemetic prophylaxis. Residual neuromuscular blockade was reversed with pyridostigmine 0.2 mg/kg and glycopyrrolate 0.01 mg/kg IV. The patients were then transferred to the postanesthesia care unit (PACU).

Postoperative pain intensity was assessed using a numerical rating scale (NRS: 0, no pain to 10, worst pain) at 30 minutes and at 2, 6, 12, and 24 hours. When the NRS score was > 4 or when the patient requested analgesics, fentanyl 50 μg was administered IV. In addition, patient-controlled analgesia (PCA) was infused immediately after PACU arrival. The PCA device was set to deliver 0.38 μg/kg/hr of fentanyl as a basal infusion rate and 20 μg on demand with a 15-minute lockout time [6]. If the pain was poorly controlled, additional fentanyl (50 μg) was administered. The total PCA volume and number of patients requiring rescue analgesics were recorded. The incidence of postoperative nausea and vomiting (PONV) and use of rescue antiemetics were also recorded 24 hours after surgery. Ramosetron 0.3 mg was administered when the patients experienced vomiting or required antiemetics. Other adverse events such as respiratory depression, headache, and dizziness were also recorded. All anesthetic procedures and study assessments were performed by an anesthesiologist who was blinded to the group assignments and study protocols.

2. Statistical analyses
We estimated the sample size using the NRS score (at 30 minutes postoperatively) from our preliminary study [2]. The mean ± standard deviation (SD) of NRS score was 7.0 ± 6.0 in the PR group and 7.6 ± 7.8 in the SR group. Thus, based on a power of 80% and an α error of 5%, 23 patients were required in each group. Therefore, 52 patients were enrolled to compensate for potential dropouts. Statistical analyses were performed using IBM SPSS ver. 23 (IBM Corp., Armonk, NY, USA). Continuous data were analyzed using t-tests and are expressed as mean ± SD, whereas categorical data were analyzed using the chi-square test or Fisher exact tests as appropriate and are expressed as number (%). A p-value of < 0.05 was considered statistically significant.

Results

Among the 52 patients screened for eligibility, data from 48 of them were analyzed; three patients refused to participate and one did not meet the inclusion criteria.

There were no significant differences between the two groups with respect to age, sex, ASA PS classification, height, weight, or duration of surgery (Table 1). The pain NRS did not significantly differ at any time point, but the magnitude of the pain scores was lower in the PR group than in the SR group (Table 2). Regarding the use of postoperative analgesics, no difference was observed between the two groups in terms of fentanyl consumption via PCA. Likewise, the total dose of rescue drugs did not differ significantly; however, the SR group showed a tendency for higher postoperative analgesic use than the PR group (Table 3). The incidence of PONV and need for antiemetics did not differ between the groups (Table 4). No significant differences were observed in postoperative adverse events such as headache, dizziness, and respiratory depression (Table 4).
Table 1. Demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PR group</th>
<th>SR group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.4±9.9</td>
<td>58.4±9.0</td>
<td>0.544</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>15.9</td>
<td>16.8</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>ASA PS classification, I/II</td>
<td>16.8</td>
<td>14.10</td>
<td>0.766</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.6±7.5</td>
<td>164.5±8.6</td>
<td>0.326</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.8±9.5</td>
<td>66.6±9.3</td>
<td>0.988</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>135.2±47.5</td>
<td>122.5±51.2</td>
<td>0.960</td>
</tr>
</tbody>
</table>

Values are presented as number or mean ± standard deviation.
PR, propofol-remifentanil; SR, sevoflurane-remifentanil; ASA, American Society of Anesthesiologists; PS, physical status.

Table 2. Postoperative pain intensity during the first 24 hours after surgery

| Time   | Pain score PR group (n = 24) | Pain score SR group (n = 24) | p-value*
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>30 min</td>
<td>6.79±1.14</td>
<td>7.12±1.03</td>
<td>0.295</td>
</tr>
<tr>
<td>2 hr</td>
<td>5.37±1.27</td>
<td>5.91±1.05</td>
<td>0.117</td>
</tr>
<tr>
<td>6 hr</td>
<td>3.20±1.41</td>
<td>3.95±1.26</td>
<td>0.059</td>
</tr>
<tr>
<td>12 hr</td>
<td>1.75±0.73</td>
<td>1.95±0.62</td>
<td>0.296</td>
</tr>
<tr>
<td>24 hr</td>
<td>0.95±0.46</td>
<td>1.08±0.40</td>
<td>0.327</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation.
PR, propofol-remifentanil; SR, sevoflurane-remifentanil.

*Statistically significant at p<0.05.

Table 3. Cumulative fentanyl consumption and rescue analgesics during the first 24 hours after surgery

| Variable                           | PR group (n = 24) | SR group (n = 24) | p-value*
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose of PCA (µg)</td>
<td>595.0±176.1</td>
<td>672.6±92.0</td>
<td>0.064</td>
</tr>
<tr>
<td>Rescue analgesics needed</td>
<td>13 (54.2)</td>
<td>19 (79.2)</td>
<td>0.066</td>
</tr>
<tr>
<td>Total dose of rescue fentanyl (µg)</td>
<td>47.9±54.1</td>
<td>75.0±46.6</td>
<td>0.070</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number (%).
PR, propofol-remifentanil; SR, sevoflurane-remifentanil; PCA, patient-controlled analgesia.

*Statistically significant at p<0.05.

Table 4. Reported side effects during the first 24 hours after surgery

| Side effect                | PR group (n = 24) | SR group (n = 24) | p-value*
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td>3 (12.5)</td>
<td>3 (12.5)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Rescue antiemetics needed</td>
<td>1 (4.2)</td>
<td>2 (8.3)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (4.2)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

Values are presented as number (%).
PR, propofol-remifentanil; SR, sevoflurane-remifentanil; PONV, postoperative nausea and vomiting.

*Statistically significant at p<0.05.

Discussion

In this study, we did not observe a significant difference in postoperative pain intensity between PR and SR anesthesia. Postoperative opioid consumption and analgesic requirements were also comparable in the first 24 hours after surgery, demonstrating that there was no benefit in choosing one general anesthetic over the other for patients undergoing TSA.

TSA is a surgical procedure used to improve the functional outcomes of glenohumeral arthritis [7]. Most patients experience substantial postoperative pain; thus, adequate control of acute postoperative pain contributes to early recovery by maintaining motor function and reducing the risk of developing chronic pain [8]. A multimodal approach to postoperative pain management has been applied, including pharmacologic and nonpharmacologic adjuvants such as opioids administered IV local analgesic infiltration, and peripheral nerve block [9,10]. The present study aimed to assess the effects of propofol and sevoflurane as general anesthetics on postoperative pain in patients undergoing TSA.

Previous studies have investigated the effects of propofol- and inhalation-based anesthesia on postoperative pain. While some studies have shown less postoperative pain after propofol anesthesia [2,3], Cheng et al. [2] demonstrated that maintenance with propofol provided better postoperative analgesia and less morphine consumption than isoflurane. In a study by Li et al. [3], propofol anesthesia was associated with less postoperative pain than sevoflurane anesthesia in patients who underwent gynecological laparoscopies, while others have reported no beneficial effects on pain control. Fassoulaki et al. [4] showed that there was no difference in the intensity of pain after surgery and in morphine requirements between the sevoflurane and propofol groups of their study. Pokkinen et al. [5] showed that the choice of anesthetic (sevoflurane or propofol) had no effect on postoperative pain and oxycodone use. Comparing the two agents, there is some evidence supporting the mixed effects of propofol or sevoflurane on acute postoperative pain.

The antinociceptive properties of propofol include neuronal suppression of the dorsal horn by interaction with GABAergic and glycine receptors, which leads to decreased transmission of nociceptive stimuli. Some studies have shown less postoperative pain after propofol anesthesia [6,7], while others have reported no beneficial effects on pain control. The present study aimed to assess the effects of propofol and sevoflurane as general anesthetics on postoperative pain in patients undergoing TSA.

In this study, we did not observe a significant difference in postoperative pain intensity between PR and SR anesthesia. Postoperative opioid consumption and analgesic requirements were also comparable in the first 24 hours after surgery, demonstrating that there was no benefit in choosing one general anesthetic over the other for patients undergoing TSA.
thetic interactions such as isoflurane intensify pain sensitivity by inhibiting nicotinic receptors in the spinal cord and, thus, hinder norepinephrine release [19]. The results of the present study are comparable to those reported previously. We found no significant differences in pain intensity and post-opioid consumption at any time point, although we did observe a lower magnitude of pain scores and use of postoperative analgesics in the PR group than in the SR group.

The use of intraoperative opioids is important for achieving balanced anesthesia. Remifentanil, an ultra-short-acting opioid, is widely used in general anesthesia to provide hemodynamic stability, anesthetic-sparing, and rapid cognitive effects [20,21]. However, remifentanil-induced hyperalgesia (RIH) is challenging in postoperative pain management. The possible mechanism of RIH is attributed to a pain-facilitating system involving rapid and prolonged upregulation of N-methyl-D-aspartate (NMDA) receptors [22,23]. However, inhalational or intravenous anesthetics might modulate postoperative hyperalgesia by inhibiting NMDA receptor function [24-26]. Shin et al. [27] showed that remifentanil hyperalgesia was induced during SR anesthesia but not during PR anesthesia. Moreover, they found that RIH was activated by a high dose (4 ng/mL with TCI) but not a low dose (1 ng/mL with TCI) of remifentanil. The better postoperative analgesic effects of propofol can be attributed to the direct activation of R-aminobutyric acid type A receptors by propofol, which inhibits NMDA receptors and modulates calcium ion channels [28]. In the present study, we used intraoperative remifentanil (3–4 ng/mL) and observed a comparable postoperative analgesic pattern in both groups, which suggests that we could not identify a potent antagonistic interaction between propofol and remifentanil that might affect NMDA receptor activation.

Without prophylaxis, the use of inhalational anesthetics and opioids may increase the risk of PONV by 30% [29]. In the present study, however, we did not observe any difference in PONV incidence between the two groups, indicating that ramsohetron might have affected prophylaxis.

This study had several limitations. First, in addition to the anesthetic regimen, postoperative pain can be affected by many factors including patient anxiety, mood, and genetic differences in response to analgesics. We did not assess these parameters preoperatively. Second, the pain scores after TSA were high; thus, the anesthetic regimen might have been underpowered to detect significant differences in early analgesic effects. Third, we did not evaluate the long-term analgesic effects of the two general anesthetics. Further studies with follow-up times longer than 24 hours postoperatively are required to investigate this effect. Finally, we set the intraoperative remifentanil level at 3 to 4 ng/mL in both groups, but the total dose of remifentanil was not included. Based on the results of a comparable postoperative analgesic pattern in both groups, we postulate that there was no antagonistic interaction between propofol and remifentanil. However, assessment of intraoperative remifentanil use might be needed for more precise comparison.

In conclusion, the postoperative analgesic effects were comparable between PR and SR as anesthetic regimens in patients who underwent TSA.

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

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Author contributions
Conceptualization, Data curation: all authors; Formal analysis: EKC, DyK; Methodology: DyK; Visualization: SK; Resources: EKC, SK; Software: SK, DyK; Supervision: EKC; Writing-original draft: EKC, SK; Writing-review & editing: EKC, SK, DyK.

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References
Novel cystography parameter to predict early recovery from urinary continence after radical prostatectomy for prostate cancer: a retrospective study

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**Background:** The purpose of this study was to investigate whether postoperative cystography findings can predict early and long-term recovery from incontinence after radical prostatectomy (RP), compared with the other cystography parameters.

**Methods:** I retrospectively reviewed 118 patients who underwent robot-assisted RP (RARP) for localized prostate cancer at a single institution between January 2016 and April 2021. One hundred and seven patients were included in the study. Postoperative cystography was routinely performed 7 days after surgery. The bladder neck to pubic symphysis ratio, vesicourethral angle, and bladder neck anteroposterior length (BNAP) ratio (the bladder neck-posterior margin distances divided by the anteroposterior lengths) were evaluated. Continence was defined as cessation of pad use. The association between these variables and urinary incontinence was also analyzed.

**Results:** The urinary incontinence recovery rates 1, 3, 6, and 12 months after RARP were 43.92%, 66.35%, 87.85%, and 97.19%, respectively. Multivariate logistic regression analysis demonstrated that a lower BNAP ratio and wider vesicourethral angle were significantly associated with continence restoration at 1, 3, and 6 months after surgery. In addition, in terms of days of pad usage, lower BNAP ratio, wider vesicourethral angle, and bladder neck preservation were significantly associated with recovery from urinary incontinence within 12 months as assessed by Cox proportional hazard analysis.

**Conclusion:** This study demonstrated that vesicourethral angle and BNAP ratio were independent predictors of early recovery from post-prostatectomy incontinence. I suggest that both the sagittal and coronal views of postoperative cystography help anticipate early continence restoration after RARP.

**Keywords:** Cystography; Prostate neoplasms; Prostatectomy; Urinary incontinence

**Introduction**

Radical prostatectomy (RP) is the definitive treatment for localized prostate cancer. However, post-prostatectomy incontinence (PPI) is a significant surgical complication after RP that can influence a patient’s quality of life. The major causes of PPI include damage to the urethral sphincter, bladder instability, and destruction of pelvic support [1-3]. Despite the fact that there are several surgical techniques for preventing PPI, such as nerve-sparing techniques, bladder neck preservation, and posterior reconstruction [4-6], PPI remains a major obstacle.

Recent studies have indicated that perioperative imaging can be
used to predict PPI. Mendoza et al. [7] reported that longer urethral lengths on preoperative magnetic resonance imaging (MRI) were associated with faster continence recovery at all postoperative time points. Coakley et al. [8] also found that a longer membranous urethra on endorectal MRI before RP was significantly associated with a more rapid return to continence [8]. However, immediate assessment of postoperative urethral length may be more important than preoperative urethral length in predicting PPI because urethral length can be shorter after surgery.

In contrast, several studies have reported that postoperative cystography, a simple method that is routinely performed to check for urinary leakage after surgery, can predict PPI. Olgin et al. [9] reported that the post-prostatectomy bladder neck location on cystography correlates with continence rates and predicts patients at risk of prolonged incontinence [9]. Sugi et al. [10] also demonstrated that a narrow vesicourethral angle measured by cystography is a useful predictor of PPI.

Although these studies have shown promising results, the efficacy of postoperative cystography in predicting early recovery from PPI is controversial because there are no systematic reviews or randomized controlled trials on the efficacy of postoperative cystography. In addition, previous studies on the efficacy of postoperative cystography assessed only two-dimensional aspects, such as the coronal view. Therefore, I focused on the three-dimensional aspect as a predictor of early recovery from PPI by using not only the coronal view but also the sagittal view on cystography. In this study, I investigated the efficacy of a new cystography parameter (i.e., the sagittal view) to predict early and long-term recovery from incontinence after RP, comparing it with a well-known previous cystography parameter (i.e., the coronal view) on postoperative cystography.

Methods

**Ethical statements**: The study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2020-04-061-001), which waived the need for informed consent owing to the retrospective design of the study.

**1. Study populations**
I retrospectively reviewed 118 patients who underwent robot-assisted RP (RARP) for localized prostate cancer at single institution between January 2016 and April 2021. One hundred and seven patients were included in the study. The exclusion criteria were as follows: radiation therapy within 1 year, urine leakage from the anastomosis during cystography, previous urethral or prostate surgery, and no nerve-sparing procedure.

**2. Surgical procedures**
All patients underwent RARP performed by an experienced surgeon at a single institution. The surgeon performed the procedures as follows: bladder neck reconstruction (if needed), posterior reconstruction, and vesicourethral anastomosis. All patients underwent posterior reconstruction using the Rocco stitch [11]. Vesicourethral anastomosis was performed using a bidirectional barbed (V-Loc 90; Medtronic, Minneapolis, MN, USA) running suture in all patients. Unilateral or bilateral neurovascular bundle (NVB) sparing procedures were performed in all patients according to their clinical stage.

**3. Postoperative cystography**
Cystography was routinely performed postoperatively 7 days before urethral catheter removal. The bladder was filled with 150-mL saline solution with contrast medium, and front, semilateral, and lateral-view images were acquired. If vesicourethral anastomosis leakage was observed, the cystography was repeated after 7 days.

**4. Cystography parameters**
I calculated the bladder neck to pubic symphysis (BNPS) ratio (defined as the bladder neck-pubis symphysis distance divided by the total pubis symphysis height) (Fig. 1A) and vesicourethral angle (measured as the angle of the bladder neck relative to the bilateral margin over the pelvic inlet) (Fig. 1B). I also calculated the anteroposterior length of the bladder and distance from the most posterior margin of the bladder to the bladder neck using lateral-view cystography. To control for potential differences in magnification by cystography, the bladder neck-posterior margin distances were divided by the anteroposterior lengths, called the bladder neck anteroposterior length (BNAP) ratio (Fig. 1C). All cystography parameters were analyzed by a single urologist who was blinded to the continence results.

**5. Outcome assessment**
All 107 patients were routinely followed up at 1, 3, 6, and 12 months after RARP. The patients reported daily pad use and the last date of pad usage at each visit. Continence was defined as the cessation of pad usage.

**6. Statistical analysis**
Univariate analysis was performed using the Student t-test for continuous variables and the chi-square test for categorical variables at 1, 3, 6, and 12 months after surgery. Multivariate logistic regression
analysis was used to confirm independent predictive factors for urinary incontinence. According to the time of pad use, the Cox proportional hazard model was used to identify predictors of recovery from urinary incontinence. In addition, cut-off values for independent factors of urinary incontinence on cystography parameters were determined using receiver operating characteristic (ROC) curves. All analyses were performed using IBM SPSS ver. 19.0 (IBM Corp. Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

**Results**

The patient characteristics are shown in **Table 1**. The recovery rates for urinary incontinence at 1, 3, 6, and 12 months after surgery were 43.92%, 66.35%, 87.85%, and 97.19%, respectively. The cumulative recovery curve for urinary incontinence is shown in **Fig. 2**.

Univariate analysis for predictive factors of continence recovery at 1, 3, 6, and 12 months after surgery is shown in **Table 2**. In the univariate analysis, bladder neck preservation was significantly associated with early continence restoration 1 month after RARP. Lower BNAP ratio and wider vesicourethral angle were statistically significant predictors of PPI at 1, 3, 6, and 12 months after RARP. However, a lower BNPS ratio was associated with continence recovery at 1, 3, and 6 months after surgery. Multivariate logistic regression analysis demonstrated that a lower BNAP ratio and wider vesicourethral angle were significantly associated with continence restoration at 1, 3, and 6 months after surgery (Table 3). The Cox-Snell R-squared values were 0.577, 0.579, and 0.375 at 1, 3, and 6 months after surgery, respectively. Meanwhile, in terms of the days of pad usage, lower BNAP ratio, wider vesicourethral angle, and bladder neck preservation were significantly associated with recovery from urinary incontinence within 12 months in the Cox proportional hazard analysis (Table 4).

In the ROC curve analysis, the BNAP ratio and vesicourethral angle were superior to the bladder neck location in terms of sensitivity, specificity, and Youden’s index (Table 5). In addition, the areas under the curve of the BNAP ratio and vesicourethral angle 1 month after surgery were higher than those of the BNPS ratio (0.898, 0.918, and 0.650, respectively). The optimal cut-off values

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**Table 1. Characteristics of all patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>107</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>$66.50 \pm 6.29$</td>
</tr>
<tr>
<td>Prostate volume (mL)</td>
<td>$30.26 \pm 12.52$</td>
</tr>
<tr>
<td>Preoperative PSA (ng/mL)</td>
<td>$17.46 \pm 27.42$</td>
</tr>
<tr>
<td>Duration of catheterization (day)</td>
<td>$8.16 \pm 3.11$</td>
</tr>
<tr>
<td>Pathologic state</td>
<td></td>
</tr>
<tr>
<td>≤ T2</td>
<td>57 (53.3)</td>
</tr>
<tr>
<td>≥ T3</td>
<td>50 (46.7)</td>
</tr>
<tr>
<td>NVB sparing</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>24 (22.4)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>83 (77.6)</td>
</tr>
<tr>
<td>Bladder neck preservation</td>
<td>67 (62.6)</td>
</tr>
<tr>
<td>Recovery of incontinence (mo)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>47 (43.9)</td>
</tr>
<tr>
<td>3</td>
<td>71 (66.4)</td>
</tr>
<tr>
<td>6</td>
<td>94 (87.9)</td>
</tr>
<tr>
<td>12</td>
<td>104 (97.2)</td>
</tr>
<tr>
<td>Regain of continence (day)</td>
<td>$79.88 \pm 86.21$</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).

PSA, prostate-specific antigen; NVB, neurovascular bundle.

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**Fig. 1. Postoperative cystography parameters. (A) Bladder neck to pubic symphysis, (B) vesicourethral angle, and (C) bladder neck anteroposterior (BNAP) length. BNPS, bladder neck to pubic symphysis.**

**Table 2. Univariate analysis for predictive factors of continence recovery at 1, 3, 6, and 12 months after surgery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive factor</td>
<td></td>
</tr>
<tr>
<td>Lower BNPS ratio</td>
<td></td>
</tr>
<tr>
<td>Wider vesicourethral angle</td>
<td></td>
</tr>
<tr>
<td>Bladder neck preservation</td>
<td></td>
</tr>
<tr>
<td>Recovery of incontinence (mo)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>47 (43.9)</td>
</tr>
<tr>
<td>3</td>
<td>71 (66.4)</td>
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<tr>
<td>6</td>
<td>94 (87.9)</td>
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<tr>
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</tr>
<tr>
<td>Regain of continence (day)</td>
<td>$79.88 \pm 86.21$</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).

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**Table 3. Multivariate logistic regression analysis of continence recovery at 1, 3, 6, and 12 months after surgery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive factor</td>
<td></td>
</tr>
<tr>
<td>Lower BNAP ratio</td>
<td></td>
</tr>
<tr>
<td>Wider vesicourethral angle</td>
<td></td>
</tr>
<tr>
<td>Bladder neck preservation</td>
<td></td>
</tr>
<tr>
<td>Recovery of incontinence (mo)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>47 (43.9)</td>
</tr>
<tr>
<td>3</td>
<td>71 (66.4)</td>
</tr>
<tr>
<td>6</td>
<td>94 (87.9)</td>
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<tr>
<td>12</td>
<td>104 (97.2)</td>
</tr>
<tr>
<td>Regain of continence (day)</td>
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</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).

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**Table 4. ROC curve analysis of continence recovery at 1, 3, 6, and 12 months after surgery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive factor</td>
<td></td>
</tr>
<tr>
<td>Lower BNPS ratio</td>
<td></td>
</tr>
<tr>
<td>Wider vesicourethral angle</td>
<td></td>
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<td>Bladder neck preservation</td>
<td></td>
</tr>
<tr>
<td>Recovery of incontinence (mo)</td>
<td></td>
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<tr>
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<td>47 (43.9)</td>
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<td>3</td>
<td>71 (66.4)</td>
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<td>104 (97.2)</td>
</tr>
<tr>
<td>Regain of continence (day)</td>
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</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).

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**Table 5. ROC curve analysis of continence recovery at 1, 3, 6, and 12 months after surgery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictive factor</td>
<td></td>
</tr>
<tr>
<td>Lower BNPS ratio</td>
<td></td>
</tr>
<tr>
<td>Wider vesicourethral angle</td>
<td></td>
</tr>
<tr>
<td>Bladder neck preservation</td>
<td></td>
</tr>
<tr>
<td>Recovery of incontinence (mo)</td>
<td></td>
</tr>
<tr>
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<td>94 (87.9)</td>
</tr>
<tr>
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<tr>
<td>Regain of continence (day)</td>
<td>$79.88 \pm 86.21$</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).
continence at any point in this study. I hypothesized that, despite the location of the bladder neck and recovery of urinary incontinence, there was no statistically significant difference between the location of the bladder neck and recovery of urinary incontinence. However, there was no significant difference in the bladder neck location and change in the vesicourethral angle. They also reported that a lower bladder neck position may predict prostatomegaly, which suspend and support the bladder. Kageyama et al. [8] reported a correlation between bladder neck location and change in the vesicourethral angle. They argued that a higher location of the bladder neck leads to a higher rate of early recovery from PPI. However, immediate postoperative MRI may facilitate PPI prognosis. However, immediate postoperative MRI is expensive for assessing only the early recovery from PPI in real practice. Thus, many studies have reported the efficacy of postoperative cystography to determine the location of the bladder neck and surgical techniques related to early recovery from urinary incontinence after robot-assisted radical prostatectomy. They argued that a lower bladder neck position may predict postoperative cystography as a predictive factor for early recovery from PPI [9,10].

Table 2. Univariate analysis for predictive factors of PPI at 1, 3, 6, and 12 months after surgery

<table>
<thead>
<tr>
<th>Factor</th>
<th>1 Mo (n = 60)</th>
<th>3 Mo (n = 47)</th>
<th>6 Mo (n = 94)</th>
<th>12 Mo (n = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>66.23 ± 6.17</td>
<td>66.83 ± 6.48</td>
<td>65.92 ± 6.14</td>
<td>66.79 ± 6.38</td>
</tr>
<tr>
<td>Prostate volume (mL)</td>
<td>32.45 ± 14.56</td>
<td>27.46 ± 8.64</td>
<td>29.92 ± 12.35</td>
<td>30.43 ± 12.68</td>
</tr>
<tr>
<td>Preoperative PSA (ng/mL)</td>
<td>16.05 ± 24.06</td>
<td>19.26 ± 31.37</td>
<td>20.27 ± 29.64</td>
<td>16.04 ± 26.32</td>
</tr>
<tr>
<td>Pathologic stage (n)</td>
<td>0.115</td>
<td>0.115</td>
<td>0.942</td>
<td>0.524</td>
</tr>
<tr>
<td>T2</td>
<td>36</td>
<td>19</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>T3</td>
<td>24</td>
<td>17</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>NVB sparing (n)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.345</td>
<td>0.345</td>
</tr>
<tr>
<td>Unilateral</td>
<td>14</td>
<td>10</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Bilateral</td>
<td>46</td>
<td>26</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Bladder neck preservation</td>
<td>29</td>
<td>19</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative cystography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>parameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNAP ratio</td>
<td>0.267 ± 0.059</td>
<td>0.188 ± 0.022</td>
<td>0.299 ± 0.047</td>
<td>0.198 ± 0.031</td>
</tr>
<tr>
<td>Vesicourethral angle</td>
<td>98.51 ± 12.14</td>
<td>116.29 ± 5.41</td>
<td>94.84 ± 11.26</td>
<td>121.15 ± 9.85</td>
</tr>
<tr>
<td>BNPS ratio</td>
<td>0.509 ± 0.163</td>
<td>0.410 ± 0.155</td>
<td>0.526 ± 0.165</td>
<td>0.434 ± 0.160</td>
</tr>
</tbody>
</table>

Values are presented as mean ± standard deviation or number.
PPI, post-prostatectomy incontinence; PSA, prostate-specific antigen; NVB, neurovascular bundle; BNAP, bladder neck anteroposterior length; BNPS, bladder neck to pubic symphysis.

As early recovery from PPI is still an important factor associated with the patients’ quality of life, many perioperative parameters and surgical techniques related to early recovery from urinary incontinence after surgery were 0.224, 108.5, 0.584, respectively.

Fig. 2. Cumulative recovery curve from urinary incontinence after robot-assisted radical prostatectomy.
Several recent studies have reported that a wide bladder neck angle on postoperative cystography is a predictive factor for PPI recovery. Sugi et al. [10] reported that a narrow vesical angle is significantly associated with urinary incontinence at 1 month and 1 year after RARP. Shao et al. [14] also suggested that a shaped bladder neck angle was a significant predictor of urinary incontinence 6 months after RARP. However, there were several limitations in previous studies regarding the vesicourethral angle. For example, in Sugi et al. [10], several surgeons performed RARP. In this study, patients with a wide bladder neck angle on postoperative cystography showed early restoration of urinary incontinence after RARP, as the clinical variables were completely controlled. At the onset of the normal voiding phase in men, the bladder neck is opened and the posterior vesicourethral angle changes sharply, with striated urethral sphincter relaxation and anterior fibromuscular stroma contraction [15]. I anticipated that as the urethral stump and bladder neck were more tensioned when vesicourethral anastomosis was performed, the shape of the bladder would be more prolate, and the bladder neck angle would be narrow. Therefore, a narrow bladder neck angle is associated with restoration of urinary incontinence.

A unique aspect of the present study was that the BNAP ratio was associated with early continence recovery after RARP. In previous studies, postoperative cystography parameters were only measured in the coronal view of cystography [9,10,12-14,16]. However, I anticipated that the force transmission of urine from the bladder neck to the urethra could be three-dimensional rather than two-dimensional. Therefore, I focused on the sagittal view of postoperative cystography, which is an important parameter related to PPI recovery. Therefore, I must consider why a lower BNAP ratio is associated with early continence recovery. When abdominal pressure increases, stable urethral support is an important mechanism for controlling urinary incontinence [17]. Because the mechanism of urinary incontinence after RP is similar to that of stress urinary incontinence in women, posterior reconstruction of the rhabdosphincter in RARP can be helpful for early continence recovery [11]. I hypothesized that urethral support would be more stable if the bladder neck was located more posteriorly after posterior reconstruction. In addition, it can be anticipated that as the bladder neck becomes more posterior, the vesicourethral angle may narrow. Therefore, I anticipated that a low BNAP ratio would influence early recovery from PPI.

The NVB-sparing procedure has been strongly associated with early continence recovery after RARP in many studies [18]. Therefore, I analyzed the differences in postoperative cystography features according to the state of NVB sparing. In the current study,

### Table 3. Multivariate logistic regression analysis for predictive factors of PPI at 1, 3, and 6 months after surgery

<table>
<thead>
<tr>
<th>Factor</th>
<th>Postoperative 1 mo (47/107)</th>
<th>Postoperative 3 mo (71/107)</th>
<th>Postoperative 6 mo (94/107)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.943 (0.838–1.062)</td>
<td>0.336</td>
<td>1.039 (0.888–1.217)</td>
</tr>
<tr>
<td>Prostate volume (mL)</td>
<td>1.092 (1.020–1.170)</td>
<td>0.012</td>
<td>1.030 (0.950–1.118)</td>
</tr>
<tr>
<td>Preoperative PSA (ng/mL)</td>
<td>0.997 (0.968–1.027)</td>
<td>0.851</td>
<td>1.036 (1.000–1.074)</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td>1.248 (1.192–0.906)</td>
<td>0.817</td>
<td>0.142 (0.013–1.499)</td>
</tr>
<tr>
<td>NVB sparing</td>
<td>1.684 (0.188–15.065)</td>
<td>0.641</td>
<td>0.044 (0.002–1.223)</td>
</tr>
<tr>
<td>No bladder neck preservation</td>
<td>0.279 (0.057–1.367)</td>
<td>0.115</td>
<td>4.290 (0.369–49.912)</td>
</tr>
<tr>
<td>BNAP ratio</td>
<td>3.795 (2.829–5.089)</td>
<td>0.006</td>
<td>3.867 (2.181–5.384)</td>
</tr>
<tr>
<td>Vescicourethral angle</td>
<td>0.800 (0.701–0.913)</td>
<td>0.001</td>
<td>0.885 (0.806–0.971)</td>
</tr>
<tr>
<td>BNPS ratio</td>
<td>0.098 (0.000–34.073)</td>
<td>0.436</td>
<td>0.013 (0.000–9.100)</td>
</tr>
</tbody>
</table>

PPI, post-prostatectomy incontinence; OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen; NVB, neurovascular bundle; BNAP, bladder neck anteroposterior; BNPS, bladder neck to pubic symphysis.

### Table 4. Cox proportional hazard analysis for predictive factors of PPI within 12 months after surgery

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>1.029 (0.995–1.063)</td>
<td>0.092</td>
</tr>
<tr>
<td>Prostate volume (mL)</td>
<td>0.993 (0.976–1.010)</td>
<td>0.412</td>
</tr>
<tr>
<td>Preoperative PSA (ng/mL)</td>
<td>1.001 (0.993–1.009)</td>
<td>0.880</td>
</tr>
<tr>
<td>Pathologic stage (T3)</td>
<td>0.786 (0.501–1.232)</td>
<td>0.293</td>
</tr>
<tr>
<td>Bilateral NVB sparing</td>
<td>1.061 (0.527–2.138)</td>
<td>0.868</td>
</tr>
<tr>
<td>No bladder neck preservation</td>
<td>0.608 (0.393–0.938)</td>
<td>0.025</td>
</tr>
<tr>
<td>BNAP ratio</td>
<td>0.416 (0.146–0.987)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vescicourethral angle</td>
<td>1.056 (1.032–1.080)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNPS ratio</td>
<td>0.924 (0.208–4.109)</td>
<td>0.917</td>
</tr>
</tbody>
</table>

PPI, post-prostatectomy incontinence; HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; NVB, neurovascular bundle; BNAP, bladder neck anteroposterior; BNPS, bladder neck to pubic symphysis.
Table 5. Comparison of the cystography parameters for predictive factors of continence recovery 1 month after surgery in ROC curve analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden's index</th>
<th>Optimal cut-off</th>
<th>AUC</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNPS ratio</td>
<td>0.350</td>
<td>0.957</td>
<td>0.307</td>
<td>0.584</td>
<td>0.650</td>
<td>0.546–0.754</td>
<td>0.008</td>
</tr>
<tr>
<td>Vesicourethral angle</td>
<td>0.915</td>
<td>0.817</td>
<td>0.732</td>
<td>108.5</td>
<td>0.918</td>
<td>0.866–0.970</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNAP ratio</td>
<td>0.800</td>
<td>0.979</td>
<td>0.779</td>
<td>0.224</td>
<td>0.898</td>
<td>0.835–0.961</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; BNPS, bladder neck to pubic symphysis; BNAP, bladder neck anteroposterior.

there was no significant difference in the BNPS ratio, vesicourethral angle, and BNAP ratio between the unilateral and bilateral NVB-sparing procedures. Therefore, the vesicourethral angle and BNAP ratio could be predictive factors for early continence recovery after RARP regardless of NVB sparing.

By analyzing the ROC curve, I evaluated the statistical significance of the BNAP ratio compared to other cystography parameters such as bladder neck location and vesicourethral angle. In the ROC curve, the BNAP ratio and vesicourethral angle values were superior to those of the bladder neck location in terms of sensitivity and specificity. Therefore, the BNAP ratio can effectively predict early recovery from PPI. In addition, the combination of these parameters could predict more outcomes than each parameter alone, although I only evaluated the efficacy of each postoperative cystography parameter.

This study had several limitations. First, this was a retrospective study conducted at a single center. Second, I did not use the 1-hour pad test to assess the degree of incontinence on each follow-up day. Finally, preoperative cystography to measure baseline parameters was not performed in this study. Nevertheless, this is the first study to assess the efficacy of predictive parameters for PPI recovery using three-dimensional aspects of postoperative cystography. In addition, the current study presents a new concept for predicting continence recovery after RARP using postoperative cystography.

In conclusion, this study demonstrated that the BNAP ratio and vesicourethral angle are associated with the prediction of early recovery from urinary incontinence after RARP. Sagittal and coronal cystography views may help predict early restoration of urinary continence. In addition, the use of a combination of cystography parameters may be more helpful than the use of any single parameter alone.

Notes

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

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Impact of Controlling Nutritional Status score on short-term outcomes after carotid endarterectomy: a retrospective cohort study

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Background: Malnutrition and impaired immune responses significantly affect the clinical outcomes of patients with atherosclerotic stenosis. The Controlling Nutritional Status (CONUT) score has recently been utilized to evaluate perioperative immunonutritional status. This study aimed to evaluate the relationship between immunonutritional status, indexed by CONUT score, and postoperative complications in patients undergoing carotid endarterectomy (CEA).

Methods: We retrospectively evaluated 188 patients who underwent elective CEA between January 2010 and December 2019. The preoperative CONUT score was calculated as the sum of the serum albumin concentration, total cholesterol level, and total lymphocyte count. The primary outcome was postoperative complications within 30 days after CEA, including major adverse cardiovascular events, pulmonary complications, stroke, renal failure, sepsis, wounds, and gastrointestinal complications. Cox proportional hazards regression analysis was used to estimate the factors associated with postoperative complications during the 30-day follow-up period.

Results: Twenty-five patients (13.3%) had at least one major complication. The incidence of postoperative complications was identified more frequently in the high CONUT group (12 of 27, 44.4% vs. 13 of 161, 8.1%; p < 0.001). Multivariate analyses showed that a high preoperative CONUT score was independently associated with 30-day postoperative complications (hazard ratio, 5.98; 95% confidence interval, 2.56–13.97; p < 0.001).

Conclusion: Our results showed that the CONUT score, a simple and readily available parameter using only objective laboratory values, is independently associated with early postoperative complications.

Keywords: Carotid endarterectomy; Nutritional status; Postoperative complications; Prognosis

Introduction

Stroke is the second leading cause of mortality and adult disability [1]. Extracranial carotid artery disease accounts for 20% of all stroke cases. Previous studies have shown that carotid endarterectomy (CEA) is significantly effective in preventing cerebrovascular events in patients with high-grade stenosis of the carotid artery and, thus, is regarded as a “gold standard” treatment [2,3]. However, the benefits of CEA shown in previous studies may be limited at any time because of the development of perioperative complications that are influenced by patient-related factors. Indeed, patients undergoing CEA have a residual risk of future stroke or major car-

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In carotid endarterectomy (CEA), the cause of this increased risk of postoperative complications in patients with CEA is unclear. Malnutrition and immune responses are involved in the atherosclerotic process; their content is associated with the recurrence of stroke or cardiovascular events and is an important cause of postoperative complications in various surgeries [4,5]. Therefore, malnutrition-immune data may be necessary for categorizing risk and understanding the residual risk in patients undergoing CEA.

The Controlling Nutritional Status (CONUT) score can be determined from one immune marker (total lymphocyte count) and two metabolic parameters (serum albumin concentration and total cholesterol levels), which are representative indicators of immune defense, protein reserves, and lipid metabolism, respectively. A decrease in each parameter is assigned a higher score, with higher scores indicating poorer nutritional status. Compared to traditional screening tools, these CONUT score parameters consider the influence of non-nutritional factors. Although the CONUT score has recently been considered as a scoring system for predicting postoperative morbidity and evaluating nutritional status in various settings, including oncology therapy and cancer surgery, clinical data using the CONUT score to predict unfavorable prognosis in CEA patients are scarce [6,7]. Given that the CONUT score is a marker of nutritional and immune responses, this study aimed to confirm whether the CONUT score can predict postoperative complications independent of other known prognostic factors.

**Methods**

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Ulsan University Hospital (IRB No: 2021-05-038), and the requirement for informed consent was waived.

**1. Study design and patient population**

A total of 198 patients who underwent CEA between January 2010 and December 2019 were retrospectively evaluated. Patients who underwent an emergency CEA procedure (n = 4), underwent other surgeries concurrently (n = 3), or had incomplete or missing data (n = 3) were excluded from this analysis. Thus, 188 patients were enrolled in the present study (Fig. 1). Clinical data, including demographic characteristics, comorbidities, postoperative complications, surgery side, degree of stenosis, and shunting, were reviewed using a computerized patient record system (Ulsan University Hospital Information of Clinical Ecosystem).

**2. Markers of nutritional status**

Blood samples were routinely collected within 1 week preceding CEA in all patients. The detection indices included white blood cells, lymphocyte counts, platelets, hemoglobin, C-reactive protein, albumin, blood urea nitrogen, serum creatinine, total cholesterol, total bilirubin, and uric acid. The immunonutritional status of each patient was evaluated based on the CONUT score. A score of > 2 indicated malnutrition (Fig. 2) [8]. The CONUT score was calculated as the sum of three laboratory parameters: serum albumin level (g/dL), total lymphocyte count (cells/µL), and total cholesterol level (mg/dL), as summarized in Fig. 2.

**3. Outcomes**

The primary endpoint in our analysis was a composite of the main complications throughout the 30 days following CEA. The 30-day postoperative complications were selected according to the European Perioperative Clinical Outcome definitions [9] as follows: (1) major adverse cardiovascular events (e.g., malignant ventricular arrhythmia, myocardial infarction, and heart failure); (2) pulmonary complications; (3) stroke; (4) renal complications; (5) sepsis; (6) wound complications; (7) gastrointestinal complications; and (8) death. As secondary clinical outcomes, the duration of intensive care and hospitalization and readmission within 30 days after CEA were confirmed.

**4. Statistical analysis**

Descriptive variables are expressed as numbers (proportions), mean ± standard deviation (SD), or medians (interquartile ranges [IQR]). Continuous variables were compared using the Student t-test, whereas the chi-square or Fisher exact test was used for categorical variables. Cox proportional hazards regression analysis was used to estimate the factors associated with postoperative complications during the 30-day follow-up period. Unadjusted relationships between risk factors and 30-day postoperative complications were es-

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**Fig. 1.** Flow chart of patient selection and classification.
timated using univariate Cox proportional hazards regression analysis and Kaplan-Meier curves. Only variables with a p-value of < 0.05 on univariate analysis were incorporated into the backward multivariate analysis. Therefore, we adjusted for preoperative heart failure, clamping time, and serum albumin levels as potential confounders in the multivariate analysis. Statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA) and R software ver. 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

**Results**

1. **Baseline characteristics of patients**
   The overall patient cohort had an average age of 67.14 ± 8.04 years, and 79.3% were men. In total, 112 patients (59.6%) were symptomatic (Table 1). In our study, 32.4% of the patients were malnourished. Systolic blood pressure and diastolic blood pressure were 139.07 ± 20.24 and 79.49 ± 13.19 mmHg (mean ± SD). Shunting was performed in 131 CEA procedures. All procedures were performed under general anesthesia. Detailed patient information is presented in Table 1.

2. **Clinical outcomes**
   The postoperative outcomes of the study are summarized in Table 2. At least 13.3% of the patients had one acute postoperative complication, and it was confirmed that the high CONUT group had a higher incidence of complications (12 of 27, 44.4% vs. 13 of 161, 8.1%; p < 0.001) (Table 2). The CONUT score of the patients who underwent CEA and the distribution of postoperative complications based on the CONUT score are presented in Fig. 1. Concerning secondary clinical outcomes, it was confirmed that hospital stay was also extended in the group with a high CONUT score (median, 7 days [IQR, 6–17 days] vs. 6 days [IQR, 6–8 days], p = 0.022) (Table 2).

3. **Prognostic factors for postoperative complications**
   Univariate and multivariate analyses were performed to identify prognostic factors for acute complications after surgery. The presence of heart failure (hazard ratio [HR], 8.43; 95% confidence interval [CI], 2.87–24.74; p < 0.001), clamping time (HR, 0.97; 95% CI, 0.93–1.00; p = 0.04), albumin (HR, 0.27; 95% CI, 0.14–0.53; p < 0.001), and CONUT score (HR, 6.47; 95% CI, 2.95–14.20; p < 0.001) were prognostic markers for postoperative complications. After adjusting for confounders, the CONUT score (HR, 5.98; 95% CI, 2.56–13.97; p < 0.001) was an independent prognostic marker of acute postoperative complications (Table 3). Kaplan-Meier curves showed that the possibility of complications after CEA was significantly higher for patients with higher CONUT scores than for those with lower CONUT scores (p < 0.001) (Fig. 3).
Table 1. Preoperative clinical characteristics of study participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Composite = 0</th>
<th>Composite = 1</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>188</td>
<td>163</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67.14 ± 8.04</td>
<td>66.94 ± 7.99</td>
<td>68.44 ± 8.41</td>
<td>0.39</td>
</tr>
<tr>
<td>Male sex</td>
<td>149 (79.3)</td>
<td>129 (79.1)</td>
<td>20 (80.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.34 ± 3.14</td>
<td>24.56 ± 3.02</td>
<td>23.95 ± 3.56</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75.78 ± 13.94</td>
<td>75.56 ± 14.18</td>
<td>77.20 ± 12.46</td>
<td>0.59</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>139.07 ± 20.24</td>
<td>138.10 ± 19.60</td>
<td>145.40 ± 23.48</td>
<td>0.09</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>79.49 ± 13.19</td>
<td>78.96 ± 13.09</td>
<td>82.96 ± 13.58</td>
<td>0.16</td>
</tr>
<tr>
<td>Symptomatic lesion</td>
<td>112 (59.6)</td>
<td>93 (57.1)</td>
<td>19 (76.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Ipsilateral stenosis, &gt; 70%</td>
<td>169 (89.9)</td>
<td>147 (90.2)</td>
<td>22 (88.0)</td>
<td>0.55</td>
</tr>
<tr>
<td>ASA PS classification</td>
<td>3.18 ± 0.82</td>
<td>3.14 ± 0.82</td>
<td>3.40 ± 0.82</td>
<td>0.34</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>75 (39.9)</td>
<td>67 (41.1)</td>
<td>8 (32.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>128 (68.1)</td>
<td>114 (69.9)</td>
<td>14 (56.0)</td>
<td>0.16</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>24 (12.8)</td>
<td>24 (14.7)</td>
<td>0 (0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6 (3.2)</td>
<td>2 (1.2)</td>
<td>4 (16.0)</td>
<td>0.003</td>
</tr>
<tr>
<td>Previous MI</td>
<td>29 (15.4)</td>
<td>25 (15.3)</td>
<td>4 (16.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>2 (1.1)</td>
<td>2 (1.2)</td>
<td>0 (0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Atrial fibrillation history</td>
<td>18 (9.6)</td>
<td>14 (8.6)</td>
<td>4 (16.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Previous arterial disease</td>
<td>48 (25.5)</td>
<td>41 (25.2)</td>
<td>7 (28.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>179 (95.2)</td>
<td>155 (95.1)</td>
<td>24 (96.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>&gt; 1 Antiplatelet</td>
<td>116 (61.7)</td>
<td>100 (61.4)</td>
<td>16 (64.0)</td>
<td>0.80</td>
</tr>
<tr>
<td>Statin use</td>
<td>163 (86.7)</td>
<td>142 (87.1)</td>
<td>21 (84.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hematologic biomarker</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39.49 ± 4.97</td>
<td>39.66 ± 4.88</td>
<td>38.34 ± 5.46</td>
<td>0.22</td>
</tr>
<tr>
<td>Lymphocyte (cells/μL)</td>
<td>1,896.4 ± 644.7</td>
<td>1,881.3 ± 637.1</td>
<td>2,010.3 ± 704.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.12 ± 0.46</td>
<td>4.17 ± 0.40</td>
<td>3.80 ± 0.66</td>
<td>0.01</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.54 ± 0.34</td>
<td>0.52 ± 0.30</td>
<td>0.64 ± 0.50</td>
<td>0.27</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.04 ± 0.84</td>
<td>1.05 ± 0.88</td>
<td>0.96 ± 0.53</td>
<td>0.51</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>5.41 ± 1.63</td>
<td>5.43 ± 1.60</td>
<td>5.30 ± 1.85</td>
<td>0.71</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>146.88 ± 42.07</td>
<td>148.99 ± 40.83</td>
<td>133.12 ± 48.06</td>
<td>0.08</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>136.2 ± 104.4</td>
<td>135.5 ± 106.3</td>
<td>142.3 ± 90.5</td>
<td>0.79</td>
</tr>
<tr>
<td>High-density lipoprotein (mg/dL)</td>
<td>40.32 ± 10.91</td>
<td>40.53 ± 10.20</td>
<td>38.99 ± 14.94</td>
<td>0.62</td>
</tr>
<tr>
<td>Low-density lipoprotein (mg/dL)</td>
<td>98.51 ± 38.40</td>
<td>99.11 ± 38.58</td>
<td>94.60 ± 37.72</td>
<td>0.59</td>
</tr>
<tr>
<td>Intraoperative variable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt use</td>
<td>131 (69.7)</td>
<td>116 (71.2)</td>
<td>15 (60.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>202.69 ± 47.53</td>
<td>203.56 ± 46.75</td>
<td>197 ± 53.05</td>
<td>0.32</td>
</tr>
<tr>
<td>Clamping time (min)</td>
<td>56.63 ± 13.97</td>
<td>57.36 ± 14.02</td>
<td>51.08 ± 12.52</td>
<td>0.04</td>
</tr>
<tr>
<td>Operation side</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>88 (46.8)</td>
<td>76 (46.6)</td>
<td>12 (48.0)</td>
<td>0.90</td>
</tr>
<tr>
<td>Right</td>
<td>100 (53.2)</td>
<td>87 (53.4)</td>
<td>13 (52.0)</td>
<td>0.82</td>
</tr>
<tr>
<td>Nutrition index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONUT score</td>
<td>2.05 ± 1.68</td>
<td>1.85 ± 1.31</td>
<td>3.40 ± 2.87</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%).
ASA, American Society of Anesthesiologists; PS, physical status; MI, myocardial infarction; CABG, coronary artery bypass grafting; CONUT, Controlling Nutritional Status.
Table 2. Postoperative outcomes for CONUT groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 188)</th>
<th>Low CONUT (n = 161)</th>
<th>High CONUT (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative complication</td>
<td>25 (13.3)</td>
<td>13 (8.1)</td>
<td>12 (44.4)</td>
</tr>
<tr>
<td>Major adverse cardiovascular events</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Renal complications</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Wound complications</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal complications</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive care unit stay (hr)</td>
<td>33.7 ± 84.3</td>
<td>34.2 ± 90.8</td>
<td>30.9 ± 20.9</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>7 (6–8)</td>
<td>6 (6–8)</td>
<td>7 (6–17)*</td>
</tr>
<tr>
<td>30-Day readmission</td>
<td>2 (1.1)</td>
<td>1 (0.6)</td>
<td>1 (3.7)</td>
</tr>
</tbody>
</table>

Values are presented as number (%), number only, mean ± standard deviation, or median (interquartile range).

CONUT, Controlling Nutritional Status.

*p < 0.05 vs. the low CONUT group.

Discussion

We evaluated the short-term prognostic value of the immunonutrition state using the CONUT score in patients who underwent CEA. Our findings showed a higher prevalence of postoperative complications in patients experiencing malnourishment than in those with normal nutrition.

Various nutritional screening tools are currently used to assess patient prognosis, as several studies have shown that malnutrition can lead to unfavorable outcomes [10]. Subjective Global Assessment and Mini Nutritional Assessment (MNA) are based on subjective data assessed by trained healthcare practitioners [11,12], whereas Prognostic Nutritional Index (PNI), Nutritional Risk Index (NRI), and CONUT scores are based on clinical or objective biochemical data [13,14]. To properly reflect the nutritional status of a patient, it would be more accurate to confirm both subjective and objective information. However, in a clinical setting, an objective, practical, and simple measurement method for primary nutritional screening may be more important. Several scoring systems, such as the PNI, NRI, and CONUT scores, have been proposed as reliable tools. Among the malnutrition scores, the CONUT score revealed the highest predictive ability for major adverse events in patients who underwent carotid artery stenting (CAS) [15]. The CONUT score was initially proposed by Ignacio de Ulibarri et al. [16] as an easy and efficient nutritional screening tool for identifying malnutrition in hospitalized patients. A recent meta-analysis found that malnutrition calculated by the CONUT score was related to poor prognosis in surgical patients with hepatopancreatobiliary and gastrointestinal cancers [17]. Another study demonstrated an association between CONUT score and unfavorable clinical prognosis in hospitalized patients with various cardiovascular diseases [18]. Despite substantial evidence demonstrating the effectiveness of the CONUT score as an indicator of malnutrition for clinically unfavorable outcomes in various diseases, only one study has used the CONUT score as a prognostic indicator in patients undergoing CAS [15]. The results revealed that higher CONUT scores were associated with a clinically unfavorable prognosis in patients with CAS. In our study, CONUT score was positively associated with acute postoperative complications. However, more research is needed to assess which nutritional-immunological screening tools are the most practical and accurate in predicting clinically unfavorable prognosis after CEA.

Malnutrition accounts for a significant proportion of patients with stroke and neurological impairment, ranging from 6.1% to 62% [19]. According to the CONUT guidelines of our study, 32.4% of patients undergoing CEA were classified as malnourished. Thus, it is essential to elucidate how nutritional status affects acute postoperative complications in patients undergoing CEA. However, the exact pathophysiological mechanism underlying the association between CONUT score and increased postoperative morbidity remains unknown. Indeed, the mechanism of the relationship between CONUT score and increased risk of postoperative complications is considered multifactorial. Other investigators have hypothesized that malnutrition increases major postoperative complications owing to alterations in protein metabolism or decreased physiological reserves to cope with acute surgical stress.
### Table 3. Predictors associated with acute postoperative complications in patients undergoing carotid endarterectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.96 (0.36–2.56)</td>
<td>0.94</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (0.97–1.08)</td>
<td>0.35</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.85 (0.74–0.98)</td>
<td>0.44</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.67 (0.29–1.56)</td>
<td>0.35</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.98 (0.94–1.02)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.56 (0.25–1.23)</td>
<td>0.15</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0.40 (0.00–6.57)</td>
<td>0.22</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8.43 (2.87–24.74)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Previous ischemic heart disease</td>
<td>1.07 (0.37–3.13)</td>
<td>0.90</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.78 (0.61–5.17)</td>
<td>0.29</td>
</tr>
<tr>
<td>Baseline heart rate</td>
<td>1.01 (0.98–1.04)</td>
<td>0.60</td>
</tr>
<tr>
<td>Baseline systolic blood pressure</td>
<td>1.02 (0.99–1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure</td>
<td>1.02 (1.00–1.04)</td>
<td>0.09</td>
</tr>
<tr>
<td>Symptomatic lesion</td>
<td>2.29 (0.91–5.73)</td>
<td>0.08</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>1.20 (0.16–8.88)</td>
<td>0.86</td>
</tr>
<tr>
<td>Antiplatelet, &gt; 1</td>
<td>1.17 (0.51–2.64)</td>
<td>0.71</td>
</tr>
<tr>
<td>Intraoperative variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt use</td>
<td>0.64 (0.29–1.43)</td>
<td>0.28</td>
</tr>
<tr>
<td>Operation time</td>
<td>1.00 (0.99–1.00)</td>
<td>0.54</td>
</tr>
<tr>
<td>Clamping time</td>
<td>0.97 (0.93–1.00)</td>
<td>0.04</td>
</tr>
<tr>
<td>Operation side, left</td>
<td>1.03 (0.47–2.27)</td>
<td>0.93</td>
</tr>
<tr>
<td>Ipsilateral stenosis, &gt; 70%</td>
<td>1.16 (0.35–3.88)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hematologic biomarker and nutrition index</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>0.96 (0.89–1.03)</td>
<td>0.23</td>
</tr>
<tr>
<td>Albumin</td>
<td>0.27 (0.14–0.53)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>0.99 (0.98–1.00)</td>
<td>0.09</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.82 (0.35–1.94)</td>
<td>0.66</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.96 (0.74–1.23)</td>
<td>0.71</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1.00 (0.99–1.01)</td>
<td>0.81</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>0.99 (0.95–1.03)</td>
<td>0.53</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>1.00 (0.99–1.01)</td>
<td>0.60</td>
</tr>
<tr>
<td>CONUT score, &gt; 2</td>
<td>6.47 (2.95–14.20)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; CONUT, Controlling Nutritional Status.

*Adjusted for heart failure, clamping time, and albumin level.

In other words, malnutrition itself may lead to a poor prognosis after surgery due to multifactorial consequences such as decreased protein synthesis, increased inflammatory response, and changes in immune function. Interestingly, immunonutritional status was readily assessed using the CONUT score based on serum albumin, total cholesterol, and lymphocyte count because a decrease in the response of each variable with acute disease or acute surgical stress may reflect a low immune nutritional status. Of the three CONUT components, serum albumin level was the most critical parameter. It is generally considered a biomarker of nutritional and systemic inflammatory status. Therefore, hypoalbuminemia may contribute to the progression and development of atherosclerosis [21].

Furthermore, hypoalbuminemia is associated with reduced antioxidant and antiplatelet aggregation activities, which result in increased central mediators of cardiovascular stenosis and increased oxidative stress and blood viscosity, leading to cardiovascular complications. In our study, these mechanisms may have influenced the association between malnutrition and cardiovascular complications. Moreover, lymphocytopenia affected the postoperative...
complications in patients who underwent CEA in our study. Indeed, low lymphocyte counts may indicate impaired host immunity and poor nutrient intake [22]. Lymphocytopenia has also been studied in association with malnutrition and systemic inflammatory conditions. It has been speculated that specific pathophysiological courses may cause an acute increase in stress-related steroid levels, leading to a decrease in lymphocyte count [23]. In addition, low cholesterol levels may indicate progressive disease and systemic inflammatory activation [24]. Therefore, the CONUT score assesses the immunonutritional status of patients with caloric depletion, reduced protein reserves, and impaired immune defenses, which may serve as incremental values in predicting postoperative complications.

Our results suggest that screening the nutritional status of patients admitted for CEA can identify those at a higher risk of postoperative complications. Additionally, identifying malnutrition in patients undergoing CEA may lead to interventions for secondary prevention such as oral nutritional supplements, dietary counseling, food/fluid enrichment, and educational interventions [25]. There are many malnutrition screening tools, but there are still no standard guidelines for treating patients undergoing CEA. The management of atherosclerotic carotid stenosis is still under development, and the prognostic capabilities of the nutritional index have been found to be valuable and practical in several studies [26]. Therefore, the CONUT score, an easy and objective scoring system, may be selected as a valuable nutritional index for predicting unfavorable clinical outcomes in patients undergoing CEA, in addition to traditional parameters.

Our study has some limitations. First, this was a single-center retrospective observational study with a relatively small patient cohort. Second, our study assessed CONUT scores only on admission and did not evaluate CONUT scores after hospital discharge. Third, we only evaluated CONUT scores as indicators of malnutrition. Due to the retrospective nature of our study, other nutritional indicators, such as the Maastricht Index, MNA Short-Form scale, and NRI, were not used. Fourth, considering the retrospective nature of this study, we verified the post hoc power of the sample size. The incidence of acute postoperative complications after CEA in patients enrolled in this study was 13%. For the sample size of 188 people, when an alpha error of 0.05 was considered, only 85% of the post-test power was confirmed. These limitations require further investigation to validate the results. Large multicenter and prospective studies with larger numbers of patients are needed.

In conclusion, this study revealed that malnutrition assessment using the CONUT score can identify patients undergoing CEA who are at elevated risk for postoperative complications. Evaluation of immunonutritional status by CONUT score may help stratify the risk of acute postoperative complications and encourage improvement in nutritional status.
Notes

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

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Author contributions
Conceptualization, Formal analysis: HWS, GY, SJL, JO; Investigation: HWS, GY, SJL; Data curation: HWS, SJL; Methodology: GY, SJL; Project administration, Validation: JO; Visualization, Supervision: HWS, JO; Software: SJL; Writing-original draft: HWS, JO; Writing-review & editing: HWS, JO.

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Rates and subsequent clinical course of fetal congenital anomalies detected by prenatal targeted ultrasonography of 137 cases over 5 years in a single institute: a retrospective observational study

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Background: With the establishment of international guidelines and changes in insurance policies in Korea, the role of targeted ultrasonography has increased. This study aimed to identify the rates and clinical course of anomalies detected using prenatal targeted ultrasonography.

Methods: This study was a retrospective analysis of all pregnancies with targeted ultrasonography performed in a single secondary medical center over 5 years.

Results: Fetal anomalies were detected by targeted ultrasonography in 137 of the 8,147 cases (1.7%). The rates of anomalies were significantly higher in female fetuses (2.0% vs. 1.3%). In cases of female fetuses, the rate of anomalies was significantly higher in the advanced maternal age group (2.4% vs. 1.2%). In cases of male fetuses, the rate of anomalies was significantly higher in nulliparous (2.4% vs. 1.5%) and twin (5.7% vs. 1.9%) pregnancies. Pulmonary anomalies were significantly more common in the multiparity group (17.6% vs. 5.8%). Among the 137 cases, 17.5% terminated the pregnancy, 16.8% were diagnosed as normal after birth, and 42.3% were diagnosed with anomalies after birth or required follow-up.

Conclusion: Through the first study on the rates and clinical course of anomalies detected by targeted ultrasonography at a single secondary center in Korea, we found that artificial abortions were performed at a high rate, even for relatively mild anomalies or anomalies with good prognosis. We suggest the necessity of a nationwide study to establish clinical guidelines based on actual incidences or prognoses.

Keywords: Congenital abnormalities; Prenatal diagnosis; Prenatal ultrasonography

Introduction

Current ultrasonography, with its high resolution and sensitive Doppler imaging, is a noninvasive and safe method suitable for monitoring fetal growth and well-being, and for identifying structural fetal abnormalities. The Eurofetus study examined the accu-
racy of routine midtrimester ultrasonographic examinations in unselected populations. Of 4,615 malformations, 2,593 were detected (sensitivity, 56.2%) before 24 weeks of gestation. Detection sensitivity was higher for major abnormalities than for minor abnormalities (73.7% vs. 45.7%) [1]. With the development of ultrasonography and the establishment of international guidelines, ‘targeted ultrasonography’ that is more accurate and comprehensive than conventional routine ultrasonography has become possible. In a recent retrospective study, the congenital malformation detection rate was compared in those that underwent routine conventional obstetric ultrasonography vs. targeted ultrasonography. The sensitivity, specificity, and diagnostic coincidence rate were 53.33%, 53.81%, and 53.75%, respectively, in the routine conventional group and 90.00%, 84.76%, and 86.67%, respectively, in the targeted ultrasonography group [2].

The main purpose of mid-trimester targeted ultrasonography is to provide accurate diagnostic information for the delivery of optimized antenatal care, with the best possible outcomes for the mother and fetus. To reduce the burden on families and society, the timely detection of severe fetal malformations and improving the quality of newborns are important issues in current antenatal care. Prenatal diagnosis can lead to improved outcomes for fetuses requiring in utero fetal intervention or for newborns requiring neonatal surgery or neonatal intensive care by ensuring that delivery is performed in a hospital equipped with the necessary facilities and personnel. Some structural anomalies are associated with genetic conditions, and recognition can lead to prenatal genetic diagnosis. Parents have the option of either terminating or continuing with the pregnancy after proper counseling.

Although targeted ultrasonography was initially performed mainly in mothers with risk factors, its importance for all pregnant women has become apparent. Most major countries, including the United States, United Kingdom, Australia, and New Zealand, have reached a consensus that all pregnant women should be offered targeted ultrasound for the detection of fetal structural anomalies and pregnancy complications. The International Society of Ultrasound in Obstetrics and Gynecology recommends that targeted ultrasonography be performed between 18 and 22 weeks; by developing guidelines for examination, this has contributed to improving the consistency and quality of examinations [3].

In Korea, targeted ultrasonography has been paid for by the National Health Insurance Corporation since October 2016. Accordingly, as economic accessibility increases, the role of targeted ultrasonography is expected to increase. Meanwhile, as the age of first marriage is delayed, the proportion of pregnancies in older women is gradually increasing, and promoting the health of the fetus and newborn is an important public health issue.

In Korea, a few recent studies have examined the rates and subsequent clinical course of fetal anomalies detected by prenatal targeted ultrasonography. The most recent study by Lee et al. [4] was published in 2010 and was limited to congenital heart anomalies diagnosed between 1994 and 2005. Considering the results of the study by Jang et al. [5] that the rates of congenital anomalies were high in newborns from multicultural families, it is also necessary to investigate the current status of prenatal diagnosis in multicultural families.

The purpose of this study was to identify the rates and subsequent clinical course of congenital anomalies detected by prenatal targeted ultrasonography, including pregnancies in multicultural families.

**Methods**

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUMC 2018-05-003), and the requirement for informed consent was waived.

This study was a retrospective analysis of 8,147 pregnancies (including 224 twins) with targeted ultrasonography from September 15, 2012 to September 14, 2017, in a single secondary obstetrical medical center in Daegu, Korea. Targeted ultrasonography was performed between 20 and 26 weeks of gestational age by a registered diagnostic medical sonographer with an obstetrics and gynecology specialty. The ultrasonograms were then interpreted and diagnosed by obstetricians.

The ultrasound machine used for diagnosis was a Voluson 730 Expert (GE Healthcare, Chicago, IL, USA) with a convex array ultrasound probe, type 4C-A (GE Healthcare). Fetal anomalies were classified according to the organ in which the anomaly was diagnosed: central nervous system (CNS), face and neck, cardiac and pulmonary systems, gastrointestinal system, genitourinary system, musculoskeletal system, skin and soft tissue, multiple anomalies, and other anomalies. Cases with two or more anomalies were classified as having multiple anomalies. Other anomalies included umbilical cord anomalies, hydrops fetalis, and abdominal masses of unknown origin. Among prenatal ultrasound diagnoses, the findings that could be improved during prenatal and postnatal follow-up, such as renal pelvis dilatation [6], choroid plexus cyst [7], mild lateral ventricle dilatation [8], and transient fetal arrhythmias [9], were excluded from the analysis.

Statistical analyses were performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). The rates of fetal anomalies ac-
According to maternal age, parity, race, residential locality, number of fetuses, and fetal sex were analyzed using the chi-square test and Fisher exact test, as appropriate. The rate of each affected organ according to maternal age, parity, and fetal sex was analyzed using the chi-square test and Fisher exact test, as appropriate.

**Results**

1. **Rates of fetal anomalies detected by targeted ultrasonography according to maternal characteristics and fetal sex**

Of the 8,147 cases in which targeted ultrasonography was performed, fetal anomalies were detected in 137 (1.7%). Among the fetuses, 84 (61.3%) were male and 53 (38.7%) were female.

The rates of targeted ultrasonography-found anomalies organized by maternal age were as follows: 0% (0 of 33) for mothers younger than 21 years, 1.7% (7 of 422) for those aged 21 to 25 years, 1.9% (51 of 2,772) for those aged 26 to 30 years, 1.4% (55 of 3,834) for those aged 31 to 35 years, 2.0% (21 of 1,028) for those aged 36 to 40 years, and 2.8% (3 of 108) for those older than 40 years. The rates according to parity were 1.8% (86 of 4,746) for primiparous women, 1.4% (40 of 2,896) for para 1 multiparous women, and 2.2% (11 of 505) for para 2+ or greater multiparous women. The rates according to maternal race were 1.7% (135 of 8,050) for Koreans, 2.3% (1 of 44) for Vietnamese, 0% (0 of 22) for Chinese, and 3.2% (1 of 31) for others. The races in ‘others’ included, in decreasing prevalence, Filipinos, Cambodians, and Thais, among other races. The rates according to region of residence were 1.6% (111 of 6,856) for Daegu, 1.9% (20 of 1,079) for Gyeongsangbuk-do, and 2.8% (6 of 212) for other regions. The regions in ‘other’ included, in decreasing prevalence, Gyeongsangnam-do, Gyeonggi-do, and Ulsan, among other areas.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male</th>
<th>p-value (OR, 95% CI)</th>
<th>Female</th>
<th>p-value (OR, 95% CI)</th>
<th>Total</th>
<th>p-value (OR, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 35</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 35</td>
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<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nulliparity</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Multiparity</td>
<td></td>
<td></td>
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</tr>
<tr>
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<tr>
<td>Korean</td>
<td></td>
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<tr>
<td>Foreigner</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Residential locality</td>
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<td></td>
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</tr>
<tr>
<td>Daegu</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>No. of fetuses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singleton</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number only or number (%) unless otherwise specified.

OR, odds ratio; CI, confidence interval.

The p-values and ORs (95% CIs) were analyzed by chi-square test or Fisher exact test as appropriate.

*p < 0.05.

https://doi.org/10.12701/jyms.2022.00514
rates according to fetus number were 1.6% (129 of 7,923) for singleton pregnancies and 3.6% (8 of 224) for twin pregnancies.

The rate of total anomalies according to fetal sex was significantly higher in the male fetal group than in the female fetal group (2.0% vs. 1.3%, p = 0.023; odds ratio [OR], 1.49). In the case of female fetuses, the rate of ultrasonography-found anomalies was significantly higher in the advanced maternal age group (>35 years) (2.4% vs. 1.2%, p = 0.024; OR, 2.04). In the case of male fetuses, the rate of ultrasonography-found anomalies was significantly higher in the nulliparity (2.4% vs. 1.5%, p = 0.041; OR, 0.62) and twin (5.7% vs. 1.9%, p = 0.018; OR, 3.13) groups. Considering all fetuses regardless of sex, there was no significant difference in the rate of ultrasonography-found anomalies according to maternal age, parity, race, residential locality, and number of fetuses. However, the rate tended to be higher in the advanced maternal age (>35 years), nulliparity, foreigner, other residential locality, and twin pregnancy groups (Table 1).

### 2. Rates of involved organ systems of fetal anomalies detected by targeted ultrasonography according to maternal age, parity, and fetal sex

The rates of involved organ systems of targeted ultrasonography-found anomalies were as follows: 19.0% (26 cases) for cardiac, 18.2% (25 cases) for musculoskeletal, 12.4% (17 cases) for CNS, and 12.4% (17 cases) for genitourinary anomalies. Among the cardiac anomalies, ventricular septum defects were the most common, followed by tetralogy of Fallot (TOF) and transposition of the great arteries. Polydactyly was the most common musculoskeletal anomaly. CNS anomalies included ventriculomegaly, agenesis of the corpus callosum, and holoprosencephaly.

Pulmonary anomalies were significantly more common in the multiparity group (17.6% vs. 5.8%, p = 0.027; OR, 3.47) (Table 2). In addition, there was no significant difference in the rate of involved organ systems of ultrasonography-found anomalies according to maternal age, maternal parity, and fetal sex.

### 3. Clinical course of fetal anomalies detected by targeted ultrasonography

Among the 137 cases of fetal anomalies detected by targeted ultrasonography, there were 24 cases (17.5%) of artificial abortion, 81 cases (59.1%) of postpartum follow-up, and 32 cases (23.4%) that could not be traced after being transferred to other medical centers. The postpartum follow-up group was divided into three types: 23 cases (16.8% of 137 cases) diagnosed as normal after birth, five cases (3.6%) as requiring follow-up with age, and 53 cases (38.7%) as anomalies (consistent with the prenatal diagnosis or other additional anomalies) (Table 3).

In 24 cases of artificial abortion, four (16.7%) were CNS anomalies, four (16.7%) were face anomalies, four (16.7%) were cardiac anomalies, three (12.5%) were pulmonary anomalies, and one (4.2%) was a musculoskeletal anomaly. Regarding face anomalies, in four of nine cases (44.4%) the mother opted for artificial abortion, the highest rate for a single anomaly.

For a normal postpartum diagnosis, the prenatal ultrasonography-found diagnosis was ventriculomegaly, muscular ventricular septal defect, dilatation of the renal pelvis, and hydronephrosis. The five cases that required follow-up with age were mild ventriculomegaly and hydronephrosis. The group with anomalies requir-

### Table 2. Involved organ system of fetal anomalies according to the maternal age, maternal parity, and fetal sex

<table>
<thead>
<tr>
<th>Involved organ system</th>
<th>Total</th>
<th>Maternal age (yr)</th>
<th>p-value</th>
<th>Maternal parity</th>
<th>p-value</th>
<th>Fetal sex</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≤35</td>
<td>&gt;35</td>
<td></td>
<td>≤35</td>
<td>&gt;35</td>
<td></td>
</tr>
<tr>
<td>CNS anomaly</td>
<td>17 (12.4)</td>
<td>14 (12.4)</td>
<td>3 (12.5)</td>
<td>&gt;0.999</td>
<td>12 (14.0)</td>
<td>5 (9.8)</td>
<td>0.476</td>
</tr>
<tr>
<td>Face anomaly</td>
<td>9 (6.6)</td>
<td>6 (5.3)</td>
<td>3 (12.5)</td>
<td>0.193</td>
<td>6 (7.0)</td>
<td>3 (5.9)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Cardiac anomaly</td>
<td>26 (19.0)</td>
<td>21 (18.6)</td>
<td>5 (20.8)</td>
<td>0.779</td>
<td>17 (19.8)</td>
<td>9 (17.6)</td>
<td>0.760</td>
</tr>
<tr>
<td>Pulmonary anomaly</td>
<td>14 (10.2)</td>
<td>13 (11.5)</td>
<td>1 (4.2)</td>
<td>0.463</td>
<td>5 (5.8)</td>
<td>9 (17.6)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Gastrointestinal anomaly</td>
<td>5 (3.6)</td>
<td>5 (4.4)</td>
<td>0 (0)</td>
<td>0.586</td>
<td>3 (3.5)</td>
<td>2 (3.9)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Genitourinary anomaly</td>
<td>17 (12.4)</td>
<td>14 (12.4)</td>
<td>3 (12.5)</td>
<td>&gt;0.999</td>
<td>8 (9.3)</td>
<td>9 (17.6)</td>
<td>0.152</td>
</tr>
<tr>
<td>Musculoskeletal anomaly</td>
<td>25 (18.2)</td>
<td>19 (16.8)</td>
<td>6 (25.0)</td>
<td>0.385</td>
<td>18 (20.9)</td>
<td>7 (13.7)</td>
<td>0.291</td>
</tr>
<tr>
<td>Skin and soft tissue anomaly</td>
<td>4 (2.9)</td>
<td>4 (3.5)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
<td>3 (3.5)</td>
<td>1 (2.0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Multiple anomalies</td>
<td>10 (7.3)</td>
<td>8 (7.1)</td>
<td>2 (8.3)</td>
<td>0.688</td>
<td>9 (10.5)</td>
<td>1 (2.0)</td>
<td>0.090</td>
</tr>
<tr>
<td>Other anomalies</td>
<td>10 (7.3)</td>
<td>9 (8.0)</td>
<td>1 (4.2)</td>
<td>&gt;0.999</td>
<td>5 (5.8)</td>
<td>5 (9.8)</td>
<td>0.500</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

CNS, central nervous system.

The p-values are analyzed by chi-square test or Fisher exact test as appropriate.

*Odds ratio, 3.47 (95% confidence interval, 1.09–11.02).

*p < 0.05.
Table 3. Clinical course of fetal anomalies detected by targeted ultrasonography

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Termination</th>
<th>Normal on postpartum FU</th>
<th>Required to FU</th>
<th>Anomaly on postpartum FU</th>
<th>FU loss</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS anomaly</td>
<td>4 (23.5)</td>
<td>5 (29.4)</td>
<td>1 (5.9)</td>
<td>1 (5.9)</td>
<td>6 (35.3)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Face anomaly</td>
<td>4 (44.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (22.2)</td>
<td>3 (33.3)</td>
<td>9 (100)</td>
</tr>
<tr>
<td>Cardiac anomaly</td>
<td>4 (15.4)</td>
<td>5 (19.2)</td>
<td>0 (0)</td>
<td>13 (50.0)</td>
<td>4 (15.4)</td>
<td>26 (100)</td>
</tr>
<tr>
<td>Pulmonary anomaly</td>
<td>3 (21.4)</td>
<td>5 (35.7)</td>
<td>0 (0)</td>
<td>3 (21.4)</td>
<td>3 (21.4)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Gastrointestinal anomaly</td>
<td>0 (0)</td>
<td>1 (20.0)</td>
<td>0 (0)</td>
<td>2 (40.0)</td>
<td>2 (40.0)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Genitourinary anomaly</td>
<td>0 (0)</td>
<td>4 (23.5)</td>
<td>4 (23.5)</td>
<td>9 (52.9)</td>
<td>0 (0)</td>
<td>17 (100)</td>
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<tr>
<td>Musculoskeletal anomaly</td>
<td>2 (8.0)</td>
<td>3 (12.0)</td>
<td>0 (0)</td>
<td>15 (60.0)</td>
<td>5 (20.0)</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Skin and soft tissue anomaly</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (50.0)</td>
<td>2 (50.0)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Multiple anomalies</td>
<td>4 (40.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (30.0)</td>
<td>3 (30.0)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Other anomalies</td>
<td>3 (30.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (30.0)</td>
<td>4 (40.0)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>24 (17.5)</td>
<td>23 (16.8)</td>
<td>5 (3.6)</td>
<td>53 (38.7)</td>
<td>32 (23.4)</td>
<td>137 (100)</td>
</tr>
</tbody>
</table>

Values are presented as number or number (%).
FU, follow-up; CNS, central nervous system.

The association between maternal age and congenital malformations remains controversial. Most experts agree that the rate of congenital malformations increases with increasing maternal age and that malformations also occur in mothers younger than 20 years [12]. In a large prospective cohort study, Hollier et al. [13] demonstrated that women aged 25 years or older at delivery had significantly and progressively greater risk of having fetuses with nonchromosomal malformations compared with women aged 20 to 24 years. By 35 years of age, the additional age-related risk of having infants with nonchromosomal malformations was approximately 1%, and for women aged 40 years or older, the increase in risk was approximately 2.5% over that of women younger than 25 years. In this study, no fetal anomalies were detected by targeted ultrasonography in women younger than 20 years, and the highest rate of 2.8% was found in women who were older than 40 years. Statistically significant differences were only found in the case of female fetuses, with a higher rate in women of advanced maternal age.

Discussion

Congenital anomalies are the three leading causes of spontaneous abortions and perinatal deaths. According to data from 1998 to 2011 provided by the European Surveillance of Congenital Anomalies, among 73,337 cases of perinatal mortality, the rate of congenital anomaly was 1.27 per 1,000 births [10]. In Korea, according to an online publication on ‘infant, maternal and perinatal mortality statistics’ provided by the Korean Statistical Information Service (KOSIS), ‘congenital anomalies, deformities, and chromosomal abnormalities’ was the third leading cause of infant mortality in 2020, accounting for 16.2% of all infant deaths [11].

However, the association between maternal age and congenital malformations remains controversial. Most experts agree that the rate of congenital malformations increases with increasing maternal age and that malformations also occur in mothers younger than 20 years [12]. In a large prospective cohort study, Hollier et al. [13] demonstrated that women aged 25 years or older at delivery had significantly and progressively greater risk of having fetuses with nonchromosomal malformations compared with women aged 20 to 24 years. By 35 years of age, the additional age-related risk of having infants with nonchromosomal malformations was approximately 1%, and for women aged 40 years or older, the increase in risk was approximately 2.5% over that of women younger than 25 years. In this study, no fetal anomalies were detected by targeted ultrasonography in women younger than 20 years, and the highest rate of 2.8% was found in women who were older than 40 years. Statistically significant differences were only found in the case of female fetuses, with a higher rate in women of advanced maternal age.

The association between fetal sex and obstetric complications has rarely been studied and remains controversial. The emerging concept of differences according to fetal sex focuses on sexual dimorphism in maternal-fetal-placental interplay. A recent meta-analysis strengthened the hypothesis that pregnancies with a male fetus are more susceptible to abnormal placental development, which is associated with obstetric complications such as gestational hypertension, preeclampsia, gestational diabetes, and placental abruption [14]. In the case of congenital anomalies, there was a recent meta-analysis on the association between fetal sex and surgically correctable anomalies. The authors found that esophageal atresia, anorectal malformation, Hirschsprung disease, congenital diaphragmatic hernia, omphalocele, malrotation, congenital pulmonary airway malformation, intestinal atresia, and gastrochisis were significantly more common in males, and biliary atresia and choledochal cysts were significantly more common in females [15]. However, previous studies differ from the present study because they analyzed anomalies among neonates, not those found before birth or abortion. The results of our study are consistent with those of other studies that advocate considering male fetuses as a risk factor for congenital anomalies.
In our study, nulliparity and twins significantly increased the rate of ultrasonography-found anomalies only in the male fetus group. In several previous studies, the risk of congenital anomalies has been shown to be higher in twins than in singletons [16]. In a statewide population-based study in Florida, male fetuses had a 29% higher risk of congenital anomalies than their twin sisters [17]. In terms of the association between maternal parity and congenital anomalies, some studies have indicated an increased risk of specific categories of congenital anomalies among women with their first child. In contrast, other studies have shown a protective effect in the first child in a few categories [18]. In our study, among the organ systems involved in ultrasonography-found anomalies, only pulmonary anomalies were found to have a significantly different rate according to parity, being higher for multiparity (5.8% vs. 17.6%, p = 0.027; OR, 3.47). However, we do not yet understand the mechanism underlying the association between congenital anomalies and fetal sex, parity, and twin pregnancies.

In this study, the organ system with the highest rate of anomalies detected by targeted ultrasonography was cardiac, with 26 of 137 cases (19.0%). Among them, 15.4% of pregnancies were terminated due to abortion. Of the remaining births, 50.0% were diagnosed with anomalies after birth. According to the online publication on ‘infant, maternal and perinatal mortality statistics’ provided by KOSIS, in 2020, there were 115 infant deaths due to ‘congenital malformations, deformations, and chromosomal abnormalities,’ and the most common anomalies were cardiac-related in 41 cases [11]. Furthermore, in the case of infant death in Korea, autopsies are often not performed; therefore, it can be estimated that the mortality rate due to congenital malformations is much higher. Accordingly, in particular, it is necessary to accurately diagnose cardiac anomalies during antepartum evaluation, provide mothers with accurate and complete information about prognosis and treatment, and then actively consult with them.

The proportion of births from multicultural families among all births was 6.0% in 2020, an increase of 1.7% from 4.3% in 2010. According to recent statistics on multicultural families, the age of pregnant women in multicultural families is increasing similarly to that of Korean pregnant women. The proportion of those aged 30 to 34 was highest at 32.3%, and the average age of childbirth was 30.7 years, an increase of 2.7 years from 2010. The average age of first childbirth increased to 29.6 years, the second childbirth to 31.7 years, and the third childbirth to 33.5 years [19]. Furthermore, several studies have indicated that advanced paternal age is associated with many congenital anomalies [20]. According to the 2020 Statistics Korea report, in the case of multicultural families, the proportion of husbands aged 45 years or older was 28.6%, followed by 19.4% in their early 30s, and 17.9% in their late 30s [19].

As a result, the need for antenatal examinations has increased in pregnant women from multicultural families; however, there are restrictions on the use of medical services due to lack of communication, lack of information, and cost burdens. Therefore, there is a need for greater concern and diverse social support in antenatal medical services for multicultural families.

In a recent retrospective study in Nigeria, abortion was performed in 32.8% of major anomalies detected on prenatal ultrasonography [21]. In the present study, among the 137 cases, 24 (17.5%) involved artificial abortions. In terms of the ratio of abortion cases to the total number of diagnosed cases for each single organ involved, the abortion rate was highest in the following order: 44.4% for face anomalies (4 of 9 cases), 23.5% for CNS anomalies (4 of 17 cases), 21.4% for pulmonary anomalies (3 of 14 cases), and 15.4% for cardiac anomalies (4 of 26 cases). Relatively mild anomalies, such as cleft lip and cleft palate or TOF with a relatively good prognosis for postpartum treatment, were included.

Losing hope for having a healthy child and making the decision to terminate the pregnancy is a traumatic event that could have long-term psychological outcomes such as posttraumatic stress, severe grief, and depression. In a qualitative content analysis through interviews, most women who had experienced pregnancy termination because of fetal anomalies expressed the need to receive information about the advantages and disadvantages of terminating the pregnancy, or the outcomes of keeping the fetus and continuing the pregnancy. The authors described that counseling, which can satisfy these needs and empower parents to intervene in their choices, can avoid long-term undesirable psychological outcomes, facilitate the conditions for their return to normal life, and ultimately promote their health [22]. However, counseling is difficult due to the lack of actual data in Korea, such as the actual concordance between prenatal ultrasonographic diagnosis and postpartum diagnosis, the common clinical course of pregnancies with ultrasonography-diagnosed fetal anomalies, and the outcome of each type of anomaly after birth.

This study has limitations, such as the small number of independent variables that can be analyzed due to record-based analysis, and the small number of mothers from multicultural families, which was too low to obtain statistical significance among races. In addition, there was a limitation because of follow-up data loss in the patient group transferred to a tertiary hospital after an anomaly was detected by targeted ultrasonography.

As artificial abortion was illegal in South Korea until 2021, it is estimated that the actual rate of artificial abortion was higher than the reported rate. While a large number of terminations have been performed in primary and secondary medical centers, most studies are published with data from tertiary medical centers; therefore, it...
is difficult to collect actual data about the clinical course after diagnosis. In this respect, the results of this study are noteworthy. To our knowledge, this is the first study on the rates, types of involved organs, and outcomes of anomalies detected by targeted ultrasonography at a single secondary obstetrical medical center in Korea.

Through this study, we identified some associations between ultrasonography-found anomalies and several variables, such as fetal sex, maternal parity, and number of fetuses. Moreover, we realized that artificial abortions were performed at a high rate in anomalies diagnosed with targeted ultrasound, even with relatively mild anomalies or anomalies with a good prognosis. The lack of information about postnatal confirmed rates or postnatal outcomes can cause fear and anxiety in patients and may lead to pregnancy termination. Furthermore, in the case of artificial abortions, accurate and sufficient information in the decision-making process plays an important role in the psychological health of patients. Therefore, it is necessary to analyze the prognosis of anomalies identified by ultrasonography through a nationwide study, and based on it, establish policies and guidelines including indications for artificial abortion.

Notes

Conflicts of interest
Joon Sakong has been an editorial board member of Journal of Youngnam Medical Science since 2004. He was not involved in the review process of this manuscript. There is no conflict of interest to declare.

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Author contributions
Conceptualization: HC, HSK; JS; Investigation: HC; Data curation: HC, HSK; Formal analysis, Supervision: HSK, JS; Methodology, Validation: JS; Writing-original draft: HC; Writing-review & editing: HSK.

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References


Bleeding and thrombosis are major complications associated with high mortality in extracorporeal membrane oxygenation (ECMO) management. Anticoagulant therapy should be adequate to reduce thrombosis. However, related studies are limited.

Methods: We retrospectively reviewed all patients supported with ECMO at a single institution between January 2014 and July 2022 and included those on all types of ECMO using the Permanent Life Support System. Patients were classified into two groups according to their measured mean activated partial thromboplastin time (aPTT) during ECMO management: a high-anticoagulation (AC) group (aPTT, ≥ 55 seconds; n = 52) and a low-AC group (aPTT, < 55 seconds; n = 79). The primary outcome was thrombotic or bleeding events during ECMO.

Results: We identified 10 patients with bleeding; significantly more of these patients were in the high-AC group (n = 8) than in the low-AC group (15.4% vs. 2.5%, \( p = 0.01 \)). However, thrombus events and oxygenator change-free times were not significantly different between the two groups. Four patients in the high-AC group died of bleeding complications (brain hemorrhage, two; hemopericardium, one; and gastrointestinal bleeding, one). One patient in the low-AC group developed a thrombus and died of ECMO dysfunction due to circuit thrombosis.

Conclusion: Heparin did not significantly improve thrombotic outcomes. However, maintaining an aPTT of ≥ 55 seconds was a significant risk factor for bleeding events, especially those associated with mortality.

Keywords: Anticoagulants; Heparin; Oxygenators; Thrombosis

Safety of low-dose anticoagulation in extracorporeal membrane oxygenation using the Permanent Life Support System: a retrospective observational study

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Background: Bleeding and thrombosis are major complications associated with high mortality in extracorporeal membrane oxygenation (ECMO) management. Anticoagulant therapy should be adequate to reduce thrombosis. However, related studies are limited.

Methods: We retrospectively reviewed all patients supported with ECMO at a single institution between January 2014 and July 2022 and included those on all types of ECMO using the Permanent Life Support System. Patients were classified into two groups according to their measured mean activated partial thromboplastin time (aPTT) during ECMO management: a high-anticoagulation (AC) group (aPTT, ≥ 55 seconds; n = 52) and a low-AC group (aPTT, < 55 seconds; n = 79). The primary outcome was thrombotic or bleeding events during ECMO.

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Conclusion: Heparin did not significantly improve thrombotic outcomes. However, maintaining an aPTT of ≥ 55 seconds was a significant risk factor for bleeding events, especially those associated with mortality.

Keywords: Anticoagulants; Heparin; Oxygenators; Thrombosis

Introduction

In extracorporeal membrane oxygenation (ECMO) management, anticoagulation (AC) is essential to prevent clotting in the ECMO circuit. According to the Extracorporeal Life Support Organization (ELSO) guidelines, the recommended activated partial thromboplastin time (aPTT) target in AC management during ECMO is 1.5 to 2.5 times the baseline aPTT of patients [1]. However, this recommended target is not based on randomized controlled trials, and references regarding target aPTT during ECMO management are lacking.

Some studies have sought to identify adequate AC strategies for...
ECMO [2-6]. These studies indicated that AC management, especially with heparin and aPTT maintenance over 1.5 times patients’ baseline aPTT, did not improve the results of thrombotic events or mortality and caused more bleeding complications. However, the authors divided their cohort according to the patients’ target aPTT and not the actual aPTT levels. Hence, a discrepancy may exist between the assigned group of patients and their actual measured aPTT values. For example, patients with disseminated intravascular coagulation can maintain high aPTT levels; however, if their target aPTT was <60 seconds, they would be assigned to the low-aPTT group rather than the high-aPTT group. To control this discrepancy, we divided patients according to their actual measured aPTT values, not their target aPTT and conducted an analysis to identify adequate AC strategies during ECMO.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Keimyung University Dongsan Medical Center (IRB No: 2022-12-038), and the requirement for informed consent was waived owing to the retrospective nature of the study.

1. Study design

We retrospectively reviewed all the patients who received ECMO at a single institution between January 2014 and July 2022. The patients were identified using a prospectively maintained database of all patients who received ECMO at our institution. Patients undergoing all types of ECMO (venovenous or venoarterial) using the Permanent Life Support (PLS) system (Maquet, Rastatt, Germany) were included. We excluded patients who were under 18 years of age, died in the first 24 hours of ECMO initiation, received other AC therapies (e.g., nafamostat and argatroban), underwent cardiovascular surgery, had coronavirus disease 2019 pneumonia, had heparin contraindications, had active bleeding during the first 24 hours of ECMO initiation, and were transferred to other hospitals.

AC management during ECMO was reviewed. Furthermore, we divided the patients into two groups according to their measured mean aPTT during ECMO: a high-AC group (aPTT ≥ 55 seconds) and a low-AC group (aPTT < 55 seconds) (Fig. 1). Considering the loading dose of heparin at ECMO initiation, we did not include the first measured aPTT after starting ECMO in the calculation of the mean aPTT. We collected aPTT data at least 6 hours after ECMO initiation.

For the subgroup analysis, we further divided the patients into three groups (patients without AC, patients with heparinization and mean aPTT of < 55 seconds, and patients with heparinization and mean aPTT of ≥ 55 seconds) to determine the effects of ECMO management without AC.

2. Data collection

Data regarding patient characteristics, ECMO indications, oxygenator change time, laboratory values, and ECMO support duration were collected from a prospectively maintained institutional ECMO database. We also retrospectively reviewed the patients’ charts to gather supplemental data and confirm the incidence of complications, relevant imaging findings, and outcomes throughout the hospital stay.

3. Outcomes

The primary outcomes were oxygenator change-free time and overall rate of hemorrhagic or thrombotic complications. Hemorrhagic complications included hemorrhagic cerebrovascular accidents, bleeding requiring intervention, and gastrointestinal bleeding requiring endoscopic evaluation. Ischemic cerebral vascular accidents, limb thrombosis, intracardiac thrombus, pulmonary embolism, and thrombosis formation in the ECMO circuit indicated thrombotic complications. According to the ELSO guidelines, the indications for oxygenator change after oxygenator failure are as follows: visible thrombus in the oxygenator, sudden increase in pressure difference before and after oxygenator change, continuously increasing oxygen demand, and decreasing capacity for carbon dioxide washout [1].

![Fig. 1. Patient selection and study cohorts. ECMO, extracorporeal membrane oxygenation; EBS, emergency bypass system; PLS, permanent life support; AC, anticoagulation; COVID-19, coronavirus disease 2019; aPTT, activated partial thromboplastin time (sec).](https://doi.org/10.12701/jyms.2023.00339)
outcomes included the rate of ECMO weaning and overall in-hospital mortality.

4. Extracorporeal membrane oxygenation system and anticoagulation

Patients started on ECMO at our institution received a 50 IU/kg bolus of heparin before peripheral cannulation unless they were coagulopathic. None of the patients underwent heparin reversal with protamine treatment. Bedside peripheral cannulation was performed using the over-the-wire Seldinger technique in all patients in the final cohort. All arterial cannulas measured 15–17 French (Fr; HLS Cannula, Maquet), with 15 Fr used most frequently, whereas the venous cannulas measured 23 Fr (HLS Cannula, Maquet). The patients were monitored in the intensive care unit by a multidisciplinary team. Laboratory tests were performed twice daily as a standard of care, but the frequency was increased as clinically indicated.

5. Statistical analysis

Categorical variables, presented as numbers (percentages), were compared using Pearson chi-square test, whereas continuous variables, presented as means and standard deviations, were compared using the independent t-tests in the main analysis and using analysis of variance in the subgroup analysis. Oxygenator change-free time was calculated using the Kaplan-Meier method and compared using log-rank tests. All statistical data were analyzed using IBM SPSS ver. 20 (IBM Corp., Armonk, NY, USA). Furthermore, the p-values of < 0.05 were considered statistically significant.

Results

1. Patient characteristics

Fig. 1 depicts patient eligibility for this study. Of the 246 adult patients who received PLS-ECMO, 115 (46.7%) were excluded. In the final cohort, 79 (60.3%) and 52 patients (39.7%) were classi-

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low-AC group</th>
<th>High-AC group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>79</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60.3 ± 12.1</td>
<td>61.3 ± 12.9</td>
<td>0.665</td>
</tr>
<tr>
<td>Male sex</td>
<td>62 (78.5)</td>
<td>37 (71.2)</td>
<td>0.208</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.73 ± 0.21</td>
<td>1.73 ± 0.21</td>
<td>0.926</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.1 ± 3.7</td>
<td>24.0 ± 4.1</td>
<td>0.172</td>
</tr>
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<td>Medication</td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>38 (48.1)</td>
<td>23 (44.2)</td>
<td>0.552</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>34 (43.0)</td>
<td>21 (40.4)</td>
<td>0.650</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Ischemic cardiogenic shock</td>
<td>42 (53.2)</td>
<td>24 (46.2)</td>
<td>0.434</td>
</tr>
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<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>24 (30.4)</td>
<td>24 (46.2)</td>
<td>0.089</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (43.0)</td>
<td>29 (55.8)</td>
<td>0.211</td>
</tr>
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<td>Chronic kidney disease</td>
<td>12 (15.2)</td>
<td>15 (28.8)</td>
<td>0.071</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>11 (13.9)</td>
<td>11 (21.2)</td>
<td>0.324</td>
</tr>
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<td>Cardiovascular diseases</td>
<td>59 (74.7)</td>
<td>36 (69.2)</td>
<td>0.333</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>14 (17.7)</td>
<td>3 (5.8)</td>
<td>0.064</td>
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<tr>
<td>Valvular heart diseases</td>
<td>7 (8.9)</td>
<td>3 (5.8)</td>
<td>0.735</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>10 (12.7)</td>
<td>6 (11.5)</td>
<td>0.797</td>
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<td>Laboratory data</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.0 ± 1.9</td>
<td>10.0 ± 2.2</td>
<td>0.968</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>28.5 ± 5.6</td>
<td>29.1 ± 7.1</td>
<td>0.608</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>31.2 ± 13.9</td>
<td>31.3 ± 14.1</td>
<td>0.991</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.8 ± 1.5</td>
<td>1.8 ± 1.5</td>
<td>0.963</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.0 ± 0.8</td>
<td>1.7 ± 2.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Platelet count (× 10⁹/μL)</td>
<td>130.2 ± 59.4</td>
<td>122.5 ± 80.7</td>
<td>0.531</td>
</tr>
<tr>
<td>WBC count (× 10⁹/μL)</td>
<td>12.4 ± 5.8</td>
<td>11.9 ± 5.0</td>
<td>0.570</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>31.9 ± 14.9</td>
<td>30.5 ± 13.1</td>
<td>0.879</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± standard deviation, or number (%). AC, anticoagulation; BUN, blood urea nitrogen; WBC, white blood cell; aPTT, activated partial thromboplastin time.

*Statistically significant.
fied into the low-AC and high-AC groups, respectively. In the low-AC group, 32 patients were treated without AC.

Table 1 shows the patient characteristics of the two groups. Patient age was similar between the low-AC group (60.3 ± 12.1 years) and high-AC group (61.38 ± 12.9 years) (p = 0.67). Regarding the laboratory results obtained immediately before ECMO initiation, total bilirubin was significantly different between the low-AC and high-AC groups (1.04 ± 0.82 mg/dL vs. 1.74 ± 2.00 mg/dL, respectively; p = 0.007). In contrast, baseline aPTT before ECMO initiation (31.9 ± 14.9 in the low-AC group vs. 30.5 ± 13.1 in the high-AC group; p = 0.88) and other values including comorbidities were not significantly different between the two groups.

2. Results of extracorporeal membrane oxygenation management

Of the total cohort, 117 patients (89.3%) received venoarterial ECMO (VA-ECMO). Regarding clinical outcomes (Table 2), the low-AC group had a significantly longer ECMO management time than the high-AC group (206.3 ± 176.5 hours vs. 142.0 ± 126.2 hours, p = 0.02) but had a significantly lower mean aPTT during this time (44.0 ± 12.2 seconds vs. 90.0 ± 32.4 seconds, p < 0.001). However, there were significantly more patients undergoing ECMO with hemodialysis in the high-AC group than in the low-AC group (51.9% vs. 25.3%, p = 0.03).

3. Primary and secondary outcomes

In the primary outcomes (Table 2), 10 major bleeding events occurred in both groups, with two in the low-AC group and eight in the high-AC group; however, the incidence of bleeding events was significantly higher in the high-AC group (15.4% vs. 2.5%, p = 0.01). In the low-AC group, the bleeding events resulted from gastrointestinal bleeding and ECMO catheterization. These two patients survived and were eventually discharged from the hospital. In the high-AC group, the bleeding events were caused by brain hemorrhage, intrathoracic bleeding, and gastrointestinal bleeding in three, two, and three patients, respectively; among them, four died (brain hemorrhage, two; intrathoracic bleeding, one; and gastrointestinal bleeding, one).

Table 3 shows the details of bleeding complications.

One patient in the low-AC group developed a major thrombus, and the ratio of thrombus event occurrence was not significantly different between the two groups (p > 0.99). The patient underwent VA-ECMO after cardiogenic shock from myocardial infarction, and aPTT was maintained at 30 to 40 seconds. Unfortunately, aPTT, activated partial thromboplastin time; ECMO, extracorporeal membrane oxygenation; AC, anticoagulation; AMI, acute myocardial infarction; GI, gastrointestinal; ICH, intracerebral hemorrhage; DCM, dilated cardiomyopathy; SAH, subarachnoid hemorrhage.

Table 2. Results of extracorporeal membrane oxygenation management

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-AC group (n = 79)</th>
<th>High-AC group (n = 52)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMO time (hr)</td>
<td>206.3 ± 176.5</td>
<td>142.0 ± 126.2</td>
<td>0.023*</td>
</tr>
<tr>
<td>ECMO flow rate (L/min)</td>
<td>3.0 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>0.698</td>
</tr>
<tr>
<td>Distal perfusion</td>
<td>15 (19.0)</td>
<td>17 (32.7)</td>
<td>0.092</td>
</tr>
<tr>
<td>Venoarterial ECMO</td>
<td>70 (88.6)</td>
<td>47 (90.4)</td>
<td>0.853</td>
</tr>
<tr>
<td>ECMO with HD</td>
<td>20 (25.3)</td>
<td>27 (51.9)</td>
<td>0.030*</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>44.0 ± 12.2</td>
<td>90.0 ± 32.4</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Primary outcomes
- Total adverse event: 3 (3.8%) vs. 8 (15.4%) (p = 0.034*);
- Bleeding event: 2 (2.5%) vs. 8 (15.4%) (p = 0.011*);
- Thrombosis: 1 (1.3%) vs. 0 (0%) (p = 0.999).

Secondary outcomes
- ECMO weaning: 53 (67.1%) vs. 20 (38.5%) (p = 0.001*);
- 30-Day mortality: 29 (36.7%) vs. 36 (69.2%) (p = 0.001*).

Values are presented as mean ± standard deviation or number (%). Ac, anticoagulation; ECMO, extracorporeal membrane oxygenation; HD, hemodialysis; aPTT, activated partial thromboplastin time.

aStatistically significant.
ly, the patient died of ECMO dysfunction owing to circuit thrombosis.

The mean oxygenator change-free time was 223 ± 57 hours in the low-AC group and 179 ± 58 hours in the high-AC group, but the difference was not significant \((p = 0.22)\). Overall, 14 patients experienced oxygenator changes, 10 in the low-AC group and four in the high-AC group. In other patients, fibrin deposition and thrombus formation were not observed in the oxygenator after ECMO device removal. Kaplan-Meier analysis revealed no significant difference in the results of oxygenator change-free time between the two subgroups (Fig. 2). Regarding secondary outcomes, the low-AC group had a higher rate of ECMO weaning than the high-AC group (67.1% vs. 38.5%, \(p = 0.001\)) and a lower 30-day mortality rate (36.7% vs. 69.2%, \(p < 0.001\)). In the subgroup analysis (Tables 4, 5), patients who did not receive AC therapy showed no adverse events. The incidence of major adverse events was not significantly different between patients who did and did not receive AC therapy (Table 4). However, in the results comparing no AC and high AC (aPTT, ≥ 55 seconds), there were significantly more major bleeding events in the high-AC group than in the no-AC group (15.4% vs. 0%, \(p = 0.02\)) (Table 5).

**Discussion**

This study has two strengths compared to other related reports. First, we classified patients according to their actual measured aPTT values and not according to their target aPTT levels. Second, this study only included ECMO cases using PLS because the types of ECMO machines and circuits are also important factors for bleeding or thrombus events.

The primary outcomes of this study were the effects of AC on hemorrhagic events, thrombotic events, and oxygenator change-free times. However, the optimal AC strategy for VA-ECMO management remains controversial. Various factors such as mechanical stress, blood-circuit interactions, and inflammatory cytokine release place patients at an increased risk of thrombotic and hemorrhagic complications \([7-9]\). However, in the present study, the lack of systemic AC and low-dose heparinization did not increase the thrombotic events in the ECMO circuit. Additionally, there

![Fig. 2. Oxygenator change-free time in low-AC and high-AC group (Kaplan-Meier analysis). AC, anticoagulation; ECMO, extracorporeal membrane oxygenation.](https://doi.org/10.12701/jyms.2023.00339)

**Table 4. Subanalysis of patients without anticoagulation vs. patients with heparinization**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients without anticoagulation (n = 32)</th>
<th>Patients with heparinization (n = 99)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMO time (hr)</td>
<td>208.2 ± 198.8</td>
<td>171.3 ± 146.4</td>
<td>0.257</td>
</tr>
<tr>
<td>ECMO flow rate (L/min)</td>
<td>3.0 ± 0.5</td>
<td>3.1 ± 0.5</td>
<td>0.187</td>
</tr>
<tr>
<td>Distal perfusion</td>
<td>5 (15.6)</td>
<td>26 (26.3)</td>
<td>0.338</td>
</tr>
<tr>
<td>Venoarterial ECMO</td>
<td>27 (84.4)</td>
<td>90 (90.9)</td>
<td>0.330</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>38.4 ± 16.3</td>
<td>70.4 ± 31.9</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total adverse event</td>
<td>0 (0)</td>
<td>11 (11.1)</td>
<td>0.072</td>
</tr>
<tr>
<td>Bleeding event</td>
<td>0 (0)</td>
<td>10 (10.1)</td>
<td>0.122</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0 (0)</td>
<td>1 (1.0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO weaning</td>
<td>18 (56.3)</td>
<td>55 (56.6)</td>
<td>0.954</td>
</tr>
<tr>
<td>Mortality</td>
<td>16 (50.0)</td>
<td>49 (49.5)</td>
<td>0.963</td>
</tr>
<tr>
<td><strong>Patients with oxygenator change</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO circuit change</td>
<td>3 (9.4)</td>
<td>11 (11.1)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>41.1 ± 4.3</td>
<td>54.4 ± 14.1</td>
<td>0.021(^a)</td>
</tr>
<tr>
<td>ECMO flow (L/min)</td>
<td>3.5 ± 0.6</td>
<td>3.3 ± 0.4</td>
<td>0.475</td>
</tr>
<tr>
<td>ECMO time (hr)</td>
<td>723 ± 120</td>
<td>452.4 ± 150.1</td>
<td>0.011(^a)</td>
</tr>
<tr>
<td>Circuit change time (hr)</td>
<td>223 ± 57</td>
<td>211.2 ± 59.9</td>
<td>0.574</td>
</tr>
</tbody>
</table>

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

ECMO, extracorporeal membrane oxygenation; aPTT, activated partial thromboplastin time.

\(^a\)Statistically significant.
was no significant difference in oxygenator change-free time (Fig. 2), and fibrin deposition and thrombus formation were not found in the oxygenators of patients who did not require oxygenator change after ECMO removal. Several studies have reported ECMO management with a lower target aPTT or no AC [10-16]. According to these reports, the lack of systemic AC did not increase thrombotic events in the ECMO circuit. Pump failure or circuit clots did not occur in the patients who did not receive AC therapy. Lamarche et al. [15] reported a low incidence of oxygenator failure (9%) in 32 patients who received VA-ECMO without AC, and similar results were reported in other reports [7,17]. The low risk of thromboembolic complications in ECMO with a lower aPTT or no heparin use may be related to improvements in the design of cannulas and oxygenators, while improving oxygenation and flow capabilities [18].

Regarding primary outcomes (Table 2), bleeding complications occurred significantly more frequently in the high-AC group. Among the eight patients with bleeding complications in the high-AC group, four died. No mortality was related to bleeding complications in the low-AC group. Previous reports on VA-ECMO supported with low activated clotting time (140–160 seconds) or no AC therapy have similarly demonstrated a decreased incidence of major bleeding events and blood product transfusions, with no significant increase in thrombotic complications [15,19].

This study had several limitations. First, both venovenous ECMO and VA-ECMO were included. Thus, we could not exclude the effect on patient outcomes of the characteristics of each mode of ECMO according to the ECMO type. However, most of our patients (117 of 131, 89.3%) received VA-ECMO, and we believe that the mode of ECMO did not significantly affect the results of heparin use for thrombus, bleeding, and oxygenator survival. Second, patients were divided into two groups according to their measured aPTT levels. Hence, patients who were in poor condition, such as those with sepsis or multiple organ failure, tended to be assigned to the high-AC group because these patients usually had high aPTT levels, even though they had been managed with low target aPTT therapy or without AC. This study mainly aimed to determine the effect of aPTT levels on bleeding events, thrombosis events, and oxygenator survival time. Therefore, we set mortality and ECMO weaning rates as secondary rather than primary outcomes. However, a prospective randomized trial is required to confirm our findings.

Heparin use did not significantly improve the outcome of thrombotic events and the oxygenator change-free times during the ECMO period. Maintaining an aPTT of ≥ 55 seconds was a significant factor in the occurrence of bleeding events, especially those associated with mortality. Although our study does not warrant changing AC guidelines for ECMO because of its small sample size, the safety of using less or no heparin during ECMO is supported.

Table 5. Subanalysis of patients by anticoagulation and aPTT status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 32)</th>
<th>Group 2 (n = 47)</th>
<th>Group 3 (n = 52)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECMO time (hr)</td>
<td>208.2 ± 198.8</td>
<td>201.6 ± 161.4</td>
<td>143.9 ± 126.7</td>
<td>0.072</td>
</tr>
<tr>
<td>ECMO flow rate (L/min)</td>
<td>3.0 ± 0.5</td>
<td>3.0 ± 0.5</td>
<td>3.2 ± 0.5</td>
<td>0.653</td>
</tr>
<tr>
<td>Distal perfusion</td>
<td>5 (15.6)</td>
<td>9 (19.1)</td>
<td>17 (32.2)</td>
<td>0.684</td>
</tr>
<tr>
<td>Venoarterial ECMO</td>
<td>27 (84.4)</td>
<td>44 (93.6)</td>
<td>46 (88.5)</td>
<td>0.248</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>38.4 ± 16.3</td>
<td>48.9 ± 9.4</td>
<td>89.8 ± 32.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total adverse event</td>
<td>0 (0)</td>
<td>3 (6.4)</td>
<td>8 (15.4)</td>
<td>0.072</td>
</tr>
<tr>
<td>Bleeding event</td>
<td>0 (0)</td>
<td>2 (4.3)</td>
<td>8 (15.4)</td>
<td>0.345</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0 (0)</td>
<td>1 (2.1)</td>
<td>0 (0)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO weaning</td>
<td>18 (56.3)</td>
<td>35 (74.5)</td>
<td>20 (38.5)</td>
<td>0.090</td>
</tr>
<tr>
<td>Mortality</td>
<td>16 (50.0)</td>
<td>13 (27.7)</td>
<td>36 (69.2)</td>
<td>0.044</td>
</tr>
<tr>
<td>Patient with oxygenator change</td>
<td>3 (9.4)</td>
<td>7 (14.9)</td>
<td>4 (7.7)</td>
<td>0.733</td>
</tr>
<tr>
<td>ECMO circuit change</td>
<td>41.1 ± 4.3</td>
<td>46.1 ± 9.6</td>
<td>68.8 ± 5.4</td>
<td>0.424</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>3.5 ± 0.6</td>
<td>3.4 ± 0.3</td>
<td>3.2 ± 0.3</td>
<td>0.682</td>
</tr>
<tr>
<td>ECMO flow (L/min)</td>
<td>723 ± 120</td>
<td>443 ± 139</td>
<td>468 ± 188</td>
<td>0.009</td>
</tr>
<tr>
<td>ECMO time (hr)</td>
<td>223 ± 57</td>
<td>250 ± 57</td>
<td>179 ± 58</td>
<td>0.658</td>
</tr>
</tbody>
</table>

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

Group 1, patients without anticoagulation; Group 2, patients with heparinization but aPTT of < 55 sec; Group 3, patients with heparinization and aPTT of ≥ 55 sec.

Statistically significant.
Notes

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

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Author contributions
Conceptualization, Formal analysis: KS, JBK; Data curation, Investigation, Visualization: KS; Project administration, Supervision: JBK; Writing-original draft: KS; Writing-review & editing: KS, JBK.

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References

Severe congenital neutropenia mimicking chronic idiopathic neutropenia: a case report

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Severe chronic neutropenia is classified as severe congenital, cyclic, autoimmune, or idiopathic. However, there is a lot of uncertainty regarding the diagnosis of severe congenital neutropenia (SCN) and chronic idiopathic neutropenia, and this uncertainty affects further evaluations and treatments. A 20-year-old man presented with fever and knee abrasions after a bicycle accident. On admission, his initial absolute neutrophil count (ANC) was 30/µL. He had no medical history of persistent severe neutropenia with periodic oscillation of ANC. Although his fever resolved after appropriate antibiotic therapy, ANC remained at 80/µL. Bone marrow (BM) aspiration and biopsy were performed, and a BM smear showed myeloid maturation arrest. Moreover, genetic mutation test results showed a heterozygous missense variant in exon 4 of the neutrophil elastase \textit{ELANE}: c597+1G > C (pV190-F199del). The patient was diagnosed with SCN. After discharge, we routinely checked his ANC level and monitored any signs of infection with minimum use of granulocyte colony-stimulating factor (G-CSF), considering its potential risk of leukemic transformation. Considering that SCN can be fatal, timely diagnosis and appropriate management with G-CSF are essential. We report the case of a patient with SCN caused by \textit{ELANE} mutation who had atypical clinical manifestations. For a more accurate diagnosis and treatment of severe chronic neutropenia, further studies are needed to elucidate the various clinical features of \textit{ELANE}.

Keywords: Bone marrow examination; Granulocyte colony-stimulating factor; Leukemia; Mutation; Neutropenia

Introduction

Neutropenia is a hematological condition characterized by a reduced absolute neutrophil count (ANC) of < 1,500/µL [1]. Severe neutropenia with an ANC of < 500/µL increases susceptibility to serious bacterial or fungal infections [2]. Severe chronic neut-
troponia that lasts for > 3 months is categorized as severe congeni-
tal, cyclic, autoimmune, or idiopathic neutropenia [1-3]. Severe
congenital neutropenia (SCN) occurs in only two cases per mil-
ion people, whereas cyclic neutropenia (CyN) occurs in 0.6 cases
per million people [4]. Chronic idiopathic neutropenia (CIN) and
autoimmune neutropenia (AIN) are also rare diseases. The preva-
ience of CIN is approximately 1 to 2 cases per million people
among children and adults [2,5].

Genetic mutation is the most important feature that distinguishes
congenital and CyN from other types of neutropenia [4]. EL-
ANE (NM_001972) gene mutations are observed in 40% to 60%
of SCN cases and in 80% to 100% of CyN cases [6]. CyN is char-
acterized by regular oscillations in peripheral blood neutrophils
with a 21-day periodicity, whereas SCN is a more severe disease
with a consistently low ANC of < 200/µL. CIN is characterized by
a normal bone marrow (BM) karyotype without a definable ge-
netic cause, and negative serum anti-neutrophil antibodies [7].
Previous studies have suggested that CIN is caused by im-
mune-mediated BM impairment of neutrophil production, but its
etiology has not been fully elucidated [5].

Granulocyte colony-stimulating factor (G-CSF) is the most ef-
effective treatment option for severe chronic neutropenia; however,
G-CSF should be used very cautiously [2,5,7]. Leukemic transfor-
mation is one of the most frequently reported problems caused by
the long-term use of G-CSF, which increases the risk of leukemia,
particularly in patients with SCN, but not in patients with CIN
[1,3,5]. However, there are not enough data on the pathophysiol-
ogy of SCN and the genes responsible for it [3]. Moreover, there are
many uncertainties regarding the diagnosis of SCN and CIN that
affect further evaluation and management. Here, we present a rare
case of SCN that mimicked CIN.

Case

Ethical statements: This study was approved by the Institu-
tional Review Board (IRB) of Kyungpook National Universi-
ty Hospital (IRB No: KNUCH 2022-04-038). Written in-
fomed consent for publication was obtained from the patient.

The patient had a history of profound neutropenia with an ANC
of < 200/µL, with bronchiolitis and asthmatic bronchitis occur-
rning in the first 3 months of life. Whenever this patient arrived
at the hospital during his childhood, his initial ANC was > 1,500/µL,
which decreased to < 200/µL during his hospital stay (Fig. 1). Fur-
thermore, his ANC returned to normal after appropriate antibiotic
treatment. However, the patient had no regular periodic oscilla-
tions in his ANC (Fig. 1). He had a history of oral ulceration and
glossitis when he was 13 years old; however, he had no history of
parodontopathy, edentulism, or aphthosis. When he was 15 years
old, the workup for neutropenia revealed a latent tuberculosis in-
fec tion (LTBI). After 9 months of isoniazid treatment, the patient
was cured of the LTBI. Since 2018, his ANC peak had decreased to
< 1,300/µL. Nevertheless, he had never undergone BM examina-
tion or G-CSF treatment. Although the patient’s mother also had
a history of neutropenia, a specific hematologic disorder was not
identified in a BM study, and genetic testing, such as DNA se-
quencing, was not performed.

In May 2021, he was admitted to our hospital with fever and su-
perficial soft tissue injuries caused by a bicycle accident. After ad-
mission to our infectious disease department, a physical examina-
tion revealed a body temperature of 38°C, blood pressure of
118/72 mmHg, pulse rate of 76 beats/min, and superficial abra-
sions over the proximal anterior tibia. At the time of admission, his
complete blood cell count revealed a white blood cell count of
3,620/µL, ANC of 30/µL, hemoglobin level of 11.7 g/dL, platelet
count of 209,000/µL, and serum C-reactive protein (CRP) level
of 19.8 mg/dL. However, antinuclear antibody test results were nega-
tive. After he received piperacillin/tazobactam (4.5 g every 8
hours) for 3 days, his serum CRP level decreased to 6.2 mg/dL; his
fever resolved on the second day of treatment. However, his ANC
remained at 80/µL during the first 3 days (Fig. 2). The patient was
referred to the hematology department, where BM aspiration and
biopsy were performed. A BM smear showed abnormal differen-
tiation of the myeloid lineage (Fig. 3). The granulocytic series
showed maturation arrest in the myelocyte stage with few seg-
mented neutrophils (Fig. 3).

Based on the patient’s medical records, it was reasonable to be-
gin G-CSF pending genetic testing. Lenograstim was adminis-
tered to the patient at 2 µg/kg/day for 2 days. Although a G-CSF
dose of 2-10 µg/kg/day is usually used for patients with SCN,
we started with the lowest possible effective dose before con-
fiming the presence of genetic mutations in this patient [8]. His
ANC increased to 2,640/µL on the third day with 2 µg/kg/day
lenograstim for 2 days. He was discharged from the hospital in a
healthy condition after 7 days of treatment for severe neutrope-
nia (Fig. 2). Finally, the genetic mutation test results showed that
his severe neutropenia was caused by a heterozygous in-frame
deletion in the neutrophil elastase ELANE, with a nucleotide
substitution in intron 4 (IVS4+1G > C) located in the consensus
splice donor site, resulting in a missense variant in exon 4 of EL-
ANE: c597+1G > C (pV190-F199del) (Table 1, Supplementary
Fig. 1) [9]. Therefore, the patient was diagnosed with SCN.
Three weeks after discharge, his ANC decreased to < 500/µL.
Fig. 1. Time courses of absolute neutrophil count (ANC) throughout the patient’s lifetime.

Nevertheless, the patient no longer had fever or signs of infection. G-CSF was not routinely administered and was reserved for episodes of infection.

**Discussion**

A nonfunctional, misfolded neutrophil elastase encoded by a mutated ELANE gene accelerates the apoptosis of granulocytic precursors of myeloid cells, causing myeloid maturation arrest [9,10]. ELANE gene mutations are the main cause of SCN and CyN [9]. Some researchers have considered SCN and CyN to represent a continuum with phenotypic variability [10]. It has been suggested that the clinical manifestations of patients with SCN and CyN might be influenced not only by a single genetic factor such as ELANE mutations but also by other genetic or epigenetic factors [11]. Therefore, it is possible to make an accurate initial diagnosis based on an accurate understanding of the pathogenic aspects of congenital neutropenia [12]. SCN is rare but can also be fatal. Furthermore, SCN has various phenotypes that are sometimes atypical, as in the present case.

Several reports have shown that the ANC is consistently < 200/μL in patients with SCN [6]. However, no evidence of constant severe neutropenia (ANC < 200/μL) was detected in our patient before 20 years of age. Severe neutropenia followed by recurrent infections is also a typical pattern of SCN and CyN [4]. In contrast, when the patient arrived at a hospital during his childhood, his initial ANC was > 1,500/μL, which decreased to < 200/μL during his hospital stay; this presentation was incompatible with SCN. Furthermore, the patient did not show regular periodic oscillations in his ANC. Thus, the patient’s nonperiodic mild-to-moderate neutropenia with no evidence of infection and a negative test result for autoimmune disease might have led the previous healthcare workers to consider the diagnosis to be CIN or acquired neutropenia due to infection, and delay a BM examination [8,13-15]. CIN
Fig. 2. Time courses of absolute neutrophil count (ANC) during hospitalization. G-CSF, granulocyte colony-stimulating factor.

Fig. 3. Histopathology of the (A) peripheral blood and (B–D) bone marrow (Wright-Giemsa stain). (A) Neutrophils are present at high magnification (×1,000). (B) Hypercellularity is present at low magnification. Scale bar represents 100 μm. (C) Neutrophils are present at high magnification (×1,000). (D) The granulocytic series are hyperplastic and show a maturation arrest in the myelocyte stage with few segmented neutrophils. Scale bar represents 20 μm.
is considered a benign disease and is often self-limiting [2,7]. In young children, approximately 1/3 of CIN cases resolve spontaneously, whereas remission is uncommon in adults [5]. Thus, BM examination should always be considered when chronic neutropenia, which began in early childhood, persists. Considering that the risk of bacterial infection and leukemic transformation in ELANE-related neutropenia is high, precise diagnosis of SCN and early identification are essential for appropriate treatment with G-CSF and further management such as hematopoietic stem cell transplantation (HSCT) [16,17].

Extensive studies have shown that myeloid proliferation and maturation are stimulated by G-CSF, which can be used to treat severe chronic neutropenia [5,18]. However, since its introduction in 1998, G-CSF has attracted considerable attention owing to its potential risk of malignancy [5,19]. Recently, a strong relationship between G-CSF treatment and malignant transformation in SCN has also been reported [3,17]. In contrast, there is no evidence that G-CSF predisposes leukemic transformation in CIN and AIN [5]. Therefore, the dose, timing, and duration of G-CSF therapy should be very carefully determined in patients with congenital neutropenia, such as SCN and CyN [17,20]. Although we do not consider the long-term use of high-dose G-CSF unless there is sufficient evidence of infection, we do take G-CSF therapy and HSCT into consideration depending on how low the patient’s ANC level falls and the existence of any signs of infection [19].

Here, we report the case of a patient with SCN that mimicked CIN. We hope that patients with atypical features of SCN can be diagnosed in a timely manner and receive appropriate G-CSF treatment. Further studies are needed to elucidate the various clinical phenotypes of ELANE to obtain a more specific and precise diagnosis and treatment of severe chronic neutropenia. Moreover, clinical trials for patients with SCN to establish an appropriate ANC cutoff for G-CSF treatment are warranted to minimize the risk of malignant transformation, depending on the specific ELANE mutation.

### Supplementary materials

Supplementary Fig. 1 can be found via https://doi.org/10.12701/jyms.2022.00353.

### Notes

**Conflicts of interest**

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**Author contributions**

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**References**


### Table 1. The pathogenic variant detected in the ELANE gene

<table>
<thead>
<tr>
<th>Location</th>
<th>DNA change</th>
<th>Predicted AA change</th>
<th>Zygosity</th>
<th>OMIM disease</th>
<th>Inheritance</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intron 4</td>
<td>c.597+1G &gt; C</td>
<td>pV190-F199del</td>
<td>Het</td>
<td>CN, CyN</td>
<td>AD</td>
<td>PV</td>
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</tbody>
</table>

AA, amino acid; OMIM, Online Mendelian Inheritance in Man; G, guanine; C, cytosine; Het, heterozygous; CN, congenital neutropenia; CyN, cyclic neutropenia; AD, autosomal dominant; PV, pathogenic variant.
Crowned dens syndrome as a rare cause of anterior neck pain after transurethral resection of the prostate: a case report

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We describe the case of a 79-year-old man who presented with progressive aggravation of severe axial neck pain and fever 3 days after transurethral resection of the prostate (TURP), despite maintaining neutral neck posture during surgery. Laboratory examination revealed markedly elevated C-reactive protein levels and erythrocyte sedimentation rates. Computed tomography revealed crown-like calcifications surrounding the odontoid process. We diagnosed crowned dens syndrome (CDS) as the cause of acute-onset neck pain after TURP. The patient was treated with nonsteroidal anti-inflammatory drugs for 5 days, and his symptoms resolved completely. CDS is a rare disease characterized by calcific deposits around the odontoid process with acute onset of severe neck pain and restricted motion. Evidence of inflammation on serological testing and fever are typical of CDS. However, the prevalence and pathophysiology of CDS remain unclear. We hypothesized that systemic inflammation after prostate surgery may have induced a local inflammatory response involving calcification around the odontoid process.

Keywords: Inflammation; Neck pain; Odontoid process; Transurethral resection of prostate

Introduction

Crowned dens syndrome (CDS) is a rare condition that presents as acute onset of severe axial neck pain with restricted cervical motion in patients who are elderly [1]. It is characterized by calcific deposits around the odontoid process, creating the appearance of a half-ringed crown [2]. Clinicians tend to conduct many laboratory and imaging tests and even invasive diagnostic procedures before diagnosing CDS. The exact prevalence and pathophysiology of CDS remain unclear [3-5]. CDS resulting in severe axial neck pain with restriction of cervical motion after transurethral resection of the prostate (TURP) has not been reported previously.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Keimyung University Dongsan Hospital (IRB No: DSMC 2021-06-006). Written informed consent was obtained from the patient to participate in the study.
A 79-year-old man underwent TURP for benign prostate hyper trophy in the urology department of a tertiary hospital. He presented with acute-onset, unbearable, and intractable axial neck pain, which was accompanied by fever, 3 days after surgery. A neutral neck posture was maintained during the TURP, and no neck pain was observed for 2 days after surgery. The patient worked as a driver but had retired 10 years ago. He denied experiencing recent trauma and did not have a history of musculoskeletal illness. His medical history included chronic kidney disease and hypertension. His neck pain had progressively worsened, with marked restriction of neck motion. The patient's body temperature, systolic/diastolic blood pressure, and pulse rate were 38.7°C, 160/90 mmHg, and 100 beats/min, respectively. On physical examination, his cervical motion was found to be restricted in all directions. His laboratory test results were as follows: white blood cell count, 7,360/µL (range, 4,000–10,000/µL); neutrophils, 63.4% (range, 39%–73%); C-reactive protein (CRP), 10.6 mg/dL (range, 0–0.5 mg/dL); erythrocyte sedimentation rate (ESR), 59 mm/hr (range, 0–15 mm/hr); procalcitonin, 0.1 µg/L (range, < 0.1 µg/L); rheumatoid factor, 53.7 IU/mL (range, 0–14 IU/mL); and anticyclic citrullinated peptide, < 8.0 U/mL (range, 0–17 U/mL). The patient did not have any neurological deficits but presented with severe neck pain and rigidity during Kernig test.

Cerebrospinal fluid was collected via lumbar puncture and examined for the differential diagnosis of central nervous system infections such as meningitis, but the findings were within the normal range. Although plain radiography revealed spondylosis, the atlantoaxial joint appeared normal, which could not explain the cause of the patient's condition. Computed tomography (CT) of the cervical spine revealed crown-shaped calcium deposits surrounding the odontoid process (Fig. 1). Degenerative osteoarthritis was excluded due to elevated ESR and CRP levels. By integrating the results of the examinations listed above, we diagnosed CDS as the cause of the acute neck pain after TURP. A short course of nonsteroidal anti-inflammatory medication (aceclofenac, 100 mg/day for 5 days) completely resolved the neck pain and fever. The results of a follow-up serological test performed 5 days after administration of aceclofenac showed no evidence of an inflammatory reaction suggestive of CDS.

Discussion

The calcifications in CDS have been postulated to be composed of calcium pyrophosphate dihydrate or hydroxyapatite [6]. Calcium pyrophosphate deposition disease affects 4% to 7% of the adult population in the United States and Europe [7]. A recent large cross-sectional study indicated a point prevalence of 5.2 per 1,000, an average patient age of 68 years, and 95% male prevalence in the United States [8]. Acute pain attacks often occur after trauma, acute illness, or during a postoperative period [7].

The diagnosis of CDS is based on a combination of clinical symptoms, biological inflammatory markers, radiologic findings, and therapeutic responses [9]. Patients with CDS typically present with acute attacks of severe axial pain and restriction of cervical motion [9]. The C1 and C2 segment includes the odontoid process and provides a large range of cervical rotation; therefore, it is presumed that periodontoid calcifications may provoke neck pain during rotation [10]. The acute inflammatory features of CDS are often accompanied by fever and increased levels of inflammatory markers such as ESR and CRP.

It may be difficult to differentially diagnose CDS from other diseases that present with similar clinical symptoms, such as meningitis, spondylodiscitis, epidural abscess, osteomyelitis, polymyalgia rheumatica, giant cell arteritis, metastatic bone disease, and tumors.

![Fig. 1. (A) Axial, (B) sagittal, and (C) coronal computed tomography scans at the C1 and C2 level demonstrate crown-shaped calcium deposits (arrows) at the posterolateral side of the odontoid process.](https://doi.org/10.12701/jyms.2022.00388)
CT is the gold standard imaging method for identifying periodontoid calcific deposits with a half-ringed appearance [6]. Magnetic resonance imaging (MRI) can reveal inflammatory changes; however, MRI is less effective in showing calcifications than CT imaging [1]. Single-photon emission CT (SPECT) can assist with differential diagnosis in cases with subacute or chronic features, such as degenerative pain [1]. The appropriate treatment for CDS remains debatable; however, its prognosis is generally good. In many cases, a short regimen of anti-inflammatory agents, including nonsteroidal anti-inflammatory drugs, corticosteroids, colchicine, or combination therapy, can alleviate symptoms [11].

The exact prevalence, cause, and pathophysiology of CDS remain unclear. CDS predominantly affects women over 60 years of age [3,4]. Possible risk factors include recent surgery, invasive procedures, trauma, serious illness, and electrolyte abnormalities due to the use of diuretics or from dehydration [4,5]. Some authors have hypothesized reasonable theories regarding the pathogenesis of CDS related to inflammatory reactions [4,6]. CDS may involve phagocytosis of calcifications by inflammatory cells, which can evoke inflammatory responses in the joint [4]. The periodontoid calcifications may mechanically damage nearby structures, which can cause an inflammatory reaction [6]. The production of prostanoids induced by the calcification may also lead to clinical symptoms of CDS [1].

While recent surgery is known to be a risk factor for CDS, no study has reported CDS development after TURP [1,12]. In previous studies, the occurrence of CDS after surgery included drainage of the subdural hematoma and endoscopic submucosal dissection for gastric cancer [5,13]. We assume that systemic inflammation after TURP may have been the main etiology of CDS in this case. Systemic inflammation due to surgery can trigger CDS, inducing a local inflammatory response in periodontoid calcifications [4]. These inflammatory reactions can cause symptoms attributed to CDS, such as axial neck pain, restricted neck motion, and fever in patients who are elderly. More cases are needed to determine whether these factors are associated with the onset of CDS. Our patient presented with pain 3 days after surgery and denied experiencing any symptoms between the immediate postoperative period and 2 days after surgery. The patient had no specific findings related to his urological surgery; thus, his symptom relief may not have been related to his postoperative recovery.

To the best of our knowledge, this is the first case report of CDS causing severe axial neck pain and fever after TURP. CDS should be considered in the differential diagnosis of patients with unexplained fever and acute onset of axial neck pain after TURP in order to perform appropriate management without unnecessary and aggressive examinations, inappropriate management, or long-term hospitalization. Although the patient was diagnosed with post-TURP-related CDS, he refused additional evaluations, such as MRI and SPECT, and the absence of such procedures is a limitation of this study. Clinicians should consider the possibility of CDS in patients with calcifications around the odontoid process even if they are asymptomatic at the time of examination after TURP. Appropriate recognition, accurate diagnosis, and prompt management are essential to minimize the impact of this condition and prevent postoperative neck pain in patients who are elderly.

Notes

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

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Author contributions
Conceptualization: MGJ, BSP, ESS; Data curation: MGJ, ESS; Resources: ESS; Software: MGJ; Investigation: BSP; Funding acquisition, JHC; Writing-original draft: MGJ, BSP; Writing-review & editing: JHC.

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References


Oral mucosal burns may be caused by exposure to a variety of chemical agents, including medications, dental materials, non-pharmacological substances, and illicit drugs [1]. Soft tissue injuries vary widely in severity and presentation, from superficial desquamation of the epithelium to full-thickness destruction of the oral mucosa [2]. The severity of mucosal damage depends on various factors, including the acidity or alkalinity of the substance, the amount of the agents, and the duration of exposure [2,3].

Policresulen (50% w/w solution; Albothyl, Celltrion Pharm Inc., Cheongju, Korea) is a frequently used over-the-counter topical medication used to treat stomatitis. This agent selectively coagulates pathologically altered tissues, promoting their regeneration and reepithelialization [4,5]. However, it carries a possible risk of oral mucosal injury due to its high acidity and should be used with caution [6]. This report describes a case of oral mucosal burns resulting from the misuse of policresulen.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University Medical Center (IRB No: CR-22-089-L). The requirement for written informed consent from the patient was waived by the IRB.

A 61-year-old man with a 3-month history of severe pain caused by ulceration of the right maxillary buccal vestibule was referred to the Department of Dentistry, Daegu Catholic University Medical Center by a local clinician. The oral lesion had developed after the
patient started wearing a new maxillary complete denture. He had undergone denture adjustment several times and was prescribed nonsteroidal anti-inflammatory drugs and antibiotics; however, his symptoms gradually worsened. The patient was therefore referred for evaluation and treatment of a refractory ulcerative lesion, which was suspected to be malignant. The patient had no significant relevant medical history.

Intraoral examination revealed a mucosal ulcer in the right maxillary buccal vestibule covered with a necrotic, sloughing pseudomembrane, which was painful on palpation (Fig. 1). Mechanical irritation by the buccal flange of the maxillary denture was not observed (Fig. 2), and there was no evidence of any other definite lesion in the oral cavity. On questioning, the patient disclosed that he had been applying Albothyl topically to the affected area for approximately 3 months to alleviate pain from a traumatic ulcer. Panoramic radiography revealed no remarkable findings (Fig. 3).

Based on the appearance of the lesion and clinical history, we diagnosed the patient with an oral mucosal chemical burn resulting from the misuse of policresulen. Other abnormal conditions, including squamous cell carcinoma or deep fungal infection, were included in the differential diagnosis but were considered less likely. The patient was instructed to discontinue the use of Albothyl in his vestibule because of its deleterious effect on the oral soft tissue, and was treated with a combined topical regimen of corticosteroids and antibiotics (prednisolone 0.3 mg and amoxicillin 10 mg in 5 mL of water as a mouthwash, three times a day). The patient did not attend his 1-week recall appointment but reported remarkable improvement in symptoms during the follow-up phone call. At the 2-week review, the patient reported no pain, and clinical examination revealed almost complete resolution of the oral lesion (Fig. 4).

Discussion

Policresulen is a polymolecular organic acid that is produced by the condensation reaction between metacresol sulfonic acid and

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**Fig. 1.** Clinical photograph shows mucosal ulcer covered with a necrotic, sloughing pseudomembrane in the right maxillary buccal vestibule.

**Fig. 2.** Clinical photograph shows the oral lesion with the maxillary denture in place.

**Fig. 3.** Panoramic radiography demonstrates no remarkable findings.

**Fig. 4.** Clinical photograph shows regression of the lesion following treatment.
formaldehyde [4,6]. Policresulen is a commonly used topical antiseptic, which topped the Korean stomatitis drugs market with a 28.7% share in 2020. Although policresulen is indicated for the treatment of stomatitis and bacterial vaginosis, it is contraindicated in patients with hypersensitivity to any of the drug components. Policresulen causes selective coagulation of damaged tissues, while leaving normal tissues unharmed, allowing rapid reepithelialization [4,5]. This drug also has antimicrobial, astringent, and anti-inflammatory properties [4]. According to the manufacturer’s instructions, when used to treat stomatitis, a policresulen solution should be applied cautiously to the affected area using a cotton swab. Then, a thorough mouth rinse with water is required to remove the residual substance. Improper use of this agent can induce epithelial necrosis and subsequent development of white sloughing pseudomembranes covering the underlying ulceration. Additionally, it may cause erosion of the tooth enamel owing to its high acidity (pH 0.6). To the best of our knowledge, very few cases of oral mucosal burns resulting from topical application of policresulen have been reported in the literature [6]. Although the mechanism by which policresulen causes oral mucosal damage is still unclear, organic and inorganic acids are known to denature epithelium proteins, triggering coagulative necrosis of cells [1]. Therefore, it is reasonable to assume that the mucosal burn could probably be attributed to tissue protein denaturation caused by policresulen.

Exposure to a wide variety of chemicals may lead to soft tissue injuries in the oral mucosa. Agents associated with oral mucosal damage include dental materials (e.g., phosphoric acid etching solutions, ferric sulfate, calcium hydroxide, sodium hypochlorite, hydrofluoric acid, and formocresol), medications (e.g., aspirin and alendronate), non-pharmaceutical substances (e.g., mouthwashes, hydrogen peroxide, denture cleansers, and garlic), and illicit drugs (e.g., cocaine and amphetamine) [1,7-17]. Chemical burns can occur at any oral mucosal site, but the labial and buccal mucosae are the most commonly affected [1]. The severity of the oral mucosal injury depends upon multiple factors, including the pH and concentration of the substance, the amount of the agents, duration of exposure, and mechanism of action [2].

A diagnosis of oral chemical burns is usually made based on the clinical history and physical examination, and comprehensive history taking is important to identify the causative agent. Contact with a potentially harmful agent causes oral mucosal erythema and subsequent development of necrotic, sloughing pseudomembranes covering the underlying ulceration [1,16]. Biopsy of the oral lesion is rarely required unless a patient’s history is difficult to obtain or appears to be intentionally misleading. Histopathological examination of chemical burns generally reveals areas of focal coagulative necrosis of the epithelium, subepithelial inflammatory cell infiltrate, and ulceration; however, these findings are not pathognomonic [1,16].

Successful treatment of oral mucosal chemical burns depends on the identification and withdrawal of causative agents. Patient education is crucial in preventing mucosal trauma due to improper use of various chemical agents. Chemical burns usually present as mild to moderate mucosal damage which resolves spontaneously within 7 to 15 days; thus, only supportive care is required in many cases [18]. However, in cases of more severe mucosal injury, the application of topical corticosteroids may be beneficial [19]. Tissue destruction due to massive exposure to corrosive agents may require surgical debridement and antibiotic administration [1,16].

Policresulen is an over-the-counter topical medication that is used to treat stomatitis. As inadequate self-treatment with this agent may lead to oral soft tissue injury, taking a detailed clinical history and providing appropriate patient education is of great importance to clinicians. Policresulen-induced mucosal burns should be included in the differential diagnosis of oral ulceration and necrotic tissue, and there is also a need to raise awareness of this adverse drug event in consumers and health professionals.

Notes

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

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Author contributions
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References

The coronavirus disease 2019 (COVID-19) pandemic has been ongoing for more than 2 years. Many patients who recover from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection continue to have aftereffects such as dyspnea and fatigue, which may lead to functional decline. Therefore, the need for managing these symptoms using methods such as pulmonary rehabilitation (PR) has emerged. The purpose of this study was to report the effectiveness of PR in five patients with acute COVID-19. PR was performed in patients with persistent dyspnea and oxygen demand after COVID-19. All five patients were able to maintain an independent functional status before COVID-19. However, after acute COVID-19, they were unable to walk independently and needed assistance for activities of daily living due to dyspnea and fatigue. Therefore, they were referred to rehabilitation units, and PR was performed. The modified Medical Research Council dyspnea scale, maximal expiratory pressure (MEP), 6-minute walking test, forced vital capacity, and grip strength were assessed before and after PR, and the results were compared. After PR, the parameters improved, except for the MEP in one patient (patient 3) and the grip strength in another patient (patient 4). After PR, two out of five patients returned to work and the other three returned home. Therefore, we conclude that PR is necessary for patients with acute COVID-19 with activity limitations.

Keywords: COVID-19; Dyspnea; Pulmonary fibrosis; Rehabilitation

Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19) in 2019, pandemic infection has been ongoing for more than 2 years. It has been reported that many patients who recovered from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection continue to have aftereffects even 3 to 4 weeks after the onset [1,2]. This manifestation is called post-acute COVID-19 syndrome [1,2]. Dyspnea, fatigue, chest pain, and cognitive disturbances are common symptoms of post-acute COVID-19 syndrome, which lead to decreased exercise capacity, functional decline, and thus, poor quality of life [3,4]. Since these aftereffects persist, there are some reports on the effectiveness and necessity of pulmonary rehabilitation (PR) [5]. Many patients were admitted to our medical center because of SARS-CoV-2 infection, and some experienced dyspnea and fatigue after acute treatment of SARS-CoV-2 infection. Therefore, we report a case series of PR performed in patients with acute COVID-19.
Cases

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Seoul Medical Center (IRB No: 2022-08-002), and the requirement for informed consent from the patient was waived by the IRB.

Among COVID-19–infected patients, PR was conducted on five severe patients who needed oxygen therapy. The patients were diagnosed using polymerase chain reaction tests, and all of them were treated with steroids, remdesivir (VEKLURY, Gilead Sciences, Foster City, CA, USA), and oxygen therapy. Three participants were treated with high-flow oxygen therapy, one of which was placed on a mechanical ventilator for 21 days. The characteristics of the five patients are shown in Table 1.

According to the medical records, all patients were able to maintain an independent functional status before COVID-19. However, after acute COVID-19 and treatment, they were unable to walk independently and needed assistance in activities of daily living due to dyspnea and fatigue. Therefore, they were referred to the rehabilitation units of our hospital and PR was performed.

At the time of transfer, chest computed tomographies of each patient was taken and pulmonary fibrosis was found (Fig. 1). After their transfer, 17 to 21 sessions of PR were provided at the Department of Rehabilitation of Seoul Medical Center between March 2021 and February 2022. Four patients were hospitalized during the PR sessions, and the other patient was treated in an outpatient clinic. We used the following measurements to assess PR outcomes: modified Medical Research Council (mMRC) dyspnea scale, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), 6-minute walking test (6 MWT), forced vital capacity (FVC), and grip strength. These indicators were evaluated and compared before and after the PR. The PR program comprised warm-up (5–10 minutes), main (30 minutes), and cool-down (5–10 minutes) exercises. The main exercises included flexibility exercise, inspiratory muscle strengthening, limb muscle strength training, and aerobic exercise. Aerobic exercise was mainly carried out as a treadmill exercise or cycle ergometer exercise. Aerobic exercise was performed at moderate intensity, targeting 60% of the maximal heart rate. The modified Borg scale (MBS) measures dyspnea to assess the patient’s tolerance. When the MBS score exceeded 3 points (i.e., moderate dyspnea), a short break was taken. During PR, oxygen was supplied if necessary to maintain an oxygen saturation above 90%. These all exercises were performed by a more experienced physical therapist. One patient (patient 3) did not require an oxygen supply during the first PR session. The remaining four patients initially required 1 to 5 L/min of oxygen. As the PR program progressed, the four patients who needed oxygen supply could taper out oxygen. Oxygen saturation was well maintained during the exercise without oxygen supply, and the patient’s dyspnea was tolerable. Subjective breathing difficulties were evaluated using mMRC. The results of the mMRC scale improved in all five patients after PR (Table 2 [6-8]). Among the three patients who started PR at mMRC level 4, two patients improved to level 1, and one patient improved to level 2. The other two patients started PR at mMRC level 3 and ended at level 2. MIP and MEP tests were performed to evaluate respiratory muscle strength. After PR, MIP and MEP results improved in all five patients, except for the MEP value of one patient (patient 3). The 6 MWT was performed to test endurance, and all five patients showed substantial improvement in distance. The FVC of all five patients also improved after PR. Grip strength was measured to determine the patients’ overall strength [9]. The grip strength of the four patients

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
</tr>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>74</td>
<td>60</td>
<td>55</td>
<td>65</td>
<td>64</td>
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<tr>
<td>Sex</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
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<tr>
<td>PR sessions</td>
<td>17</td>
<td>21</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<tr>
<td>O₂ therapy (day)</td>
<td>46</td>
<td>17</td>
<td>27</td>
<td>31</td>
<td>52</td>
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<tr>
<td>Mechanical ventilator use</td>
<td>(–)</td>
<td>(–)</td>
<td>(–)</td>
<td>(–)</td>
<td>(+)</td>
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<tr>
<td>High-flow nasal cannula (day)</td>
<td>25</td>
<td>0</td>
<td>13</td>
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<td>36</td>
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<tr>
<td>Start of PR until O₂ cessation (day)</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>15</td>
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<tr>
<td>Length of stay in hospital (day)</td>
<td>76</td>
<td>46</td>
<td>30</td>
<td>61</td>
<td>74</td>
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<tr>
<td>Steroid use (day)</td>
<td>118</td>
<td>58</td>
<td>83</td>
<td>73</td>
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<tr>
<td>Hypertension</td>
<td>(+)</td>
<td>(–)</td>
<td>(–)</td>
<td>(–)</td>
<td>(+)</td>
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<td>Diabetes mellitus</td>
<td>(–)</td>
<td>(–)</td>
<td>(–)</td>
<td>(–)</td>
<td>(+)</td>
</tr>
</tbody>
</table>

PR, pulmonary rehabilitation; O₂, oxygen.
Table 2. The change in various parameters after PR program

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient 1 Before PR</th>
<th>Patient 1 After PR</th>
<th>Patient 2 Before PR</th>
<th>Patient 2 After PR</th>
<th>Patient 3 Before PR</th>
<th>Patient 3 After PR</th>
<th>Patient 4 Before PR</th>
<th>Patient 4 After PR</th>
<th>Patient 5 Before PR</th>
<th>Patient 5 After PR</th>
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<tbody>
<tr>
<td>mMRC dyspnea scale</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3, 2</td>
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<tr>
<td>MEP (cmH₂O) [6]</td>
<td>32 (42.7)</td>
<td>49 (64.5)</td>
<td>75 (60.0)</td>
<td>86 (69.4)</td>
<td>128 (100.0)</td>
<td>114 (89.1)</td>
<td>72 (59.5)</td>
<td>103 (85.8)</td>
<td>42 (34.7)</td>
<td>83 (68.6)</td>
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<tr>
<td>MIP (cmH₂O) [6]</td>
<td>32 (61.5)</td>
<td>53 (98.1)</td>
<td>45 (47.9)</td>
<td>69 (73.4)</td>
<td>116 (119.6)</td>
<td>118 (121.5)</td>
<td>62 (66.0)</td>
<td>76 (81.5)</td>
<td>46 (52.1)</td>
<td>86 (91.5)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>1.59 (87.4)</td>
<td>2.35 (90.0)</td>
<td>2.81 (70.3)</td>
<td>4.70 (71.1)</td>
<td>3.81 (76.4)</td>
<td>4.15 (80.4)</td>
<td>2.76 (70.1)</td>
<td>3.16 (80.2)</td>
<td>3.12 (78.0)</td>
<td>3.97 (89.6)</td>
</tr>
<tr>
<td>6 MWT (m) [7]</td>
<td>221 (49.7)</td>
<td>265 (59.6)</td>
<td>250 (46.5)</td>
<td>475 (88.3)</td>
<td>467 (78.4)</td>
<td>540 (90.6)</td>
<td>330 (62.5)</td>
<td>440 (83.3)</td>
<td>325 (62.7)</td>
<td>450 (86.8)</td>
</tr>
<tr>
<td>Grip strength (kg) [8]</td>
<td>15.5 (79.5)</td>
<td>18.0 (92.3)</td>
<td>38.8 (99.4)</td>
<td>42.0 (107.7)</td>
<td>34.5 (78.4)</td>
<td>45.5 (103.3)</td>
<td>20.0 (51.3)</td>
<td>19.0 (48.7)</td>
<td>14.0 (35.9)</td>
<td>20.0 (51.2)</td>
</tr>
</tbody>
</table>

Values are presented as score only or data (% predicted).

PR, pulmonary rehabilitation; mMRC, modified Medical Research Council; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; FVC, forced vital capacity; 6 MWT, 6-minute walking test.

Fig. 1. Chest computed tomography of patient 2. (A) Axial view and (B) coronal view (before pulmonary rehabilitation [PR]). Ground glass opacities and pulmonary fibrosis are present in both lungs. (C) Axial view and (D) coronal view (4-month follow-up after PR). Ground-glass opacities and pulmonary fibrosis of both lungs decreased compared to panels A and B.
increased after PR. Finally, after PR, two out of five patients returned to work and the other three returned home.

Discussion

COVID-19 pneumonia causes pulmonary fibrosis [10], and PR after pulmonary fibrosis helps reduce dyspnea, improve exercise capacity, and improve the quality of life [11]. Since exercise also works positively for the psychological, neurological, cardiovascular, respiratory, musculoskeletal, and immune systems [12], PR may also help the overall recovery of COVID-19 patients. Yet, the benefits of PR, including improvement in dyspnea, exercise capacity, and quality of life, are usually well described in chronic obstructive pulmonary disease (COPD) [13]. However, the effectiveness of PR for COVID-19 has not yet been clearly described. Currently, there is no panacea for COVID-19; therefore, the importance of adding PR to antiviral and anti-inflammatory drugs and symptom control is emerging.

In our report, we evaluated the mMRC, MEP/MIP, 6 MWT, FVC, and grip strength in five patients with acute COVID-19. mMRC scale assessed the degree of subjective dyspnea. MEP/MIP evaluated respiratory muscle performance [14,15], 6 MWT tested endurance and FVC estimated lung function after pulmonary fibrosis. Grip strength measured a patient’s overall strength, including muscle mass and physical function [9]. The parameters (mMRC, MEP/MIP, 6 MWT, FVC, and grip strength) improved, except for the MEP in one patient (patient 3) and grip strength in another patient (patient 4). For patient 3 whose MEP value did not improve after PR, the initial MEP result before PR was already 100% of the expected value. In other words, there may have been fewer opportunities for improvement. As the PR sessions progressed, dyspnea improved, as shown by improvement in the mMRC scale. The oxygen demand also decreased. As dyspnea is known to significantly impact the quality of life [3,16], it can be inferred that the quality of life of patients who received PR has improved. In addition, increased exercise capacity, indicated by improvements in the 6 MWT results, helped return to daily life. Even after the end of the PR sessions, the patients continued to visit the Department of Pulmonology and Rehabilitation Medicine for outpatient treatment. Later, when tracking the medical records, all five patients were found to have improved enough to experience no problems in their activities of daily living. Based on our findings, we suggest that PR may be helpful in treating COVID-19, as in previous COPD studies.

This study had some limitations. First, patients’ underlying conditions, such as preexisting respiratory disorder, comorbidity, premorbid activity level, or smoking history, were not considered. Second, the number of PR sessions was different for each patient. Therefore, it is difficult to propose a regular protocol for PR. Third, the sample size is relatively small. Additionally, there was only one intensive care unit case, and the disease level and severity level of the participant group was not consistently controlled. Fourth, there is a gender imbalance in the sample. Four of the five patients were men, and only one woman was included. Finally, this study can only be reported as a case series. Since COVID-19 has been a pandemic, it was difficult to conduct this study as a case-control study or randomized controlled trial due to the limited hospitalization period and bed use.

In this study, we performed PR testing in patients with acute COVID-19. After receiving PR, patients were able to return to their daily lives with improved function. Therefore, we conclude that intensive PR is necessary for patients with acute COVID-19 with activity limitations. In the future, large-scale studies comparing PR groups to non-PR groups and follow-up studies on the long-term prognosis of PR conducted in patients with acute COVID-19 will be helpful.

Notes

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

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References

Three-dimensional printing of temporary crowns with polylactic acid polymer using the fused deposition modeling technique: a case series

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With recent developments in digital dentistry, research on techniques and materials for three-dimensional (3D) printing is actively underway. We report the clinical applications and outcomes of 3D printing of temporary crowns fabricated with polylactic acid (PLA) using a fused deposition modeling (FDM) printer. Five participants were recruited from among patients scheduled to be treated with a single full-coverage crown at a dental clinic in a university medical center from June to August 2022. We used 3D-printed crowns fabricated with PLA using an FDM printer as temporary crowns and were assessed for discomfort, fracture, and dislodging. The 3D-printed temporary crowns were maintained without fracture, dislodging, or discomfort until the permanent prosthesis was ready. The average time required for printing the temporary crowns was approximately 7 minutes. The 3D printing of temporary crowns with PLA using an FDM printer is a convenient process for dentists. However, these crowns have some limitations, such as rough surface texture and translucency; therefore, the 3D printing process should be improved to produce better prostheses.

Keywords: Digital dentistry; Polylactic acid; Temporary dental restoration; Three-dimensional printing

Introduction

Temporary crowns are a critical part of fixed prosthodontic treatment because they protect the prepared teeth, provide positional stability, and maintain functions, such as mastication and esthetics [1]. Temporary crowns can be fabricated directly on the prepared tooth or indirectly on a model of the prepared tooth [2]. The direct method is convenient but entails significant disadvantages such as irritation to the adjacent tissue and polymer shrinkage [3]. In addition, the chemical odor generated during polymerization causes severe discomfort to patients. The conventional indirect fabrication method can overcome these shortcomings [2], but additional processes, such as impression making and plaster modeling, may be required. If the temporary crown is prepared arbitrarily before tooth preparation, its accuracy is reduced, causing similar problems in the relining process as in the direct method. If the temporary crown is prepared by an indirect method after tooth preparation, the chair time will increase because of the impression and model-making processes.

However, with the recent development of digital dentistry, an indirect temporary prosthesis fabrication method using three-dimensional (3D) printing has been introduced and is being actively developed to overcome the limitations of the conventional indirect method. For fabricating 3D objects from 3D digital data, 3D print-
ing is an additive manufacturing technique. A 3D-printed temporary crown is manufactured through a digital flow process that includes 3D scanning of the prepared tooth, digitalization on a computer, transfer to the 3D printer, and fabrication of the 3D structure [4].

The 3D-printing technologies commonly used for preparing dental polymers include stereolithography apparatus (SLA), digital light processing (DLP), material jetting (MJT), and fused deposition modeling (FDM) [5]. SLA and DLP are currently the most popular technologies in dentistry. Both processes produce 3D structures by the photopolymerization of a liquid photopolymer and can quickly produce high-resolution restorations [6]. MJT is a direct 3D-printing process in which molten droplets of material are ejected onto a heated build platform and bonded; MJT is also accurate and fast, but it is expensive. In the FDM technique, 3D structures are fabricated such that the solid filament material is melted in a nozzle, polymerized while being extruded, and stacked layer by layer. The equipment and materials required for FDM are less expensive and more convenient to use than those required for SLA or DLP. However, although 3D objects printed by FDM have appropriate physical properties, they are not popular in dentistry because they require a long printing time and have low resolution [4].

Interest in the 3D printing of temporary crowns has been increasing, but limited studies have assessed the use of 3D-printing technologies and materials used for manufacturing temporary prostheses. A few studies on 3D printing of temporary crowns have focused on SLA and DLP [7,8]. However, FDM has advantages such as being economical, highly convenient, and producing material with appropriate physical properties. If the shortcomings of the rough surface of the end product and slow working speed are improved, FDM could be successfully used in dental clinics.

Herein, we report our experience with the printability and clinical application of a relatively convenient filamentous polymer (polylactic acid [PLA]; QUVE Co. Ltd., Seoul, Korea), which has been developed and marketed as a temporary restoration material for use in FDM 3D printers (CUBICON Style Plus - A15D; CUBICON Co. Ltd., Seoul, Korea).

**Cases**

**Ethical statements:** This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUMC-2021-07-019). Written informed consent was obtained from the patients for the publication of this case series and accompanying images.

Potential participants were recruited from among patients who visited a dental clinic in Yeungnam University Medical Center from June to August 2022. Five patients were enrolled, and five teeth were scheduled for treatment with a single full-coverage restoration. The teeth were prepared by an experienced dentist, and 3D-printed temporary crowns were luted onto the prepared teeth with Temp-Bond NE (Kerr Dental, Brea, CA, USA) and maintained until the final prosthesis was ready.

After tooth preparation, intraoral scanning of the prepared tooth was performed using a 3D scanner (Medit i500; MEDIT Corp., Seoul, Korea).
Seoul, Korea) (Fig. 1). The digital data were then transferred to a NexWay platform (QUVE Co. Ltd.) as an STL file, and the temporary crown was designed by an experienced dental technician using computer-aided design/computer-aided manufacturing (CAD/CAM) software (Exocad GmbH, Darmstadt, Germany) (Fig. 2). Finally, the design was transferred to an FDM 3D printer (CUBICON Style Plus - A15D) installed in the dental clinic and printed into a 3D structure using PLA polymer (Fig. 3).

1. Case 1
A 59-year-old man complained of pain emanating from tooth #15 during mastication. The patient was diagnosed with cracked tooth #15 based on clinical and radiographic data; therefore, he underwent root canal treatment and core build-up. A porcelain-fused-to-metal (PFM) crown was planned to cover the treated tooth, which was prepared according to the preparation requirements of PFM crowns. A temporary crown was fabricated with PLA using the FDM method.

2. Case 2
A 45-year-old woman visited our clinic because her old crown on tooth #36 was dislodged. Secondary caries were present in tooth #36, and an infection was found in the previously treated root canal system. Restoration with a gold crown after repeated root canal treatments was planned. A temporary crown was fabricated with PLA using the FDM method.

3. Case 3
A 34-year-old man presented with the chief complaint of spontaneous pain emanating from tooth #37. Clinical and radiographic examinations revealed irreversible pulpitis of tooth #37. Restoration with a gold crown was planned after root canal treatment. A temporary crown was fabricated with PLA using the FDM method.

4. Case 4
A 54-year-old woman visited our clinic for prosthetic treatment of tooth #46 after root canal treatment. Restoration with a gold crown was planned, and a temporary crown for the tooth was fabricated with PLA using the FDM method.

Fig. 2. Crown design using computer-aided design/computer-aided manufacturing (CAD/CAM) software (Exocad GmbH, Darmstadt, Germany). (A) Lateral view. (B) Occlusal view.

Fig. 3. Fabrication of a three-dimensional (3D)-printed temporary crown using the fused deposition modeling (FDM) method and polylactic acid (PLA) polymer. (A) FDM 3D printer (CUBICON Style Plus - A15D; CUBICON Co. Ltd., Seoul, Korea). (B) Nexway PLA (QUVE Co. Ltd., Seoul, Korea). (C, D) Fabrication of a single temporary crown using PLA. (E) Single temporary crown made with PLA.
5. Case 5
An 80-year-old man complained of pain emanating from tooth #14 when biting, and chewing difficulty over the entire dentition. The maxillary right first premolar was diagnosed with irreversible pulpitis. He experienced prolonged abnormal occlusion due to missing teeth #15, 16, 17, 45, 46, and 47; therefore, the remaining anterior teeth showed severe pathological attrition, and there was no space for the prosthesis in the mandible. Root canal treatment was planned for tooth #14, which was subsequently covered with a surveyed crown so that it could be used as an abutment for removable partial dentures. Owing to the short clinical crown length and low esthetic expectations, a gold crown was planned, and a temporary crown was fabricated with PLA using the FDM method.

The printing process for each crown took approximately 7 minutes. The workplace was not polluted by noise or dust and was kept clean. No failure occurred due to fracture or dislodging of the temporary crown, and no complaints of discomfort, poor esthetics, or surface roughness were reported during the temporary restoration period, which took an average of 7 days (Table 1). Occlusal adjustment was achieved using a denture bur, as would be performed with a temporary, conventional direct resin crown. However, these single provisional crown cases required almost no occlusal adjustment, as few high spots or guide interferences were observed.

Discussion
With the recent development of digital equipment and materials in the dental field, the popularity of digital dental technologies has increased [9-11]. The digital process of printing crowns is a novel method that is highly accurate and has low technique sensitivity, allowing dental prostheses to be manufactured by 3D printing, including model-making, without complex lab work [12-14].

Although 3D printing is fast and precise and most printed objects have smooth surface, it is mostly used to produce temporary prostheses. The brittleness, easy deformability, poor weather resistance, and low biocompatibility of 3D-printed objects fabricated using the photo-curing technique limit their performance [15]. Various types of 3D printers and materials are used in the 3D printing of temporary prostheses; however, evidence of their clinical application is still lacking. Therefore, advanced research on materials for the 3D printing of temporary restorations is needed [4]. Convenience, cost, and accuracy are more important factors for temporary crowns than for permanent prostheses.

The equipment and materials involved in SLA are expensive and inconvenient for clinical handling because of the sticky and messy photopolymer used. SLA also produces large amounts of waste material [4,5]. However, the equipment and materials involved in FDM are relatively economical, easy to handle, and possess excellent strength [16].

PLA is one of the most commonly used materials in FDM printers. PLA is biocompatible and nontoxic because it is synthesized from renewable resources, such as sugarcane or cornstarch [17]. In a few in vitro studies, 3D-printed temporary crowns fabricated with PLA using an FDM printer were appropriate in terms of fit and mechanical strength. Molinero-Moureille et al. [18] reported that the mean marginal fit of PLA provisional crowns was 122.89 ± 26.04 µm, which was clinically acceptable. Crenn et al. [19] reported that PLA temporary crowns had superior flexural strength (115.8 ± 2.11 MPa), hardness (Vickers hardness number of 17.5 ± 0.7), and elastic modulus (3,784 ± 98.9 MPa) compared with those of temporary crowns fabricated with poly(methyl methacrylate), which is an autopolymerizing temporary resin used in the conventional direct method. However, there is a lack of evidence regarding the clinical application of PLA provisional crowns.

Hence, we examined the efficiency of PLA as a temporary crown material fabricated using an FDM dental 3D printer. We used the PLA polymer that was made by blending less than one part polybutylene adipate-co-terephthalate with more than nine parts PLA. All 3D temporary crowns manufactured using this PLA were simply and accurately applied after intraoral scanning.

Both the printer and PLA were easy to handle in the clinic, the workload of the dental staff was reduced owing to digitalization, and contamination of the clinic by volatile liquids was reduced.

Table 1. Characteristics of the patients and three-dimensional printing of temporary crowns

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/age (yr)</th>
<th>Tooth No.</th>
<th>Working time (min:sec)</th>
<th>Failure of the temporary restoration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male/59</td>
<td>#15</td>
<td>7:02</td>
<td>No event</td>
</tr>
<tr>
<td>2</td>
<td>Female/45</td>
<td>#36</td>
<td>7:12</td>
<td>No event</td>
</tr>
<tr>
<td>3</td>
<td>Male/34</td>
<td>#37</td>
<td>7:10</td>
<td>No event</td>
</tr>
<tr>
<td>4</td>
<td>Female/54</td>
<td>#46</td>
<td>7:08</td>
<td>No event</td>
</tr>
<tr>
<td>5</td>
<td>Male/80</td>
<td>#14</td>
<td>6:58</td>
<td>No event</td>
</tr>
</tbody>
</table>

The working time was length of the time required to manufacture the temporary crown.
There were no complaints of patient discomfort and no failures, including fractures and dislodgements, occurred until the final prosthesis was ready. However, PLA products tend to undergo thermal degradation, making high-speed polishing difficult. Therefore, it is important to find ways to reduce the surface roughness of PLA crowns.

The average working time for the 3D printing of temporary crowns is \(21 \pm 5\) minutes, which is shorter than the time taken for the direct method, and similar to the time required for impression taking, enabling the efficient use of chair time.

In the 3D-printing process, after tooth preparation, points that require correction can be checked and corrected immediately on the screen by direct communication between the dental technician and the dentist. Digital data can also be used to fabricate permanent prostheses.

However, our reported cases were limited to single restorations in the posterior region, which is associated with the fact that the accuracy of oral scanning is limited to single-tooth or short-span prostheses. Along with improvements in digital scanning, further research on long-span 3D-printed prostheses should be conducted. Because of the limited surface texture of PLA temporary crowns, their application was limited to the posterior teeth; this limitation should be addressed in future studies to enable the use of 3D-printed crowns for anterior teeth. In addition, assessment of the patients in this study was subjective. Further studies are needed to evaluate PLA 3D-printed crowns using objective data.

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

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Author contributions
Conceptualization, Funding acquisition, Validation: EK, EYP, SK; Formal analysis, Supervision: EK, SK; Methodology: EYP; Project administration, Investigation, Resources: SK; Visualization: EK; Writing-original draft: EK; Writing-review & editing: EK, EYP.

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References


Morgagni-Stewart-Morel (MSM) syndrome is characterized by the thickening of the frontal bone of the skull (hyperostosis frontalis interna), obesity, neurological symptoms, and hypertrichosis. We present the case of a 76-year-old patient who complained of confusion, extreme irritability, and headache and was diagnosed with MSM based on examination, imaging, and test results.

Keywords: Endocrine system; Hirsutism; Hyperostosis frontalis interna; Hyperparathyroidism

Introduction

Morgagni-Stewart-Morel (MSM) syndrome is characterized by the thickening of the frontal bone of the skull (hyperostosis frontalis interna), obesity, neurological symptoms, and hypertrichosis [1-3]. In addition, diabetes, hyperparathyroidism, and other endocrine problems may accompany this condition. Headache, atrophy of the frontal lobe, a decreased sense of sight and smell, parkinsonism, anxiety, depression, confusion, cognitive disorders, and seizures may accompany the neurological symptoms [4,5]. The etiology of MSM syndrome is not fully understood. The syndrome was described in 1719 by pathologist Giovanni Battista Morgagni, in 1928 by neurologist Roy Mackenzie Stewart, and in 1930 by psychiatrist Ferdinand Morel [1,2,4].

Case

A 76-year-old female patient was brought to the emergency department with confusion, dizziness, and extreme nervousness that had started 2 days earlier. In the anamnesis, it was found that she had a headache for years, did not enjoy life occasionally, and was extremely nervous. On physical examination, the patient's general condition was good, body temperature was normal, and vital signs were stable. On neurological examination, there were no signs other than orientation and limited cooperation, and the patient did not have neck stiffness. Other system examinations were normal. No acute pathology was detected on brain computed tomography (CT) and magnetic resonance imaging (MRI) performed in the emergency department. An axial cranial CT scan showed bilateral thickening of the inner table of the frontal bone (Fig. 1).

She was administered irbesartan 150 mg/day for hypertension. The patient had no history of trauma or febrile illness and was admitted to our hospital for further examination and treatment. Routine blood tests, whole blood, vitamin B12 levels, ammonia, thyroid function tests, hemoglobin A1c, erythrocyte sedimentation rate, serum electrophoresis, autoantibody screening (antinuclear antibody, anti-SSA, and anti-SSB), antithyroid antibodies, syphilis serology (fluorescent treponemal antibody), and Schirmer's test...
were normal. Enzyme-linked immunosorbent assay tests and pathergy tests for Behçet disease were negative. The complete urinalysis results were within normal limits. Screening for viral meningitis and Brucella yielded negative results.

The patient’s blood biochemistry results showed high urea, high parathormone (82.7 ng/L; range, 15–65 ng/L), and low 25-hydroxyvitamin D levels. There were mild signs of hirsutism and progesterone, testosterone, 17β-estradiol levels were normal. A score of 19 was obtained on the Mini-Mental State Examination (MMSE). Growth hormone and somatomedin C indicative of acromegaly were within normal limits. The patient was referred to endocrinology, and vitamin D treatment was administered.

Brain MRI of the patient revealed no findings other than hyperostosis frontalis interna. Sagittal T1-weighted MRI and an axial section cranial scan showed nodular bony overgrowth involving the frontal endocranium (Fig. 2). The patient’s body mass index (BMI) was 30 kg/m². Electroencephalography (EEG) revealed seizure activity, and our patient was started on levetiracetam 500 mg twice a day. No significant pathology was found in the breast examination for Paget disease or a bone survey X-ray taken for lytic lesions.

The patient was diagnosed with MSM syndrome based on anamnesis, examination findings, and imaging results. She was discharged with the recommendation of a neurology outpatient follow-up, with treatment for her current complaints.

Discussion

MSM syndrome was first described by Giovanni Battista Morgagni in 1719 as a thickening of the inner layer of the skull in an obese female patient with hirsutism and hyperostosis frontalis interna observed during autopsy. In 1928, Stewart reported three cases found during autopsy. In 1930, Morel reported the first living case. MSM syndrome presents with endocrinological, metabolic, and neuropsychiatric symptoms [1-5].

Our patient had extreme irritability, confusion, and headaches. Seizure activity was also detected in the EEG results. Our patient had hypertension but did not have diabetes. She showed signs of hirsutism and a BMI of 30 kg/m². Hyperostosis frontalis was detected in the imaging results of our patient, and the laboratory findings revealed high urea, high parathormone, and low vitamin D levels. Fibrous dysplasia, acromegaly, and Paget disease were excluded in the differential diagnosis. The first MMSE score was 19 points, and the repeated MMSE score was 26 points. MSM syndrome is rare and usually occurs in women. The mean age of onset is 45 years. Reported cases in literature are predominantly women [1-3]. The patient was a 76-year-old female. Although the pathophysiology of MSM syndrome has not been clearly determined, it is believed to be related to long-term exposure to estrogen, obesity, high leptin levels, and genetics [3,4]. Genetic transmission is believed to be autosomal dominant.
Treatment of MSM syndrome is symptom-based and usually includes weight-control medications, as well as diet and lifestyle changes. Seizures and headaches associated with hyperostosis frontalis interna are treated using standard medications [1,4,5]. As a result, MSM syndrome should be considered in patients presenting with similar symptoms. Thorous anamnesis should be taken, radiological imaging performed, metabolic parameters tested, and symptomatic treatment administered after the diagnosis is made.

**Notes**

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

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

**References**

Thallium poisoning is usually accidental. We present a case of a 51-year-old woman who was evaluated in June 2018 for myalgia, vertigo, asthenia, and abdominal pain. Physical examination revealed temporal-spatial disorientation, jaundice, and asterixis. The laboratory reported the following: bilirubin, 10.3 mg/dL; aspartate transaminase, 78 U/L; alanine transaminase, 194 U/L; albumin, 2.3 g/dL; prothrombin time, 40%; and platelet count, 60,000/mm$^3$. Serology performed for hepatitis A, B, and C; Epstein-Barr virus; cytomegalovirus; and human immunodeficiency virus was negative, and a collagenogram was negative. Physical reevaluation revealed alopecia on the scalp, armpits, and eyebrows; macules on the face; plantar hyperkeratosis; and ulcers on the lower limbs. Tests for lead, arsenic, copper, and mercury were carried out, which were normal; however, elevated urinary thallium (540 µg/g; range, 0.4–10 µg/g) was observed. The patient was treated with D-penicillamine 1,000 mg/day and recovered her urinary thallium levels were within normal range at annual follow-up. Thallium poisoning is extremely rare and can be fatal in small doses. An adequate clinical approach can facilitate early diagnosis.

**Keywords:** Alopecia; Intoxication; Liver failure; Thallium

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**Introduction**

Thallium is a colorless, odorless, heavy metal present in the air, water, and soil. Its initial use in pesticides led to multiple reports of intoxication and death from exposure, which is why its domestic use has been prohibited since the 1960s, relegating it to limited industrial applications.

Thallium enters the body via digestive, respiratory, and skin routes. It widely distributes, fixing itself in the nervous system, skin and appendages, muscle, liver, kidneys, and adipose tissue, and can cross the placental barrier and cause fetal damage [1].

It does not undergo metabolism and rapidly reaches the enterohepatic circulation, which can prolong its half-life for up to 4 days (occasionally more than 30 days). It is excreted mainly through the kidneys and the digestive tract over several weeks, which explains the presence of high levels of the compound in 24-hour urine tests (the most reliable method) in contrast to the low plasma levels after more than 4 days have elapsed postexposure. The lethal dose of thallium is 10 to 15 mg/kg [2,3].

Although the exact mechanism of its toxicity is still not clear, thallium is known to exchange with intracellular potassium and have a high affinity for the sulfhydryl groups of mitochondrial
membrane proteins, resulting in the inhibition of glycolysis and energy production in the Krebs cycle and oxidative phosphorylation [4].

After ingestion of thallium, vomiting and abdominal pain are noted within minutes; dry mouth and diarrhea (or constipation) may persist for days or weeks. Alopecia and encephalopathy (dementia, confusion, ataxia, and coma) are dependent on the amount, duration, and dose of thallium [3,4].

Cases of poisoning are extremely rare and mostly accidental. In the Argentine Republic, 335 thallium poisoning cases were reported from 1977 to 1985, after which the use of this compound was completely prohibited in the manufacture of rodenticides. Since then, there have been no other official reports because the detection of new cases has been extremely rare [5].

Case

Ethical statements: This study was exempt from review by the Institutional Review Board (IRB) of Sanatorio de la Providencia (IRB No: 014-2022). Written informed consent was obtained from the patient to participate in the study.

A 51-year-old female patient, a lawyer by profession, living in a residential area of Buenos Aires, presented with a relative to the emergency department in June 2018 due to myalgia and vertigo that had persisted for 1 month and was associated with abdominal pain, daily emesis (up to three episodes), and progressive asthenia over the previous week. She had a history of irritable bowel syndrome and hypothyroidism (treated with levothyroxine 50 µg daily for 2 years and strictly controlled by an endocrinologist).

Physical examination revealed vital signs within normal parameters, with evidence of temporal-spatial disorientation, incoherent speech, generalized jaundice, and flapping. Her laboratory test results were as follows: total bilirubin, 10.3 mg/dL; direct bilirubin, 5 mg/dL; aspartate transaminase, 78 U/L; alanine transaminase, 194 U/L; prothrombin time, 40%; international normalized ratio, 1.7; albumin, 2.3 g/dL; platelet count, 60,000/mm³; lactate dehydrogenase, 1,130 U/L; and C-reactive protein, 69 mg/dL. The remaining initial tests, including sodium, potassium, calcium, phosphorus, magnesium, ammonium, and chlorine levels, were unremarkable. Likewise, brain computed tomography was performed without contrast, which did not reveal morphological compromise of the central nervous system.

The patient was hospitalized on the basis of a diagnosis of acute liver failure. Serology was performed for hepatitis A, B, and C; Epstein-Barr virus; cytomegalovirus; human immunodeficiency virus; and antibodies to detect autoimmune disorders (antimitochondrial antibody, anti-liver-kidney microsomal antibody, smooth muscle antibody, and factor associated with neutral sphingomyelinase activation), which were all negative. It was decided to perform a thyroid profile based on the patient’s pathological history, revealing normal values (thyroid-stimulating hormone, 1.9 µU/mL; free thyroxine, 70 nmol/L; and triiodothyronine, 2 nmol/L).

After a second physical evaluation, the following were found: alopecia on the scalp, armpits, and eyebrows (Fig. 1); brown macules on the face; dry and rough skin with anhidrosis; generalized hypotonia; plantar hyperkeratosis (Fig. 2A); and ulcers on both limbs (Fig. 2B), in addition to weakness and hyporeflexia associated with decreased sensitivity in the four extremities. When the patient was again questioned to obtain another history of exposure, she denied the use of alcoholic beverages, tobacco, therapy with herbs or plants, direct contact with insecticides or poisons, or consumption of medications other than levothyroxine. She stated that she had always lived within the same area, which was strictly residential without nearby factories or industrial activity. She also said
that she was unaware of any reports of poisoning in people in her close circle or the appearance of symptoms similar to hers in the people with whom she lived or in the neighbors with whom she had constant communication.

Brain computed tomography and abdominal ultrasound were repeated, which did not show any pathological findings. Due to suspicion of intoxication by heavy metals, they were measured in her plasma (p) and 24-hour urine (u), resulting in the following values: p lead, 5.5 µg/dL (range, < 30 µg/dL); p arsenic, 0.4 µg/dL (range, < 0.4 µg/dL); u arsenic, < 0.1 µg/g creatinine (Cr) (range, < 10 µg/g Cr); p copper, 68 µg/dL (range, 70–160 µg/dL); u copper, 57.4 µg/24 hr (range, 15–64 µg/24 hr); p mercury, < 0.5 µg/L (range, < 15 µg/L); u mercury, 2.6 µg/g Cr (range, < 50 µg/g Cr); p thallium, 12 µg/dL (range, < 80 µg/dL); and TLU, 540 µg/g Cr (range, 0.4–10 µg/g Cr).

After making the diagnosis of chronic thallium intoxication, chelation therapy was started with oral D-penicillamine 250 mg every 6 hours. The patient presented a favorable evolution after 2 weeks of treatment and was discharged. Monthly follow-ups were carried out, in which an average decrease in TLU levels of 10% was observed at each appointment; all symptoms (including alopecia) resolved after 6 months of treatment.

After 1 year of treatment, her TLU levels were measured and found to be within normal limits (2.3 µg/g Cr). At the date of this publication, the source of poisoning is still unknown.

Discussion

The findings presented in our clinical case are consistent with those of other cases published in the literature, in which the appearance of a characteristic triad has been shown, leading to the suspicion of thallium intoxication [2,6,7]. This triad consists of the presence of abdominal pain, evidence of a motor or sensory neurological deficit, and alopecia. The pattern of presentation usually develops in the following order after exposure to thallium: nausea, vomiting, and abdominal pain appearing during the first hours after exposure, followed by the appearance of peripheral sensorimotor neuropathy after 72 or more hours, and finally generalized alopecia weeks later (Table 1). Thus, based on the data mentioned in Table 1, as well as the clinical manifestation of our patient, it can be inferred that these symptoms are related to thallium intoxication that has progressed between 2 and 4 weeks [8-10].

Although thallium affects organs in a generalized way, the liver is one of the most affected. Acute liver failure has not been reported as an isolated symptom, but rather as part of multi-organ toxicity. As part of the neurological involvement, painful peripheral neuropathy (“burning feet syndrome”) was the most frequently described, which differs from this case in which the neuropathy was characterized as hypoesthesia and was not painful [11,12].

With regard to treatment, it is now known that the antidote for thallium intoxication is Prussian blue (3 g daily for adults), usually administered with a cathartic for better adsorption and elimination of the metal. Despite this, the available data are insufficient to comment definitively on its effectiveness. Thus, the management of thallium intoxication does not seem to be systematized because it is subject to multiple controversies [13]. In this case, D-penicillamine was chosen as the chelating treatment for several reasons. First, D-penicillamine was immediately available, as opposed to Prussian blue. Second, the patient’s chronic constipation contraindicated the use of Prussian blue. Third, Prussian blue is recommended for acute thallium poisoning.

We considered the importance of presenting this case because thallium poisoning can be fatal in small doses in a very short period of time. In addition, such cases are extremely infrequent and have a highly variable clinical presentation, resulting in many misdiagnoses. Because of this, it is necessary to understand the clinical manifestations of thallium poisoning, with a high index of suspicion involving the presence of alopecia (a characteristic sign) associated with various manifestations, the most frequent being gastrointestinal symptoms in the early stage and nervous system alterations in the late stage.

Notes

Conflicts of interest

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

Funding

None.

Author contributions

Conceptualization: all authors; Investigation: OJ, LS; Formal analysis, Supervision: HC, LG, JAAR; Resources: OJ, HC, MM; Vali-

Table 1. Symptoms associated with thallium poisoning

<table>
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<tr>
<th>Period after poisoning</th>
<th>Symptom</th>
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<tr>
<td>3–4 hours</td>
<td>Nausea, vomiting, diarrhea, and hematemesis</td>
</tr>
<tr>
<td>5 hours–14 days</td>
<td>Disorientation, coma, psychosis, seizures, heart failure, acute pulmonary edema, optic neuritis, acne, hyperhidrosis, gray gum lines, hair root pigmentation, and anhidrosis</td>
</tr>
<tr>
<td>15–30 days</td>
<td>Dry and scaly skin, alopecia, and white stripes on the nails</td>
</tr>
<tr>
<td>&gt;30 days</td>
<td>Ataxia, foot hyperextension, and memory loss</td>
</tr>
</tbody>
</table>
References

An 87-year-old woman presented to the emergency department with right-sided chest pain and dyspnea. The patient had been undergoing outpatient internal medical follow-up for a hepatic cyst 10 years previously (Fig. 1A). One month before visiting the hospital, she underwent computed tomography (CT) due to pain in the upper abdomen, which revealed that the size of the hepatic cyst had increased considerably (Fig. 1B). However, her symptoms were not severe and the patient was older. She only wanted to control her symptoms. At the time of admission to the emergency room, a large amount of pleural fluid was observed on CT, and the size of the hepatic cyst had decreased (Fig. 1C), resulting in empyema thoracis as the hepatic cyst had ruptured through the diaphragm and into the thoracic cavity [1,2]. The patient was immediately treated with closed-tube thoracostomy. After the procedure, approximately 2,000 mL of pleural effusion was drained, and her dyspnea improved. The pH of the drained pleural fluid was 6.57, with a glucose level of 6 mg/L, lactate dehydrogenase level of 51,361 IU/L, and white cell count of 176,000/μL. Empyema was diagnosed based on these results, and intravenous piperacillin/tazobactam antibiotics were initiated. Although a diaphragmatic defect or fistula was not clearly visible on the CT scan, > 150.0 μmol/L of bile acid was found in the pleural fluid, confirming empyema from the hepatic lesion. Five days after the procedure, the patient’s symptoms significantly improved, and a follow-up CT scan was performed. The large hepatic cyst had almost disappeared, and the empyema was well drained (Fig. 1D). Escherichia coli was identified in the pleural effusion, and piperacillin/tazobactam was continued because E. coli is highly sensitive to this antibiotic combination. The chest tube was removed on the 19th day of hospitalization. She was discharged without any discomfort 2 days after removal of the chest tube. On the 9th day after discharge, she visited the outpatient clinic, and chest radiography

Image vignette

Effective treatment of empyema thoracis caused by a ruptured large hepatic cyst

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Fig. 1. (A) Hepatic cyst (10 cm, arrow) noted by abdominal computed tomography (CT) 10 years ago. (B) CT scan taken at the internal medicine outpatient department 1 month before the visit to the emergency room shows the existing hepatic cyst enlarged to approximately 19 cm (arrow). (C) Abdominal CT at the time of admission to the emergency room shows a large amount of pleural effusion (arrow) and the hepatic cyst (arrowhead), which is significantly smaller than 1 month earlier. (D) One week after chest tube insertion, CT scan shows that most of the pleural effusion has drained, and the giant hepatic cyst has disappeared.
confirmed that her right lung had improved. It has been 2 years since the patient was treated and discharged from our hospital. She is currently being followed up at the neurology department of a local medical center for dementia. She has had no subsequent symptoms such as dyspnea or abdominal pain.

Hepatic cysts are usually asymptomatic; however, in rare cases, a liver abscess may occur as a complication of an infection. Pyogenic liver abscess (PLA) is primarily caused by bacteria, such as *E. coli*, *Streptococcus* spp., and *Klebsiella pneumoniae* [3]. PLA is rare; however, empyema caused by a liver abscess that bursts through the diaphragm into the chest cavity is much rarer [4]. As the risk of death is high if treatment is not initiated quickly, effective drainage and appropriate use of antibiotics are required to treat patients [3].

Notes

Ethical statements
This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUMC 2023-03-030). Informed consent was waived because of the retrospective nature of the image vignette.

Conflicts of interest
Hyuckgoo Kim has been an editorial board member of *Journal of Yeungnam Medical Science* since 2021. He was not involved in the review process of this manuscript. There is no conflict of interest to declare.

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Author contributions
Conceptualization, Data curation, Resources: SSL, HK; Formal analysis, Visualization, Software, Supervision: SSL; Writing-original draft: SSL, HK; Writing-review & editing: SSL.

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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 pathognomic 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
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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.

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Research and publication ethics

Enactment May 22, 2012

Research ethics


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