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Risk Factors for Heterotopic Ossification in Traumatic Brain Injury: An Analysis of the Korean National Health Insurance Service Data

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Purpose: This study investigated the risk factors for heterotopic ossification (HO) in patients with traumatic brain injury (TBI).
Materials and Methods: This was a retrospective study using the Korean National Health Insurance Service (KNHIS) database and included as many relevant factors as possible. Data were collected from the KNHIS cohort, a nationwide cohort covering the entire Korean population. Patients diagnosed with TBI from 2004 to 2018 were included. TBI was defined as individuals who 1) had been hospitalized, 2) were diagnosed with TBI under ICD-10 code S06, and 3) underwent brain imaging within 1 week before or after diagnosis. Among 637315 adult patients, 1909 (0.30%) developed HO. This study aimed to clarify the relationship between HO and various factors, including demographic and medical history, medication history, complications, and accompanying injuries in TBI patients.
Results: Among TBI patients, HO was more common in female and peaked in patients in their 50s, with a lower incidence in their 70s. Preobesity and obesity were significant risk factors, while smokers had a reduced risk. HO was more common in patients with rheumatic diseases and medical comorbidities, and those who had undergone tracheostomies. The use of antiseptics was associated with an increased risk, whereas anticonvulsants, antithrombotics, steroids, and non-steroidal anti-inflammatory drugs were associated with lower risks. HO was more common in registered patients with disability due to brain lesion.
Conclusion: In conclusion, middle-age range, female sex, obesity, comorbidities, injury severity, systemic inflammation, and bony metabolism-affecting medications appear to increase the risk of HO in patients with TBI.

Key Words: Traumatic brain injury, heterotopic ossification, risk factors, big data, logistic regression

INTRODUCTION

Heterotopic ossification (HO), a lamellar bone formation in ectopic regions, primarily large joints, can occur in neurologic and musculoskeletal injuries, including traumatic brain injury (TBI), spinal cord injury, burns, amputation, and joint replacement.[1]

HO typically involves large joints and often limits their range of motion. The hip joint is most frequently affected by HO, followed by the elbow joint.[2] HO is also reportedly the cause of poor outcomes and low home discharge rates among the patients with a TBI.[3] Therefore, an early diagnosis is important to prevent progression. HO causes symptoms such as swelling, heating sensations, and pain in the affected region. As these symptoms may not be obvious in patients with a TBI with motor or cognitive impairment, early diagnosis often relies on the clinician's experience.

Many studies on HO risk factors have involved hip replacement, a relatively common surgical condition, and meta-analyses of the risk factors for HO occurrence in patients with hip

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replacement and spinal cord injury have been published.[4,5] However, although TBI is as prevalent as these conditions, relatively few studies have been conducted on the risk factors for developing HO in TBI.

Although the exact mechanism of HO is yet to be elucidated, it is thought to be caused primarily by mechanical and neurological mechanisms.[6] In conditions without neurologic deficits, mechanical factors may be responsible for HO, whereas HO in traumatic central nervous system injuries, such as spinal cord injury and TBI, is related to neurogenic processes. Since TBI and spinal cord injury have different disease characteristics and clinical features, the risk factors for HO development after these two conditions could be different. Various brain-related factors, including osteogenic factors, neuropeptides, hormones, and blood-brain barrier permeability, have been suggested to be associated with HO in TBI.[7] Therefore, we aimed to identify the TBI-specific risk factors for HO by analyzing the Korean National Health Insurance Service (KNHIS) cohort, a large nationwide cohort covering the entire Korean population. In this study, we investigated various risk factors for HO at any joint in the body among patients with TBI.

MATERIALS AND METHODS

Definition of research patients

This study was approved by the Institutional Review Board (IRB) of the National Health Insurance Service Ilsan Hospital (IRB No. NHIMC 2022-07-029). As all data were provided by the KNHIS and fully anonymized, the IRB of the National Health Insurance Service Ilsan Hospital allowed the omission of informed consent.

In Korea, all citizens are obligated to join the KNHIS, which is the only insurer operated by the Korean government. Among Koreans, 97.2% have medical insurance and the other 2.8% are medical beneficiaries. The KNHIS database provides information on a wide range of medical and sociodemographic variables. This anonymized database contains information about the insured person, such as insurance eligibility, utilization of healthcare resources, and national public health screening, as well as data from medical institutions. In this database, diagnosis is based on the International Classification of Diseases, Tenth Revision (ICD-10). The national public health screening data includes body measurements and a self-reported lifestyle questionnaire.

We selected patients who were diagnosed with TBI from 2002 to 2018. Patients with TBI were defined as individuals who 1) had been hospitalized, 2) were diagnosed with TBI under ICD-10 code S06, and 3) underwent brain imaging (CT or MRI) within 1 week before or after the TBI diagnosis. To include only newly diagnosed TBI cases after 2004, we excluded patients with a history of healthcare utilization for TBI from 2002 to 2003 (washout period: 2 years). Pediatric patients younger than 18 years were excluded from the study. HO occurrence was defined using ICD-10 codes (M610, 612, 614, 615, and 619) after the onset of TBI. HO occurring in any joint of the body was included in the analysis.

The existing literature was extensively searched to identify as many risk factors as possible. Since the nature of the KNHIS database precludes the use of clinical data, we included as many factors as possible that could be obtained from claim-based data.

Demographic and medical history

Body mass index (BMI) and smoking history were extracted from the public health examination data at the closest point before the onset of TBI. BMI was divided into five classifications according to the obesity treatment guidelines of the Korean Society for the Study of Obesity: low (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), preobesity (23–24.9 kg/m^2), obesity (25–29.9 kg/m^2), and severe obesity (≥30 kg/m^2).[8] Smoking history classifications included never-smoker, ex-smoker, and current smoker. Rheumatic diseases included rheumatoid arthritis (ICD-10 codes M05, M060, M068, and M069), ankylosing spondylitis (ICD-10 code M45), systemic lupus erythematosus (ICD-10 codes M321, M328, and M329), dermatomyositis/polymyositis (ICD-10 code M330), and fibrodysplasia ossificans progressiva (ICD-10 code M611). A disease was considered present if there was a medical record of rheumatic disease within 2 years prior to the onset of TBI. In addition, for previous medical comorbidities, the Charlson Comorbidity Index (CCI), based on the records from 2 years before TBI, was used (Supplementary Table 1, only online).[9]

Medication

Drugs expected to be potential risk factors for HO, such as anticonvulsants, antispastics, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antithrombotics, calcium, and steroids, were also included. We defined administration of each medication as the use of the drug for more than 30 days after the onset of TBI.

Complications and accompanying injuries

Long bone and vertebral fractures (ICD-10 codes S32, S33, S42, S52, S62, S72, S82, S92, and T02), but not skull and facial bone fractures, were included as risk factors. The accompanying fractures were reclassified as single or multiple fractures. Information on red blood cell transfusions, tracheostomies, and head surgeries was extracted from medical practice codes. The length of stay in an intensive care unit was analyzed by dividing stays into <1 week and ≥1 week. Neurogenic bladder was defined as the administration of anticholinergics for more than 1 month or the implementation of cystostomy. Deep vein thrombosis (ICD-10 code I802) and pulmonary thromboembolism (ICD-10 code I267) were also included. In Korea, disability can be registered based on a modified Barthel Index

score, which reflects the functional status more than 6 months after a brain lesion. The registered disability due to brain lesions was classified as none, mild, or severe.

Statistical analysis

Chi-squared tests (for categorical variables) and independent t-tests (for continuous variables such as CCI score and number of head surgeries) were performed to compare the characteristics of patients with and without HO. To determine the impact of various factors on the development of HO, we conducted univariable logistic regression, followed by multivariable logistic regression analysis. Various factors that may influence the outcome—including sociodemographic, anthropometric, and lifestyle factors; medication use; comorbidities; and medical conditions such as tracheotomy or number of head surgeries—were adjusted for in the multivariable logistic regression analysis. SAS software (version 9.4; SAS Institute, Cary, NC, USA) was used for the analysis.

RESULTS

Data from 637315 adult patients diagnosed with TBI from 2004 to 2018 were analyzed (Fig. 1). A total of 1909 patient with HO accounted for 0.30% of all patients.

The proportion of female in the HO group was higher than that in the group without HO. The HO group had a higher prevalence of rheumatic disease than those without HO, and CCI scores were also higher in the HO group. Significant differences in age, BMI, and smoking history were evident between patients with and without HO (Table 1).

With regard to medication use, the HO group received more antispastics and fewer NSAIDs and antithrombotics than the non-HO group (Table 2). The incidence of HO was higher in patients who were hospitalized in an intensive care unit for at least 7 days, tracheostomized after TBI, or accompanied by deep vein thrombosis/pulmonary thromboembolism, and those who received red blood cell transfusion. The average number of head surgeries was higher in the HO group (0.14±0.47) than in the non-HO group (0.09±0.32) (Table 3).

Table 4 shows the results of univariable and multivariable logistic regression analyses for all potential risk factors. Female were at an increased risk of HO after TBI compared to male. HO occurrence was significantly higher in individuals in their 40s and 50s and lower in those aged 70 years or older than in those younger than 40 years. HO was more common in the

Table 1. Heterotopic Ossification, Demographics, and Medical History in Patients with Traumatic Brain Injury

	Heterotopic ossification		$p^{\dagger}$
	No (n=635406)	Yes (n=1909)	
Sex			<0.0001*
Male	380552 (59.89)	1048 (54.90)	
Female	254854 (40.11)	861 (45.10)	
Age, yr			<0.0001*
<40	125380 (19.73)	291 (15.24)	
40–49	95856 (15.09)	391 (20.48)	
50–59	121565 (19.13)	480 (25.14)	
60–69	109059 (17.16)	386 (20.22)	
70–79	113706 (17.90)	272 (14.25)	
≥80	69840 (10.99)	89 (4.66)	
Body mass index, kg/m^2			<0.0001*
Low (<18.5)	22176 (3.49)	58 (3.04)	
Normal (18.5–22.9)	187143 (29.45)	530 (27.76)	
Preobesity (23–24.9)	117373 (18.47)	406 (21.27)	
Obesity (25–29.9)	145228 (22.86)	545 (28.55)	
Severe obesity (≥30)	19774 (3.11)	67 (3.51)	
Data missing‡	143712 (22.62)	303 (15.87)	
Cigarette smoking			<0.0001*
None	274134 (43.14)	1004 (52.59)	
Ex-smoker	69277 (10.90)	202 (10.58)	
Current smoker	138113 (21.74)	380 (19.91)	
Data missing‡	153882 (24.22)	323 (16.92)	
Rheumatic disease			<0.0001*
None	618336 (97.31)	1818 (95.23)	
Yes	17070 (2.69)	91 (4.77)	
Charlson Comorbidity Index	1.82±2.17	2.01±2.10	0.0338*

Data are presented as n (%) or mean±standard deviation.
*p<0.05; †Chi-square test except for Charlson Comorbidity Index (independent t-test); ‡Data missing from the national public health screening.

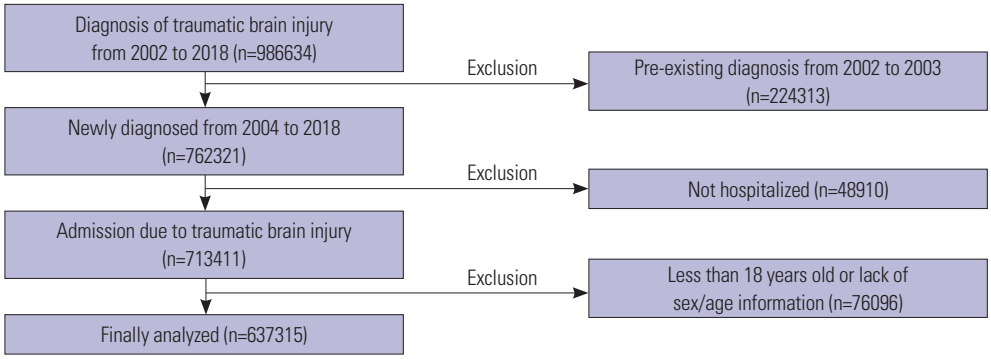

Fig. 1. Flowchart for selection of study population from the Korean National Health Insurance Service claims data.

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Table 2. Heterotopic Ossification and Medication in Patients with Traumatic Brain Injury

	Heterotopic ossification		$p^{\dagger}$
	No (n=635406)	Yes (n=1909)	
Anticonvulsant			0.8827
None	491185 (77.30)	1473 (77.16)	
Yes	144221 (22.70)	436 (22.84)	
Antispastics			0.0006*
None	285246 (44.89)	782 (40.96)	
Yes	350160 (55.11)	1127 (59.04)	
NSAIDs			0.0029*
None	221672 (34.89)	728 (38.14)	
Yes	413734 (65.11)	1181 (61.86)	
Antibiotics			0.7207
None	31816 (5.01)	99 (5.19)	
Yes	603590 (94.99)	1810 (94.81)	
Antithrombotics			0.0278*
None	443958 (69.87)	1378 (72.18)	
Yes	191448 (30.13)	531 (27.82)	
Calcium			0.4542
None	582175 (91.62)	1740 (91.15)	
Yes	53231 (8.38)	169 (8.85)	
Steroids			0.9438
None	457128 (71.94)	1372 (71.87)	
Yes	178278 (28.06)	537 (28.13)	

NSAID, non-steroidal anti-inflammatory drug.
Data are presented as n (%).
*p<0.05; †Chi-square test.

Table 3. Heterotopic Ossification, Complications, and Accompanied Injuries in Traumatic Brain Injury

	Heterotopic ossification		$p^{\dagger}$
	No (n=635406)	Yes (n=1909)	
Bony fracture (except for skull)			0.6303
None	270648 (42.59)	802 (42.01)	
Single site	236965 (37.29)	732 (38.34)	
Multiple sites	127793 (20.11)	375 (19.64)	
ICU length of stay (days)			<0.0001*
<7 days	541804 (85.27)	1489 (78.00)	
≥7 days	93602 (14.73)	420 (22.00)	<0.0001*
No. of head surgery (cont.)	0.09±0.32	0.14±0.47	
Tracheostomy			<0.0001*
None	618626 (97.36)	1701 (89.10)	
Yes	16780 (2.64)	208 (10.90)	
DVT/PTE			0.0068*
None	625889 (98.50)	1866 (97.75)	
Yes	9517 (1.50)	43 (2.25)	
RBC transfusion			<0.0001*
None	500402 (78.75)	1405 (73.60)	
Yes	135004 (21.25)	504 (26.40)	
Neurogenic bladder			0.1399
None	548276 (86.29)	1625 (85.12)	
Yes	87130 (13.71)	284 (14.88)	
Registered disability of brain lesion			<0.0001*
None	605434 (95.28)	1587 (83.13)	
Mild	8753 (1.38)	48 (2.51)	
Severe	21219 (3.34)	274 (14.35)	

ICU, intensive care unit; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; RBC, red blood cell.
Data are presented as n (%) or mean±standard deviation.
*p<0.05; †Chi-square test except for no. of head surgery (independent t-test).

preobesity and obesity groups than in the group of patients with a normal BMI and was less common in current smokers than in non-smokers. The risk of HO was significantly higher in patients with a history of rheumatic disease and in those who underwent tracheostomy after injury. A high CCI score was related to the occurrence of HO after TBI. The occurrence of HO was higher in the antispastic administration group, whereas anticonvulsants, NSAIDs, antithrombotics, and steroids were associated with lower risk of HO. There was a higher risk of HO in patients with registered disability due to brain injury; however, bony fractures and neurogenic bladder were not associated with HO development. Several variables, such as the number of head surgeries, length of stay in the intensive care unit, and deep vein thrombosis/pulmonary thromboembolism, showed significant relationships with HO in the univariable analysis but not in multivariable analysis after adjusting for other variables.

DISCUSSION

This study is the first nationwide population-based cohort study to investigate the risk factors for HO in patients with TBI, involving the largest number of patients compared to previous studies. A wide range of risk factors was explored, and several were identified as novel.

The incidence of HO in TBI patients is reported to range from 4% to 20%, depending on diagnostic methods and study populations.[10,11] Since previous reports were conducted for screening purposes in specialized neurotrauma centers, there is a possibility that severely injured patients were under close surveillance, leading to the detection of even non-significant small HO.[10,12,13] The HO cases accounted for using the ICD-10 codes in this study are considered to be clinically significant. Moreover, a considerable proportion of the study population may have had mild injuries without critical neurological deficits. We considered classifying TBI patients according to disease severity but found that severity based on claims data alone would not be reliable. Instead, we adjusted for variables related to disease severity, such as tracheostomy, ICU stay length, and comorbidities. A previous retrospective study using ICD-10 codes, conducted in a single institution, showed no cases of HO in 3172 neurologically injured patients.[14] In burn patients, who are known to be associated with HO, the incidence of HO also var-

Table 4. Logistic Regression Models for Heterotopic Ossification in Patients with Traumatic Brain Injury

	Univariable models†		Multivariable model‡	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex				
Male	1 (ref)		1 (ref)	
Female	1.227 (1.121–1.342)	<0.0001*	1.350 (1.190–1.531)	<0.0001*
Age, yr				
<40	1 (ref)		1 (ref)	
40–49	1.757 (1.510–20.46)	<0.0001*	1.599 (1.332–1.919)	<0.0001*
50–59	1.701 (1.470–1.968)	<0.0001*	1.476 (1.234–1.766)	<0.0001*
60–69	1.525 (1.309–1.776)	<0.0001*	1.156 (0.952–1.405)	0.1442
70–79	1.031 (0.873–1.216)	0.7205	0.736 (0.593–0.914)	0.0055*
≥80	0.549 (0.433–0.697)	<0.0001*	0.448 (0.333–0.604)	<0.0001*
Body mass index, kg/m^2				
Low (<18.5)	0.924 (0.704–1.121)	0.0730	0.992 (0.754–1.306)	0.9547
Normal (18.5–22.9)	1 (ref)		1 (ref)	
Preobesity (23–24.9)	1.221 (1.073–1.390)	0.1279	1.205 (1.057–1.373)	0.0053*
Obesity (25–29.9)	1.325 (1.176–1.494)	0.0013*	1.297 (1.148–1.466)	<0.0001*
Severe obesity (≥30)	1.196 (0.927-1.543)	0.5391	1.171 (0.906–1.512)	0.2278
Cigarette smoking				
None	1 (ref)		1 (ref)	
Ex-smoker	0.796 (0.684–0.926)	0.0032*	0.874 (0.738–1.035)	0.1182
Current smoker	0.751 (0.668–0.846)	<0.0001*	0.792 (0.688-0.913)	0.0013*
Rheumatic disease	1.813 (1.468-2.240)	<0.0001*	1.719 (1.367-2.162)	<0.0001*
Charlson Comorbidity Index (cont.)	1.039 (1.019–1.059)	<0.0001*	1.046 (1.021–1.071)	0.0002*
Bony fracture (except for skull)				
None	1 (ref)		1 (ref)	
Single site	1.042 (0.943–1.152)	0.3380	1.052 (0.932–1.187)	0.4143
Multiple sites	0.990 (0.876–1.120)	0.5963	0.978 (0.842–1.138)	0.7771
ICU length of stay				
<7 days	1 (ref)		1 (ref)	
≥7 days	1.633 (1.465–1.820)	<0.0001*	0.976 (0.811–1.174)	0.7962
No. of head surgery (cont.)	1.406 (1.269–1.558)	<0.0001*	1.006 (0.875–1.157)	0.9329
Tracheostomy	4.509 (3.901–5.211)	<0.0001*	2.922 (2.289–3.728)	<0.0001*
DVT/PTE	1.516 (1.119–2.052)	0.0072	1.363 (0.973–1.909)	0.0719
RBC transfusion	1.330 (1.201–1.473)	<0.0001*	1.012 (0.874–1.173)	0.8724
Medication				
Anticonvulsant	1.008 (0.906–1.122)	0.8824	0.876 (0.772–0.994)	0.0397*
Antispastics	1.174 (1.072–1.286)	0.0006*	1.378 (1.207–1.574)	<0.0001*
NSAIDs	0.869 (0.792–0.953)	0.0030*	0.799 (0.692–0.923)	0.0022*
Antibiotics	0.963 (0.787–1.179)	0.7161	0.863 (0.677–1.100)	0.2335
Antithrombotics	0.894 (0.808–0.988)	0.0278*	0.838 (0.741–0.949)	0.0052*
Calcium	1.062 (0.907–1.244)	0.4543	0.929 (0.778–1.110)	0.4198
Steroids	1.004 (0.908–1.109)	0.9438	0.873 (0.775–0.984)	0.0263*
Neurogenic bladder	1.100 (0.969–1.248)	0.1399	1.031 (0.894–1.190)	0.6762
Registered disability with brain lesion				
None	1 (ref)		1 (ref)	
Mild	2.092 (1.569–2.790)	<0.0001*	1.797 (1.286–2.511)	0.0006*
Severe	4.929 (4.333–5.608)	<0.0001*	3.255 (2.690–3.939)	<0.0001*

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; RBC, red blood cell; NSAID, non-steroidal anti-inflammatory drug.
*p<0.05; †Results including only the individual variable; ‡Adjusted for all the variables in this table.

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ied widely, from 0.15% to 23%, depending on the population and severity.[15,16]

In previous studies, HO was predominantly reported in male patients, especially in cases of hip replacement and spinal cord injury.[5,17] However, the findings in TBI patients vary. Some studies report no sex predominance,[14,18] while others have shown a female predominance,[13] which aligns with findings that bone formation tends to increase in aging females.[19] The role of sex in HO occurrence in TBI patients requires further investigation. Age-related risk for HO also varies. While some studies find no correlation between age and HO development,[10,18] others have found higher rates in young adults.[12] Our study differs from previous ones by including a larger proportion of older adults, with 28.9% of participants aged 70 or older. We believe the risk of developing HO may be lower in extremely old patients due to decreased metabolic activity.

Obesity is another risk factor for abnormal ossification in ectopic sites.[20] Leptin, a hormone released by adipose cells, is thought to play a role in abnormal bone formation.[7] TBI itself has also been shown to increase leptin levels in cerebrospinal fluid.[21] Although obesity is a well-known risk factor for HO in skeletal injury and hip replacement,[22,23] few studies have explored the relationship between obesity and neurologic HO in TBI patients. The reports about the effect of smoking on HO have also been inconsistent. Some studies reported that smoking increases the incidence of HO in traumatic spinal cord injury patients,[24] while others found no association.[25] One study reported that smoking increases HO occurrence in lumbar disc arthroplasty,[26] whereas another study has shown a protective effect of cigarette smoking on HO in patients who underwent orthopedic surgery.[27] Although studies on the association between HO and smoking are insufficient, clear medical evidence shows that cigarette smoking inhibits bone growth.[28,29]

The exact mechanism of HO remains unclear, but exaggerated inflammatory responses are believed to play a crucial role. Inflammatory factors can promote bone formation, and NSAIDs have been shown to inhibit osteogenic differentiation.[30] While NSAIDs are known to prevent HO in hip replacement and spinal cord injury,[31,32] their effect on TBI patients is still unconfirmed. Similarly, steroids, which have anti-inflammatory effects, were associated with a lower rate of HO development in this study, aligning with animal studies suggesting steroids suppress abnormal bone formation.[33] Vascular stasis and thrombogenic mechanisms are implicated in HO development.[7] In patients undergoing hip arthroplasty, the use of antithrombotic agents has been shown to reduce the incidence of HO.[34] Warfarin is also considered to have sufficient evidence for prophylaxis against HO in spinal cord injury.[35] To our knowledge, no studies have evaluated the effect of antithrombotic agents on HO in TBI patients. We expected that the administration of anticonvulsants would reflect TBI severity and increase the risk of HO, but the results were contrary to this expectation. The adverse effects of anticonvulsants on bone health, such as reduced bone mineral density and increased fracture risk,[36] may relate to the findings of this study.

The increased risk of HO in rheumatic disease appears to contradict previous studies showing that rheumatoid arthritis lowers HO prevalence in hip arthroplasty patients.[4] However, these studies have shown a comparatively lower incidence of HO in rheumatoid arthritis than in other conditions requiring hip joint replacement, such as osteoarthritis, avascular necrosis, and hip fractures, indicating that rheumatoid arthritis does not absolutely reduce the risk of HO. The relatively decreased HO may reflect the effect of regular administration of anti-inflammatory drugs rather than rheumatoid arthritis itself.[4] As studies suggest that ankylosing spondylitis increases the risk of HO,[37] rheumatic diseases that cause systemic inflammation may be linked to HO development.

Spasticity is another well-established risk factor for neurogenic HO.[12] Since physical examination data were not available in the database, we defined spasticity based on the administration of antispastic medications, which were linked to an increased incidence of HO. It is generally known that the severity of neurological or musculoskeletal injuries increases the risk of HO.[38,39] Functional outcomes in TBI and the level or injury completeness in spinal cord injury are important risk factors for HO.[11,13] We used various indicators to adjust for the severity of TBI, such as tracheostomy, length of ICU stays, number of head surgeries, and registered disability. Tracheostomy and registered disability showed a significant relationship with HO occurrence. Tracheostomy is a critical risk factor for HO development in traumatic spinal cord injury as well.[24] Registered disability is a parameter directly reflecting injury severity compared to other factors. It is likely that not only the severity of the brain injury but also poor medical condition or comorbidity prior to injury may be related to HO, as its incidence was related to the sum of the CCI scores.

Bony fractures are often considered a risk factor for HO, as skeletal fractures may synergize with neurological injury mechanisms to increase HO occurrence.[18] However, our study found no statistically significant association between skeletal fractures and HO incidence. The nature of the data may have diluted the effects of fractures, as the specific locations of fractures were not matched with the HO regions.

This study has several limitations. Some causes of TBI were not included, making it difficult to generalize the findings. TBI resulting from motor vehicle or industrial accidents were excluded as their medical expenses were not covered by the KNHIS. Additionally, the study was conducted in a single Asian country, which limits its generalizability across different ethnic groups. Bone formation and turnover may differ among ethnicities.[40] Furthermore, the study analyzed medical claims data, which lacked clinical details such as laboratory findings, level of consciousness, and physical function. Without imaging data, the accuracy and severity of HO diagnoses could not be fully assessed. Finally, some drugs related to bone metabolism were

excluded from the analysis. The number of patients receiving vitamin D, calcitonin, parathyroid hormone, selective estrogen receptor modulators, or denosumab was too small for proper analysis. Particularly, it was also unrealistic to include various bisphosphonates in the analysis, due to the differences in half-life among these drugs.

In conclusion, various factors, including middle age, female sex, obesity, medical comorbidities, injury severity, and systemic inflammation, were found to increase the risk of HO in TBI patients. These findings offer valuable insights for early detection of HO in high-risk patients and provide a foundation for further research into the prevention and treatment of HO in TBI patients.

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