Effect of Anti-Hypertensive Drugs in Geriatric Trauma Patients: A Single-Centre, Retrospective Cohort Study

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Abstract

Background: The relationship between the administration of oral anti-hypertensive drugs and mortality after hospitalisation in trauma patients has not yet been investigated. We conducted a single-centre, retrospective cohort study to determine the effect of anti-hypertensive drugs on mortality and complications in geriatric trauma patients.

Methods: Trauma patients aged ≥ 65 years who were admitted to our hospital between January 2018 and December 2020 were analysed. Patients who had not received anti-hypertensive drugs before admission [AHT(–) group] and those who had received anti-hypertensive drugs before admission [AHT(+) group] were compared using 1:1 propensity score-matched analysis. The primary outcome was 28-day mortality, and the secondary outcomes were in-hospital mortality and the incidence of complications during hospitalisation. Outcomes were analysed by calculating the relative risk.

Results: A total of 637 patients were included in our study. After propensity score matching, each study group had 223 patients. There was no significant difference in the primary outcome between the two groups [28-day mortality: AHT(–) group vs. AHT(+) group: 3.6% vs. 3.6%, respectively; adjusted relative risk: 1.00; 95% confidence interval: 0.38–2.62]. Regarding secondary outcomes, only the incidence of in-hospital delirium was significantly different between the AHT(–) group and the AHT(+) group (25.1% vs. 13.9%, respectively; adjusted relative risk: 0.55; 95% confidence interval: 0.37–0.82).

Conclusions: Regular use of anti-hypertensive drugs did not affect the outcome of geriatric trauma patients. However, the incidence of in-hospital delirium was reduced in patients regularly receiving anti-hypertensive drugs.

Background

The world population is aging and will continue growing older, including in Japan. Older adults have higher trauma mortality rates due to various factors, such as multidrug administration, a medical history, muscle weakness, poor nutrition, and weakened immunity [1–5]. In addition, they often die from complications (e.g., infections and embolism), even if the trauma itself is mild [5–8].

On the one hand, the regular administration of anti-hypertensive drugs is a risk factor for falls in older adults [9–12]. On the other hand, anti-hypertensive drugs are expected to exhibit anti-inflammatory effects [13]. Particularly in patients with sepsis, a better prognosis has been reported in those regularly taking anti-hypertensive drugs [14–17]. To our knowledge, the relationship between the administration of oral anti-hypertensive drugs and mortality after hospitalisation in trauma patients has not yet been investigated.

Herein, we present the potential effects of anti-hypertensive drugs in trauma patients. This study contributes to a growing body of evidence for improved care after admission for this vulnerable

population. It is expected that this study will further research on medication management following admission.

We hypothesised that trauma patients receiving anti-hypertensive drugs would have a better prognosis than those who did not receive anti-hypertensive drugs. This was assessed by evaluating 28-day mortality, the primary outcome of this study.

Methods

Study design and setting

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The protocol for this single-centre, retrospective cohort study was approved by the Medical Ethics Committee of Juntendo University Shizuoka Hospital (approval number: E21-0089). This institution delivers critical trauma care to an area with a population of 1,500,000. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [18].

Selection of participants

We collected the data of older trauma patients (≥ 65 years) who were admitted to our hospital between January 2018 and December 2020. Patients admitted for cardiac arrest, burns, toxins, asphyxiation, near-drowning, or hanging were excluded. Moreover, patients who were transferred to another hospital within 3 days of admission, and those with unclear medical and drug histories, were excluded.

Measurements

This observational study used a medical chart review to collect data. In this study, collectors who were not authors collected the necessary information from the medical records. Next, supervisors checked and anonymised the collected data. After these processes, the authors analysed the data. The following data were collected: patient demographics, medical history, injury severity score (ISS), vital signs upon arrival (Glasgow coma scale score, systolic blood pressure, heart rate, respiratory rate, and body temperature), in-hospital complications (acute kidney injury, acute respiratory distress syndrome, arrhythmia, bleeding, cardiovascular disease, delirium, infections, stroke, and venous thromboembolism [VTE]), 'do not attempt resuscitation' orders, invasive treatments received within 24 hours of admission (blood transfusion, emergency operation under general anaesthesia, interventional radiology, and tracheal intubation), and 28-day or in-hospital mortality.

Definition

In this study, we defined 'anti-hypertensive medication' as a history of prescribing anti-hypertensive drugs and taking these medications within 28 days before the injury.

Outcomes

The primary outcome was 28-day mortality, which was selected with reference to the results of previous studies [14–17]. The secondary outcomes were in-hospital mortality and the incidence of in-hospital complications (acute kidney injury, acute respiratory distress syndrome, arrhythmia, bleeding, cardiovascular disease, delirium, infections, stroke, and VTE). These variables were selected based on their impact on the prognosis of trauma patients after admission.

Statistical analyses

Patients who had not received anti-hypertensive drugs before hospital admission [AHT(–) group] and those who had received anti-hypertensive drugs before hospital admission [AHT(+) group] were compared using 1:1 propensity score-matched analysis. Logistic regression analysis was used to estimate propensity scores. The variables included in the model were age, sex, type of injury, vital signs on arrival, ISS, ‘do not attempt resuscitation’ orders, treatments received within 24 hours of admission, and comorbidities. We used a calliper width of 0.2 of the standard deviation of the logit of the propensity score. The balance between both groups was evaluated using the standardised mean difference (SMD), with an SMD > 0.1 as a significant imbalance. Data are presented as the median (interquartile range), or as the number (percentage), as appropriate. Thereafter, outcomes were compared in the matched cohort. The relative risk (RR) was calculated, and the difference—along with the 95% confidence interval (CI)—are reported herein.

Missing values were handled using pairwise methods. All statistical analyses were performed using EZR 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) [19]. For sensitivity analysis, matching was also performed on patients with an ISS ≥ 16 , and the same outcomes were evaluated.

All results were considered statistically significant based on a *P*-value < 0.05, or the width of the 95% CI.

Results

Characteristics of the study subjects

A total of 5,641 trauma patients were treated in our emergency room, of whom 1,043 satisfied the inclusion criteria. After excluding 406 patients, 637 patients were analysed in our study. Based on the medication history, we divided this population into two groups: the AHT(–) and AHT(+) groups. Using the propensity score estimated by a multivariable logistic regression analysis of 637 patients, we obtained 223 patients in each group (Fig. 1). The c-statistic for the goodness-of-fit model was 0.70 (95% CI: 0.66–0.74). Table 1 shows the baseline characteristics of the patients before propensity score matching. In the matched population, there were no significant differences in the baseline characteristics of the patients between the two groups (Table 2).

Table 1

Baseline characteristics of older trauma patients who had and had not received anti-hypertensive drugs

Characteristics	AHT(−) group (n = 331)	AHT(+) group (n = 306)	<i>P</i> -value	SMD
Age, years	75 [70, 82]	78 [72, 84]	< 0.001	0.273
Sex, n (%)			0.570	0.050
Male	205 (61.9)	182 (59.5)		
Female	126 (38.1)	124 (41.5)		
Type of injury, n (%)			0.302	0.092
Blunt	321 (97.0)	301 (98.4)		
Penetrative	10 (3.0)	5 (1.6)		
Injury severity score	10 [5, 17]	9 [5, 16]	0.156	0.091
Vital signs upon arrival				
Systolic blood pressure, mmHg	144 [120, 162]	148 [128, 164]	0.143	0.116
Heart rate, bpm	80 [69, 93]	81 [70, 93]	0.633	0.007
Respiratory rate, bpm	20 [17, 23]	20 [16, 21]	0.125	0.160
Glasgow coma scale	15 [14, 15]	15 [14, 15]	0.137	0.039
Body temperature, °C	36.5 [36.2, 36.8]	36.5 [36.1, 36.8]	0.223	0.003
Comorbidities, n (%)				
Autoimmune disease	8 (2.4)	8 (2.6)	1.000	0.013
Chronic heart failure	7 (2.1)	13 (4.2)	0.172	0.122
Chronic kidney disease	10 (3.0)	30 (9.8)	< 0.001	0.280
Chronic liver disease	8 (2.4)	11 (3.6)	0.486	0.069
Chronic lung disease	14 (4.2)	18 (5.9)	0.368	0.075
Dementia	22 (6.6)	22 (7.2)	0.876	0.021
Diabetes mellitus	50 (15.1)	80 (26.1)	0.001	0.275

All categorical variables are presented as numbers and percentages (%), whereas all numerical variables are presented as medians (interquartile range). The balance between the two groups was evaluated using the SMD, with an SMD > 0.1 as a significant imbalance.

Abbreviations: AHT, anti-hypertensive drug; DNAR, do not attempt resuscitation; SMD, standardised mean difference.

Characteristics	AHT(−) group (n = 331)	AHT(+) group (n = 306)	<i>P</i> -value	SMD
Malignancy	17 (5.1)	16 (5.2)	1.000	0.004
Old myocardial infarction	8 (2.4)	28 (9.2)	< 0.001	0.291
Psychiatric disease	10 (3.0)	10 (3.3)	1.000	0.014
Stroke	20 (6.0)	52 (17.0)	< 0.001	0.348
DNAR order, n (%)	2 (0.6)	4 (1.3)	0.435	0.072
Treatment received within 24 hours of admission, n (%)				
Blood transfusion	69 (20.8)	60 (19.6)	0.767	0.031
Emergency operation	49 (14.8)	50 (16.3)	0.662	0.042
Interventional radiology	14 (4.2)	15 (4.9)	0.708	0.032
Tracheal intubation	42 (12.7)	34 (11.1)	0.625	0.049
All categorical variables are presented as numbers and percentages (%), whereas all numerical variables are presented as medians (interquartile range). The balance between the two groups was evaluated using the SMD, with an SMD > 0.1 as a significant imbalance.				
Abbreviations: AHT, anti-hypertensive drug; DNAR, do not attempt resuscitation; SMD, standardised mean difference.				

Table 2
Characteristics of the study population after propensity score matching

Characteristics	AHT(−) group (n = 223)	AHT(+) group (n = 223)	P-value	SMD
Age, years	77 [71, 83]	77 [72, 84]	0.723	0.037
Sex, n (%)			1.000	0.009
Male	130 (58.3)	129 (57.8)		
Female	93 (41.7)	94 (42.2)		
Type of injury, n (%)			1.000	0.036
Blunt	220 (98.7)	219 (98.2)		
Penetrative	3 (1.3)	4 (1.8)		
Injury severity score	9 [5, 17]	9 [4, 14]	0.426	0.057
Vital signs upon arrival				
Systolic blood pressure, mmHg	147 [124, 165]	148 [128, 164]	0.956	0.028
Heart rate, bpm	80 [68, 90]	81 [69, 91]	0.429	0.058
Respiratory rate, bpm	20 [16, 22]	20 [16, 22]	0.785	0.052
Glasgow coma scale	15 [14, 15]	15 [14, 15]	0.109	0.020
Body temperature, °C	36.5 [36.3, 36.8]	36.5 [36.1, 36.8]	0.268	0.090
Comorbidities, n (%)				
Autoimmune disease	5 (2.2)	4 (1.8)	1.000	0.032
Chronic heart failure	6 (2.7)	7 (3.1)	1.000	0.027
Chronic kidney disease	10 (4.5)	13 (5.8)	0.669	0.061
Chronic liver disease	7 (3.1)	7 (3.1)	1.000	< 0.001
Chronic lung disease	11 (4.9)	11 (4.9)	1.000	< 0.001
Dementia	16 (7.2)	18 (8.1)	0.859	0.034
Diabetes mellitus	45 (20.2)	41 (18.4)	0.719	0.045

All categorical variables are presented as numbers and percentages (%), whereas all numerical variables are presented as medians (interquartile range). The balance between the two groups was evaluated using the SMD, with an SMD > 0.1 as a significant imbalance.

Abbreviations: AHT, anti-hypertensive drug; DNAR, do not attempt resuscitation; SMD, standardised mean difference.

Characteristics	AHT(–) group (n = 223)	AHT(+) group (n = 223)	<i>P</i> -value	SMD
Malignancy	13 (5.8)	13 (5.8)	1.000	< 0.001
Old myocardial infarction	8 (3.6)	8 (3.6)	1.000	< 0.001
Psychiatric disease	7 (3.1)	8 (3.6)	1.000	0.025
Stroke	20 (9.0)	21 (9.4)	1.000	0.016
DNAR order, n (%)	2 (0.9)	3 (1.3)	1.000	0.043
Treatment received within 24 hours of admission, n (%)				
Blood transfusion	69 (20.8)	60 (19.6)	0.767	0.031
Emergency operation	49 (14.8)	50 (16.3)	0.662	0.042
Interventional radiology	14 (4.2)	15 (4.9)	0.708	0.032
Tracheal intubation	42 (12.7)	34 (11.1)	0.625	0.049
All categorical variables are presented as numbers and percentages (%), whereas all numerical variables are presented as medians (interquartile range). The balance between the two groups was evaluated using the SMD, with an SMD > 0.1 as a significant imbalance.				
Abbreviations: AHT, anti-hypertensive drug; DNAR, do not attempt resuscitation; SMD, standardised mean difference.				

Main results

Table 3 shows the outcomes of the matched cohort. There was no significant difference in terms of the primary outcome (i.e., 28-day mortality) between the two groups [AHT(–) group vs. AHT(+) group: 3.6% vs. 3.6%, respectively; adjusted RR: 1.00; 95% CI: 0.38–2.62]. Regarding secondary outcomes, only the incidence of in-hospital delirium was significantly different between the two groups, with that in the AHT(+) group being significantly lower than that in the AHT(–) group [13.9% vs. 25.1%, respectively; adjusted RR: 0.55; 95% CI: 0.37–0.82]. Table 4 summarises the total causes of death during hospitalisation in the matched cohort. There was no significant difference in the causes of death between the two groups.

Table 3
Primary and secondary outcomes

Variables	AHT(−) group, (n = 223)	AHT(+) group, (n = 223)	Relative risk [95% CI]
28-day mortality, n (%)	8 (3.6)	8 (3.6)	1.000 [0.382–2.618]
In-hospital mortality, n (%)	11 (4.9)	11 (4.9)	1.000 [0.443–2.259]
Complications, n (%)			
Acute kidney injury	8 (3.6)	7 (3.1)	0.875 [0.323–2.372]
ARDS	8 (3.6)	6 (2.7)	0.750 [0.265–2.126]
Arrhythmia	19 (8.5)	17 (7.6)	0.895 [0.478–1.676]
Bleeding	7 (3.1)	4 (1.8)	0.571 [0.170–1.925]
Cardiovascular disease	6 (2.7)	6 (2.7)	1.000 [0.328–3.053]
Delirium	56 (25.1)	31 (13.9)	0.554 [0.372–0.824]
Infections	48 (21.5)	46 (20.6)	0.958 [0.669–1.373]
Stroke	7 (3.1)	4 (1.8)	0.571 [0.170–1.925]
VTE	11 (4.9)	4 (1.8)	0.364 [0.118–1.125]
All results were considered statistically significant based on the width of the 95% CI.			
Abbreviations: AHT, anti-hypertensive drug; ARDS, acute respiratory distress syndrome; CI, confidence interval; VTE, venous thromboembolism.			

Table 4
Causes of death in the matched cohort

Causes of death	AHT(–) group (n = 11)	AHT(+) group (n = 11)	<i>P</i> -value
Bleeding, n (%)	0 (0.0)	1 (9.1)	1.000
Brain death, n (%)	6 (54.5)	3 (27.3)	0.387
Heart failure, n (%)	1 (9.1)	1 (9.1)	1.000
Infection, n (%)	3 (27.3)	2 (18.2)	1.000
Others ^a , n (%)	1 (9.1)	4 (36.4)	0.311
Data were compared using Fisher's exact test. Results were considered statistically significant based on a <i>P</i> -value < 0.05.			
^a Others include aortic dissection, terminal cancer, multiple organ failure, and natural death. Abbreviation: AHT, anti-hypertensive drug.			

In the sensitivity analysis, 187 patients with an ISS ≥ 16 were extracted from the study population, and 55 patients were matched in both groups (**Table 5**). In the matched cohort, some variables (age, sex, comorbidities [dementia and diabetes mellitus]) were not balanced. In this analysis, the incidence of delirium was also lower in the AHT(+) group than in the AHT(–) group (19.1% vs. 46.9%, respectively; adjusted RR: 0.39; 95% CI: 0.20–0.77) (**Table 6**).

Table 5
Characteristics of patients with an ISS ≥ 16 after propensity score matching

Characteristics	AHT(−) group (n = 55)	AHT (+) group (n = 55)	P-value	SMD
Age, years	76 [70, 84]	75 [71, 81]	0.584	0.144
Sex, n (%)			0.687	0.116
Male	38 (69.1)	35 (63.6)		
Female	17 (21.9)	20 (36.4)		
Type of injury, n (%)			1.000	< 0.001
Blunt	54 (98.2)	54 (98.2)		
Penetrative	1 (1.8)	1 (1.8)		
Injury severity score	22 [17, 26]	18 [17, 27]	0.455	0.033
Vital signs upon arrival				
Systolic blood pressure, mmHg	141 [112, 160]	139 [115, 160]	0.733	0.072
Heart rate, bpm	78 [67, 94]	82 [67, 94]	0.528	0.057
Respiratory rate, bpm	20 [16, 24]	20 [18, 22]	0.866	0.047
Glasgow coma scale	14 [12, 15]	14 [12, 15]	0.269	0.076
Body temperature, °C	36.4 [36.0, 36.7]	36.4 [35.9, 36.6]	0.774	0.067
Comorbidities, n (%)				
Autoimmune disease	3 (5.5)	2 (3.6)	1.000	0.087
Chronic heart failure	2 (3.6)	3 (5.5)	1.000	0.087
Chronic kidney disease	2 (3.6)	2 (3.6)	1.000	< 0.001
Chronic liver disease	4 (7.3)	3 (5.5)	1.000	0.075
Chronic lung disease	3 (5.5)	2 (3.6)	1.000	0.087
Dementia	4 (7.3)	2 (3.6)	0.679	0.161
Diabetes mellitus	10 (18.2)	14 (25.5)	0.489	0.177

All categorical variables are presented as numbers and percentages (%), whereas all numerical variables are presented as medians (interquartile range). The balance between the two groups was evaluated using the SMD, with an SMD > 0.1 as a significant imbalance.

Abbreviations: AHT, anti-hypertensive drug; DNAR, do not attempt resuscitation; SMD, standardised mean difference.

Characteristics	AHT(–) group (n = 55)	AHT (+) group (n = 55)	P-value	SMD
Malignancy	2 (3.6)	3 (5.5)	1.000	0.087
Old myocardial infarction	3 (5.5)	2 (3.6)	1.000	0.087
Psychiatric disease	1 (1.8)	1 (1.8)	1.000	< 0.001
Stroke	5 (9.1)	6 (10.9)	1.000	0.061
DNAR order, n (%)	1 (1.8)	1 (1.8)	1.000	< 0.001
Treatment received within 24 h upon admission, n (%)				
Blood transfusion	25 (45.5)	26 (47.3)	1.000	0.036
Emergency operation	16 (29.1)	16 (29.1)	1.000	< 0.001
Interventional radiology	6 (10.9)	6 (10.9)	1.000	< 0.001
Tracheal intubation	17 (30.9)	19 (34.5)	0.839	0.078
All categorical variables are presented as numbers and percentages (%), whereas all numerical variables are presented as medians (interquartile range). The balance between the two groups was evaluated using the SMD, with an SMD > 0.1 as a significant imbalance.				
Abbreviations: AHT, anti-hypertensive drug; DNAR, do not attempt resuscitation; SMD, standardised mean difference.				

Table 6
Relative risk of outcomes analysed using sensitivity analysis

Variables	AHT(–) group (n = 55)	AHT(+) group (n = 55)	Relative risk [95% CI]
28-day mortality, n (%)	6 (10.9)	6 (10.9)	1.000 [0.344–2.910]
Delirium, n (%)	23 (46.9)	9 (19.1)	0.391 [0.199–0.768]
All the results were considered statistically significant based on the width of the 95% CI.			
Abbreviations: AHT, anti-hypertensive drug; CI, confidence interval.			

Discussion

To our knowledge, the relationship between the use of anti-hypertensive drugs and mortality or morbidity rates after injury has not yet been investigated. Thus, this is the first study to reveal that the use of anti-

hypertensive drugs may not affect mortality in older trauma patients, although it may reduce the risk of delirium during hospitalisation.

Delirium is a clinically influential event that commonly occurs in hospitalised geriatric patients. Patients with hypertension or those receiving anti-hypertensive drugs were previously reported to be at risk of developing delirium [20, 21]. However, our study showed opposite results. Because there has been no previous study on the relationship between the use of anti-hypertensive drugs and delirium, no evidence has been shown to support the direct effect that anti-hypertensive drugs have on reducing the risk of delirium. On the one hand, a systemic inflammatory response is induced after trauma [22]. On the other hand, systemic inflammation and endothelial dysfunction are involved in delirium [23–25]. Thus, it has been hypothesised that the anti-inflammatory effect or protective effect of the endothelial function of anti-hypertensive drugs [13] may have suppressed post-traumatic inflammation and endothelial dysfunction, resulting in a reduced risk of delirium. One basis for this hypothesis is the incidence of VTE, which has also been reported to be at risk due to an acute inflammatory response and endothelial damage after trauma [26]. Although we did not report any statistically significant differences, the risk of VTE tended to be lower in the AHT(+) group.

Previous studies on sepsis showed that the use of anti-hypertensive drugs reduced the risk of in-hospital mortality [14–17]. However, in this study, similar results were not found. One possible reason for this is the small number of outcomes. Our study population had an in-hospital mortality rate of approximately 5%; however, previous studies had 30- to 90-day mortality rates of approximately 20%–40%.

In retrospect, a study of cases involving a cluster of severe traumas may be helpful. The difference in mortality among patients with an ISS ≥ 16 was also examined, although the results appeared to have insufficient detection ability, because of the small study population. Alternatively, the degree of systemic inflammation may be small, and the anti-inflammatory effect of anti-hypertensive drugs may not have affected the mortality of trauma patients.

Consequent complications, such as delirium [27, 28], worsen the prognosis of geriatric patients with trauma [8]. Therefore, the prevention of delirium is important. Although the use of anti-hypertensive drugs before the injury may have a preventive effect on delirium, one of the limitations of this study is whether the re-administration or the induction of anti-hypertensive drugs after hospitalisation has a preventive effect on delirium. In cases of polytrauma, older patients may be likely to experience haemorrhagic shock during the acute phase, or may be suddenly exacerbated due to infection or re-bleeding, even after overcoming the hyperacute phase. Thus, there is no clear recommendation regarding when to resume the oral administration of anti-hypertensive drugs. Further studies should investigate the appropriate time to resume the use of anti-hypertensive drugs and the mechanism underlying their preventive effect on delirium.

This study has some limitations. First, this was a retrospective cohort study conducted in a single centre. Thus, we could not eliminate the bias in the backgrounds of our study population. Second, we used propensity score matching, which could not access the effect of unknown variables that might have led

to biased results. Third, due to the retrospective design, there was no data on patient compliance until the day before the injury. If patients have a history of oral anti-hypertensive drug administration without actually taking oral anti-hypertensive drugs, then the interpretation of the results may be different.

Conclusions

Regular use of anti-hypertensive drugs did not affect the outcome of geriatric trauma patients. In addition, many in-hospital complications were not affected by anti-hypertensive drugs; however, the incidence of delirium was reduced in patients who regularly received anti-hypertensive drugs.

List Of Abbreviations

AHT(+)	Patients who had received anti-hypertensive drugs before admission
AHT(−)	Patients who had not received anti-hypertensive drugs before admission
CI	Confidence interval
ISS	Injury severity score
RR	Relative risk
SMD	Standardised mean difference
VTE	Venous thromboembolism

Declarations

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The protocol for this single-centre, retrospective cohort study was approved by the Medical Ethics Committee of Juntendo University Shizuoka Hospital (approval number: E21-0089). The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [18].

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: HN and YY designed the study. KI and HO supervised the data collection. SO, KIM, YK, and KJ corrected the data. HN conducted the literature search and statistical analysis, interpreted the data, and drafted the manuscript. All authors read and approved the final manuscript. HN takes responsibility for the paper as a whole.

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Figures

Figure 1

Flow chart of participant inclusion.