Are Preinjury Anticoagulant and Antiplatelet Medications a Pitfall in the Bleeding Tendencies of Elderly Trauma Patients in Intensive Care?

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Abstract

Purpose: The elderly are more likely to be on anticoagulant or antiplatelet medications, which increase bleeding. We aimed to determine the effect of preinjury anticoagulant or antiplatelet medications on required blood transfusions and the trauma outcomes of elderly patients.

Methods: We retrospectively reviewed the medical records of all elderly trauma patients admitted to Chungbuk National University Hospital from January 2016 to June 2019. We compared the required number of blood transfusion units, complications, and mortality rate between those on anticoagulant or antiplatelet medications and those that were not, using the chi-squared test, independent t-test, liner regression analysis, and logistic regression analysis.

Results: Out of 466 patients, 142 were on anticoagulant or antiplatelet medications while 324 were not. There was a significant statistical difference in the unit amount of red blood cells transfused within 4 hours of arriving at the hospital between the medicated and non-medicated groups (0.89 vs 1.43 units, respectively, p = 0.02); however, multivariate analysis showed no statistical difference (p = 0.28). The medication group showed a higher rate of complications compared to the non-medicated group (47.9% vs. 29.6%, respectively, p = 0.001), bleeding (17.6% vs 2.8%, respectively, p = 0.001), and pneumonia (24.4% vs 14.2%, respectively, p =0.01). There was no statistical difference in the mortality rate (16.9% vs. 22.2%, respectively, p = 0.21).

Conclusion: Preinjury anticoagulant or antiplatelet medications in elderly trauma patients increased bleeding and complications such as pneumonia but did not affect transfusion requirement, or mortality rate.

Introduction

The proportion of people that are considered elderly (older than 65 years) in the Republic of Korea in 2019 is 14.9%, and according to Statistics Korea, this proportion is expected to reach 28.5% in 2035 [1]. Advancement of medicine and social environments has resulted in more active elderly people, along with increased risk of trauma, such as falls and traffic accidents [2]. The elderly are more susceptible to complications and death following a trauma. One study reported that a large proportion of trauma patients (21.7%) were older than 75 years [3, 4]. The elderly are susceptible to more severe injuries than younger individuals, and may have a compromised physiology [5]. Recently, special trauma teams applying more aggressive initial treatments and intensive care have started to show progression in treating major trauma patients [6].

It was reported in 2004 that brain injuries were the main cause of death in trauma patients, but death due to haemorrhagic shock had decreased [7]. A study in 2010 [8] continued to report that brain injuries were the main cause of death, and haemorrhage as the second. However, another study [4] reported that in 2014, haemorrhage was the main cause of death following trauma, implying that active treatment of haemorrhages is key in trauma patients. The elderly are more likely to be on anticoagulant or antiplatelet

medications than younger individuals, due to underlying disease [9], which increases the risk of bleeding, making initial fluid therapy and intensive monitoring even more important following an accident [10-13]. Several studies have reported that anticoagulant and antiplatelet medications affect mortality and the outcomes in traumatic brain injury patients [14, 15]. However, there are very few studies assessing the effect these medications have on other areas of the body, such as the chest, abdomen, and pelvis of trauma patients [11, 13, 16, 17].

The aim of this study was to determine the effect preinjury anticoagulant and antiplatelet medications have on the requirement for blood transfusions and on the outcomes in elderly trauma patients, regardless of location of injury, who were admitted to the intensive care unit (ICU).

Methods

Study design, population and data collection

This study was approved by the Institutional Review Board of Chungbuk National University Hospital (approval number: 2019-09-009). The inclusion criteria for this study was: admittance to the Chungbuk National Hospital as a trauma patient between January 2016 and June 2019, aged over 65 years, and admitted to the ICU. Patients were excluded if they were under 65 years of age, were not admitted to the ICU, or were transferred to a different hospital. We retrospectively reviewed the eligible patients medical records for blood examinations, imaging studies, blood transfusions, complications following their trauma, and whether they were on anticoagulant or antiplatelet medications. These medications included aspirin, clopidogrel, warfarin, and non-vitamin K antagonist oral anticoagulants (NOAC).

Blood examination and transfusions

Coagulation ability was determined with a prothrombin time (PT) test the results of which were used to generate an international normalized ratio (INR), and activated partial thromboplastin time (aPTT). We checked what the patients haemoglobin levels, INR, and platelet count were at the initial time of hospital arrival, 4 hours after arrival, and 24 hours after arrival. The Patients' transfusion record was reviewed, including individual component transfusions (red blood cell, plasma, and platelets) within 4 hours of hospital arrival and we determined if a patient had received a massive transfusion by counting the total transfusions administered within 24 hours of arrival.

Definitions and complications

The eligible patients were divided into 2 groups, those taking anticoagulant or antiplatelet medications (medicated group) and those that were not (non-medicated group). Injury severity was determined with the Injury Severity Score (ISS), and consciousness level was determined with the Glasgow Coma Scale (GCS). A massive transfusion was defined as the requirement of more than 10 units of red blood cells within 24 hours of hospital arrival [18]. Regarding complications, pneumonia was defined as clinical symptoms including cough and sputum, positive imaging studies on a plain x-ray or computed

tomography (CT) scan, and growth of pathogens following a microbiological culture, that required antibiotic treatment. Increased bleeding was defined as prolonged haemorrhaging detected clinically or by radiologic evaluation, or when continued postoperative bleeding was identified. Infection was defined as redness and/or a feeling of heat at the injury site or surgical site, or growth of pathogens following a wound swab.

Statistical analysis

Mortality, embolisations, operations, massive transfusions, and complications were compared between the two groups with the chi-squared test. Comparisons between age, ISS, laboratory data, length of ICU stay and amount of transfusions required were analysed with the independent t-test. A multivariable liner regression analysis was used to determine if preinjury anticoagulant or antiplatelet medications affected the need for blood transfusions. A multivariable logistic regression analysis was used to determine if there was a difference in the trauma outcomes between the two groups. All statistical analyses were calculated using SPSS software ver. 23.0(IBM Co., Armonk, NY, USA). A value of $p < 0.05$ was considered statistically significant.

Results

Participant selection

A total of 5,736 trauma patients were admitted to the Chungbuk National University Hospital between January 2016 and June 2019. Out of these patients 1,388 were admitted to the ICU and 478 were older than 65 years (35.7%). Twelve patients were excluded because they were transferred to other facilities. Therefore, the total number of patients enrolled in this study was 466. The medicated group consisted of 142 (30%) patients that were taking preinjury anticoagulant or antiplatelet agents including aspirin (72 patients), clopidogrel (25 patients), warfarin (9 patients), NOAC (12 patients), or a combination of these medications (24 patients). Therefore, the non-medicated group was made up of 324 (70%) patients (Fig, 1). The proportion of patients older than 65 years among all the trauma patients admitted to hospital from January 2016 to June 2019 increased gradually from 34% to 38% (Fig. 2).

Participant characteristics

The average age of the participants was 75.7 years (standard deviation [SD], 6.88 years), 311 were male and 155 were female. The past medical history of the patients were as follows: 71 had cardiovascular disease, 27 had cerebrovascular disease, 223 had hypertension, and 114 had diabetes. The most common mechanism of injury, making up 23% of all cases, was pedestrian traffic accidents, followed by motorcycle accidents (18.2%), falls (16.3%), motor vehicle accidents (13.7%), slipping down (13.1%), other (10.3%), and bicycle accidents (5.4%). The ISSs ranged between 4 and 75 (average 19.58) (Table 1).

Comparison of participant groups

The average age of the patients in the medicated group was 76.6 years (SD, 6.87 years), older than the average age of the patients in the non-medicated group, which was 75.3 years (SD, 6.85 years), but without statistical significance (p = 0.06). The medicated group were more likely to have cardiovascular disease than the non-medicated group (21.8% vs. 12.3%, respectively, p = 0.01), and cerebrovascular disease (11.3% vs 3.4%, respectively, p = 0.02). The medicated group's average ISS was 18.19, lower than the 20.19 of the non-medicated group (p = 0.03). The average Glasgow coma score (GCS) of the medicated group was 12.19, while that of the non-medicated group was 11.46 (p = 0.09) (Table 1). In total 96 patients died during treatment (20.6%), while 239 (51.3%) underwent operations, and 101 (21.7%) received angioembolisation. Red blood cell transfusions were received by 197 patients, plasma by 137, and platelets by 89. Of the 225 patients (48.3%) who required mechanical ventilation, 53 needed long-term ventilation and received a tracheostomy. Complications occurred in 164 patients, with pneumonia being the most common developing in 17.2% (Table 2).

Requirements for transfusion

We compared the required amount of blood transfusions within 4 hours of hospital arrival, and within the next 20 hours between the two groups. There was a statistically significant difference in the amount of blood transfused within 4 hours between the medicated and non-medicated groups, 0.89 units and 1.43 units, respectively (p = 0.03), while no differences were demonstrated for any other types of transfusion (Table 3). A multiple linear regression analysis of ISS and preinjury antiplatelet or anticoagulant medications showed no relationship with the transfusion amount of red blood cells, p = 0.48; plasma, p = 0.35; or platelets, p = 0.59. However, a positive relationship was observed between the higher ISSs and the need for more transfusions (p=0.00) (Table 4). Massive transfusions were given to 30 patients, but no relationship with preinjury anticoagulant or antiplatelet medications was detected (Table 5). The average ISS was higher (33.43) in the massive transfusion group (p=0.00). There was also a statistically significant difference in the GCS and initial blood examinations. The multivariate analysis demonstrated that patients had an increased risk of needing a massive transfusion if they had a higher ISS and a high initial INR and aPTT. Within the massive transfusion group, there was no significant statistical difference in the amount of red blood cells (p = 0.61), plasma (p = 0.23), or platelets (p = 0.55) transfused between the medicated group and the non-medicated group (Table 6).

Patient Outcomes

The patients in the medicated group underwent more operations than those in the non-medicated group (51.9% vs. 50.0%, respectively, p = 0.76), and more angioembolisations (24.1% vs. 16.2%, respectively, p = 0.67), but without statistical significance. There were no significant statistical differences in the number of days spent in ICU (9.50 vs. 7.98, respectively, p = 0.24), or days on mechanical ventilation (6.08 vs. 6.34, respectively, p = 0.85) (Table 7). The complication rate was higher in the medicated group than the non-medicated group (47.9% vs. 29.6%, respectively, p = 0.001) with an odds ratio of 2.18 (95% confidence interval [CI]: 1.453 -3.277). Bleeding was more frequent in the medicated group (17.6% vs. 2.8%, respectively, p = 0.001), odds ratio of 7.48 (95% CI: 3.391-16.493), as was pneumonia (24.4% vs.

14.2%, respectively, p = 0.01), odds ratio of 1.90 (95% CI: 1.159-3.124). A multivariate analysis showed that patients taking preinjury medications were at a 1.79-fold risk of suffering 2 or more complications.(p = 0.04) (Table 8). The mortality rate was higher in the medicated group than the non-medicated group (22.2% vs. 16.9%, respectively, p = 0.21) but without statistical significance.

Discussion

The severity of injury has a strong relationship with the course of treatment and mortality. It also affects transfusion requirement during initial treatment [5]. In the present study there was no statistical difference in the amount of massive transfusions administered to the elderly that took preinjury anticoagulants or antiplatelets, and those that did not. The medicated group received less red blood cells within 4 hours of hospital arrival. However, a multivariate analysis that included ISS showed that blood, plasma, and platelet transfusions were impacted on by injury severity. Ferraris et al. also reported that preinjury antiplatelet medication does not affect bleeding following an injury [13]. However, other studies have reported that elderly trauma patients on warfarin are at an increased risk of needing a massive transfusion [19, 20]. Ohmori et al. reported that patients taking anticoagulants had a 4.91-fold or antiplatelets 3.67-fold increased risk of needing a massive transfusion following a trauma, however, this study was conducted with a small sample [20]. These conflicting results regarding the effect anticoagulant and antiplatelet medications have on bleeding and transfusions warrant further discussions and studies with greater sample sizes.

Complication rates increase as patients became older and vary depending on the past medical history, according to one study [21]. In contrast, a different study reported that past medical history had no effect on the course of trauma treatment [22]. In the present study, the majority of the elderly patients had chronic diseases, and many were taking anticoagulant or antiplatelet medications, thus the discrepancy in the complication rate, with some previous studies, may be due to past medical histories, rather than blood thinning medications. Nevertheless, it has been reported that elderly patients taking anticoagulants are at a higher risk of complications following a trauma, particularly acute respiratory failure, acute renal failure, and pneumonia [17]. The patients taking preinjury anticoagulant or antiplatelet medications in the present study had a higher rate of bleeding and pneumonia, along with a higher risk of suffering from more than two complications.

The results of the present study did not reveal any significant statistical differences in the length of ICU stay or mechanical ventilation between the medicated and non-medicated groups. However, the ICU stay was significantly longer for patients that had a higher ISS or received a massive transfusion. Similarly, the studies by Boltz et al. and Julien et al. reported no effect of preinjury anticoagulant or antiplatelet medications on the length of ICU stay or mechanical ventilation [23, 24]. Coleman et al. reported that taking preinjury clopidogrel did not affect the length of ICU stay, but did affect the total time spent in hospital [25], and Bonville et al. also reported that preinjury antiplatelet medication affected the total hospital stay, but not the length of time spent in ICU [17]. Although more studies are needed for

confirmation, the evidence suggests that the length of time spent in ICU following a trauma is affected by the ISS and not the taking of preinjury anticoagulant or antiplatelet medications.

Several studies have reported that preinjury anticoagulant or antiplatelet medications affect the mortality of traumatic brain injury (TBI) patients [15, 26-28], however there are also some reports with contradicting results. Dosset et al. reported that warfarin is a significant risk factor of mortality in all trauma patients [11], and Bonville et al. also reported high mortality in TBI patients on warfarin [17]. However, Wojcik et al. reported that warfarin did not affect mortality [16]. Coleman et al. reported a higher mortality rate in elderly patients on clopidogrel [25]. Boltz et al. reported a higher mortality rate in geriatric fall patients on anticoagulants, and a higher proportion of deaths in patients with skull fractures and cerebral haemorrhages [23]. In the present study, the medicated group had a lower ISS and mortality rate, but without statistical significance. Rather, the mortality rate was affected by ISS. Unlike previous studies that assessed the effect each anticoagulant and antiplatelet medication had on mortality, the present study did not have a large enough sample size to perform individual analyses on each medication and its effect on mortality. Further studies to analyse the individual anticoagulants and antiplatelets have an effect on the mortality of trauma patients are required.

This study had several limitations. First, this was carried out at a single institute with only 466 patients. To increase the sample size and to confirm our results, a study will need to be conducted in conjunction with other hospitals. A larger sample size will allow individual anticoagulant and antiplatelet medications to be investigated and the effect they each have on trauma patients. Second, there were variations in the initial treatment responses, dependent upon the medical staff attending the patient. The initial amount of fluid and blood administered is decided by the first attending medical staff, thus some patients may have received more transfusions while others less. Further studies with fixed initial treatment protocols will assure standardised treatment and more reliable results. Third, this study was carried out retrospectively, reviewing patients' records for medication history. The patients or guardians' comments may not have been accurate, and the medical histories of patients who died prematurely could not be acquired. Lastly, since this study only included patients who were admitted to the ICU, those that died in the emergency department were excluded, therefore not all major trauma patients have been represented.

Conclusion

This study revealed that preinjury anticoagulant and antiplatelet medications increased the risk of complications including bleeding and infections, such as pneumonia, but showed no statistical difference in transfusion requirement, length of ICU stay, or mortality rate. Careful consideration of pneumonia and bleeding is warranted when treating trauma patients on anticoagulant or antiplatelet medications.

Declarations

Author contributions

SH Kim: Acquisition of data, analysis and interpretation of the data, and drafting of the manuscript; YH Sul: Study conception and design, acquisition of data, and critical revision of the manuscript; JY Lee: Acquisition of data; JB Ye: Acquisition of data; JS Lee: Acquisition of data; HR Kim: Acquisition of data, SY Yoon: Acquisition of data; JS Kim: critical revision of the manuscript. All authors reviewed and approved the final submitted manuscript.

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Conflicts of interest:

All authors have no conflict of interest to declare

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Tables

Table 1. Demographics and clinical data for the 466 elderly patients

	Total patients	Non-medicated group	Medicated group	p value
Age*	75.7 (6.88)	75.3 (6.85)	76.6 (6.87)	0.06
Sex, n (%)				0.74
Male	311 (66.7%)	218 (67.3%)	93 (65.5%)	
Female	155 (33.3%)	106 (32.7%)	49 (34.5%)	
Past medical history, n (%)				
HTN	223 (47.9%)	153 (47.2%)	70 (49.3%)	0.68
DM	114 (24.5%)	72 (22.2%)	42 (29.6%)	0.10
Cardiovascular disease	71 (15.2%)	40 (12.3%)	31 (21.8%)	0.01
Cerebrovascular disease	27 (5.8%)	11 (3.4%)	16 (11.3%)	0.00
Other	161 (34.5%)	109 (33.6%)	52 (36.6%)	0.59
Mechanism of injury, n (%)				0.01
Fall	76 (16.3%)	53 (16.4%)	23 (16.2%)	
Slip down	61 (13.1%)	25 (7.7%)	36 (25.4%)	
Motorcycle	85 (18.2%)	66 (20.4%)	19 (13.4%)	
Motor vehicle	64 (13.7%)	48 (14.8%)	16 (11.3%)	
Bicycle	25 (5.4%)	20 (6.2%)	5 (3.5%)	
Pedestrian traffic accident	107 (23.0%)	80 (24.7%)	27 (19.0%)	
Other	48 (10.3%)	32 (9.9%)	16 (11.3%)	
GCS score*	11.68 (4.45)	11.46 (4.57)	12.19 (4.14)	0.09
ISS*	19.58 (10.06)	20.19 (10.59)	18.19 (8.59)	0.03

HTN: hypertension, DM: diabetes mellitus, GCS: Glasgow coma scale, ISS: injury severity score

* Average (Standard deviation)

Table 2. Clinical outcomes of the 466 elderly trauma patients

	No. patients (%)
Mortality	96 (20.6%)
Operation	239 (51.3%)
NS	96 (20.6%)
OS	100 (21.5%)
TS	49 (10.5%)
CS	8 (1.7%)
Other	13 (2.8%)
Embolisation	101 (21.7%)
Transfusion	
RCC	197 (42.3%)
FFP	137 (29.4%)
PC	89 (19.1%)
Massive Transfusion	30 (6.4%)
Ventilator care	225 (48.3%)
Tracheostomy	53 (11.4%)
Complications	164 (35.2%)
Pneumonia	80 (17.2%)
Bleeding	34 (7.3%)
Infection	32 (6.9%)
Pleural effusion	31 (6.7%)
Other	72 (15.5%)
Suffered 2 or more complications	63 (13.5%)

NS: neurosurgery, OS: orthopaedics surgery, TS: trauma surgery, CS: cardiovascular surgery, RCC: red cell concentration, PC: platelet concentration, FFP: fresh frozen plasma

Table 3. Transfusion and laboratory data for the non-medicated and medicated groups

Transfusion type (time)	No anticoagulation or antiplatelets (units)	Anticoagulation or antiplatelets (units)	p value
RCC (≤4 hr)*	1.43	0.89	0.02
FFP (≤4 hr)*	0.55	0.67	0.58
PC (≤4 hr)*	0.28	0.33	0.79
RCC (≤24 hr)**	1.13	0.96	0.51
FFP (≤24 hr)**	1.15	1.01	0.60
PC (≤24 hr)**	1.98	1.33	0.12
Total RCC†	2.56	1.85	0.12
Total FFP†	1.70	1.68	0.95
Total PC†	2.26	1.66	0.22
Massive Transfusion, n (%)	22 (6.8%)	8 (5.6%)	0.69
Lab data††			
Initial INR	1.16 (0.31)	1.23 (0.52)	0.12
Initial aPTT	33.44 (20.67)	32.89 (18.22)	0.78
Initial Hb	11.87 (2.32)	12.04 (2.22)	0.49
INR after 24 hr	1.32 (0.34)	1.30 (0.30)	0.58
aPTT after 24 hr	40.39 (23.29)	38.95 (16.03)	0.09
Hb after 24 hr	10.91 (2.00)	11.09 (1.84)	0.36

RCC: red cell concentration, FFP: fresh frozen plasma, PC: platelet concentration, INR: international normalized ratio, aPTT: activated partial thromboplastin time, Hb: haemoglobin

* Transfusion within 4 hours of hospital arrival, ** Transfusion within 24 hours of hospital arrival, † Total transfusion units administered within 24 hours of hospital arrival, †† Average (Standard deviation)

Table 4. Multivariable multiple linear regression analysis of transfusions administered to patients taking anticoagulant or antiplatelet medications

Transfusion	Regression coefficient (95% CI)			
	Anticoagulant or antiplatelet medications		Injury severity score (ISS)	
RRC (≤4 hr)*	-0.29 (-.0.79~0.19)	p = 0.28	0.11 (0.09~0.14)	p = 0.00
FFP (≤4 hr)*	0.26 (-0.08~0.61)	p = 0.14	0.07 (0.05~0.08)	p = 0.00
PC (≤4 hr)*	0.09 (-0.24~0.42)	p = 0.59	0.02 (0.01~0.03)	p = 0.00
RRC (≤24 hr)**	0.01 (-0.46~0.49)	p = 0.94	0.09 (0.07~0.11)	p = 0.00
FFP (≤24 hr)**	0.07 (-0.42~0.57)	p = 0.76	0.11 (0.08~0.13)	p = 0.00
PC (≤24 hr) **	-0.33 (-1.13~0.46)	p = 0.41	0.15 (0.11~0.19)	p = 0.00
Total RRC†	-0.28 (-1.07~0.51)	p = 0.48	0.21 (0.17~0.24)	p = 0.00
Total FFP†	0.33 (-0.37~1.05)	p = 0.35	0.18 (0.14~0.21)	p = 0.00
Total PC†	-0.24 (-1.15~0.66)	p = 0.59	0.17 (0.13~0.21)	p = 0.00

CI: confidence interval, RRC: red cell concentration, FFP: fresh frozen plasma, PC: platelet concentration

* Transfusion within 4 hours of hospital arrival, ** Transfusion within 24 hours of hospital arrival, † Total transfusion units administered within 24 hours of hospital arrival

Table 5. Comparison of the clinical data between massive transfusion and non-massive transfusion elderly trauma patients

Clinical data	MT (n = 30)	Non-MT (n = 436)	p value	Adjusted p value†
Age*	75.65 (6.88)	76.37 (6.89)	0.58	0.67
ISS*	18.62 (9.01)	33.43 (13.85)	0.00	0.00
GCS*	11.92 (4.30)	8.30 (5.24)	0.00	0.30
Initial Hb*	12.02 (2.23)	10.62 (2.63)	0.00	0.16
Initial aPTT*	31.63 (16.78)	57.00 (39.11)	0.00	0.00
Initial INR*	1.15 (0.37)	1.47 (0.47)	0.00	0.01
Total ICU days*	7.68 (10.68)	19.53 (27.65)	0.02	0.00
Preinjury anticoagulant or antiplatelet agent use, n (%)	8 (26.7%)	134 (30.7%)	0.83	0.59

MT: massive transfusion, ISS: injury severity score, GCS: Glasgow coma scale, Hb: haemoglobin, aPTT: activated partial thromboplastin time, INR: international normalized

ratio, ICU = intensive care unit

* Average (Standard deviation)

† Multivariable logistic regression analysis including ISS and GCS score

Table 6. A comparison of the massive transfusions administered to the non-medicated and medicated groups

	N=30	No anticoagulation or antiplatelets group (n=22)	Anticoagulation or antiplatelets group (n=8)
Total RRC†	16.47 (6.21)	16.82 (6.64)	15.50 (5.16)
Total FFP†	12.87 (7.91)	11.50 (6.38)	16.63 (10.72)
Total PC†	11.37 (8.17)	10.82 (6.61)	11.37 (8.17)

RRC: red cell concentration, FFP: fresh frozen plasma, PC: platelet concentration

†Average (Standard deviation)

Figures

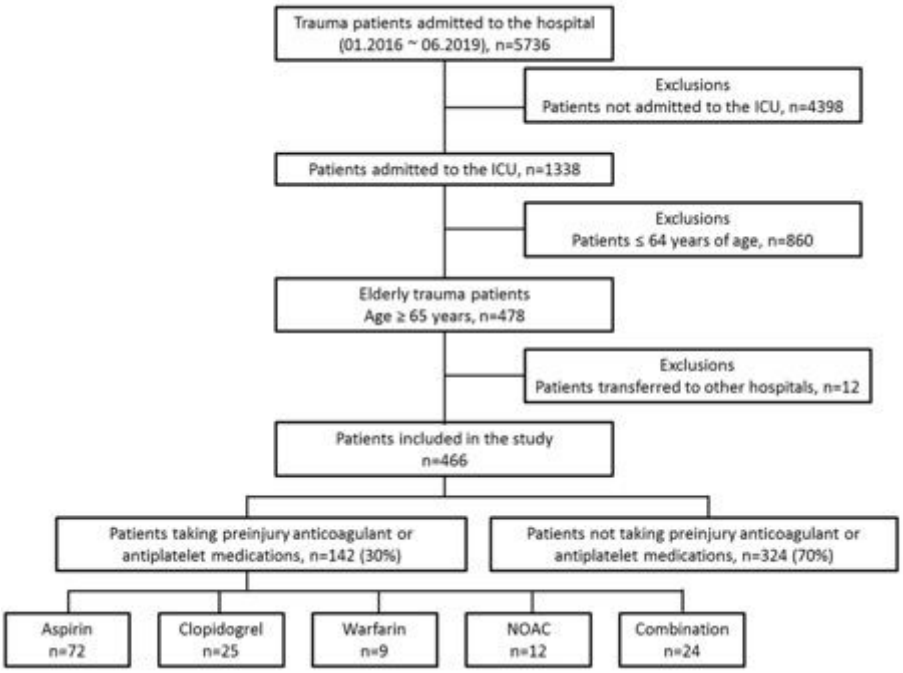

Figure 1

Flowchart of the study population and patient selection. Abbreviations: ICU, intensive care unit, NOAC, non-vitamin K antagonist oral anticoagulant

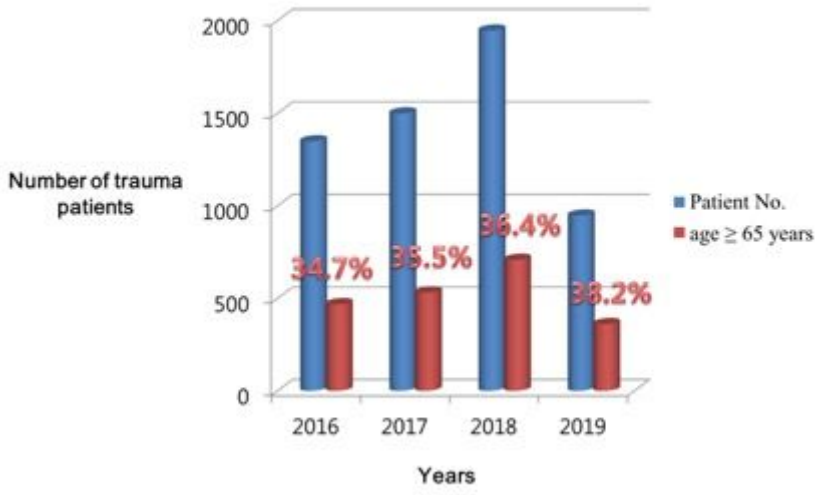

Figure 2

The total number of patients and the percentage of whom were elderly, who visited the trauma centre of Chungbuk National University Hospital from 2016 to 2019