Int J Burn Trauma 2023;13(2):65-77
www.IJBT.org /ISSN:2160-2026/IJBT0148722

Original Article

Use of preinjury antiplatelet and oral anticoagulant agents on outcomes following blunt trauma in an Asian population: a 1:2 propensity score matched study

Kai Siang Chan[1,2], Karen Tsung Shyen Go[1], Li Tserng Teo[1], Serene Si Ning Goh[1,2]

[1]MOH Holdings Pte Ltd, Singapore 099253, Singapore; [2]Department of General Surgery, Tan Tock Seng Hospital, Singapore 308433, Singapore

Received December 23, 2022; Accepted March 28, 2023; Epub April 15, 2023; Published April 30, 2023

Abstract: Background: Bleeding is a feared complication of antiplatelets (APTs) and oral anti-coagulants (OACs) use. Asians are at higher risk of bleeding from APT/OAC compared to Western population. Our study aims to investigate the impact of preinjury APT/OAC use on outcomes of moderate to severe blunt trauma. Methods: This is a retrospective cohort study from Jan 2017 - Dec 2019 of all patients with moderate to severe blunt trauma. A 1:2 propensity score matching (PSM) analysis was performed to address for confounding factors. Our primary outcome was in-hospital mortality. Our secondary outcomes were severity of head injury and need for emergency surgery within the first 24 hours. Results: There were 592 patients (APT/OAC n=72, no APT/OAC n=520) included in our study. The median age was 74 years in APT/OAC and 58 years in no APT/OAC. PSM resulted in 150 patients (APT/OAC n=50, no APT/OAC n=100). In the PSM cohort, more patients with APT/OAC use had ischemic heart disease (76% vs 0%, P<0.001). APT/OAC use was independently associated with higher in-hospital mortality (22.0% vs 9.0%, Odds ratio (OR) 3.00, 95% Confidence interval (CI): 1.05, 8.56, P=0.040) Severity of head injury (abbreviated injury scale in APT/OAC: 3.33 ± 1.53, vs 2.97 ± 1.43, P=0.380) and need for emergency surgery (APT/OAC 16.2% vs 11.0%, P=0.434) was comparable between APT/OAC and no APT/OAC. Conclusions: Preinjury APT/OAC use was associated with higher in-hospital mortality. Severity of head injury and need for emergency surgery within 24 hours from admission were comparable between APT/OAC use and no APT/OAC use.

Keywords: Anti-coagulants, anti-platelets, anti-thrombotic agents, emergency surgery, trauma

Introduction

Bleeding is the most feared complication of antiplatelets (APTs) and oral anti-coagulants (OACs) use. There has been a concerning increase in prevalence of metabolic syndrome across all ages in the recent decade [1], with consequent increase in atherosclerotic cardiovascular disease (ASCVD). Of 964 patients surveyed in the National Health and Nutrition Examination Survey, the percentage of aspirin use was 73.8% in diabetic patients with ASCVD in the United States [2]. There has also been an increasing use of oral anticoagulant (OAC) in recent years, especially with establishment of safety of direct OACs (DOACs) in elderly populations [3]. The landmark Perioperative Ischemic Evaluation 2 (POISE-2) trial in 2014 on 10,010 patients showed that aspirin was associated with 23 percent higher risk of major bleeding in patients undergoing non-cardiac surgery [4]. Use of warfarin and rivaroxaban was also associated with increased risk of intra-cranial haemorrhage (ICH) [5].

Bleeding is a significant concern following traumatic injuries. About 4% of trauma patients are on OACs due to underlying atrial fibrillation, thromboembolic events or other cardiovascular diseases [6, 7]. Existing literature demonstrated that preinjury APT/OAC may be associated with increased risk of mortality [8-12], but results have been conflicting [13-16]; Spektor et al. showed that preinjury aspirin did not increase the risk of intracranial haemorrhage (ICH) [13], and Wojcik et al. showed that preinjury warfarin did not increase mortality or length of stay in both patients with head injury and no

head injury [14]. However, Inamasu et al. showed that use of warfarin was associated with worse outcomes in patients with ICH [16].

To add on, majority of these studies were conducted in the Western populations. Bleeding risk may be higher in the East Asian population compared to Western population with APT or OAC use [17-19]. To our knowledge, there has been no study conducted in the local Singaporean population to report on the outcomes of preinjury APT/OAC following trauma. The aim of this study is to investigate the impact of preinjury APT/OAC use on outcomes following moderate to severe blunt trauma in the local population. We hypothesize that preinjury APT/OAC use results in higher in-hospital mortality compared to no APT/OAC use.

Materials and methods

This is a retrospective cohort study of sequential patients from Jan 2017 to Dec 2019 who were admitted to our tertiary institution (Tan Tock Seng Hospital (TTSH)) for blunt traumatic injuries comparing the outcomes of patients with preinjury APT and/or OAC use compared to no APT and/or OAC use. Our institution is the designated anchor regional trauma centre for the central region of Singapore. We included patients who were aged ≥16 years old and had Injury Severity Score (ISS) ≥9. Patients with penetrating trauma or demised on arrival to the emergency department were excluded from this study. All patients were identified electronically using our institution's electronic health record system (Computerised Patient Support System (CPSS) 2.0, Integrated Health Information Systems, Singapore) through our locally approved prospective trauma registry. This study was approved by our local institutional review board (National Healthcare Group Domain Specific Review Board Ref: 2022/00438). This study's conduct was in concordance with the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) statement for retrospective cohort studies [20].

Study variables and outcomes

Patient demographics and clinical outcomes were studied. Patient demographics included age, gender, race, body mass index (BMI), comorbidities, systolic blood pressure on triage, injury characteristics (location of injury with respective Abbreviated Injury Scale (AIS) and ISS) and use of APT and/or OAC. The AIS is a 6-point ordinal scoring system (1: minor, 6: maximal i.e. untreatable) which classifies the extent of injury in each body region. ISS is a composite score (ranging 3-75) used to assess trauma severity and is calculated by the sum of the squares of the three highest AIS severity across nine body regions [21]; ISS of <9, 9-15, 16-24 and ≥25 are defined as mild, moderate, severe and profound respectively. For the purpose of this study, APT/OAC was defined as the use of APT and/or OAC. No APT/OAC was defined as no use of both APT and OAC. Our study outcomes included need for platelet, fresh frozen plasma (FFP) and packed cells transfusion within the first 24 hours, need for angioembolization and surgery within the first 24 hours, need for intensive care unit (ICU) admission, high dependency unit (HDU) admission, length of stay (LOS), any morbidity and in-hospital mortality. Any morbidity was defined as presence of any complications, acute urinary retention, urinary tract infection (UTI), acute kidney injury, sepsis, pneumonia and venous thromboembolism. However, only data on UTI and pneumonia were collected for the specific type of morbidity. In-hospital mortality was defined as death within the same admission. Our primary outcome was in-hospital mortality. Our secondary outcomes were severity of head injury, need for emergency surgery within 24 hours of presentation and LOS. Severity of injuries were measured using the AIS during the initial presentation to the emergency department after radiological imaging (if performed) [21]. While data on the need for emergency transfusions (packed cells, platelets and/or FFP) was collected, this was not one of our main outcomes in view of the retrospective nature of this study and lack of definitive criteria for emergency transfusion (described in our treatment protocol).

Treatment protocol

All patients admitted to the emergency department for trauma were seen by a dedicated trauma team in our institution. Subspecialties (e.g. orthopedic surgery, plastics and reconstructive surgery, neurosurgery) were consulted if clinically indicated. Management of trauma patients was guided by the principles of Advanced

Trauma and Life Support (ATLS) [22]. All patients who were on APT and/or OAC based on their clinical records were withheld the medications on admission. Indications for platelet transfusion were presence of head injury with absolute platelet count of less than 100 × 10^9/L, presence of coagulopathy with platelet count of less than 20 × 10^9/L, or based on surgeon's preference. All patients who were on warfarin and were hemodynamically unstable were administered 4-factor prothrombin complex concentrate (PCC) or FFP. Intravenous vitamin K was given for patients who were on warfarin and sustained head injury or had significant bleeding (e.g. intra-abdominal bleeding). With regards to the reversal agents for DOACs, this was only available for dabigatran i.e. idarucizumab. Decision to start 4-factor PCC and idarucizumab for warfarin and dabigatran respectively was made after hematology consult. Indications for massive transfusion protocol were presence of multiple fractures with major bleeding and/or the lack of adequate response to intravenous fluid resuscitation. Intravenous tranexamic acid (TXA) was given 1 g over 10 minutes within 3 hours, followed by 1 g over 8 hours in the presence of non-compressible haemorrhage or haemodynamic instability [23]. All patients were provided deep vein thrombosis prophylaxis with TED (Thrombo-Embolus Deterrent) stockings and/or pneumatic calf compressors unless contraindicated. Decision for pharmacological DVT prophylaxis was based on surgeon's preference; while there is evidence for early pharmacological DVT prophylaxis in moderate to severe trauma, the timing of initiation of pharmacological DVT prophylaxis in patients with active bleeding or coagulopathy is not well-defined in current literature [24].

Statistical analysis

Categorical values were described as n (%) and were analysed by chi-square test. Continuous variables were expressed as median (interquartile range (IQR)) and were analyzed by Mann-Whitney U test as the data did not follow a normal distribution. A 1:2 propensity score matching (PSM) was performed to reduce selection bias. Patients were adjusted for a total of eleven factors: six factors (age ≥65, gender, race, hypotension, ISS >15 and diabetes mellitus) were reported to impact morbidity and mortality of patients in trauma [25], and five factors (presence of hypertension, hyperlipidemia, chronic kidney disease, cirrhosis and history of cancer) had statistically significant intergroup differences (defined as P< 0.10). Hypotension was defined as systolic blood pressure of <90 mmHg on presentation to the emergency department. Patients were not matched based on incidence of ischemic heart disease (IHD), peripheral vascular disease (PVD) and transient ischemic attack or cerebrovascular accident as majority of patients who were on APT/OAC had these co-morbidities (**Table 1**); matching for these variables would result in very low sample size in the APT/OAC group. PSM was performed with a ratio of 1:2 using a caliper width of 0.2 of the standard deviation (SD) of the logit of the propensity score [26, 27]. Standardized mean difference (SMD), Hansen and Bowers test and Iacus, King and Porro test were used to assess for covariate and global imbalance respectively [28]. Adequate covariate balance was defined as SMD <0.250. PSM was performed using R software (R-3.3.3) and subsequent statistical analysis was performed using SPSS version 25 (SPSS, SPSS Inc., Chicago, IL, USA). Multivariate logistic regression was performed to assess the impact of the use of APT/OAC on clinical outcomes; the variables used in the multivariate logistic regression model were the same as the variables included in the PSM model. Both PSM and multivariate logistic regression was performed using the same variables as double adjustment has been shown to reduce imbalance [29]. Subgroup analysis was also performed for elderly patients (defined as age ≥65 years). A value of P<0.05 was used to define statistical significance.

Results

Baseline demographics and injury severity

There were 592 patients included in this study, of which 72 (12.2%) had APT/OAC use. Of those with APT/OAC, there were 8 patients (11.1%) who used both APT and OAC, 59 patients (81.9%) who used only APT, and 5 patients (6.9%) who only used OAC. Patients in the APT/OAC group were older, with a median age of 74 (IQR 64.3-84) years as compared to 58 (IQR 33-75) years in the no APT/OAC group. The APT/OAC group had significantly more co-

Table 1. Patient demographics and injury severity after blunt trauma in patients who received antiplatelets and/or anticoagulants versus those without in both the unmatched and matched cohort

	Overall cohort, n=592				PSM cohort, n=150			
	Anticoagulants/ antiplatelets (n=72)	No anticoagulants/ antiplatelets (n=520)	*P* value	SMD	Anticoagulants/ antiplatelets (n=50)	No anticoagulants/ antiplatelets (n=100)	*P* value	SMD
Age, years, median (IQR)	74 (64.3-84)	58 (33-75)	<0.001		73.5 (64-84)	74 (63-84)	0.902	
Age ≥65 years^	54 (75.0)	220 (42.3)	<0.001	0.701	37 (74.0)	73 (73.0)	0.896	0.022
Gender, male (%)^	40 (68.1)	349 (67.1)	0.873	0.020	34 (68.0)	62 (62.0)	0.470	0.125
Race, n (%)^			0.035	0.314			0.331	0.133
Chinese	55 (76.4)	330 (63.5)			38 (76.0)	79 (79.0)		
Malay	7 (9.7)	84 (16.2)			5 (10.0)	14 (14.0)		
Indian	10 (13.9)	68 (13.1)			7 (14.0)	6 (6.0)		
Others	0 (0)	38 (7.3)			0 (0)	1 (1.0)		
BMI, median (IQR)	23.1 (19.7-26.0)	23.0 (20.8-25.1)	0.867		23.4 (19.7-25.8)	23.9 (21.1-26.9)	0.250	
BMI >27.5	10/68 (14.7)	60/409 (14.7)	0.994		7/47 (14.9)	15/78 (19.2)	0.537	
Co-morbidities, n (%)								
Diabetes mellitus^	31 (43.1)	50 (9.6)	<0.001	0.816	19 (38.0)	42 (42.0)	0.638	0.081
Hypertension^	59 (81.9)	93 (17.9)	<0.001	1.662	37 (74.0)	79 (79.0)	0.491	0.117
Hyperlipidemia^	51 (70.8)	78 (15.0)	<0.001	1.360	31 (62.0)	64 (64.0)	0.811	0.041
Ischemic heart disease	54 (75.0)	0 (0)	<0.001		38 (76.0)	0 (0)	<0.001	
Chronic kidney disease/end-stage renal failure^	17 (23.6)	12 (2.3)	<0.001	0.665	8 (16.0)	12 (12.0)	0.497	0.115
Peripheral vascular disease	6 (8.3)	2 (0.4)	<0.001		3 (6.0)	0 (0)	0.013	
Transient ischemic attack/cerebrovascular accident	18 (25.0)	11 (2.1)	<0.001		8 (16.0)	10 (10.0)	0.286	
COPD	1 (1.4)	3 (0.6)	0.431		0 (0)	0 (0)	N/A	
Liver cirrhosis	4 (5.6)	6 (1.2)	0.007	0.245	2 (4.0)	4 (4.0)	1.000	<0.001
History of malignancy^	11 (15.3)	16 (3.1)	<0.001	0.430	4 (8.0)	12 (12.0)	0.454	0.133
Systolic blood pressure, mmHg, median (IQR)	134 (118-156)	132 (114-151)	0.335		132 (114-153)	146 (125-160)	0.021	
Hypotension#,^	1 (1.4)	25 (4.8)	0.185	0.198	1 (2.0)	4 (4.0)	0.520	0.117
Lactate, median (IQR)	2.09 (1.45-3.20)	2.26 (1.60-3.22)	0.348		2.00 (1.48-2.60)	2.10 (1.39-3.09)		
Elevated (≥2)	19/43 (44.2)	191/427 (44.7)	0.945		14/35 (40.0)	26/63 (41.3)	0.902	
Hemoglobin, g/dL	12.5 (10.7-13.2)	13.5 (12.1-14.8)	<0.001		12.3 (10.5-13.2)	12.6 (11.0-13.7)	0.249	
Platelets, 10^9/L	207 (172-270)	253 (210-300)	<0.001		207 (172-263)	240 (185-285)	0.080	
Type of injury, location								
Head	30 (41.7)	199 (38.3)	0.579		21 (42.0)	32 (32.0)	0.227	
AIS, mean (SD)	3.27 (1.39)	3.11 (1.25)	0.529		3.33 (1.53)	2.97 (1.43)	0.380	
Face	9 (12.5)	108 (20.8)	0.099		4 (8.0)	18 (18.0)	0.103	
AIS, mean (SD)	1.67 (0.50)	1.69 (0.50)	0.878		1.50 (0.58)	1.56 (0.51)	0.849	
Neck	1 (1.4)	8 (1.5)	0.923		1 (2.0)	1 (1.0)	0.615	
AIS, mean (SD)	3.00 (N/A)	2.38 (0.92)	0.541		3.00	2.00	N/A	

Thorax	28 (38.9)	193 (37.1)	0.771		22 (44.0)	38 (38.0)	0.480	
AIS, mean (SD)	2.96 (1.37)	2.78 (0.76)	0.297		3.09 (1.44)	2.97 (0.72)	0.676	
Abdomen	11 (15.3)	77 (14.8)	0.916		10 (20.0)	13 (13.0)	0.262	
AIS, mean (SD)	2.45 (0.52)	2.58 (0.88)	0.635		2.40 (0.52)	2.31 (0.75)	0.743	
Spine	20 (27.8)	166 (31.9)	0.478		14 (28.0)	35 (35.0)	0.389	
AIS, mean (SD)	2.75 (0.79)	2.58 (0.76)	0.362		2.71 (0.83)	2.66 (0.68)	0.804	
Upper extremity	19 (26.4)	163 (31.3)	0.393		12 (24.0)	23 (23.0)	0.891	
AIS, mean (SD)	1.95 (0.23)	2.00 (0.69)	0.740		1.92 (0.29)	2.00 (0.30)	0.437	
Lower extremity	31 (43.1)	252 (48.5)	0.389		22 (44.0)	50 (50.0)	0.488	
AIS, mean (SD)	2.52 (0.72)	2.81 (0.51)	0.033		2.50 (0.74)	2.76 (0.52)	0.145	
External and others	42 (58.3)	307 (59.0)	0.909		27 (54.0)	44 (44.0)	0.248	
AIS, mean (SD)	1.00 (0)	1.01 (0.13)	0.620		1.00 (0)	1.00 (0)	N/A	
Injury severity score (ISS)^, median (IQR)	10 (9-18.8)	13 (9-19.8)	0.458		10 (9-22)	10 (9-18)	0.480	
ISS >15, yes^	23 (31.9)	196 (37.7)	0.344	0.120	17 (34.0)	32 (32.0)	0.806	0.042
Injury severity score (ISS), category							0.180	
Moderate (9-15)	49 (68.1)	324 (62.3)			33 (66.0)	68 (68.0)		
Severe (16-24)	10 (13.9)	120 (23.1)			6 (12.0)	20 (20.0)		
Profound (≥25)	13 (18.1)	76 (14.6)			11 (22.0)	12 (12.0)		

All continuous variables were expressed as median (IQR (interquartile range)) unless specified. All categorical variables were expressed as n (%) unless otherwise specified. Values in bold indicate statistical significance, where P<0.05. ^Propensity score matching was performed for these variables due to potential and/or significant effects on clinical outcomes, or due to significant differences in demographics between the two study groups. #Hypotension was defined as systolic blood pressure of <90 mmHg. AIS: Abbreviated injury scale; BMI: Body mass index; ISS: Injury severity score; IQR: Interquartile range; PSM: propensity score matched; SD: Standard deviation; SMD: standardized mean difference.

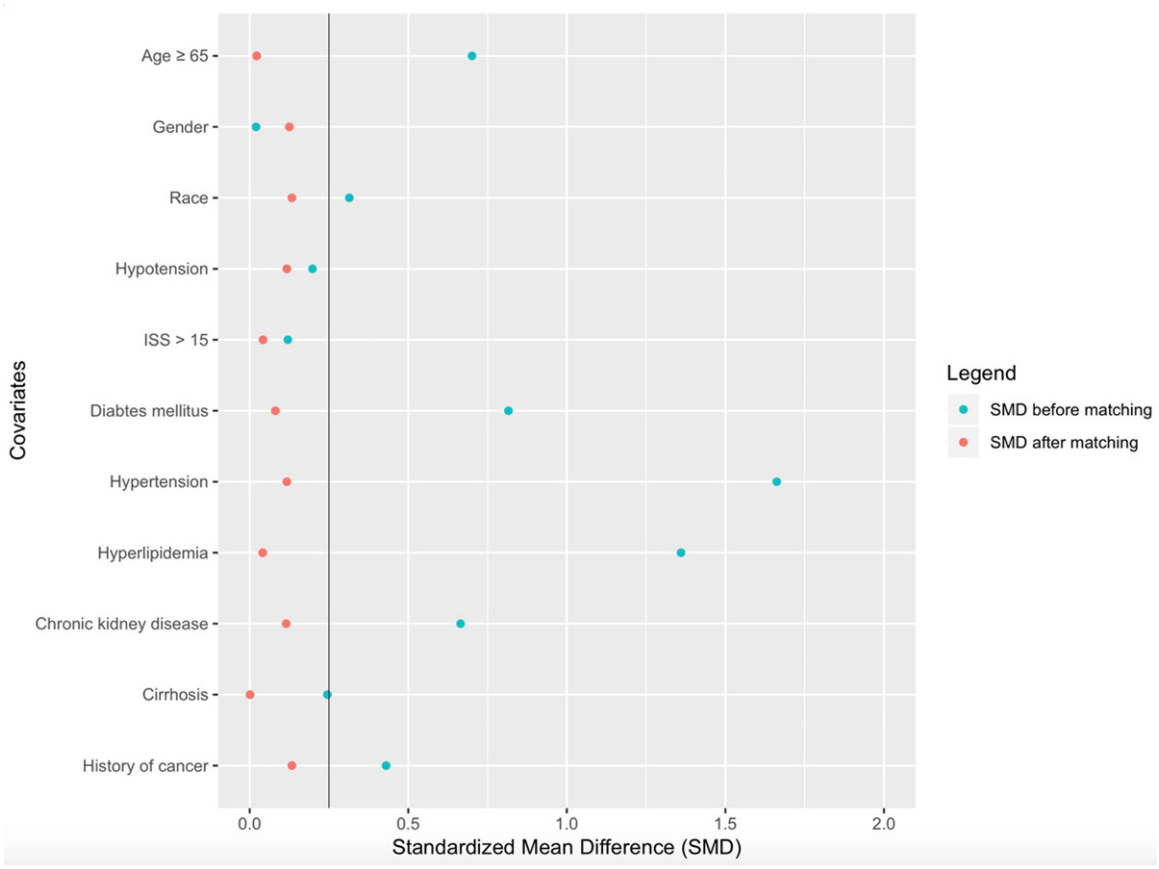

Figure 1. Plot of standardised mean difference (SMD) in covariates: before propensity score matching (blue) and after propensity score matching (red). SMD <0.250 indicates adequate balance. ISS: Injury Severity Score.

morbidities such as IHD, PVD, cerebrovascular disease, diabetes mellitus, hypertension, hyperlipidemia, chronic kidney disease, liver cirrhosis and history of malignancy (**Table 1**). ISS was comparable between both groups (APT/OAC: median 10 (IQR 9-18.8), No APT/OAC: median 13 (IQR 9-19.8), P=0.458).

After PSM, there were 150 patients (APT/OAC n=50, No APT/OAC n=100). Of those with APT/OAC use, there were 3 patients (6%) who used both APT and OAC, 43 patients (86%) who used APT only, and 4 patients (8%) who used OAC only. All matched covariates had SMD <0.250 following PSM, suggesting adequate and improved balance (**Figure 1**). Hansen and Bowers test for global significance did not demonstrate any statistical significance in the matched cohort (before PSM: χ^2=183, P<0.001; after PSM: χ^2=3.81, P=0.975). Iacus, King, and Porro test demonstrated improvement in the overall balance after matching (before PSM: L1=0.870; after PSM: L1=0.660). Majority of patient demographics were comparable after PSM, except for the incidence of IHD and PVD (**Table 1**). Median ISS was comparable (APT/OAC: 10 (IQR 9-22), no APT/OAC: 10 (IQR 9-18), P=0.480).

Clinical outcomes

Table 2 summarizes the clinical outcomes of patients who had preinjury APT/OAC versus no APT/OAC in both the unmatched and matched cohorts. In the unmatched cohort, need for platelet transfusion within the first 24 hours was higher in APT/OAC compared to no APT/OAC (OR 5.08, 95% CI: 2.67, 9.66, P<0.001). Multivariate analysis showed that APT/OAC use was independently associated with increased need for platelet transfusion (OR 18.14, 95% CI: 5.60, 58.82, P<0.001). Need for FFP, packed cells transfusion, angioembolization and surgery within 24 hours, incidence of ICU and HDU admission and any morbidity were comparable between APT/OAC and no APT/OAC.

Table 2. Outcomes after blunt trauma in patients who received antiplatelets and/or anticoagulants versus those without in both the unmatched and matched cohort

	Overall cohort, n=592						PSM cohort, n=150					
	Antico-agulants/ antiplatelets (n=72)	No antico-agulants/ antiplatelets (n=520)	Univariate analysis		Multivariate analysis		Anticoagu-lants/anti-platelets (n= 50)	No antico-agulants/ antiplatelets (n=100)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value			OR (95% CI)	*p* value	OR (95% CI)	*p* value
Need for transfusion within the first 24 hours												
Platelets	18 (25.0)	32 (6.2)	5.08 (2.67, 9.66)	<0.001	18.14 (5.60, 58.82)	<0.001	12 (24.0)	3 (3.0)	10.21 (2.73, 38.21)	<0.001	15.23 (3.05, 76.04)	0.001
Median, mL (IQR)	315 (268-343)	344 (322-623)	-	0.020	-	-	311 (277-348)	300 (248-N/A)	-	0.365	-	-
Fresh frozen plasma	5 (6.9)	36 (6.9)	1.00 (0.38, 2.65)	0.995	-	-	3 (6.0)	4 (4.0)	1.53 (0.33, 7.13)	0.584	-	-
Median, mL (IQR)	527 (387-1314)	916 (530-1330)	-	0.188	-	-	527 (254-N/A)	645 (526-1178)	-	0.400		-
Packed cells	19 (26.4)	135 (26.0)	1.02 (0.58, 1.79)	0.938	-	-	9 (18.0)	25 (25.0)	0.66 (0.28, 1.54)	0.334	-	-
Median, mL (IQR)	563 (284-819)	851 (530-1653)	-	0.043	-	-	567 (281-800)	687 (524-1806)	-	0.224	-	-
Management within 24 hours												
Surgery, n (%)	11 (15.3)	112 (21.5)	0.66 (0.33, 1.29)	0.220	-	-	10 (20.0)	15 (15.0)	1.42 (0.59, 3.43)	0.439	-	-
Angioembolisation, n (%)	2 (2.8)	11 (2.1)	1.32 (0.29, 6.09)	0.719	-	-	0 (0)	2 (2.0)	N/A	0.314	-	-
ICU admission, yes (%)	11 (15.3)	91 (17.5)	0.85 (0.43, 1.68)	0.640	-	-	8 (16.0)	22 (22.0)	0.68 (0.28, 1.65)	0.386	-	-
Length of ICU stay, median (IQR)	4 (1-6)	5 (2-8)	-	0.315	-	-	4.5 (1-12)	3 (1-8)		0.774		
HDU admission, yes (%)	31 (43.1)	193 (37.1)	1.28 (0.78, 2.11)	0.330	-	-	19 (38.0)	37 (37.0)	1.04 (0.52, 2.10)	0.905	-	-
Length of HDU stay, median (IQR)	2 (1-4)	2 (1-4)	-	0.652	-	-	2 (1-4)	2 (1-3)	-	0.812	-	-
Length of hospitalisation stay, days, median (IQR)	16 (8-36.5)	12 (6-25)	-	0.021	-	-	15.5 (7.5-35.5)	12.0 (8-20)	-	0.180	-	-
Any morbidity, n (%)	13 (18.1)	80 (15.4)	1.21 (0.64, 2.31)	0.559	-	-	14 (28.0)	31 (31.0)	0.87 (0.41, 1.83)	0.705	-	-
Morbidity, n (%)												
Urinary tract infection	18 (25.0)	56 (10.8)	2.76 (1.51, 5.04)	0.001	1.10 (0.52, 2.38)	0.799	10 (20.0)	23 (23.0)	0.84 (0.36, 1.93)	0.676	-	-
Pneumonia	16 (22.2)	39 (7.5)	3.52 (1.85, 6.71)	<0.001	1.69 (0.72, 3.94)	0.228	10 (20.0)	17 (17.0)	1.22 (0.51, 2.91)	0.652	-	-
In-hospital mortality, n (%)	12 (16.7)	26 (5.0)	3.80 (1.82, 7.92)	<0.001	2.02 (0.78, 5.23)	0.149	11 (22.0)	9 (9.0)	2.85 (1.10, 7.43)	0.027	3.00 (1.05, 8.56)	0.040

All continuous variables were expressed as median (IQR (interquartile range)) unless specified. All categorical variables were expressed as n (%) unless otherwise specified. Values in bold indicate statistical significance, where P<0.05. CI: Confidence interval; HDU: High dependency unit; ICU: Intensive care unit; IQR: Interquartile range; OR: Odds ratio; PSM: Propensity score matched.

LOS was higher in the APT/OAC group (median 16 days (IQR 8-36.5), vs median 12 days (IQR 6-25), P=0.021). Univariate analysis showed that incidence of UTI (OR 2.76, 95% CI: 1.51, 5.04, P=0.001) and pneumonia (OR 3.52, 95% CI: 1.85, 6.71, P<0.001) were higher in the APT/OAC group. In-hospital mortality was also higher in the APT/OAC group (OR 3.80, 95% CI: 1.82, 7.92, P<0.001). However, multivariate analysis showed that APT/OAC use was not independently associated with increased UTI, pneumonia and in-hospital mortality.

In the PSM cohort, need for platelet transfusion within 24 hours (OR 10.21, 95% CI: (2.73, 38.21), P<0.001) and in-hospital mortality (OR 2.85, 95% CI: 1.10, 7.43, P=0.027) were similarly higher in APT/OAC. Multivariate analysis showed that APT/OAC use was independently associated with increased need for platelet transfusion (OR 15.23, 95% CI: 3.05, 76.04, P=0.001) and in-hospital mortality (OR 3.00, 95% CI: 1.05, 8.56, P=0.04). Unlike the unmatched cohort, the PSM cohort had similar LOS, incidence of UTI and pneumonia between APT/OAC use and no APT/OAC use (**Table 2**).

Subgroup analysis of elderly patients ≥65 years old in the unmatched cohort (APT/OAC n=54, no APT/OAC n=220) similarly showed increased need for platelet transfusion, incidence of UTI, pneumonia and in-hospital mortality in the unmatched cohort (**Table 3**). However, in the PSM cohort (APT/OAC n=37, no APT/OAC n=73), univariate analysis only showed increased need for platelet transfusion (16.2% vs 4.1%, P=0.029). Multivariate analysis did not show that APT/OAC was independently associated with increased platelet transfusion (OR 4.89, 95% CI: 0.83, 28.77, P=0.079). There was a trend towards higher in-hospital mortality with APT/OAC use but did not reach statistical significance (21.6% vs 9.6%, P=0.082).

Discussion

Preinjury APT/OAC use is concerning for increased bleeding risk following moderate to severe blunt trauma. This is especially so in the Asian context, where the Asian population has been shown to have higher bleeding risk with APT/OAC use compared to the Western population [17-19]. Evidence on preinjury APT/OAC use on outcomes is equivocal. Our study demonstrated higher in-hospital mortality with the use of preinjury APT/OAC following moderate to severe blunt trauma in both the unmatched and matched cohorts. Patients who had preinjury APT/OAC were more likely to have IHD and PVD. Severity of head injury and need for emergency surgery was comparable in both the unmatched and matched cohorts.

Several studies had explored the prognostic factors and predictors of mortality following moderate to severe blunt trauma [30, 31]; These include increased age, deranged biochemical investigations such as prolonged partial thromboplastin time, increased INR, initial hemoglobin levels, and characteristics of injury (presence of head injury and severity of injury) [21]. Use of APT/OAC predisposes patients to increased bleeding risk, which may lower initial hemoglobin levels and prolong INR, resulting in increased mortality. However, as there are several confounding factors for mortality in trauma, we used PSM to match for those variables (e.g. age ≥65 years, presence of hypotension and ISS >15). Even after PSM and multivariate logistic regression, our study demonstrated higher in-hospital mortality with preinjury APT/OAC use. This finding is consistent with the study by Kerschbaum et al. on 254 elderly patients (age ≥65) with ISS ≥16, which showed significantly higher 30-day mortality in elderly patients with APT/OAC use (APT/OAC 38.5% vs no APT/OAC 24.8%, P=0.019) [32]. However, it is noteworthy that other secondary outcomes i.e. severity of head injury, need for emergency surgery and LOS were comparable between APT/OAC vs no APT/OAC in our study. Severity of other injuries were also comparable. To add on, incidence of IHD and PVD were higher in patients with preinjury APT/OAC (since these variables were not matched). Therefore, it is possible that higher in-hospital mortality in the APT/OAC group may be due to worse co-morbidities instead of the use of APT/OAC. Presence of IHD was shown to be a significant predictor of mortality (odds ratio = 1.80) following trauma [33].

We also demonstrated higher incidence of platelet transfusion with APT/OAC in both the matched and unmatched cohorts. Common APTs include aspirin and clopidogrel. Aspirin inhibits thromboxane A_2 synthesis, a promoter of platelet aggregation, while the active metabolite of clopidogrel irreversibly inhibits the

Table 3. Outcomes after blunt trauma in elderly patients (age ≥65) who received antiplatelets and/or anticoagulants versus those without in both the unmatched and matched cohort

	Overall cohort, n=274						PSM cohort, n=110					
	Antico-agulants/ antiplatelets (n=54)	No antico-agulants/ antiplatelets (n=220)	Univariate analysis		Multivariate analysis		Antico-agulants/ antiplatelets (n=37)	No antico-agulants/ antiplatelets (n=73)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p* value	OR (95% CI)	*p* value			OR (95% CI)	*p* value	OR (95% CI)	*p* value
ISS >15, yes	12 (22.2)	58 (26.4)	0.80 (0.39, 1.62)	0.532	-	-	9 (24.3)	16 (21.9)	1.15 (0.45, 2.91)	0.776	-	-
Type of injury, head	20 (37.0)	79 (35.9)	1.05 (0.57, 1.95)	0.877	-	-	14 (37.8)	24 (32.9)	1.24 (0.55, 2.84)	0.605	-	-
AIS, mean (SD)	2.90 (1.29)	3.10 (1.33)	-	0.544	-	-	2.86 (1.35)	2.92 (1.48)	-	0.902	-	-
Need for transfusion within the first 24 hours												
Platelets	11 (20.4)	14 (6.4)	3.76 (1.60, 8.85)	0.001	7.61 (2.03, 28.49)	0.003	6 (16.2)	3 (4.1)	4.52 (1.06, 19.23)	0.029	4.89 (0.83, 28.77)	0.079
Median, mL (IQR)	317 (269-339)	340 (318-418)	-	0.134	-	-	302 (267-327)	300 (248-N/A)		0.714	-	-
Fresh frozen plasma	4 (7.4)	10 (4.5)	1.68 (0.51, 5.58)	0.392	-	-	2 (5.4)	4 (5.5)	0.99 (0.17, 5.65)	0.987	-	-
Median, mL (IQR)	536 (321-1695)	775 (524-1543)	-	0.374	-	-	403 (254-N/A)	645 (526-1178)	-	0.533	-	-
Packed cells	15 (27.8)	49 (22.3)	1.34 (0.68, 2.64)	0.392	-	-	7 (18.9)	18 (24.7)	0.71 (0.27, 1.90)	0.497	-	-
Median, mL (IQR)	567 (284-1097)	846 (536-1800)	-	0.143	-	-	567 (295-781)	832 (500-2200)		0.714	-	-
Management within 24 hours												
Surgery, n (%)	7 (13.0)	25 (11.4)	1.16 (0.47, 2.85)	0.743	-	-	6 (16.2)	8 (11.0)	1.57 (0.50, 4.93)	0.434	-	-
Angioembolisation, n (%)	2 (3.7)	2 (0.9)	4.19 (0.58, 30.46)	0.125	-	-	1 (1.4)	0 (0)	N/A	0.474	-	-
ICU admission, yes (%)	9 (16.7)	34 (15.5)	1.09 (0.49, 2.44)	0.826	-	-	6 (16.2)	13 (17.8)	0.89 (0.31, 2.58)	0.835	-	-
Length of ICU stay, median (IQR)	4 (1-10)	3 (1-7)	-	0.797	-	-	4.5 (1-14.8)	2 (1-4.5)		0.274	-	-
HDU admission, yes (%)	22 (40.7)	84 (38.2)	1.11 (0.61, 2.04)	0.729	-	-	12 (32.4)	26 (35.6)	0.87 (0.38, 2.01)	0.740	-	-
Length of HDU stay, median (IQR)	2.5 (1-6)	2 (1-3)	-	0.331	-	-	3 (1-6)	2 (1-3)		0.461	-	-
Length of hospitalisation stay, days, median (IQR)	16 (7.8-34.3)	16 (10-31)		0.629	-	-	14 (5.5-30.5)	14 (9-24)		0.902	-	-
Any morbidity, n (%)	10 (18.5)	38 (17.3)	1.09 (0.50, 2.35)	0.829	-	-	10 (27.0)	25 (34.2)	0.71 (0.30, 1.70)	0.442	-	-
Morbidity, n (%)												
Urinary tract infection	14 (25.9)	25 (11.4)	2.73 (1.31, 5.71)	0.006	1.15 (0.47, 2.81)	0.769	7 (18.9)	17 (23.3)	0.77 (0.29, 2.06)	0.600	-	-
Pneumonia	12 (22.2)	15 (6.8)	3.91 (1.71, 8.94)	0.001	1.65 (0.60, 4.52)	0.329	7 (18.9)	13 (17.8)	1.08 (0.39, 2.98)	0.887	-	-
In-hospital mortality, n (%)	9 (16.7)	16 (7.3)	2.55 (1.06, 6.14)	0.032	1.89 (0.63, 5.69)	0.256	8 (21.6)	7 (9.6)	2.60 (0.86, 7.85)	0.082	-	-

All continuous variables were expressed as median (IQR (interquartile range)) unless specified. All categorical variables were expressed as n (%) unless otherwise specified. Values in bold indicate statistical significance, where P<0.05. CI: Confidence interval; HDU: High dependency unit; ICU: Intensive care unit; IQR: Interquartile range; ISS: Injury severity score; OR: Odds ratio; PSM: Propensity score matched.

platelet adenosine diphosphate $P2Y_{12}$ receptor, which is essential for platelet activation [34-36]. This results in platelet dysfunction which warrants the need for platelet transfusion. The increased need for platelet transfusion in the APT/OAC group may be due to increased hemorrhage attributed to platelet dysfunction or inherent selection bias from the lack of standardized criteria for platelet transfusion. Recommendations from the British Committee for Standards in Haematology in 2016 suggested platelet transfusion to maintain platelet count >100 × 10^9/L in patients with multiple trauma or traumatic brain injury (level 2C evidence), and to consider the use of platelet transfusion as an additional measure to general hemostatic measures and TXA for critical bleeding (level 2C evidence) [37]. It is important to know that while APT use results in platelet dysfunction, absolute platelet count is not reduced [38, 39]. This was similarly demonstrated in our study where hemoglobin and platelet counts were comparable between APT/OAC and no APT/OAC groups after PSM. Decision for platelet transfusion based on platelet count with preinjury APT use in trauma should not be advised.

As old age is a predictor of mortality following trauma [30, 31], we performed subgroup analysis to evaluate the impact of preinjury APT/OAC use on outcomes in patients with age ≥65 years old. While there was a trend towards higher in-hospital mortality (21.6% vs 9.6%, P=0.082), this did not reach statistical significance in the PSM cohort. This is contrary to the study by Kerschbaum et al. which assessed 254 elderly patients with severe trauma [32]. The lack of statistical significance in our study may be due to a smaller sample size and lack of power to detect statistically significant differences after PSM and subgroup analysis. Nevertheless, the absolute difference in in-hospital mortality was 13.0% higher in the APT/OAC group, which is of clinical significance. We caution to conclude that preinjury APT/OAC use has comparable mortality with no APT/OAC use in elderly patients.

Interestingly, univariate analysis in the unmatched cohort showed higher incidence of UTI and pneumonia in the APT/OAC group in both the overall cohort (n=592) and elderly cohort (n=274). This was not seen in our PSM cohort, nor following multivariate analysis. There was significantly higher number of elderly patients in the unmatched cohort (75% vs 42.3%, P<0.001). Reduced physiological reserves in elderly patients and presence of multiple co-morbidities predispose them to nosocomial infections such as pneumonia [40]. Need for immobilization for lower extremity fractures and spinal fractures also predisposes patients to acute retention of urine, increasing risk of UTI [41]. Subgroup analysis of the elderly patients in our unmatched cohort similarly showed increased UTI and pneumonia in APT/OAC. This may also be due to the higher incidence of co-morbidities and lower physiological reserves in patients who are on APT/OAC compared to no APT/OAC. Therefore, following multivariate analysis and in our PSM cohort, there was no correlation between APT/OAC use and incidence of UTI and pneumonia.

Our study has its strengths. Firstly, this is one of the largest studies on the use of preinjury APT/OAC in the Asian population following moderate to severe trauma. Our study included patients with blunt trauma only and excluded patients with penetrating trauma to reduce heterogeneity. We also included the use of PSM analysis and multivariate analysis to balance confounding effects on outcomes, especially in the context of APT/OAC use, where majority of patients who require the use of APT/OAC are elderly patients with co-morbidities which are poor prognostic factors following trauma [42].

However, there are limitations to our study. Firstly, this is a retrospective cohort study with inherent selection bias. However, this was mitigated through the use of PSM which reduces bias unlike traditional retrospective observational studies [26]. While the aim of this study is to identify the impact of preinjury APT/OAC use on clinical outcomes following moderate to severe trauma in an East Asian population, we were unable to compare the outcomes of different races as majority of the included patients were Chinese. We did not collect data on the type of APT and OAC used; However, a recent meta-analysis on the use of APT in traumatic brain injury failed to show any difference between the use of aspirin vs clopidogrel on mortality [43]. There was no data on whether single APT or dual APT agents were used. Additionally, while our study compared APT/OAC with no APT/OAC use, majority of the

included patients in the APT/OAC group received only APT. Results may not be generalizable to those with both APT and OAC use, or OAC use only. There was also no data collected on the mechanism of injury (e.g. fall from height versus road traffic accident) and cause of mortality. However, patients were grouped according to the severity of injury using the ISS. The severity of head injury was measured only during the initial presentation to the emergency department and may not capture progression or worsening of head injury throughout the admission. Subgroup analysis for patients with head injury was not performed, as the sample size will be too small (n=53 in the PSM cohort) to detect any statistical significance. Data on the incidence of DVT and pulmonary embolism were also not collected.

Conclusion

Preinjury APT/OAC use was associated with higher in-hospital mortality in the East Asian population following moderate to severe blunt trauma. This may be contributed by higher incidence of comorbidities in the APT/OAC group. Severity of head injury and need for emergency surgery within 24 hours from admission were comparable between APT/OAC use and no APT/OAC use.

Disclosure of conflict of interest

None.

Address correspondence to: Serene Si Ning Goh, MOH Holdings Pte Ltd, 1 Maritime Square, Singapore 099253, Singapore; Department of General Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore. ORCID: 0000-0003-4916-2142; E-mail: serene.goh@mohh.com.sg

References

[1] Hirode G and Wong RJ. Trends in the prevalence of metabolic syndrome in the United States, 2011-2016. JAMA 2020; 323: 2526-2528.

[2] Wang X, Hao G, Chen Z, Zhang L, Kang Y, Yang Y, Zheng C, Zhou H, Chen L, Wang Z and Gao R. Aspirin use in patients with diagnosed diabetes in the United States and China: nationally representative analysis. Diab Vasc Dis Res 2021; 18: 14791641211067416.

[3] Ilomäki J, Fanning L, Keen C, Sluggett JK, Page AT, Korhonen MJ, Meretoja A, Mc Namara KP and Bell JS. Trends and predictors of oral anticoagulant use in people with Alzheimer's disease and the general population in Australia. J Alzheimers Dis 2019; 70: 733-745.

[4] Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S and Yusuf S. Aspirin in patients undergoing noncardiac surgery. N Engl J Med 2014; 370: 1494-1503.

[5] Wu T, Lv C, Wu L, Chen W, Lv M, Jiang S and Zhang J. Risk of intracranial hemorrhage with direct oral anticoagulants: a systematic review and meta-analysis of randomized controlled trials. J Neurol 2022; 269: 664-675.

[6] Dossett LA, Riesel JN, Griffin MR and Cotton BA. Prevalence and implications of preinjury warfarin use: an analysis of the National Trauma Databank. Arch Surg 2011; 146: 565-570.

[7] Lippi G, Mattiuzzi C, Cervellin G and Favaloro EJ. Direct oral anticoagulants: analysis of worldwide use and popularity using Google Trends. Ann Transl Med 2017; 5: 322.

[8] Franko J, Kish KJ, O'Connell BG, Subramanian S and Yuschak JV. Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma. J Trauma 2006; 61: 107-110.

[9] Lavoie A, Ratte S, Clas D, Demers J, Moore L, Martin M and Bergeron E. Preinjury warfarin use among elderly patients with closed head injuries in a trauma center. J Trauma 2004; 56: 802-807.

[10] Karni A, Holtzman R, Bass T, Zorman G, Carter L, Rodriguez L, Bennett-Shipman VJ and Lottenberg L. Traumatic head injury in the anticoagulated elderly patient: a lethal combination. Am Surg 2001; 67: 1098-1100.

[11] Ivascu FA, Howells GA, Junn FS, Bair HA, Bendick PJ and Janczyk RJ. Predictors of mortality in trauma patients with intracranial hemorrhage on preinjury aspirin or clopidogrel. J Trauma 2008; 65: 785-788.

[12] Jones K, Sharp C, Mangram AJ and Dunn EL. The effects of preinjury clopidogrel use on older trauma patients with head injuries. Am J Surg 2006; 192: 743-745.

[13] Spektor S, Agus S, Merkin V and Constantini S. Low-dose aspirin prophylaxis and risk of intracranial hemorrhage in patients older than 60 years of age with mild or moderate head injury:

a prospective study. J Neurosurg 2003; 99: 661-665.
[14] Wojcik R, Cipolle MD, Seislove E, Wasser TE and Pasquale MD. Preinjury warfarin does not impact outcome in trauma patients. J Trauma 2001; 51: 1147-1151; discussion 1151-1152.
[15] Fortuna GR, Mueller EW, James LE, Shutter LA and Butler KL. The impact of preinjury antiplatelet and anticoagulant pharmacotherapy on outcomes in elderly patients with hemorrhagic brain injury. Surgery 2008; 144: 598-603; discussion 603-5.
[16] Inamasu J, Nakatsukasa M, Miyatake S and Hirose Y. Influence of warfarin and low-dose aspirin on the outcomes of geriatric patients with traumatic intracranial hemorrhage resulting from ground-level fall. Geriatr Gerontol Int 2012; 12: 667-672.
[17] Shen AY, Yao JF, Brar SS, Jorgensen MB and Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol 2007; 50: 309-315.
[18] Huang WY, Saver JL, Wu YL, Lin CJ, Lee M and Ovbiagele B. Frequency of intracranial hemorrhage with low-dose aspirin in individuals without symptomatic cardiovascular disease: a systematic review and meta-analysis. JAMA Neurol 2019; 76: 906-914.
[19] Cho H, Kang J, Kim HS and Park KW. Ethnic differences in oral antithrombotic therapy. Korean Circ J 2020; 50: 645-657.
[20] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC and Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007; 147: 573-577.
[21] Baker SP, O'Neill B, Haddon W Jr and Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. J Trauma 1974; 14: 187-196.
[22] American College of Surgeons. Committee on trauma. Advanced Trauma Life Support: student course manual. Chicago, IL: 2018.
[23] Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, Cook L, Kawahara T, Perel P, Prieto-Merino D, Ramos M, Cairns J and Guerriero C. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess 2013; 17: 1-79.
[24] Ley EJ, Brown CVR, Moore EE, Sava JA, Peck K, Ciesla DJ, Sperry JL, Rizzo AG, Rosen NG, Brasel KJ, Kozar R, Inaba K and Martin MJ. Updated guidelines to reduce venous thromboembolism in trauma patients: a Western Trauma Association critical decisions algorithm. J Trauma Acute Care Surg 2020; 89: 971-981.
[25] Ahmad R, Cherry RA, Lendel I, Mauger DT, Service SL, Texter LJ and Gabbay RA. Increased hospital morbidity among trauma patients with diabetes mellitus compared with age- and injury severity score-matched control subjects. Arch Surg 2007; 142: 613-618.
[26] Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983; 70: 41-55.
[27] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011; 10: 150-161.
[28] Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009; 28: 3083-3107.
[29] Nguyen TL, Collins GS, Spence J, Daurès JP, Devereaux PJ, Landais P and Le Manach Y. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol 2017; 17: 78.
[30] Kunitake RC, Kornblith LZ, Cohen MJ and Callcut RA. Trauma Early Mortality Prediction Tool (TEMPT) for assessing 28-day mortality. Trauma Surg Acute Care Open 2018; 3: e000131.
[31] MacLeod J, Lynn M, McKenney MG, Jeroukhimov I and Cohn SM. Predictors of mortality in trauma patients. Am Surg 2004; 70: 805-810.
[32] Kerschbaum M, Lang S, Henssler L, Ernstberger A, Alt V, Pfeifer C, Worlicek M and Popp D. Influence of oral anticoagulation and antiplatelet drugs on outcome of elderly severely injured patients. J Clin Med 2021; 10: 1649.
[33] Morris JA Jr, MacKenzie EJ and Edelstein SL. The effect of preexisting conditions on mortality in trauma patients. JAMA 1990; 263: 1942-1946.
[34] Savi P, Pereillo JM, Uzabiaga MF, Combalbert J, Picard C, Maffrand JP, Pascal M and Herbert JM. Identification and biological activity of the active metabolite of clopidogrel. Thromb Haemost 2000; 84: 891-896.
[35] Mikhailidis DP and Jagroop IA. Is clopidogrel markedly superior to aspirin in patients with peripheral vascular disease? Platelets 1998; 9: 273-278.
[36] Wilde JI, Retzer M, Siess W and Watson SP. ADP-induced platelet shape change: an investigation of the signalling pathways involved

and their dependence on the method of platelet preparation. Platelets 2000; 11: 286-295.
[37] Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP, Mumford AD, Stanworth SJ and Tinegate H; British Committee for Standards in Haematology. Guidelines for the use of platelet transfusions. Br J Haematol 2017; 176: 365-394.
[38] Erhart S, Beer JH and Reinhart WH. Influence of aspirin on platelet count and volume in humans. Acta Haematol 1999; 101: 140-144.
[39] Grau AJ, Reiners S, Lichy C, Buggle F and Ruf A. Platelet function under aspirin, clopidogrel, and both after ischemic stroke: a case-crossover study. Stroke 2003; 34: 849-854.
[40] Bergeron E, Lavoie A, Clas D, Moore L, Ratte S, Tetreault S, Lemaire J and Martin M. Elderly trauma patients with rib fractures are at greater risk of death and pneumonia. J Trauma 2003; 54: 478-485.
[41] Borrie MJ, Campbell K, Arcese ZA, Bray J, Hart P, Labate T and Hesch P. Urinary retention in patients in a geriatric rehabilitation unit: prevalence, risk factors, and validity of bladder scan evaluation. Rehabil Nurs 2001; 26: 187-191.
[42] Morgan CJ. Reducing bias using propensity score matching. J Nucl Cardiol 2018; 25: 404-406.
[43] Cheng L, Cui G and Yang R. The impact of pre-injury use of antiplatelet drugs on outcomes of traumatic brain injury: a systematic review and meta-analysis. Front Neurol 2022; 13: 724641.