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Effect of gender on 28-day survival rates and transfusion volume in severe trauma patients:
a multicenter observational study

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21

22

Abstract:

Background: This study clarified the relationship between sex with survival and transfusion volume in severe trauma cases.

Methods: A multicenter, collaborative post-hoc analysis of patients with trauma in Japan was conducted. Patients aged ≥ 18 years with severe trauma indicated by an Injury Severity Score (ISS) of 16 or higher were enrolled. Patients were matched and analyzed by gender based on propensity score with factors determined at the time of injury. Subgroup analysis was performed on patients younger than 50 years and older than 50 years. The significance level was defined as $p < 0.05$.

Results: The 1,189 patients included in this registry were divided into adjusted groups of 226 male and female patients each. In the main analysis, 28-day survival rates in females were significantly higher than those in males ($p=0.046$). In the subgroup analyses, there was no statistically significant prognostic effect of gender. Secondary outcomes, including transfusion volume, showed no significant gender-based variations. Logistic regression analyses consistently demonstrated that female sex was a significant favorable prognostic factor in all ages. This was true for the over-50 group on subgroup analysis, but no significant gender-prognosis relationship was identified in the under-50 age group. High ISS were

associated with poorer outcomes across all age groups.

Conclusion: In severe trauma, survival at 28 days was significantly lower in males. However, this trend was not observed in patients aged <50 years. Factors other than sex hormones may be responsible for differences in posttraumatic outcomes by gender.

Keywords: gender difference, sex dimorphisms, mortality, trauma, prognosis, sex hormone, massive transfusion

Introduction

Several studies have investigated the relationship between sex and prognosis following trauma with conflicting results.¹⁻⁸ Mixed reports suggest females have a better,^{1,3,8} similar,^{2,4,5} or worse prognosis.⁶ In patients with isolated traumatic brain injury, worsening of coagulation-fibrinolysis markers immediately after injury may have been associated with unfavorable neurologic prognosis in males but not in females.⁷ In trauma populations not limited to head trauma, there are also reports of a relatively higher mortality rate for male patients in the older population.⁹

Females and males have different coagulation functions, with higher coagulability observed in females.¹⁰ This is a physiological function of the female-specific event of pregnancy and delivery, and estrogen has been hypothesized to be involved in the modulation of immune responses in trauma and hormone-induced hypercoagulability.¹¹ Hormone-induced hypercoagulability may affect the response to hemorrhage and critical injury in premenopausal females, and some studies have focused their analysis on the age of female patients with trauma, particularly around menopause.^{4,7,12,13} These sex comparative studies are also inconclusive, with mixed reports of changes in prognosis and coagulopathy by age group^{7,12,13} and no change in prognosis or coagulopathy.⁴

Previous studies on sex differences in transfusion volume have shown that there was no difference in transfusion volume between males and females after trauma,^{14,15} but none of these analyses considered the timing of menopause. Another study in patients with trauma who required a massive transfusion protocol reported that sex was not associated with survival.¹⁶

Therefore, consistent evidence has not been obtained regarding the impact of sex differences on the prognosis of trauma patients and the amount of blood transfusions. In trauma, the number of patients, injury mechanism, and underlying medical conditions differ significantly by sex. Therefore, background-adjusted analysis is required, but large-scale studies with detailed adjustments for confounding factors in males and females are very limited.

In this study, we used data from a national trauma registry to identify the relationship between sex, post-trauma prognosis, and transfusion volume, and age-specific analysis to determine the impact of sex hormones on the prognosis of patients with trauma.

Materials and Methods

Study design and setting

86 This was a post-hoc analysis of adult patients with trauma enrolled in the Japanese
87 Observational Study for Coagulation and Thrombolysis in Early Trauma 2 (J-OCTET 2)
88 study, a multicenter observational study conducted by the Japanese Association for The
89 Surgery of Trauma.

90 Participating institutions were 23 critical care centers nationwide in Japan, and
91 eligible patients were those who suffered injuries between September 2018 and March 2022.

92

93 Variables, Outcomes, and Definitions

94 In the J-OCTET2 study, the recorded parameters included age, sex, daily
95 medications (antiplatelet/ anticoagulant), past medical history (myocardial infarction/
96 congestive heart failure/ peripheral vascular disease/ hemiplegia or cerebrovascular disease
97 / dementia/ chronic obstructive pulmonary disease/ connective tissue disease/ ulcer disease/
98 diabetes/ renal disease/ liver disease/ metastatic or any tumor/ lymphoma/ leukemia/
99 acquired immunodeficiency syndrome), time from accident to hospital arrival, pre-hospital
100 care by a physician, mechanisms of injury, traumatic brain injury, pelvic fracture, femoral
101 fracture, vital signs on arrival (systolic blood pressure/ diastolic blood pressure/ heart rate/
102 respiratory rate/ Glasgow coma scale/ body temperature), blood test findings on arrival

(hemoglobin/ hematocrit/ platelet count/ pH/ base excess/ lactate/ prothrombin time- international normalized ratio (PT-INR)/ fibrin-fibrinogen degradation products/ d-dimer/ fibrinogen), findings of focused assessment with sonography in trauma (FAST), Abbreviated Injury Scale (AIS), Injury Severity Score (ISS), treatment strategy (rapid fluid infusion/ avoid fluid resuscitation), and type of treatment (aortic clamp/ resuscitative endovascular balloon occlusion of the aorta (REBOA)/ transcatheter arterial embolization (TAE)/ surgical hemostatic intervention/ use of tranexamic acid). The method of treatment was left to each facility. No clear definition was provided for rapid fluid infusion.

The primary outcome was survival at 28 days, and the secondary outcome was transfusion volume within 24 hours (red blood cell/ platelet concentrate/ fresh frozen plasma) and percentage of massive transfusion. Massive transfusion was defined as more than 10 units of red blood cells administered within 24 hours.

Patients

Selection criteria were (a) severe trauma with ISS $\geq$ 16, (b) 18 years of age or older. Exclusion criteria were (a) patients, their family members, or surrogates who indicated their intention not to participate in the study, (b) patients whose time of injury was unclear, (c)

patients who were transferred to a participating institution after initial treatment at another institution, (d) patients who declined aggressive treatment (including cases in which patients declined necessary transfusion therapy or surgery), (e) patients who presented with out-of-hospital cardiopulmonary arrest, (f) patients with severe burns, (g) pregnant female, and (h) patients with a history of liver cirrhosis.

Statistical analysis

The patient cohort was divided into males and females and evaluated for characteristics and outcomes. To precisely evaluate the impact of the patient's sex on outcomes, analyses were performed using propensity score matching. For propensity score matching, the covariates were age, daily medications, past medical history, time from accident to hospital arrival, pre-hospital care by a physician, mechanisms of injury, traumatic brain injury, pelvic fracture, femoral fracture, FAST, AIS, and ISS findings.

For subgroup analysis, the patients were divided into two groups (≥ 50 years and < 50 years) to examine the effect of pre- and post-menopause. The age threshold was set based on the mean age of menopause for Japanese females aged 49.33 years.¹⁷ Propensity score matching under the same conditions as above was used for the subgroup analysis.

The goodness-of-fit of the propensity score was verified with the concordance statistics.

For sensitivity analysis, logistic regression was performed on the adjusted patient population. In this analysis, 28-day survival was the dependent variable, and age, sex, traumatic brain injury, ISS, and daily platelet/coagulant use were the explanatory variables. Because the number of cases applicable to daily use of anti-platelet/coagulant was extremely small for patients aged <50 years, that variable was excluded.

Continuous variables are presented as medians with interquartile ranges. Categorical data are presented as frequencies and percentages. Patient characteristics and outcomes between the two groups were compared using the Mann–Whitney U test (for numerical variables), Fisher’s exact test (for categorical variables), and the chi-square test (for categorical variables). All analyses were performed using IBM SPSS software version 25 (IBM Japan, Tokyo, Japan). All reported p-values were two-tailed, and differences were considered statistically significant at $p < 0.05$.

Ethical statement

Because this was an observational study conducted using only existing medical information, without obtaining new samples or information, individual patient consent was

not necessarily required. Information about the conduct of the study, including the purpose of the study, was published on the website, and this procedure ensured that participants had the opportunity to refuse participation in the study. The protocol for the J-OCTET 2 study was approved by the Institutional Review Board of Tohoku University, the leading institution for the study (approval number: 2020-1-898). Each facility participating in the J-OCTET 2 study registered patient data after obtaining approval from the ethics committee of each facility. The STROBE guideline was used to ensure proper reporting of the methods, results, and discussion.

Results

The population in this study is shown in Figure 1. The J-OCTET 2 study enrolled a total of 1,189 patients aged > 18 years with severe trauma from 23 critical care centers. Eligible patients were divided into male and female groups, with 71.3% being male. The baseline characteristics of the overall patient population, categorized by sex, are shown in Table 1.

As a result of propensity score matching, the flowchart of eligible patients is shown in Figure 1. The main analysis compared 226 males and 226 females (Figure 1A). After

adjustment, there were no differences in background and treatment factors between the male and female groups (Supplemental Table 1). There were differences by sex with respect to several factors measured after trauma (diastolic blood pressure, lactate, hemoglobin, and hematocrit). A comparison of 28-day survival rates between the two groups showed that females had a significantly favorable prognosis ($p=0.046$) (Table 2). However, there were no significant differences in the secondary outcomes, transfusion volume, and massive transfusion (Table 2).

A flowchart of the patients included in the subgroup analysis is shown in Figure 1B. There were no differences in background characteristics between the population aged < 50 and those aged ≥ 50 years (data not shown). The 28-day survival rate did not show significant differences in any of the analyses; however, among the group of patients aged ≥ 50 years ($p=0.065$), females tended to have a better prognosis (Table 2). In contrast, there was no difference between male and female patients in the analysis of patients aged < 50 years ($P=0.644$) (Table 2). In any subgroup analysis, there were no significant differences in the secondary outcomes, transfusion volume, or percentage of massive transfusion (Table 2).

The concordance statistics of the propensity score models used in these analyses were 0.720 (main analysis), 0.758 (subgroup analysis for those aged < 50 years), and 0.731

(subgroup analysis for those aged > 50 years), indicating adequate discriminatory power.

The results of the logistic regression analysis are shown in Figure 2. Female sex was a significantly favorable prognostic factor in the all-age population (odds ratio [OR]: 1.954, 95% confidence interval [CI]: 1.000–3.819) and in the population aged > 50 years (OR: 2.336, 95% CI: 1.096–4.982), whereas no significant relationship was observed between sex and prognosis in the population aged < 50 years (OR: 1.097, 95% CI: 0.227–5.293). This result is the same as that of the main and subgroup analyses, indicating the robustness of the analysis. In all groups, a high ISS was shown to be a poor prognostic factor.

Discussion

This study used 28-day survival and blood transfusion volume up to 24 hours after injury as outcomes to evaluate the effect of sex on those outcomes. The results of the main analysis, adjusted for background variables, showed that the 28-day survival rate was better in females. In the subgroup analysis, which is a comparison of males and females with a threshold of 50 years of age, the 28-day survival rate was not significantly different in any of the analyses. There were no significant differences in the secondary outcomes of transfusion volume and massive transfusion in either the main or sub-analysis. In the logistic regression

analysis, female sex was a significant favorable prognostic factor in the all-ages population and in the population aged >50 years.

In trauma, the number of patients and the injury mechanism differ according to sex, and it is known that severely injured patients are more likely to be male.^{4,18,19} Therefore, in trauma, it is very important to match the background of patient characteristics in this type of study. In this study, as in previous reports, injury severity scores tended to be higher for males, although the differences were not significant. In the present study, propensity score matching was used to analyze a group with a high-quality match of background between sexes.

The main analysis of this study revealed that females have a better prognosis when transported to a hospital with trauma of the same severity. The result that females have a better prognosis in trauma is similar to previous reports.²⁰ In contrast, subgroup analyses showed no survival advantage in females aged <50 years. This result is slightly different from some previous studies.^{12,13} However, as in the present study, there are also reports of no difference in prognosis between young female and male patients.⁴ Pre-clinical trauma studies with rodents show clear and strong benefits in females, unlike the present study.²¹ There are two possible reasons for the discrepancy between studies using rodents and studies on people, including this study: a) rodents do not reflect sex characteristics encountered in human

patients, b) there are too many confounders in the analyzed human patients, and an existing sex effect cannot be exposed due to the heterogeneity of the analyzed groups.

The finding of no female advantage in the <50 years of age population supports the finding that factors other than sex hormones influence the prognosis of patients with trauma. The effects of sex hormones in trauma have been investigated and discussed in many previous studies.^{11,19,22} Based on the results, progesterone was administered to patients with traumatic brain injury, but the administration did not produce any beneficial effects.²³ Meanwhile, some reports indicated that in all age groups, females have a better prognosis than males,²⁰ and the difference is more pronounced in older age groups, as in this study.⁹ The present study also measured several coagulation-fibrinolysis markers at the time of admission; however, the only significant differences were prolonged PT-INR and decreased fibrinogen levels in the under-50 age group, with no gender differences in coagulation-fibrinolysis markers in the under-50 age group (data not shown). Thus, these findings suggest that factors other than sex hormones may be responsible for differences in post-traumatic outcomes by sex.²⁰

Reported prognostic factors other than sex hormones include post-traumatic complications and differences in physiologic reactivity. Previous reports suggest that females

are less likely to suffer complications such as pneumonia and sepsis after trauma,²⁴⁻²⁷ and that post-traumatic lactate levels in females are lower, with a better physiologic response than males to the same level of shock or trauma.³

Although the dataset used in this study lacked information on complication frequency, it revealed significantly lower lactate levels in females, even after trauma of the same severity. Concerning survival within 24 hours post-injury, females showed a trend toward higher survival rates, although the difference was not statistically significant (Supplemental Table 1). These results suggest a potential difference in the response in the hyperacute phase of trauma based on sex, potentially influencing prognosis.

In addition, females do not have a poorer survival rate after trauma than males, even though their hemoglobin and hematocrit levels are inherently lower. This fact alone may support the idea that females are more resilient to trauma. In this study, hemoglobin and hematocrit levels also differed between sexes, but the transfusion volume and other treatments did not differ. It can be suggested that in trauma, female patients had lower diastolic blood pressure, hemoglobin, and hematocrit values than male patients; however, the difference was not significant enough to change the clinician's judgment.

Limitations

Although we attempted to minimize the effects of confounders as much as possible, this study had some limitations. First, the registry data were collected from a limited number of institutions, including trauma centers, potentially introducing selection bias. Second, inherent limitations in registry measures and numerous unmeasured confounders might have influenced the findings. Third, although relatively large registry datasets were used, the number of cases may have been insufficient. In particular, the number of young patients was small, which may have rendered the results statistically unstable. Finally, this study was conducted in Japan; therefore, the results may not be generalizable to regions with different healthcare systems and ethnicities.

In conclusion, in severe trauma cases with an Injury Severity Score of 16 or higher, survival at 28 days after injury was significantly lower in males. This trend was not observed in a subgroup analysis of patients aged <50 years. There was no effect of gender on the amount of blood transfused up to 24 hours after injury. These results suggest that factors other than sex hormones may be responsible for sex differences in posttraumatic outcomes.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or

financial relationships that could be construed as a potential conflict of interest.

Author Contributions

TT and TW contributed to research conception, analysis, and manuscript preparation. AM, ST, TN and AS contributed to the collection and registration of data. All authors read and approved the final version of the manuscript prior to submission.

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

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Figure legends

Figure 1. Flow chart of study population. (A) Flow chart of main analysis, (B) Flow chart of subgroup analysis.

Figure 2. Results of logistic regression analysis for 28-day survival.

Odds ratios for each factor for 28-day survival. Older age and higher ISS were associated with lower survival rates. Survival was lower in male and in those with traumatic brain injury.

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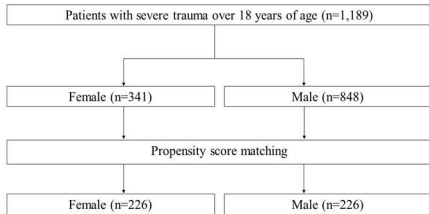
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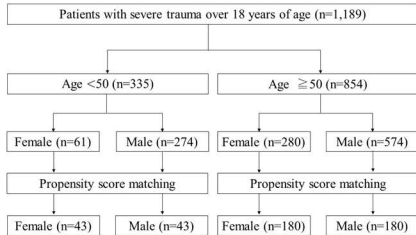
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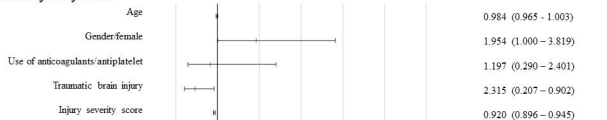
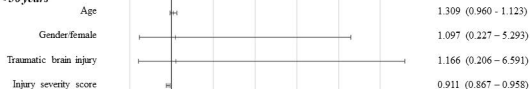
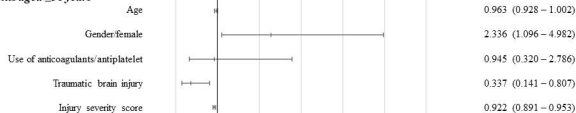
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A)



B)



All patients after adjustment**Patients aged < 50 years****Patients aged ≥ 50 years**

0 1 2 3 4 5 6

Odds ratio

TABLE 1. Baseline characteristics of patients

	Female (n=341)	Male (n=848)	<i>p</i> -Value
Age, yr	71.0 (57.0-81.0)	63.0 (45.0-75.0)	<0.001
Medicine for daily use			
Antiplatelet therapy, n (%)	28 (8.2)	77 (9.1)	0.366
Anticoagulant therapy, n (%)	22 (6.5)	43 (5.1)	0.206
Past medical history			
Myocardial infarction, n (%)	8 (2.3)	26 (3.1)	0.325
Congestive heart failure, n (%)	16 (4.7)	17 (2.0)	0.012
Peripheral vascular disease, n (%)	7 (2.0)	9 (1.0)	0.143
Hemiplegia or cerebrovascular disease, n (%)	21 (6.2)	50 (5.9)	0.468
Dementia, n (%)	35 (10.3)	35 (4.1)	<0.001
Chronic obstructive pulmonary disease, n (%)	1 (0.3)	14 (1.7)	0.043
Connective tissue disease, n (%)	10 (2.9)	3 (0.4)	<0.001
Ulcer disease, n (%)	5 (1.5)	16 (1.9)	0.417
Diabetes, n (%)	30 (8.8)	121 (14.3)	0.006
Renal disease, n (%)	5 (1.4)	21 (2.5)	0.200
Liver disease, n (%)	9 (3.6)	21 (2.5)	0.500
Metastatic or any tumor, n (%)	11 (3.2)	35 (4.1)	0.295
Lymphoma, n (%)	1 (0.3)	2 (0.2)	0.637
Leukemia, n (%)	0 (0.0)	0 (0.0)	-
Acquired immunodeficiency syndrome, n (%)	0 (0.0)	0 (0.0)	-
Types of injuries			0.421
Blunt, n (%)	330 (96.8)	824 (97.2)	
Penetrating, n (%)	11 (3.2)	24 (2.8)	
Traumatic brain injury, n (%)	207 (60.7)	422 (49.8)	0.001
Pelvic fracture, n (%)	72 (21.1)	124 (14.6)	0.005
Femoral fracture, n (%)	15 (4.4)	43 (5.1)	0.374
Pre hospital care by a physician, n (%)	77 (22.6)	160 (18.9)	0.083
Time from accident to hospital arrival	45 (32.0-65.5)	44 (33.0-60.0)	0.492
Vital signs upon arrival			
Glasgow coma scale	14 (10-15)	14 (10-15)	0.441
E	4 (3-4)	4 (3-4)	0.307
V	4 (2-5)	4 (3-5)	0.776
M	6 (5-6)	6 (5-6)	0.964
Systolic blood pressure (mmHg)	132 (108-158)	134 (111-155)	0.707
Diastolic blood pressure (mmHg)	78 (64-90)	83 (68-96)	0.001
Heart rate (/min)	85 (74-100)	84 (71-101)	0.692
Respiratory rate (/min)	20 (18-24)	20 (17-24)	0.288

Body temperature (°C)	36.3 (36.0-36.7)	36.4 (35.9-36.8)	0.507
Blood test results upon arrival			
pH	7.38 (7.33-7.42)	7.38 (7.33-7.41)	0.159
Lactate (mmol/L)	2.1 (1.6-3.2)	2.6 (1.7-4.0)	0.001
Base excess	-0.9 (-3.3-1.1)	-1.3 (-3.7-0.7)	0.189
Platelet (*10 ⁴ /μL)	20.5 (16.7-25.8)	21.6 (17.3-26.0)	0.164
Hemoglobin (g/dL)	12.0 (10.7-13.1)	13.6 (12.3-14.8)	<0.001
Hematocrit (%)	36.4 (32.3-39.0)	40.1 (36.5-43.5)	<0.001
PT-INR	1.03 (0.98-1.13)	1.03 (0.97-1.11)	0.188
D-dimer (μg/mL)	38.5 (10.3-85.6)	23.4 (8.0-56.7)	<0.001
Fibrin-fibrinogen degradation products (μg/mL)	70.0 (21.6-168.5)	49.5 (16.8-116.0)	0.002
Fibrinogen (mg/dL)	238 (185-297)	241 (192-285)	0.641
Findings of FAST positive, n (%)			
Pericardiac	6 (1.8)	13 (1.5)	0.482
Left thoracic cavity	7 (2.1)	10 (1.1)	0.193
Right thoracic cavity	5 (1.5)	10 (1.1)	0.446
Perihepatic	9 (2.6)	35 (4.1)	0.135
Perisplenic	7 (2.1)	21 (2.5)	0.411
Pelvic	6 (1.8)	20 (3.4)	0.337
Injury severity score	24.0 (17.0-29.0)	25.0 (24.0-25.0)	0.087
Abbreviated injury scale			
Head	3 (0-4)	3 (0-4)	0.004
Neck	0 (0-0)	0 (0-0)	0.258
Face	0 (0-0)	0 (0-0)	0.107
Thorax	0 (0-3)	0 (0-3)	0.836
Abdomen	0 (0-0)	0 (0-0)	0.980
Upper extremity	0 (0-2)	0 (0-2)	0.012
Lower extremity	0 (0-0)	0 (0-0)	0.441
Surface	0 (0-0)	0 (0-0)	0.876
Cervical vertebrae	0 (0-0)	0 (0-0)	0.001
Thoracic vertebrae	0 (0-0)	0 (0-0)	0.270
Lumbar vertebrae	0 (0-0)	0 (0-0)	0.391
Treatment			
Rapid fluid infusion, n (%)	156 (45.7)	381 (44.9)	0.430
Avoid fluid resuscitation, n (%)	50 (14.7)	155 (18.2)	0.078
Aortic clamp, n (%)	5 (1.5)	16 (1.9)	0.414
REBOA, n (%)	23 (6.7)	33 (3.9)	0.028
Surgical hemostatic intervention, n (%)	61 (17.9)	130 (15.3)	0.156
transcatheter arterial embolization, n (%)	52 (15.2)	100 (11.7)	0.064
Tranexamic acid, n (%)	177 (51.9)	380 (44.8)	0.016
Survival at 24 hours (n, %)	320 (93.8)	800 (94.3)	0.416

Outcome			
Survival at 28 days (n, %)	301 (88.2)	765 (90.2)	0.186
Massive transfusion	49 (14.3)	114 (13.4)	0.369
Red blood cell transfusion (mL)	0 (0-560)	0 (0-280)	0.009
Fresh frozen plasma transfusion (mL)	0 (0-900)	0 (0-480)	0.068
Platelet concentrate (mL)	0 (0-0)	0 (0-0)	0.045

Data presented as median (25th-75th percentile), percentage or numbers.

FAST; focused assessment with sonography in trauma, PT-INR; prothrombin time-international normalized ratio, REBOA; Resuscitative endovascular balloon occlusion of the aorta

Table 2. Results of primary and secondary outcomes in the main and subgroup analyses

Main analysis			
	Female (n=226)	Male (n=226)	p Value
Survival at 28 days (n, %)	208 (92.0)	196 (86.7)	0.046
Massive transfusion	34 (15.0)	40 (17.7)	0.263
Red blood cell transfusion (mL)	0 (0-560)	0 (0-280)	0.454
Fresh frozen plasma transfusion (mL)	0 (0-900)	0 (0-480)	0.682
Platelet concentrate (mL)	0 (0-0)	0 (0-0)	0.756
Subgroup analysis (patients aged < 50 years)			
	Female (n=43)	Male (n=43)	p Value
Survival at 28 days (n, %)	39 (90.7)	39 (90.7)	0.644
Massive transfusion	11 (25.6)	9 (20.9)	0.400
Red blood cell transfusion (mL)	0 (0-560)	0 (0-280)	0.787
Fresh frozen plasma transfusion (mL)	0 (0-720)	0 (0-480)	0.855
Platelet concentrate (mL)	0 (0-0)	0 (0-0)	0.890
Subgroup analysis (patients aged ≥ 50 years)			
	Female (n=180)	Male (n=180)	p Value
Survival at 28 days (n, %)	165 (91.7)	155 (86.1)	0.065
Massive transfusion	25 (13.9)	28 (15.6)	0.383
Red blood cell transfusion (mL)	0 (0-560)	0 (0-280)	0.444
Fresh frozen plasma transfusion (mL)	0 (0-720)	0 (0-480)	0.699
Platelet concentrate (mL)	0 (0-0)	0 (0-0)	0.829
Results in unadjusted population			
	Female (n=341)	Male (n=848)	p Value
Survival at 28 days (n, %)	301 (88.3)	765 (90.2)	0.186
Massive transfusion	49 (14.4)	114 (13.4)	0.369
Red blood cell transfusion (mL)	0 (0-560)	0 (0-280)	0.009
Fresh frozen plasma transfusion (mL)	0 (0-900)	0 (0-480)	0.068
Platelet concentrate (mL)	0 (0-0)	0 (0-0)	0.045

Data presented as median (25th-75th percentile), percentage or numbers.