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Age and sex differences in blood product transfusions and mortality in trauma patients at a level I trauma center

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ABSTRACT

Objectives: Hemorrhage is a common complication of trauma. We evaluated age and sex differences in treatment with blood product transfusions and massive transfusions as well as in-hospital mortality following trauma at a Level 1 Trauma Center.

Methods: This cross-sectional study evaluated trauma data from a Level 1 trauma center registry from January 2013 to December 2017. The primary outcome was amount of blood products (packed red blood cells (PRBCs), plasma, platelets), and massive transfusion (MT) by biological sex and by age group: 16-24 (youth), 25-59 (middle age), and >=60 (older age) The secondary outcome was in-hospital mortality to hospital discharge.

Results: There were 13596 trauma patients in the registry, mean age was 48 years, 4589 (34%) female and 9007 (66%) male, and median ISS of 9. Male patients received significantly more PRBC transfusions than female patients within 4-hours 6.6% vs 4.4%, and 24-hours 6.7% vs 4.5% respectively. Older patients received significantly fewer PRBC transfusions within 4-hours and 24-hours than their younger counterparts, with 6.9% in the youth group, 6.8% in the middle age group, and 3.9% in the older group ($p<0.001$). When adjusted for injury severity, the odds of receiving a blood transfusion within 4 hours of injury was significantly lower in older females. Using multivariate analysis, predictors of mortality included (in order of significance) injury severity, older age, transfusion within 4 hours of injury, penetrating trauma, and male sex.

Conclusion: In this large trauma cohort, older female trauma patients were less likely to receive blood products compared to younger females and to their older male counterparts, even after adjusting for injury severity. Predictors of mortality included injury severity, older age, early transfusion, penetrating trauma, and male sex. Following trauma, older women appear vulnerable to undertreatment. Further study is needed to determine the reasons for these differences and their impact on patient outcomes.

1. Introduction

Timely management of hemorrhage in the acute trauma setting is critical [1,2]. Balanced blood component transfusion resuscitation with packed red blood cells, fresh frozen plasma, and platelet concentrates is a potentially life-saving intervention in the

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resuscitation of a trauma patient but is not administered homogenously [3]. It also carries risk of complications such as coagulopathy, hypothermia, citrate toxicity, volume overload, and metabolic derangements [4,5]. Despite these risks, transfusions can improve chances of survival and massive transfusions of packed red blood cells (>10 units of in a 24-h period) may be required [2,6].

There is controversy surrounding the topic of sex differences in trauma treatment and outcome. Preclinical models of hemorrhagic shock have suggested that females are more resistant to shock than males and exogenous estrogens have even been suggested as possible adjuvant treatment for hemorrhagic shock [7–14]. However, many clinical studies, including large multicenter clinical cohorts, do not support this observation [15–19]. In a recent study severely injured trauma patients in shock there was no significant association between female sex and mortality, ICU admission, mechanical ventilation, other complications and packed red blood cells transfusion [18]. Interestingly, studies in female trauma patients have found that severely injured females have a more hypercoagulable profile than males [19], but these sex differences in coagulation profile do not result in a survival advantage for females who require massive transfusions [17].

Many studies on trauma transfusion protocols focus on young trauma patients [20] and very few address trauma in the elderly [21]. In addition to injury severity scores and massive transfusion, factors that impact the elderly such as comorbidities, dementia, and restrictive advanced directives are all associated with earlier trauma mortality [22]. Elderly patients may have relatively minor mechanisms of injury and benign clinical presentations yet harbor significant injuries. Elderly trauma patients have been observed to suffer more bleeding complications than their younger counterparts and therefore, an increased likelihood of requiring blood products [23]. There are important benefits to treating elderly using an evidence-based approach. In a retrospective cohort analysis, older trauma patients receiving massive transfusion a 1:1 ratio of PRBCs to FFP were more likely to survive than when other transfusion ratios were used [21,24]. Even massive transfusions for elderly patients with multiple injuries have been shown to reduce mortality and improve outcome [24–26].

Given the controversies surrounding age and sexes differences in trauma care as well as the differences in transfusion rates that have been observed in patients of varying ages and sex, it is important to explore these relationships further in different trauma populations. Additionally, many trauma studies evaluate age and sex differences separately. Therefore, the objective of this study was to investigate the association between sex, age, and number of blood product transfusions/massive transfusions among trauma patients presenting to a level one trauma center. Factors associated with mortality outcome in these patients were also assessed.

2. Methods

2.1. *Design and setting*

This retrospective cross-sectional study evaluated trauma data from a state-accredited Level 1 Trauma Center Registry from January 2013 to December 2017. The trauma center is an is an 898-bed surgical, medical, rehabilitation and emergency acute-care academic medical center in downtown Orlando, Florida with ACGME accredited emergency medicine and general surgery residency programs. It is one of the largest tertiary facilities in the region and sees approximately 100,000 ED visits per year. This trauma center is located in the southeastern United States. The study was granted a waiver of consent by the Orlando Health Institutional Review Board (approval 2061536-1).

2.2. *Population*

Inclusion criteria for entry into the database were all trauma patients aged 16 years or older presenting to the emergency department with traumatic injuries who required inpatient admission with a length of stay greater than or equal to 24 h. Patients were excluded if they were under 16 years old, discharged from the ED, or inadvertently left out of the registry.

2.3. *Measures*

Demographic (age, biological sex, race/ethnicity), injury severity scores, transfusion, and outcome parameters for all adult male and female patients were collected from the Trauma Registry and placed into a Microsoft Excel (Microsoft Corporation, Washington, United States) spreadsheet. Injury severity was classified by the injury severity score (ISS) and the Glasgow Coma Scale Score (GCS). The mechanism of injury was either blunt or penetrating. Blunt injuries were the result of direct contact of a blunt object with the body whereas penetrating trauma was defined as injury caused by stabbing or gunshot wounds.

2.4. *Outcome measures*

The main outcome measures were treatment with blood products including packed red blood cells (PRBCs), plasma, platelets, and massive transfusion (MT) defined by 10 or more units of PRBCs in 24 h [27]. Blood product use was compared in different age groups: 16–24 (youth), 25–59 (middle age), and ≥ 60 (older age) as well as by biological sex (male vs female). Although sex and gender are often used interchangeably, we used the term “sex” as it includes the biological attributes based on reproductive organs and chromosomes complement (gender reflects non-biological traits and behaviors ascribed to men and women) [28]. The secondary outcome was in-hospital mortality and patients were divided into survivors and non-survivors.

2.5. Data analysis

Data were analyzed using frequencies and means with 95% confidence intervals (CIs). Median and interquartile ranges (IQR) were given for skewed distributions. Univariate data analysis was performed to compare differences between groups. Independent sample t-tests with pooled and separate variance along with Mann–Whitney *U* test were used to compare means between two groups. Categorical variables were expressed as proportions and compared using Chi-square tests. Multivariable logistic regression analyses were performed with adjustment for injury severity score (ISS) and penetrating trauma to determine if age and sex were associated with transfusion and mortality. Missing data was not imputed, and only complete cases were included in the analysis. Regression analysis results were expressed as odds ratios (OR) with 95%CIs. Two-sided testing with a p-value <0.05 set as statistically significant. All analyses were performed using the statistical software package SPSS 29.0 (IBM Corporation®, Somers NY).

3. Results

3.1. Sex differences

There were 13,596 trauma patients in the registry, 9,007 (66%) males and 4,589 (34%) females. Mean overall age was 48 years. Male trauma patients were significantly younger than female trauma patients (44 years vs 57 years). There were significantly more Black and Hispanic male patients than female patients (47% vs 33%). The median injury severity score (ISS) was 9 (4–14) in males and 9 (4–10) in females with the average higher in male patients. A larger proportion of male patients had penetrating trauma than female patients (20% vs 6%) and trauma alert activation occurred more frequently in males (50% vs 32%) (Table 1).

Flow diagram of included patients by age, sex and transfusion status is provided in Fig. 1. Overall, 796 (5.9%) patients received PRBC transfusions. Male patients received significantly more PRBC transfusions than female patients at 4 h 6.6% vs 4.4%, and at 24 h 6.7% vs 4.5% respectively (Table 1). Mean PRBC units transfused within 4-h of presentation was 0.46 (95%CI 0.40–0.51) in males and 0.32 (0.20–0.44) in females ($p = 0.02$) (Fig. 2). Mean PRBC units transfused within 24-h of presentation was 1.46 (1.28–1.64) in males and 1.18 (0.61–1.76) in females) ($p = 0.257$).

Plasma and platelets were transfused in higher proportions in males versus females at both 4- and 24-h post injury (Fig. 2). Mean units of plasma within 4-h were 0.59 (0.48–0.70) in males versus 0.34 (0.23–0.44) in females ($p < 0.001$). Mean units of platelets within 4-h were 0.07 (0.05–0.09) in females and 0.12 (0.10–0.14) in males ($p < 0.001$) (Fig. 2).

Of the patients who received PRBCs within 24-h, 594 (4.4%) received less than 10 units and 212 (1.6%) received ≥10 units (massive transfusion; MT). Of the 212 patients who received MT, 167 (78%) were male and 45 (22%) were female.

Table 1
Demographics by gender.

	Male Gender N = 9,007	Female Gender N = 4,589	Total N = 13,596	*P*-Value
Age	43.8 (43.3–44.2)	56.5 (55.8–57.2)	48.1 (47.7–48.4)	<0.001
Race				<0.001
Asian	110 (1%)	85 (2%)	195 (1%)	
Black	2,171 (24%)	743 (16%)	2,914 (21%)	
Hispanic	2,057 (23%)	761 (17%)	2,818 (21%)	
White	4,351 (48%)	2,872 (63%)	7,223 (53%)	
American Indian	7 (0.1%)	5 (0.1%)	12 (0.1%)	
Native Hawaiian	11 (0.1%)	10 (0.2%)	21 (0.2%)	
Other Race	201 (2%)	77 (2%)	278 (2%)	
Unknown	99 (1%)	36 (1%)	135 (1%)	
INJURY SEVERITY				
Blunt Trauma	6,749 (80%)	4,107 (94%)	10,856 (84%)	<0.001
GCS Score				<0.001
3–8	960 (11%)	293 (7%)	1,253 (10%)	
9–12	317 (4%)	112 (3%)	429 (3%)	
13–15	7,328 (85%)	3,926 (91%)	11,254 (87%)	
Injury Severity Score (ISS)				<0.001
Mean	10.6 (10.4–10.9)	9.5 (9.3–9.8)	10.3 (10.1–10.4)	
Median	9 (4–14)	9 (4–10)	9 (4–13)	
Trauma Alert Activation	4,475 (50%)	1,447 (32%)	5,922 (44%)	<0.001
MORTALITY				
Overall Hospital Mortality	587 (6.5%)	211 (4.6%)	798 (5.9%)	<0.001
TRANSFUSIONS				
Received a Blood Transfusion in 4 h	596 (6.6%)	200 (4.4%)	796 (5.9%)	<0.001
Received a Blood Transfusion in 24 h	599 (6.7%)	207 (4.5%)	806 (5.9%)	<0.001
Received Massive Transfusion (≥ 10 Units of blood in 24 h)	167 (1.9%)	45 (1.0%)	212 (1.6%)	<0.001

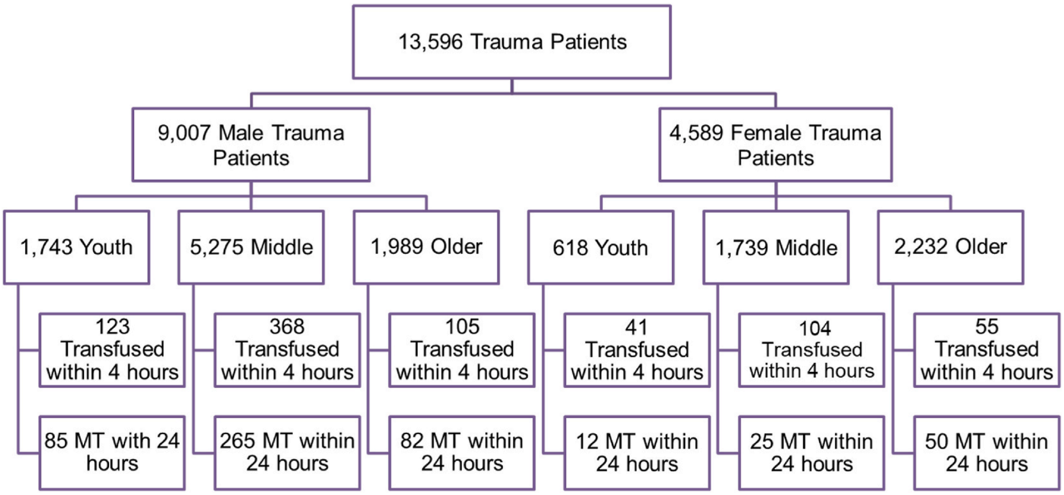


Fig. 1. Flow diagram.

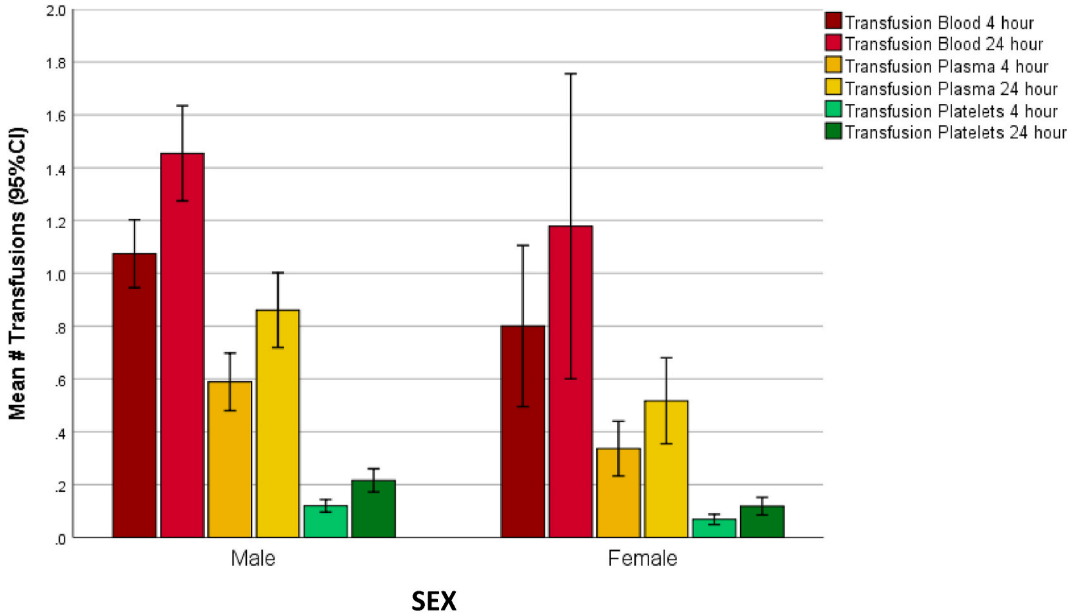


Fig. 2. Number of transfusions by sex.

3.2. Age differences

Of the 13,596 trauma patients, 2,361 were in the youth group (16–24 years), 7,014 in the middle age group (25–59 years), and 4,221 were in the older group ($\geq$60 years) (Fig. 1). The youth group had significantly more penetrating injuries (27%) than the middle (19%) and older age groups (3%) ($p < 0.001$). Median injury severity score by age group was 9 (4–14), 8 (4–14), and 9 (4–10) respectively ($p < 0.001$) (Table 2). Older patients received significantly fewer PRBC transfusions within 4-h and 24-h of presentation than their younger counterparts, with 6.9% in the youth group, 6.8% in the middle age group, and 3.9% in the older group in the same proportions at 4-h and 24-h ($p < 0.001$) (Table 2).

Mean PRBC units transfused within 4-h of presentation was 0.50 (95%CI 0.39–0.61) in youth, 0.51 (0.41–0.60) in middle age, and 0.20 (0.14–0.25) in older ($p < 0.001$) (Fig. 3). Mean PRBC units transfused within 24-h of presentation was 1.60 (95%CI 1.23–1.97) in youth, 1.60 (1.22–1.98) in middle age, and 0.78 (0.58–0.97) in older ($p = 0.005$) (Fig. 3).

Plasma and platelets were transfused in significantly higher proportions in youth and middle age than older patients at both 4- and 24-h post injury (Fig. 3). Mean units of plasma within 4-h were 0.63 (0.45–0.82) in youth, 0.61 (0.48–0.74) in middle age, and 0.22 (0.14–0.29) in older patients ($p < 0.001$). Mean units of platelets within 4-h were 0.12 (0.08–0.16) in youth, 0.12 (0.09–0.15) in

Table 2
Demographics by age.

	Age Group 16–24 years N = 2,361	Age Group 25–59 years N = 7,014	Age Group ≥ 60 years N = 4,221	Total N = 13,596	*P*-Value
Age	21 (SD 2)	41 (SD 11)	76 (SD 10)	48 (SD 22)	<0.001
Gender (%male)	1,743 (74%)	5,275 (75%)	1,989 (47%)	9,007 (66%)	<0.001
Race					<0.001
Asian	29 (1%)	100 (1%)	66 (2%)	195 (1%)	
Black	748 (32%)	1,727 (25%)	439 (10%)	2,914 (21%)	
Hispanic	586 (25%)	1,666 (24%)	566 (13%)	2,818 (21%)	
White	916 (39%)	3,273 (47%)	3,034 (72%)	7,223 (53%)	
American Indian	2 (0.1%)	5 (0.1%)	5 (0.1%)	12 (0.1%)	
Native Hawaiian	4 (0.2%)	14 (0.2%)	3 (0.1%)	21 (0.2%)	
Other Race	48 (2%)	157 (2%)	73 (2%)	278 (2%)	
Unknown	28 (1%)	72 (1%)	35 (1%)	135 (1%)	
INJURY SEVERITY					
Blunt Trauma	1,653 (73%)	5,264 (81%)	3,939 (97%)	10,856 (84%)	<0.001
GCS Score					<0.001
3–8	263 (12%)	710 (11%)	280 (7%)	1,253 (10%)	
9–12	85 (4%)	226 (3%)	118 (3%)	429 (3%)	
13–15	1,922 (85%)	5,787 (86%)	3,545 (90%)	11,254 (87%)	
Injury Severity Score (ISS)					<0.001
Mean	10.8 (10.4–11.3)	10.4 (10.1–10.6)	9.8 (9.5–10)	10.3 (10.1–10.4)	
Median (IQR)	9 (4–14)	8 (4–14)	9 (4–10)	9 (4–13)	
Trauma Alert Activation	1,353 (57%)	3,465 (49%)	1,104 (26%)	5,922 (44%)	<0.001
MORTALITY					
Overall Hospital Mortality	136 (5.8%)	384 (5.5%)	278 (6.6%)	798 (5.9%)	0.051
TRANSFUSIONS					
Received a Blood Transfusion in 4 h	164 (6.9%)	472 (6.8%)	160 (3.9%)	796 (5.9%)	<0.001
Received a Blood Transfusion in 24 h	164 (6.9%)	478 (6.8%)	164 (3.9%)	806 (5.9%)	<0.001
Received Massive Transfusion (≥ 10 Units of blood in 24 h)	50 (2.1%)	130 (1.9%)	32 (0.8%)	212 (1.6%)	<0.001

*802 patients were not admitted.

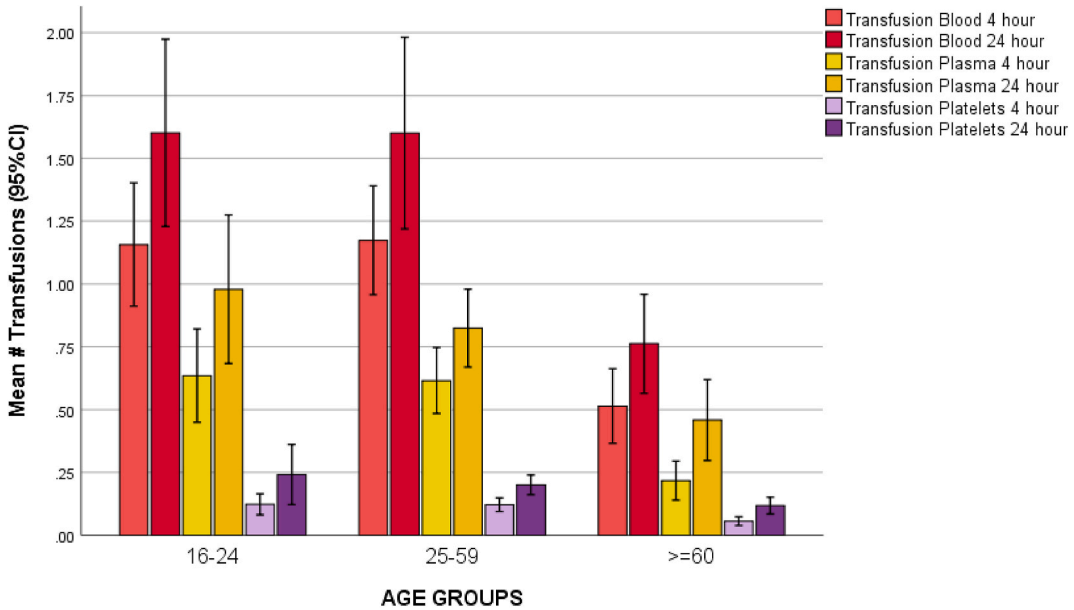


Fig. 3. Transfusions by age groups.

middle age and, 0.06 (0.04–0.07) in older patients (p = 0.004). Mean units of plasma within 24-h were 0.98 (0.68–0.1.27) in youth, 0.82 (0.67–0.98) in middle age, and 0.46 (0.30–0.62) in older patients (p = 0.003). Of the 212 patients who received MT, 50 (23%) were in the youth group, 130 (61%) were in the middle age group, and 32 (15%) in the older group.

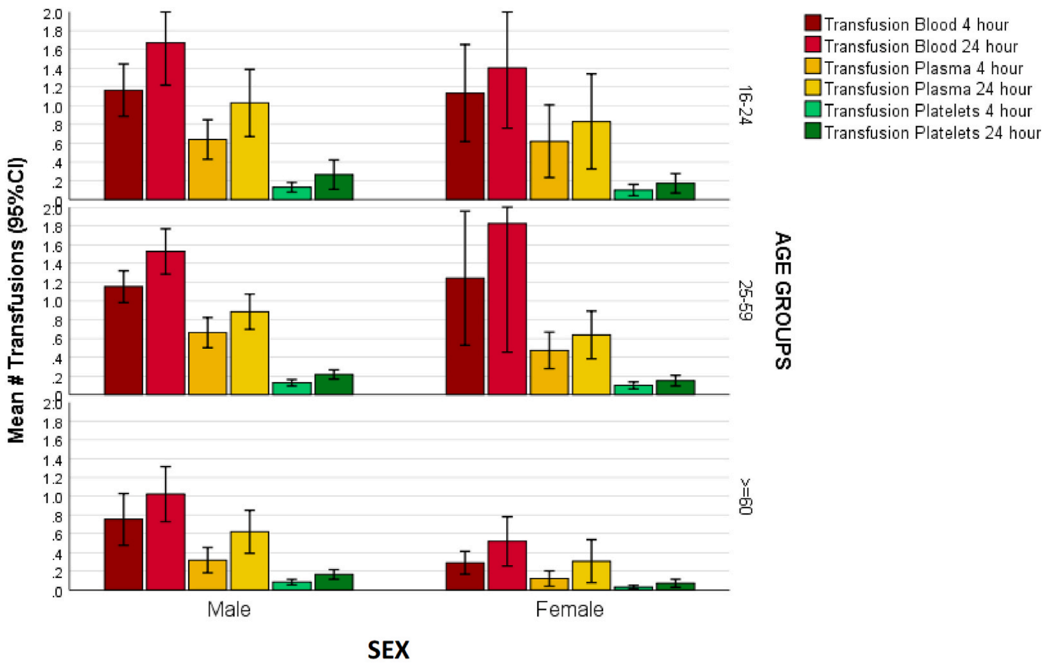
3.3. Sex and age - transfusion and in-hospital mortality

When comparing differences in transfusions of all blood products, the sex differences became insignificant in the youth and middle age groups but remained significantly different in the older age group (Fig. 4). When adjusted for injury severity, the odds of receiving a blood transfusion within 4 h of injury was significantly lower in females OR = 0.774 (95%CI 0.642–0.932) and significantly lower in older patients OR = 0.991 (95%CI 0.987–0.995). However, when adjusted for penetrating injury, sex and age were no longer significant.

Mortality was significantly higher in male (6.5%) than female patients (4.6%) ($p < 0.001$). Mortality was higher in the older age group (6.6%) compared to the middle (5.5%) and younger groups (5.8%) ($p = 0.051$) (eFig. 1). However, mortality differences among the sexes varied significantly by age group. In the youth group mortality in male versus female patients was 6.0% vs 5.0% ($p = 0.421$); in the middle age group 5.7% vs 4.9% ($p = 0.225$) respectively. Mortality in the older age group was 9.2% vs 4.3% respectively ($p < 0.001$) (eFig. 1). There were significantly more transfusions of PRBCs, plasma, and platelets in patients who did not survive to hospital discharge in both sexes and among all age groups (eFig. 1 and eFig. 2) ($p < 0.001$).

Overall, the mean number of units of PRBC transfused was 0.3 (95%CI 0.2–0.3) units in survivors and 4.0 units (95%CI 3.2–4.8) in non-survivors (p 0.001). Among those who received a massive transfusion, mortality was 8.2% in youth, 8.6% in middle age, and 13% in the older age group. When adjusted for injury severity, the odds of receiving a blood transfusion within 4 h of injury was significantly lower in females OR = 0.774 (95%CI 0.642–0.932) and significantly lower in older patients OR = 0.991 (95%CI 0.987–0.995).

Using multivariate analysis, predictors of mortality included (in order of significance) worse injury severity (ISS), older age, requiring a transfusion within 4 h of injury, having penetrating trauma, and male sex (Table 3).



Number of Transfusions versus Sex in different Age groups (p-values)

	AGE 16-24	AGE 25-59	AGE ≥60
PRBC 4 HOURS	NS	NS	0.002
PRBC 24 HOURS	NS	NS	0.012
PLASMA 4 HOURS	NS	NS	0.015
PLASMA 24 HOURS	NS	NS	0.059
PLATELETS 4 HOURS	NS	NS	0.003
PLATELETS 24 HOURS	NS	NS	0.006

***Not statistically significant (p>0.05)**

Fig. 4. Number of transfusions by age and sex.

Table 3
Odds ratios of variables predictive of mortality.

	Wald	OR (95%CI)	Significance
Sex (male)	6	1.30 (1.05–1.59)	0.014
Age	102	1.02 (1.02–1.03)	<0.001
ISS	805	1.12 (1.11–1.13)	<0.001
Penetrating Trauma	63	2.57 (2.03–3.26)	<0.001
Transfusion within 4-h	89	2.99 (2.38–3.75)	<0.001

4. Discussion

In this large retrospective study of over 13,500 trauma patients presenting to a tertiary care level one trauma center, PRBCs, plasma and platelets were transfused in higher proportions in males versus females at both 4- and 24-h post injury. Additionally, all blood products were transfused in significantly higher proportions in youth and middle age than older patients at both 4- and 24-h post injury. When age and sex were factored together, sex differences in transfusion rates became insignificant in the youth and middle age groups but remained significantly different in the older age group. When transfusion rate was adjusted for injury severity, the odds of receiving a blood transfusion within 4 h of injury was significantly lower in females than males and significantly lower in older patients. However, when adjusted for penetrating injury mechanism, transfusion rate discrepancies between sexes and different age groups were no longer significant. Overall, injury severity, older age, early transfusion (within 4 h of arrival), penetrating trauma, and male sex, were all important predictors of in-hospital mortality.

4.1. Sex differences

In this analysis, male sex was a predictor of need for PRBC transfusion and need for massive transfusion. The odds of receiving blood, even when adjusted for ISS, remained lower in the female group. Unlike previous data suggesting that younger, hormonally active women are protected against trauma [9,19], women in the young and middle-aged groups in this cohort did not receive significantly fewer transfusions than men. While women of all age groups tended to receive fewer transfusions, only the older female group reached statistical significance. Whether there is an unconscious bias of transfusing older women less aggressively or whether inherent physiology may play a role in need for fewer transfusions, it is likely that injury pattern and other variables not accounted for in this analysis contribute to the relative fewer transfusions in women, particularly older women [19].

4.2. Age differences

Overall, this study showed that all patients aged 60 years and older received significantly fewer blood transfusions (and massive transfusions) than their younger counterparts with similar injury severity scores (an ISS of only 1 point lower than the younger age groups). They also had trauma alert activation initiated 26% of the time, as opposed to 49%–57% of the time in the younger age groups. This is consistent with another larger study of over 126,000 trauma patients that showed trauma patients over 60 received fewer interventions and that this approach led to increased mortality [29]. It is unclear if there is inherent physician bias toward more aggressive care in younger patients, or whether these differences in transfusion rates could be related to injury mechanism/pattern, complicating comorbidities, or physiologic changes of aging. For instance, heart rate may not reflect serious hemorrhage in this population, a sign that is often used to recognize severity of injury [30]. Moreover, physicians may be less likely to initiate massive transfusion in patients who may have a decreased ejection fraction and would poorly tolerate volume. Nonetheless, massive transfusion protocols have been shown to effectively decrease mortality in elderly trauma patients, especially early in administration [24–27]. In addition, massive transfusion has been shown to improve coagulation function, alleviate organ dysfunction, and shorten the length of ICU stay in elderly populations [31].

It is possible that when caring for elderly patients, physicians may choose a less aggressive strategy due to perceived futility, however this decision may be biased by the age of the patient. According to EAST trauma guidelines, while advanced patient age is associated with poor outcomes, it was not an independent predictor of mortality in trauma and "should not be used as the sole criterion for denying or limiting care." [32].

4.3. Mortality

Women in our study had an increased odds of survival compared to men, but on average women had a lower ISS, were more likely to suffer blunt trauma, and were less likely to result in trauma alert activation. While many factors drive potential sex differences in outcomes after trauma, including injury pattern, hypercoagulability, and risk of subsequent complications such as sepsis and organ failure, this study does not support the premise that female trauma patients have better outcomes than male trauma patients. Prior data evaluating sex differences in mortality and need for blood transfusion after trauma are mixed. In a retrospective review of 6044 trauma patients, George et al. reported a 2.5 times increase in survival rate in pre-menopausal women as opposed to men of similar age and injury severity after blunt trauma [8]. Pape et al. in a review of 6865 polytrauma patients who presented to any of three level 1 trauma centers reported no difference in mortality between men and women, however reported that ISS and ICU admission were significantly greater in men in that cohort [33]. A review of sex disparities in trauma by Marcolini et al. suggests that increased odds for mortality in men may be driven by differing injury pattern or increased risk of subsequent organ failure, sepsis, or pneumonia after trauma [34]. In our cohort, male sex was associated with increased risk for mortality (OR 1.3), but men were more likely to suffer penetrating injury (20% versus 6%), were more likely to have an initial GCS <13 (15% versus 10%), and were more likely to meet criteria for trauma alert activation (50% versus 32%). Which suggests that men had more severe injury patterns than women on average at presentation.

Growing data suggests that age is not an independent risk factor for increased mortality after trauma and elderly patients who otherwise meet criteria for transfusion have better outcomes when transfused aggressively [24–26]. The factors that contribute to increased mortality in older trauma patients are multifactorial and more data are required to further guide clinical practice.

4.4. Limitations

We recognize that there are limitations to our study. This analysis represents data from a single tertiary care level one trauma center and, although may be reflective of other trauma centers in the US, may not reflect practices in non-trauma centers. Our findings were, however, consistent with other recent studies. The number of patients receiving transfusions, relative to the entire cohort, was small. This study was also limited by inherent problems with retrospective trauma registry research.

5. Conclusion

In this large trauma cohort, older female trauma patients were less likely to receive blood products compared to younger females and to their older male counterparts, even after adjusting for injury severity. Predictors of mortality included injury severity, older age, early transfusion, penetrating trauma, and male sex. Following trauma, older women appear vulnerable to undertreatment. Further study is needed to determine the reasons for these differences and their impact on patient outcomes.

Declarations

Funding/support

This study was supported by Award Number R01NS057676 (Papa, PI) from the National Institute of Neurological Disorders and Stroke. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders And Stroke or the National Institutes of Health.

Role of the sponsor

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Ethics approval

This study was approved by the Orlando Regional Medical Center Institutional Review Board in accordance with Federal Regulations for Research in the United States of America. The study was granted a waiver of consent (approval 2061536-1).

Author contribution statement

Linda Papa: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Lindsay Maguire: Analyzed and interpreted the data; Wrote the paper.

Josef G Thundiyil; Jay G Ladde: Contributed reagents, materials, analysis tools or data; Wrote the paper.

Susan A Miller: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

The authors do not have permission to share data.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18890.

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