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# Sex differences in trauma resuscitation: different early treatment patterns of transfusion and fluid therapy without differences in clinical outcome

**Alomar-Dominguez Cristina**
Medical University Innsbruck
**Bachler Mirjam**
Medical University Innsbruck
**Wallner Bernd**
bernd.wallner@i-med.ac.at

Medical University Innsbruck
**Tscholl Pia**
Non-University Research Institution
**Fries Dietmar**
Medical University Innsbruck
**Niederbrunner Daniel**
Medical University Innsbruck
**Stürzel Daniel**
Medical University Innsbruck
**Lichtenberger Philipp**
Medical University Innsbruck
**Jallali Thara**
Medical University Innsbruck
**Argreiter Debora**
Medical University Innsbruck
**Vorhofer Magdalena**
Medical University Innsbruck
**Gebetsberger Jennifer**
UMIT – University for Health Sciences, Hall in Tyrol

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## Abstract

# Purpose

We aimed to investigate sex-related differences in trauma resuscitation while considering physiological characteristics relevant to treatment decisions.

# Methods

In this retrospective single-center study, trauma patients admitted to the intensive care unit (ICU) were analyzed. Sex-related differences in transfusion practices, fluid therapy, and coagulation management were assessed across various pre-ICU and ICU phases. Multivariable regression models adjusted for injury severity and shock parameters were applied. Trigger-adjusted analyses accounted for hemoglobin concentration at emergency department (ED) admission and body weight.

# Results

Among 219 patients, 54 (24.7%) were female. Women had lower body weight and hemoglobin concentrations at ED admission. Female patients received higher weight-adjusted red blood cell (RBC) transfusion volumes in the pre-ICU phase. After additional normalization to hemoglobin concentration at ED admission, female sex remained associated with higher normalized RBC transfusion volumes. Female sex was associated with higher administration of both colloids (β = 3.6 mL/kg, $p = 0.011$) and crystalloids (β = 4.72 mL/kg, $p = 0.008$). Female patients showed a modest increase in cumulative fluid overload (β = 0.55%, $p = 0.023$). Sex was not associated with mortality, and renal findings were not consistent across modeling approaches.

# Conclusion

Sex-related differences in trauma resuscitation were particularly observed during the pre-ICU phase and involved both RBC transfusions and fluid administration. Interpretation of sex-related differences in transfusion practice should account for physiological baseline characteristics, including body size and hemoglobin concentration. Despite differences in early management, sex was not an independent predictor of mortality, which was instead primarily determined by physiological derangement.

## 1. Introduction

Trauma remains a major cause of death and long-term disability, with uncontrolled hemorrhage accounting for a substantial proportion of potentially preventable early deaths after severe injury.[1, 2] Hemorrhagic shock is frequently accompanied by trauma-induced coagulopathy (TIC), which may already be present at hospital admission and is independently associated with increased transfusion

requirements, organ dysfunction, and mortality.[3–5] TIC is a dynamic disorder arising from the interaction of tissue injury and hypoperfusion with endothelial activation, platelet dysfunction, fibrinogen depletion, and dysregulated coagulation and fibrinolysis.[2, 5, 6] These endogenous alterations may be further aggravated during resuscitation by hypothermia, acidosis, and hemodilution, making early hemorrhage control and targeted hemostatic resuscitation central components of contemporary trauma care.[2, 6, 7]

In addition to injury- and treatment-related mechanisms, biological sex may influence the hemostatic response to trauma.[8] Women generally exhibit a more procoagulant profile than men, with reported differences in clot formation kinetics, clot strength, platelet contribution to clot formation, fibrinogen biology and fibrinolytic activity.[8–10] In a thromboelastographic study, women demonstrated shorter clot formation times, greater alpha angles, and higher clot strength than men, suggesting baseline sex dimorphism in coagulation.[9] Clinical trauma studies have similarly reported sex differences in viscoelastic profiles and fibrinolytic phenotypes, although results are not uniform across injury mechanisms and levels of physiological derangement.[8]

The mechanisms underlying these observations are likely multifactorial. Sex hormones may affect platelet reactivity, endothelial function, vascular regulation, and the expression of coagulation and fibrinolytic proteins, while genetic and body-composition differences may further modify the response to hemorrhage and tissue injury.[8, 11, 12]

Whether sex-related physiological differences translate into clinically relevant differences in trauma management or outcome remains uncertain. Some observational studies have reported lower blood-product utilization, lower rates of massive transfusion, or improved survival among women after severe injury, whereas other investigations have found no independent association between sex and mortality after accounting for injury severity and physiological status.[8, 13, 14] A secondary analysis of the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial found sex-related differences in blood-product administration but did not demonstrate an independent mortality difference attributable to sex.[13] The broader trauma literature therefore does not support a uniform female survival advantage or a consistent sex-specific transfusion pattern across all patient populations.[8, 14]

Potential sex differences in trauma care may also reflect variation in clinical treatment rather than biological mechanisms alone. Sex-related disparities have been described in access to trauma services, the use of hemostatic interventions and transfusion practices.[15] However, apparent differences in treatment exposure are difficult to interpret because resuscitation decisions are guided by injury severity, hemodynamic instability, laboratory findings, suspected blood loss, and the clinician’s assessment of the patient’s response to therapy.[7, 15] Differences observed in retrospective datasets may therefore represent biological variation, variation in treatment thresholds, residual confounding, or combinations of these factors.

Physiological baseline characteristics are particularly important when transfusion and fluid administration are compared between women and men. Healthy adult women have, on average, around

12% lower hemoglobin concentrations than men,[16] lower total hemoglobin mass and circulating blood volume as well as smaller body size and body composition.[17] Consequently, identical absolute volumes of RBCs or intravenous fluids result in different clinical responses according to the baseline characteristics.[16, 17]

These methodological considerations may partly explain the heterogeneous findings of previous studies. Many investigations have focused on isolated endpoints such as massive transfusion, coagulation parameters, or mortality, while fewer have examined multiple components of resuscitation across distinct phases of care.[8, 13–15] Furthermore, absolute or weight-adjusted treatment volumes are often interpreted without simultaneously considering hemoglobin concentrations, indicators of hemorrhagic shock, and other physiological characteristics relevant to treatment exposure. This limits the ability to determine whether sex-related differences are confined to early resuscitation or persist during subsequent, more standardized intensive care management.

Therefore, the aim of the present retrospective cohort study was to investigate sex-related differences in trauma resuscitation and clinical outcomes across the pre-ICU and ICU phases of care. We evaluated RBC transfusion, crystalloid and colloid administration, coagulation therapy, cumulative fluid balance, renal outcomes, and mortality while considering established indicators of injury severity, hemorrhagic shock, and physiological derangement. RBC exposure was additionally examined after normalization to hemoglobin concentration at ED admission to provide a complementary physiological perspective on transfusion volume. By evaluating several treatment modalities over time, we sought to determine whether sex-related differences were primarily confined to the early resuscitation phase and whether they were associated with differences in subsequent clinical outcomes.

## 2. Materials and methods

# 2.1. Study design

This retrospective observational study was conducted at the Department of Anaesthesia and Intensive Care Medicine of the Medical University of Innsbruck, Austria. The study included all trauma patients admitted to the intensive care unit (ICU) over a period of around 4 years and 8.5 months, namely from 18.12.2014 to 06.09.2019.

The study adhered to the RECORD (Reporting of studies Conducted using Observational Routinely-collected health Data) recommendations,[18] and the protocol was approved by the local ethics committee of the Medical University of Innsbruck (1399/2020). The study was conducted in accordance with the principles of the Declaration of Helsinki and adhered to the ethical regulations established by the Austrian Medical Association. All patient data were anonymized prior to analysis, and strict confidentiality was maintained throughout the study. Due to the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived.

# 2.2. Participants

All patients admitted to the ICU due to traumatic injury during the study period were eligible for inclusion. Clinical data were collected at predefined time points along the clinical trajectory of trauma care. These included the prehospital phase, defined as data obtained from the external emergency physician or referring hospital, arrival at the emergency department (ED), and the intraoperative period in cases where surgical intervention was performed. Subsequent data collection included the early ICU phase on day 1, which was subdivided into the first 6 hours, the first 12 hours, and the first 24 hours after ICU admission. Additional data were recorded daily for each patient from ICU-day 2 until day 7.

# 2.3. Data collection

Clinical and laboratory data were retrospectively extracted from the institutional electronic medical database and patient data management system.

Collected variables included demographic characteristics such as age, body weight, height, and sex, as well as information on pre-existing medical comorbidities. Trauma characteristics were documented and included the type of trauma (burn injury, blunt trauma, penetrating trauma, or polytrauma). Injury severity was assessed using several established scoring systems, including the Abbreviated Injury Scale and Injury Severity Score (AAAM-ISS), the ISS according to the German Trauma Society (ISS-DGU), and the local institutional ISS classification (ISS-IBK). Additional severity scores recorded at admission included the Trauma Associated Severe Hemorrhage (TASH) score at the ED, the Simplified Acute Physiology Score (SAPS 3) at ICU admission, the Therapeutic Intervention Scoring System (TISS), the Revised Trauma Score (RTS), and the Trauma and Injury Severity Score (TRISS).

Vital parameters and laboratory values were recorded at the predefined clinical time points throughout the study period. These included standard physiological parameters as well as routine blood tests and coagulation parameters obtained during trauma care.

Information on administered therapies during the study period was also collected. This included the transfusion of blood products such as erythrocyte concentrates, thrombocyte concentrates, and fresh frozen plasma. In addition, the administration of coagulation factor concentrates, and hemostatic agents was documented, including fibrinogen and FXIII concentrate, tranexamic acid, prothrombin complex concentrate, antithrombin, recombinant factor VII, factor VIII concentrate, von Willebrand factor concentrate, and desmopressin.

Fluid therapy was recorded as the total administered infusion volume of crystalloids and colloids, including Elo-Mel®, Gelofusin®, hydroxyethyl starch (HES), albumin, sodium chloride (NaCl), Ringer lactate, and Perflux®. Additional medication potentially influencing fluid balance, such as anticoagulation therapy and diuretics, was also documented.

The primary analyses focused on potential sex-related differences in treatment strategies, including the administration of fluids, blood products, and coagulation factor concentrates. Secondary analyses evaluated potential sex-related differences in clinical outcomes, including post-treatment fluid balance parameters (fluid input, fluid output, cumulative fluid balance, and fluid overload), organ dysfunction

assessed by the Sequential Organ Failure Assessment (SOFA) score, the occurrence of acute kidney injury according to KDIGO criteria, and mortality outcomes including ICU mortality, 30-day mortality, and in-hospital mortality.

## 2.4. Statistical methods

All statistical analyses were performed using R, version 4.5.3 at a 5% significance level. Analyses were based on complete cases for each variable; no imputation was performed. Given the exploratory nature of this study, no correction for multiple testing was applied. All results should be interpreted as hypothesis-generating.

For the cohort overview, continuous variables are presented as medians with interquartile ranges (IQR), and categorical variables as counts and percentages. Differences in demographic and baseline characteristics between female and male patients were assessed using the Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables; p-values are reported throughout.

To evaluate sex-related differences in treatment strategies and outcomes across both the pre-ICU phase and the ICU stay (days 1–7), linear and logistic mixed-effects regression models were applied, with patient ID included as a random intercept to account for the autocorrelation arising from repeated measurements within individual patients. Linear mixed-effects models were used for continuous outcome parameters (e.g., fluid administration, transfusion volumes, coagulation factor use), while logistic mixed-effects models were applied for binary outcomes (e.g., SOFA renal component ≥ 2). Models including an additional random intercept for measurement time point (e.g. ICU day) were also evaluated but did not improve model fit and showed unstable convergence; a random-intercept-only structure for patient ID was therefore retained for all models.

In a first step, unadjusted models were fitted with sex as the sole fixed-effect variable. Subsequently, models were adjusted for predefined clinical confounders reflecting injury severity and shock, including the Injury Severity Score (ISS), Trauma Associated Severe Hemorrhage (TASH) score, systolic blood pressure, and base excess, to ensure that observed effects could be attributed to sex rather than confounding factors. Where clinically appropriate, transfusion variables were additionally adjusted for hemoglobin concentration at ED admission, and treatment volumes were normalized to body weight. These adjustments were designed to distinguish true sex-related treatment differences from differences driven by physiological baseline characteristics.

For linear mixed-effects models, beta estimates, standard errors, and p-values are reported; for logistic mixed-effects models, odds ratios and p-values are reported.

Mortality outcomes (ICU, 30-day, and in-hospital mortality) were analyzed using standard logistic regression models without mixed effects. As with the mixed-effects models, unadjusted models were first fitted with sex as the sole predictor, followed by adjusted models including a predefined set of clinical confounders: fluid balance on ICU day 1, age, coagulation comorbidity, arterial lactate, base excess, hemoglobin, shock index, and fibrinogen at ICU admission. Odds ratios and p-values are

reported. Confounders were selected a priori and separately for each outcome, based on clinically plausible pathophysiological pathways, rather than a single uniform set across all models.

# 3. Results

## 3.1. Patient characteristics

A total of 219 patients were included in the analysis, of whom 165 (75.3%) were male and 54 (24.7%) were female (Table 1).

Median age was comparable between groups, with 51 years (IQR 35–63) in males and 51 years (IQR 31.25–69.5) in females ($p = 0.7449$). Female patients were significantly smaller and lighter than male patients, with a median height of 166.5 cm (IQR 163–170) versus 178 cm (IQR 175–183) and a median body weight of 65 kg (IQR 60–75) versus 80 kg (IQR 75–90), respectively (both $p < 0.0001$). Accordingly, BMI was also lower in women (23.59 [IQR 21.97–26.06] vs. 24.84 [IQR 23.88–27.76], $p = 0.0011$).

The cohort represented a severely injured trauma population with comparable injury severity across sexes. Median ISS Score DGU was 22 (IQR 14–34) in male patients and 29 (IQR 17–38) in female patients, without a statistically significant difference between sexes ($p = 0.0792$). Likewise, median TASH score at hospital arrival was 6 (IQR 4–11) in men and 7 (IQR 4–11.5) in women ($p = 0.3723$), indicating a comparable risk of severe hemorrhage. ICU illness severity was also similar, with SAPS 3 values of 47 (IQR 35–60.5) in men and 49.5 (IQR 36.75–60.25) in women ($p = 0.5646$). TRISS scores did not differ between groups either (76.78 [IQR 47.81–95.34] in men vs. 89.4 [IQR 42.23–95.43] in women, $p = 0.974$). RTS categories were likewise not significantly different across sex.

With respect to trauma pattern, no significant sex differences were observed in the frequencies of polytrauma, burn trauma, blunt injury, or penetrating injury. Pre-existing comorbidities were similarly distributed between sexes. However, some injury-location differences were noted: severe abdominal injury was more frequent in women, with AAAM-ISS abdomen grade 5 present in 9.4% of women versus 2.4% of men ($p = 0.0403$), while facial injuries of grade 2 were less frequent in women than in men (1.9% vs. 13.9%, $p = 0.0114$).

Among prehospital vital parameters, women had significantly lower systolic and diastolic blood pressure as recorded by the emergency physician, with systolic values of 105 mmHg (IQR 88–122) versus 120 mmHg (IQR 100–142) in men ($p = 0.016$), and diastolic values of 60 mmHg (IQR 50–76.5) versus 70 mmHg (IQR 60–80), respectively ($p = 0.0184$). Despite this, the proportion of patients receiving vasoactive medication before ICU admission did not differ significantly between groups (80.0% in women vs. 73.8% in men, $p = 0.6241$).

At ED admission, female patients had significantly lower hemoglobin levels than male patients, with a median of 113.5 g/L (IQR 99–125.25) versus 125 g/L (IQR 109–138) ($p = 0.0035$). This difference was no longer present at ICU admission (95.5 g/L [IQR 88.25–103.75] in women vs. 100 g/L [IQR 88–114] in

men, $p = 0.2242$). Creatinine and urea were also lower in women at admission to the ED (creatinine: 0.86 [IQR 0.75–0.97] vs. 1.08 [IQR 0.92–1.25], $p < 0.0001$; urea: 28.2 [IQR 23.92–33.22] vs. 37.2 [IQR 30.75–45.35], $p < 0.0001$), whereas fibrinogen, base excess, lactate, platelet counts, and GFR at admission did not differ significantly between sexes. Platelet counts were significantly lower in women at ICU admission (98 [IQR 58–163] vs. 138.5 [IQR 100.75–179.5], $p = 0.003$).

Table 1
Patient characteristics (total, female versus male).

| Characteristic | Total (n = 219) | Male (n = 165) | Female (n = 54) | *p* value |
|---|---|---|---|---|
| **Age, years** | 51 (34.5–65.5) | 51 (35–63) | 51 (31.25–69.5) | 0.7449 |
| **Weight, kg** | 77 (70–90) | 80 (75–90) | 65 (60–75) | < 0.0001 |
| **Height, cm** | 175 (170–180) | 178 (175–183) | 166.5 (163–170) | < 0.0001 |
| **BMI** | 24.69 (23.15–27.41) | 24.84 (23.88–27.76) | 23.59 (21.97–26.06) | 0.0011 |
| **Polytrauma, n/N (%)** | 161/219 (73.5) | 124/165 (75.2) | 37/54 (68.5) | 0.3756 |
| **Burn trauma, n/N (%)** | 10/219 (4.6) | 7/165 (4.2) | 3/54 (5.6) | 0.7109 |
| **Blunt injury, n/N (%)** | 194/204 (95.1) | 148/154 (96.1) | 46/50 (92.0) | 0.2640 |
| **Penetrating injury, n/N (%)** | 3/201 (1.5) | 3/153 (2.0) | 0/48 (0.0) | 1.0000 |
| **ISS Score DGU** | 24 (16–34) | 22 (14–34) | 29 (17–38) | 0.0792 |
| **TASH score (at ED admission)** | 6 (4–11) | 6 (4–11) | 7 (4–11.5) | 0.3723 |
| **SAPS 3 score** | 47.5 (35.25–60.75) | 47 (35–60.5) | 49.5 (36.75–60.25) | 0.5646 |
| **TRISS score** | 83.06 (45.32–95.44) | 76.78 (47.81–95.34) | 89.4 (42.23–95.43) | 0.9740 |
| **Systolic BP, emergency doctor (mmHg)** | 120 (100–139) | 120 (100–142) | 105 (88–122) | 0.0160 |
| **Diastolic BP, emergency doctor (mmHg)** | 70 (60–80) | 70 (60–80) | 60 (50–76.5) | 0.0184 |
| **Circulation-supporting medication before ICU, n/N (%)** | 86/114 (75.4) | 62/84 (73.8) | 24/30 (80.0) | 0.6241 |
| **Hemoglobin at ED admission, g/L** | 123 (106.5–137) | 125 (109–138) | 113.5 (99–125.25) | 0.0035 |
| **Hemoglobin at ICU admission, g/L** | 98 (88–112) | 100 (88–114) | 95.5 (88.25–103.75) | 0.2242 |
| **Creatinine at ED admission, mg/dL** | 1.02 (0.86–1.21) | 1.08 (0.92–1.25) | 0.86 (0.75–0.97) | < 0.0001 |
| **Urea at ED admission, mg/dL** | 33.9 (28.85–44.15) | 37.2 (30.75–45.35) | 28.2 (23.92–33.22) | < 0.0001 |

| Characteristic | Total (n = 219) | Male (n = 165) | Female (n = 54) | *p* value |
|---|---|---|---|---|
| **Platelets at ED admission, g/L** | 191.5 (156.5–235.25) | 189.5 (156.5–228.5) | 196 (157.75–274.5) | 0.1368 |
| **Platelets at ICU admission, g/L** | 127 (93.5–177) | 138.5 (100.75–179.5) | 98 (58–163) | 0.0030 |
| **Fibrinogen at ED admission, mg/dL** | 220 (170.5–269.75) | 220 (170.5–276.5) | 220.5 (185–247.25) | 0.6412 |
| **Lactate at ED admission, mg/dL** | 21 (12–35) | 21 (12–35) | 21 (15–35) | 0.6366 |
| **BE at ED admission, mmol/L** | -4.4 (-7.4 to -1.58) | -3.95 (-6.83 to -1.35) | -4.65 (-8.15 to -3.4) | 0.2087 |

*Data are presented as median (interquartile range) or number/total number (%). P-values were calculated using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Abbreviations: BE, base excess; BMI, body mass index; BP, blood pressure; ICU, intensive care unit ; ED, emergency department; ICU, intensive care unit; ISS, Injury Severity Score; SAPS 3, Simplified Acute Physiology Score 3; TASH, Trauma Associated Severe Hemorrhage score; TRISS, Trauma and Injury Severity Score.*

## 3.2. Sex differences in trauma transfusion requirements

During the pre-ICU phase (from accident to ICU admission), female patients received significantly higher volumes of red blood cell (RBC) transfusions per kilogram body weight compared to male patients in unadjusted analyses (β = 2.58 mL/kg, standard error = 1.01, $p = 0.012$).

This association remained consistent in multivariable models adjusting for injury severity and physiological parameters (ISS, TASH, systolic blood pressure, and base excess), with female sex being associated with higher weight-adjusted RBC transfusion volumes (β = 3.6 mL/kg, standard error = 1.21, $p = 0.003$; Fig. 1A).

After additional normalization of weight-adjusted RBC transfusion volume to hemoglobin concentration at ED admission (expressed as mL/kg per g/L hemoglobin), female sex remained significantly associated with higher normalized RBC transfusion volumes (β = 0.04 mL/kg per g/L Hb, standard error = 0.01, $p = 0.003$; Fig. 1B).

Overall, transfusion requirements during the pre-ICU phase were primarily associated with clinical indicators of shock, with the TASH score showing a strong association with RBC administration (β = 0.01 mL/kg/Hb, standard error = 0; $p < 0.001$ in weight and hemoglobin adjusted model; β = 0.66 mL/kg, standard error = 0.13; $p < 0.001$ in weight adjusted model), whereas ISS ($p = 0.028$ in weight and hemoglobin adjusted model; $p = 0.076$ in weight adjusted model) and base excess ($p = 0.019$ in weight and hemoglobin adjusted model; $p = 0.064$ in weight adjusted model) showed weaker associations.

During ICU stay (days 1–7), no significant association between sex and RBC transfusion was observed ($p = 0.311$), and this remained unchanged after adjustment for hemoglobin concentration at ED admission ($p = 0.462$).

## 3.3. Sex differences in fluid therapy

To account for differences in injury severity and physiological status, all analyses of fluid administration were performed using multivariable models adjusted for ISS, TASH score, base excess, and systolic blood pressure. Regression coefficients for all models are summarized in Table 2.

**Colloids**

In the pre-ICU phase, female patients received significantly higher volumes of colloids per kilogram body weight compared to male patients (β = 3.6 mL/kg, standard error = 1.41, $p = 0.011$; Fig. 2A). This association remained significant after adjustment for all predefined covariates, indicating that female sex was an independent predictor of increased colloid administration.

Among the covariates, only the TASH score was significantly associated with colloid administration (β = 0.51, standard error = 0.16, $p = 0.001$), reflecting increased fluid requirements in patients with more severe hemorrhagic shock. ISS, base excess and systolic blood pressure were not significantly associated with colloid use in this phase.

During ICU stay (days 1–7), colloid administration was comparable between sexes, with no significant association between female sex and daily colloid volume (β = 0.1 mL/kg/day, standard error = 1.42, $p = 0.942$).

**Crystalloids**

Similarly, in the pre-ICU phase, female patients received significantly higher volumes of crystalloids per kilogram body weight compared to male patients (β = 4.72 mL/kg, standard error = 1.74, $p = 0.008$; Fig. 2B), after adjustment for injury severity and physiological parameters.

In contrast to colloid administration, none of the included covariates (ISS, TASH, base excess or systolic blood pressure) was significantly associated with crystalloid volume in this phase.

During ICU stay (days 1–7), crystalloid administration did not differ significantly between sexes (β = 1.72 mL/kg/day, standard error = 1.36, $p = 0.211$), indicating comparable fluid management under standardized intensive care conditions.

**Fluid accumulation**

Despite largely comparable fluid administration during ICU stay, female patients exhibited a modest but statistically significant increase in cumulative fluid overload compared to male patients (β = 0.55%, standard error = 0.11, $p = 0.023$; Fig. 2C).

Table 2
Linear mixed-effects regression results for fluid therapy during accident to ICU admission and ICU stay (day 1–7): effect estimates for sex and potential confounders.

| Phase | Variable | Estimate (β) | Std. Error | *p* value |
|---|---|---|---|---|
| **Pre-ICU (accident to ICU admission)** | | | | |
| | **Colloids (mL/kg)** | | | |
| | Intercept | 3.95 | 3.15 | 0.211 |
| | Female | 3.60 | 1.41 | 0.011 |
| | ISS DGU | 0.00 | 0.04 | 0.913 |
| | TASH | 0.51 | 0.16 | 0.001 |
| | Base excess | 0.06 | 0.14 | 0.647 |
| | SBP | -0.01 | 0.02 | 0.678 |
| | **Crystalloids (mL/kg)** | | | |
| | Intercept | 8.54 | 3.90 | 0.030 |
| | Female | 4.72 | 1.74 | 0.008 |
| | ISS DGU | 0.05 | 0.05 | 0.330 |
| | TASH | 0.12 | 0.20 | 0.538 |
| | Base excess | 0.29 | 0.17 | 0.096 |
| | SBP | -0.01 | 0.03 | 0.805 |
| **ICU stay (day 1–7)** | | | | |
| | **Colloids (mL/kg/day)** | | | |
| | Intercept | 38.31 | 3.58 | < 0.001 |
| | Female | 0.1 | 1.42 | 0.942 |
| | ISS DGU | -0.03 | 0.04 | 0.454 |
| | TASH | 0.16 | 0.13 | 0.242 |
| | Base excess | -1.58 | 0.18 | < 0.001 |
| | SBP | -0.18 | 0.03 | < 0.001 |

| Phase | Variable | Estimate (β) | Std. Error | *p* value |
|---|---|---|---|---|
| **Pre-ICU (accident to ICU admission)** | | | | |
| | **Colloids (mL/kg)** | | | |
| | **Crystalloids (mL/kg/day)** | | | |
| | Intercept | 14.68 | 2.61 | < 0.001 |
| | Female | 1.72 | 1.36 | 0.211 |
| | ISS DGU | -0.01 | 0.04 | 0.795 |
| | TASH | 0.07 | 0.13 | 0.592 |
| | Base excess | -0.04 | 0.12 | 0.759 |
| | SBP | -0.02 | 0.02 | 0.265 |
| | **Fluid overload (%)** | | | |
| | Female | 0.55 | 0.11 | 0.023 |

*Estimates represent regression coefficients from linear mixed-effects models. Besides sex, injury severity and shock-related parameters were included as potential confounders. Abbreviations: ISS, Injury Severity Score; TASH, Trauma Associated Severe Hemorrhage score; BE, base excess; SBP, systolic blood pressure; ICU, intensive care unit.*

# 3.4. Clinical outcomes

**Renal outcomes**

No consistent association between sex and renal dysfunction was observed across different modeling approaches.

In unadjusted analyses, female sex was not significantly associated with renal impairment as assessed by KDIGO stage (β = 0.23, *p* = 0.101) or SOFA kidney score (β = −0.17, *p* = 0.092).

In multivariable mixed-effects models, sex remained not significantly associated with KDIGO stage (β = −0.14, *p* = 0.337). In contrast, female sex was associated with lower SOFA kidney scores in confounder-adjusted models, indicating better renal function (β = −0.30, standard error = 0.11, *p* = 0.008).

However, this finding was not consistently observed across modeling approaches. In confounder-adjusted logistic regression models assessing clinically relevant renal dysfunction (SOFA kidney ≥ 2),

only a non-significant trend toward a protective effect in female patients was observed (OR 0.037, $p$ = 0.080).

Across models, renal outcomes were primarily associated with physiological parameters rather than sex. Increasing age was consistently associated with worse renal function defined as SOFA kidney ≥ 2 or KDIGO stage ≥ 2 (OR 1.09–1.11, $p \leq 0.031$), while higher hemoglobin levels at admission were associated with a reduced risk of renal impairment (OR 0.91–0.93, $p \leq 0.036$). Fluid overload showed a significant association with renal dysfunction in linear models ($p \leq 0.025$) but not in binary ones (SOFA kidney or KDIGO stage ≥ 2), whereas lactate levels were associated with renal outcomes only for KDIGO stage ≥ 2 (OR = 1.11, $p$ = 0.043).

Pre-existing renal comorbidity, fibrinogen levels, base excess, and shock index were not consistently associated with renal dysfunction.

**Mortality**

In models with and without confounders, no significant differences were observed between male and female patients with respect to ICU, 30-day, or in-hospital mortality (all $p > 0.05$), although a non-significant trend toward lower ICU-mortality in female patients was observed after adjusting for confounders (OR 0.17, $p$ = 0.093).

Arterial lactate at ED admission consistently emerged as the most robust predictor of mortality across all models (OR 1.08–1.09, $p \leq 0.002$).

Fluid balance on ICU day 1 showed a statistically significant but negligible association with ICU-mortality (OR ~ 0.999–1.000, $p$ = 0.021), whereas this effect was not observed for other mortality measures.

Base excess showed a significant association with in-hospital mortality (OR 1.31, $p$ = 0.018), but not in others, indicating limited robustness of this finding.

Other variables, including age, hemoglobin, fibrinogen levels, and shock index, were not independently associated with mortality.

# 4. Discussion

In this retrospective cohort, female patients received higher weight-adjusted and hemoglobin-adjusted volumes of RBC transfusions, crystalloids, and colloids during the pre-ICU phase. These differences were not observed during the subsequent ICU stay. Female sex was also associated with a small increase in cumulative fluid overload, but not with ICU, 30-day, or in-hospital mortality. Renal findings varied according to the outcome definition and statistical model. Overall, the results suggest that sex-related differences in treatment exposure were primarily detectable during early trauma resuscitation, without corresponding differences in the evaluated mortality outcomes.

**RBC transfusion**

Female patients received higher weight-adjusted RBC transfusion volumes before ICU admission, and this association remained statistically significant after adjustment for ISS, TASH score, systolic blood pressure, and base excess. Previous studies have reported heterogeneous sex-related transfusion patterns. The PROPPR secondary analysis found no difference between women and men in blood-product volumes administered during active hemorrhage and no independent difference in early mortality.[13] More recent observational studies have reported lower transfusion rates among women in some trauma populations, particularly among older patients, whereas other analyses of severe trauma have not identified a consistent independent association between sex, transfusion volume, and survival.[19, 20] Taken together, the literature does not support a uniform direction of sex-related differences in transfusion practice. Differences in study populations, injury severity, transfusion protocols, treatment phases, and the expression of transfusion exposure may contribute to the inconsistent findings.

The interpretation of our RBC transfusion results requires consideration of both body size and hemoglobin concentration at ED admission. Women in our cohort were smaller and lighter and had lower hemoglobin concentrations at ED admission than men. Because the same absolute RBC volume represents a greater volume per kilogram in a smaller patient, body weight normalization changes the comparison substantially. In addition, hemoglobin measured at ED admission is clinically relevant to transfusion decisions, although it should not be regarded as a true pre-injury baseline because it may already have been influenced by hemorrhage, fluid shifts, and prehospital treatment.

In an exploratory analysis, weight-adjusted RBC transfusion volume was additionally expressed relative to hemoglobin concentration at ED admission. The association with female sex remained statistically significant on this alternative scale.

To illustrate the magnitude of the observed association, model-based predictions at mean covariate values corresponded to approximately 188 mL of RBCs for a 75 kg male patient with a hemoglobin concentration of 125 g/L at ED admission versus approximately 563 mL for a female patient with the same modeled covariate values. This estimated difference of approximately 375 mL reflects the adjusted sex effect alone, independent of the sex-related differences in weight and hemoglobin observed in the cohort.

The observed difference in RBC exposure may reflect a combination of factors, including body size, hemoglobin concentration at ED admission, circulating blood volume, hemorrhage severity, transfusion thresholds, and clinical decision-making. While the consistency of the association across different expressions of transfusion exposure strengthens the observed treatment pattern, the retrospective design precludes conclusions regarding its underlying mechanism. Future studies incorporating detailed transfusion triggers, estimated blood loss, treatment timing, and product-level data may help distinguish physiological from treatment-related explanations.

**Crystalloid and colloid administration**

Female patients also received higher weight-adjusted volumes of crystalloids and colloids during the pre-ICU phase after adjustment for the measured indicators of injury severity and shock. Unlike RBC transfusion, fluid administration cannot be interpreted directly in relation to hemoglobin concentration. Nevertheless, body size remains important because fixed-volume boluses result in greater mL/kg exposure in smaller patients.

The existing literature provides little direct evidence regarding sex-specific crystalloid or colloid administration in trauma. McKinley and colleagues reported lower crystalloid requirements among women treated within a standardized shock-resuscitation protocol, but their study evaluated absolute in-hospital volumes and is therefore not directly comparable with our weight-adjusted pre-ICU analysis.[21] A recent systematic review of crystalloid versus colloid resuscitation in polytrauma patients identified very limited direct randomized evidence and found no clear difference in 28-day mortality.[22] Accordingly, the present findings add a potentially relevant observation but cannot establish whether the differences arose from patient physiology, dosing practices, or clinical decision-making.

In our study, the higher colloid administration should be interpreted particularly cautiously. The association remained significant after adjustment for the measured severity and shock variables, but this only indicates that it was not accounted for by the covariates included in the model. Residual confounding remains possible. Local practice patterns, the assessment of hypovolemia, fixed-volume administration, transport conditions, or unrecorded changes in hemodynamic status may all have contributed. Biological differences in cardiovascular regulation and vascular responses to hemorrhage are also plausible,[8, 11] but the present study cannot distinguish physiological mechanisms from treatment-related explanations.

**Fluid overload and renal outcomes**

Female sex was associated with a small increase in cumulative fluid overload despite comparable daily fluid administration during the ICU stay. This difference may reflect fluid administered before ICU admission, differences in output, body composition, or other unmeasured factors. Because the absolute effect was small, its clinical relevance remains uncertain.

Renal results were inconsistent. Female patients had lower SOFA kidney scores in one adjusted analysis, but sex was not significantly associated with KDIGO stage, and the binary analysis of clinically relevant renal dysfunction showed only a non-significant association. Previous research has suggested possible sex-related differences in acute kidney injury after severe traumatic shock,[23] but our findings do not provide sufficiently consistent evidence to support either a protective or harmful effect. The renal analyses should therefore be regarded as exploratory, particularly given the limited number of female patients and likely small number of events.

**Mortality**

Sex was not independently associated with ICU, 30-day, or in-hospital mortality. In contrast, arterial lactate was consistently associated with mortality across the evaluated models. This suggests that measured physiological derangement was more strongly associated with outcome than sex in this cohort. However, the observational analysis does not establish a causal role for lactate, which primarily reflects the severity of hypoperfusion and metabolic stress.

Previous studies of sex and trauma survival remain inconsistent. The PROPPR analysis found no independent mortality difference between women and men with severe hemorrhage,[13] whereas other large observational datasets have reported lower mortality among women after adjustment for injury severity and other factors.[14, 19] Recent severe-trauma analyses have likewise not established a uniform female survival advantage.[20] Differences in age, injury mechanism, hormonal status, shock severity, case selection, and treatment systems may explain some of this heterogeneity.

The absence of a significant association in our cohort should not be interpreted as proof of equivalent outcomes. Women represented only approximately one quarter of the study population, limiting statistical power to detect smaller sex-related effects. The treatment differences observed in the pre-ICU phase were therefore not accompanied by detectable mortality differences, but clinically relevant associations cannot be definitively excluded.

**Interpretation and implications**

Female sex was associated with higher exposure to weight-adjusted RBC transfusions, crystalloid, and colloid exposure during the pre-ICU phase, whereas treatment exposure during the ICU stay was comparable between sexes. These associations do not establish a causal effect of sex or evidence of treatment inequity. Their interpretation is influenced by anthropometric characteristics, hemoglobin concentration, transfusion thresholds, fixed-volume dosing practices, and unmeasured treatment indications. No independent association between sex and mortality was identified, while renal findings were inconsistent across analytical approaches.

Future prospective studies should record absolute and weight-adjusted treatment volumes, individual bolus sizes, transfusion units, treatment triggers, estimated blood loss, and physiological changes over time. Larger and more sex-balanced cohorts are needed to distinguish anthropometric, physiological, and treatment-related mechanisms and to evaluate potential interactions with age, menopausal status, injury mechanism, and shock severity.

**Limitations and strengths**

This study has several strengths. First, we provide a comprehensive evaluation of sex differences across both the pre-ICU and ICU phases, enabling differentiation between the early resuscitation period, where treatment decisions are less standardized, and subsequent protocol-driven intensive care management. This temporal perspective is rarely addressed in previous trauma studies and allows a more nuanced interpretation of sex-related treatment patterns.

Second, we used multivariable models incorporating established indicators of injury severity, hemorrhagic shock, and physiological derangement, including ISS, TASH score, systolic blood pressure, base excess, and lactate concentration. In addition, RBC transfusion was evaluated using both weight-normalized volumes and hemoglobin-normalized treatment exposure, providing complementary perspectives on transfusion practice. This analytical approach facilitated interpretation of treatment differences within their physiological context rather than relying solely on absolute treatment volumes.

Third, we evaluated multiple components of trauma resuscitation, including RBC transfusion, crystalloid and colloid administration, cumulative fluid balance, renal outcomes, and mortality. This comprehensive assessment provides a broader understanding of sex-related differences in early trauma care than studies focusing on individual treatment modalities or isolated clinical endpoints.

Several limitations should be considered. First, the retrospective single-center design limits generalizability and precludes causal inference. Although we adjusted for major indicators of injury severity and physiological derangement, residual confounding cannot be excluded, particularly during the pre-ICU phase, where treatment decisions are influenced by factors that cannot be fully captured in retrospective analyses.

Second, the relatively small proportion of female patients reduced statistical power for subgroup analyses and may have limited the detection of more subtle sex-specific associations. Accordingly, findings from analyses based on relatively small event numbers should be interpreted with appropriate caution.

Third, information on hormonal status, menopausal state, or circulating sex hormone levels was unavailable. These factors may influence coagulation, vascular physiology, and the response to traumatic injury and could contribute to heterogeneity within the female cohort.

Finally, some findings—particularly regarding renal outcomes—were not consistent across different statistical models. These discrepancies underscore the importance of interpreting isolated associations cautiously and emphasize the need for prospective studies using standardized treatment protocols and predefined analytical strategies to validate our observations.

# Declarations

### Ethics approval and consent to participate

The study adhered to the RECORD (Reporting of studies Conducted using Observational Routinely-collected health Data) recommendations and the protocol was approved by the local ethics committee of the Medical University of Innsbruck (1399/2020). The study was conducted in accordance with the principles of the Declaration of Helsinki and adhered to the ethical regulations established by the Austrian Medical Association.

### Consent for publication:

All patient data were anonymized prior to analysis, and strict confidentiality was maintained throughout the study. Due to the retrospective nature of the study and the use of anonymized data, the requirement for informed consent was waived.

**Availability of data and material**

The datasets used and analysed during the current study are available from the corresponding author (Bernd Wallner; bernd.wallner@i-med.ac.at ) upon reasonable request.

**Author´s Contributions**

C.A.-D. contributed to data acquisition, the design of the present analysis, and drafted the manuscript. M.B. managed the overall study, including ethics application, study coordination, data acquisition, conceptualization and critical manuscript revision. B.W. contributed to the interpretation of data and manuscript drafting. P.T. contributed to the planning of the statistical analysis, performed the statistical analyses, interpreted the data, and contributed to manuscript drafting. D.F. contributed to the study concept, interpretation of data, and critical revision of the manuscript. D.N., D.S., P.L., T.J., D.A., and M.V. made substantial contributions to data acquisition and critically revised the manuscript. J.G. made substantial contributions to the design of the work and interpretation of data, drafted and critically revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

**Competing interests or conflicts of interest:**

**Declarations of interests**

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# Figures

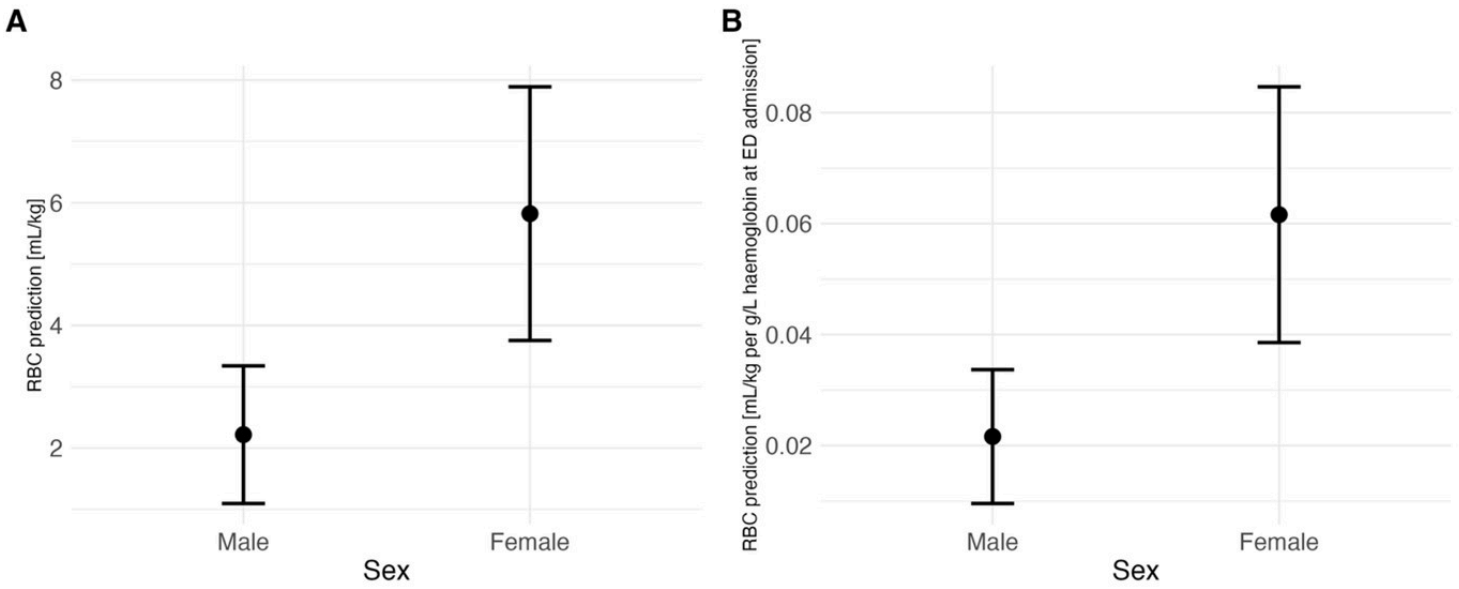



**Figure 1**

**Model-based predicted red blood cell (RBC) transfusion volume during the pre-ICU phase according to sex.** Predicted values are population-level model predictions with 95% confidence intervals derived from multivariable mixed-effects regression models. (A) Predicted RBC transfusion volume per body weight (mL/kg) for females and males. (B) Corresponding predictions after additional adjustment for hemoglobin concentration at ED admission. All continuous covariates (ISS, TASH score, base excess, systolic blood pressure) were held constant at their respective mean values.

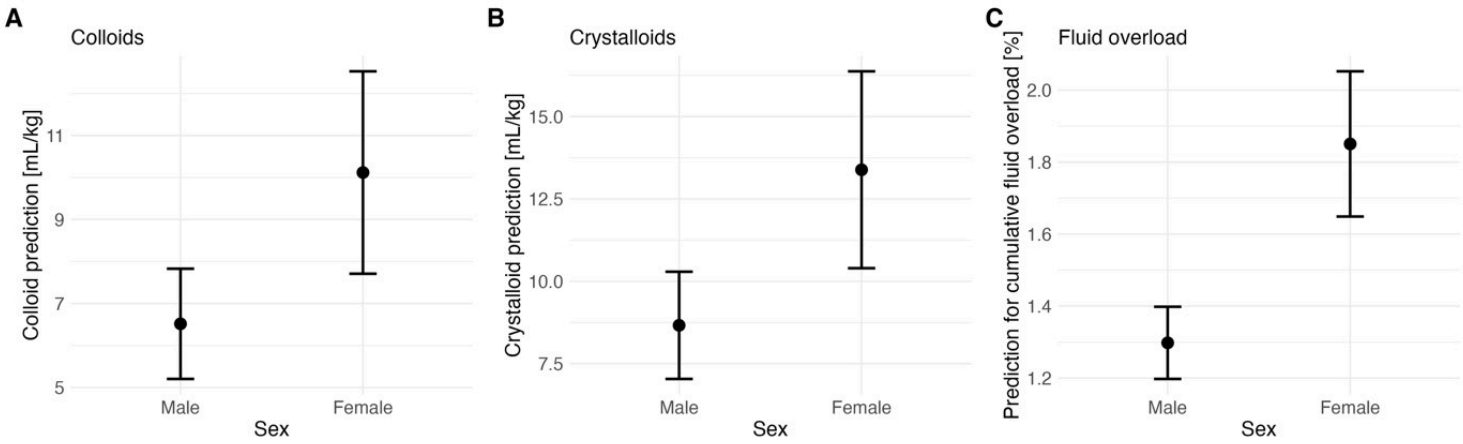



**Figure 2**

**Model-based predicted fluid administration and cumulative fluid overload according to sex.**Predicted values are population-level model predictions (random effects set to zero) with 95% confidence intervals derived from mixed-effects regression models. (A, B) Predicted colloid and crystalloid administration per body weight (mL/kg), respectively, during the pre-ICU phase, with continuous covariates (ISS, TASH score, base excess, systolic blood pressure) held constant at their respective mean values. (C) Predicted cumulative fluid overload (%) during the ICU stay; this model included sex as the only fixed effect, with no further covariate adjustment.