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Fibrinogen is an independent predictor of mortality in major trauma patients: A five-year statewide cohort study

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ABSTRACT

Introduction: Fibrinogen may be reduced following traumatic injury due to loss from haemorrhage, increased consumption and reduced synthesis. In the absence of clinical trials, guidelines for fibrinogen replacement are based on expert opinion and vary internationally. We aimed to determine prevalence and predictors of low fibrinogen on admission in major trauma patients and investigate association of fibrinogen levels with patient outcomes.

Patients and methods: Data on all major trauma patients (January 2007–July 2011) identified through a prospective statewide trauma registry in Victoria, Australia were linked with laboratory and transfusion data. Major trauma included any of the following: death after injury, injury severity score (ISS) >15, admission to intensive care unit requiring mechanical ventilation, or urgent surgery for intrathoracic, intracranial, intra-abdominal procedures or fixation of pelvic or spinal fractures. Associations between initial fibrinogen level and in-hospital mortality were analysed using multiple logistic regression.

Results: Of 4773 patients identified, 114 (2.4%) had fibrinogen less than 1 g/L, 283 (5.9%) 1.0–1.5 g/L, 617 (12.9%) 1.6–1.9 g/L, 3024 (63.4%) 2–4 g/L and 735 (15%) >4 g/L. Median fibrinogen was 2.6 g/L (interquartile range 2.1–3.4). After adjusting for age, gender, ISS, injury type, pH, temperature, Glasgow Coma Score (GCS), initial international normalised ratio and platelet count, the lowest fibrinogen categories, compared with normal range, were associated with increased in-hospital mortality (adjusted odds ratio [OR] for less than 1 g/L 3.28 [95% CI 1.71–6.28, $p < 0.01$], 1–1.5 g/L adjusted OR 2.08 [95% CI 1.36–3.16, $p < 0.01$] and 1.6–1.9 g/L adjusted OR 1.39 [95% CI 0.97–2.00, $p = 0.08$]). Predictors of initial fibrinogen <1.5 g/L were younger age, lower GCS, systolic blood pressure <90 mmHg, chest decompression, penetrating injury, ISS >25 and lower pH and temperature.

Conclusions: Initial fibrinogen levels less than the normal range are independently associated with higher in-hospital mortality in major trauma patients. Future studies are warranted to investigate whether earlier and/or greater fibrinogen replacement improves clinical outcomes.

Introduction

Major bleeding is frequent in patients following major trauma. Massive transfusions are reported in approximately 4–20% [1–5] of major trauma patients, and this is associated with poor outcomes with reported mortality of 7–26% [1–6].

Acute traumatic coagulopathy (ATC) has been demonstrated in 8–50% of trauma patients at hospital admission [1–5], with reported rates varying according to the inclusion criteria and ATC definition. ATC may contribute to major bleeding and requirement for massive transfusion. Fibrinogen is an essential protein for coagulation, and consumption of fibrinogen and fibrinolysis by the action of plasmin are key components of ATC [7]. Fibrinogen is one of the earliest coagulation proteins to fall in major bleeding [8] and fibrin strands that form in a low fibrinogen environment are more susceptible to fibrinolysis [9].

Despite the importance of fibrinogen for clot formation and its role in ATC, there is little evidence to guide clinicians on fibrinogen

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replacement during initial resuscitation. Recent systematic reviews could not identify interventional studies to inform the use of fibrinogen replacement in trauma patients [10,11], and guidelines are based primarily on expert opinion [12–14]. In the presence of active bleeding, recommended thresholds for fibrinogen replacement vary, ranging from plasma fibrinogen of <1 g/L–<1.5–2.0 g/L [12–14]. Whilst there are few data on prevalence or predictors of hypofibrinogenemia in trauma patients, studies have reported association between lower fibrinogen levels and increased mortality [1,15,16]. Furthermore, one recent observational study reported an optimal fibrinogen concentration of 2.29 g/L, showing that levels below this value were associated with reduced odds of death of 0.08 for every unit increase in fibrinogen level [15].

In this study, we aimed to determine the prevalence and predictors of low fibrinogen on admission in a cohort of major trauma patients and to investigate the association of lower fibrinogen with patient outcomes.

Methods

Patients

The Australian state of Victoria (population approximately 5.4 million people [17]) has an inclusive trauma system, with two adult hospitals (the Alfred Hospital and The Royal Melbourne Hospital) designated the major trauma services (equivalent to level-1 trauma centres).

For this study, we used the Victorian State Trauma Registry (VSTR), which prospectively collects data on all major trauma patients in Victoria, to identify patients aged 18 or older who presented to the two major trauma hospitals between January 2008 and July 2011 and who had a fibrinogen level measured during initial resuscitation. The VSTR uses on opt-out consent process, in which all eligible patients are recorded on the VSTR, provided with information regarding the registry, including data collected, and given the opportunity to be removed from the VSTR [18,19]. The VSTR has an opt-off rate of less than 0.1%, ensuring almost complete capture of all major trauma patients in the state [18,19].

Patients with major trauma were defined as those meeting any of the following criteria [19]:

- Death after injury;
- An Injury Severity Score (ISS) >15
- Admission to an intensive care unit (ICU) requiring mechanical ventilation for at least part of their ICU stay
- Urgent surgery for intrathoracic, intracranial, intra-abdominal procedures, or fixation of pelvic or spinal fractures.

Data sources

Data obtained from the VSTR were patient demographics, injury event details (time and mechanism of injury), ISS, Glasgow Coma Scale (GCS), systolic blood pressure (BP) and pulse rate recorded by ambulance and on hospital admission, pH and temperature on admission, in-hospital and 24-h mortality, intensive care unit (ICU) and hospital length of stay (LOS).

Data were obtained electronically from the hospital laboratory information system (LIS) at each of the two hospitals. This included all recorded haemoglobin (Hb) and platelet counts, coagulation studies (including international normalized ratio [INR], activated partial thromboplastin time [aPTT] and plasma fibrinogen levels), arterial blood gas results as well as information on all blood products issued, including type of component and time of issue.

The diagnostic laboratories at the participating hospitals performed the fibrinogen assays, with both using an automated Clauss assay (STA Fibrinogen, Diagnostica Stago Inc.). Both laboratories are accredited pathology providers and participate in external quality assurance programs.

Laboratory data were merged using a unique patient identifier and hospital site with the VSTR. The first laboratory results recorded after admission to hospital within the first 24 h of admission were identified for each patient.

Analysis

Descriptive statistics are reported as mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. Hypothesis testing was performed using Chi Square for categorical data and either *t*-test or Wilcoxon rank sum for continuous data depending on data distribution. Fibrinogen was categorised as <1 g/L, 1.0–1.5 g/L, 1.6–1.9 g/L, 2.0–4.0 g/L (reference category) and >4 g/L to incorporate the normal reference range, as well as the commonly used thresholds for fibrinogen supplementation [12–14]. The GCS was categorised according to clinical convention with 3–8 representing severe, 9–12 moderate and 13–15 a mild head injury. Temperature and pH were categorised according to normal ranges, with categories for below, within and above the normal range. Platelet count was categorised according to normal range, with categories for below normal range, and INR was categorised according to normal range, with categories for above normal range. Patient age and ISS were categorised into quintiles. Patients were categorized as having received a massive transfusion if they had received 10 or more units of red blood cells (RBC) during the admission.

The association between first fibrinogen levels and in-hospital mortality was modelled using multiple logistic regression. Variables considered for the multivariable models were identified *a priori,* based on previous literature, and included age, gender, ISS, pH, temperature, GCS, injury type (blunt, penetrating, other), chest decompression, pulse and systolic BP on admission, time from injury to admission, Hb, platelet count, INR, aPTT and fibrinogen level. As there were a high proportion of patients with missing values, we including a missing category for those variables with high missing rates (>5% of patients). The relationship was modelled in two ways, with fibrinogen treated as a continuous variable, and categorised as outlined above. The models were constructed using both stepwise selection and backwards elimination techniques before undergoing a final assessment for clinical and biological plausibility. Predicted mortality across the range of fibrinogen values was estimated using multiple logistic regression. The association between hospital and ICU LOS in survivors was modelled using linear regression with ICU LOS log-transformed.

Sensitivity analysis for the association between mortality and fibrinogen levels was performed. As there were a high proportion of patients with missing values, we repeated our regression analysis using only patients with complete data to assess if the inclusion of missing category altered the findings of the regression analysis.

Predictors for low fibrinogen (defined as <1.5 g/L) on initial presentation were modelled using multiple logistic regression, including categories for missing values as in the mortality model.

To increase the robustness of the study, a two-sided p-value of <0.01 was used to indicate statistical significance.

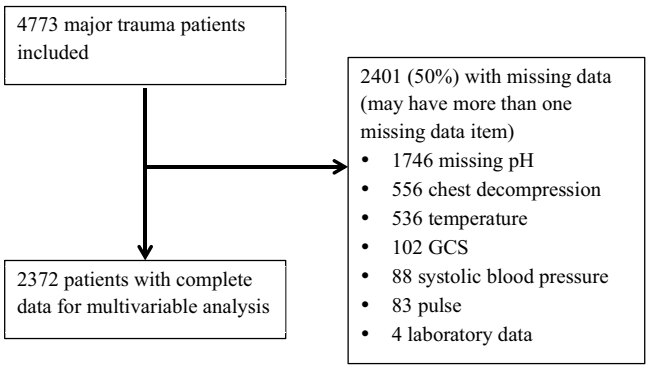

Fig. 1. Patient inclusion flow chart.

All analyses were performed using Stata/IC Version 12 (StataCorp TX USA).

The study had approval from the Alfred Hospital, Royal Melbourne Hospital and Monash University human research ethics committees.

Results

There were 4773 patients identified during the study period who met the inclusion criteria. Fig. 1 shows patient inclusion flow chart, including the variables with missing values. The most commonly missing variables were pH, followed by chest decompression and temperature on admission. Patient characteristics are shown in Table 1.

Fibrinogen levels

There were 114 (2.4%) patients who had a level less than 1 g/L, 283 (5.9%) who had a level 1–1.5 g/L, 617 (12.9%) who had a level 1.6–1.9 g/L, 3024 (63.4%) who had a level 2–4 g/L and 735 (15%) who had a level >4 g/L. Median fibrinogen level was 2.6 g/L (interquartile range 2.1–3.4). Patient characteristics according to initial fibrinogen level are shown in Table 1. Patients with lower fibrinogen levels were younger, had greater injury severity and were more likely to have lower BP, pH, temperature, GCS and higher pulse. They were also more likely to have lower Hb and

Table 1
Patient characteristics according to fibrinogen category.

Characteristic	All patients	Less 1 g/L	1-1.5 g/L	1.6–2.0 g/L	2.1–4.0 g/L	Greater than 4 g/L	p-value
Number (%)	4773 (100)	114 (2)	283 (6)	617 (13)	3024 (63)	735 (15)	
Age in years, median (IQR)	42 (26, 62)	31 (22, 49)	34 (23, 51)	31 (22, 49)	42 (26, 60)	61 (43, 77)	<0.01
Female gender (%)	1185 (24.8)	32 (28.1)	60 (21.2)	135 (21.9)	734 (24.3)	224 (30.5)	<0.01
Pre-hospital IV fluids (%)	2581 (54.2)	82 (81.2)	222 (82.5)	437 (77.6)	1579 (59.3)	261 (43.0)	<0.01
Time injury to admission, hours, median (IQR)	1.12 (1.32, 8.1)	1.79 (1.2, 4.35)	1.95 (1.33, 3.77)	1.88 (1.3, 4.17)	2.06 (1.28, 7.68)	6.47 (1.45, 23.53)	<0.01
Injury severity score, median (IQR)	17 (14, 26)	34 (25, 43)	27 (19, 38)	22 (17, 33)	17 (14, 25)	17 (13, 21)	<0.01
ISS >15 (%)	3312 (69.4)	105 (92.1)	248 (87.6)	500 (81.0)	2002 (66.2)	457 (62.2)	<0.01
SBP <90 mmHg	196 (4.2)	32 (29.9)	51 (18.3)	41 (6.8)	67 (2.2)	5 (0.7)	<0.01
Missing	88 (1.8)	7 (6.1)	5 (1.8)	11 (1.8)	45 (1.5)	20 (2.7)	
Pulse >100 bpm (%)	1748 (37.3)	83 (75.5)	178 (64.3)	314 (51.6)	991 (33.3)	182 (25.5)	<0.01
Missing	83 (1.7)	4 (3.5)	6 (2.1)	8 (1.3)	45 (1.5)	20 (2.7)	
GCS (%)							
3–8	1319 (28.2)	72 (66.7)	160 (57.8)	266 (44.0)	732 (24.7)	89 (12.5)	<0.01
9–12	226 (4.8)	8 (7.4)	16 (5.8)	39 (6.4)	123 (4.1)	40 (5.6)	
>12	3126 (66.9)	28 (25.9%)	101 (36.5)	300 (49.6)	2112 (71.2)	585 (81.9)	
Missing	102 (2.1)	6 (5.3)	6 (2.1)	12 (1.9)	57 (1.9)	21 (2.9)	
pH (%)							
< 7.25	709 (23.4)	72 (64.9%)	124 (46.3)	167 (32.6)	313 (17.0)	33 (11.2)	<0.01
7.25–7.34	1377 (45.5)	23 (20.7)	107 (39.9)	220 (42.9)	900 (48.9)	127 (43.2)	
7.35–7.45	837 (27.7)	15 (13.5)	33 (12.3)	119 (23.2)	547 (29.7)	123 (41.8)	
>7.45	104 (3.4)	1 (0.9)	4 (1.5)	7 (1.4)	81 (4.4)	11 (3.7)	
Missing	1746 (36.6)	3 (2.6)	15 (5.3)	104 (16.9)	1183 (39.1)	441 (60.0)	
Temperature (%)							
<35 °C	428 (10.1)	35 (44.9)	70 (30.4)	101 (18.1)	204 (7.5)	18 (2.8)	<0.01
35–36.5	1732 (40.9)	32 (41.0)	104 (45.2)	239 (42.9)	1141 (41.9)	216 (33.4)	
36.6–37.5	1782 (42.1)	10 (12.8)	48 (20.9)	181 (32.5)	1204 (44.2)	339 (52.5)	
>37.5	295 (7.0)	1 (1.3)	8 (3.5)	36 (6.5)	177 (6.5)	73 (11.3)	
Missing	536 (11.2)	36 (31.6)	53 (18.7)	60 (9.7)	298 (9.9)	89 (12.1)	
Injury type (%)							
Blunt	4324 (90.6)	101 (88.6)	249 (88.0)	552 (89.5)	2731 (90.3)	691 (94.0)	<0.01
Penetrating	233 (4.9)	12 (10.5)	22 (7.8)	28 (4.5)	149 (4.9)	22 (3.0)	
Burns	184 (3.9)	1 (0.9)	11 (3.9)	35 (5.7)	118 (3.9)	19 (2.6)	
Other	32 (0.7)	0 (0.0)	1 (0.4)	2 (0.3)	26 (0.9)	3 (0.4)	
Hb, g/L mean (SD)	129 (23)	86 (27)	102 (27)	121 (25)	134 (19)	131 (20)	<0.01
Platelet count × 10^9/L, mean (SD)	229 (79)	125 (73)	176 (77)	214 (77)	237 (74)	247 (84)	<0.01
Abnormal coagulation studies[a] (%)	1364 (28.6)	111 (97.4)	253 (89.4)	334 (54.1)	539 (17.8)	127 (17.3)	<0.01
One or more RBC (%)	1560 (32.7)	97 (85.1)	203 (71.7)	324 (52.5)	800 (26.5)	136 (18.5)	<0.01
One or more PLT (%)	507 (10.6)	80 (70.2)	112 (39.6)	122 (19.8)	169 (5.6)	24 (3.3)	<0.01
One or more FFP (%)	782 (16.4)	96 (84.2)	162 (57.2)	200 (32.4)	287 (9.5)	37 (5.0)	<0.01
One or more Cryo (%)	424 (8.9)	90 (78.9)	131 (46.3)	115 (18.6%	85 (2.8)	3 (0.4)	<0.01

IQR – interquartile range; SBP – systolic blood pressure; bpm – beats per minute; GCS – Glasgow Coma Scale; ISS – Injury Severity Score; SD – standard deviation; RBC – red blood cell; PLT – platelet; FFP – fresh frozen plasma.

[a] Defined as INR >1.2 and/or APTT time above laboratory reference range; Reported for non-missing.

Table 2
Patient outcomes according to fibrinogen level on admission.

Outcome	Less 1 g/L	1–1.5 g/L	1.6–2.0 g/L	2.1–4.0 g/L	Greater than 4 g/L	p-value
Massive transfusion	63 (55.3%)	93 (32.9%)	104 (16.9%)	124 (4.1%)	12 (1.6%)	<0.01
ICU LOS days[a], mean (95% CI)	8 (6, 11)	7.5 (6, 9)	6 (5, 7)	5 (4, 5)	5 (4, 5)	<0.01
Hospital LOS days[a], mean (95% CI)	21 (17, 26)	17 (15, 19)	12 (11, 13)	8 (8, 9)	9 (8, 10)	<0.01
24-h mortality	36 (31.6%)	29 (10.2%)	24 (3.9%)	44 (1.5%)	3 (0.4%)	<0.01
In-hospital mortality	54 (47.4%)	71 (25.1%)	77 (12.5%)	186 (6.2%)	53 (7.2%)	<0.01

ICU – intensive care unit; LOS – length of stay.
[a] Restricted to patients who survived until hospital discharge.

platelet counts, abnormal coagulation results and to require transfusion of RBC, fresh frozen plasma (FFP), platelets and cryoprecipitate.

Fibrinogen levels and outcomes

Observed 24-h and in-hospital mortality according to fibrinogen levels are shown in Table 2. Patients with lower initial fibrinogen levels had higher in-hospital and 24-h mortality in comparison with those patients with a fibrinogen in the normal range. Patients with lower fibrinogen were more likely to receive a massive transfusion and had longer hospital and ICU LOS than survivors (see Table 2).

After adjusting for age, gender, ISS, injury type, pH, temperature, GCS, initial INR and platelet count, the odds ratio for every 1 g/L increase in fibrinogen was 0.86 (95% CI 0.76–0.97, p = 0.01). The predicted probability of death as a function of fibrinogen levels is shown in Fig. 2.

When considering fibrinogen as a categorical variable, the two lowest fibrinogen categories were associated with increased risk of death after adjustment compared with the reference category (2–4 g/L): fibrinogen <1 g/L adjusted OR 3.28 (95% CI 1.71–6.28, p < 0.01), 1–1.5 g/L adjusted OR 2.08 (95% CI 1.36–3.16, p < 0.01). Fibrinogen 1.6–1.9 g/L was not associated with in-hospital mortality (adjusted OR 1.39 (95% CI 0.97–2.00, p = 0.08, see Fig. 3)). The full model results are shown in Table 3. When compared against fibrinogen concentration above the normal range (>4 g/L), the two lowest fibrinogen categories had significantly greater risk of death: fibrinogen <1 g/L adjusted OR 3.16 (95% CI 1.52–6.61, p < 0.01), 1–1.5 g/L adjusted OR 2.01 (95% CI 1.17–3.45, p < 0.01). Fibrinogen remained associated with mortality at each stage of the model construction.

Finally, repeating the complete case analysis did not alter the association between fibrinogen and mortality (see Appendix A).

Predictors for low fibrinogen

Patient and injury factors independently associated with an initial fibrinogen level less than 1.5 g/L in multivariable analysis were younger age (less than 25 years OR 1.99 [95% CI 1.35–2.94, p < 0.01] and 26–40 years OR 1.59 [95% CI 1.07–2.35, p = 0.02] with age >60 reference), lower GCS (GCS 3–8 OR 1.80 [95% CI 1.34–2.42, p < 0.01] and 9–12 OR 1.78 [95% CI 1.03–3.06, p = 0.03] with >12 reference), systolic BP <90 mmHg (OR 3.43 [95% CI 2.27–5.19, p < 0.01]), chest decompression (OR 1.77 [95% CI 1.25–2.50, p < 0.01]), penetrating injury (OR 1.89 [95% CI 1.07–2.50, p = 0.02] compared with blunt injury as reference), ISS greater than 25 (OR 2.29 [95% CI 1.40–3.74, p < 0.01]), pH <7.25 (OR 2.64 [95% CI 1.79–3.88, p < 0.01] with pH 7.35–7.45 reference) and temperature less than 35 (OR 2.60 [95% CI 1.77–3.85, p < 0.01]) and 35–36.5 °C (OR 1.60 [95% CI 1.14-2.25, p < 0.01, with temperature 36.5–37.5 °C reference).

Discussion

In this multi-centre study of major trauma patients with recorded fibrinogen levels identified through an inclusive trauma registry, we have confirmed that lower fibrinogen levels are

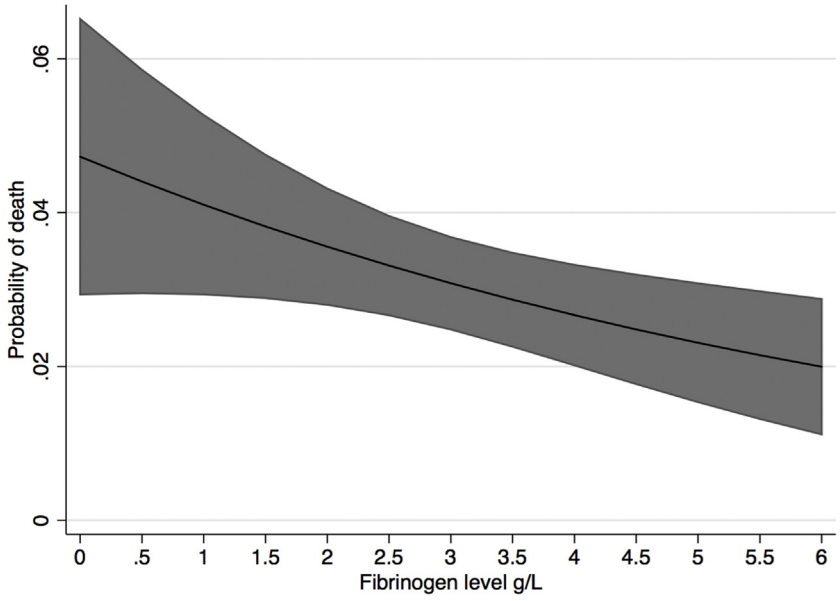

Fig. 2. Adjusted odds ratio for in hospital mortality by fibrinogen category.

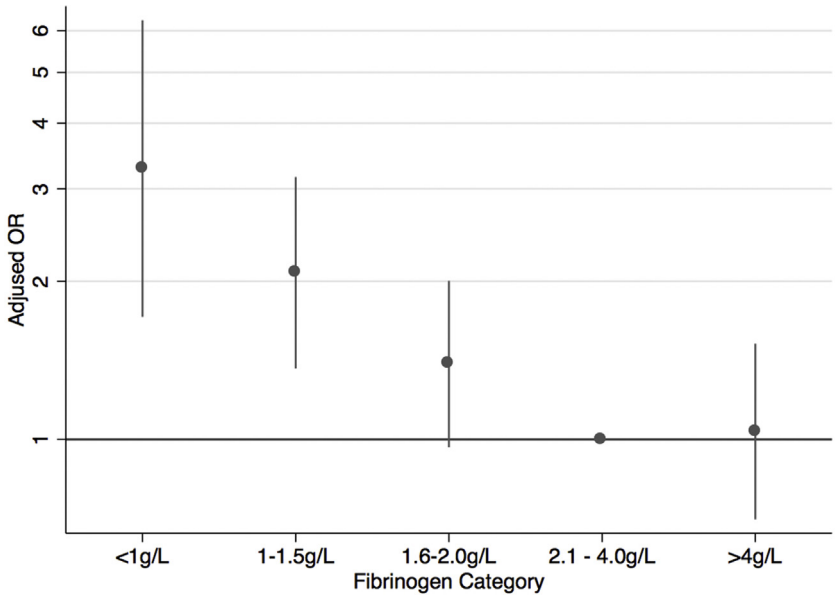

Fig. 3. Predicted adjusted mortality according to fibrinogen level on admission.
Probability of death as a function of fibrinogen level on admission, adjusted for ISS, injury type, age, GCS, pH, temperature, gender and INR. Probability shown at mean values for the other variable.

associated with increased risk of in-hospital mortality, massive transfusion and longer ICU LOS in survivors. The association with in-hospital mortality remained after adjusting for potential confounders. We also identified that younger age, worse GCS, lower systolic BP, chest decompression, penetrating injury, higher ISS, lower pH and temperature were all independent predictors of lower fibrinogen on presentation.

Comparison with the literature

Our findings support previous studies that have reported associations between fibrinogen level and mortality. Rourke et al. in a prospective cohort of 517 trauma patients who met local criteria for a trauma team activation reported an association between fibrinogen levels (treated as a continuous variable) and mortality (OR 0.22, 95% CI 0.10–0.47) after adjusting for injury severity, systolic blood pressure, base deficit, aPTT, gender, age and mechanism of injury. Hagemo et al. in a prospective study of 1133 major trauma patients from four centres reported an association between fibrinogen and mortality after adjusting for ISS, age, time from injury, mechanism of injury, base excess, INR, platelet count and gender. The patient cohort was similar to our current study, with a mean fibrinogen level of 2.6 g/L and 8% of patients with a level $\leq$1.5 g/L on presentation. The study authors reported a statistically significant breakpoint for the association at a fibrinogen concentration of 2.29 g/L, with a 90% reduction in the odds of mortality for each unit increase in fibrinogen concentration. In their analysis they were unable to adjust for hypothermia, which is known to be associated with reduced fibrinogen, which they acknowledged may have influenced their results. In a smaller study of 260 patients who had undergone a massive transfusion after injury, Inaba et al. reported that fibrinogen $<$1 g/L was independently associated with 24-h and in hospital mortality [16].

A number of factors can lead to reduced fibrinogen levels in trauma patients. Acute loss of fibrinogen from haemorrhage and dilutional coagulopathy may lead to reduced fibrinogen concentrations. Early decrease in fibrinogen concentration during haemorrhage and before resuscitation has been demonstrated in animal models [20]. A swine model of haemorrhagic shock found that the rate of loss of fibrinogen was greater than the rate of synthesis by the liver [21]. In addition to increased loss, hyperfibrinolysis is a recognised component of ATC [22], with up to 57% of patients showing evidence of moderate fibrinolytic activation in one study [9]. Finally, both acidosis and hypothermia have been shown in animal models to have effects on fibrinogen metabolism. In a swine model, acidosis was shown to result in increased fibrinogen breakdown, with no effects on synthesis [23], whilst hypothermia has been shown to reduce fibrinogen synthesis [24].

In addition to hypothermia and acidosis, we found younger age associated with lower fibrinogen levels. Plasma fibrinogen levels are known to increase with age [25], and this may account for our observation. It may also be due to differences in mechanism and severity of injury in older patients compared with younger patients. We found that greater injury severity, penetrating injury and chest decompression were associated with lower fibrinogen on presentation. Hypotension was associated with lower fibrinogen, and this is consistent with previous studies that have shown association between shock and lower fibrinogen levels [1]. Finally, we found low GCS was associated with low fibrinogen. A previous prospective study of patients with severe traumatic brain injury also found GCS $\leq$8 was an independent predictor of coagulopathy [26].

INR was associated with mortality in our study cohort even after adjusting for fibrinogen level. Peltan et al. reported that higher INR on admission was an independent predictor of mortality in a cohort of 1031 major trauma patients. In their study, using an INR greater than 1.5 (but not 1.2) identified a cohort of patients who experienced worse outcomes, including mortality, massive transfusion, ICU LOS and multi-organ failure. [5] This study did not include fibrinogen in the adjusted analysis, and other studies that have included fibrinogen have not found INR to be independently associated with mortality [15]. However, we found both elevated INR and reduced fibrinogen concentrations were associated with worse mortality. Lower platelet count was associated with in-hospital mortality after adjusting for other factors in our study, similar to a previous study that reported platelet count to be a predictor of mortality [27]. However, that study did not adjust for other coagulation parameters in the analysis, and did show that platelet count was correlated with INR.

Table 3
Variables associated with in hospital mortality including missing category for variables with more than 5% missing rate[a].

	Unadjusted OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Fibrinogen (2.4 g/L reference)				
Less than 1 g/L	13.73 (9.24, 20.41)	<0.001	3.28 (1.71, 6.28)	<0.001
1-1.5 g/L	5.11 (3.75, 6.94)	<0.001	2.08 (1.36, 3.16)	0.001
1.6–1.9 g/L	2.18 (1.64, 2.89)	<0.001	1.39 (0.97, 2.00)	0.08
>4 g/L	1.19 (0.86, 1.63)	0.291	1.04 (0.70, 1.52)	0.86
Age (<24 year reference)				
24–34	0.94 (0.67, 1.33)	0.721	0.93 (0.60, 1.46)	0.76
35–48	0.91 (0.64, 1.29)	0.596	1.24 (0.79, 1.94)	0.36
49–66	1.37 (0.99, 1.88)	0.054	2.51 (1.64, 3.84)	<0.001
>67	3.60 (2.72, 4.77)	<0.001	11.91 (7.88, 18.00)	<0.001
ISS (<12 reference)				
13–16	0.39 (0.26, 0.58)	<0.001	0.70 (0.42, 1.16)	0.17
17–19	0.42 (0.27, 0.64)	<0.001	0.69 (0.41, 1.16)	0.17
20–25	1.32 (0.94, 1.85)	0.113	1.29 (0.83, 2.00)	0.26
>25	3.39 (2.51, 4.58)	<0.001	1.81 (1.19, 2.74)	0.005
Injury type (Blunt reference)				
Penetrating	0.94 (0.61, 1.46)	0.780	1.09 (0.58, 2.07)	0.79
Burns	2.10 (1.43, 3.10)	<0.001	1.41 (0.82, 2.44)	0.21
Other	6.80 (3.36, 13.75)	<0.001	6.69 (2.29, 19.54)	0.001
GCS (>12 reference)				
3–8	11. 04 (8.80, 13.84)	<0.001	7.42 (5.32, 10.36)	<0.001
9–12	5.98 (4.05, 8.82)	<0.001	3.54 (2.16, 5.81)	<0.001
Temperature (36.6–37.5 °C reference)				
<35 °C	9.56 (7.09, 12.89)	<0.001	1.91 (1.28, 2.85)	0.002
35–36.5 °C	2.12 (1.62, 2.79)	<0.001	1.11 (0.80, 1.56)	0.53
>37.5 °C	0.85 (0.46, 1.57)	0.597	0.72 (0.35, 1.50)	0.38
Temperature missing	6.69 (5.02, 8.92)	<0.001	2.40 (1.62, 3.57)	<0.001
pH (7.35–7.46 reference)				
<7.25	3.21 (2.43, 4.23)	<0.001	2.06 (1.39, 3.04)	<0.001
7.25–7.34	1.06 (0.79, 1.39)	0.706	1.25 (0.87, 1.79)	0.23
>7.45	0.96 (0.48, 1.90)	0.898	0. 89 (0.41, 1.92)	0.76
pH missing	0.34 (0.25, 0.47)	<0.001	1.18 (0.75, 1.90)	0.83
INR (<1.5 reference)				
1.5–1.9	10.26 (7.48, 14.05)	<0.001	3.23 (2.12, 4.92)	<0.001
>2.0	13.29 (9.42, 18.74)	<0.001	3.02 (1.82, 5.03)	<0.001
Platelet count (>150 × 10^9/L reference)				
<100	4.44 (3.20, 6.16)	<0.001	0.50 (0.30, 0.84)	0.009
100–150	2.56 (1.97, 3.32)	<0.001	0.98 (0.69, 1.40)	0.91

ISS – Injury Severity Score; GCS – Glasgow Coma Scale; INR – International Normalised Ratio.
[a] 4656 patients included in the analysis.

Strengths and limitations

Our study's strengths include the large sample size, and the inclusion of more than one site and use of a prospective trauma registry to identify all eligible patients, thereby ensuring the generalizability of our findings. The limitations to our study include its retrospective and observational design, meaning that fibrinogen levels were not measured at standard times but instead according to local protocol or clinician preference, which may introduce some variability into the timing of the first fibrinogen level. The large number of patients with missing data may be a source of bias in our study. The two most frequently missing variables were pH and temperature, with pH more likely to be measured and temperature more likely to be missing in those patients with lower fibrinogen level on admission. We attempted to address this by including a category for missing in variables with >5% missing data to allow us to perform the analysis with all cases. Although there are limitations with this approach, using the alternative method of handling missing data with multiple imputations was not possible, as our data clearly did not meet the missing at random assumption. As this is an observational study, we cannot make any conclusions about causality, and while we did make efforts to control for potential confounders, we cannot exclude the omission of other relevant risk factors. Finally, we did not model whether any factors measured after presentation, including changes in laboratory values or fibrinogen supplementation, were associated with patient outcomes. However, this could be explored with future studies which consider such factors as time-varying variables, including fibrinogen supplementation.

Implications for future research

Australian national clinical practice guidelines recommend replacement of fibrinogen after levels fall to <1 g/L, whilst other international guidelines recommend higher thresholds (1.5–2.0 g/L). The finding in our study, and in that by Hagemo et al., of worse patient outcomes associated with below normal range fibrinogen levels, raises the question of whether a trigger of 1 g/L for fibrinogen replacement is too low, and supports the need to study the effects of earlier (i.e. at higher levels) fibrinogen replacement in patients with haemorrhage following trauma. A

small pilot study of early fibrinogen replacement in trauma with cryoprecipitate has recently been published [28], and other studies are underway.

Conclusion

In a large, unselected cohort of major trauma patients, we found low initial fibrinogen concentrations in 21% of patients, and this was associated with increased in-hospital mortality, with a progressive increase in the adjusted OR with decreasing fibrinogen levels. Younger age, lower GCS, systolic blood pressure <90 mmHg, chest decompression, penetrating injury, greater ISS, lower pH and temperature were all associated with lower fibrinogen levels. Studies to investigate the effects of earlier and/or greater fibrinogen replacement on patient outcomes are warranted.

Author contributions

ZM contributed to the study conception and design, acquisition of the data, data analysis and interpretation and drafting the manuscript. EW, PC and DJC contributed to study conception and design, interpretation of the data and critical revision of the manuscript. MB contributed to the data analysis and interpretation and critical revision of the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

The authors have no conflict of interest to disclose.

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Appendix A.

See Table A1.

Table A1
Variables associated with in hospital mortality – complete case analysis.[a]

	Adjusted OR (95% CI)	P-value
Fibrinogen (2.4 g/L reference)		
Less than 1 g/L	4.79 (2.21–10.38)	<0.001
1–1.5 g/L	2.24 (1.39–3.63)	0.001
1.6–1.9 g/L	1.48 (0.99–2.22)	0.06
>4 g/L	0.78 (0.44–1.38)	0.39
Age (<24 year reference)		
24–34	0.79 (0.47, 1.33)	0.38
35–48	1.26 (0.75, 2.11)	0.37
49–66	2.34 (1.44, 3.79)	0.001
>67	11.54 (7.14, 18.65)	<0.001
ISS (<12 reference)		
13–16	0.85 (0.43, 1.70)	0.65
17–19	0.98 (0.51, 1.90)	0.96
20–25	1.78 (1.02, 3.10)	0.043
>25	2.30 (1.36, 3.87)	0.002
Injury type (Blunt reference)		
Penetrating	1.29 (0.59, 2.83)	0.53
Burns	1.36 (0.75, 2.46)	0.31
Other	9.18 (3.02, 27.87)	<0.001
GCS (>12 reference)		
3–8	5.35 (3.68, 7.79)	<0.001
9–12	3.02 (1.55, 5.87)	0.001
Temperature (36.6–37.5 °C reference)		
<35 °C	058 (0.41, 0.83)	0.003
35–36.5 °C	0.45 (0.29, 0.71)	0.001
>37.5 °C	0.48 (0.22, 1.03)	0.06
pH (7.35–7.46 reference)		
<7.25	1.90 (1.24, 2.92)	0.003
7.25–7.34	1.15 (0.78, 1.69)	0.48
>7.45	0.84 (0.36, 1.96)	0.68
INR (<1.5 reference)		
1.5–1.9	2.46 (1.51, 4.01)	<0.001
>2.0	2.43 (1.26, 4.71)	0.008
Platelet count (>150 × 10^9/L reference)		
<100	0.54 (0.30, 0.96)	0.036
100–150	0.77 (0.50, 1.18)	0.23

ISS – Injury Severity Score; GCS – Glasgow Coma Scale; INR – International Normalised Ratio.
[a] 2625 patients included in the analysis.

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