

# Association Between Blood Donor Demographics and Post-injury Multiple Organ Failure after Polytrauma

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**Objective:** To test the hypothesis that blood donor demographics are associated with transfused polytrauma patients' post-injury multiple organ failure (MOF) status.

**Summary of Background Data:** Traumatic shock and MOF are preventable causes of death and post-traumatic hemorrhage is a frequent indication for transfusion. The role of blood donor demographics on transfusion recipients is not well known.

**Methods:** A log-linear analysis accounting for the correlated structure of the data based on our prospective MOF database was utilized. Tests for trend and interaction were computed using a likelihood ratio procedure.

**Results:** A total of 229 critically injured transfused trauma patients were included, with 68% of them being males and a mean age of 45 years. On average 10 units of blood components were transfused per patient. A total of 4379 units of blood components were donated by donors aged 46 years on average, 74% of whom were males. Blood components used were red blood cells (47%), cryoprecipitate (29%), fresh frozen plasma (24%), and platelets (less than 1%). Donor-recipient sex mismatched red blood cells transfusions were more likely to be associated with MOF ( $P = 0.0012$ ); fresh frozen plasma and cryoprecipitate recipients were more likely to experience MOF when transfused with a male (vs female) component ( $P = 0.0014$  and  $<0.0001$ , respectively). Donor age was not significantly associated with MOF for all blood components.

**Conclusions:** Blood components donor sex, but not age, may be an important factor associated with post-injury MOF. Further validation of our findings will help guide future risk mitigation strategies specific to blood donor demographics.

**Keywords:** blood components, blood donor demographics, polytrauma, post-injury multiple organ failure, transfusion

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Injury is a well-established cause of death in the young<sup>1</sup> and its burden is of worldwide public concern.<sup>2</sup> Traumatic shock and subsequent post-injury multiple organ failure (MOF) are potentially preventable causes of death among the severely injured, with MOF being the most common cause of late trauma mortality and associated with excessive resource utilization.<sup>3</sup> Optimisation of blood and blood products transfusion is a focus in trauma care.<sup>4</sup> Transfusion medicine is an evolving speciality<sup>5</sup> with perfectible interventions: transfusions, which are the most frequently performed in-hospital surgical procedures,<sup>6</sup> especially for hemorrhaging patients. Trauma is, in fact, a common and often unquestioned indication for acute transfusion.<sup>7</sup>

The age and sex of the donor of blood components (BC) may affect post-transfusion outcomes, similarly to transfusion-related acute lung injury and storage age.<sup>8</sup> Blood donor characteristics are a recent focus in transfusion medicine<sup>9</sup> and improved transfusion-related outcomes will likely be expected by patients and medical practitioners.

Our objective was to explore the hypothesis that blood donor age and sex were associated with MOF in severely traumatized patients receiving BC.

## METHODS

This population-based study analyzed prospectively collected data from the post-injury MOF database at John Hunter Hospital (JHH), New South Wales, Australia, between December 2005 and December 2014. JHH is the single Level I trauma center for the Hunter New England Local Health District, covering a geographic area of 130,000 km<sup>2</sup>, providing care to ~840,000 residents and admitting ~1500 trauma patients per year. JHH is the only hospital in this region managing polytrauma patients at risk of MOF. All these patients are either primarily admitted or transferred to JHH within 24 hours of injury. Trauma care level is determined by the Royal Australasian College of Surgeons' Trauma Verification Program. Ethics review and approval was obtained from The Hunter New England Human Research Ethics Committee.

Trauma patients presenting to JHH in the study period were triaged after consistent and pre-determined criteria based on mechanism, injury, and vital signs. The inclusion criteria for the MOF database were chosen to capture patients at high risk of developing MOF, namely those surviving more than 48 hours, admitted to the intensive care unit (ICU) with an injury severity score (ISS) > 15, and age above 15 years. Non-mechanical trauma (burns, hanging, electrocution, poisoning, or drowning) and serious head injury patients (head Abbreviated Injury Scale > 3) were excluded owing to different physiologic response, morbidity, and mortality profile. Those who received BC were eligible for inclusion in our study. Patients were followed-up until death, discharge from ICU, or for a maximum of 28 days.

The Transfusion Service at JHH Pathology Department provided BC information (e.g. ABO type, pack number, and transfusion date) for packed red blood cells (RBC), fresh frozen plasma (FFP), cryoprecipitate (CRYO), and platelets (PLT). PLT were routinely collected from a single donor through apheresis or pooled from multiple donations; pooled PLTs were excluded from our analysis owing to their multi-donor origin. Australian Red Cross Lifeblood, which is the national provider of blood and blood products for the Australian community, provided blood donor age and sex for all single donor BC. The JHH MOF database provided recipient demographics (age and sex), clinical characteristics, ISS, new injury severity score (NISS), volume of infused crystalloids, and shock parameters (base deficit and lactate).

Incidence of MOF, as defined by the Denver score,<sup>3</sup> was analyzed using uni and multivariable log-linear models accounting for the correlated structure of the data (multiple donations per recipient).<sup>10,11</sup> Odds ratios (OR) and 95% confidence intervals were the measure of association and hereafter referred to as risk. Blood donor age and sex were the exposure variables. Estimates were adjusted for NISS, number of transfusions, base deficit, RBC leukocyte filtration status, and lactate. In the analysis, NISS was preferred to ISS being a better predictor of MOF.<sup>12</sup> Results were stratified by BC type. Donor and recipient age were recorded as continuous variables and, given their contiguous structure, categorized into tertiles based on recipient age. Analysis included BC transfused from admission to MOF or to 28 ICU days. The likelihood ratio method was used to test for interactions by donor and recipient sex, and to test for trend across donor and recipient age categories. A generalized procedure for the family of logistic models was used to test for goodness of fit.<sup>13</sup> Statistical significance was defined as  $P \leq 0.05$ . SAS statistical software (version 9.4, SAS Institute Inc., Cary, NC) was used for all analyses.

## RESULTS

The total number of trauma activations during the study period was 8794, with 1331 patients admitted to ICU. Of these, 304 met the inclusion criteria for the MOF database, with 229 patients receiving BC. These constituted our study population (Fig. 1). Fifty-two patients developed MOF (22.7%). 1583 BC transfusions were given to patients who developed MOF, 2796 to those without MOF.

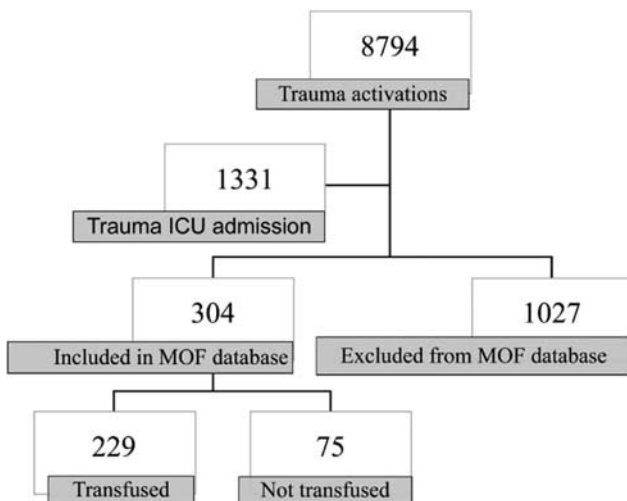


FIGURE 1. Study population.

TABLE 1. Participant Characteristics

Characteristic	n (%) Median [IQR]
Recipient (N = 229)	
Age (yr)	45 [36]
Base deficit (mmol/L)	-5.1 [6.1]
Lactate (mmol/L)	3.6 [2.6]
NISS	34 [14]
Male	156 (68)
Transfusions per patient	10 [23]
Donations* (N = 4379)	
Age (yr)	46 [25]
Male	3222 (74)
Transfused blood component type	
Cryoprecipitate	1271 (29)
Fresh frozen plasma	1030 (24)
Platelets apheresis	36 (<1)
Red blood cells	2042 (47)

\*May include multiple donations made by the same donor and multiple transfusions given to the same recipient. IQR indicates interquartile range; L, liters; mmol, millimolar; yr, year.

Most patients were males (68%), with a median age of 45 years, and received 10 transfusions on average. Median values for base deficit, lactate, and NISS were -5.1 mmol/L, 3.6 mmol/L, and 34 respectively, as expected in our major trauma population. Blood donations came from patients on average greater than 46 years of age and predominantly male (74%). RBC (47%) were the most commonly transfused BC type followed by CRYO (29%), FFP (24%), and PLT (<1%). The latter were excluded from further consideration because of their small number (Table 1).

As commonly described in a trauma population recipient age and sex, base deficit, lactate, NISS, and number of transfusions were significantly associated with MOF in the univariable analysis. Base deficit was not associated with MOF in the multivariable analysis (Table 2). Patients in the MOF and non-MOF group received a median of 4.0 and 5.5 liters ( $P > 0.05$ ) of crystalloids early (first 12 hours) and a median of 2.0 and 2.0 liters ( $P > 0.05$ ) late (second 12 hours) during their admission, respectively.

A correlation was found between blood donor sex and MOF: sex matched RBC transfusions were associated with reduced risk of MOF, while sex-mismatched RBC transfusions were associated with increased risk of MOF. FFP and CRYO from male donors were associated with an increased risk of MOF for both recipient sexes, while FFP and CRYO from female donors had a protective effect, for both recipient sexes. All confidence intervals spanned unity except for male recipients receiving FFP and CRYO from either sex. Likelihood ratio test for interaction were significant for all BC (Table 3).

TABLE 2. Predictors of MOF

Characteristic*	Univariable P-value	Multivariable P-value
Recipient		
Age	<0.0001	<0.0001
Sex	<0.0001	<0.0001
Base deficit	<0.0001	0.77
Lactate	<0.0001	<0.0001
NISS	<0.0001	0.013
Number of transfusions	<0.0001	<0.0001

\*Accounting for multiple blood donations which may be given to each patient (correlated data structure). MOF indicates post-injury multiple organ failure; NISS, new injury severity score.

TABLE 3. Association Between Sex and MOF

Characteristic*		Recipient†		P-value Interaction‡
		Male OR (95% CI)	Female OR (95% CI)	
Red blood cells Donor	Male	0.899 (0.703–1.125)	1.266 (0.747–2.145)	0.0038
	Female	1.125 (0.889–1.423)	0.790 (0.466–1.338)	
Fresh frozen plasma Donor	Male	2.226 (1.134–4.369)	1.872 (0.448–7.814)	0.0001
	Female	0.449 (0.229–0.882)	0.534 (0.128–2.231)	
Cryoprecipitate Donor	Male	7.342 (1.957–27.536)	1.294 (0.296–5.645)	<0.0001
	Female	0.136 (0.036–0.511)	0.773 (0.177–3.373)	

\*Accounting for multiple blood donations which may be given to each patient (correlated data structure).

†Adjusted for patient and donor age, NISS, number of transfusions, base deficit, RBC leukocyte filtration status, and lactate.

‡Likelihood ratio test for interaction. CI indicates confidence interval; MOF, post-injury multiple organ failure; NISS, new injury severity score; OR, odds ratio.

When analyzing the association between age and MOF, tertiles were defined by age cut-off values of 35 and 55 years (Table 1 Supplemental, <http://links.lww.com/SLA/C908>). With regards to donor age, transfusing FFP from donors older than 35 years was associated with an increased risk of MOF for middle-aged recipients only, while CRYO from donors older than 35 years was associated with an increased risk of MOF in older recipients. The following donor-recipient age group correlations were associated with a reduced risk of MOF: RBC from donors older than 35 years transfused to recipients older than 35 years, FFP from donors older than 35 years transfused to recipients older than 55 years, and CRYO from donors older than 35 years transfused to recipients younger than 35 years. All respective confidence intervals spanned unity. Likelihood ratio tests for trend were non-significant for all BC. With regards to recipient age, transfusing any BC from donors of any age was associated with an increased risk of MOF if the recipient was >35 years. Only 3 out of 18 donor-recipient age groups interactions had confidence intervals which did not span unity. Likelihood ratio tests for trend were significant for all BC excluding FFP from donors >55 years (Table 1 Supplemental, <http://links.lww.com/SLA/C908>).

## DISCUSSION

We observed a statistically significant association between donor sex and MOF but not between donor age and MOF in a critically injured polytrauma population. MOF is understood today as the result of uncontrolled and dysfunctional inflammatory response, resulting in severe secondary tissue damage, leading to respiratory, liver, cardiac, and/or kidney failure, with physiological exhaustion. The risk of developing MOF depends on host factors (age, genetic polymorphism, individual response to injury), tissue injury (injury severity, injury pattern), shock factors (severity, duration), treatment, and iatrogenic factors (resuscitation, surgical procedures with associated tissue damage). MOF was the outcome of interest for our analysis because it represents the most significant complication of polytrauma patients surviving the first day after injury and is responsible for most post-injury deaths beyond 48 hours. MOF is also responsible for excessive resource utilization and poor long term outcomes. It is a frequent occurrence in our trauma patient population and its correlation to infused fluids is well-described in the literature.<sup>14–16</sup> Considering the small amounts of crystalloids infused in our cohort MOF is not related to crystalloids in our cohort, may directly reflect post-transfusion effects and can be measured daily with validated scales like the Denver score. An advantage of this score is that time-dependent analysis

could be used, accounting for the patient's BC exposure changing over time.

The importance of sex differences in clinical research is long recognised<sup>17</sup> and efforts have recently been made to translate this concept to pre-clinical research advocating implementations of policies encouraging inclusion of sex and gender records in the biomedical field.<sup>18</sup>

Our results suggest a protective effect against MOF associated with transfusions of CRYO and FFP from female donors; this association was stronger for male recipients. These findings diverge from what was found on previous work on transfusion-related acute lung injury<sup>19</sup> which has led to policies deferring previously pregnant female donors unless tested for antibodies against human leukocyte antigens. Previous studies on donor-recipient sex match status related outcomes concentrated mainly on RBC transfusions.<sup>20</sup> Contradicting observations highlight the importance to focus further investigations on all BC types, rather than RBC only. Additionally, we found transfusion of CRYO and FFP from males to be associated with increased MOF risk; this association appeared stronger when the recipient was a male. In contrast, previous allogenic transplantation studies of hematopoietic stem cell recipients show improved outcomes with male-donated cells.<sup>21</sup>

Regarding our RBC related results, donor-recipient sex mismatch was recognized as a risk factor for MOF, with a recipient-dependent effect. This is consistent with what is known in heart transplantation, where sex mismatch is a recognized risk factor for decreased survival.<sup>22</sup> Similarly, a recent publication found the outcome of patients receiving RBC correlated with recipient sex,<sup>23</sup> particularly for patients receiving RBC from females who had previously been pregnant. Blood donor pregnancy status before donation, represents another interesting aspect of this emerging research stream, as it does in trauma patient cohorts. Hormonal changes of pregnancy may play a role in determining trauma patients' outcome by altering immune function. Donor and recipient hormonal status at the time of donation and transfusion might impact transfusion outcomes and collecting such data in a future study would be informative. Hormonal status relates to the concept of andro and menopause, and perhaps overlaps with aging. Hormonal status could therefore be an underlying link between donor-recipient age-sex interactions. Expanding research in this direction may support the identification of a biologically justified age limit to be used for research in this field.

Documenting donor-recipient sex interaction can be approached binarily (sex-matched vs sex-mismatched exposure-

outcome interactions) or directionally through 4 possible exposure combinations (female or male BC transfused to female or male recipient). We chose the second option because identifying directional effects could better inform sector-specific guidelines. A recent meta-analysis, that includes some relevant work on transfused cardiovascular surgery patients, concluded that sex-mismatched RBC transfusions are associated with increased risk of death and highlighted the need for further research.<sup>20</sup>

With respect to blood donor age and recipient outcomes, no correlation was identified in our cohort. Recent laboratory animal studies observed a rejuvenating effect on older recipients exposed to blood from young donors,<sup>24</sup> suggesting a beneficial therapeutic effect on multiple organs including heart, bones, and nervous system,<sup>25</sup> that have not been replicated in humans. Following this, multiple studies have focused on blood donor age as the next frontier for transfusion medicine quality improvement with conflicting results.

Two recent studies by Loftus et al identified RBC donations from older individuals being associated with increased risk of nosocomial infection in trauma patients<sup>26</sup> and deleterious effects of RBC from older donors in patients undergoing hepatectomy for non-hepatocellular malignancy.<sup>27</sup> Similarly to our study, 1 of these 2 populations involved trauma patients, however for both studies patients received smaller amounts of RBC compared to our cohort. Noticeably, their hypothesis related to immunosenescence and analyzed a small single-etiology sample.

By contrast, 2 previous studies analyzed large multi-etiology cohorts exploring the hypothesis that donor's demographics correlate with outcomes of patients receiving RBC transfusions.<sup>28,29</sup> Chasse et al identified an increased risk of death associated with RBC from younger donors, while Edgren et al found RBC donor age not to be associated with patient mortality. Edgren's work followed Chasse's using similar methods and discrepant findings were attributed to residual confounding in the latter, complex statistics are in fact required for this type of analysis. Furthermore, results from Heddle et al identified RBC donor age being associated with recipient in-hospital mortality.<sup>30</sup> Previous work also failed to identify an association between donor age and survival of transfused patients from a large population database<sup>31</sup> and in a large sample of patients undergoing cardiac surgery.<sup>32</sup>

Multiple reasons may explain why different studies found discrepant results to a very similar research question. Analyzing populations with multiple aetiologies identified from large databases and comparing recipients of large and small quantities of BC for acute and non-acute indications might be important confounding factors. A yet-to-be-discovered underlying mechanism could rationalize the approach to this research topic.<sup>33</sup> Despite hypothesized short term mechanisms<sup>34</sup> supporting the validity of short term outcomes, long term outcomes have been used in the past to correlate donor demographics and recipient outcomes 5, 10, or 12 years post transfusion, in small<sup>26,27</sup> and large population-based studies.<sup>28,29</sup> A dose effect may better explain donor-recipient interactions and make the polytrauma population receiving high volumes of BC over a short period of time an ideal group of patients in which to test this hypothesis. Definitive answers on this topic require results to be validated in interventional trials on homogeneous single-etiology populations.

One limitation of our study relates to the way we counted BC: our analysis is based on products released from the blood bank, not those actually transfused. There is a possibility that some BC were released but not given, however, we believe this to be negligible given the strict BC transfusion policies and procedures at our institution. Also, adjustment for patient comorbidities was not

possible as this information was not recorded in our database; despite trauma typically affecting a young and therefore likely healthy population, patients' comorbidity status may be an important variable. Additionally, RBC administered by the pre-hospital service or BC given in other hospitals before transfer to our institution were not accounted for. However, we believe the impact of this is also negligible as the option to transfuse pre-hospital RBC was only available for the last 10 months of our 9-year recruitment period and because all severe trauma patients populating our study cohort received a total of 112 BC before transfer to JHH. Volume of blood component per BC packs is not recorded in our study; currently it is not possible to estimate the significance of this limitation, but future studies confirming a dose-related mechanism might make this a relevant limitation. Another potential limitation of this study is the lack of documentation regarding donors and recipients taking hormone supplementation or birth control tablets and their hormonal status in general, which may affect outcomes. And also, unappreciated practice changes may have involved the BC manufacturing process or everyday clinical practice over 10 years, nevertheless no specific concern is reported with this regards.

Multiple variables specific to each BC could play a role in the causal pathway determining recipients' outcomes. In particular RBC storage age and lesions have been extensively investigated for their potential to cause harm.<sup>35</sup> This was investigated in the trauma population primarily in observational studies<sup>36</sup> even though randomized data justifies utilization of older RBC.<sup>8</sup> RBC storage lesions have been studied as potentially hindering RBC ability to restore viscosity in microcirculation which may intertwine with oxygen delivery.<sup>37</sup> RBC storage lesions also have been associated with RBC microparticles scavenging nitric oxide<sup>38</sup> and endothelium-derived nitric oxide has been hypothesized as a potential short term mechanism to explain why RBC could negatively impact on females outcomes when donated by males.<sup>20</sup> Different aspects relating to thawed FFP also are worth noting, namely product age and varying protein concentration which may impact on the patients' physiology and outcomes.<sup>39</sup> Storage age has been studied for PLT components, with older product age proving inferior to fresher components when transfused for trauma<sup>40</sup> and in non-trauma situations.<sup>41</sup> Multiple aspects relating to the quality of PLT have been explored in the literature. Apheresis PLT were associated with improved survival in combat casualties when transfused with specific ratios.<sup>42</sup> However, any generalization is challenging in the context of multiple indications and BC manufacturing methods worldwide.<sup>43</sup>

Strengths of this work include the fact that our subset of severely injured trauma patients with frequent transfusions and at high risk for developing post-injury MOF places this study in a unique position to detect time and cause-effect relationship between BC transfusions and MOF. Our strict inclusion criteria single etiology cohort may suffer less bias; innumerable confounders could, in fact, compromise reliability of outcomes measured long after transfusion in multi-etiology cohorts.

In conclusion, until interventional prospective studies demonstrate or refute a causal relationship between exposure and outcomes, findings need to be cautiously interpreted given the analytic complexity required to extrapolate results. More work needs to be done to confer external validity to our results. Importantly, BC manufacturing varies across jurisdictions around the world hampering the generalization of results. There is a demand for further implementation of vein-to-vein databases to facilitate data collection and streamline results. Compared with donor age, donor sex seems to hold better potential for being associated with transfused trauma patients' MOF status,

nevertheless further research is required to focus hypotheses, define findings, and support or discourage any future risk mitigation strategy specific to BC donor demographics.

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