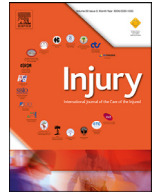




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Evaluation of blood product transfusion therapies in acute injury care in low- and middle-income countries: a systematic review



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ABSTRACT

Background: Worldwide, injuries account for approximately five million mortalities annually, with 90% occurring in low- and middle-income countries (LMICs). Although guidelines characterizing data for blood product transfusion in injury resuscitation have been established for high-income countries (HICs), no such information on use of blood products in LMICs exists. This systematic review evaluated the available literature on the use and associated outcomes of blood product transfusion therapies in LMICs for acute care of patients with injuries.

Methods: A systematic search of PubMed, EMBASE, Global Health, CINAHL and Cochrane databases through November 2018 was performed by a health sciences medical librarian. Prospective and cross-sectional reports of injured patients from LMICs involving data on blood product transfusion therapies were included. Two reviewers identified eligible records ($\kappa=0.92$); quality was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. Report elements, patient characteristics, injury information, blood transfusion therapies provided and mortality outcomes were extracted and analyzed.

Results: Of 3411 records, 150 full-text reports were reviewed and 17 met inclusion criteria. Identified reports came from the World Health Organization regions of Africa, the Eastern Mediterranean, and South-East Asia. A total of 6535 patients were studied, with the majority from exclusively inpatient hospital settings (52.9%). Data on transfusion therapies demonstrated that packed red blood cells were given to 27.0% of patients, fresh frozen plasma to 13.8%, and unspecified product types to 50.1%. Among patients with blunt and penetrating injuries, 5.8% and 15.7% were treated with blood product transfusions, respectively. Four reports provided data on comparative mortality outcomes, of which two found higher mortality in blood transfusion-treated patients than in untreated patients at 17.4% and 30.4%. The overall quality of evidence was either low (52.9%) or very low (41.2%), with one report of moderate quality by GRADE criteria.

Conclusion: There is a paucity of high-quality data to inform appropriate use of blood transfusion therapies in LMIC injury care. Studies were geographically limited and did not include sufficient data on types of therapies and specific injury patterns treated. Future research in more diverse LMIC settings with improved data collection methods is needed to inform injury care globally.

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Introduction

Injuries account for approximately five million deaths annually. Road traffic injuries (RTIs) account for 24% of injury deaths world-

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wide and are projected to become the seventh leading cause of death by 2030 [1,2]. Approximately 90% of the injury burden is in low-and middle-income countries (LMICs), accounting for 12% of all deaths in Sub-Saharan Africa, Latin America and the Caribbean compared to 6% in high-income countries (HICs) [2–4]. Globally, injury is responsible for the majority of deaths among those aged 15–44 years [5].

Hemorrhage is the most common potentially preventable cause of death in LMICs [6, 7]. Resuscitation of patients with traumatic hemorrhage is centered on controlling blood loss and providing blood transfusion therapies [8]. This approach has been relatively well-studied in military settings [9–12] and in some civilian population from HICs [6,13]. Treatment of injury-related hemorrhage with blood transfusion therapies attempts to either provide whole blood or a balanced red blood cell-plasma-platelet component strategy, and such approaches have been associated with improved outcomes [14–16]. In HICs, contemporary data indicate that injury mortality related to hemorrhage has likely decreased due to improved injury care, including advances in blood product transfusion strategies [17].

Consensus clinical guidelines with patient- and injury-specific recommendations exist in HICs for the treatment of injured patients with blood product transfusions [18–20]. In LMICs, however, where the vast majority of injuries occur, there are no such international consensus guidelines to inform the care of injured patients. Epidemiologic characteristics of patients in LMICs are different from those in HICs, with greater baseline rates of anemia and infectious diseases; thus, extrapolation of research and guidelines from HICs may not be appropriate [21–24]. Additionally, injury care is further complicated by differences in access to resources and more limited availability of blood products in many LMIC settings. In sub-Saharan Africa, studies demonstrate that less than half of the estimated blood needed for treatment is available, resulting in common shortages in blood resources for resuscitative care [25,26].

Given the global magnitude of injuries in LMICs and the absence of appropriate consensus guidelines from these settings, evaluation and characterization of the available data on the use of blood products in injury treatments in LMICs is a crucial foundational step for informing clinical practice and future research. To address this need, a systematic review assessing the literature on the use of blood product transfusion therapies in LMICs and associated outcomes of patients with injuries was performed.

Methods

Search strategies

A search strategy was designed by a health sciences medical librarian following Cochrane Collaboration protocol guidelines. The search strategy identified reports from LMICs that described and evaluated the use of blood product transfusion therapies in LMICs for acute care of patients with injuries. A secondary aim was to assess the impact of blood product transfusion therapies on mortality among the same population. Classification of LMICs followed criteria used by The World Bank [27]. Acute physical trauma was defined using standardized World Health Organization (WHO) and Centers for Disease Control (CDC) reference definitions [28,29].

Inclusion criteria

- All prospective or cross-sectional reports from LMICs with data on the use of blood product transfusion therapies for emergency and/or acute care of patients with injuries.
- Blood transfusion therapies include: Whole blood, Red blood cells, Plasma, Cryoprecipitate and Platelets.

Exclusion criteria

- Study types: retrospective studies, reviews, case-control, case reports, case-series, editorials
- Reports studying non-physical injuries
- Reports studying patients during only the rehabilitation phases of injury treatment
- Reports studying patients in combat or military settings
- Non-English language reports

PubMed, EMBASE, Global Health, CINAHL and Cochrane Library databases were searched from each database's inception through 1st November 2018. Structured computer-assisted search protocols using combinations of key words, free text terms, subsets and exploded medical subject headings (MeSH) were employed (Supplement S1). Additionally, citation lists of included reports were reviewed for relevant records. The primary authors of all reports that met inclusion criteria were contacted to identify additional data pertinent to the aims of the systematic review.

Data processing

After removal of duplicates, titles, and abstracts of identified records were assessed for eligibility by two independent reviewers, disagreements were adjudicated by a third reviewer as needed. Full-text reports of potentially relevant records were reviewed in their entirety. For reports that met inclusion parameters, data were extracted using a pre-designed form. Data elements included: report characteristics (e.g., first author, publication year, study design, country); patient characteristics (e.g., number of injured patients, types of blood products transfusion therapies used, volume of transfused products); and mortality, if presented. Mortality outcomes were assessed as all-cause without delineation of the etiology. Injury types, when identifiable from the primary reports, were classified as general (i.e., all patients without restrictions on included injuries), penetrating, blunt or burns. When specific mechanisms of injuries or anatomical regions were identified in a given report, these were recorded. Healthcare research settings were defined as inpatient (within hospital), outpatient (clinic or emergency care facility) or mixed, if data were drawn from both inpatient and outpatient settings. Multinational reports were assessed for extraction of data pertaining to LMICs, and contact with the authors was attempted if the data could not be disaggregated from the source report. To facilitate data synthesis and comparative analyses, volumes of packed red blood cells (PRBCs) and fresh frozen plasma (FFP) were standardized at 300 milliliters (mL) per unit of blood product [30,31]. For reports that represented the volumes of blood products transfused in milliliters, the quantities of PRBCs or FFP were standardized by dividing the reported volumes by 300 mL to convert them to blood product units. In reports that represented volumes transfused in milliliters per kilogram (kg), a standard patient weight of 70 kg was used, and the volume in mL/kg was divided by 300 mL and multiplied by 70 kg to yield the number of units.

The quality of included studies was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [32–34]. The systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (Registration Number:

CRD42020119538) [35]. Reporting adhered to the criteria proposed by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Statistical methods

Data analyses were performed using STATA v15.0 (StataCorp; College Station, USA). Inter-observer agreement for included re-

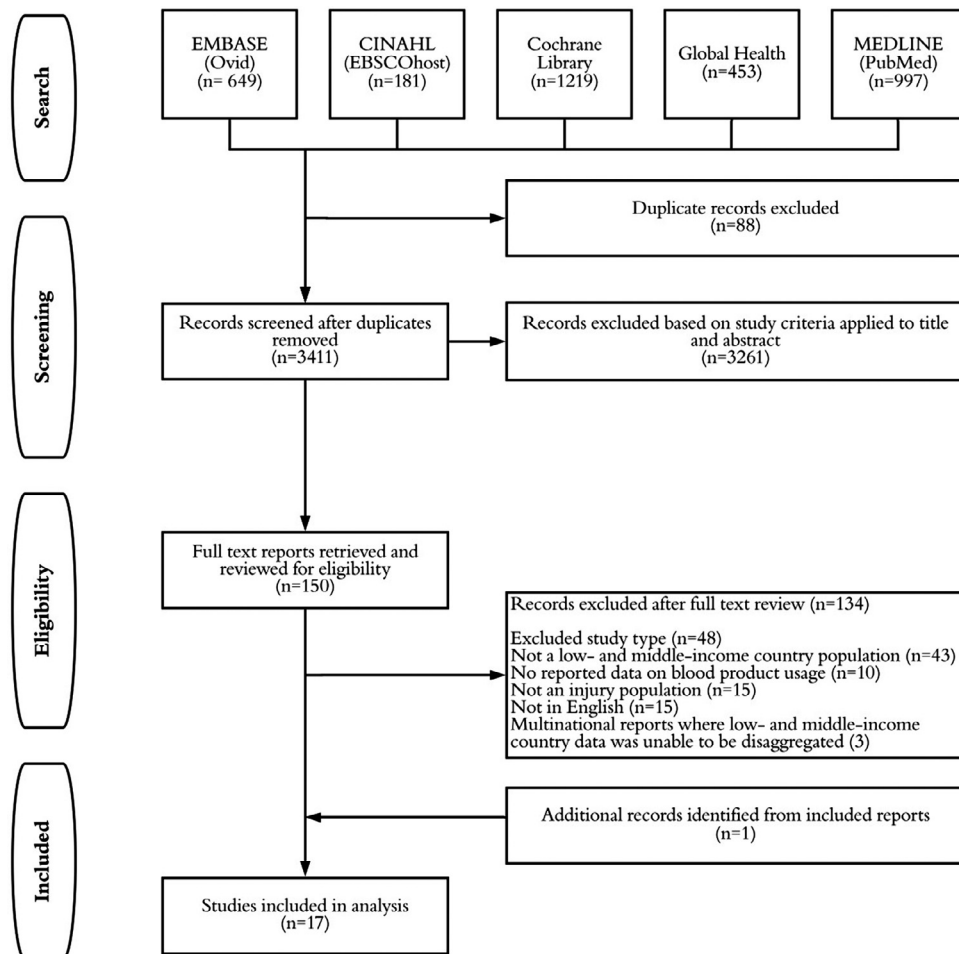


Fig. 1. Report selection process.

ports was assessed using Cohen's kappa (κ) [36,37]. Data were analyzed descriptively and summarized based on parameters of geographic distribution, types of blood product transfusion therapies used and study types. As differences in volume resuscitation approaches in injuries caused by blunt versus penetrating mechanisms exist, data were stratified and evaluated based on mechanism of injury [38–40]. Volumes of blood product transfusion therapies and mortality outcomes among those exposed to transfusion therapies and those not exposed were explored and compared when data were available. Due to the substantial clinical heterogeneity in the included reports, meta-analysis of the data was deemed inappropriate and not performed.

Results

The search strategy generated 3411 individual reports from all databases evaluated. After review of titles and abstracts, 3261 reports were excluded and 150 underwent full-text review. From these, 134 were excluded and sixteen reports met full inclusion criteria. One additional report meeting inclusion criteria was identified and added after review of references of the primary included reports (Fig. 1), yielding a total of seventeen included reports. Inter-observer agreement for report selection was excellent ($\kappa=0.92$) [36,37].

Characteristics of included reports

Included reports were derived from Ghana (1) [41], India (4) [42–45], Iran (4) [46–49], Kenya (4) [50–53], South Africa (2) [54,55], Turkey (1) [56] and Uganda (1) [57]. The cumulative number of patients studied in all reports was 6535. The global distribution of patients studied, based on the countries and WHO regions of the included reports, is shown in Fig. 2. The majority of patients studied were from the African Region (52.5%) [41,50–53,57], with smaller percentages from the South-East Asia Region [42–45], European Region [56] and Eastern Mediterranean Region [46–49]. There was limited representation of nations within each WHO region, as only one country was represented in the European Region, one in the Eastern Mediterranean Region, one in the South-East Asia Region, and four in the African Region. There were no available reports from the Americas or the Western Pacific regions (Fig. 2).

The majority of the reports were conducted in the inpatient setting (52.9%) [42,45,49–54,57], while four were conducted in the outpatient setting (23.5%) [43,46,47,55] and four in mixed settings (23.5%) [41,44,48,56]. Included reports were published between 2001 and 2018. Study methodologies were predominantly cross-sectional (58.8%) [41,45–49,51–53,56]. There were six cohort studies (35.3%) [42–44,50,55,57] and one randomized controlled trials (RCTs) (5.9%) [54,58]. Approximately half of the reports were conducted on general injured populations (47.1%) [41–

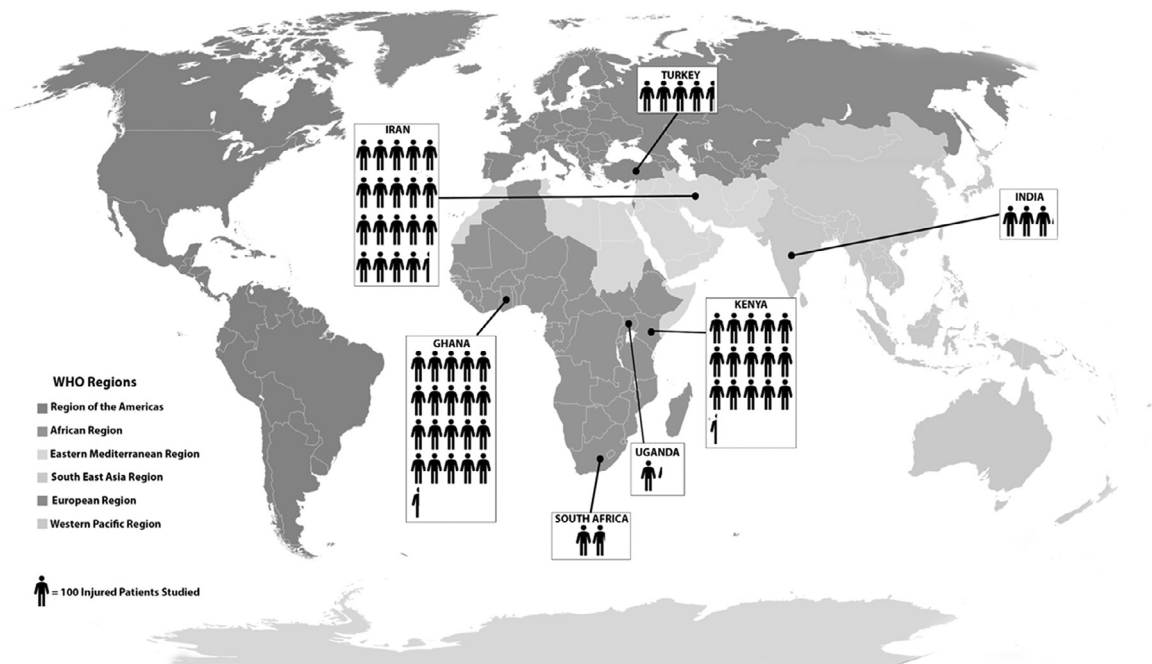


Fig. 2. Global distribution of patients studied across World Health Organization Regions.

Table 1
Characteristics of included reports.

| Author (year) | Study Design | Country | HealthCare Setting | Mechanism of Injury | Patients Studied | Type of Blood Products(s) |
|--------------------------|------------------|--------------|--------------------|----------------------|------------------|---|
| Alimohammadi (2017) [46] | Cross-sectional | Iran | Outpatient | General | 793 | Not specified |
| Bowley (2006) [54] | RCT ^a | South Africa | Inpatient | Penetrating | 44 | PRBC ^b (Allogeneic or Allogeneic & Autologous) |
| Hommes (2015) [55] | Cohort | South Africa | Outpatient | Blunt | 134 | PRBC |
| Jana (2008) [42] | Cohort | India | Inpatient | General ^c | 52 | Not specified |
| Javali (2017) [43] | Cohort | India | Outpatient | General ^d | 100 | Not specified |
| Kilyewala (2017) [57] | Cohort | Uganda | Inpatient | Burn | 112 | Not specified |
| London (2001) [41] | Cross-sectional | Ghana | Mixed | General | 2022 | Whole blood |
| Mofidi (2010) [47] | Cross-sectional | Iran | Outpatient | Blunt | 400 | Not specified |
| Musau (2006) [50] | Cohort | Kenya | Inpatient | General ^e | 80 | Not specified |
| Newton (2015) [51] | Cross-sectional | Kenya | Inpatient | General | 227 | Not specified |
| Otieno (2004) [52] | Cross-sectional | Kenya | Inpatient | General | 202 | Not specified |
| Sadeghi (2017) [48] | Cross-sectional | Iran | Mixed | General | 37 | PRBC |
| Saidi (2014) [53] | Cross-sectional | Kenya | Inpatient | Blunt | 1013 | Not specified |
| Sokhal (2017) [44] | Cohort | India | Mixed | Burn | 78 | Not specified |
| Srikant (2003) [45] | Cross-sectional | India | Inpatient | Blunt | 72 | Not specified |
| Tavousi (2018) [49] | Cross-sectional | Iran | Inpatient | Burn | 701 | PRBC FFP Platelets Cryoprecipitate PRBC |
| Yanar (2008) [56] | Cross-sectional | Turkey | Mixed | Blunt | 468 | PRBC |

^a RCT abbreviates for Randomized Controlled Trial

^b PRBC abbreviates for Packed Red Blood Cells

^c Report included only non-obstetric gynecological injuries

^d Report excluded severe head injuries with Glasgow Coma Scale ≤ 8 with intracranial hemorrhage

^e Report included only abdominal injuries

43,46,48,50–52], while five reports solely studied blunt injuries (29.4%) [45,47,53,55,56] and one examined only penetrating injuries (5.9%) [54]. Three reports were conducted on patients with isolated burn injuries (17.6%) [44,49,57]. A single report evaluated isolated abdominal injuries [50] and a single report evaluated non-obstetric gynecological injuries (Table 1) [42].

The majority of reports did not specify types of blood products used (64.7%) [42–47, 50–53,57]. Three reports provided data solely on PRBCs (17.6%) [48,55,56], one of which examined allogeneic and autologous PRBCs [54], and one report provided data on the use of PRBCs, FFP, platelets, and cryoprecipitate [49]. Evalua-

tion of patient level data extracted from the reports demonstrated that of the 881 patients who received blood products, 50.1% received unspecified blood products, 27.0% received PRBCs, 13.8% received FFP, 8.3% received whole blood, 0.7% received platelets and 0.1% received cryoprecipitate (Fig. 3). In assessing types of blood products used based on WHO regions, there was a lower proportion of patients treated with unspecified product types from the Eastern Mediterranean region at 25.4% compared to the African region (69.0%) and the Southeast Asia region (100.0%) (Fig. 4).

In stratified analyses based on mechanism of injury, of the 4067 patients with blunt mechanisms, 236 (5.8%) patients had reported

Table 2
Characteristics of populations stratified by injury mechanism.

| Blunt Mechanisms of Injury | | | | | |
|----------------------------------|----------------------------|-----------------------|--------------------------------------|--|---|
| Author (year) | Number of Patients Studied | Overall Mortality (%) | Type of Blood product(s) Reported on | Number of Patients Treated with Blood Product(s) | Volume of Blood product per patient (units) |
| London (2001) [41] | 1728 | Not reported | Whole blood | Not reported | Not reported |
| Mofidi (2010) [47] | 400 | Not reported | Not specified | 56 | Not reported |
| Musau (2006) [50] | 27 | 22.2% | Not specified | 8 | Not reported |
| Newton (2015) [51] | 210 | Not reported | Not specified | Not reported | Not reported |
| Otieno (2004) [52] | 149 | Not reported | Not specified | Not reported | Not reported |
| Saidi (2014) [53] | 1013 | 17.4% | Not specified | 172 | Not reported |
| Srikant (2003) [45] | 72 | 21.0% | Not specified | Not reported | 2.0 |
| Yanar (2008) [56] | 468 | 1.7% | PRBC | Not reported | 4.3-11.5 ^a |
| Penetrating Mechanisms of Injury | | | | | |
| Author (year) | Number of Patients Studied | Overall Mortality (%) | Type of Blood product(s) Reported on | Number of Patients Treated with Blood Product(s) | Volume of Blood product per patient (units) |
| Bowley (2006) [54] | 44 | 66.0% | PRBC ^b (Allogenic) | 23 | 11.2 |
| | | | PRBC (Allogenic & Autologous) | 21 | 11.5 |
| London (2001) [41] | 121 | Not reported | Whole blood | Not reported | Not reported |
| Musau (2006) [50] | 53 | 7.5% | Not specified | 15 | Not reported |
| Newton (2015) [51] | 16 | Not reported | Not specified | Not reported | Not reported |
| Otieno (2004) [52] | 10 | Not reported | Not specified | Not reported | Not reported |

^a Conversion of mL/kg reported in the study assuming average 70kg male with 1 unit = 300 mL Packed Red Blood Cells

^b PRBC abbreviates for Packed Red Blood Cells

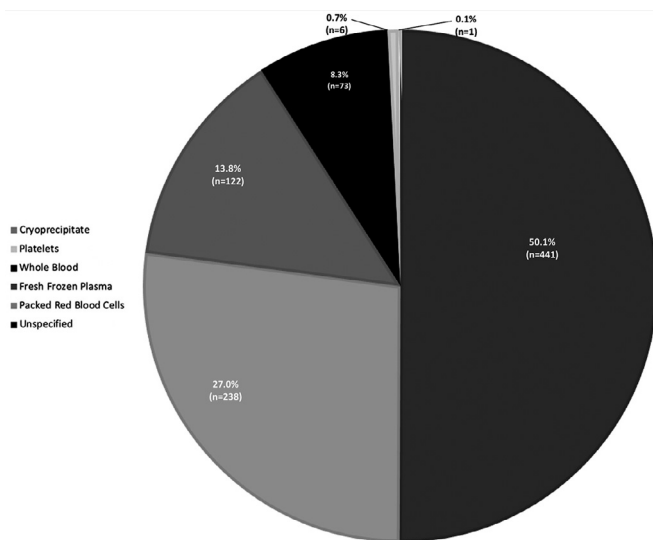


Fig. 3. Reported blood product transfusion therapies used^a
^a Data derived from reports which specified transfusions at the level of individual patients ($n = 981$)

data pertaining to treatment with blood products transfusion therapies. Two reports on patients with blunt injury mechanisms specified types of blood products transfused: whole blood [41] and PRBCs [56]. Two reports included volumes of blood products provided, which were 2 units per patient in one report from India [45] and a range of 4.3-11.5 units per patient in a report from Turkey [56].

Of the 244 patients with penetrating mechanisms of injury, 59 (24.2%) total patients drawn from two reports had data on blood product treatments [50,54]. One of these reports provided data on volumes of blood product transfusion therapies used. A RCT from South Africa studied two transfusion strategies [54]: providing allogeneic PRBCs compared to providing both allogeneic and autologous PRBCs. The allogeneic PRBCs group included 23 patients who received 11.2 units per patient, while the allogeneic and autologous

PRBCs group included 21 patients who received 11.5 units per patient.

Mortality outcomes

Of the patients with blunt mechanisms of injury, 1580 total patients (38.8%) from four studies had data on overall mortality [45,50,53,56]. The largest study was a cross-sectional report from India with 1013 patients, of which mortality occurred in 17.4%. In that report, 17.0% of patients received blood products [53]. A cross-sectional report from Turkey had an overall mortality prevalence of 1.7% [56], while cohort data from Kenya demonstrated 22.2% mortality among those with blunt mechanisms of injury [50].

For patients with penetrating mechanisms of injury, two reports provided mortality outcomes for 97 patients [50,54]. Overall mortality prevalence ranged from 7.5% [50] to 66.0%. Only one report specified blood product types used in treatment. This report was the RCT of 44 patients performed in South Africa that compared mortality outcomes between allogeneic and allogeneic plus autologous PRBCs transfusions and found an overall mortality of 66.0% that did not significantly differ between groups [54].

Four of the reports, comprising 1189 patients in total, included data on comparative mortality between injured patients exposed to blood products and those who were not exposed (Table 3) [42,50,53,54]. Two of these reports were conducted in Kenya [50,53], one in South Africa [54] and one in India [42]. Neither of the reports from Kenya specified the types of blood products used [50, 53]. One report from Kenya analyzed patients who suffered only abdominal injuries [50], while the other examined patients treated for RTIs [53]. In the study on abdominal injury, mortality was higher in patients who received blood product transfusions (30.4%) than in those not treated with blood products (5.26%) [50]. In the report on RTIs, 28.8% of the patients received blood product transfusion therapies. There was higher observed mortality in the patients that received blood products (17.4%) than in those who did not receive transfusions (6.6%) [53]. The single report from India studying non-obstetric lower genitourinary injuries in 52 patients, of which 28.8% were treated with blood products, had no mortality events [42]. The RCT from South Africa studying patients with penetrating injuries demonstrated that a combination of autolo-

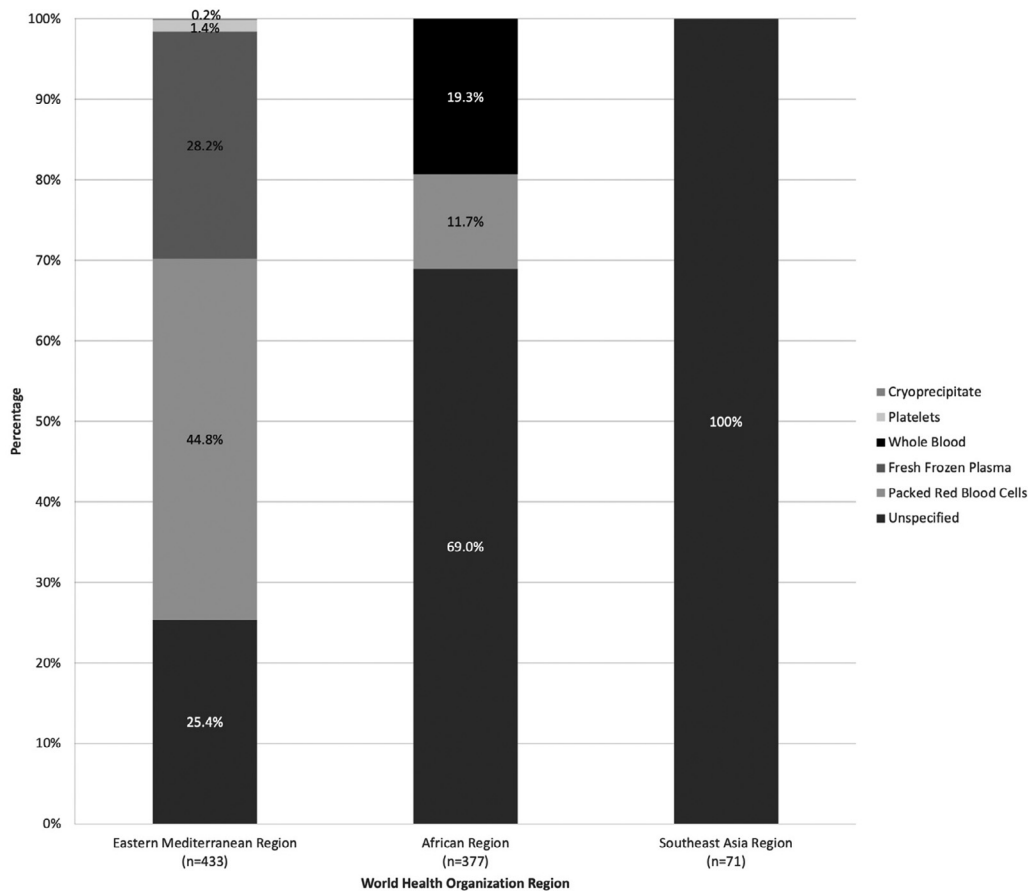


Fig. 4. Blood product transfusion therapies used by World Health Organization Regions ^a

^a Data derived from reports which specified transfusions at the level of individual patients ($n = 981$)

Table 3

Mortality outcomes by exposure to blood product transfusion therapies.

| Author (year) | Injury Type | Number of Patients Studied | Overall Mortality (%) | Patients Treated with Blood Product | Mortality blood-product non-treated | Type of Blood Product(s) | Volume of Blood Product (units /patient) | Mortality blood-product treated |
|--------------------|----------------------|----------------------------|-----------------------|-------------------------------------|-------------------------------------|--------------------------------|--|---------------------------------|
| Bowley (2006) [54] | Penetrating | 44 | 66.0% | 44 ^a | Not applicable | PRBC ^b (Allogeneic) | 11.2 | 65.2% |
| | | | | | | PRBC (Allogeneic & Autologous) | 11.5 | 66.7% |
| Musau (2006) [50] | General ^c | 80 | 12.5% | 23 | 5.3% | Not specified | Not reported | 30.4% |
| Jana (2008) [42] | General ^d | 52 | 0.0% | 15 | 0.0% | Not specified | Not reported | 0.0% |
| Saidi (2014) [53] | Blunt | 1013 | 7.7% | 172 | 6.6% | Not specified | Not reported | 17.4% |

^a 23 patients received PRBC (allogeneic) and 21 patients received PRBC (allogeneic & autologous)

^b PRBC abbreviates for Packed Red Blood Cells

^c Report included only abdominal injuries

^d Report included only non-obstetric gynecological injuries

gous and allogeneic PRBCs resulted in similar mortality outcomes as solely allogeneic PRBCs [54].

Quality assessment

The quality of reports and assessment of bias based on the GRADE criteria are shown in Table 4 [32–34]. The overall quality of the sixteen included observational reports was either low (56.3%) or very low (37.5%), with one report [43] assessed to be of moderate quality (6.3%). The quality of evidence for the one included RCT was very low. The most commonly identified limitations of reports were failure to control for confounders (82.4%), imprecision of outcomes measures (58.8%) and incomplete follow-up (53.0%).

Discussion

Available data from the systematically identified research demonstrates that there is insufficient high-quality evidence to inform the use of blood product transfusion therapies for injury care in LMICs. The gaps in the evidence base pertain to specific types of transfusion therapies, geographic representation and blood product resuscitation treatments across differing injury patterns and mechanisms. With the far-reaching impacts of injuries in LMICs [1–5, 29] and the limited available research from these settings, additional study of blood product therapies, which are key to combating injury-related mortality, is crucial for informing clinical practice and policy.

Table 4
Quality assessment of included reports using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Criteria [32–34].

| Observational Studies^a | | |
|--|---|--|
| Author (Year) | Existing Limitations | Overall Quality of Evidence |
| Alimohammadi (2017) [46] | 3, 4, 5 | Very Low |
| Hommel (2015) [55] | 1, 3, 4 | Very Low |
| Jana (2008) [42] | 3, 5 | Low |
| Javali (2017) [43] | 3 | Moderate |
| Kilyewala (2017) [57] | 3, 4, 5 | Very Low |
| London (2001) [41] | 2, 4 | Low |
| Mofidi (2010) [47] | 2, 4, 5 | Very Low |
| Musau (2006) [50] | 3, 4 | Low |
| Newton (2015) [51] | 1, 3, 4, 5 | Very Low |
| Otieno (2004) [52] | 3, 4 | Low |
| Sadeghi (2017) [48] | 2, 3 | Low |
| Saidi (2014) [53] | 3, 5 | Low |
| Sokhal (2017) [44] | 3, 5 | Low |
| Srikant (2003) [45] | 1, 3, 4 | Very Low |
| Tavousi (2018) [49] | 3, 5 | Low |
| Yanar (2008) [56] | 3, 4 | Low |
| Randomized Trials^b | | |
| Author (Year) | Existing Limitations | Overall Quality of Evidence |
| Bowley (2006) [54] | 1, 2, 5 Assessed Limitations Observational Studies ^a 1. Poorly developed and applied eligibility criteria 2. Flawed exposure and outcome measurements 3. Failure to control for confounders or fully evaluate prognostic factors 4. Imprecision of outcome measures 5. Incomplete follow up | Very Low Assessed Limitations Randomized Trials ^b 1. Lack of allocation concealment 2. Lack of blinding 3. Incomplete accounting of patients and outcome events 4. Selective outcome reporting bias 5. Other limitations (early stoppage, unvalidated outcome measures, carryover effects, recruitment bias) |

There is substantial research, including well-performed RCTs from HICs, that has led to development of consensus guidelines on the use of blood products in the treatment of acute injuries [14–16,18,59,60] [8,18,61,62]. Even though the global burden of injuries lies predominantly in LMICs [1–5,29], this systematic review demonstrates that there is a paucity of high-quality research from these settings. This discordance likely contributes to perpetuating the asymmetric morbidity and mortality outcomes observed between higher-resourced and lower-resourced settings. Although it has been proposed that injury care in LMICs could be guided by extrapolation from combat setting research, this approach may not be appropriate, as unique resources and injury patterns exist in the military context that are unlike those in civilian populations [11,63]. Furthermore, as controlled trials evaluating HIC care protocols for sepsis have been shown to result in increased mortality in African settings [64,65], gathering setting-specific data to inform treatments in LMICs is essential to delivering appropriate and safe healthcare to injured patients.

This review not only emphasizes the scarcity of available data on the use of blood product transfusion therapies in acute injury care in LMICs but also identifies priority focus areas for future investigation. The included reports illustrate geographic deficiencies in the data, as no LMICs from the Americas or the Western Pacific WHO regions were identified. These regions account for a large proportion of worldwide injury-related mortality and several nations from these regions (Philippines [66], China [67] and Brazil [68,69]) contribute substantially to the global burden of RTIs [2]. In addition, the majority of reports from LMICs in this review failed to define the types of blood products transfused [42–47,50–

53,57]. Measures of data collection were also inconsistent across the included reports, as many studies did not indicate the volumes of types of blood products used. Future LMIC injury research would be enhanced by employing reproducible reporting metrics that could be standardized across settings on the types and volumes of blood product transfusion therapies provided in injury care. Use of such metrics would advance scientific understanding while also contributing to improved infrastructure for global monitoring and evaluation [70].

This review yielded minimal data informing the variable use of blood product transfusions in blunt versus penetrating injuries. As there are differing treatment paradigms of blood product usage and associated clinical targets based on mechanism of injury [38–40], more data related to these variable presentations from LMICs are needed. Furthermore, future studies should take into account the anatomical location of injuries, as the impact of blood product therapies may vary across injury phenotypes; for example, anemia in traumatic brain injury has been associated with poorer outcomes [71,72]. In penetrating mechanisms, the impact of blood product therapies may be modulated by the presence and extent of vascular injuries. Future studies should aim to provide a more thorough understanding of both the use of blood product therapies in general and the injury populations in LMICs based on mechanisms and types of injuries.

Only four identified reports provided comparative mortality outcomes between patients treated and not treated with blood product therapies [42,50,53,54]. Two of the reports demonstrated a greater overall proportional mortality with the use of blood products [50,53]. However, as the source data did not adequately control for potential confounders such as injury severity, comorbidities and additional interventions, the relationship between injury treatments with blood products and mortality in LMICs is inconclusive. Given the role of blood product transfusions in injury care and the mortality burden of injuries in LMICs [1–5], there is an imperative to better understand the impacts of blood product therapies on patient-centered outcomes so that limited and often scarce blood product resources are allocated most appropriately. It would also be beneficial to characterize morbidity outcomes associated with hemorrhagic injuries such as acute respiratory distress syndrome, venous thromboembolism and infection, in LMIC settings where resources to address such complications may be less available [73].

Limitations

While this systematic review used a comprehensive search protocol and the identified reports are representative of the body of available literature on blood product transfusion therapies in LMICs, limitations do exist. It is possible that some relevant data were not included. Specifically, there were three multinational reports meeting inclusion criteria for which the data could not be disaggregated, and although the corresponding authors were contacted to obtain the source data, extraction was not possible [74–76]. As well, non-English language reports were not included and this may have limited the identification of possibly relevant data. Additionally, although by design, conference proceedings and grey literature were excluded, which could have biased the findings. However, the review aimed to identify high-quality peer-reviewed data. Thus, the findings allow reasonable conclusions to be drawn from the best available evidence on the use of blood product transfusion therapies in LMICs and can therefore inform future research priorities. This review was limited to non-retrospective reports to identify the most methodologically robust data, but the included reports were found to be predominantly of low or very low quality. The most common methodological weakness across the reports was failure to control for confounders. Although this does inhibit

the analysis, it should not impact the results relevant to the primary aim of characterizing the available literature on blood product transfusion therapies for injury care in LMICs. As discussed, the data deficiencies in the use of varying blood product types and volumes were abundant in the identified reports. Due to these discrepancies, assumptions were employed based on standardized blood product volumes and weights [30,31]. While this strategy allowed for a more uniform and comprehensive reporting of the data, the assumption may not be completely congruent with the source reports. Additionally, a pre-defined time frame for mortality outcomes was not used to extrapolate from the existing data because this information was difficult to ascertain from the included reports. These challenges again point to the need for higher-quality research with standardized monitoring and evaluation to improve understanding of the usage and impact of blood products during injury care in LMICs [70].

Conclusions

This systematic review characterizes the literature pertaining to the use of blood product transfusion therapies in LMICs and associated outcomes of acute care of patients with injuries. The results illustrate the paucity of available high-quality data and identify key areas for further investigation. Future research in LMICs should focus on enhancing understanding of the impact of specific types of transfusion therapies, expanding the knowledge base on blood product resuscitation treatments across injury patterns and mechanisms and increase geographic representation in the data. Furthermore, these future works should aim to use standardized and translatable data collection methods in the study of blood product therapies in LMIC injury care.

Author contributions

LY, JSR, AS and ARA conceived the study and supervised the conduct of data collection and management. LY, JSR, AS and ARA developed the statistical plan and analyzed the data. All authors took part in drafting and revising the manuscript. ARA takes responsibility for the manuscript in its entirety.

Declaration of Competing Interest

The authors have no competing interests to declare. All authors had full access to all study data and had final responsibility for the decision to submit for publication. The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the views of the affiliated academic organizations.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.injury.2020.05.007](https://doi.org/10.1016/j.injury.2020.05.007).

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