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ΘΡΟΜΒΩΣΗ ΚΑΙ ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ

Μεταπτυχιακή Διπλωματική Εργασία

"ΒΕΛΤΙΣΤΗ ΣΤΡΑΤΗΓΙΚΗ ΜΑΖΙΚΗΣ ΜΕΤΑΓΓΙΣΗΣ ΣΕ ΑΣΘΕΝΗ ΜΕ ΟΞΕΙΑ ΔΙΕΓΧΕΙΡΗΤΙΚΗ ΑΙΜΟΡΡΑΓΙΑ"

υπό

ΚΩΝΣΤΑΝΤΙΝΟΥ Π. ΜΠΟΥΡΑΝΤΑ

Ειδικευόμενο Γενικής Χειρουργικής

Υπεβλήθη για την εκπλήρωση μέρους των
απαιτήσεων για την απόκτηση του
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Επιβλέπων:

Αθανάσιος Χαλκιάς, Επίκουρος Καθηγητής Αναισθησιολογίας, Τμήμα Ιατρικής,
Πανεπιστήμιο Θεσσαλίας

Τριμελής Συμβουλευτική Επιτροπή:

1. Ελένη Αρναούτογλου, Καθηγήτρια Αναισθησιολογίας, Τμήμα Ιατρικής,
   Πανεπιστήμιο Θεσσαλίας

2. Μεταξία Μπαρέκα, Επίκουρος Καθηγήτρια Αναισθησιολογίας, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας

3. Μαρία Νταλούκα, Επιμελήτρια Β΄ Αναισθησιολογίας, Π.Π.Γ.Ν. Λάρισας

Αναπληρωματικό μέλος:
Μιλτιάδης Ματσάγκας, Καθηγητής Αγγειοχειρουργικής, Τμήμα Ιατρικής, Πανεπιστήμιο Θεσσαλίας

Τίτλος εργασίας στα αγγλικά:

“OPTIMAL STRATEGY FOR MASSIVE TRANSFUSION IN SEVERE INTRAOPERATIVE BLEEDING: A SYSTEMATIC REVIEW AND META-ANALYSIS”

ΕΥΧΑΡΙΣΤΙΕΣ

Επιθυμώ να εκφράσω την πιο βαθιά μου ευγνωμοσύνη στον κ.Αθανάσιο Χαλκιά, Επίκουρο Καθηγητή της Αναισθησιολογίας και επιβλέποντα της διπλωματικής μου εργασίας, για την ανιδιοτελή βοήθειά του, την στοχευμένη καθοδήγησή του και την ειλικρινή υποστήριξη κατά την εκπόνηση της διπλωματικής εργασίας.

Περίληψη

Εισαγωγή: Η μαζική μετάγγιση χρησιμοποιείται ευρέως σε ασθενείς με οξεία διεγχειρητική αιμορραγία. Παρότι προτείνονται διάφορες αναλογίες παραγόντων αίματος στα πρωτόκολλα μαζικής μετάγγισης, εξακολουθεί να υπάρχει αντιπαράθεση σχετικά με την επίδρασή τους στην έκβαση των ασθενών. Στόχος της παρούσας ανασκόπησης και μετα-ανάλυσης είναι η εκτίμηση της επίδρασης των στρατηγικών μαζικής μετάγγισης στην μετεγχειρητική θνητότητα των ασθενών με σοβαρή διεγχειρητική αιμορραγία.

Μεθοδολογία: Διενεργήθηκε ενδελεχής αναζήτηση για σχετικά άρθρα στις βάσεις δεδομένων PubMed και του clinicaltrials.gov από τον Γενάρη του 2000 έως και τον Απρίλιο 2022. Ακολούθως, διενεργήθηκε και δεύτερη αναζήτηση με συνδυασμό ελεύθερων και καταχωρημένων όρων. Τέλος, διενεργήθηκε και τρίτη αναζήτηση με βάση της βιβλιογραφικές αναφορές των άρθρων που βρέθηκαν από τις προηγούμενες αναζητήσεις. Στην αναζήτηση συμπεριλήφθηκαν τυχαιοποιημένες και μη κλινικές μελέτες. Οι ασθενείς χωρίστηκαν σε δύο ομάδες, αυτούς που έλαβαν συμπυκνωμένα ερυθρά:πλάσμα σε αναλογία ≥1.5:1 και αυτούς που έλαβαν με αναλογία <1.5:1. Το πρωτογενές καταληκτικό σημείο ήταν η μετεγχειρητική θνησιμότητα στις 24 ώρες και 30 ημέρες. Μελετήθηκε επίσης η επίδραση των διαφόρων αναλογιών παραγόντων αίματος στην θνητότητα των ασθενών. Ο κίνδυνος συστηματικού σφάλματος εκτιμήθηκε με την κλίμακα Newcastle-Ottawa Quality Assessment Scale, ενώ η συνολική ποιότητα των μελετών αξιολογήθηκε με το εργαλείο MINORS.

Αποτελέσματα: Σε αυτήν την συστηματική ανασκόπηση και μετα-ανάλυση συμπεριλήφθηκαν 22 μελέτες με 84955 ασθενείς. Μετά από μαζική μετάγγιση, η πιθανότητα (odds ratio) θανάτου στις 24 ώρες και 30 ημέρες είναι 0.22 (95% CI: 0.16-0.30) και 0.27 (95% CI: 0.20-0.37), αντίστοιχα. Η πιθανότητα (odds ratio) θανάτου κατά την νοσηλεία στο νοσοκομείο είναι 0.23 (95% CI:0.12-0.44). Δεν βρέθηκε σημαντική διαφορά στην θνητότητα μεταξύ ασθενών που έλαβαν παράγωγα σε υψηλή αναλογία και αυτών που έλαβαν σε χαμηλή αναλογία [0.24 (95% C.I.: 0.15 to 0.37) vs. 0.28 (95% C.I.: 0.21 to 0.37)]. Παρατηρήθηκε υψηλή ετερογένεια μεταξύ των μελετών.

Συμπεράσματα: Η παρούσα συστηματική ανασκόπηση και μετα-ανάλυση δεν βρήκε σημαντικές διαφορές μεταξύ των διαφόρων αναλογιών χορήγησης παραγόντων αίματος όσον αφορά την επιβίωση. Ο βαθμός ετερογένειας των μελετών επισημαίνει την ανάγκη για υψηλής ποιότητας

κλινικές μελέτες, ώστε να να προσδιοριστεί το βέλτιστο πρωτόκολλο μαζικής μετάγγισης με στόχο την βελτίωση της επιβίωσης των ασθενών με διεγχειρητική αιμορραγία.

Λέξεις-κλειδιά: μαζική μετάγγιση, πρωτόκολλο μαζικής μετάγγισης, συμπυκνωμένα ερυθρά, φρέσκο κατεψυγμένο πλάσμα, διεγχειρητική περίοδος, χειρουργείο, τραύμα, αιμορραγία

ABSTRACT

Background: Massive transfusion is widely used in patients with severe intraoperative hemorrhage. Although different ratios of blood products are proposed for massive transfusion protocols, significant controversy exists regarding their effect on outcome.The purpose of this systematic review and meta-analysis was to assess the effect of massive transfusion strategies on postoperative mortality in patients suffering severe intraoperative bleeding.

Methods: A systematic search of PubMed and clinicaltrials.gov databases was conducted for articles from January 2000 to April 2022. A second search was carried out by combining free text words and indexed terms with Boolean operators. A third search was conducted with the reference lists of all identified reports and articles for additional studies. Inclusion criteria were randomized controlled and non-randomized trials. Case reports and case series, review and meta-analysis articles, book chapters, non-peer-reviewed articles, experimental studies, studies including obstetric and pediatric patients, and non-English literature were excluded. Patients were divided into two groups, the HIGH group including studies with pRBC:FFP ratio ≥1.5:1 and the LOW group including studies with pRBC:FFP ratio <1.5:1. Mortality at 24-hours and 30-day postoperative mortality were the primary outcomes. The effect of different ratios and/or blood products on mortality of patients was investigated as a secondary outcome. Risk of bias was evaluated with the Newcastle-Ottawa Quality Assessment Scale, while the overall quality of the studies was assessed by the MINORS tool.

Results: This systematic review and meta-analysis included 22 studies and 84955 patients.After massive transfusion, the odds ratio of 24-hour and 30-day mortality is 0.22 (95% CI: 0.16-0.30) and 0.27 (95% CI: 0.20-0.37), respectively. The odds ratio of in-hospital mortality is

0.23 (95% CI: 0.12-0.44). No significant difference between mortality of trauma and non-trauma patients was observed [0.80 (95% CI: 0.42-1.53)]. Also, there was no significant difference in mortality between the HIGH and the LOW group [0.24 (95% C.I.: 0.15 to 0.37) vs. 0.28 (95% C.I.: 0.21 to 0.37)]. The included studies showed high heterogeneity.

Conclusions: This systematic review and meta-analysis did not reveal significant differences among different RBC:FFP ratios in terms of survival. The level of heterogeneity of the included studies highlights the need for high quality clinical trials to identify the optimal massive transfusion protocol and to improve survival of patients with severe intraoperative hemorrhage.

Key words: massive transfusion, massive transfusion protocol, packed red blood cells, fresh frozen plasma, platelets, intraoperative, surgery, trauma, bleeding, hemorrhage

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Chapter 1 Introduction

1.1 Massive hemorrhage

A main cause of perioperative morbitity and mortality is intraoperative hemorrhage. This applies especially in patients undergoing emergency surgery. Of note, about 30% of deaths in elective procedures are caused by unexpected injury of an organ or a vessel. [1–6]

Massive hemorrhage is defined as any of the following: (1) blood loss that exceeds the circulating blood volume of a patient within 24 hours; (2) blood loss that exceeds half (50%) of the circulating blood volume within a 3-hour-period; (3) blood loss that exceeds 150 ml min^{-1}, or (4) blood loss that requires platelet and plasma transfusion. Nevertheless, there are cases of massive hemorrhage that do not fulfil the abovementioned criteria. Other factors having a crucial role in massive hemorrhage are the volume and the speed of blood loss, pre-existing co-morbidities or abdominal adhesions, and factors associated with the administered blood products. All the aforementioned may provoke a rapid deterioration of the bleeding patient. In either case, early recognition and adequate management are essential in order to prevent hemorrhagic shock and secondary organ injury[7–9]. In addition, several human factors can provoke or aggravate intraoperative hemorrhage, such as inexperienced personnel, delay in recognizing blood loss, or inappropriate handling of surgical instruments and devices. The communication between surgical and anesthesia teams can also affect outcomes after severe intraoperative hemorrhage. [2,10]

1.2 Massive transfusion

Hypovolemic shock induces tissue hypoperfusion, decreases cellular oxygenation, and causes coagulation abnormalities, which can be further aggravated by acidosis, hypocalcemia and hypothermia. These disturbances are often present in patients with severe bleeding even before the onset of hypotension, and can result in altered enzymatic activity and organ injury or failure.

The transfusion of at least 10 units of packed red blood cells (pRBCs) within 24 hours is defined as massive transfusion. Massive transfusion aims at restoring tissue perfusion and oxygen delivery to the cells, and coagulation disorders[11–13] As a matter of fact, massive transfusion protocols (MTPs) include consideration of several parameters, such loss of blood volume, tissue oxygenation, acid-base balance and coagulation.[14]

Massive transfusion protocols are predefined protocols of blood and blood products activated for controlling massive hemorrhage, and are offered in ratios of packed red blood cells (PRBC) to fresh frozen plasma (FFP) to platelets (PLT) of 1:1:1, or 1:1:2. These protocols are usually activated in the hospital setting, yet most studies on massive transfusion have extracted data from military or civilian trauma patients. Up to date, although the incidence of massive transfusion is considered to be low, mortality of these patients is relatively high. [13]

1.3 Guidelines on intraoperative massive transfusion

Restoration of circulatory volume aims at improving tissue perfusion and oxygenation and is a main therapeutic modality along with surgical hemostasis and correction of coagulopathy. The main goals of massive transfusion include maintaining hemoglobin 7-9g/dL, mean arterial pressure (MAP) 60-65mmHg, INR <1.5, fibrinogen >1.5-2 g/L, normal pH (7.35-7.45), and core temperature >35 ^{o}C. [15]

Development of MTPs requires a multidisciplinary approach and specialties, including anesthesiologists, surgeons, transfusion specialists, nursing staff, and hospital administrators. [1,6,16] Various protocols are available worldwide, with the relevant evidence, coming from military trauma patients, suggesting that massive transfusion with fresh whole blood may improve outcome. [13,17–19] However, administration of fresh whole blood remains impractical in the civil setting, and thus, massive transfusion protocols use ratios of PRBCs, FFP, and PLTs as substitute to whole blood. Fresh frozen plasma provides the much-needed coagulation factors, while cryoprecipitate, recombinant factor VIIIa, and fibrinogen concentrate are widely used, but research so far has failed to provide safe conclusions. In both the military and civilian settings, tranexamic acid (TXA) has also proven to be efficient against coagulopathy and can improve survival if administered within the first 3 hours of hemorrhage onset. [6,13,15]

In trying to maintain a balanced resuscitation via component therapy, many questions have arisen as to the appropriate balance of components during the management of massive trauma. The Pragmatic, Randomised, Platelet and Plasma Ratios trial (PROPPR) offers the best evidence of massive tranfusion component ratio. They compared the ratios of 1:1:1 and 1:1:2 in PRBC:FFP:PLT. While unable to find a statistically significant difference in mortality at 24 hours and 30 days, Holcomb et al. did demonstrate that the 1:1:1 ratio achieved faster hemostasis and fewer deaths due to exsanguination at 24 hours.[20] Although component therapy is a viable option for the patient that can produce good clinical outcomes, it remains unknown which resuscitation strategy is best for the patient in the short- and long-term.

This systematic review and meta-analysis was carried out to assess the effect of massive transfusion strategies on postoperative mortality in patients with severe intraoperative bleeding.

Chapter 2 Materials & Methods

2.1 Protocol and registration

The protocol was submitted in the PROSPERO register of systematic reviews on May 27, 2022 (CRD42022335803). This systematic review and meta-analyses were reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist. [21]

2.2 Inclusion and exclusion criteria

The inclusion criteria of the current systematic review and meta-analysis were: (1) randomised controlled trials (RCTs), non-randomised trials, and observational studies; (2) adults (≥ 18 years old); (3) intraoperative period; (4) severe bleeding requiring massive transfusion.

Exclusion criteria include case studies and case series, review articles, meta-analysis articles, book chapters, non-peer-reviewed articles, articles in languages other than English or Greek, studies on laboratory animal models, or in-vitro studies. We also excluded articles with solely obstetric and pediatric patients.

2.3 Outcomes of interest

The primary outcome was mortality at 24-hours and at 30-day postoperative mortality. Secondary outcome was to investigate the effect of different ratios and/or blood products on mortality of patients with severe intraoperative bleeding.

2.4 Search strategy

All available published and unpublished studies from January 2000 to April 2022 were explored. A comprehensive initial search was employed in PubMed (MEDLINE) and clinicaltrials.gov databases with any of the following MeSH® terms in the abstract or title: hemorrhage, blood transfusion, blood component transfusion, or any of the following terms;

massive transfusion, bleeding, RBC, platelets, plasma, ratio, strategy, blood loss, blood products, complications, outcome, survival and the wildcard term hemorrhag*. A second search was conducted by combining free text words (intraoperative period, surgery, or surgical, intraoperative care, surgical procedures, operative) and indexed terms with Boolean operators. A third search was conducted with the reference lists of all identified reports and articles for additional studies.

2.5 Data extraction

Two independent researchers extracted the data from every study using a customized format. Any disagreements between the two independent researchers were resolved by two other researchers. Publication details (authors, year), study information (design, population, follow-up, inclusion-exclusion criteria, number of cases/cohort-size, and subgroups), type of surgery, massive transfusion strategy/ratio hospital length of stay, length of mechanical ventilation, ICU length of stay and outcome (at hospital discharge, 30 days and 90 days) will be extracted in a pre-designed Excel spreadsheet.

2.6 Assessment of methodological quality

Two independent researchers assessed the retrieved articles for methodological quality before inclusion in the review. The overall quality of the included observational studies was assessed using the MINORS tool, while the risk of bias was evaluated with the Newcastle-Ottawa Quality Assessment Scale. Any disagreements between the researchers appraising the articles were resolved through discussion with the other researchers.

2.7 Data analysis and synthesis

Effect size was estimated by computing the standardized error of the mean (SEM) taking into consideration the number of patients presenting the result (outcome) of question within the sample and the sample size of each study. Data synthesis in adequate software was performed with the standard random-effects models, as described by DerSimonian and Laird. [59] Random-effects models is preferred over the fixed-effects model due to the expected high heterogeneity between the included studies regarding the different settings, type of patients and procedures, as well as outcome definition. The significance level is set at $p < 0.05$. Heterogeneity among studies was assessed by the I^2 statistic, with significance level of P value < 0.05 or a value of $I^2 > 50\%$. Many of the studies reported mortality outcome by categories, mainly by surgery type, and not overall. In order to be as precise as possible, if synthesis of surgical cases alone was possible, the mortality was summed up, as well as the sample size, while other non-surgical medical conditions requiring massive transfusion were excluded. In case the outcome (mortality) was reported in total, if surgical cases were more than 75%, the study was included in the meta-analysis. If the non-surgical cases were more than the abovementioned percentage and the outcome (mortality) was reported in total, the study was excluded from meta-analysis.

As the number of studies included in our analysis is higher than ten, funnel plot of studies is presented for every analysis we performed. Subgroup analysis of studies based on trauma and non-trauma patients, as well as analysis of blood product ratios were performed from available data. All analyses were performed using Review Manager software (RevMan 5.3) and MiniMeta online tool.

Chapter 3 Results

3.1 Search Results

The selection process results of this study is depicted Figure 1.

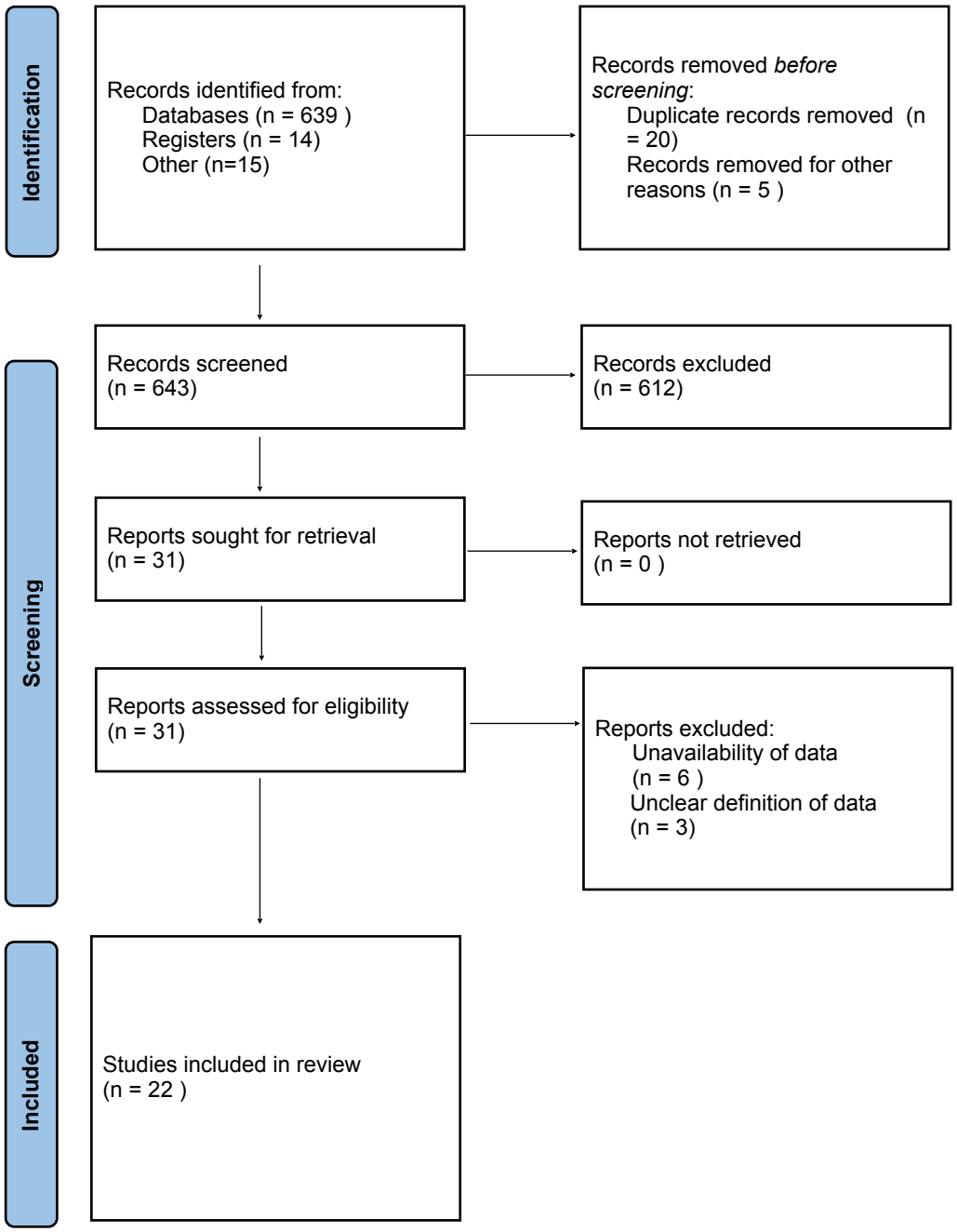


Figure 1. Prisma Flowchart

Altogether, 643 relevant citations were identified and screened, while 31 studies were included in our final assessement for possible data extraction .(Fig. 1) In total, data extraction was possible in 22 studies. The basic characteristics of these studies are summarised below in Table 1.

Table 1. Basic characteristics of the included studies

Study ID	Study type	Setting	Study size (participants)	Patient characteristics	Male (%)	Mean Age
Tennyson 2021	Retrospective	Addenbrooke's Hospital, Cambridge, UK (2015-2018)	27	Cardiac surgery, Thoracic surgery, Solid organ transplant	70.4 %	57.3
Hu 2021	Retrospective	University Hospital in University of Alabama, Birmingham (2018-2020)	235	Trauma	79.6 %	36
Hess 2018	Retrospective	Records from Harborview Transfusion Service,Washington (2016)	309	Trauma, AAA ruptured, Other surgery/OR, GI bleeding, other ward/ ICU, Obstetric surgery	NA	NA
Rankin 2017	Retrospective	The Ohio State University Wexner Medical Center (2008-2012)	25	Neurosurgical / Orthopedic (or combined)	56%	50.5
Mesar 2017	Retrospective	Massahusetts General Hospital, Boston (2009 - 2012)	865	Cardiac surgery, Liver transplant, Trauma surgery, General surgery, Vascular surgery, Other medical issues, Orthopedic surgery, Cardiopulmonary transplant surgery, Obstetric surgery, Urology surgery, Neurosurgery, Burns, Thoracic surgery, Otolaryngology	67%	59.6
Halmin 2016	Retrospective	Sweeden & Norway (1987-2010)	72257	Trauma, Obstetric,Cardiac/ Vascular surgery, Cancer surgery, Other surgery	NA	NA (graph)

Turan 2013	Retrospective	Records from Database of American College of Surgeons National surgical quality improvement program (2006-2009)	5143	Surgical patients	38.6 %	69
Cap 2012	Retrospective	The United States military hospital in Baghdad, Iraq (2004-2006)	414	Iraq soldiers and casualties, not burns, only patients receiving MT during first 24h and not died during 1st hour	93-99%	26
Wijaya 2016	Retrospective	Changi General Hospital (CGH), Singapore (2011-2013)	18	Trauma and Non-Trauma patients	NA	NA
Kauvar 2012	Retrospective	Records of University of Utah, Lake City (1989-2009)	89	RAAA	81%	74
Sisak 2012	Retrospective	John Hunter Hospital and University of Newcastle, New South Wales, Australia (2001 - 2009)	58	Trauma	74%	46.0
Van der Meij 2019	Prospective	Liverpool Hospital, Sydney, Australia (2002-2016)	168	Trauma	76-83%	43
Sinha 2011	Retrospective	Flinders Medical Centre & Repatriation General Hospital, Australia (1998-2006)	220	Trauma or Surgery (AAA, Trauma, Cardiothoracic surgery, liver transplantation, abdominal/orthopedic surgery, OB)	73.5 %	63
Sinha 2017	Retrospective	Flinders Medical Centre (2010 - 2014)	190	Gastro-intestinal haemorrhage, trauma, cardiothoracic surgery, other surgery, liver transplant/surgery, vascular surgery, obstetric haemorrhage, medical/other	62%	60
Morse 2012	Prospective	Grady Memorial Hospital, Georgia (2007-2011)	439	Trauma	78%	37.5

Warner 2020	Retrospecti ve	Mayo Clinic,Rochester, Minessota (2011 - 2015)	2385	Intraoperative - cardiac surgery, general surgery, solid organ transplant, vascular surgery	57.7 %	62.9
Sharpe 2012	Prospective	Presley Regional Trauma Center (2006-2009)	135	Trauma	74%	36
Cotton 2009	Retrospecti ve	Vanderbilt University Medical Center (2004-2008)	266	Trauma	87%	38.5
Dente 2009	Prospective	Grady Memorial hospital, Georgia (2005-2008)	73	Trauma	82-8 4%	36
Matthay 2021	Retrospecti ve	Multicenter, 17 trauma centers (2014 – 2019)	461	Trauma	82%	35
Hong 2021	Retrospecti ve	University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA (2009-2018)	126	Cardiac Surgery	91.3 %	62.5
Tsukinag a 2018	Retrospecti ve	National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka, Japan (2012-2016)	1052	Cardiac Surgery	65%	71

Study Demographic Characteristics

We included adults of both sexes, with younger men predominating especially among trauma studies.[22–29] On the contrary, cardiovascular surgery or ruptured abdominal aortic aneurysm studies included older patients. [30–36] We observed significant heterogeneity in hospital setting, such as Level 1 Trauma Centers, Military and Civilian Hospitals in war zones, especially in Iraq, and large hospitals.

Study intervention and outcomes characteristics

This systematic review and meta-analysis investigated massive transfusion among surgical patients of any type (trauma, obstetrics, abdominal aortic aneurysm, cardiothoracic surgery, solid organ transplantations, general surgery). No restrictions on blood product ratios or implementation of MTPs were applied. Most studies included trauma patients, either civilian trauma or military trauma cases. [22,24–29,37] On the other hand, there were studies including patients of both surgical and trauma cases that received massive transfusion. [38–42] However, there are studies of either emergency or elective surgical cases that required massive transfusion. [30–33,35,36,40,42,43] Some studies included patients of national records of massive transfusion, regardless of the cause, and we pooled the surgical cases out of the total amount of patients. [38–40,42,43]

All the included studies presented percentages of either in-hospital mortality, 24-hour mortality, or 30-day mortality. [22,25,26,28–30,32,33,37,42–44]Studies presenting none of the above outcomes, or mortality measured otherwise or unclearly defined, were excluded.

Excluded studies

Nine studies were excluded by full text, mainly due to mortality definition issues or unclear results that were presented only on graphics, thus it was impossible to draw the numeric values with certainty. Twenty-two studies were included in this systematic review and meta-analysis. (Table 1)

3.2 Risk of Bias (Quality) Assesment

Risk of bias was evaluated with the Newcastle-Ottawa Quality Assessment Scale. Studies were evaluated for selection bias, comparability bias, and outcome bias. Risk of bias performance of each study in every bias category is presented in Figure 2.

The MINORS tool was utilised to assess the quality of the studies, which ranged between 5 and 7. (Figure 2) Risk of bias assessment was performed with the Cochrane Collaboration tool available on software of Review Manager version 5.3 (RevMan 5.3, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Short term mortality was recorded at 24-hours; thus, the short-term effect of massive transfusion resuscitation could be properly evaluated. We considered in-hospital mortality as inadequate length of follow-up and 30-day mortality as adequate follow-up. Studies were accredited

a point for 30-day mortality rates, while those presenting only in-hospital mortality, or 24-hour mortality lost the point in risk of bias assessment.

Most studies were not sponsored by any company or institution. Study results are based on national or hospital records that could not be altered or biased by any means.

The observational non-randomised studies included in this review and meta-analysis have a low grade in quality of evidence according to GRADE criteria.

Figure 2. Risk of bias (NOS)

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of Exposure	Demonstration that outcome of interest was not present at start of study	Comparability	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total
Tennyson 2021	*	*	*	*		*	*	*	7
Hu 2021	*	*	*	*		*	*	*	7
Matthay 2021	*	*	*	*		*		*	6
Rankin 2017	*	*	*	*		*	*	*	7
Mesar 2017	*	*	*	*		*	*	*	7
Halmin 2016	*	*	*	*		*	*	*	7
Mazzeffi 2017	*	*	*			*	*	*	6
Turan 2013	*	*	*	*		*	*	*	7
Cap 2012	*	*	*	*		*	*	*	7
Wijaya 2016	*	*	*	*		*	*	*	7
Kauvar 2012	*	*	*	*		*		*	6
Sisak 2012	*	*	*	*		*			5
Van der meij 2019	*	*	*	*		*		*	6
Sinha 2011	*	*	*	*		*		*	6
Sinha 2017	*	*	*	*		*			5
Unlu 2021	*	*	*	*		*		*	6
Hong 2021	*	*	*	*		*	*	*	7
Morse 2012	*	*	*	*		*	*	*	7

Warner 2020	*	*	*	*		*		*	6
Sharpe 2012	*	*	*	*		*		*	6
Cotton 2009	*	*	*	*		*	*	*	7
Dente 2009	*	*	*	*		*	*	*	7

Selection bias

Our study included both retrospective and prospective surgical cohorts of patients undergoing massive transfusion. All studies provided adequate information about sample and patients' records. Furthermore, patients who didn't receive massive transfusion were drawn from the same population as those who received. All data were pooled from databases or records held in surgical departments of hospitals or blood bank departments. Patients who died in less than an hour after hospital admission were excluded in most studies. However, these cases could not significantly alter the outcome of the present study, as they would not have survived to receive massive transfusion.

Comparability

This systematic review and meta-analysis were not intended to compare different interventions or study groups, but to observe the mortality rates of surgical patients receiving massive transfusion. Transfusion ratios of RBCs, Platelets, FFP were recorded when provided by the included studies and, if adequate, were analyzed as subgroup analysis.

3.3 Mortality (24-hour)

Fifteen out of 22 included studies provided data on hospital mortality at 24-hours, resulting in a total population of 5212 individuals. (Table 2)

Table 2. Studies reporting 24-hour mortality outcome

Study	Study size	24 hour mortality (N)	24-hour mortality (%)
Tennyson 2021	27	3	11.1
Hu 2021	235	36	15.3
Matthay 2021	461	207	45
Cap 2012	414	83	20
Wijaya 2016	18	6	33.3
Kauvar 2012	89	18	20.2
Sisak 2012	58	19	32.8
Van der meij 2019	168	56	33.3
Sinha 2011	220	40	18.2
Sinha 2017	190	14	7.4
Morse 2012	439	137	31
Warner 2020	2385	193	8.1
Sharpe 2012	135	31	22.9
Cotton 2009	266	124	46.6
Dente 2009	73	13	17.6

In our study, meta-analysis of 24-hour mortality rates among the included studies revealed that Odds Ratio of 24-hour mortality is 0.22 (95% CI: 0.16-0.30). There are specific studies that report very low mortality rates, such as these by Sinha et al. and Warner et al. [43,44], while others report mortality rates of up to 46.6% [28,29]. It is possible that the different settings or type of patients could interpret this heterogeneity of mortality rates. On the other hand, there are studies with very small study size, thus it is difficult to draw safe conclusions. [30,41]

Of these 5212 patients who received massive transfusion, 930 patients died within the first 24-hours (mortality rate 18.8%). The studies showed high heterogeneity, with mortality rate fluctuating from 7.4% to 46.6% among them. (Figure 4)

Figure 3. Forest plot of 24-hour mortality

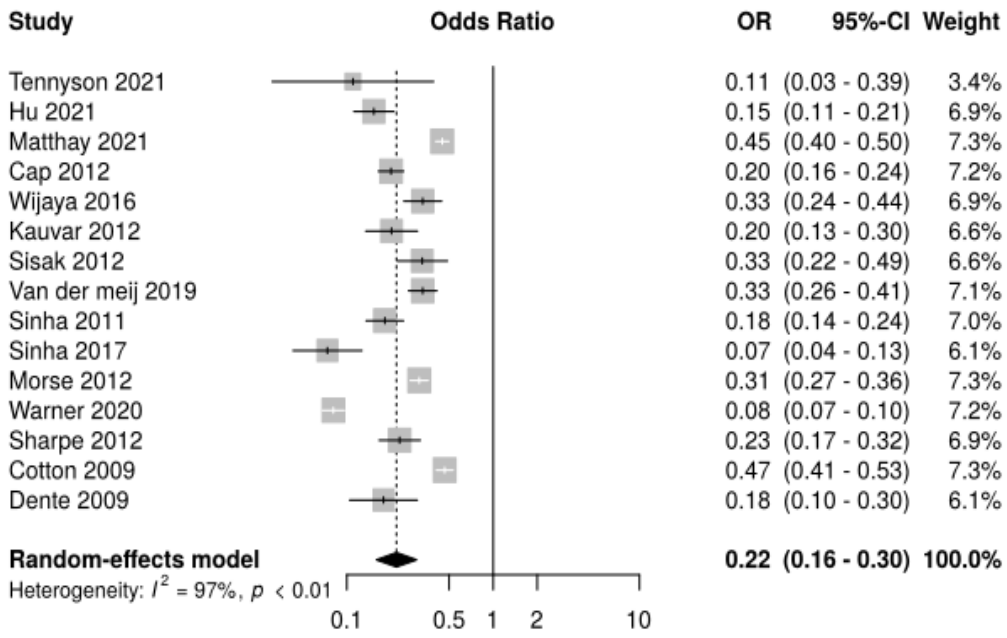
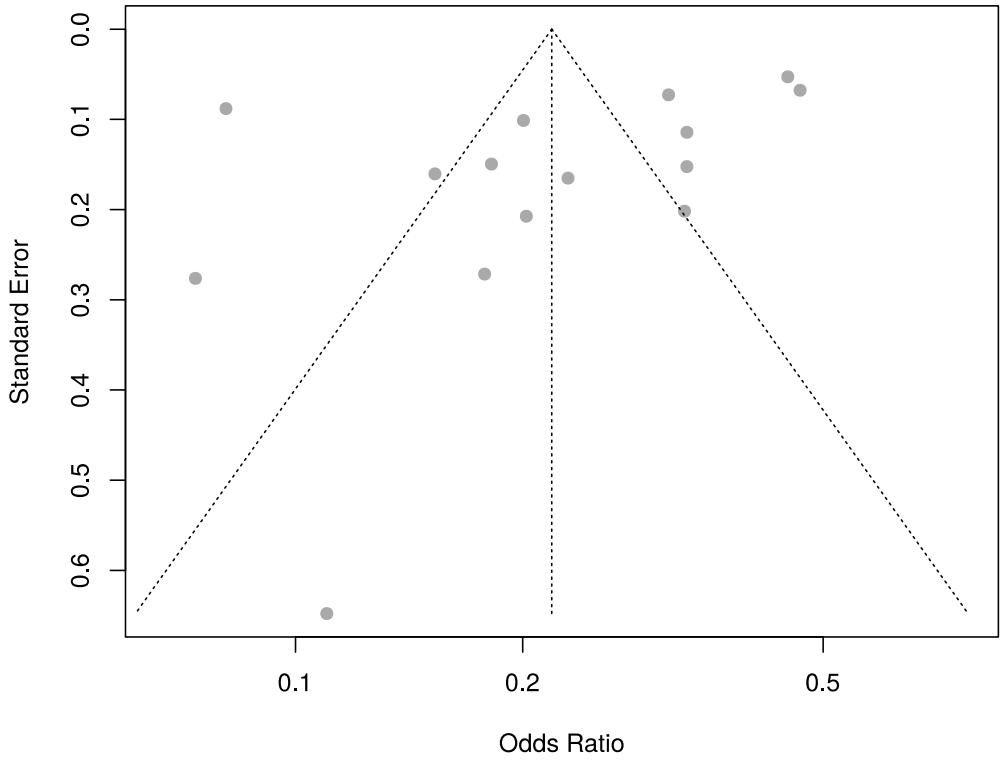


Figure 4. Funnel plot of 24-hour mortality



3.4 Mortality (in-hospital)

The total number of participants of the studies reporting in-hospital mortality outcome were 5009. (Table 3)

Table 3. Studies reporting in-hospital mortality outcome

Study	Study size	In-hospital Mortality (N)	In-hospital Mortality (%)
Sinha 2011	220	49	22
Kauvar 2012	89	39	43,8
Sharpe 2012	135	51	38
Sinha 2017	190	51	26.7
Hess 2018	309	66	21,4
Van der meij 2019	168	74	44
Warner 2020	2385	203	6
Matthay 2021	461	300	65
Tsukinaga 2018	1052	49	4.7

Meta-analysis of in-hospital mortality rates showed that Odds Ratio of in-hospital mortality is 0.23 (95% CI: 0.12-0.44). Specific studies with large samples report very low mortality rates [36,43]. On the other hand, Matthay et al. reported 65% of in-hospital mortality, possibly due to severe trauma necessitating the transfusion of more than 20 pRBCs [28]. Warner et al. included undergoing elective surgery of various types in an organized setting who suffered less critical or urgent hemorrhage [43]. These could also interpret the high heterogeneity in mortality rates. (Figure 6)

Of the 5009 patients who received massive transfusion, 882 died during hospitalization (mortality rate 17.6%). Data provided by the included studies have high heterogeneity, with mortality rate fluctuating from 4.7% to 65% among the different studies.

Figure 5. Forest plot of in-hospital mortality

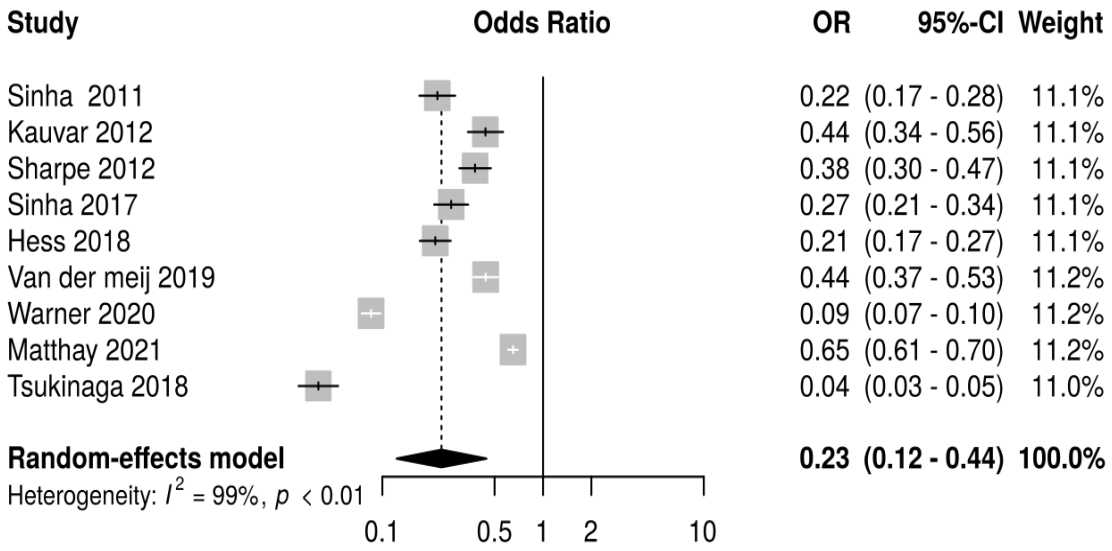
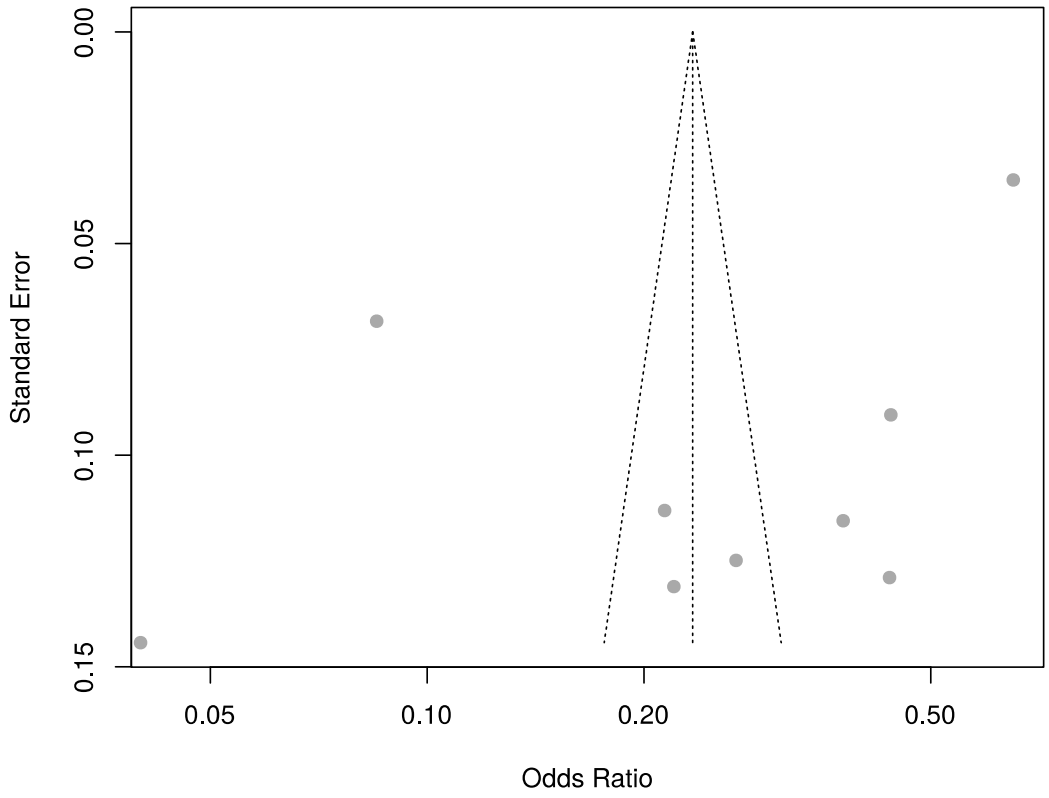


Figure 6. Funnel plot of in-hospital mortality



3.5 Mortality (30 days)

The total number of participants of the studies that report 30-day mortality outcome was 79888. These were derived from 12 studies. (Table 4)

Meta-analysis of 30-day mortality rates among the included studies showed that Odds Ratio of 30-day mortality is 0.27 (95% CI: 0.20-0.37). One study included 72.257 [39], but others report very low mortality rates, such as Rankin et al. [31], while others report mortality of up to 68.7% [29]. Different settings, type of patients, and type of surgery could interpret the high heterogeneity of the mortality rates.

Of the 79888 patients who received massive transfusion, 17420 died within the first 30 days (mortality rate of 21.8%). Data provided by the included studies have high heterogeneity, with mortality rate fluctuating from 4% to 68.7% .(Figure 8)

Table 4. Studies reporting 30-day mortality outcome

Study	Study size	30-day mortality (N)	30-day mortality (%)
Tennyson 2021	27	6	22.2
Hu 2021	235	61	26
Rankin 2017	25	1	4
Mesar 2017	865	229	26.4
Halmin 2016	72257	15720	21.7
Turan 2013	5143	867	17
Cap 2012	414	112	27
Wijaya 2016	18	8	44.4
Hong 2021	126	9	7.1
Morse 2012	439	196	45
Cotton 2009	266	183	68.7
Dente 2009	73	28	38.4

Figure 7. Forest plot of 30-day mortality

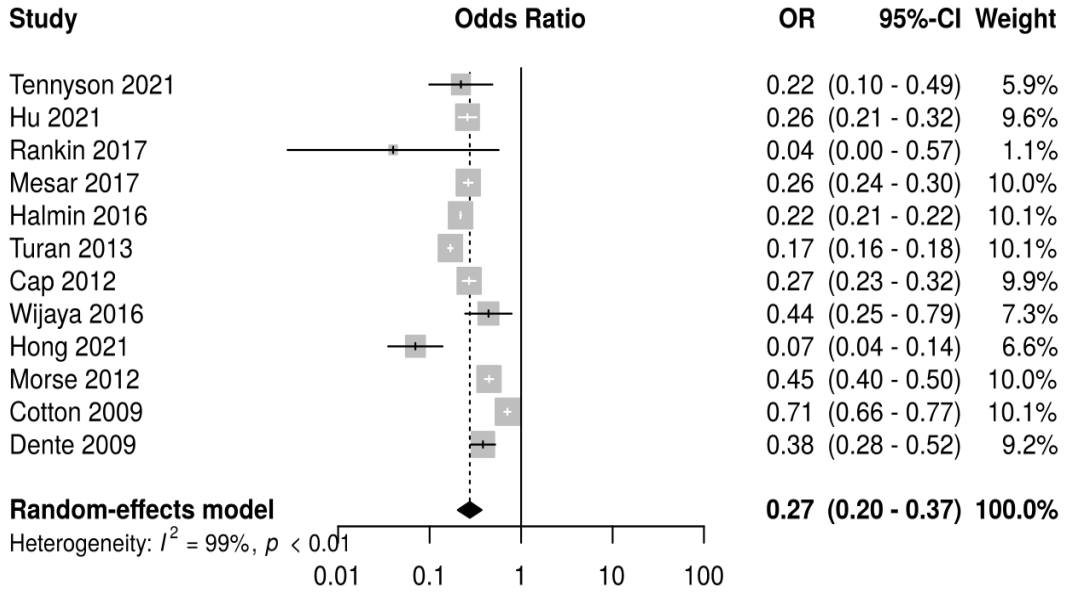
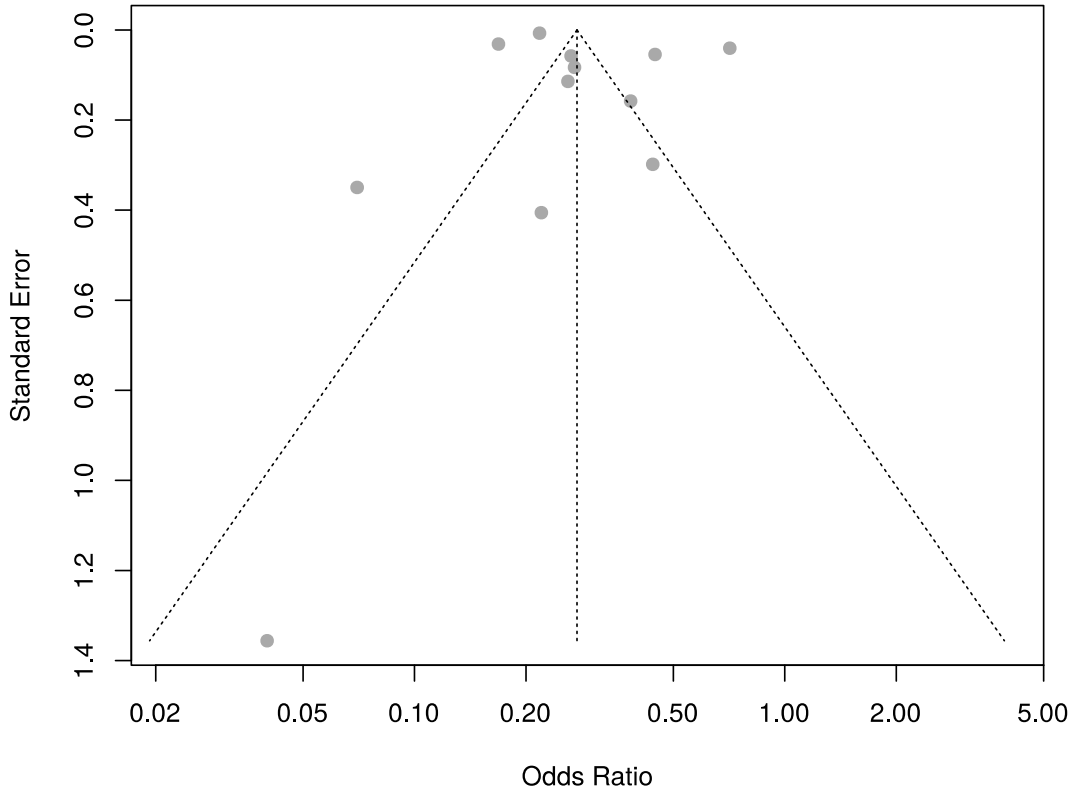


Figure 8. Funnel plot of 30-day mortality



3.6 Mortality rates in trauma and non-trauma patients

Some studies included both trauma and non-trauma patients, while others included only trauma patients or focused on specific type of surgeries. Specifically, nine studies included only trauma patients that required massive transfusion [22,24–28,37,45,46], six studies included non-trauma patients [30,31,33,35,36,40,43], while six studies included both trauma and non-trauma patients [32,38,39,41,42,44]. Overall mortality was defined as the longest available provided in the studies presenting data from both trauma and non-trauma patients.

There is no significant difference between mortality of trauma patients that underwent massive transfusion versus non-trauma patients. (Figure 9) However, these results are limited, as the trauma exclusive studies that also include combat trauma report even higher mortality rates than those with civilian trauma. Heterogeneity was also high, due to small number of studies included in the subgroup meta-analysis. (Figure 10)

Figure 9. Forest plot of trauma VS non-trauma overall mortality after massive transfusion (Experimental = trauma, Control = Non-trauma)

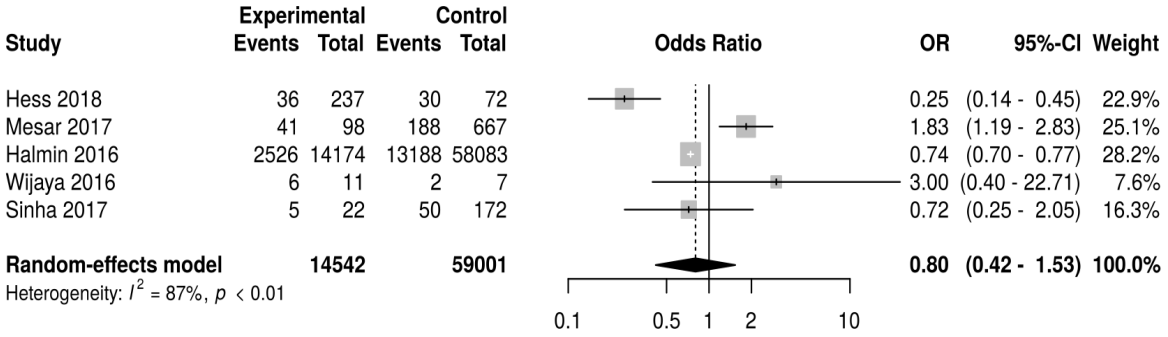
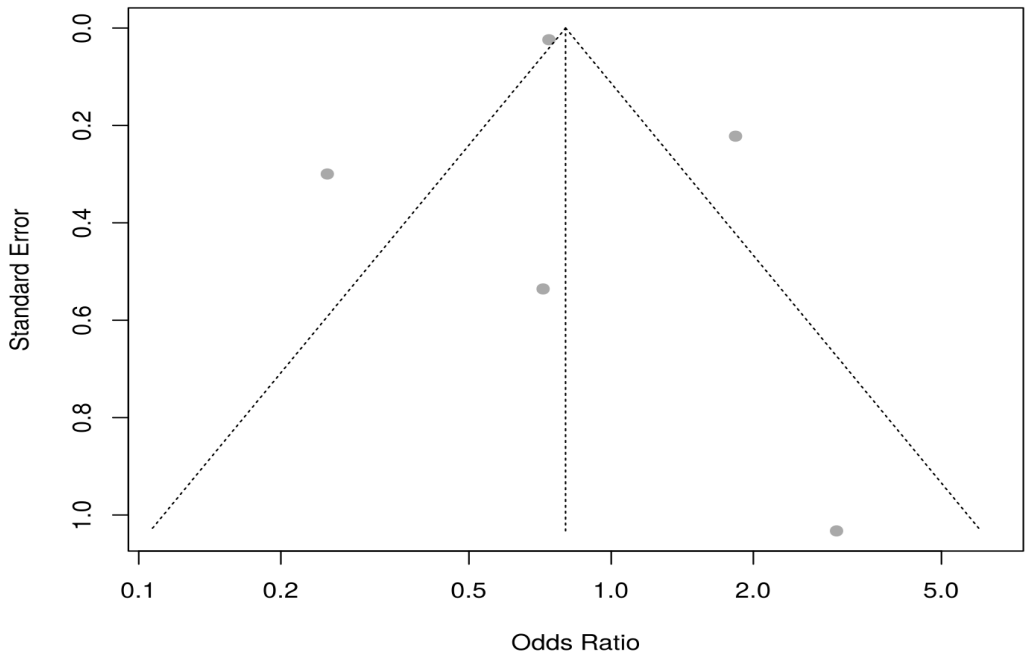


Figure 10. Funnel plot of trauma VS non-trauma mortality after massive transfusion



3.7 Overall mortality and RBC:FFP ratio

The included studies presented different MTP ratios of pRBC and FFP. However, there were studies where transfusion failed to meet the predefined ratios. For this meta-analysis, the intended pRBC:FFP ratio was taken into consideration. For this reason, included studies were divided into two groups. HIGH group included studies with pRBC:FFP ratio equal or over 1.5:1, while the LOW group included studies with pRBC:FFP ratio lower than 1.5:1. Overall mortality is considered to be the mortality in longest available follow-up, thus includes both in-hospital and 30-day mortality. When both available, the 30-day mortality rates were considered to be the longest follow-up. Only one study did not report any data about blood product ratios. [40]

Based on our meta-analysis, there is no significant difference between the two groups, with HIGH group Odds Ratio being 0.24 (95% C.I.: 0.15 to 0.37), while the LOW group reports an Odds ratio of 0.28 (95% C.I.: 0.21 to 0.37). Overall Odds Ratio of mortality rates 0.26 (95% C.I.: 0.19 to 0.35). (Figure 11) However, heterogeneity is high. (Figure 12)

Figure 11. Forest plot of overall mortality & FFP:RBC ratio

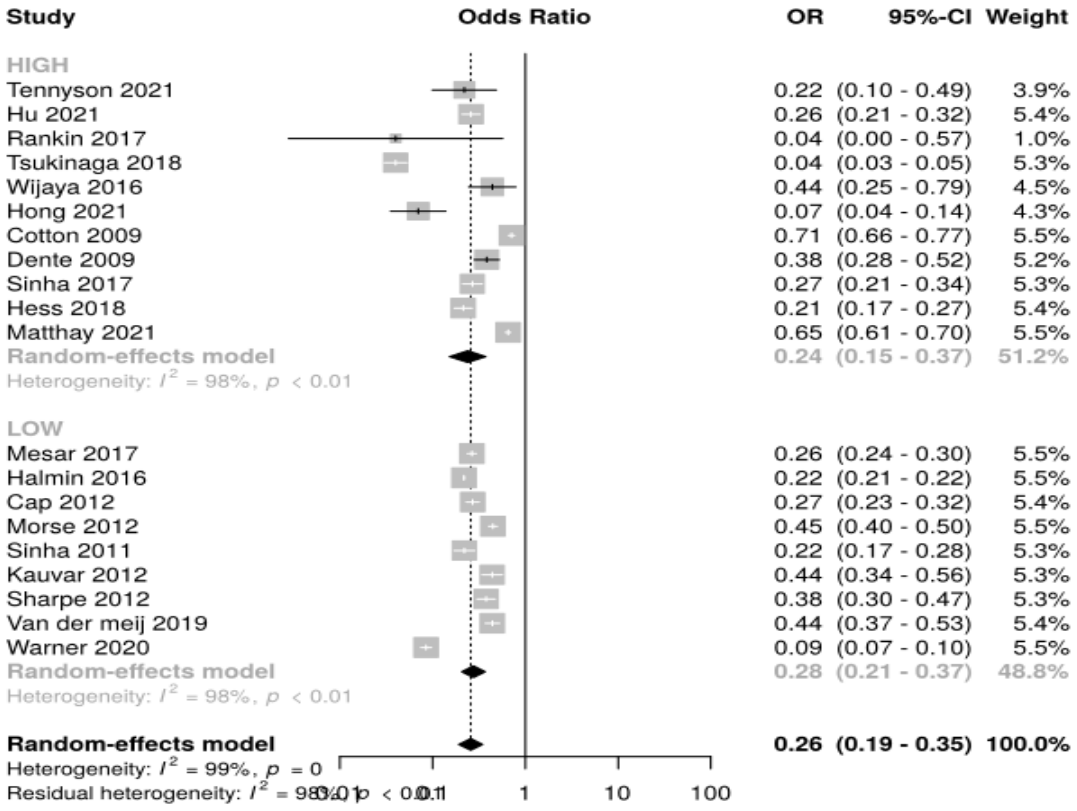
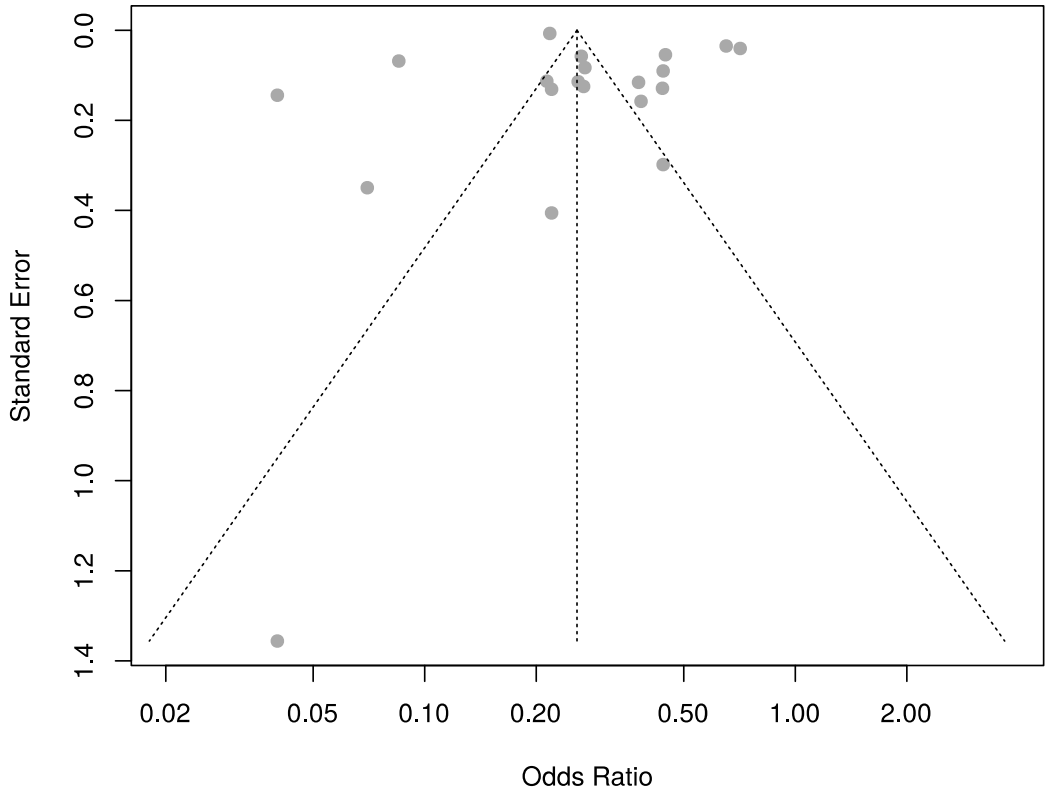


Figure 12. Funnel plot of overall mortality studies



Chapter 4 Discussion

Summary of findings

In this systematic review and meta-analysis, we investigated the massive transfusion strategies in patients with severe intraoperative haemorrhage. Specifically, we assessed the 24-hour mortality, in-hospital mortality, and 30-day postoperative mortality. Furthermore, we compared mortality between trauma and non-trauma patients and assessed the effect of different MTP ratios. The main results of this study are: (1) the Odds Ratio of 24-hour mortality is 0.22 (95% CI: 0.16-0.30); (2) the Odds Ratio of 30-day mortality is 0.27 (95% CI: 0.20-0.37); (3) the Odds Ratio of in-hospital mortality is 0.23 (95% CI: 0.12-0.44); (4) there is no significant difference between mortality of trauma vs. non-trauma patients [0.80 (95% CI: 0.42-1.53)]; (5) there is no significant difference between the HIGH and the LOW group [0.24 (95% C.I.: 0.15 to 0.37) vs. 0.28 (95% C.I.: 0.21 to 0.37)]

The present systematic review and meta-analysis included 22 studies and 84955 patients. The heterogeneity was high in all outcome analyses, yet this can be explained by numerous factors, such as the different type of the included patients, the different ratios of blood products, or the small sample in some studies. In addition, the outcomes and follow-up time was not the same among all studies. Nevertheless, our results are intriguing considering that we did not observe significant differences in overall mortality of either high or low pRBC:FFP ratio. Specifically, Hong et al. (2021) and Kauvar et al. (2012) reported no significant decrease in mortality with liberal use of FFP.[33,35] The same results were reported by Cap et al. (2012) for unadjusted data; the same authors also reported better survival in high PLT:RBC with adjusted data[45] However, the high PLT:RBC ratio was also associated with higher FFP:RBC ratio. On the other hand, Matthay et al. (2021) reported that an FFP:RBC ratio of < 1:1.5 is significantly associated with mortality [28]. Only one trial investigated different ratios of blood products. Holcomb et al. (2015) showed that the pRBC:FFP:PLT ratio of 1:1:1 is associated with improved survival rates in severely injured trauma patients at 3-hours and 24-hours follow-up, compared to pRBC:FFP:PLT ratio of 2:1:1.[20]

Trauma patients and patients undergoing emergency surgeries are more common to suffer severe intraoperative hemorrhage. Although the implementation of MTPs has not yet proven their effectiveness in terms of outcomes, they increase the availability of blood products when needed. However, mortality is not significantly reduced with MTPs, possibly due to delayed activation of the protocol [47]. In major trauma patients, massive transfusion protocol is usually activated upon arrival at the Emergency Department, so as the blood products are not readily available for use.[48]

Non-trauma surgical patients may have less prominent signs of hemorrhage due to the continuous anesthetic support, and unless bleeding is visible in surgical field, it may take longer to be detected and treated. On the other hand, in case of elective surgery, blood products are probably already cross-matched and are readily available to use in the operating theater. Martinez et al. (2016) reported that MTP is initiated early in less than 20% of non-trauma patients, while in the remaining, it is activated by the blood bank after transfusion of eight pRBCs.[47] However, the activation of MTP leads to earlier delivery of other blood products .[47–49]

Non-initiation of an MTP can be due to late activation of trauma team or due to the retrospective design of the studies that may not include such information. We observed an overactivation of MTPs in several studies, where blood products weren't eventually administered to the bleeding patient. In clinical practice, these problems could be eliminated after defining universal criteria for MTP activation both in trauma and non-trauma patients; however, criteria for MTP activation have been established for trauma patients, such as the Massive Transfusion Score, the Assesment of Blood Consumption Score, or the McLaughlin et al algorithm for combat casualties.[46,50–54]

Our results raise the issue of blood product waste, considering the low availability worldwide, especially during the COVID-19 pandemic. However, very few studies report the waste of blood products in MTPs. Of note, McDaniel et al. (2013) reported an increased waste of PLTs after the initiation of MTP use.[49] This waste could be eliminated with careful activation of MTPs under strict criteria. In addition, MTPs should also be terminated as early as possible. The ACS TQIP has formed specific criteria for MTP termination, including surgical control of hemorrhage, vessel embolization, or successful resuscitation without active bleeding and correction of coagulopathy and anemia. Finally, MTP could be terminated in cases where further resuscitation is futile. [46]

Limitations of the study

We acknowledge some limitations. Our search was limited to PubMed; however, this is the largest database used in medical research. Another limitation is the differences between the number and definitions of outcomes among the included studies. For example, through online database search, we identified five previous pooled analyses of massive transfusion in trauma and non-trauma patients with severe hemorrhage [48,55–58]. However, we could not include all these studies in our analyses due to the variety in outcomes. Improving the consistency of outcomes is urgently

needed in order to improve outcomes research. Also, we identified only one clinical trial investigating massive transfusion in massive intraoperative hemorrhage. Thus, we pooled data from observational studies, either retrospective or prospective, after careful inspection by risk of bias tool. The conclusions drawn from this review must be cautious and reserved, since the level of heterogeneity was high. Lack of standard reporting may also constrain the ability to pool data and perform in depth analyses. Finally, non-English publications were not included.

Chapter 5 Conclusions

The present systematic review and meta-analysis did not reveal significant differences among different RBC:FFP ratios in terms of survival. The level of heterogeneity of the included studies mandates for high quality clinical trials to identify the optimal MTP and improve survival in patients with severe intraoperative hemorrhage.

References

1. Moorthy K, Munz Y, Forrest D, et al. Surgical crisis management skills training and assessment: a simulation[corrected]-based approach to enhancing operating room performance. *Ann Surg*. 2006;244(1):139-147. doi:10.1097/01.SLA.0000217618.30744.61
2. Irita K. Risk and crisis management in intraoperative hemorrhage: Human factors in hemorrhagic critical events. *Korean Journal of Anesthesiology*. 2011;60(3):151. doi:10.4097/KJAE.2011.60.3.151
3. Dutton RP, Lee LA, Stephens LS, Posner KL, Davies JM, Domino KB. Massive HemorrhageA Report from the Anesthesia Closed Claims Project. *Anesthesiology*. 2014;121(3):450-458. doi:10.1097/ALN.0000000000000369
4. Graling P, Dort J, Moynihan J. Crisis management of a hemorrhagic emergency in the OR. *AORN J*. 2014;99(4):510-516. doi:10.1016/J.AORN.2014.02.008
5. Ghadimi K, Levy JH, Welsby IJ. Perioperative management of the bleeding patient. *Br J Anaesth*. 2016;117(suppl 3):iii18-iii30. doi:10.1093/BJA/AEW358
6. Dhoon TQ, Raphael D, Rajan GR, Vaughn D, Engwall S, Vakharia S. Management of Massive Intraoperative Hemorrhage. *Anesthesia Patient Safety Foundation*. 2021;36(2). Accessed April 7, 2022. https://www.apsf.org/article/management-of-massive-intraoperative-hemorrhage/
7. Hellstern P, Haubelt H. Indications for plasma in massive transfusion. *Thromb Res*. 2002;107 Suppl:S19-22. doi:10.1016/s0049-3848(02)00147-0
8. Irita K, Kawashima Y, Morita K, et al. [Supplemental survey in 2003 concerning life-threatening hemorrhagic events in the operating room]. *Masui*. 2005;54(1):77-86.
9. Katz SC, Shia J, Liau KH, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann Surg*. 2009;249(4):617-623. doi:10.1097/SLA.0b013e31819ed22f
10. Bundgaard-Nielsen M, Secher NH, Kehlet H. "Liberal" vs. "restrictive" perioperative fluid therapy--a critical assessment of the evidence. *Acta Anaesthesiol Scand*. 2009;53(7):843-851. doi:10.1111/j.1399-6576.2009.02029.x
11. Hu P, Uhlich R, Gleason F, Kerby J, Bosarge P. Impact of initial temporary abdominal closure in damage control surgery: a retrospective analysis. *World J Emerg Surg*. 2018;13(1). doi:10.1186/S13017-018-0204-3
12. Weiniger CF, Yakirevich-Amir N, Sela HY, Gural A, Ioscovich A, Einav S. Retrospective study to investigate fresh frozen plasma and packed cell ratios when administered for women with postpartum hemorrhage, before and after introduction of a massive transfusion protocol. *Int J Obstet Anesth*. 2018;36:34-41. doi:10.1016/J.IJOA.2018.08.001
13. Jennings LK, Watson S. Massive Transfusion. *StatPearls*. Published online August 30, 2021. Accessed April 7, 2022. https://www.ncbi.nlm.nih.gov/books/NBK499929/
14. Aubron C, Aries P, le Niger C, Sparrow RL, Ozier Y. How clinicians can minimize transfusion-related adverse events? *Transfusion clinique et biologique : journal de la Societe francaise de transfusion sanguine*. 2018;25(4):257-261. doi:10.1016/J.TRACLI.2018.08.158
15. Stainsby D, MacLennan S, Hamilton PJ. Management of massive blood loss: a template guideline. *BJA: British Journal of Anaesthesia*. 2000;85(3):487-491. doi:10.1093/BJA/85.3.487
16. Bracco F, de Tonetti G, Masini M, Passarelli M, Geretto F, Celleno D. Crisis Resource Management in the Delivery Room: Development of Behavioral Markers for Team Performance in Emergency Simulation. *Int J Environ Res Public Health*. 2018;15(3). doi:10.3390/IJERPH15030439

17. Flint AWJ, McQuilten ZK, Wood EM. Massive transfusions for critical bleeding: is everything old new again? *Transfus Med*. 2018;28(2):140-149. doi:10.1111/TME.12524
18. Harvey CJ. Evidence-Based Strategies for Maternal Stabilization and Rescue in Obstetric Hemorrhage. *AACN Adv Crit Care*. 2018;29(3):284-294. doi:10.4037/AACNACC2018966
19. Tang J, Shi Z, Hu J, et al. Optimal sequence of surgical procedures for hemodynamically unstable patients with pelvic fracture: A network meta-analysis. *Am J Emerg Med*. 2019;37(4):571-578. doi:10.1016/J.AJEM.2018.06.027
20. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471-482. doi:10.1001/jama.2015.12
21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372. doi:10.1136/bmj.n71
22. Hu P, Uhlich R, Black J, Jansen JO, Kerby J, Holcomb JB. A new definition for massive transfusion in the modern era of whole blood resuscitation. *Transfusion (Paris)*. 2021;61 Suppl 1:S252-S263. doi:10.1111/trf.16453
23. Cap AP, Spinella PC. Severity of head injury is associated with increased risk of coagulopathy in combat casualties. *J Trauma*. 2011;71(1 Suppl):S78-81. doi:10.1097/TA.0b013e3182218cd8
24. Sisak K, Soeyland K, McLeod M, et al. Massive transfusion in trauma: blood product ratios should be measured at 6 hours. *ANZ J Surg*. 2012;82(3):161-167. doi:10.1111/j.1445-2197.2011.05967.x
25. van der Meij JE, Geeraedts LMGJ, Kamphuis SJM, et al. Ten-year evolution of a massive transfusion protocol in a level 1 trauma centre: have outcomes improved? *ANZ J Surg*. 2019;89(11):1470-1474. doi:10.1111/ans.15416
26. Morse BC, Dente CJ, Hodgman EI, et al. Outcomes after massive transfusion in nontrauma patients in the era of damage control resuscitation. *Am Surg*. 2012;78(6):679-684.
27. Dente CJ, Shaz BH, Nicholas JM, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. *J Trauma*. 2009;66(6):1616-1624. doi:10.1097/TA.0b013e3181a59ad5
28. Matthay ZA, Hellmann ZJ, Callcut RA, et al. Outcomes after ultramassive transfusion in the modern era: An Eastern Association for the Surgery of Trauma multicenter study. *J Trauma Acute Care Surg*. 2021;91(1):24-33. doi:10.1097/TA.0000000000003121
29. Cotton BA, Au BK, Nunez TC, Gunter OL, Robertson AM, Young PP. Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. *J Trauma*. 2009;66(1):41-49. doi:10.1097/TA.0b013e31819313bb
30. Tennyson M, Redlaff J, Biosse-Duplan G, Lewin M, Jones N, Layard Horsfall H. Massive blood loss protocol “Code Red” at Papworth Hospital: A closed loop audit. *J Perioper Pract*. 2021;31(9):334-340. doi:10.1177/1750458920943361
31. Rankin D, Zuleta-Alarcon A, Soghomonyan S, Abdel-Rasoul M, Castellon-Larios K, Bergese SD. Massive blood loss in elective spinal and orthopedic surgery: Retrospective review of intraoperative transfusion strategy. *J Clin Anesth*. 2017;37:69-73. doi:10.1016/j.jclinane.2016.10.017
32. Mesar T, Larentzakis A, Dzik W, Chang Y, Velmahos G, Yeh DD. Association Between Ratio of Fresh Frozen Plasma to Red Blood Cells During Massive Transfusion and Survival Among Patients Without Traumatic Injury. *JAMA Surg*. 2017;152(6):574-580. doi:10.1001/jamasurg.2017.0098

33. Kauvar DS, Sarfati MR, Kraiss LW. Intraoperative blood product resuscitation and mortality in ruptured abdominal aortic aneurysm. *J Vasc Surg*. 2012;55(3):688-692. doi:10.1016/j.jvs.2011.10.028
34. Warner DL, Cabaret J, Velling D. Ketamine plus midazolam, a most effective paediatric oral premedicant. *Paediatr Anaesth*. 1995;5(5):293-295. Accessed June 9, 2019. http://www.ncbi.nlm.nih.gov/pubmed/7489470
35. Hong Y, Dufendach K, Wang Y, Thoma F, Kilic A. Impact of early massive transfusion and blood component ratios in patients undergoing left ventricular assist device implantation. *Journal of Cardiac Surgery*. 2021;36(12):4519-4526. doi:https://doi.org/10.1111/jocs.16010
36. Tsukinaga A, Maeda T, Takaki S, Michihata N, Ohnishi Y, Goto T. Relationship between fresh frozen plasma to packed red blood cell transfusion ratio and mortality in cardiovascular surgery. *J Anesth*. 2018;32(4):539-546. doi:10.1007/s00540-018-2508-6
37. Sharpe JP, Weinberg JA, Magnotti LJ, et al. Accounting for differences in transfusion volume: Are all massive transfusions created equal? *J Trauma Acute Care Surg*. 2012;72(6):1536-1540. doi:10.1097/TA.0b013e318251e253
38. Hess JR, Ramos PJ, Sen NE, et al. Quality management of a massive transfusion protocol. *Transfusion (Paris)*. 2018;58(2):480-484. doi:10.1111/trf.14443
39. Halmin M, Chiesa F, Vasan SK, et al. Epidemiology of Massive Transfusion: A Binational Study From Sweden and Denmark. *Crit Care Med*. 2016;44(3):468-477. doi:10.1097/CCM.0000000000001410
40. Turan A, Yang D, Bonilla A, et al. Morbidity and mortality after massive transfusion in patients undergoing non-cardiac surgery. *Canadian journal of anaesthesia = Journal canadien d'anesthesie*. 2013;60(8):761-770. doi:10.1007/s12630-013-9937-3
41. Wijaya R, Cheng HMG, Chong CK. The use of massive transfusion protocol for trauma and non-trauma patients in a civilian setting: what can be done better? *Singapore Med J*. 2016;57(5):238-241. doi:10.11622/smedj.2016088
42. Sinha R, Roxby D. Any changes in recent massive transfusion practices in a tertiary level institution? *Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis*. 2017;56(4):558-562. doi:10.1016/j.transci.2017.05.013
43. Warner MA, Frank RD, Weister TJ, Madde NR, Gajic O, Kor DJ. Ratios of Plasma and Platelets to Red Blood Cells in Surgical Patients With Acute Intraoperative Hemorrhage. *Anesth Analg*. 2020;131(2):483-493. doi:10.1213/ANE.0000000000004609
44. Sinha R, Roxby D. Transfusion practices in massive haemorrhage in pre-intensive and intensive care. *Vox Sang*. 2011;101(3):230-236. doi:10.1111/j.1423-0410.2011.01482.x
45. Cap AP, Spinella PC, Borgman MA, Blackbourne LH, Perkins JG. Timing and location of blood product transfusion and outcomes in massively transfused combat casualties. *J Trauma Acute Care Surg*. 2012;73(2 Suppl 1):S89-94. doi:10.1097/TA.0b013e318260625a
46. Nunez TC, Voskresensky I v, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *J Trauma*. 2009;66(2):346-352. doi:10.1097/TA.0b013e3181961c35
47. Martínez-Calle N, Hidalgo F, Alfonso A, et al. Implementation of a management protocol for massive bleeding reduces mortality in non-trauma patients: Results from a single centre audit. *Medicina Intensiva (English Edition)*. 2016;40(9):550-559. doi:10.1016/j.medin.2016.05.003
48. Sommer N, Schnüriger B, Candinas D, Haltmeier T. Massive transfusion protocols in nontrauma patients: A systematic review and meta-analysis. *J Trauma Acute Care Surg*. 2019;86(3):493-504. doi:10.1097/TA.0000000000002101

49. McDaniel LM, Neal MD, Sperry JL, et al. Use of a massive transfusion protocol in nontrauma patients: activate away. *J Am Coll Surg*. 2013;216(6):1103-1109. doi:10.1016/j.jamcollsurg.2013.02.008
50. Callcut RA, Cotton BA, Muskat P, et al. Defining when to initiate massive transfusion: a validation study of individual massive transfusion triggers in PROMMTT patients. *J Trauma Acute Care Surg*. 2013;74(1):59-65,67. doi:10.1097/TA.0b013e3182788b34
51. McLaughlin DF, Niles SE, Salinas J, et al. A predictive model for massive transfusion in combat casualty patients. *J Trauma*. 2008;64(2 Suppl):S57-63; discussion S63. doi:10.1097/TA.0b013e318160a566
52. Yücel N, Lefering R, Maegele M, et al. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *J Trauma*. 2006;60(6):1227-1228. doi:10.1097/01.ta.0000220386.84012.bf
53. Cantle PM, Cotton BA. Prediction of Massive Transfusion in Trauma. *Crit Care Clin*. 2017;33(1):71-84. doi:10.1016/j.ccc.2016.08.002
54. Cotton BA, Dossett LA, Haut ER, et al. Multicenter validation of a simplified score to predict massive transfusion in trauma. *J Trauma*. 2010;69 Suppl 1:S33-9. doi:10.1097/TA.0b013e3181e42411
55. Mitra B, O'Reilly G, Cameron PA, Zatta A, Gruen RL. Effectiveness of massive transfusion protocols on mortality in trauma: a systematic review and meta-analysis. *ANZ J Surg*. 2013;83(12):918-923. doi:10.1111/ans.12417
56. Vogt KN, van Koughnett JA, Dubois L, Gray DK, Parry NG. The use of trauma transfusion pathways for blood component transfusion in the civilian population: a systematic review and meta-analysis. *Transfus Med*. 2012;22(3):156-166. doi:10.1111/j.1365-3148.2012.01150.x
57. Consunji R, Elseed A, El-Menyar A, et al. The effect of massive transfusion protocol implementation on the survival of trauma patients: a systematic review and meta-analysis. *Blood Transfus*. 2020;18(6):434-445. doi:10.2450/2020.0065-20
58. Yoon KW, Cho D, Lee DS, et al. Clinical impact of massive transfusion protocol implementation in non-traumatic patients. *Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis*. 2020;59(1):102631. doi:10.1016/j.transci.2019.07.007
59. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. doi: 10.1016/0197-2456(86)90046-2. PMID: 3802833.