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Beyond Damage Control: A Scoping Review Investigating Resuscitation for Trauma Patients in the Post-Hemostatic Period

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ABSTRACT

Background: Quality improvement for the surgical care of trauma patients has focused predominantly on interventions within the first 24 hours after injury and has yielded significant improvements outcomes in recent decades. However, many trauma patients require multiple procedures coordinated with a variety of subspecialty services during their initial hospitalization, and late outcomes after traumatic injury are often driven by management of medical comorbidities.

Methods: This scoping review seeks to determine what is known about best practices for fluid management and resuscitation later in trauma care after hemostasis has been achieved. A standardized three-stage search revealed 41 papers for review, of which 12 met criteria.

Results: After the post-hemostatic period (>24 hours after injury), the incidence of multiple organ failure among trauma patients remains high, as does morbidity and mortality among these patients. Data from the orthopedic literature suggest that lower hemoglobin transfusion triggers might be well-tolerated later in the post-hemostatic period, and repeat doses of tranexamic acid (TXA) are associated with decreased intraoperative blood loss but not increased incidence of venous thromboembolism (VTE). Balanced crystalloids are associated with lower volumes of fluid required, and, if transfusion is required, whole blood is not associated with increased transfusion reactions. Finally, for those trauma patients who survive to ICU admission, a composite score of common biometric data and laboratory results may predict which trauma patients have higher resuscitation needs, and providing balanced crystalloids early in ICU admission is associated with a lower volume of resuscitation required.

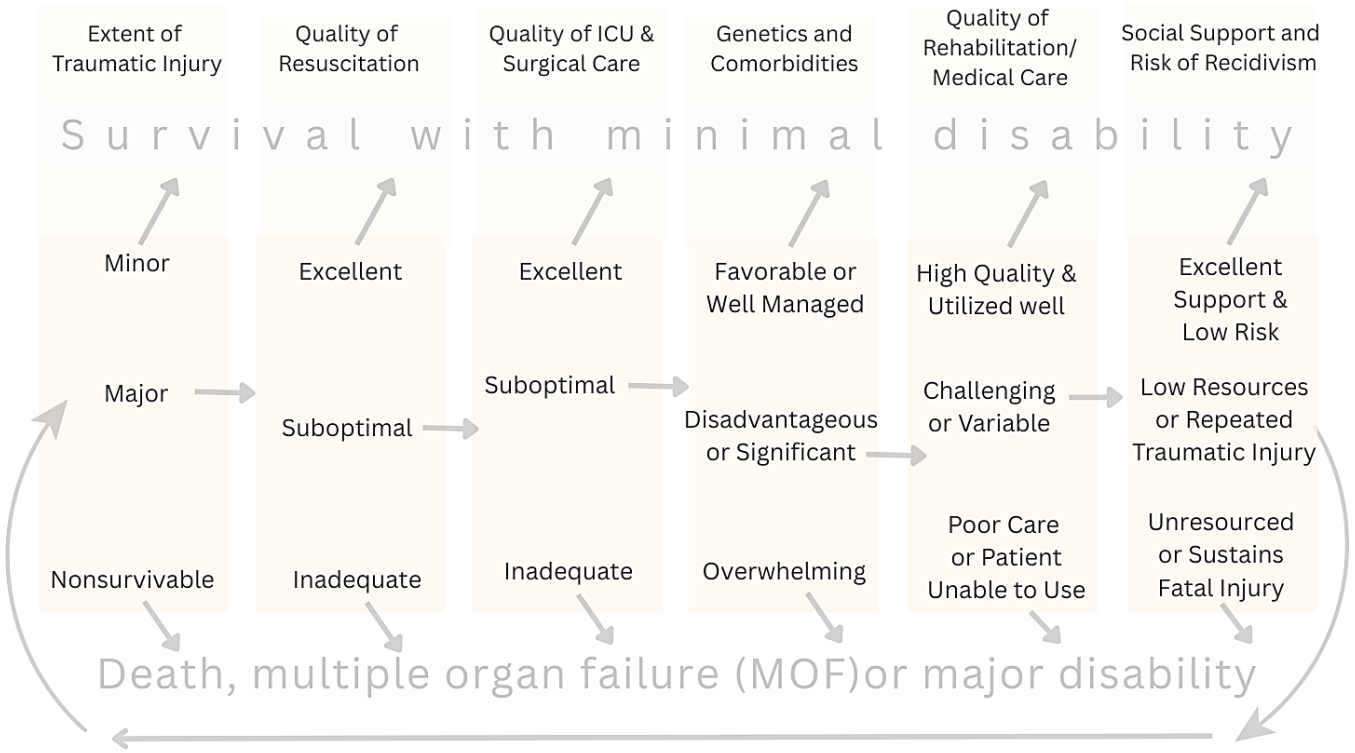
Conclusions: Relatively few publications address ongoing resuscitation and fluid management for trauma patients in the post-hemostatic period (>24 hours after injury). Better outcomes are observed when balanced crystalloids are used early in ongoing resuscitation after hemostasis. Multiple organ failure (MOF) after trauma remains a dangerous syndrome, and the lack of a standardized definition hinders future research to define best practices for fluid management for patients with and without MOF. The study was limited by the lack of standardized terminology and approach to studying outcomes later in trauma care after hemostasis has been achieved.

Background

Trauma is the leading cause of death for individuals up to age below age 40 in the United States.[1] Globally, on a yearly basis, trauma causes 6 million deaths, roughly equivalent to the population of Denmark or El Salvador. And, in a given year, traumatic injuries permanently impact the health of 40 million people and temporarily affect 100 million people, the human magnitude of which equals the entire population of Russia.[2] Given the effect of traumatic injury on the mental and physical health of millions of people and the economic impact of traumatic injury and death particularly among people in their prime working years, significant research on how to best prevent and manage traumatic injuries has been undertaken.

The overlap of the quality of trauma & medical care, the magnitude of other post-injury pathologies, the extent of pre-existing patient comorbidities, and genetic factors govern whether hospitalized survivors of trauma survive and whether they progress into critical illness or multiple organ failure. The confluence of these factors, along with the patient's social support network and likelihood of trauma recidivism, also subsequently dictate whether, after discharge, a given trauma patient survives and is permanently injured or survives to full recovery. (see Figure 1)

Figure 1: Factors Contributing to Lifetime Trauma Outcomes



The majority of deaths subsequent to traumatic injury occur in a bimodal distribution in the prehospital setting and then again within hours of hospital admission.[3,4] In the prehospital setting and within the first 24 hours after admission, about 80% of early patient deaths after trauma can be attributed to nonsurvivable traumatic brain injury (TBI) and exsanguination. Robust, evidence-based guidelines have been crafted to guide trauma care in the pre-hospital setting and within the first 24 after admission.[5,6]

In the pre-hospital setting and within the first 24 hours of admission, evidence indicates that the following resuscitation techniques convey a mortality benefit:

- transfusion of whole blood or blood components at a 1:1:1 ratio,[7–10]
- permissive hypotension, especially in the setting of thoracic trauma,[5,6]
- limitation of crystalloid administration,[5,11]

- use of transexamic acid,[5,12–14] and
- avoidance of hypocalcemia[15–17]

These resuscitation techniques, along with specific surgical and diagnostic elements that are outside the scope of this review comprise the elements of damage control surgery and damage control resuscitation for trauma patients immediately post-injury.

Twenty-four to 48 hours after injury until death or discharge - a time alternately called late trauma resuscitation, post-stablization, or post-hemostatic period[18,19] - post-injury pathology or exacerbation of comorbidities, often coalescing into multiple organ failure (MOF), emerge as the leading causes of death.[20] The evidence for different resuscitation strategies that might positively affect this diverse set of disease processes and change patient outcomes is much less well studied than the first 24-48 hours after injury.[18,21] One of the challenges to studying this phase of trauma care is that multiple teams and specialties are involved and invested in a diverse set of medical and surgical outcomes. This scoping review aims to summarize the literature from diverse specialties on best practices for trauma resuscitation in the post-hemostatic/post-stablization phase of care (> 24 hours post-injury).

Methods

To be included in the review, papers needed to elaborate on one or more aspects of the resuscitation of trauma patients, e.g. trauma-induced coagulopathy, hemostatic resuscitation, intravenous fluid management, or care in the post-resuscitation phase. Peer-reviewed papers needed to focus on the time >24 hours from injury to discharge or death, be published in English, and discuss trauma patient care.

Military experience from the war in Afghanistan as well as the influx of information from large databases and several multi-center collaborative trials resulted in a major shit occurred in trauma management guidelines. Goal-directed coagulation management, damage control surgery, permissive hypotension, restrictive fluid resuscitation, utilizing whole blood or blood component therapy in a 1:1:1 ratio, and administration of tranexamic acid (TXA) was becoming common practice in the early 2010s.[19,22,23] Given this change in the standard of care for trauma patients in the immediate post-injury phase, only papers published after 2010 were considered. Papers from the sphere of orthopedics, otolaryngology, and ormaxillofacial surgery were also included given their critical role in managing trauma patients undergoing non-emergent surgeries in the immediate post-injury period. Papers which focused on pediatric populations, burn patients, or patients with traumatic brain injury (TBI) were excluded due to the unique management required.

This scoping review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The PRISMA extensions for Scoping Reviews (PRISMA-ScR) checklist was utilized to ensure a comprehensive and transparent reporting of the methodology and results.[24]

To identify potentially relevant papers, searches were performed on electronic databases including PubMed, Ovid MEDLINE, and Google Scholar. The primary search included papers published from January 1, 2010 to present with the assistance of UAB Department of Anesthesiology and Perioperative Medicine librarian using the key words: trauma coagulopathy, trauma resuscitation, orthopedic trauma, fluid management and trauma, trauma and multiorgan failure, Intensive care and trauma. Papers discussing pediatrics, burn patients, TBI patients, and papers published before 2010 were excluded. A secondary search was performed with an emphasis on publications discussing the subspecialty care of trauma patients in the post-resuscitation and pre-discharge time period.

Acknowledging the challenge of a lack of accepted terminology to describe the post-hemostatic/post-stabilization period of trauma resuscitation, the search strategy was expanded by leveraging key articles identified as highly relevant to trace additional

sources through citation tracking and reference mining. This tertiary search was conducted by the authors to investigate studies cited in papers from the primary and secondary search as well as those cited in practice guidelines.[25,26] This approach facilitated the identification of pertinent studies that may not have surfaced in the initial database queries, ensuring a more comprehensive synthesis of the existing literature. The final results were exported to a citation management program (Mendeley by Elsevier Inc., Frisco, CO) and duplicates were removed.

The primary search yielded 24 results. From the initial 24 publications, papers were omitted based on their relevance to the subject matter, leaving 16 papers from the initial search. A second search focused on the subspecialties of orthopedic trauma, otolaryngology, and oromaxillofacial surgery in the post-resuscitation and pre-recovery period. This second search yielded 46 additional papers. Publications were further screened based on the aforementioned exclusion criteria and relevance to the scoping review topic, leaving 13 papers from the second search. An additional 12 papers were identified in the tertiary search for a total of 41 references.

These 41 articles were reviewed in full by both authors. Studies that did not have an experimental focus on late trauma resuscitation or the post-hemostatic period, studies that were narrative or unstructured reviews, or studies that did not provide any data on resuscitation (e.g. those focused on a specific surgical outcome) were excluded, leaving 12 relevant articles.[27–38] Information on current and best practices (e.g. timing, type, and volume of fluid administration, coagulopathy management, blood product administration, and care in the post-hemostatic resuscitation period) for the care of trauma patients was extracted and summarized below.

Results

Compared to the large volume of epidemiologic, observational, and experimental research conducted on both civilian and military trauma patients in the immediate post-injury period, this scoping review found comparatively few studies focusing on optimization, ongoing resuscitation, transfusion, or fluid management of trauma patients more than 24-48 hours post-injury.

Beginning with the epidemiology of later mortality after traumatic injury, Dr. Matthias Fröhlich and colleagues from The Intensive Care and Trauma Management (Sektion NIS) of the German Trauma Society published an epidemiologic study of 31,154 looking at mortality and the incidence of Multiple Organ Failure (MOF) among trauma patients from the TraumaRegister DGU database who had traumatic injury with Injury Severity Score >16 and survived to ICU admission between 2002 and 2011. They found that, while trauma mortality decreased over the study period (18.1% vs.15.3%, $p < 0.001$), the incidence of MOF increased (24.6% vs. 31.5%, $p < 0.001$). In this study, though MOF was more common, the mortality among patients with MOF was noted to decrease between 2002 and 2014 (42.6% vs. 33.3%, $p < 0.001$).[28]

Another, larger review found very little change in the incidence of multiple organ failure among patients who survived traumatic injury in the first decades of the 2000s: Dr. Ryan Ting and a multinational trauma collaborative gathered data from 106 studies from 2005 to 2022 of 351,942 trauma patients. Analysis showed an aggregate incidence of multiple organ failure of 24% (range 12.7% to 55.1% from 10 different definitions), with no change over time.[35]

Much of the credit for improved early mortality among trauma patients has been attributed to more universal application of the principles of damage control surgery[5,38] and damage control resuscitation, which includes limitation of IV fluids in favor of whole blood or a tight ratio of blood component therapies that approximate whole blood.[5,10,23,39,40] Two studies looked at the safety of damage control resuscitation and included endpoints in the post-hemostatic period. In 2022, Gelbard and colleagues at the University of Alabama at Birmingham, found that patients who (a) met criteria for activation of

massive transfusion protocol in the ED and (b) received 1-3 units of blood prior to being revealed to have a normal hemoglobin level, had clinical outcomes equivalent to those trauma patients who were anemic and received a similar transfusion.[36] Murphy et. al. looked at 6771 units of transfused blood product between 2020 and 2023 at the University of Texas – San Antonio, and found no statistical difference in hemolytic transfusion reactions, other severe transfusion reactions, or mortality between patients who received transfusion of low-titer whole blood versus standard red blood cell transfusion.[27]

While this work provides information on the longitudinal safety of transfusion early in resuscitation, few studies have looked at transfusion practices specifically among trauma patients later in the post-hemostatic phase of trauma care. We were only able to encounter one randomized control trial of transfusion triggers among subspecialty trauma surgical patients. Mullis and colleagues at the University of Indiana found no difference in major complications or musculoskeletal function at 6 months but fewer surgical site infections (0% vs. 7%, $P < 0.01$) among a cohort of young 99 orthopedic trauma patients (ages 18-50) randomized during surgery to an extremely conservative transfusion hemoglobin threshold of 5.5 mg/dL vs. a more standard threshold of 7.0 mg/dL.[33]

Two studies from the orthopaedic literature evaluated the use of tranexamic acid (TXA) to decrease intraoperative and postoperative blood loss and improve outcomes among orthopaedic trauma patients. Yakkanti et. al. performed a systematic review that included several surgical and resuscitation techniques in the treatment of traumatic pelvic and acetabular fractures; they found 2 RCTs and 2 retrospective studies that suggest the use of TXA is associated with reduced intraoperative blood loss and no increased incidence of venous thromboembolism or pulmonary embolism (VTE/PE).[31] Dr. Srivatsan Thirumalai Vasu and neurosurgical colleagues from the Medical Trust Hospital in Kochi, Kerala India performed a systematic review and meta-analysis of the use of TXA in patients undergoing surgery for traumatic thoracolumbar fractures; they found that administration of 1-3g of TXA was associated with decreased intraoperative blood loss and length of stay but not associated with increased risk of thromboembolic events.[37]

With respect to resuscitation with IV fluids after hemostasis, Tseng et. al. performed a systematic review and meta-analysis that included 10 studies evaluating IV fluid resuscitation among 5076 trauma patients. They found no difference in mortality for resuscitation with balanced crystalloids, normal saline, and hydroxyethyl starch (HES), however the patients who received balanced crystalloids required a lower total volume of IV fluid. Also, they observed that patients with TBI who were resuscitated with albumin had higher mortality than those resuscitated with normal saline.[8] Braasch et. al. conducted a small observational study of all fluids administered to 31 trauma patients during the first 72 hours after admission at the University of Kansas. They found balanced crystalloids represents the majority of fluid administered in the first 24-72 hours for critically ill trauma patients and that larger volume crystalloid administration was associated with higher rates of MOF.[32]

One group of investigators has focused on IV fluid administration in the trauma ICU. Drs. Catherine Beni, Michael Weycamp and colleagues at the University of Washington looked at fluid administration and trauma outcomes among patients who survived to ICU admission. In a retrospective cohort study linking the local trauma database to the EMR, they looked at 337 severely injured trauma patients admitted to the ICU between 2012 and 2015. They found there was a wide range of volume of intravenous fluid (IVF) administered early in the ICU admission, with median volume noted at 3.7 L (interquartile range, 1.5–6.4 L). Trauma patients who received/required IVF in the highest quartile, had higher rates of requiring operative intervention, higher injury severity scores, and higher rates of AKI as well as longer ICU stays and duration of mechanical ventilation.[38]

Further investigating this population, they looked at 7385 trauma patients between 2016 and 2019 and narrowed to focus on 333 patients who survived to the ICU, needed ongoing resuscitation, and had lactate levels documented. Among these patients, early resuscitation (defined as receiving at least a 500 mL bolus of crystalloid within the first 6 hours of ICU admission) was associated with less total resuscitation volume administered (4.1L vs. 5.5L, $p \leq 0.001$), fewer ventilator days (2 vs. 5 days, $p \leq 0.001$), shorter ICU length of stay (LOS) (5 vs. 9 days, $p \leq 0.001$), and lower rates of AKI (11% vs. 38%; $p \leq 0.001$).[29] They also found in a separate study that the need for high-intensity ICU resuscitation was retrospectively associated with shock index, lactate, base deficit, hematocrit, and INR, suggesting the possibility of prospective intervention based on these criteria.[30]

Discussion

The majority of evidence-based care guiding the care of trauma patients is derived from studies that focus on interventions in the critical period from traumatic injury to hospital admission and the first 24-48 hours after admission. This scoping review investigated resuscitation of trauma patients >24-48 hours post injury in the post-hemostatic period and identified a small amount of clinical studies and systematic reviews to guide clinical decision-making in later in resuscitation. This review identified two trends strong enough to stand as recommendations and several jumping off points for future research.

By pooling data from smaller studies, crystalloids emerge as the IV fluid of choice for resuscitation after trauma. Whereas resuscitation with colloids such as hydroxyethyl starch (HES) and albumin are more costly, outcomes are equivalent in the general trauma population, and certain subgroups of trauma patients (e.g. patients with TBI) have worse outcomes, crystalloids are recommended. Among patients with TBI, normal saline is superior, and among those without TBI, balanced crystalloids is superior.[34,42] The recommendation for balanced crystalloids correlates well with findings in the ICU literature wherein, patients undergoing resuscitation with balanced crystalloids had lower mortality despite being observed to have lower mean arterial pressure (MAP), cardiac index (CI), and central venous pressure (CVP) as compared to those receiving colloids.[43]

There is one lingering question with respect to colloid administration for trauma patients later in care. In a different group of studies in the same meta-analysis, Tseng, et. al., included a pool of 4646 general surgery patients from 23 studies; they saw improved outcomes among general surgery patients receiving colloids. General surgery patients who received colloids (albumin, hydroxyethyl starch [HES]) required significantly lower volumes of fluid and blood during surgery and had a lower incidence of Acute Kidney Injury (AKI) than those who received crystalloids.[34] It is not yet clear if or at what point after injury trauma patients might behave physiologically more like general surgery patients and thus whether they might benefit from colloids for ongoing resuscitation needs during subsequent surgeries.

The CRASH-2 trial showed a decreased risk of early and late mortality for trauma patients who received transexamic acid in the first 3 hours after injury,[14] and two studies in this review showed TXA administration during orthopaedic trauma procedures was associated with less blood loss later in trauma care. In patients treated for pelvic and acetabular fractures as well as for thoracolumbar spinal fractures found that TXA is associated with less intraoperative blood loss, is not associated with increased risk of VTE/PE.[31,37] Therefore, TXA may have a role in preventing transfusion and morbidity later in treatment of traumatic injuries. To fully study the impact of TXA, future research will need to reconcile medications administered right after injury to those administered later in the patient's admission. Neither of these reviews reported whether studies included reported prior doses of the medication, therefore it is unknown whether treatments during orthopedic surgery represent later initial doses or additional doses of TXA.

With respect to transfusions after traumatic injury, we identified two studies that showed no increase in complications for damage control resuscitation practices in the first 24 hours post injury, i.e. the early use of whole blood or equivalent component therapy.[27,41] They provide some early indication that damage control practices have a favorable safety profile later in recovery. We know from the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) Study Group that a higher ratio of FFP administered very early in resuscitation is correlated with decreased mortality,[8] and trauma patients often receive transfusions of RBCs and plasma in the days to weeks after injury. However, we could find no studies in the trauma literature looking at transfusion practices more than 48 hours out from injury.

One study from the orthopaedic trauma literature showed found fewer surgical complications among trauma patients randomized to a very conservative transfusion strategy during orthopaedic procedures in the post-hemostatic period.[33] There were some limitations of this study, including the use of musculoskeletal function as a proxy for wellbeing at 6 month follow up and low generalizability because patients selected were all under 50 years old, but these findings – which show benefit to extremely conservative transfusion strategies – are more in line with previous studies showing conservative transfusion strategies minimize complications like venous thromboembolism and surgical site infections among trauma patients.[44] Taken together, these findings suggest that early resuscitation with whole blood or equivalent components immediately post injury is beneficial, but later in resuscitation, a conservative strategy might be better. However, it is unclear where in the timeline after traumatic injury the inflection point occurs. More research evaluating outcomes for trauma patients who receive transfusions >24-48 hours after injury is needed.

Finally, several opportunities for improving terminology, definitions, and reported outcomes based on these definitions specifically for trauma patients were identified:

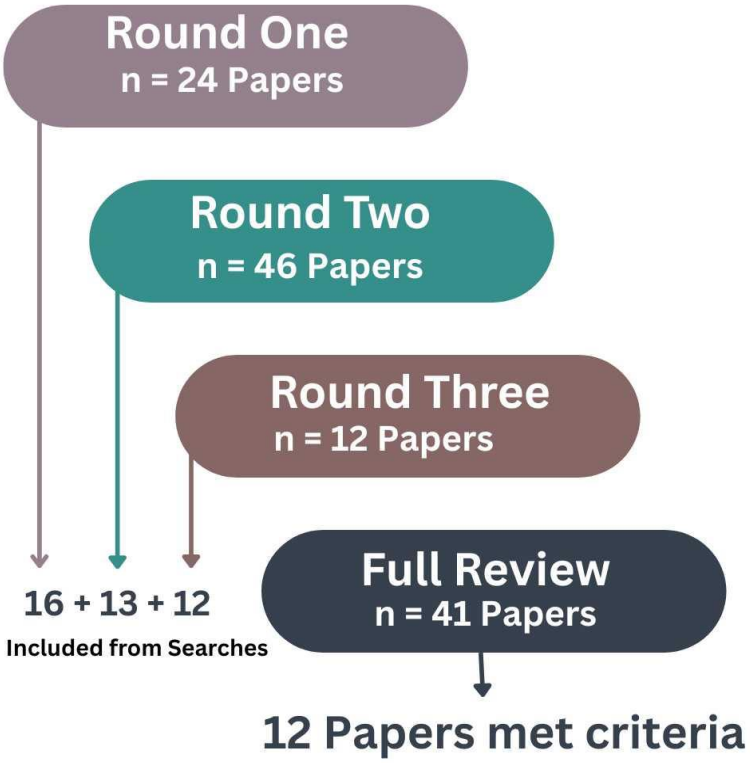
- Few studies have distinguished between early and late (pre-hemostatic and post-hemostatic) resuscitation after traumatic injury[29,46]
- Despite mutiorgan failure (MOF) being the syndrome most associate with mortality in patients who survive to ICU admission and the incidence of MOF being increased or unchanged in recent decades despite advances in early trauma care,[28,35] there is no widely accepted definition of MOF in the literature.[47]
- No studies that we could find looked at late/post-hemostatic resuscitation endpoints as predictors of progression to or recovery after MOF.

At the leading edge of investigating these questions, Drs. Beni, Weycamp, and colleagues elucidated that among trauma patients who survive to ICU admission, high resuscitation requirement was associated with five metrics (shock index, lactate, base deficit, hematocrit, and INR). They concluded that, in the future, a predictive scale might be able to differentiate between those with higher and lower resuscitations needs. Additionally, they found that those trauma patients with higher resuscitation needs seem to benefit from intervention early in their ICU course.[29,30] Future research looking at predictive capability of ICU admission data for post-traumatic resuscitation needs and clinical trials evaluating treatment protocols for high needs patients would provide valuable information to guide clinical care in the trauma ICU.

This scoping review was limited mainly by the lack of consistent terminology to differentiate the distinct periods of injury early vs. late in trauma care or prior to and after hemostasis. Searches could not rely on key words; multiple rounds of searches identified a large number of potential citations (see Figure 2), but few contained data specific to the population and time period of interest. It has been proposed, and we would agree that this lack of terminology directly contributes to the lack of research.[19,46]

Additionally, one study was underpowered,[32] and one did not adhere to PRISMA guidelines for structure and reporting of systematic reviews.[31] Given the small number of studies, the authors felt it was important to include the information while acknowledging the limitation.

Figure 2: Scoping Review Schematic



Going forward, given the volume of surgical patients and the number of practitioners, consultants, and subspecialists providing care during the late resuscitation/early recovery/post-hemostatic period of trauma care, multidisciplinary research teams could draw from: trauma surgeons, trauma anesthesiologists, critical care physicians, advanced practice nurses and nurse anesthetist, ICU nurses, blood management specialists, and social workers. These teams would need to be equipped with the information technology resources needed to integrate clinical information with large databases, ideally with the help of artificial intelligence and machine learning algorithms. And finally, to truly move the needle on reducing the incidence of multiorgan failure among critically ill trauma patients, consensus on a common definition of this high-morbidity syndrome is urgently needed.[35,48]

Conflicts of Interest:

None to Disclose

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