Prognostic factors for development of acute respiratory distress syndrome following traumatic injury: a systematic review and meta-analysis

Alexandre Tran[1,2,3], Shannon M. Fernando[3,4], Laurent J. Brochard[5,6], Eddy Fan[5,7,8], Kenji Inaba[9], Niall D. Ferguson[5,7,8], Carolyn S. Calfee[10], Karen E.A. Burns[5,6,11], Daniel Brodie[12,13], Victoria A. McCredie[5,14], Dennis Y. Kim[15], Kwadwo Kyeremanteng[3], Jacinthe Lampron[1], Arthur S. Slutsky[5,6], Alain Combes[16,17] and Bram Rochwerg[11,18]

[1]Dept of Surgery, University of Ottawa, Ottawa, ON, Canada. [2]School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada. [3]Division of Critical Care, Dept of Medicine, University of Ottawa, Ottawa, ON, Canada. [4]Dept of Emergency Medicine, University of Ottawa, Ottawa, ON, Canada. [5]Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada. [6]Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, ON, Canada. [7]Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada. [8]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada. [9]Division of Acute Care Surgery, Dept of Surgery, University of Southern California, Los Angeles, CA, USA. [10]Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, University of California San Francisco, San Francisco, CA, USA. [11]Dept of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada. [12]Division of Pulmonary, Allergy, and Critical Care Medicine, Dept of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA. [13]Center for Acute Respiratory Failure, New York-Presbyterian Hospital, New York, NY, USA. [14]Krembil Research Institute, Toronto Western Hospital, University Health Network, Toronto, ON, Canada. [15]Dept of Surgery, University of California Los Angeles, Los Angeles, CA, USA. [16]Institute of Cardiometabolism and Nutrition, Sorbonne Université, INSERM UMRS 1166, Paris, France. [17]Service de Médecine Intensive-Réanimation, Institut de Cardiologie, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France. [18]Dept of Medicine, Division of Critical Care, McMaster University, Hamilton, ON, Canada.

Corresponding author: Alexandre Tran (aletran@toh.ca)

Shareable abstract (@ERSpublications)
This systematic review identifies one important modifiable factor, the amount of crystalloid resuscitation within the first 24 h of injury, and several non-modifiable factors associated with development of post-traumatic ARDS https://bit.ly/3klhshF

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Abstract

Background Our purpose was to summarise the prognostic associations between various clinical risk factors and development of acute respiratory distress syndrome (ARDS) following traumatic injury.

Methods We conducted this review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and CHARMS (Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies) guidelines. We searched six databases from inception through December 2020. We included English language studies describing the clinical risk factors associated with development of post-traumatic ARDS, as defined by either the American–European Consensus Conference or Berlin definition. We pooled adjusted odds ratios for prognostic factors using the random effects method. We assessed risk of bias using the QUIPS (Quality in Prognosis Studies) tool and certainty of findings using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.

Results We included 39 studies involving 5 350 927 patients. We identified the amount of crystalloid resuscitation as a potentially modifiable prognostic factor associated with development of post-traumatic ARDS (adjusted OR 1.19, 95% CI 1.15–1.24 for each additional litre of crystalloid administered within the first 6 h after injury; high certainty). Non-modifiable prognostic factors with a moderate or high certainty of association with post-traumatic ARDS included increasing age, non-Hispanic White race, blunt mechanism of injury, presence of head injury, pulmonary contusion or rib fracture and increasing chest injury severity.

Conclusions We identified one important modifiable factor, the amount of crystalloid resuscitation within the first 24 h of injury, and several non-modifiable factors associated with development of post-traumatic ARDS. This information should support the judicious use of crystalloid resuscitation in trauma patients and may inform development of risk stratification tools.

Introduction

Acute respiratory distress syndrome (ARDS) is associated with substantial mortality and is relatively common, occurring in 10% of all intensive care unit (ICU) admissions [1]. In patients with severe trauma, ARDS can occur in response to direct pulmonary insult, such as pulmonary contusion, or indirect insults secondary to cellular injury and endothelial activation [2]. Outcomes following post-traumatic ARDS are often better than those associated with non-trauma-related causes, likely due to the fact that these patients tend to be younger, with a lower burden of acute and chronic illness, as well as less severe lung epithelial and endothelial injury [3]. Nonetheless, post-traumatic ARDS is independently associated with substantial mortality, increased healthcare costs and utilisation, and worse long-term quality-of-life outcomes among survivors [4–8].

Meta-analyses over the past few decades have demonstrated a relatively consistent incidence of mortality from ARDS following traumatic injury [2, 9]. However, these previous reviews did not address potentially important prognostic factors associated with development of ARDS in trauma patients. Further understanding of both modifiable and non-modifiable factors in trauma patients could help with risk stratification and potentially inform care by identifying modifiable factors to reduce the likelihood of progression to ARDS.

We conducted a systematic review and meta-analysis summarising the association between clinical risk factors and development of ARDS following trauma. In a secondary objective, we evaluated risk factors associated with mortality following post-traumatic ARDS.

Methods

We conducted this systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [10], the CHARMS (Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies) checklist [11], as well as guidelines for meta-analyses of prognostic factor studies [12]. We registered our protocol with the Open Science Framework (https://osf.io/vjz2y).

Search strategy

We searched six databases (MEDLINE, Embase, Web of Science, Scopus, Cochrane Database of Systematic Reviews and PubMed) from inception through December 2020. An experienced health sciences librarian assisted in development of the strategy. The strategy used content terms, in combination with terms related to prognostic research, consistent with similar prognostic meta-analyses [13–16], and is included in the supplementary material.

Study selection

We included all English language studies describing retrospective and prospective observational studies as well as randomised controlled trials. We included studies meeting the following criteria: 1) enrolled adult patients (⩾16 years of age) suffering traumatic injury and 2) evaluated clinical risk factors associated with development of ARDS, as defined by either the American–European Consensus Conference (AECC) [17] or Berlin definition [18]. We excluded studies evaluating the relationship between ARDS and serum markers of lung injury alone. We excluded studies that failed to provide either adjusted or unadjusted odds ratios with corresponding confidence intervals or at least adequate data to allow for calculation of unadjusted odds ratios. We contacted the corresponding author for completeness where these values could not be obtained from the reported data.

We screened studies using Covidence software (Covidence, Melbourne, Australia). We imported titles into Covidence directly from the search databases and removed duplicates. Two reviewers (A.T. and S.M.F.) independently screened the titles and abstracts of all identified citations.

We resolved disagreements by discussion; no third-party adjudication proved necessary. The same reviewers (A.T. and S.M.F.) subsequently independently assessed full texts of the selected articles following screening and again disagreements were resolved by discussion.

Data extraction and quality assessment

Two investigators (A.T. and S.M.F.) abstracted the following variables: author information, year of publication, study design, study dates, eligibility criteria, clinical risk factors, development of ARDS and mortality following ARDS. Clinical risk factors included patient-specific factors such as age and sex, injury factors such as mechanism and pattern, as well as resuscitation factors such as the administration of crystalloid, packed red blood cells (PRBCs), fresh frozen plasma (FFP) and platelets. For each prognostic factor, two investigators (A.T. and S.M.F.) independently collected unadjusted or adjusted odds ratios for development of ARDS and mortality following ARDS for each study, where available. To ensure homogeneity in control of confounding, adjusted odds ratios were selected from models that included at least one patient factor (age or comorbidity) and at least one injury factor (mechanism of injury, injury pattern or injury severity). In the event of overlapping patient cohorts, we preferentially included data from the larger patient cohort. We performed extraction using a modified CHARMS checklist for prognostic factors [11].

Using the QUIPS (Quality in Prognosis Studies) tool, two reviewers (A.T. and S.M.F.) independently assessed the risk of bias of included studies [19]. Disagreements were resolved by consensus following discussion. The QUIPS tool includes six domains for bias and applicability: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting.

Data synthesis

We extracted or calculated adjusted and unadjusted odds ratios based on the available data. We performed meta-analysis of adjusted and unadjusted odds ratios separately using the random effects method for estimation of between-study variances [20] and Review Manager (RevMan version 5.3; The Nordic Cochrane Centre, Copenhagen, Denmark). We assessed heterogeneity using the I^2 statistic, the Chi-squared test for homogeneity and visual inspection of the forest plots.

An investigator with expertise in GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (B.R.) assessed overall certainty in pooled estimates using the GRADE approach [21]. The overall certainty in estimates was categorised into one of four levels: high, moderate, low or very low. In keeping with GRADE guidance for prognostic studies, cohort data start as high certainty evidence but could be lowered for concern in any one of the following domains: precision, consistency, risk of bias, directness or publication bias. A GRADE evidence profile was created using the guideline development tool (https://gradepro.org).

For each prognostic factor, we present both but highlight the analysis (adjusted or unadjusted) with the higher certainty evidence as determined by the GRADE assessment. In the event of equivalent certainty, we highlight the adjusted analysis, in keeping with best practice guidelines for reporting of meta-analyses of prognostic factor studies [12]. High certainty associations are characterised as “is associated”, moderate certainty as “probably associated”, low certainty as “may be associated” and very low certainty as “uncertain”.

Upon reviewer request, we conducted several *post hoc* sensitivity analyses. For all prognostic factors, we conducted sensitivity analyses 1) including only prospective cohort studies and 2) including only studies using the Berlin definition for ARDS. For non-Hispanic White race, reviewers requested an additional subgroup analysis comparing studies done in North America to those from other continents; however, we did not have data to allow for this additional analysis.

Results

Search results

The search yielded 1396 citations (figure 1). Following removal of duplicates, we screened 955 studies, of which 87 underwent full-text review. We included 39 studies involving 5 350 927 patients in the meta-analysis. Included studies were predominantly observational cohorts of North American patients with mixed mechanisms of injury (table 1).

Risk of bias and quality assessments

Using the QUIPS tool [20], most studies were judged to be at low risk of bias in the domains of study attrition, prognostic factor measurement and outcome measurement (supplementary material). A few studies were judged to be at moderate risk of bias for study participation due to targeted subpopulations of trauma patients (due to specific injury patterns (head or chest injury only)) [22–33] and other studies were judged to be at moderate risk of bias for confounding due to lack of adjusted analyses [27, 29, 32, 34–39]. Most studies

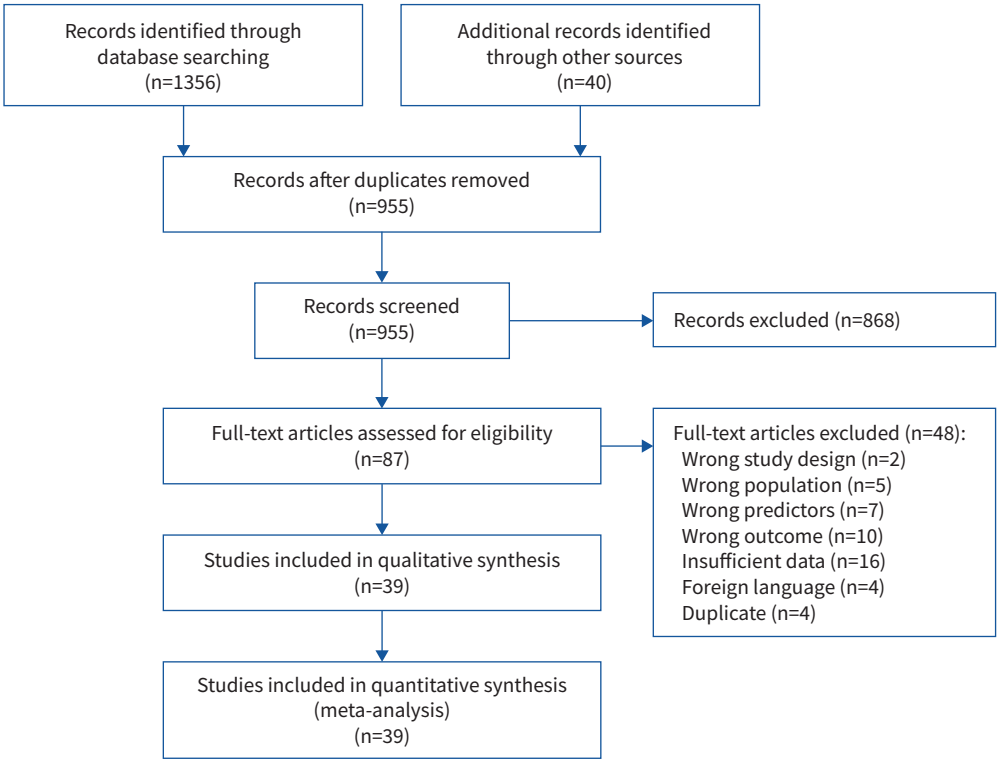

FIGURE 1 PRISMA flow diagram.

were judged to be at moderate risk of bias for statistical analysis and reporting (due to lack of adherence to best practice guidelines for prognostic model development and validation) [23, 24, 27–29, 31–55].

Predictors of ARDS development

We present the forest plots for adjusted (figure 2 and table 2) and unadjusted analyses (supplementary material and table 2). Of the patient factors, male sex may increase the odds of ARDS (n=6 studies; adjusted odds ratio (aOR) 1.33, 95% CI 0.90–1.97), although this is based on a low certainty of evidence. Non-Hispanic White race (n=11; unadjusted odds ratio (uOR) 1.22, 95% CI 1.11–1.34) and increasing age (n=7; aOR 1.14, 95% CI 1.07–1.21 per 10 year increase) were probably associated with increased odds of ARDS (moderate certainty). For sensitivity analyses including only prospective cohort studies, male sex and increasing age demonstrated uncertain association with ARDS due to serious imprecision. Sensitivity

TABLE 1 Characteristics of included studies (n=39)

Study origin	
North America	28 (71.8)
Europe	5 (12.8)
Asia	6 (15.4)
Study design	
Retrospective cohort	27 (69.2)
Prospective cohort	12 (30.8)
Patient population	
Mixed mechanism	29 (74.4)
Blunt mechanism only	10 (25.6)
ARDS definition	
American–European Consensus Conference	24 (61.5)
Berlin	15 (38.5)

Data are presented as n (%). ARDS: acute respiratory distress syndrome.

Study or subgroup	Log(OR)	SE	Weight	OR IV, Random (95% CI)
Patient factors				
Male *versus* female				
Daher 2018	0.2927	0.1545	24.9%	1.34 (0.99–1.81)
Hendrickson 2016	1.0647	0.4418	12.0%	2.90 (1.22–6.89)
Martin 2005	–0.1985	0.1767	23.8%	0.82 (0.58–1.16)
Park 2016	0.9632	0.3942	13.7%	2.62 (1.21–5.67)
Robinson 2018	0.2231	0.4007	13.4%	1.25 (0.57–2.74)
Senekjian 2020	–0.2485	0.4389	12.1%	0.78 (0.33–1.84)
Total (95% CI)			**100.0%**	**1.33 (0.90–1.97)**
Heterogeneity: Tau²=0.14; Chi²=14.04, df=5 (p=0.02); I²=64%				
Test for overall effect: Z=1.43 (p=0.15)				
Age (10 year increase) *versus* none				
Avci 2019	0.198	0.005	14.4%	1.22 (1.21–1.23)
Chaiwat 2009	0.149	0.0076	14.3%	1.16 (1.14–1.18)
Daher 2018	0.159	0.003	14.4%	1.17 (1.17–1.18)
Park 2016	0.07	0.0118	14.1%	1.07 (1.05–1.10)
Robinson 2018	0.1	0.0102	14.2%	1.11 (1.08–1.13)
Senekjian 2020	0	0.0051	14.4%	1.00 (0.99–1.01)
Watkins 2012	0.22	0.01	14.2%	1.25 (1.22–1.27)
Total (95% CI)			**100.0%**	**1.14 (1.07–1.21)**
Heterogeneity: Tau²=0.01; Chi²=1040.86, df=6 (p<0.00001); I²=99%				
Test for overall effect: Z=4.26 (p<0.0001)				
Injury factors				
Blunt *versus* penetrating mechanism				
Daher 2018	0.9163	0.2958	25.4%	2.50 (1.40–4.46)
Kornblith 2019	0.5822	0.3452	22.3%	1.79 (0.91–3.52)
Martin 2005	0.2231	0.1564	34.9%	1.25 (0.92–1.70)
Robinson 2018	1.2837	0.438	17.5%	3.61 (1.53–8.52)
Total (95% CI)			**100.0%**	**1.94 (1.21–3.12)**
Heterogeneity: Tau²=0.14; Chi²=8.32, df=3 (p=0.04); I²=64%				
Test for overall effect: Z=2.74 (p=0.006)				
Pulmonary contusion *versus* none				
Avci 2019	2.3693	0.4415	49.0%	10.69 (4.50–25.40)
Watkins 2012	0.599	0.361	51.0%	1.82 (0.90–3.69)
Total (95% CI)			**100.0%**	**4.33 (0.76–24.54)**
Heterogeneity: Tau²=1.40; Chi²=9.64, df=1 (p=0.002); I²=90%				
Test for overall effect: Z=1.66 (p=0.10)				
Chest injury severity by AIS (1 point increase) *versus* none				
Kornblith 2019	0.3031	0.0745	63.1%	1.35 (1.17–1.57)
Robinson 2018	0.3393	0.1018	33.8%	1.40 (1.15–1.71)
van Wessem 2018	0.2287	0.3357	3.1%	1.26 (0.65–2.43)
Total (95% CI)			**100.0%**	**1.37 (1.22–1.54)**
Heterogeneity: Tau²=0.00; Chi²=0.15, df=2 (p=0.93); I²=0%				
Test for overall effect: Z=5.29 (p<0.00001)				
Resuscitation factors				
Early PRBCs (1 unit increase) *versus* none				
Kornblith 2019	–0.112	0.0599	35.7%	0.89 (0.80–1.01)
Robinson 2018	0.004	0.0446	64.3%	1.00 (0.92–1.10)
Total (95% CI)			**100.0%**	**0.96 (0.90–1.03)**
Heterogeneity: Tau²=0.00; Chi²=2.41, df=1 (p=0.12); I²=59%				
Test for overall effect: Z=1.04 (p=0.30)				
Late PRBCs (1 unit increase) *versus* none				
Kornblith 2019	–0.006	0.1237	23.6%	0.99 (0.78–1.27)
Robinson 2018	–0.0161	0.0687	76.4%	0.98 (0.86–1.13)
Total (95% CI)			**100.0%**	**0.99 (0.88–1.11)**
Heterogeneity: Tau²=0.00; Chi²=0.01, df=1 (p=0.94); I²=0%				
Test for overall effect: Z=0.23 (p=0.82)				
Early FFP (1 unit increase) *versus* none				
Chaiwat 2009	0.5092	0.325	50.3%	1.66 (0.88–3.15)
van Wessem 2018	–0.107	0.328	49.7%	0.90 (0.47–1.71)
Total (95% CI)			**100.0%**	**1.22 (0.67–2.24)**
Heterogeneity: Tau²=0.08; Chi²=1.78, df=1 (p=0.18); I²=44%				
Test for overall effect: Z=0.66 (p=0.51)				

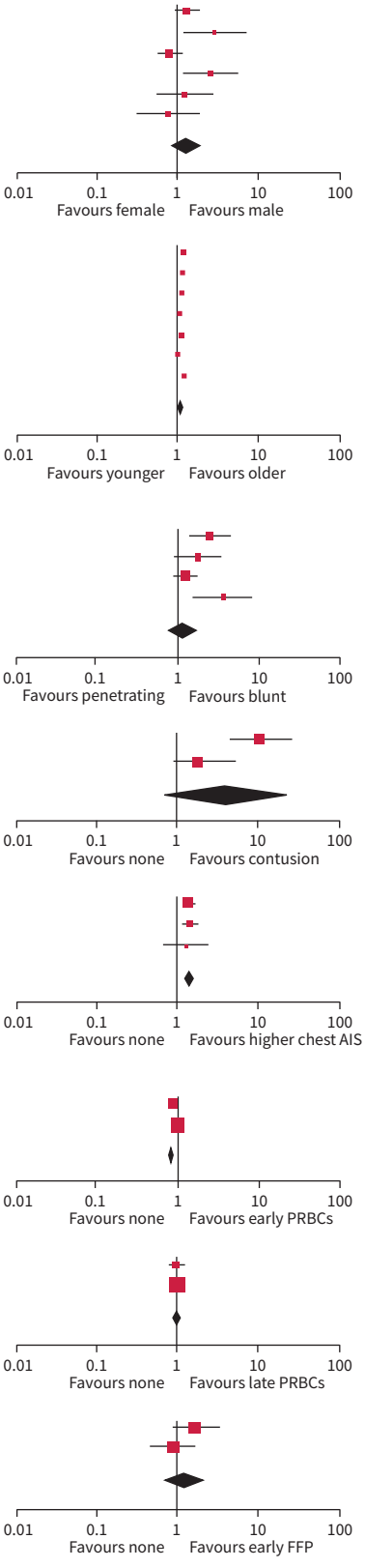

FIGURE 2 Continued on next page.

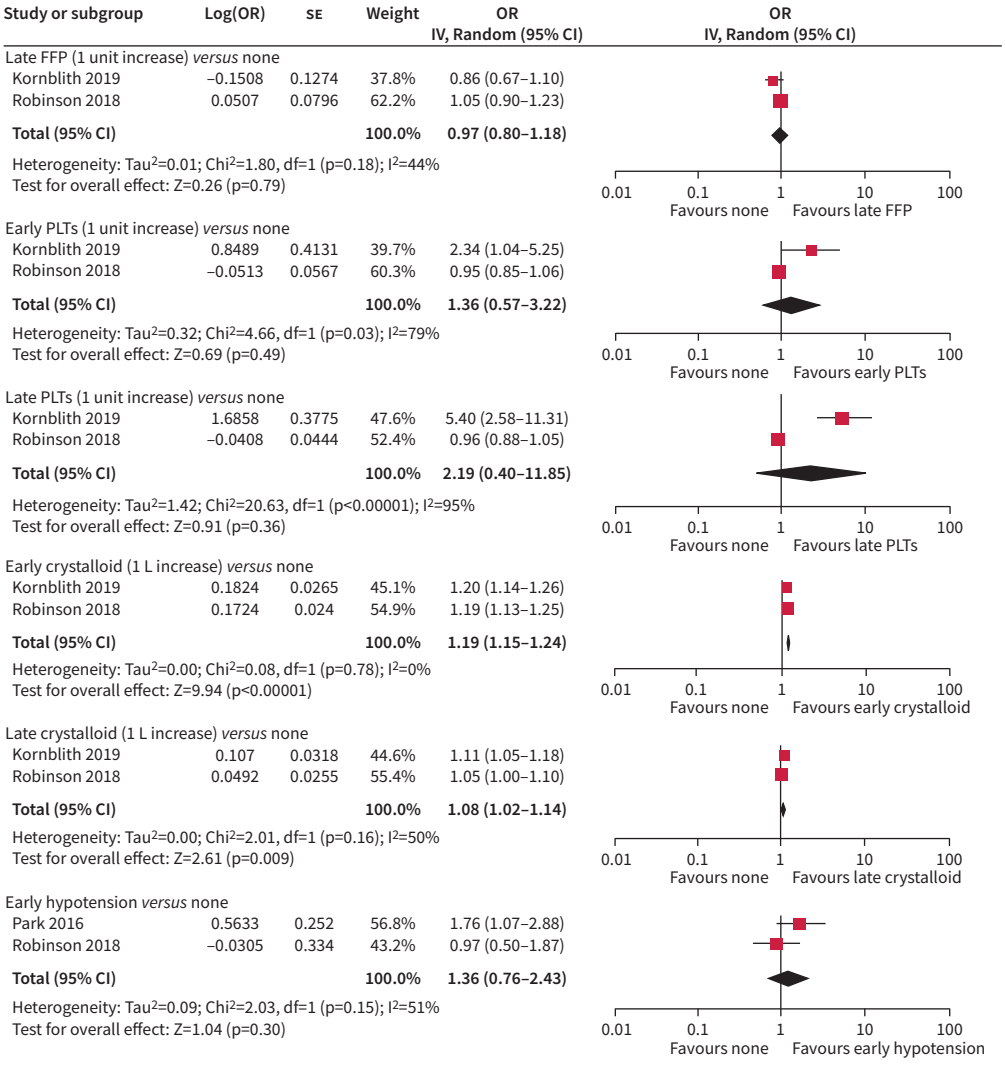

FIGURE 2 Forest plots: adjusted analyses. IV, Random: inverse variance random effects method; AIS: Abbreviated Injury Scale; PRBC: packed red blood cell; FFP: fresh frozen plasma; PLT: platelet.

analyses including only studies using the Berlin definition for ARDS did not identify any important differences in results.

With regard to injury factors, chest injury severity, per 1 point increase in Abbreviated Injury Scale (n=3; aOR 1.37, 95% CI 1.22–1.54), was associated with increased odds of ARDS (high certainty). The presence of head injury (n=11; uOR 2.57, 95% CI 1.63–4.08), presence of pulmonary contusion (n=5; uOR 4.42, 95% CI 2.78–7.02) and presence of at least one rib fracture (n=6; uOR 2.39, 95% CI 1.75–3.28) were probably associated with increased odds of ARDS (moderate certainty). The adjusted analysis for pulmonary contusion was consistent although rated as very low certainty due to imprecision [43, 56]. Sensitivity analyses including only prospective cohort studies and only those using the Berlin definition for ARDS did not identify any important differences in results.

Of the resuscitation factors, each additional litre of crystalloid administered within the first 6 h (early) after injury (n=2; aOR 1.19, 95% CI 1.15–1.24) was associated with increased odds of ARDS (high certainty). A similar association was observed with each additional litre of crystalloid administered between 7 and 24 h (late) after injury (n=2; aOR 1.08, 95% CI 1.02–1.14; moderate certainty). The administration of PRBCs within the first 6 h (early) after injury was probably not associated with an increased risk of ARDS (n=2; aOR 0.96, 95% CI 0.90–1.03; moderate certainty). There was an uncertain effect of early FFP or

TABLE 2 Prognostic factors associated with development of acute respiratory distress syndrome

	Studies (n)	Pooled OR (95% CI)	p-value	I^2 (%)	GRADE certainty
Unadjusted analyses					
Male *versus* female	30	1.14 (1.00–1.30)	<0.04	97	Very low
Non-Hispanic White race *versus* other	11	1.22 (1.11–1.34)	<0.0001	95	Moderate
Blunt *versus* penetrating	19	1.59 (1.34–1.89)	<0.00001	85	Moderate
Head injury *versus* none	11	2.57 (1.63–4.08)	<0.0001	99	Moderate
Pulmonary contusion *versus* none	5	4.42 (2.78–7.02)	<0.00001	91	Moderate
Rib fracture *versus* none	6	2.39 (1.75–3.28)	<0.00001	84	Moderate
Adjusted analyses					
Male *versus* female	6	1.33 (0.90–1.97)	0.15	64	Low
Age (per 10 year increase)	7	1.14 (1.07–1.21)	<0.0001	99	Moderate
Blunt *versus* penetrating	4	1.94 (1.21–3.12)	0.006	64	Moderate
Pulmonary contusion *versus* none	2	4.33 (0.76–24.54)	0.10	90	Very low
Chest injury severity by AIS (per 1 point increase)	3	1.37 (1.22–1.54)	<0.00001	0	High
Early PRBCs (per 1 unit increase)	2	0.96 (0.90–1.03)	0.30	59	Moderate
Late PRBCs (per 1 unit increase)	2	0.99 (0.88–1.11)	0.82	0	Moderate
Early FFP (per 1 unit increase)	2	1.22 (0.67–2.24)	0.51	44	Very low
Late FFP (per 1 unit increase)	2	0.97 (0.80–1.18)	0.79	44	Low
Early PLTs (per 1 unit increase)	2	1.36 (0.57–3.22)	0.49	79	Very low
Late PLTs (per 1 unit increase)	2	2.19 (0.40–11.85)	0.36	95	Very low
Early crystalloid (per 1 L increase)	2	1.19 (1.15–1.24)	<0.00001	0	High
Late crystalloid (per 1 L increase)	2	1.08 (1.02–1.14)	0.009	50	Moderate
Early hypotension *versus* none	2	1.36 (0.76–2.43)	0.30	51	Very low

AIS: Abbreviated Injury Scale; PRBC: packed red blood cell; FFP: fresh frozen plasma; PLT: platelet.

platelet administration on the risk of ARDS (very low certainty). Late administration of PRBCs (n=2; aOR 0.99, 95% CI 0.88–1.11; moderate certainty) or FFP (n=2; aOR 0.97, 95% CI 0.80–1.18; low certainty) between 7 and 24 h after injury probably had no effect on the risk of ARDS. There was an uncertain effect of early hypotension or late administration of platelets on the risk of ARDS (very low certainty). Sensitivity analyses including only prospective cohort studies did not identify any important differences in results. During sensitivity analyses including only studies using the Berlin definition for ARDS, late platelet administration demonstrated a low certainty of association with ARDS. Otherwise, there were no important differences in results.

Predictors of ARDS mortality

Of the patient factors, older age (n=3; aOR 4.79, 95% CI 2.75–8.35) had increased odds of mortality following ARDS (high certainty) (figure 3 and table 3). Older age was variably defined as ⩾65 years old [55], ⩾75 years old [8] or ⩾80 years old [57]. Of the injury factors, the presence of trauma coagulopathy (n=3; aOR 1.95, 95% CI 1.22–3.12) was also probably associated with increased odds of mortality (moderate certainty). Of the resuscitation factors, early hypotension (n=2; aOR 1.73, 95% CI 1.28–2.36) was associated with increased odds of mortality following ARDS (high certainty). Sensitivity analyses including only prospective cohort studies and only those using the Berlin definition for ARDS did not identify any important differences in results.

Discussion

In this systematic review and meta-analyses, we found that the amount of crystalloid resuscitation within the first 24 h of traumatic injury is a potentially modifiable prognostic factor associated with development of post-traumatic ARDS. Non-modifiable prognostic factors with a moderate or high certainty of association with development of ARDS included increasing age, non-Hispanic White race, blunt mechanism of injury, presence of head injury, pulmonary contusion or rib fracture and increasing chest injury severity. Modifiable risk factors with a moderate or high certainty of association with development of ARDS included increasing crystalloid administration, notable in both the early and late phase of post-injury resuscitation. Poor prognostic factors for mortality after ARDS included increasing age, development of trauma coagulopathy and early hypotension.

The most important potentially modifiable risk factor for post-traumatic ARDS was the volume of crystalloid administered during the first 24 h after injury. Large-volume crystalloid resuscitation has

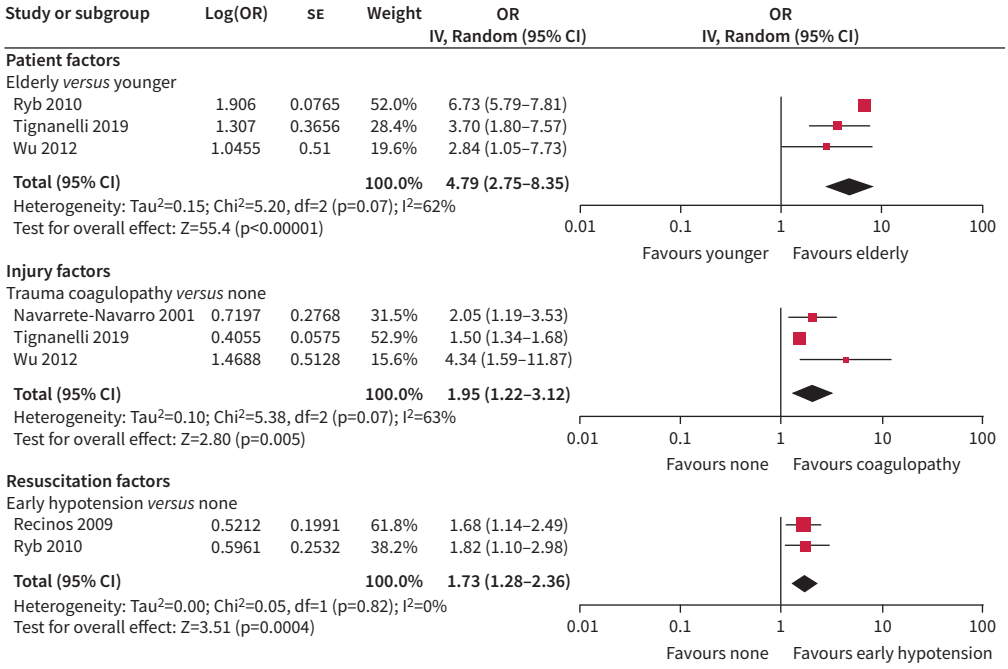

FIGURE 3 Forest plots: adjusted analyses (mortality). IV, Random: inverse variance random effects method.

typically been discouraged in the trauma setting due to its association with cardiac and pulmonary complications, inflammatory mediator dysfunction, and dilutional coagulopathy [58, 59]. Similarly, a prior meta-analysis has suggested mortality benefit for restricted fluid strategies in the pre-hospital and early resuscitation phases for trauma patients [60]. Instead, damage control resuscitation has been encouraged, incorporating early provision of blood products, reduced crystalloid administration, permissive hypotension where appropriate and prioritisation of haemostatic manoeuvres [61–63]. Despite this, aggressive crystalloid use continues to occur during resuscitation of bleeding trauma patients. A large multicentre cohort study noted that a median of 17.2 L crystalloid was used in the first 24 h in conjunction with massive transfusion and most patients received a greater than 1:1 ratio of crystalloid (litres) to units of PRBCs [64]. Despite similar clinical and biochemical resuscitation end-points, the authors demonstrated that a crystalloid to PRBC ratio >1.5 had a significantly increased risk of multiorgan failure, ARDS and abdominal compartment syndrome. Similarly, a cohort study by Robinson *et al.* [7], included in this review, demonstrated that the deleterious effect of crystalloid volume was independent of injury severity, presenting haemodynamics and mechanism of injury. These considerations suggest that excessive resuscitation with crystalloid remains a common but modifiable risk factor to reduce the incidence of post-traumatic ARDS. We did not identify any eligible studies evaluating the association between colloid administration and development of ARDS.

We found with moderate certainty that advanced age and non-Hispanic White race were associated with post-traumatic ARDS, a finding previously observed in non-trauma patients [65]. However, we also noted that the influence of race/ethnicity on the pathophysiology and risk of ARDS continues to be unclear. In particular, other studies have demonstrated contrasting findings where Black and Hispanic patients were more likely to develop respiratory complications and mortality from ARDS than non-Hispanic White

TABLE 3 Prognostic factors associated with mortality following post-traumatic acute respiratory distress syndrome (adjusted analyses)

	Studies (n)	Pooled OR (95% CI)	p-value	I^2 (%)	GRADE certainty
Elderly *versus* younger	3	4.79 (2.75–8.35)	<0.00001	62	High
Trauma coagulopathy *versus* none	3	1.95 (1.22–3.12)	0.005	63	Moderate
Early hypotension *versus* none	2	1.73 (1.28–2.36)	0.0004	0	High

patients [66]. Whether these findings reflect fundamental differences in disease pathophysiology or discrepancies in provision of care remains unclear. With regard to specific injury patterns, we found with moderate certainty that blunt mechanism of injury, presence of head injury, pulmonary contusion or rib fracture and increasing chest injury severity increased the odds of developing post-traumatic ARDS. In particular, the association with chest injury patterns supported a mechanism of predominantly direct lung injury in the trauma population, as opposed to indirect lung injury [67]. This distinction suggests potential differences in the underlying molecular phenotypes, cellular pathophysiology, treatment responses and clinical outcomes [68]. Interestingly, while direct injury ARDS is classically characterised by more severe lung epithelial injury and worse clinical outcomes in the general population [68], trauma patients have been shown to have lower plasma levels of biomarkers for endothelial and lung epithelial injury reflecting less severe disease processes [3]. Whether these differences in molecular phenotypes and clinical outcomes reflect a fundamental contrast in disease pathophysiology or underlying host factors between post-traumatic ARDS and non-traumatic ARDS remains unclear.

While many of the identified risk factors in this review were non-modifiable, their consideration may prompt clinicians to identify and react earlier to a potential ARDS diagnosis in trauma patients. A missed or delayed diagnosis of ARDS continues to be a frequent occurrence among critically ill patients and leads to a failure to institute measures to minimise the progression of lung injury, such as fluid restriction, protective ventilation strategies and consideration of prone positioning [69, 70].

With regard to prognostic factors associated with mortality among patients who develop post-traumatic ARDS, we found with high certainty that older age conferred higher odds of mortality, a finding similar to non-trauma patients [70]. However, we noted that in the absence of available co-adjustment, advanced age likely functions as an imperfect surrogate for clinical frailty, which has previously been identified as an important independent predictor of mortality and adverse outcomes in mechanically ventilated patients [71]. We additionally found with moderate certainty that presence of coagulopathy and with high certainty that occurrence of early hypotension are important independent predictors of mortality. Prior literature has demonstrated that the presence of trauma-induced coagulopathy likely reflects a higher burden of cellular injury and hypoperfusion, and is associated with higher transfusion requirements, incidence of organ dysfunction and mortality [72]. Similarly, early hypotension likely reflects a higher severity of injury and period of hypoperfusion with increased likelihood of need for high-volume crystalloid resuscitation, massive transfusion and aggressive intervention [16, 73]. We did not find any studies specifically evaluating the association between volume of crystalloid resuscitation and ARDS mortality.

Strengths and limitations

This review was strengthened by conduct of a comprehensive search, adherence to recommendations for meta-analysis of prognostic studies [12], and use of GRADE to evaluate and clinically contextualise our findings based on overall certainty estimates [21]. The face validity, consistency, precision and generally robust effect sizes for the prognostic factors identified in this review justify their inclusion in any risk stratification framework. We reported both adjusted and unadjusted analyses, and prioritised the analysis with the highest certainty in interpreting our findings. This review also has limitations. While we pragmatically included both the Berlin and AECC definitions in this review, we acknowledge that important differences exist. The use of the Berlin definition, which includes the mild ARDS subgroup, would be expected to result in a higher incidence of ARDS but with better overall outcomes compared with the AECC definition. During sensitivity analyses including only studies utilising the Berlin definition, which functions as a surrogate for modern ARDS management, very few meaningful differences were identified and there were no changes to our conclusions. In addition, while we pre-specified the required co-adjustment of at least one patient factor and one injury factor for inclusion, the presence of residual confounding, variability in prediction model design, and variable selection and reporting strategy among included studies nonetheless remain important limitations of prognostic factor meta-analyses [12]. These considerations are reflected in the higher measures of statistical heterogeneity, which are driven predominantly by variability in estimated effect size. However, such limitations are accounted for during the GRADE assessments, which additionally consider risk of bias and consistency of direction when determining the level of confidence in a potential association. This review is not intended to determine clinically applicable effect size estimates, but rather uses those estimates in conjunction with other metrics to provide a holistic appraisal of a potentially important clinical association. The identification of clinically applicable effect size estimates is best performed by development and validation of a well-designed prognostic model, for which variable selection can be informed by the findings of this review. Importantly, while we identify the amount of crystalloid resuscitation as a potentially modifiable factor, this relies upon the assumption of a potential causal relationship. However, we acknowledge that this meta-analysis cannot directly address causation and that the association with resuscitation intensity may be an indicator of

increased severity of underlying disease that is not entirely accounted for by confounding adjustment. This review serves rather as a call for interventional studies to examine this relationship further. Similarly, we are unable to comment on the impact of mechanical ventilation strategies, which are well known to be critical determinants of ARDS incidence and outcomes [74–76]. In particular, while the body of work for ventilation strategy in trauma-related ARDS is less robust, the existing evidence similarly favours lower tidal volumes as the benchmark practice [77]. While we did not directly account for changing practice trends over time, the sensitivity analysis including only modern studies utilising the Berlin definition did not identify any meaningful differences for the majority of prognostic factors. Lastly, we note that the mortality analysis was performed only on patients who developed ARDS, which offers some guidance for prognosticating this subgroup of patients. However, we are unable to specifically address whether those prognostic factors contributed specifically to increased mortality by means of an ARDS-mediated pathway.

Conclusions

We identified one important modifiable factor, the amount of crystalloid resuscitation within the first 24 h of injury, and several non-modifiable factors associated with development of post-traumatic ARDS. These findings may allow clinicians to be more cognisant of high-risk clinical features in order to more promptly recognise and initiate strategies to mitigate acute lung injury in critically ill trauma patients.

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