RESPIRATORY CARE Paper in Press. Published on September 21, 2021 as DOI: 10.4187/respcare.09091

Epidemiology and Outcomes of ARDS After Pediatric Trauma

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BACKGROUND: Results of recent studies suggest that the incidence and mortality of ARDS may be higher than previously thought in pediatric trauma patients. We conducted a systematic review of the literature on incidence, risk factors, prognostic factors, and outcomes of ARDS after pediatric trauma in the ICU. METHODS: Medical literature databases were searched up to April 2020. Guidelines for reporting systematic reviews and meta-analyses were followed. Articles that reported quantitative data with regard to the incidence, risk factors, prognostic factors, mortality, or other outcomes for ARDS in subjects with pediatric trauma admitted to the ICU were included. Two authors independently screened and assessed eligibility of all identified studies, collected data, and assessed the methodological quality of selected studies. Data extraction was performed by using a standardized data extraction sheet. Quality assessment was performed by using the Newcastle-Ottawa scale for cohort studies. A meta-analysis was not performed because the studies used overlapping cohorts or different ARDS criteria. RESULTS: Nine studies were included. The incidence was reported in 4 studies, risk factors in 1, mortality in 7, and other outcomes in 2. The largest cohort included 148,749 subjects from a national trauma database. The ARDS incidence was 1.8%–7.6% when using adult ARDS criteria, with 1.8% in the largest cohort, and 4.2% when using pediatric ARDS criteria. Mortality was 7.6%–22.9% when using adult ARDS criteria and 11.1%–34.0% when using the pediatric ARDS criteria. Identified risk factors included mechanism of injury, higher injury severity scores, abnormal breathing frequencies, and lower Glasgow coma scale scores at hospital presentation. ARDS was associated with a longer duration of mechanical ventilation, longer ICU and hospital length of stay, and a higher likelihood of requiring post-discharge care. CONCLUSIONS: The ARDS incidence of 4.2% in the subjects with pediatric trauma in the ICU was comparable with 3.2% in the general pediatric ICU population; however, mortality associated with trauma-associated ARDS was higher and more commonly due to multi-system organ failure rather than hypoxemia. *Key words: ARDS; wounds and injuries; pediatrics; intensive care units; pediatric; epidemiology; mortality.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Trauma continues to be a major cause of morbidity and mortality among young people worldwide.[1] Outcomes can be impacted by both the direct injury and the sequelae of the injury and hospital complications. ARDS is characterized by a rapid onset neutrophil-based inflammatory response in the lungs after a clinical trigger (ie, sepsis, aspiration, trauma), which results in hypoxic respiratory failure and the need for invasive or noninvasive mechanical ventilation. Among deceased pediatric trauma patients, ARDS was the most commonly encountered complication before death.[2] Two recent studies demonstrated that the incidence and mortality of ARDS were higher than previously demonstrated in pediatric trauma patients and higher than in the general pediatric ICU population.[3,4]

Before 2015, children were diagnosed with ARDS by using 1 of 2 adult definitions for ARDS: the American-European Consensus Conference (AECC) criteria[5] beginning in 1994, and the updated Berlin criteria[6] in 2012. In 2015, the Pediatric Acute Lung Injury Consensus Conference (PALICC) recognized the need for a pediatric definition and established a new set of ARDS criteria for children.[7] The PALICC criteria[7] differed from the adult criteria in several important ways, including only requiring unilateral pulmonary infiltrates on chest imaging instead of bilateral infiltrates, allowing S_{pO_2} to be used in the definition of hypoxia rather than just P_{aO_2}, incorporating mean airway pressure ($\overline{P}_{aw}$) and F_{IO_2} into the assessment of hypoxia by using the oxygenation index ($[F_{IO_2} \times \overline{P}_{aw}] / P_{aO_2}$) or the oxygen saturation index ($[F_{IO_2} \times \overline{P}_{aw}] / S_{pO_2}$) rather than the P_{aO_2} / F_{IO_2} for children who are invasively ventilated, and establishing criteria for ARDS in children who are receiving noninvasive ventilation.

Previous studies in the general pediatric ICU population demonstrated higher incidence but lower mortality for ARDS when using the PALICC criteria[7] versus adult definitions.[8-10] In adult populations, trauma subjects with ARDS demonstrated lower mortality than non-trauma subjects with ARDS.[11] Several recent studies in pediatric subjects that used the PALICC criteria,[7] however, found a higher incidence and higher mortality for ARDS in pediatric trauma subjects versus pediatric non-trauma subjects.[3,8] It is unclear why these recent studies of pediatric trauma subjects reported such high incidences and mortalities associated with ARDS relative to previous literature. The objectives of this systematic review were to assess the incidence of ARDS, the risk factors associated with the development of ARDS, the prognostic parameters that predict outcomes of ARDS, and the mortality and other outcomes associated with ARDS in a pediatric trauma population in the pediatric ICU. A better understanding of the epidemiology and outcomes of ARDS after pediatric trauma may help improve prevention, recognition, and treatment strategies to reduce morbidity and mortality associated with ARDS.

Methods

Search Strategy and Study Selection

This systematic review followed the PRISMA guidelines.[12] PubMed and Embase databases were searched for relevant publications from the beginning of collection up to April 2020 by using the Medical Subject Heading and the key words (acute lung injury or acute respiratory distress syndrome) and (trauma or wound and injuries) and (pediatrics or pediatric intensive care units or infant or child or adolescent or minors). The complete search strategy for PubMed and Embase is provided in Appendix A (see the supplementary materials at http://www.rcjournal.com). Two authors (RH, JG) independently and blinded from each other screened and assessed the eligibility of the identified publications and extracted data from and performed quality assessment of all included publications. Disagreements were resolved by consensus.

All study designs were considered. Publications were included if they provided quantitative data with regard to incidence, risk factors, prognostic factors, mortality, or other outcomes for ARDS in pediatric trauma subjects in the pediatric ICU. Publications were excluded if they did not report data separately for trauma subjects or if they did not report data separately for subjects ≤ 18 y old in studies that included other age ranges. Other exclusion criteria were studies that included subjects not admitted to the ICU, subjects with drowning or burn injuries, animal studies, case reports, case series (that were not cohort based), literature reviews, studies not published as full reports (ie, conference abstracts, letters to the editor), no full-text availability, and publications in languages other than English or Dutch.

Data Extraction

Data extraction was performed by one researcher (RH) by using a standardized data extraction sheet for all studies and was checked for correctness and completeness by a second researcher (JG). Data elements that were extracted are as follows: (1) incidence, defined as the percentage of subjects with ARDS compared with all pediatric trauma subjects in the pediatric ICU; (2) risk factors, defined as odds ratios or relative risks for the incidence of ARDS; (3) prognostic factors, defined as odds ratio, relative risk, or a prognostic model for outcomes associated with ARDS; (4) mortality, defined as the percentage of subjects with ARDS with in-hospital death compared with all pediatric trauma subjects in the pediatric ICU; and (5) other outcomes, defined as all other outcomes associated with ARDS except for mortality. Authors of potentially eligible studies with incomplete data to calculate the aforementioned data items or relevant conference abstracts were invited to share data and/or unpublished manuscripts but none responded.

Quality Assessment and Risk of Bias

Two authors (RH, JG) independently assessed methodological quality and the risk of bias of studies by using the Newcastle-Ottawa scale for cohort studies.[13] A summary

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The authors have disclosed no conflicts of interest.

Supplementary material related to this paper is available at http://www.rcjournal.com.

This work was performed at University Medical Center Utrecht, Utrecht, The Netherlands, and at Wilhelmina Children's Hospital, Utrecht, The Netherlands.

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DOI: 10.4187/respcare.09091

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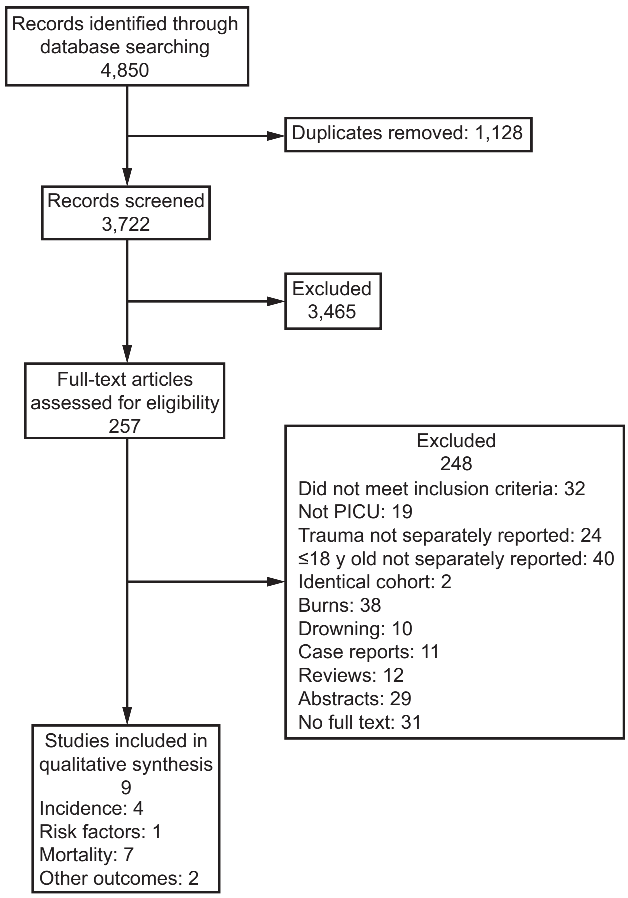

Fig. 1. Flow chart. PICU = pediatric ICU.

score was calculated for each study, ranging from 0% (no points) to 100% (maximum score). A high score indicates good methodological quality and a low risk of bias in the studies.

Statistical Analysis and Data Synthesis

For quality assessment, inter-rater reliability was tested by using the Cohen weighted κ to determine consistency among the raters. Statistical analysis was performed by using IBM SPSS Statistics for Windows, version 27 (IBM, Armonk, New York). A meta-analysis was planned but not performed due to overlapping cohorts and use of differing ARDS definitions. Three studies[18-20] were conducted by using data from the National Trauma Data Bank (NTDB) (American College of Surgeons, Chicago, IL), the national trauma registry of the United States of America and Canada. Six other studies[3,8,14-17] were conducted in centers that provided data to the NTDB over similar study periods, which effectively created 1 overlapping cohort. The use of different, sometimes unofficial, ARDS criteria was deemed to create too much heterogeneity for a high-quality comparison.

Results

Search Results and Study Selection

The initial search identified 3,722 publications potentially eligible for inclusion. After screening, 257 publications had full-text available and, of these, 9 publications were included for analysis (Fig. 1).[3,8,14-20] Three studies by Killien et al[18-20] used near-identical cohorts, but the incidence and mortality were only extracted from the most recent of these 3 studies.[20] To prevent analyzing subjects more than once, only unique data on risk factors[18] and other outcomes[19] were reported for the other 2 studies. Four unique cohorts reported the incidence of ARDS,[3,14,15,20] one described risk factors for ARDS development,[18] none reported prognostic factors for outcomes specifically for trauma patients, 7 reported mortality[3,8,14-17,20] and 2 reported other outcomes.[3,19]

Quality Assessment

Methodological quality was high and the risk of bias was low, with a median Newcastle-Ottawa Scale score of 100% (interquartile range 88.9% - 100%). Weighted κ for inter-rater reliability was 0.182 (95% CI –0.248 to 0.611; P = .39). Detailed quality assessment for all included studies is provided in Appendix B (see the supplementary materials at http://www.rcjournal.com).

Study Characteristics

Study characteristics are provided in Table 1. The 9 studies encompassed an inclusion period of 35 years and all the studies were observational. Data were collected prospectively in 4 studies.[8,14,16,17] One study[8] originated in multiple nations, including the United States, and all the other studies[3,14-20] originated in the United States. Three studies[14,15,17] were conducted in a single center, and 3 studies were conducted by using the NTDB and used near-identical cohorts.[18-20] In addition, all the trauma centers in the United States that are represented in these studies reported data to the NTDB, thus all the single- or multi-center studies that originated solely in the United States were subpopulations of the cohorts used in the NTDB studies.

Three studies included < 50 trauma subjects,[8,16,17] 2 studies included 231 trauma subjects[14] and 340 trauma subjects,[15] 1 study included 2,470 trauma subjects,[3] and 3 included nearly 150,000 trauma subjects.[18-20] Two studies were conducted before the introduction of an official ARDS definition but used the Murray lung injury score,[14,21] a predecessor of the adult ARDS definitions, or comparable definitions with the AECC criteria[5] and Berlin criteria.[6,15] One study used the AECC definition,[5,16] and 3 studies used the NTDB,[18-20] which used the AECC definition[5] from 2007–2011, the modified Berlin criteria[22]

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Table 1. Study Characteristics of Included Publications for Qualitative Synthesis

Study	Year	Study Location	Study Center	Study Period	Type of Study	ARDS Definition	Age Groups Included	Trauma Population, *n*
Davis et al[14]	1993	United States	Single center	1990–1992	Prospective	Murray lung injury score	2 mo to 21 y	231
Scannell et al[15]	1995	United States	Single center	1985–1993	Retrospective	Comparable with AECC and Berlin[6]	≤18 y	340
Zinter et al[16]	2016	United States	Multi-center	2008–2014	Prospective	AECC	30 d to 18 y	13
Yehya et al[17]	2018	United States	Single center	2011–2017	Prospective	AECC, Berlin, and PALICC	>1 mo and <18 y	35
Killien et al[18]*	2018	United States	NTDB	2007–2016	Retrospective	AECC, modified Berlin,[22] and full Berlin	<18 y	146,058
Khemani et al[8]	2019	International	Multi-center	2016–2017	Prospective	Berlin and PALICC	3.3 y (median, IQR 0.7–9.6)	27
Killien et al[19]*	2019	United States	NTDB	2007–2016	Retrospective	AECC, modified Berlin,[22] and full Berlin	<17 y	146,058
Killien et al[20]*	2019	United States	NTDB	2007–2016	Retrospective	AECC, modified Berlin,[22] and full Berlin	<17 y	148,749
Killien et al [3]	2020	United States	Two centers	2009–2017	Retrospective	PALICC	<18 y	2,470

*Identical or near-identical cohorts.
AECC = American-European Consensus Conference criteria (Reference 5)
PALICC = Pediatric Acute Lung Injury Consensus Conference criteria (Reference 7)
NTDB = National Trauma Data Bank
IQR = interquartile range

from 2012–2014, and full Berlin criteria[6,23] from 2015-present. Also, 3 studies used the PALICC criteria,[3,7,8,17] and 2 of these also used adult definitions.[8,17] Inclusion and exclusion criteria as well as included age groups were comparable for all the studies.

Incidence

Four studies reported the ARDS incidence (Table 2 and Fig. 2).[3,14,15,20] The incidence ranged from 1.7 to 6.7% across all definitions. Killien et al[20] reported an incidence of 1.8% in, by far, the largest cohort ($N = 148{,}749$) when using the NTDB and adult ARDS definitions. On subgroup analysis, they reported a higher incidence of 2.1% for children 13–17 y old. Over time, the NTDB used the AECC,[5] modified Berlin,[22] and full Berlin criteria[8] consecutively but never simultaneously. The incidence for individual ARDS definitions were not reported. Killien et al[3] reported an incidence of 4.2% over a similar study period as the NTDB studies, but it was the only study among the incidence studies that used the PALICC criteria[7] and the only one to explicitly identify subjects with ARDS by calculation of oxygenation metrics and review of chest imaging and patient charts. No comparisons were made between the PALICC criteria[7] and adult ARDS definitions in this study.

Risk Factors

Only 1 study reported risk factors for development of ARDS among pediatric trauma subjects.[18] The risk factors that remained significant after multivariate logistic regression are provided in Table 3. The risk factors associated with injury included the mechanism of injury (amputation, firearm injuries, and motor vehicle crashes) and a higher Injury Severity Score.[24] Clinical factors included any breathing frequency other than normal at the time of emergency department presentation; the Glasgow coma scale score was negatively associated with the development of ARDS. Also, chest injury characteristics associated with the development of ARDS were intrathoracic vascular injuries, pulmonary contusion, and severe chest injuries identified by an Abbreviated Injury Scale[25] severity score > 3.

Mortality

Seven studies reported mortality among the subjects with ARDS (Table 4 and Fig. 2).[3,8,14-17,20] Overall mortality in the studies with > 10 subjects ranged from 7.7% to 34.0%. One study reported 50.0% mortality in 4 subjects.[14] When using adult ARDS definitions, mortality ranged from

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Table 2. Incidence of ARDS in Pediatric Trauma Patients in the Pediatric ICU

Study	Year	Study Location	Study Center	Study Period	ARDS Definition	Subjects, *N*	Subjects With ARDS, *n*	Incidence, %
Davis et al[14]	1993	United States	Single center	1990–1992	Murray lung injury score	231	4	1.7
Scannell et al[15]	1995	United States	Single center	1985–1993	Comparable*	340	26	7.6
Killien et al[20]	2019	United States	NTDB	2007–2016	AECC, modified Berlin,[22] and full Berlin	148,749	2,615	1.8
Killien et al[3]	2020	United States	Two centers	2009–2017	PALICC	2,470	103	4.2

*Comparable with AECC and Berlin criteria.[6]
NTDB = National Trauma Data Bank
AECC = American-European Consensus Conference criteria (Reference 5)
PALICC = Pediatric Acute Lung Injury Consensus Conference criteria (Reference 7)

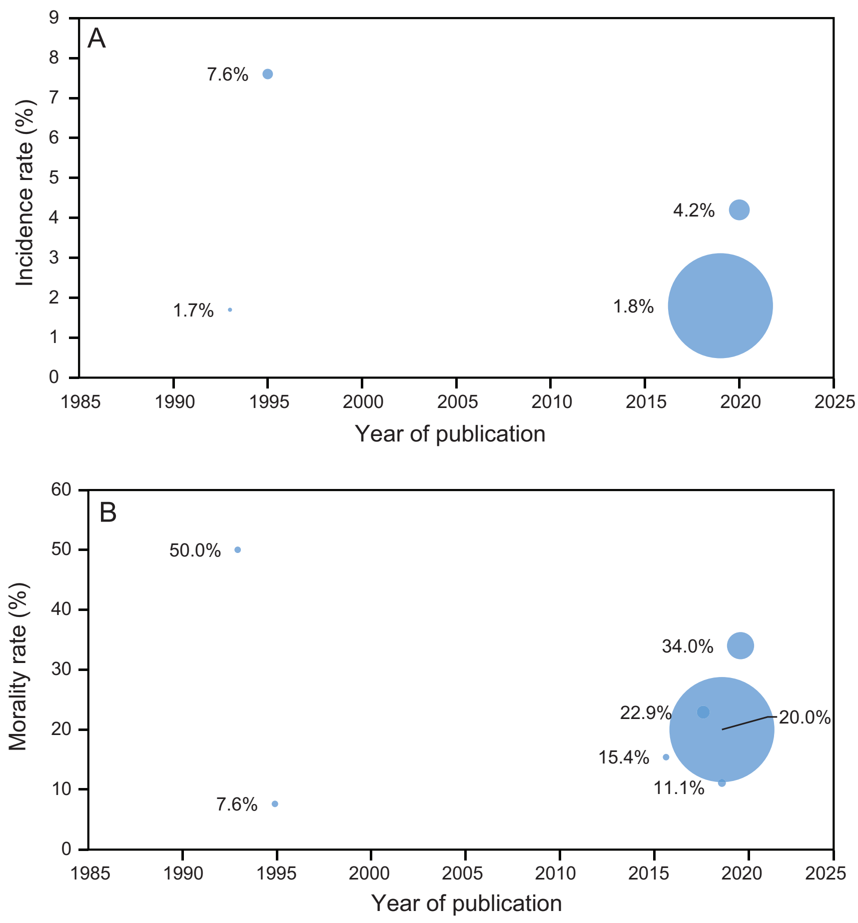

Fig. 2. Incidence and mortality of ARDS across year of publication and population size. The size of bubbles indicates the size of the study population with the incidence or mortality of ARDS relative to other studies.

15.4% to 22.9%. When using the PALICC criteria,[7] mortality ranged from 11.1% to 34.0%. The largest cohort that used the NTDB and adult ARDS definitions reported an overall mortality of 20%.[20] On subgroup analysis, mortality was higher for children ≤ 4 y old (25.2% mortality)[20] and in children with severe ARDS at onset (50.0% mortality).[3] Only one study reported the cause of death as neurologic failure (60.0%) or multi-system organ failure (34.4%) in almost all the subjects rather than refractory hypoxemia (2.9%).[3] After adjustment for confounding factors, higher

Table 3. Relative Risk Factors for the Development of ARDS in Pediatric Trauma Patients in the Pediatric ICU on Multi-variable Logistic Regression, Adjusted for Admission Year and Transfer Status*

Risk Factor	Multivariate Logistic Regression	
	Adjusted Relative Risk	95% CI
Race / ethnicity		
Non-Hispanic white	Ref	
Non-Hispanic Black	1.42	1.13–1.78
Mechanism of injury		
Fall	Ref	
Motor vehicle crash	1.91	1.57–2.31
Pedestrian or cyclist	1.41	1.17–1.70
Firearm	1.93	1.58–2.36
Chest injury	1.36	1.22–1.52
Lower extremity injury	1.26	1.10–1.44
Spinal injury	1.39	1.20–1.60
Amputation injury	2.10	1.51–2.91
Injury Severity Score		
1–8	Ref	
9–15	1.60	1.31–1.95
16–24	2.15	1.68–2.76
25–39	3.38	2.46–4.64
40–75	3.69	2.50–5.44
Breathing frequency		
Normal	Ref	
Intubated	1.64	1.23–2.26
Hypopnea	1.23	1.05–1.45
Tachypnea	1.26	1.10–1.44
Glasgow coma scale score		
15	Ref	
13–14	1.76	1.47–2.12
9–12	3.44	2.82–4.21
6–8	5.37	4.15–8.49
4–5	6.76	5.39–8.49
3	5.61	4.44–7.07
Pulmonary contusion	1.58	1.31–1.90
Intrathoracic vascular injury	1.62	1.23–2.12
Type of injury		
Penetrating	Ref	
Blunt	1.54	1.21–1.95
AIS score of chest injury		
3	Ref	
4 (severe)	1.58	1.20–2.08
5–6 (critical / maximum)	2.24	1.66–3.03

* Adapted with permission from reference number 18.
Ref = reference
AIS = Abbreviated Injury Severity Scale

adjusted relative risks for mortality were reported that ranged from 1.76 (95% CI 1.52–2.04)[19] to 3.70 (95% CI 2.00–6.90)[3] for pediatric trauma subjects with ARDS compared with pediatric trauma subjects without ARDS. On subgroup analysis, age group was negatively associated with relative risk for mortality, with a higher risk for mortality for each sequentially lower age group, the highest being 2.06 (95% CI 1.72–2.70) for children ≤ 4 y old.[20]

Other Outcomes

Two studies reported other outcomes (Table 5).[3,19] Both studies reported a longer duration of mechanical ventilation, ICU length of stay, and hospital length of stay for pediatric trauma subjects with ARDS versus pediatric trauma subjects without ARDS.[3,19] Pediatric trauma subjects with ARDS also had a higher risk for requiring ongoing care after discharge (adjusted relative risk 3.59 [95% CI 2.87-4.49]).[19] In subgroup analysis, children ages 13 - 17 years had the highest adjusted relative risk (2.26 [95% CI 1.80-2.84]) for requiring post-discharge care.[20] Killien et al[3] also reported a lower functional independence measure,[26] a scale used to measure normal functioning, for patients with ARDS versus patients without ARDS, at 7.8 / 12 (±3.3 SD) versus 11.2 / 12 (±1.6 SD), respectively ($P < .001$). No studies reported post-discharge follow-up or long-term outcomes.

Discussion

To our knowledge, this was the first large-scale systematic review of the epidemiology and outcomes of ARDS in pediatric trauma subjects in the pediatric ICU. This is an understudied topic, with only 9 studies reporting specifically on the association between pediatric trauma and ARDS. Among those, by far the largest cohorts originated from the NTDB. The incidence and mortality associated with ARDS are dependent on the ARDS definition used. When using adult definitions in pediatric trauma subjects, we found an incidence rate of 1.8%[18-20] and mortality ranged from 15.4% to 23.8%.[16,17,19,20,27,28] In a systematic review of ARDS in the general pediatric ICU population, Schouten et al[29] reported a similar pooled incidence, of 2.3%, and higher pooled mortality, of 33.7%, when using adult definitions. However, adult definitions of ARDS may not be appropriate for children because both adult definitions require invasively measured arterial blood gas sampling. Arterial blood gas sampling may not be commonly performed in children, especially when lung injury is mild or moderate. Several studies found that adult definitions of ARDS identify a smaller but more severely ill subset of subjects with higher mortality than those identified by PALICC criteria.[7-10]

When using the PALICC criteria[7] in pediatric trauma patients, the ARDS incidence was 4.3%[3] and mortality ranged from 11.1% to 34.0%,[3,8,17,27,28] with 34.0% in the largest cohort of 2,470 subjects.[3] In a large prospective multi-center study in the general pediatric ICU that used the PALICC criteria,[7] Khemani et al[8] reported an ARDS incidence of 3.2%, whereas when the Berlin criteria[6] were used, only one third of these subjects were identified with ARDS. Mortality in the general pediatric ICU population

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Table 4. Overall Mortality of ARDS in Pediatric Trauma Patients in the Pediatric ICU

Study	Year	Study Location	Study Center	Study Period	ARDS Definition	Subjects with ARDS, *n*	Died, *n*	Mortality, %
Davis et al[14]	1993	United States	Single center	1990–1992	Murray lung injury score	4	2	50.0
Scannell et al[15]	1995	United States	Single center	1985–1993	Comparable*	26	2	7.6
Zinter et al[16]	2016	United States	Multi-center	2008–2014	AECC	13	2	15.4
Yehya et al[17]	2018	United States	Single center	2011–2017	AECC, Berlin and PALICC	35	8	22.9
Khemani et al[8]	2019	International	Multi-center	2016–2017	PALICC	27	3	11.1
Killien et al[20]	2019	United States	NTDB	2007–2016	AECC, modified Berlin[22] and full Berlin	2,615	523	20.0
Killien[3]	2020	United States	Two centers	2009–2017	PALICC	103	35	34.0

*Comparable with AECC and Berlin criteria.[6]
AECC = American-European Consensus Conference criteria (Reference 5)
PALICC = Pediatric Acute Lung Injury Consensus Conference criteria (Reference 7)
NTDB = National Trauma Data Bank

Table 5. Other Outcomes

Study	Other Outcomes			
	Outcome	Outcome Measure		Value
Killien et al,[19] 2019*	Extra duration vs subjects without ARDS			
	Mechanical ventilation	Average extra days	3.10	2.74–3.47
	ICU length of stay	Average extra days	6.53	6.29–6.78
	Hospital length of stay	Average extra days	9.08	8.67–9.49
	Complications vs subjects without ARDS	aRR†		
	Tracheostomy		3.10	2.59–3.70
	Discharge disposition, all subjects	aRR†		
	Home without care		Ref	
	Ongoing post-discharge care		3.59	2.87–4.49
	Discharge disposition, survivors	aRR†		
	Home without care		Ref	
	Home health care		2.97	2.12–4.15
	Long-term care facility		5.10	3.21–8.11
	Skilled nursing facility		4.91	3.48–6.94
	In-patient rehabilitation		3.27	2.37–4.50
	Transfer to second acute care facility		2.76	2.02–3.79
Killien et al,[3] 2020‡	Extra duration vs subjects without ARDS	Average extra days		
	Mechanical ventilation	Average extra days	8.9	7.3–10.6
	ICU length of stay	Average extra days	11.4	10.5–12.4
	Hospital length of stay	Average extra days	16.5	14.6–18.3
	Post-discharge care	aRR§	1.5	1.1–2.1

*Study location: United States; NTDB; study period: 2007–2016; ARDS definition: AECC,[22] modified Berlin, Full Berlin criteria.[6]
†The aRRs are adjusted for age, Injury Severity Score, and the presence of a traumatic brain injury with an Abbreviated Injury Scale severity score ≥ 3, presence of a chest injury with an Abbreviated Injury Scale severity score ≥ 3, admission heart rate, admission hypotension, year, transfer status, and facility trauma level designation.
‡Study location: United States; study period: 2009–2017; ARDS definition: PALICC [22].
§The adjusted risk for post-discharge care relative to patients without pediatric ARDS adjusted for patient age, injury mechanism, injury severity and serious traumatic brain injury or chest injuries.
NTDB = National Trauma Data Bank
AECC = American-European Consensus Conference criteria (Reference 5)
aRR = adjusted relative risk
PALICC = Pediatric Acute Lung Injury Consensus Conference criteria (Reference 7)

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with ARDS based on the PALICC criteria[7] was 17.1%, which is lower than reported when using adult definitions.[29]

Surprisingly, the 11.1%–34.0% overall mortality of ARDS in pediatric trauma subjects when using PALICC criteria[3,7] was up to twice as high as that in the general pediatric ICU[8] and comparable with the mortality reported when using adult definitions in the general pediatric ICU population.[29] Mortality of 50% for severe ARDS in pediatric trauma subjects[3] was also higher than the mortality of 33% of severe ARDS in the general pediatric ICU population.[8] Pediatric trauma patients with ARDS thus may be more severely ill and demonstrate a higher mortality than non-trauma patients with ARDs. Even after adjustment for injury severity, hemodynamics, and other confounding factors, there still was a significant association with mortality for subjects with ARDS versus trauma subjects without ARDS with an adjusted relative risk of 3.70 (95% CI 2.00 - 6.90).[3] It is unknown whether this was due to the severity of ARDS alone or other accompanying factors, such as a different inflammatory response in children.

Several studies were excluded because they had included all pediatric trauma subjects who presented to the emergency department rather than pediatric trauma subjects in the pediatric ICU. These studies reported an ARDS incidence of 0.3% – 0.6%.[4,30-32] As expected, this is lower than in pediatric trauma patients in the pediatric ICU because only patients who are severely ill are admitted to the pediatric ICU. de Roulet et al[4] reported similar risk factors for ARDS compared with the study by Killien et al,[18] including severe chest and head injuries, although both studies used overlapping cohorts of subjects identified in the NTDB. Nair et al[33] reported a mortality of 19.0% of ARDS in all the trauma subjects when using the modified PALICC criteria,[7] in which they only included subjects with invasively measured arterial blood gas sampling (with a calculated oxygenation index). Similar to the studies in our review, the mortality for ARDS when using adult definitions in all the pediatric trauma subjects was 16.9%–18.6%.[4,32] Mortality was comparable because, most likely, all trauma patients who were severely ill and who developed ARDS would ultimately be admitted to the pediatric ICU and be included in the studies in our review.

The largest studies included in this review used the NTDB. The NTDB is the largest trauma registry in the world and contains >7 million records from > 1,000 pediatric and adult facilities in the United States and Canada.[34] Due to its sheer volume, nearly 150,000 pediatric ICU subjects in the included studies, the NTDB is an incredibly valuable research database and no other database in the world has more entries of pediatric trauma patients. However, it may not be suitable for all research questions. Trained registrars at each facility review patient charts and upload data to the NTDB. The NTDB uses only adult definitions for ARDS (AECC[5] from 2007 - 2011, modified Berlin[22] from 2012 - 2014 and full Berlin[6] from 2015-present), even for children.[23] Also, the NTDB does not record intervening events during hospital admission, such as aspiration or pneumonia, which may trigger ARDS, and thus all ARDS diagnoses in trauma patients are inclusive of these events. The accuracy of an ARDS diagnosis in the NTDB compared with oxygenation metrics, chest imaging, and chart review cannot be verified.

Studies in the pediatric ICU that diagnosed ARDS independently rather than when using the NTDB found a higher incidence of ARDS.[3,18-20] The same pattern is apparent in studies of all the pediatric trauma subjects admitted to the emergency department, where independent studies found higher incidences of ARDS than in studies that used the NTDB.[4,30-33,35] This discrepancy could partially be explained by selection bias because the independent studies were conducted in large level-1 trauma centers, whereas the NTDB cohorts included all trauma centers, including lower-tier centers with patients who were less severely injured. It may also indicate underrecognition of ARDS diagnosis in large databases. There were no studies that compared local data with an independently verified ARDS diagnosis to entries in the NTDB.

A second limitation of the NTDB is that it only contains data for patients in the United States and Canada. A systematic review of ARDS in general pediatric ICU subjects when using adult definitions by Schouten et al[29] reported a difference in the incidence of ARDS based on study location, which revealed a higher incidence in Asian versus Western countries. Only 1 study in our review contained data from subjects outside of the United States but included very few trauma subjects compared with the NTDB studies and did not provide data for different countries separately.[8] Strengths of this study included a comprehensive literature search and independent screening, assessment of eligibility, and data extraction and analysis by 2 researchers (RH, JG). Authors of potentially eligible manuscripts with incomplete data or conference abstracts were invited to collaborate, but none responded.

Our systematic review had several limitations. We only included studies written in English. A major limitation in assessing the incidence, mortality, and other parameters of ARDS in different studies is the changing definitions of ARDS. Diagnostic criteria are not interchangeable, and a significant portion of variation between studies may be attributable to the definitions of ARDS used, method of ARDS diagnosis (database or calculation of oxygenation metrics), and the populations studied. Most of the data in our study come from large studies that used the NTDB and/or adult definitions for ARDS, which both have their own limitations. Furthermore, there is a distinct underrepresentation of trauma-associated ARDS in the literature. Trauma patients are too often characterized in the "other" category in studies, and studies often do not report separate

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data for trauma patients, nor do they report separate data for pediatric trauma patients in the adult ICU, which makes adequate research in this special population particularly difficult. Data on long-term outcomes are lacking.

Conclusions

ARDS affects few pediatric trauma patients and the incidence is comparable with the general pediatric ICU population, but, once it occurs, ARDS in pediatric trauma is associated with high mortality. Although lower incidence rates are reported for younger children, they seem to have worse outcomes. Large cohort studies that used the NTDB are extremely valuable, but questions remain about validity, completeness, and accuracy of data and their use for specific research questions. In future studies, trauma should be sectioned out from the "other" category and pediatric ARDS definitions should be reported in national databases, for example, the NTDB. Future studies could be directed at assessing epidemiology and outcomes outside the United States and Canada, differences between younger and older children, causes of death, and long-term outcomes. Early identification of these patients may help to optimize treatment strategies to reduce the serious morbidity and mortality associated with ARDS in pediatric trauma patients.

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