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REVIEW ARTICLE

Prevalence and Mortality of Post-traumatic Acute Kidney Injury in Children; a Systematic Review and Meta-analysis

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Abstract: **Introduction:** Numerous studies on acute kidney injury (AKI) following trauma have been performed, and acceptable findings have been reported in the adult population. The present meta-analysis summarizes the studies performed on the pediatric population to evaluate the prevalence of AKI following trauma in this population. **Methods:** The Medline, Embase, Scopus and Web of Sciences databases were searched for articles published until the July, 31, 2021. Two independent reviewers screened observational studies performed on children with physical trauma and AKI related to it. The interested outcomes were the prevalence and mortality of trauma-related AKI in traumatized children. **Results:** Data of 9 articles were included in the present meta-analysis. The prevalence of trauma-related AKI varied between 0% and 30.30% among included studies. Pooled analysis showed that the prevalence of trauma-related AKI was 9.86% (95% CI: 8.02 to 11.84%). The prevalence of AKI after exertional rhabdomyolysis, direct physical trauma, and earthquake related injuries was 0%, 12.64% and 24.60%, respectively. There was a significant relationship between the prevalence of AKI and trauma etiology (p = 0.038). Moreover, the occurrence of AKI in children with trauma was associated with an increased risk of mortality (OR = 5.55; 95% CI: 2.14 to 13.93). **Conclusion:** The findings of the present study showed that 9.86% of children develop AKI following trauma, which may increase their risk of death by about 5.5 times. Nevertheless, since none of the studies had adjusted their analyzes for potential confounders, caution should be exercised in interpreting the relationship between trauma-related AKI and mortality.

Keywords: Multiple trauma; pediatrics; acute kidney injury; earthquakes; exercise; rhabdomyolysis

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1. Introduction

Acute kidney injury (AKI) is a serious complication in children and adolescents. It is caused by many different etiologies and if not diagnosed in time, it can quickly progress to chronic kidney disease and dialysis. The prevalence of AKI indicates that about 10% of children admitted to the intensive care unit develop AKI (1). This injury significantly affects patients' mortality (1, 2).

The risk of developing AKI increases in both children and adults following trauma. This is due to direct damage to the kidneys, shock, the use of harmful compounds for the kidneys in the diagnosis and treatment of trauma patients, and the occurrence of rhabdomyolysis (3). Current evidence show that the risk of mortality in traumatized children with

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AKI could be 3.6 times higher (4). However, there is still considerable diversity among studies.

In the last 20 years, numerous studies have been performed on AKI following trauma, and acceptable findings have been reported in adults (5-8). However, the extent of the problem in children and the effect of AKI on trauma mortality are not well understood. Based on this, the researchers of the present study intended to provide evidence by conducting a systematic review and meta-analysis on the prevalence of AKI and its relationship with mortality in traumatized children.

2. Methods

2.1. Study design and search strategy

The present meta-analysis was designed to summarize the evidence of studies performed on pediatric samples to evaluate the prevalence of AKI in traumatized pediatric patients. For the present study, the MOOSE guideline, a guide for systematic review and meta-analysis in observational research has been used (9). An extensive search of the Medline, Embase, Scopus and Web of Sciences electronic databases was conducted for articles published until the end of May 2020. The search strategy was based on keywords related to AKI, trauma and prevalence. To refine the search, the recommended Cochrane Childhood Cancer Group filter was used to find articles related to children (10). Table 1 presents the search strategy for the Medline database.

2.2. Inclusion criteria

The definition of PECO in the present study was as follows: problem or study population (P): children and adolescents with trauma; exposure (E): exposure to physical trauma; comparisons (C): with non-AKI group; and outcome (O): prevalence of AKI in children with trauma and their mortality. Therefore, the observational studies performed on traumatized children with AKI were included. Exclusion criteria were adult patients, studies performed on non-traumatic AKI, patients without AKI, penetrating injuries, and case-series studies.

2.3. Data collection and quality assessment

Two independent researchers collected the data. After conducting the search and integrating the findings obtained from databases and searching the gray literature (search in Google and Google Scholar as well as a search in the dissertation section of ProQuest database), the researchers performed an initial screening in the Endnote program (version 8.0), independently. Title and abstract of each article were studied and if the article was relevant or likely to be relevant, the full text of the study was retrieved and reviewed. The data of these studies were then summarized in a checklist designed based on PRISMA statement guidelines (11). The extracted data included information related to the study design, sample baseline characteristics (age, sex, etc.), number of samples studied, definition of AKI, prevalence of AKI and prevalence of mortality.

The articles' risk of bias was assessed using the National Heart, Lung, and Blood institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (12). In case of any disagreements, the dispute was resolved through discussion with a third reviewer.

2.4. Statistical analysis

Analyses were performed using STATA 14.0 statistical program. All studies were summarized based on the studied outcomes. These outcomes were the prevalence of AKI in traumatized children and its relationship with mortality. Prevalence data were recorded as frequency. For evaluating the prevalence of trauma-related AKI, the "Metaprop_one" command was used and a pooled prevalence with 95% confidence interval (95% CI) was reported. the relationship between trauma-related AKI and children's mortality, was assessed using the "metan" command and pooled effect size was reported as odds ratio (OR). The presence of heterogeneity was investigated using the I2 statistics. Since we expected no obvious heterogeneity among studies, a fixed effect model was used for the analyses. In case of heterogeneity, we used random effect model, and performed subgroup analysis to find the source of heterogeneity. Egger's test and funnel plot were used to examine publication bias.

3. Results

3.1. Summary of studies

The search yielded 3311 non-duplicated articles. After the initial full-text screening, 37 articles were reviewed and finally the data of 9 articles were included in the present meta-analysis (Figure 1) (13-21). There were 3 prospective cohort studies and 6 retrospective cohort studies. The etiology of trauma among patients in the included studies were direct physical trauma, exercise-related injuries, exertional rhabdomyolysis, or earthquake. These studies included data from 1,052 traumatized children. Table 2 shows a summary of the characteristics of included articles.

3.2. Risk of bias

In the quality control section, it was realized that none of the studies reported the prevalence of AKI in terms of severity of trauma (item 8); Also, the sample size calculation was reported in only one study (item 5). None of the studies adjusted the analyses for potential confounders (item 14). Moreover, the blinding status of the outcome observer was not reported in any of the studies (item 12) (Table 3).

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3.3. Meta-analysis

• Prevalence of trauma-related AKI in children

The prevalence of trauma-related AKI varied between 0% and 30.30% among included studies. Pooled analysis showed that the prevalence of trauma-related AKI was 9.86% (95% CI: 8.02 to 11.84%) (Figure 2). To investigate the cause of heterogeneity in the prevalence of AKI, subgroup analysis was performed based on the etiology of AKI. Table 4 shows the findings of this section.

Accordingly, the prevalence of AKI after exertional rhabdomyolysis, mild to severe direct trauma, and earthquake-related injuries was 0%, 12.64% and 24.60%, respectively; According to this analysis, there is a significant difference between the prevalence of AKI in terms of trauma etiology (p = 0.038).

• Relationship between trauma-related AKI and mortality in children

In this section, data from 7 studies were entered. The prevalence of mortality following trauma-related AKI in children is low (Table 2). However, the analysis showed that the occurrence of AKI in traumatized children was associated with an increased odds ratio (OR) of mortality (OR = 5.55; 95% CI: 2.14 to 13.93). Nevertheless, since none of the studies had adjusted their analyzes for potential confounders, caution should be exercised in interpreting the findings of this section (Figure 3).

3.4. Publication bias

Egger's test showed that there wasn't any publication bias in assessment of the prevalence of trauma-related AKI in children (p = 0.72) and relationship of trauma-related AKI with children's mortality (p = 0.154) (Figure 4).

4. Discussion

The present meta-analysis summarized the current evidence on the relationship between trauma and the incidence of AKI in children. The findings of the present study showed that 9.86% of children develop AKI following trauma, which may increase their risk of mortality by about 5.5 times.

The analyses of the present study showed that the cause of trauma is an important factor in the occurrence of AKI. The prevalence of AKI following exertional rhabdomyolysis is zero percent, while the prevalence increases with injury severity. Therefore, as a report, it can be said that the occurrence of AKI in children with exertional rhabdomyolysis is very rare, while almost a quarter of children with severe injuries or earthquake victims develop AKI. A finding that calls for more attention in the management of children with trauma, especially those admitted to intensive care units with severe traumas.

One of the aims of the present study was to investigate the relationship between the incidence of AKI following trauma in children and adolescents and the pertaining mortality. Although the findings of the present meta-analysis showed that the incidence of AKI is associated with an increased risk of death in traumatized children, care should be taken in interpreting this finding. Risk of bias assessment in the present study showed that none of the studies attempted to adjust the analyzes for potential confounders of mortality in trauma patients and therefore the observed relationship between the incidence of AKI and mortality of traumatized children may be a confounding relationship. Furthermore, the quality of studies was moderate, most studies were retrospective in nature, and the blinding of the outcome assessor was unclear. Therefore, in order to accurately determine the prevalence of AKI in children with trauma, it is necessary to design studies with a larger sample size and higher quality.

Another limitation in the present study was the difference in the definition of AKI in included studies. For example, in the study of Prodhan et al., they used the pRIFLE criteria to define AKI, and defined all classes of risk, injury, failure, and end-stage as AKI (20).

Whereas, in the standard definition, the risk category is not defined as documented AKI. Therefore, to overcome this problem, the risk category was left out to use a similar definition of AKI among included studies. Nonetheless, two studies (18, 19) did not provide the definition of AKI.

5. Conclusion

For the first time, the present meta-analysis summarized the existing reports on the relationship between trauma and the incidence of AKI in children. The findings of the present study showed that 9.86% of children develop AKI following trauma, which may increase their risk of death by about 5.5 times.

6. Declarations

6.1. Acknowledgments

None.

6.2. Conflict of interest statement

The authors declare that they have no conflict of interests.

6.3. Compliance with Ethical Standards

This study complies with the declaration of Helsinki and all ethical standards.

6.4. Human and Animal Rights

This article does not contain any studies with human participants or animals performed by any of the authors.

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6.6. Conflict of interest

None.

References

1. Schneider J, Khemani R, Grushkin C, Bart R. Serum creatinine as stratified in the RIFLE score for acute kidney injury is associated with mortality and length of stay for children in the pediatric intensive care unit. Crit Care Med. 2010;38(3):933-9.
2. Goldstein SL, Devarajan P. Pediatrics: Acute kidney injury leads to pediatric patient mortality. Nat Rev Nephrol. 2010;6(7):393-4.
3. Harrois A, Libert N, Duranteau J. Acute kidney injury in trauma patients. Curr Opin Crit Care. 2017;23(6):447-56.
4. Haines RW, Fowler AJ, Kirwan CJ, Prowle JR. The incidence and associations of acute kidney injury in trauma patients admitted to critical care: A systematic review and meta-analysis. J Trauma Acute Care Surg. 2019;86(1):141-7.
5. Burmeister DM, Gomez BI, Dubick MA. Molecular mechanisms of trauma-induced acute kidney injury: Inflammatory and metabolic insights from animal models. Biochim Biophys Acta Mol Basis Dis. 2017;1863(10 Pt B):2661-71.
6. Civiletti F, Assenzio B, Mazzeo AT, Medica D, Giaretta F, Deambrosis I, et al. Acute Tubular Injury is Associated With Severe Traumatic Brain Injury: in Vitro Study on Human Tubular Epithelial Cells. Sci Rep. 2019;9(1):6090.
7. Perkins ZB, Captur G, Bird R, Gleeson L, Singer B, O'Brien B. Trauma induced acute kidney injury. PLoS One. 2019;14(1):e0211001.
8. Ramirez ME, McQuillan RF. Acute Kidney Injury Secondary to Trauma-Induced Hemolysis: The Need for Increased Awareness and a Preventative Strategy. Am J Kidney Dis. 2017;69(2):320.
9. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.
10. Leclercq E, Leeflang MMG, van Dalen EC, Kremer LCM. Validation of Search Filters for Identifying Pediatric Studies in PubMed. J Pediatr. 2013;162(3):629-34.e2.
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9.
12. National Institutes of Health. National Heart Lung, and Blood Institute. Quality assessment tool for observational cohort and cross-sectional studies 2014 [Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
13. Bjornstad EC, Muronya W, Smith ZH, Gibson K, Mottl AK, Charles A, et al. Incidence and epidemiology of acute kidney injury in a pediatric Malawian trauma cohort: a prospective observational study. BMC Nephrol. 2020;21(1):1-12.
14. Chen C-Y, Lin Y-R, Zhao L-L, Yang W-C, Chang Y-J, Wu K-H, et al. Clinical spectrum of rhabdomyolysis presented to pediatric emergency department. BMC Pediatr. 2013;13(1):134.
15. Guardenier A, Peterson B, Hilfiker M, Shellington D. 1170: Acute renal failure in pediatric patients after moderate to severe traumatic brain injury. Crit Care Med. 2015;43(12):294.
16. Hatamizadeh P, Najafi I, Vanholder R, Rashid-Farokhi F, Sanadgol H, Seyrafian S, et al. Epidemiologic aspects of the Bam earthquake in Iran: the nephrologic perspective. Am J Kidney Dis. 2006;47(3):428-38.
17. Iskit SH, Alpay H, Tuğtepe H, Özdemir C, Ayyıldız SH, Özel K, et al. Analysis of 33 pediatric trauma victims in the 1999 Marmara, Turkey earthquake. J Pediatr Surg. 2001;36(2):368-72.
18. Lin H, Chie W, Lien H. Epidemiological analysis of factors influencing an episode of exertional rhabdomyolysis in high school students. Am J Sports Med. 2006;34(3):481-6.
19. Oh JY, Laidler M, Fiala SC, Hedberg K. Acute exertional rhabdomyolysis and triceps compartment syndrome during a high school football camp. Sports Health. 2012;4(1):57-62.
20. Prodhan P, McCage LS, Stroud MH, Gossett J, Garcia X, Bhutta AT, et al. Acute kidney injury is associated with increased in-hospital mortality in mechanically ventilated children with trauma. J Trauma Acute Care Surg. 2012;73(4):832-7.
21. Talving P, Karamanos E, Skiada D, Lam L, Teixeira PG, Inaba K, et al. Relationship of creatine kinase elevation and acute kidney injury in pediatric trauma patients. J Trauma Acute Care Surg. 2013;74(3):912-6.

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Table 1: Search strategy in Medline database

Database	Search terms
MEDLINE (PubMed)	1. “Wounds and Injuries”[mh] OR "Injuries"[Subheading] OR “Multiple Trauma”[mh] OR “Hemolysis”[mh] OR “Rhabdomyolysis”[mh] OR Trauma[tiab] OR Traumas[tiab] OR Multiple Trauma[tiab] OR Polytrauma[tiab] 2. “Prevalence”[mh] OR “Epidemiology”[mh] OR “Incidence”[mh] OR Prevalence[tiab] OR Epidemiology[tiab] OR Incidence[tiab] OR incidence rate[tiab] OR epidemiologic[tiab] 3. ("acute kidney injury"[MeSH Terms] OR ("acute"[All Fields] AND "kidney"[All Fields] AND "injury"[All Fields]) OR "acute kidney injury"[All Fields]) OR ("acute kidney injury"[MeSH Terms] OR ("acute"[All Fields] AND "kidney"[All Fields] AND "injury"[All Fields]) OR "acute kidney injury"[All Fields] OR ("acute"[All Fields] AND "renal"[All Fields] AND "failure"[All Fields]) OR "AKI"[All Fields]) 4. (Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*) 5. #1 AND #2 AND #3 AND #4

Table 2: The summary of the characteristics of eligible studies

Author; year; country	Study type	Population	Age	Sample size	Number of boys	AKI definition	AKI	Mortality in AKI	Mortality in Non-AKI
Bjornstad; 2020; Malawi	Prospective cohort	Mild to severe trauma	8.1	114	42	KDIGO criteria	11	4	6
Chen; 2013; Taiwan	Retrospective cohort	Trauma and exercise related injury	10.2	12	26	Serum creatinine level of more than the 97.5th percentile	0	0	0
Guardenier; 2015; United States	Retrospective cohort	Moderate to severe TBI	0-17 years	35	18	pRIFLE	5	0	0
Hatamizadeh; 2006; Iran	Retrospective cohort	Earthquake victims	0-15	49	Not specified	At least 2 reported serum creatinine values of 1.6 mg/dL or greater	14	Not specified	Not specified
Lin; 2005; Taiwan	Prospective cohort	Exertional Rhabdomyolysis	High school student	157	106	Not specified	0	0	0
Oh; 2011; United States	Retrospective cohort	Exertional Rhabdomyolysis	15.9	43	Not specified	Not specified	0	0	0
Iskit; 2001; Turkey	Retrospective cohort	Earthquake victims	8.8	33	17	Serum creatinine level above 1.2 mg/dL or oliguria	10	0	0
Prodhan; 2012; United States	Retrospective cohort	Severe ICU admitted trauma	11.6	88	58	pRIFLE	22	7	5
Talving; 2013; United States	Retrospective cohort	Mild to severe trauma	12.2	521	352	pRIFLE	70	Not specified	Not specified

AKI: Acute kidney injury; KDIGO: Kidney Disease Improving Global Outcomes; pRIFLE: Pediatric Risk, Injury, Failure, Loss , End Stage Renal Disease; TBI: Traumatic brain injury; ICU: intensive care unit.

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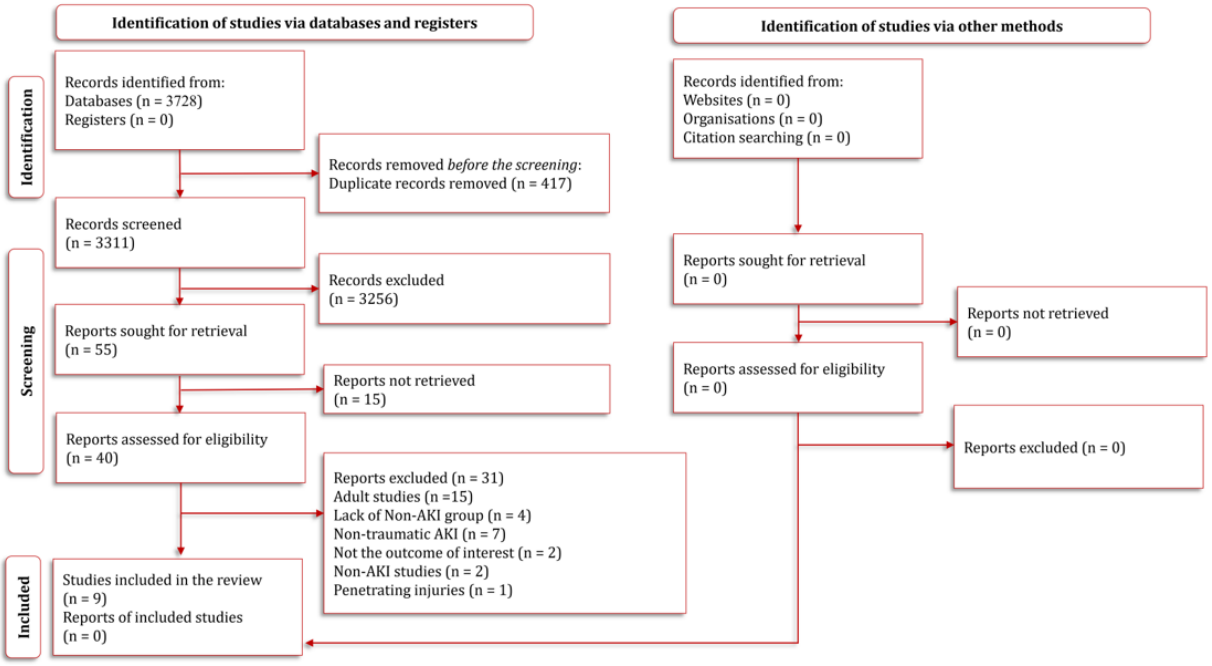

Figure 1: PRISMA flow diagram of the present study. AKI: Acute Kidney injury.

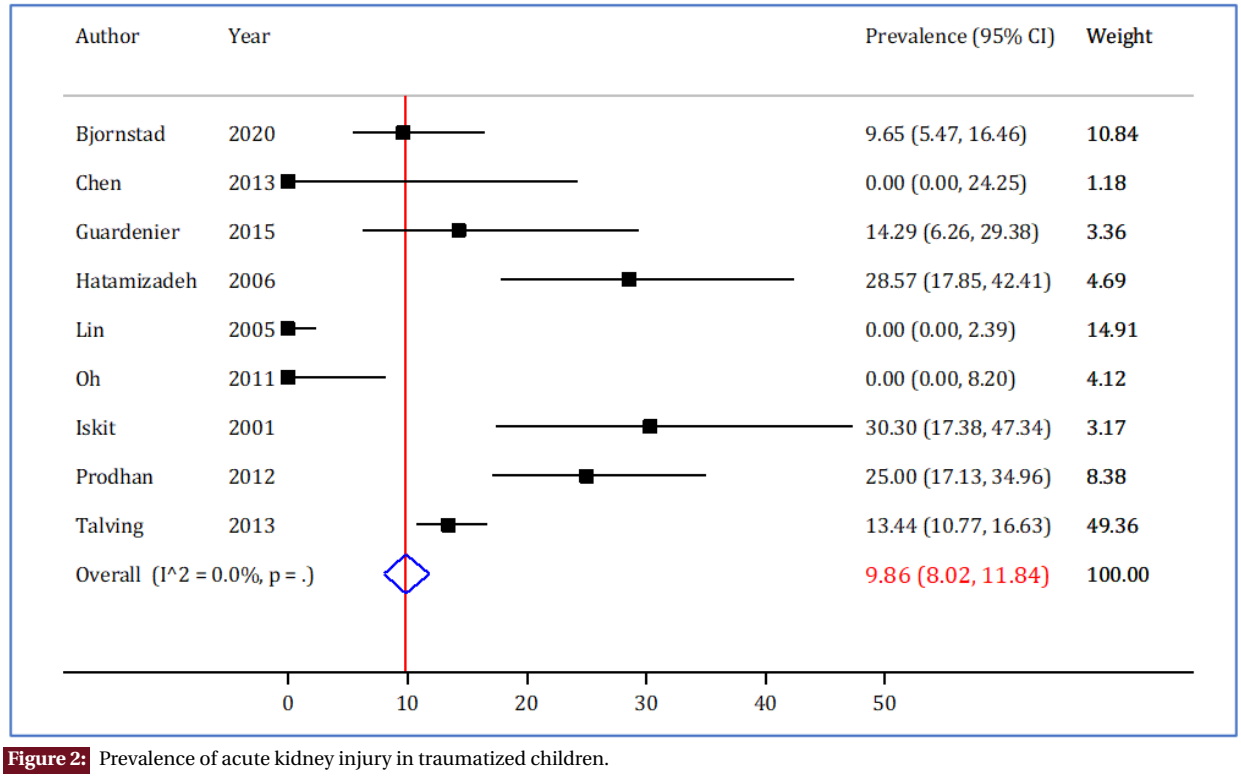

Figure 2: Prevalence of acute kidney injury in traumatized children.

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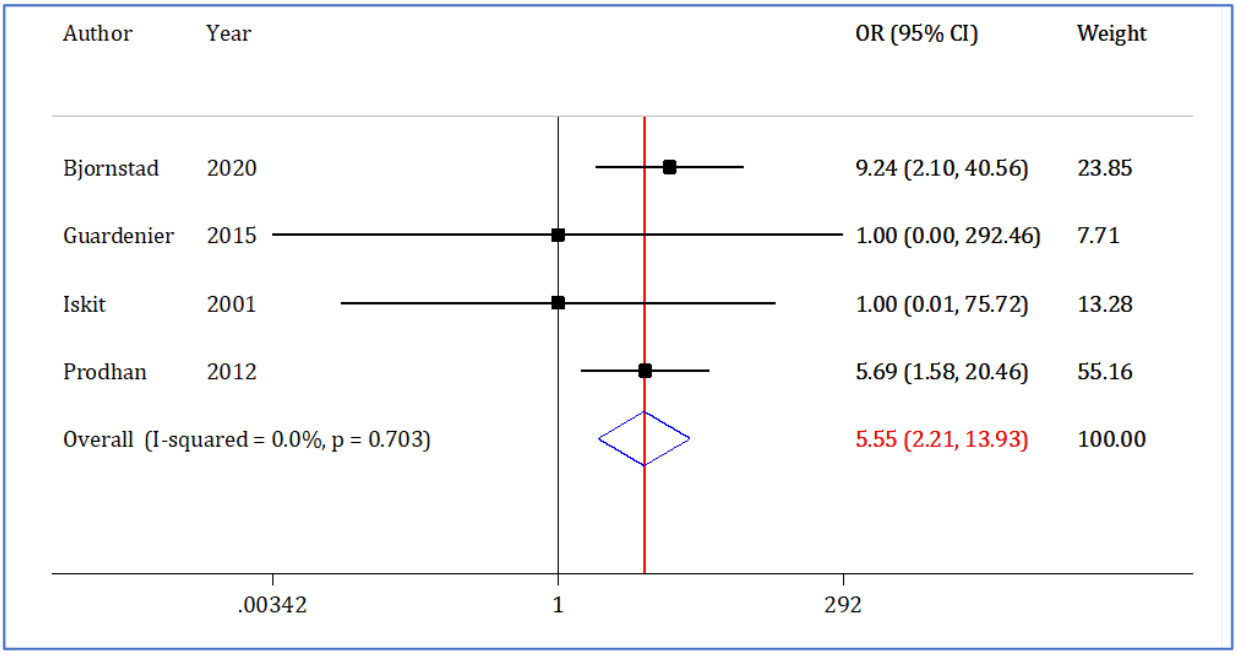

Figure 3: The pooled odds ratio (OR) of mortality following trauma-related acute kidney injury (AKI) in children. The risk of mortality of is higher in traumatized children with AKI compared to non-AKI children.

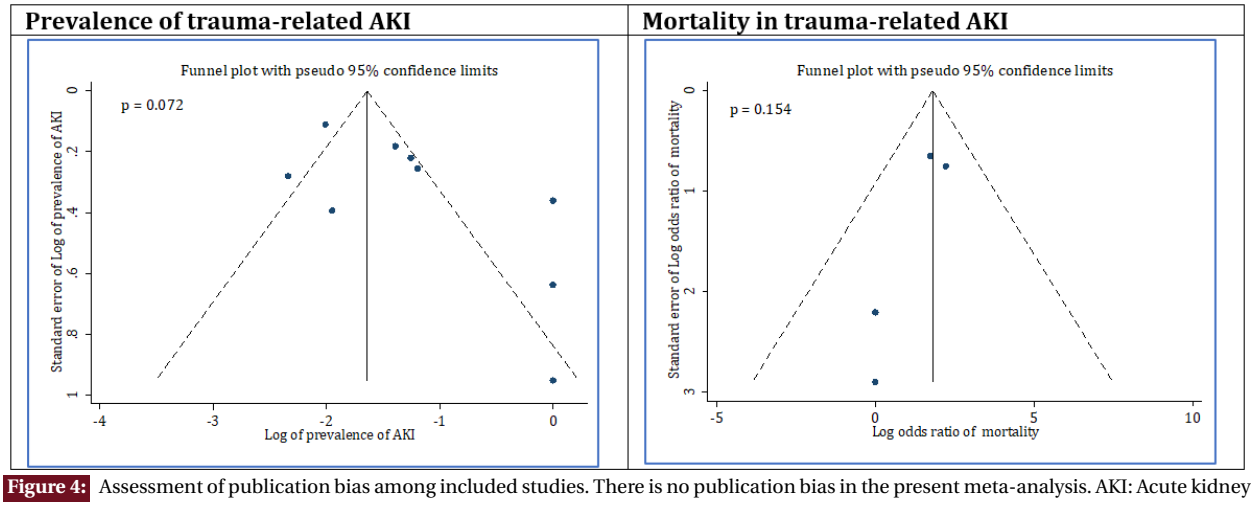

Figure 4: Assessment of publication bias among included studies. There is no publication bias in the present meta-analysis. AKI: Acute kidney injury.

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Table 3: Risk of bias assessment of included studies according to National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (12)

Study	Items													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bjornstad; 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Yes	NR	Yes	No
Chen; 2013	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	NA	Yes	NR	NR	No
Guardenier; 2015	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	NA	Yes	NR	NR	No
Hatamizadeh; 2006	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	NA	Yes	No	NR	NA
Lin; 2005	Yes	Yes	Yes	Yes	NR	Yes	ND	No	Yes	NA	Yes	No	NR	No
Oh; 2011	Yes	Yes	Yes	Yes	NR	Yes	ND	No	Yes	NA	Yes	No	NR	No
Iskit; 2001	Yes	Yes	Yes	Yes	NR	Yes	ND	No	Yes	NA	Yes	NR	No	No
Prodhan; 2012	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	NA	Yes	NR	ND	No
Talving; 2013	Yes	Yes	Yes	Yes	NR	Yes	Yes	No	Yes	NA	Yes	NR	No	No

Yes: Low risk of bias; No: High risk of bias; NA: Not applicable; ND: Not determined; NR: Not reported.

Table 4: The prevalence of acute kidney injury (16) stratified by the etiology of trauma

Etiology of AKI	Number of studies	Prevalence (95% CI)	Heterogeneity (p value)
Exertional rhabdomyolysis	3	0.00 (0.00 to 0.20)	0.0% (>0.999)
All severities	2	12.64 (10.14 to 15.37)	0.0% (>0.999)
Moderate to severe rhabdomyolysis in earthquake	4	24.60 (18.81 to 30.86)	0.0% (>0.999)
	Among subgroups		0.038

CI: Confidence interval.

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