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Assessing the value of serum and urinary interleukins for diagnosis of acute kidney injury in children and adolescents: A systematic review and meta-analysis

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ABSTRACT

Introduction: Several studies have questioned the diagnostic utility of interleukins (IL) in detecting acute kidney injury (AKI) in pediatric population. Therefore, the present systematic review and meta-analysis aims to assess the diagnostic value of ILs in pediatric AKI patients.

Method: Two independent researchers screened records acquired through searching in Medline, Embase, Scopus, and Web of Science, until the end of 2020. Articles evaluating serum and urinary levels of ILs in AKI patients were included in this study. Data were extracted and analyzed using STATA software.

Results: Twenty-one studies were included. Analyses showed that AUC, sensitivity, specificity and diagnostic odds ratio of urinary IL-18 for diagnosing AKI were 0.77 (95% CI: 0.74, 0.81), 0.64 (95% CI: 0.32, 0.87), 0.75 (95% CI: 0.62, 0.85) and 6 (95% CI: 1, 23), respectively. Those values were 0.79 (95% CI: 0.75, 0.83), 0.58 (95% CI: 0.37, 0.76), 0.87 (95% CI: 0.66, 0.96), and 9 (95% CI: 4, 20) for serum IL-6, and 0.72 (95% CI: 0.68, 0.76), 0.53 (95% CI: 0.34, 0.72), 0.79 (95% CI: 0.60, 0.91) and 4 (95% CI: 2, 8) for serum IL-8, respectively. Urinary levels of ILs 6, 8 and 10 were not significantly different between AKI patients and the non-AKI control group. Serum levels of ILs 10 and 18 were not adequately evaluated in the studies.

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Conclusion: IL-18 urinary levels and IL-6 and IL-8 serum levels are significantly higher in AKI patients compared to the non-AKI group. However, their low sensitivity and specificity in detecting AKI questions their diagnostic value.

Abbreviations

Interleukin IL
Acute Kidney Injury AKI
Area Under the Curve AUC
Confidence Interval CI
Chronic Kidney Disease CKD
Neutrophil Gelatinase-Associated Lipocalin NGAL
meta-analysis of observational studies in epidemiology MOOSE
standardized mean difference SMD

1. Introduction

Acute kidney injury (AKI) is a serious complication in children and adolescents, and if not diagnosed in a timely manner, it can progress to chronic kidney disease (CKD), rapidly [1]. AKI has much higher importance in pediatric population, compared to other populations of other age groups. Statistics show that about 10% of children hospitalized in ICU, acquire AKI [2]. Moreover, AKI mortality among children is five times higher than that of others [2,3]. Unfortunately, the onset and progression of this disease are asymptomatic in many cases, and its diagnosis is usually based on functional biomarkers, such as serum creatinine. Nevertheless, due to serious limitations related to creatinine measurement, in recent years, researchers have been looking for more reliable biomarkers [2,4–9].

Research in this field is continued, and each year, a number of new biomarkers in the detection of AKI are introduced [10]. Overall, biomarkers such as Cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) and interleukins (IL) have attracted most of the attention [11,12]. As one of the factors responsible for the inflammatory cascade, IL levels increase in response to organ injuries [11]. On the other hand, AKI is accompanied by tubular and glomerular inflammation in its early stages. Therefore, an increase in IL serum levels in patients is plausible, as mentioned in previous studies [13–15]. Yet, significant disagreements exist on the matter, and reported sensitivity and specificity values in studies, regarding the utility of ILs in the detection of AKI, has a prominent wide range. As a result, a conclusion on the use of ILs as a diagnostic tool for AKI is still to be achieved among experts and medical professionals. One of the solutions to reach such a conclusion is by conducting a systematic review and meta-analysis on the existing studies. A meta-analysis conducted in 2013 showed that IL-18 has a sensitivity of 64% and specificity of 82.1% for diagnosing AKI. However, assessing only one type of IL and low number of included studies were its limitations. It is worth mentioning that eight studies on a total of 1125 exclusive pediatric patients were included in that meta-analysis [16]. Also, another meta-analysis by Lin et al., in 2015 reported a moderate diagnostic value for IL-18. Similar to the previous meta-analysis, low number of included studies and the high heterogeneity were prominent limitations to Lin et al.' study. Moreover, the study included only four articles performed on pediatric population, with a 561 number of pediatric population [17]. As a significant number of studies have been conducted on the diagnostic value of ILs in AKI, an update to the mentioned meta-analyses is justifiable. Moreover, as apparent by the existing gap between the prior meta-analyses, a comprehensive conclusion regarding the diagnostic utility of ILs in pediatric population is needed. Therefore, the current study aims to assess the diagnostic value of serum and urinary levels of different ILs for diagnosing AKI in children and adolescents, using a systematic review and meta-analytic approach.

2. Methods

2.1. Study design

We evaluated the diagnostic value of serum and urinary ILs in the diagnosis of AKI, according to the instructions for performing meta-analyses on diagnostic studies. For the present study the MOOSE guideline (meta-analysis of observational studies in epidemiology) was adopted [18]. PICO was defined as follows: P (patient/problem/population): children aged under 18 years who were suspected of having AKI, I (index): serum and urinary IL levels, C (comparison): comparison with patients without AKI, O (outcome): evaluation of diagnostic value of ILs for AKI.

2.2. Search strategy

With the help of a nephrologist, a librarian and a researcher, familiar to conducting systematic reviews, keywords related to AKI

and ILs were extracted, and using appropriate tags for every database, a separate search term for each database was designed. Keywords were selected using MeSH and Emtree databases, reviewing related articles and consulting with a researcher specialized in the field of inflammation. Then, using the selected keywords, electronic databases of Embase, Medline, Web of Science, and Scopus were systematically searched, until the end of 2020. The search strategy for Medline is provided in Appendix 1. Moreover, Google and Google Scholar search engines, ProQuest Dissertations and Theses database were explored to search for gray literature. Also, clinical trial registry databases such as IRCT.ir and clinicaltrial.gov were searched. In addition, reference tracking and citation tracking were conducted to find additional articles. Citation section of the accessed articles were manually reviewed for any papers that might have been missed through the systematic search. Any paper that cited one of the included studies as a reference was also manually reviewed for related data.

2.3. Selection criteria

Observational studies on pediatric populations, with the purpose of assessing the value of ILs for the detection of AKI were included in the present study. Exclusion criteria were IL measurement after 72 h of patients' admission, case report and case series studies, lack of a control group, measurement of IL levels after the incidence of AKI, not evaluating AKI occurrence and duplicate studies.

2.4. Data extraction

Screening and summarizing the articles, importing the data to a checklist and finally, quality control of the articles were performed by two individuals, independently. Any disagreements were resolved by discussing it with a third reviewer. Related articles were selected through two steps of screening. In the first step, by checking titles and abstracts, possible candidates for inclusion were chosen. Then, after reviewing the full texts of the included articles, included articles were selected based on the predefined inclusion and exclusion criteria. Extracted data were sample features (age, sex, patient setting), sample size, timepoints of IL measurement, mean of serum and urinary IL levels, and diagnostic value indicators (sensitivity, specificity) of the studies. If the provided values were separated into different subgroups, such as different control groups or different sampling timepoints, the data were recorded separately.

2.5. Quality assessment

Quality assessment of the included studies was conducted based on QUADAS-2 guidelines [19]. The overall risk of bias and concern regarding applicability was defined as "low risk" if the study was rated to be as low risk in all domains, and as "at risk of bias" if the study was rated to have high or unclear risk of bias in at least one domain. Agreement between the two researchers in assessing the quality of studies was evaluated by interrater reliability, and any discrepancies were resolved by discussion with a third researcher.

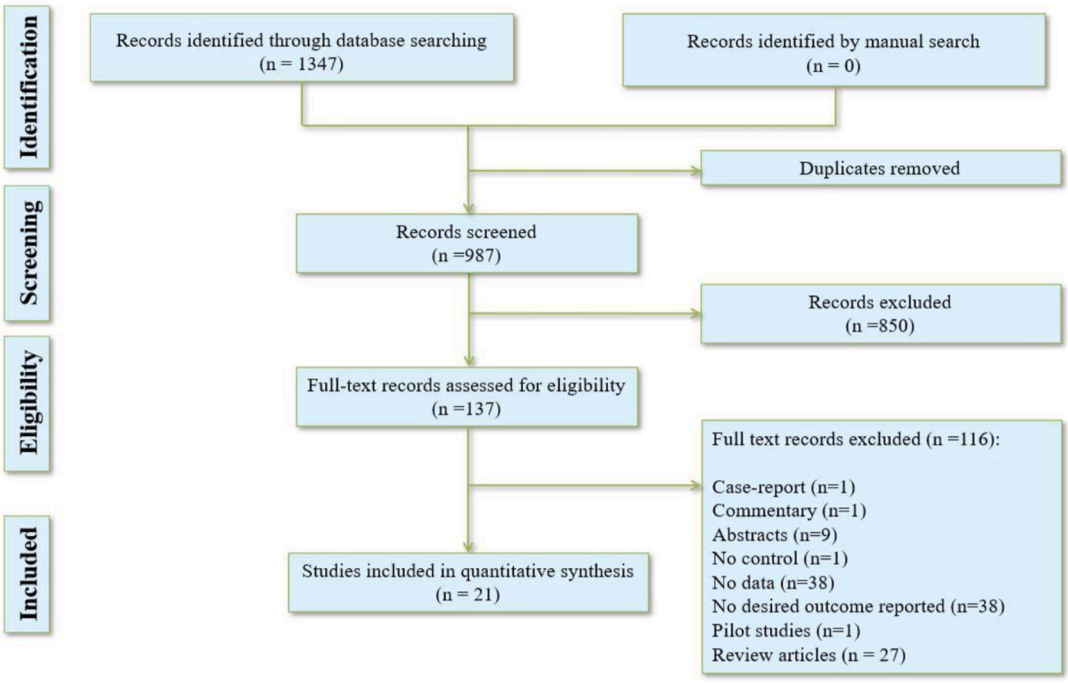

Fig. 1. PRISMA flowchart. The figure depicts the screening process performed to select included articles.

Table 1
Characteristics of included studies.

Study	AKI definition in the study	Study design	Setting	AKI*	No-AKI*	Boys in AKI group	Boys in non-AKI group	Timing#	Type of interleukins	source
Ahn, 2020, Korea [20]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days or UO < 0.5 mL/kg/h for 6–12h	PCS	Premature	13	5	8	4	24, 72	8	Urine
Baek, 2020, Korea [21]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days or UO < 0.5 mL/kg/h for 6–12h	PCS	Cardiac surgery	12	18	9	11	0, 6, 24, 48	18	Urine
Chui, 2020, Canada [22]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days	PCS	Aminoglycosides related AKI	47	66	22	33	0, 24, 48, 48	18	Urine
DeFontnouvelle, 2017, USA [23]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days	PCS	Cardiac surgery	113	95	180	232	6	8	Serum
Dennen, 2010, USA [24]	≥50% increase in sCr from pre-operative at 24h;	PCS	Cardiac surgery	10	13	5	7	2	6	Urine
Dobiliene, 2019, Lithuania [25]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days or UO < 0.5 mL/kg/h for 6–12h	PCS	Critical ill	32	75	68	39	24, 72	18	Urine
Du, 2010, Canda [26]	25% decrease in eCCl	PCS	AKI suspected	18	234	18	234	0	18	Urine
Greenberg, 2015, USA [27]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days	PCS	Cardiac surgery	56	50	28	13	24	6, 10	Urine
Hanudel, 2019, USA [28]	≥50% increase in sCr at 24h;	PCS	ARDS related AKI	35	126	21	71	24	6	Serum
Huang, 2013, China [29]	≥100% increase from baseline sCr within 48h	PCS	Acute pancreatitis AKI	52	253	39	190	0	6	Serum
Krawczeski, 2011, USA [30]	≥50% increase in sCr from pre-operative within 48h;	PCS	Cardiac surgery	60	160	26	84	0, 6, 2, 12, 24	18	Urine
Lagos-Arevalo, 2015, Canada [31]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days	PCS	PICU admitted	70	90	38	58	48	18	Urine
Liu, 2009, USA [32]	≥50% increase from baseline sCr within 3 days	PCS	Cardiac surgery	18	21	9	13	0, 2, 12, 24	6, 8	Serum
Miklaszewska, 2013, Poland [33]	25% decrease in eGFR in 24h	PCS	Cardiac surgery	19	28	9	15	0	6	Serum
Morgan, 2013, Canada [34]	25% decrease in eCCl	PCS	Cardiac surgery	76	33	41	20	4	6	Serum
Oncel, 2016, Turkey [35]	increase in sCr≥0.3 mg/dL or ≥50% increase from baseline sCr	PCS	Perinatal asphyxia	15	46	NR	NR	24	18	Urine
Palermo, 2017, Canada [36]	increase in sCr≥0.3 mg/dL in 48h or	PCS	PICU admitted	16	65	8	35	24, 48, 72	18	Urine

(*continued on next page*)

Table 1 (*continued*)

Study	AKI definition in the study	Study design	Setting	AKI*	No-AKI*	Boys in AKI group	Boys in non-AKI group	Timing#	Type of interleukins	source
	≥50% increase from baseline sCr within 7 days or UO < 0.5 mL/kg/h for 6–12h									
Uygur, 2020, Turkey [37]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days or UO < 0.5 mL/kg/h for 6–12h	PCS	PICU admitted	37	16	NR	NR	0	18	Urine
Washburn, 2007, USA [38]	25% decrease in eCCl	PCS	PICU admitted	108	34	NR	NR	24	18	Urine
Zappitelli, 2015, USA [39]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days	PCS	Cardiac surgery	74	154	46	88	24	18	Urine
Zheng, 2013, China [40]	increase in sCr≥0.3 mg/dL in 48h or ≥50% increase from baseline sCr within 7 days or UO < 0.5 mL/kg/h for 6–12h	PCS	Cardiac surgery	29	29	21	18	0, 4, 6, 12, 24	18	Urine

AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; eCCl: estimated creatinine clearance; sCr: serum creatinine; NR: Not reported; PCS: Prospective cohort study; PICU: Pediatric intensive care unit; UO: Urine output.
*, Number of subjects.
#, Time of interleukin assessment.

2.6. Statistical analysis

Statistical analyses of this study were performed in two sections. First, serum and urinary IL levels were compared between patients with and without AKI. The "metan" command in STATA 14.0 statistical software was used for this purpose. Outputs of this section are reported as standardized mean difference (SMD) with 95% confidence interval (95% CI). Second, diagnostic utility of ILs in the detection AKI in children was evaluated. Analyses in this section were conducted using "midas" command in STATA 14.0 software. Subsequent outputs are reported as sensitivity, specificity, area under the curve (AUC) and diagnostic odds ratio.

Heterogeneity of the studies was checked using I^2 test, and in cases of heterogeneity, subgroup analysis based on the time of measurement and patient setting was conducted. A sensitivity analysis was performed according to the overall quality score of the included studies. Since the number of the included studies were not adequate to perform subgroup analysis for all of the ILs, subgroup analysis based on risk of bias was only performed on data regarding IL-18. Publication bias was assessed using Egger's test.

3. Results

3.1. Study characteristics

Search in databases resulted in 987 non-duplicate articles. After screening, 21 studies [20–40] were included in the current meta-analysis (Fig. 1). All of the included studies had a prospective cohort design. Ten of the included studies were performed on patients undergoing heart surgery, and four were conducted on patients hospitalized in PICU. Included studies contained data on 910 patients with AKI and 1611 patients without AKI. Serum and urinary IL levels were evaluated in six and 15 studies, respectively. These 21 studies included 54 separate analyses. Evaluated ILs were IL-6 (12 analyses), IL-8 (8 analyses), IL-10 (2 analyses), and IL-18 (32 analyses) (Table 1).

3.2. Meta-analysis

- **Relationship between urinary ILs and the occurrence of AKI**

Analyses revealed that urinary IL-6 (SMD = 0.28; 95% CI: 0.01, 0.57; p = 0.086), IL-8 (SMD = 0.39; 95% CI: 0.35, 1.13; p = 0.798), and IL-10 (SMD = 0.06; 95% CI: 0.27, 0.39; p = 0.368) levels were not significantly different between the group with AKI and the group without AKI. Studies in this regard were homogenous (Fig. 2). However, urinary levels of IL-18 were significantly higher in the group of patients with AKI than that of non-AKI patients (SMD = 0.63; 95% CI: 0.40, 0.85; p < 0.001), and heterogeneity was observed

between the studies (I^2 = 86.9%) (Fig. 3); Therefore, subgroup analysis was conducted and showed that the timing of urinary IL measurement was the main cause of heterogeneity (Table 2). When analysis was stratified based on the timing of measurement, the amount of heterogeneity was reduced in the timepoints of 0–2 h and 4–12 h of IL measurement. It is worth noting that urinary level of IL-18 was not significantly different between AKI patients and non-AKI control group in 0–2-h IL measurement timepoint (SMD = 0.10; 95% CI: 0.09, 0.30; p = 0.289). Our analyses also showed that urinary IL-18 level is a predictor for AKI only in critical conditions (SMD = 1.02; 95% CI: 0.48, 1.55; p < 0.001) and in patients who have undergone heart surgery (SMD = 0.58; 95% CI: 0.33, 0.83; p < 0.001), while such a relationship does not exist in non-critical conditions (SMD = 0.21; 95% CI: 0.26, 0.69; p = 0.382). In addition, subgroup analysis according to the overall risk of bias score showed that the pooled effect size of urinary IL-18 in the detection of AKI is similar in both "low risk of bias" (SMD = 0.80; 95% CI: 0.29, 1.32; p = 0.002) and "at risk of bias" (SMD = 0.58; 95% CI: 0.32, 0.84; p < 0.0001) studies.

- **Relationship between serum ILs and the occurrence of AKI**

Only IL-6 and IL-8 were included in this section. Our meta-analysis showed that serum IL-6 level was significantly higher in patients with AKI (SMD = 1.33; 95% CI: 0.77, 1.89; p < 0.001). Serum IL-8 level was also significantly higher in patients with AKI compared to non-AKI patients (SMD = 1.39; 95% CI: 0.44, 2.34; p < 0.001) (Fig. 4).

- **Diagnostic value of serum and urinary ILs for AKI**

Eight studies reported sensitivity and specificity of serum and urinary ILs for diagnosing AKI. Consequently, urinary IL-18, serum IL-6, and serum IL-8 levels were compared between AKI patients and non-AKI control group. AUC of urinary IL-18 for the detection of AKI was 0.77 (95% CI: 0.74, 0.81). Furthermore, sensitivity, specificity, and diagnostic odds ratio of urinary IL-18 for the purpose was 0.64 (95% CI: 0.32, 0.87), 0.75 (95% CI: 0.62, 0.85) and 6 (95% CI: 1, 23), respectively. AUC of Serum IL-6 for diagnosing AKI was 0.79 (95% CI: 0.75, 0.83). Sensitivity, specificity and diagnostic odds ratio values of serum IL-6 levels in diagnosing AKI were equal to 0.58 (95% CI: 0.37, 0.76), 0.87 (95% CI: 0.66, 0.96) and 9 (95% CI: 4, 20), respectively. Finally, AUC of serum IL-8 for detecting AKI was 0.72 (95% CI: 0.68, 0.76) and serum IL-8 had sensitivity, specificity, and diagnostic odds ratio equal to 0.53 (95% CI: 0.34, 0.72), 0.79

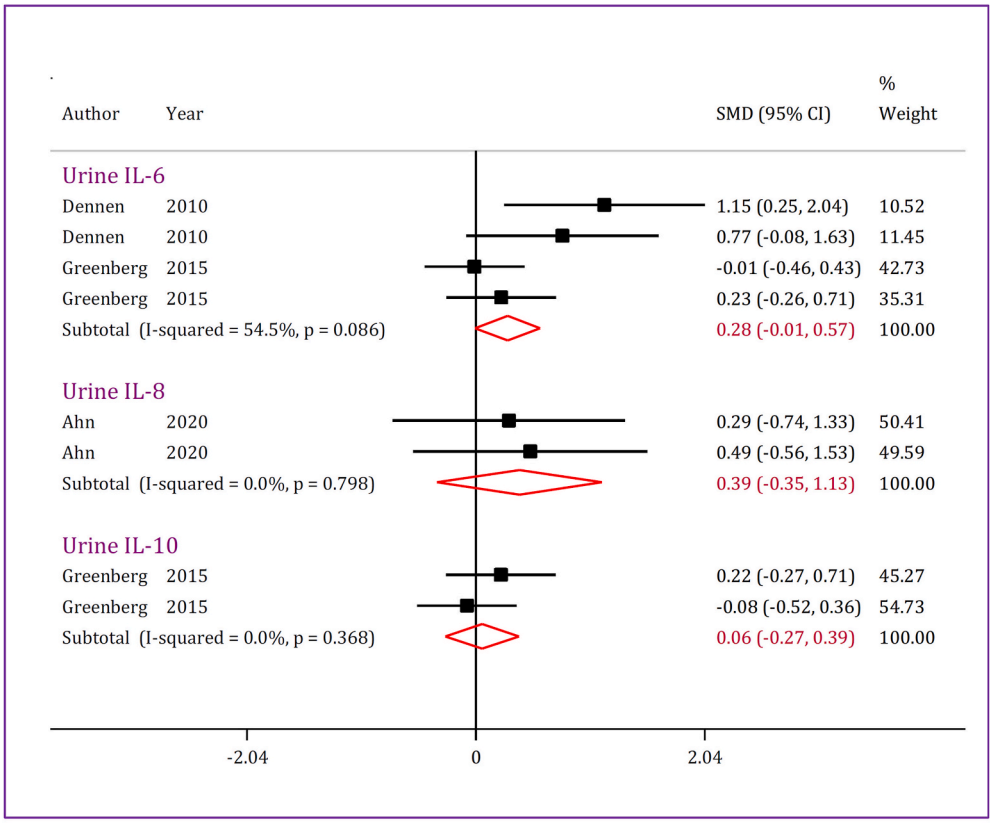

Fig. 2. Forest plot for comparison of mean urinary levels of interleukin 6 (p = 0.086), interleukin 8 (p = 0.798) and interleukin 10 (p = 0.368) in acute kidney injury and non-AKI group. It was concluded that urinary IL-6, IL-8 and IL-10 levels were not significantly different in the group with AKI and the group without AKI. CI: Confidence interval; SMD: standardized mean difference.

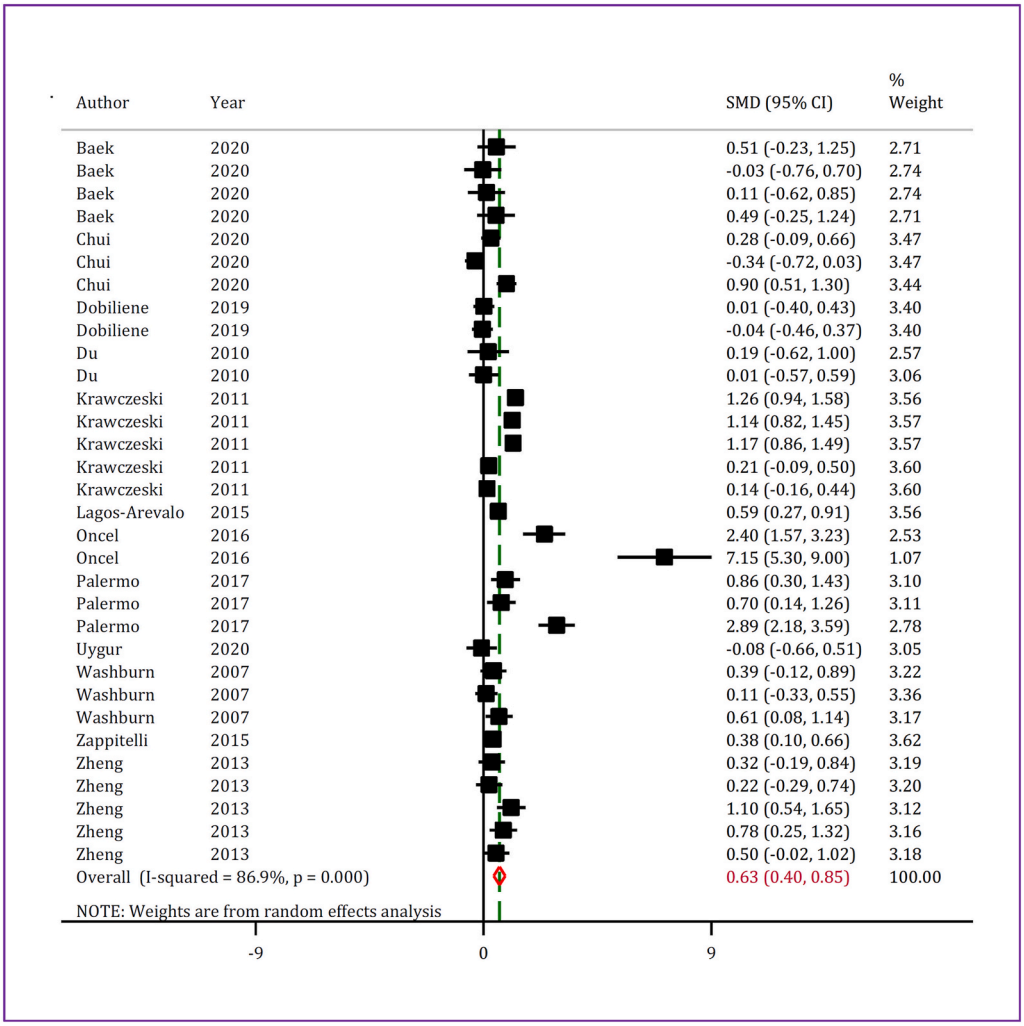

Fig. 3. Forest plot for comparison of mean urinary levels of interleukin 18 in acute kidney injury and non-AKI group ($p < 0.001$). It was concluded that urinary levels of IL-18 were significantly higher in the group of patients with AKI. CI: Confidence interval; SMD: standardized mean difference.

Table 2
Subgroup analysis for assessment of source of heterogeneity between studies in comparison of urinary interleukin 18 level.

Variable	No. of analysis	SMD (95% CI)	P	Heterogeneity (p)
Setting of patients				
Cardiac surgery	15	0.58 (0.33, 0.83)	<0.001	80.0% (<0.001)
Critical	12	1.02 (0.48, 1.55)	<0.001	91.8% (<0.001)
Non-critical	5	0.21 (−0.26, 0.69)	0.382	80.9% (<0.001)
Time of assessment				
0–2 h	8	0.10 (−0.09, 0.30)	0.289	28.6% (0.200)
4–12 h	6	0.84 (0.52, 1.16)	<0.0001	65.6% (0.012)
24 h	12	0.89 (0.47, 1.32)	<0.001	89.4% (<0.001)
48–72 h	6	0.70 (0.07, 1.33)	0.030	90.8% (<0.001)
Risk of bias				
Low risk	7	0.80 (0.29, 1.32)	0.002	87.7% (<0.0001)
At risk	25	0.58 (0.32, 0.84)	<0.0001	87.2% (<0.0001)

CI: Confidence interval.

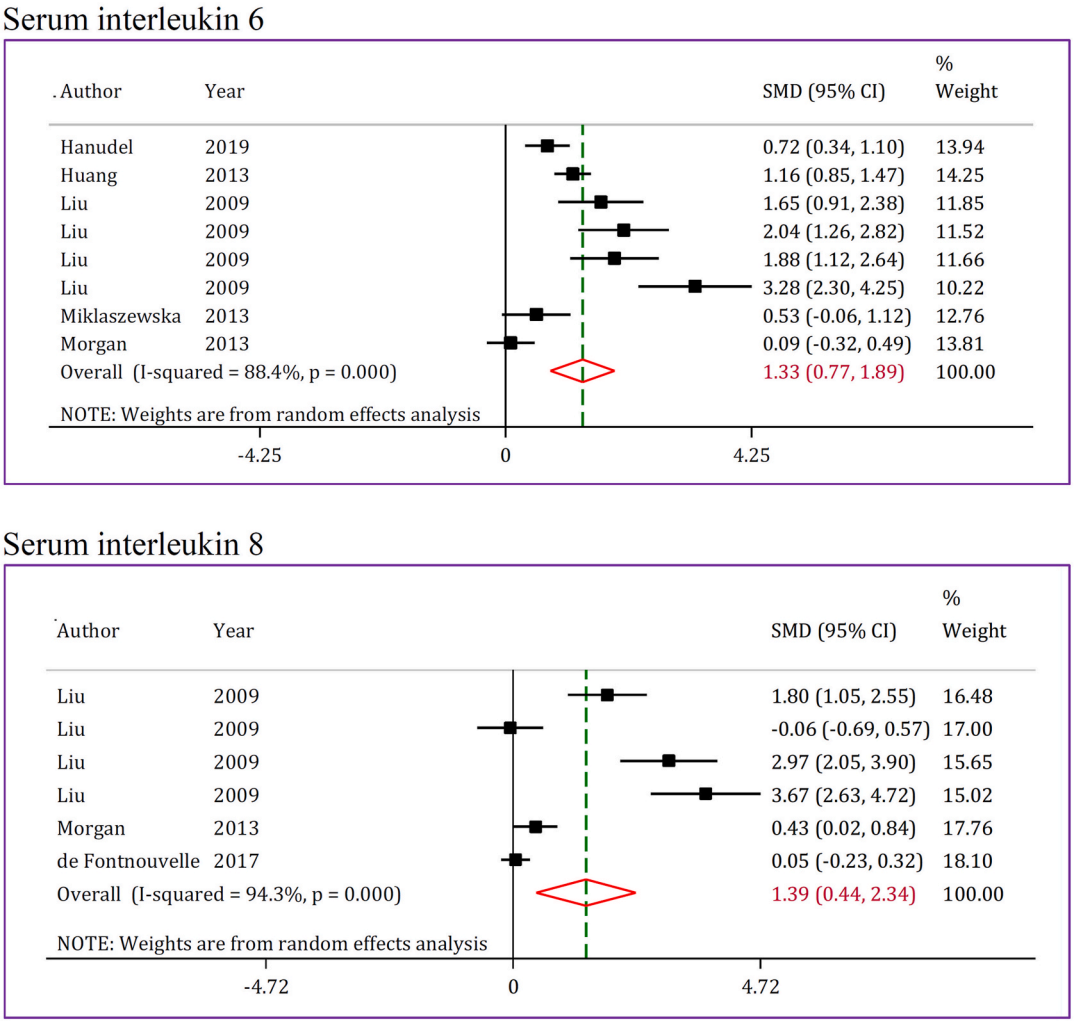

Fig. 4. Forest plot for comparison of mean serum levels of interleukin 6 ($p < 0.001$) and interleukin 8 ($p < 0.001$) in acute kidney injury and non-AKI group. It was concluded that serum IL-6 and IL-8 level were significantly higher in patients with AKI compared to non-AKI patients. CI: Confidence interval; SMD: standardized mean difference.

(95% CI: 0.60, 0.91), and 4 (95% CI: 2, 8) (Fig. 5, Table 3), respectively.

3.3. Publication bias and risk of bias assessment

Our analyses showed no publication bias regarding the relationship between urinary ILs and the occurrence of AKI ($p= 0.344$), but evidence of publication bias was found concerning the relationship between serum ILs and AKI ($p < 0.001$) (Fig. 6).

Moreover, quality assessment of the studies showed that risk of bias in patient selection item was unclear in 12 studies and high risk of bias in 2 studies. All studies scored a low risk of bias on the other items. Overall risk of bias was "low risk" in seven studies, while the other 14 studies were scored to be "at risk of bias" (Table 4). In detail, studies on urinary IL-6 levels and urinary IL-10 levels were all subjected to low risk of bias, and studies on urinary IL-8 levels were scored to be "at risk of bias". Moreover, one study on serum IL-6 levels was subjected to low risk of bias, while other studies on serum IL-6 levels were "at risk of bias". Similarly, one study on serum IL-8 levels was subjected to low risk of bias, while other articles on serum IL-8 levels were scored to be as "at risk of bias".

4. Discussion

For the first time, the present meta-analysis summarized the available evidence on the diagnostic utility of serum and urinary ILs in the detection of AKI in children. Analyses showed that urinary IL-18, serum IL-6, and serum IL-8 levels were significantly high in children with AKI, since the beginning hours of hospitalization. Therefore, it is possible that these biomarkers may be used for the early detection of AKI. However, after analyzing their diagnostic value in detecting AKI, it was shown that their sensitivity and specificity

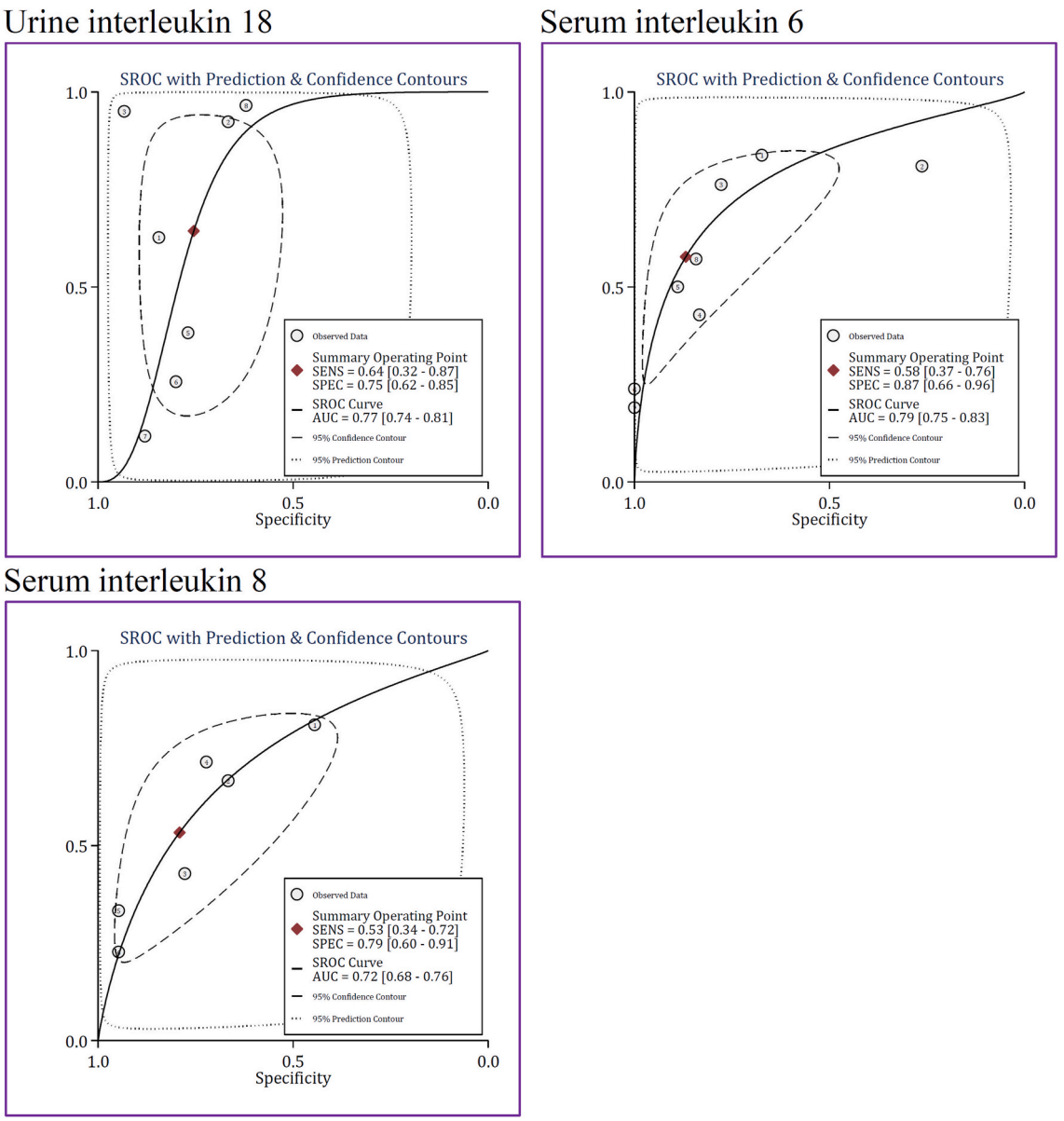

Fig. 5. Summary receiver operating characteristics curves of urinary and serum interleukins in prediction of acute kidney injury. Sensitivity, specificity and area under curve with, confidence intervals, for serum IL-6, serum IL-8 and urinary IL-18 in diagnosing AKI are depicted in the figure. AUC: Area Under the Curve; SENS: Sensitivity; SPEC: Specificity.

Table 3
Diagnostic performance of urinary and serum interleukins in detection of acute kidney injury.

Interleukins	Area under the curve	Cut-offs	Sensitivity	Specificity	Diagnostic odds ratio
Urinary IL-18	0.77 (0.74–0.81)	49 to 1135	0.64 (0.32, 0.87)	0.75 (0.62, 0.85)	6 (1, 23)
Serum IL-6	0.79 (0.75–0.83)	75 to 188	0.58 (0.37, 0.76)	0.87 (0.66, 0.96)	9 (4, 20)
Serum IL-8	0.72 (0.68–0.76)	40 to 100	0.53 (0.34, 0.72)	0.79 (0.60, 0.91)	4 (2, 8)

Data are presented as value and 95% confidence interval.

were between 0.53 to 0.64 and 0.75 to 0.87, respectively. These values, especially the low sensitivity of these biomarkers in diagnosing AKI, led us to think again about the clinical utility of the mentioned ILs for diagnostic purposes in pediatric patients dealing with AKI.

Although, in the present study, the data for assessing sensitivity and specificity of ILs were included, but the number of studies with these data was low, and the cutoff points reported in the studies were different. Therefore, further studies may be needed. Current

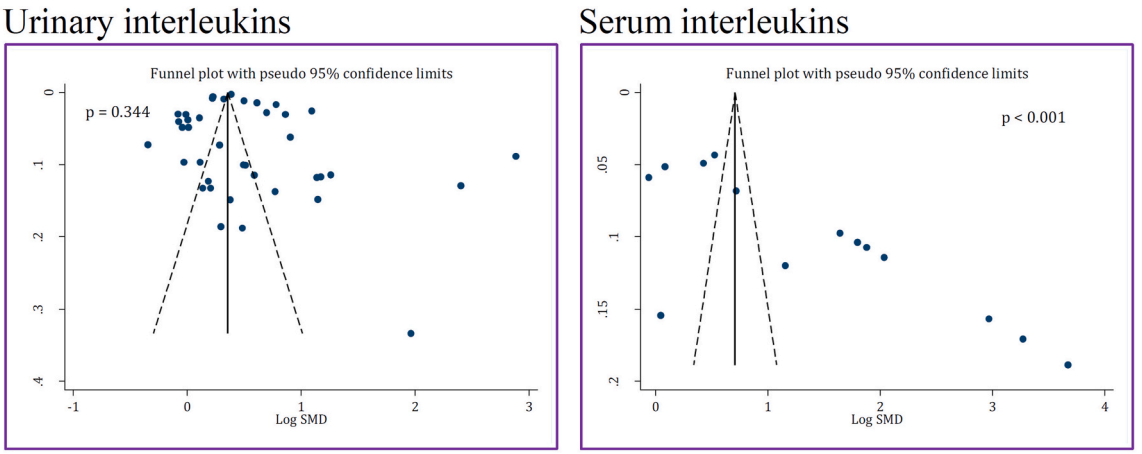

Fig. 6. Funnel plot for assessment of publication bias among included studies. No publication bias was observed regarding the relationship between urinary ILs and AKI, although publication bias was found to be present regarding the relationship between serum ILs and AKI.

Table 4
Risk of bias assessment.

Author, Year	Risk of bias				Applicability			Overall score
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard	
Ahn, 2020, Korea	Unclear	Low	Low	Low	Low	Low	Low	At risk
Baek, 2020, Korea	Unclear	Low	Low	Low	Low	Low	Low	At risk
Chui, 2020, Canada	Unclear	Low	Low	Low	Low	Low	Low	At risk
DeFontnouvelle, 2017, USA	Low	Low	Low	Low	Low	Low	Low	Low risk
Dennen, 2010, USA	Low	Low	Low	Low	Low	Low	Low	Low risk
Dobiliene, 2019, Lithuania	Unclear	Low	Low	Low	Low	Low	Low	At risk
Du, 2010, Canda	High	Low	Low	Low	Low	Low	Low	At risk
Greenberg, 2015, USA	Low	Low	Low	Low	Low	Low	Low	Low risk
Hanudel, 2019, USA	Low	Low	Low	Low	Low	Low	Low	Low risk
Huang, 2013, China	Unclear	Low	Low	Low	Low	Low	Low	At risk
Krawczeski, 2011, USA	Unclear	Low	Low	Low	Low	Low	Low	At risk
Lagos-Arevalo, 2015, Canada	High	Low	Low	Low	Low	Low	Low	At risk
Liu, 2009, USA	Unclear	Low	Low	Low	Low	Low	Low	At risk
Miklaszewska, 2013, Poland	Unclear	Low	Low	Low	Low	Low	Low	At risk
Morgan, 2013, Canada	Unclear	Low	Low	Low	Low	Low	Low	At risk
Oncel, 2016, Turkey	Unclear	Low	Low	Low	Low	Low	Low	At risk
Palermo, 2017, Canada	Low	Low	Low	Low	Low	Low	Low	Low risk
Uygur, 2020, Turkey	Unclear	Low	Low	Low	Low	Low	Low	At risk
Washburn, 2007, USA	Low	Low	Low	Low	Low	Low	Low	Low risk
Zappitelli, 2015, USA	Low	Low	Low	Low	Low	Low	Low	Low risk
Zheng, 2013, China	Unclear	Low	Low	Low	Low	Low	Low	At risk

studies show that other biomarkers, more plausible than serum and urinary ILs for the detection of AKI are available. For instance, in the previous three meta-analyses it was reported that both serum and urinary NGAL levels have significantly high diagnostic values for the detection of AKI [41]. It was also observed that serum and urinary cystatin C have considerable diagnostic utility for the aforementioned purpose [42]. Therefore, it seems that the diagnostic utility of the evaluated ILs in the detection of AKI is not clinically conceivable when compared to that of NGAL and cystatin C.

In addition, urinary levels IL-18 is frequently studied among the included articles. After conducting subgroup analysis, it was observed that in non-critical settings, urinary IL-18 levels were not significantly different between pediatric patients with AKI and non-AKI control group. Therefore, urinary IL-18 levels may not be used for diagnosing AKI in non-critical settings. On the other hand, it was found that the urinary levels of IL-18 in the first 2 h was not significantly different between the AKI group and the non-AKI group, which suggests that the increase in IL-18 urinary levels is likely to occur after these hours. Moreover, according to the sensitivity analysis performed based on the studies' risk of bias, it was observed that the diagnostic performance of IL-18 urinary levels is not affected by the risk of bias status of the studies. However, the analysis could not be performed regarding other ILs due to the few

numbers of articles studying them.

This systematic review and meta-analysis, like other review studies, was subjected to certain limitations. Due to the nature of the study, laboratory measurements were not performed in one center, and with no supervision from authors on the sampling procedure, there exists a possibility of errors and discrepancies regarding the measurements of ILs. For instance, the cut off points considered for each IL in diagnosing AKI were not exactly the same between the included studies. Also, confirming AKI diagnosis in each study was based on the number of samples, the method of sampling and the presence of urine samples and baseline serum creatinine levels before hospitalization; thus, some studies did not have a baseline serum creatinine level available and therefore considered creatinine at the time of admission as baseline. Moreover, some studies confirmed the occurrence of AKI after 24 h since the increase in serum creatinine levels, while other studies confirmed AKI after a time range varying between 24 and 72 h since the increase in serum creatinine levels. It is worth mentioning that the few numbers of studies contemplating on serum and urinary levels of other ILs was another limitation, as IL-8 and IL-10 were each studied in only one article. Thus, it is recommended that future studies be performed on the diagnostic performance of other urinary and serum IL levels, to fill the gap between the existing evidence, as well as unifying sampling methods, cut off points and other discrepancies.

5. Conclusion

The findings of the present study indicate that although urinary levels of IL-18 and serum levels of IL-6 and 8 in children with AKI are significantly higher than those of non-AKI patients, their low sensitivity and specificity in the diagnosis of AKI questions their diagnostic utility for the detection of AKI in children and adolescents.

Ethics approval and consent to participate

The study was approved by Tehran University of Medical Sciences Ethics Committee. The inform consent was not applicable for the present meta-analysis.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Role of the sponsor

Tehran university of medical sciences had no role in the design and conduct of the study; collection, management, and analysis of the data.

CRediT author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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