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SYSTEMATIC REVIEW

Acute kidney injury in trauma patients admitted to the ICU: a systematic review and meta-analysis

Signe Søvik[1,2*], Marie Susanna Isachsen[3], Kine Marie Nordhuus[2], Christine Kooy Tveiten[2], Torsten Eken[2,4], Kjetil Sunde[2,4], Kjetil Gundro Brurberg[5,6] and Sigrid Beitland[4,7]

Abstract

Purpose: To perform a systematic review and meta-analysis of acute kidney injury (AKI) in trauma patients admitted to the intensive care unit (ICU).

Methods: We conducted a systematic literature search of studies on AKI according to RIFLE, AKIN, or KDIGO criteria in trauma patients admitted to the ICU (PROSPERO CRD42017060420). We searched PubMed, Cochrane Database of Systematic Reviews, UpToDate, and NICE through 3 December 2018. Data were collected on incidence of AKI, risk factors, renal replacement therapy (RRT), renal recovery, length of stay (LOS), and mortality. Pooled analyses with random effects models yielded mean differences, OR, and RR, with 95% CI.

Results: Twenty-four observational studies comprising 25,182 patients were included. Study quality (Newcastle–Ottawa scale) was moderate. Study heterogeneity was substantial. Incidence of post-traumatic AKI in the ICU was 24% (20–29), of which 13% (10–16) mild, 5% (3–7) moderate, and 4% (3–6) severe AKI. Risk factors for AKI were African American descent, high age, chronic hypertension, diabetes mellitus, high Injury Severity Score, abdominal injury, shock, low Glasgow Coma Scale (GCS) score, high APACHE II score, and sepsis. AKI patients had 6.0 (4.0–7.9) days longer ICU LOS and increased risk of death [RR 3.4 (2.1–5.7)] compared to non-AKI patients. In patients with AKI, RRT was used in 10% (6–15). Renal recovery occurred in 96% (78–100) of patients.

Conclusions: AKI occurred in 24% of trauma patients admitted to the ICU, with an RRT use among these of 10%. Presence of AKI was associated with increased LOS and mortality, but renal recovery in AKI survivors was good.

Keywords: Acute kidney injury, Wounds and injuries, Critical illness, Risk factors, Mortality, Systematic review

*Correspondence: signe.sovik@medisin.uio.no
[1] Department of Anaesthesia and Intensive Care, Akershus University Hospital, Lørenskog, Norway
Full author information is available at the end of the article

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Introduction

Trauma patients admitted to the intensive care unit (ICU) may develop acute kidney injury (AKI), but the reported incidence of post-traumatic AKI may vary widely depending on the AKI definition used and the study population [1, 2]. Consensus definitions of AKI have been developed to include all severities of AKI and to allow comparison between studies. Such definitions include the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) [3], later modified to the Acute Kidney Injury Network (AKIN) [4] and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [5].

A number of risk factors, e.g., hypotension, hypoperfusion, inflammation, critical care medication, and rhabdomyolysis, have been found to be associated with AKI [1, 2], and several prophylactic strategies have been tested, but it remains unresolved to what degree development of AKI in trauma patients may be prevented [6]. AKI is a heterogeneous condition ranging from mild impairment of kidney function to need of renal replacement therapy (RRT). Clinical data reveal that handling of AKI and use of RRT are strongly variable across ICU departments [7].

AKI in trauma patients is associated with adverse outcomes such as increased length of stay (LOS) and mortality [1, 2]. Survivors of AKI may have variable recovery of kidney function and might be prone to develop chronic kidney disease (CKD) and late morbidity [8] and mortality [9–11]. AKI may also be a burden to the health-care system, leading to substantially increased costs especially associated with the use of RRT.

The purpose of the present study was to perform a systematic review and meta-analysis of AKI according to RIFLE, AKIN, and/or KDIGO criteria reported in studies of trauma patients admitted to the ICU. Our primary aims were to report on incidence of AKI and compare risk factors and adverse outcomes, such as increased LOS and mortality, in patients with and without post-traumatic AKI. Secondary aims were to report on use of RRT, incidence of renal recovery, and impact on health-care costs. Preliminary results of this study have been presented [12].

Methods

Study registration

This systematic review and meta-analysis was registered in the PROSPERO database on 12 May 2017 (CRD42017060420). The protocol is available at https://www.crd.york.ac.uk/PROSPEROFILES/60420_PROTOCOL_20170412.pdf. Results were reported according to PRISMA guidelines (Electronic Supplementary Material ESM1). Protocol Appendices 1–3 are ESM2–4.

Take-home message

Acute kidney injury occurs in 24% of trauma patients admitted to the intensive care unit, and 10% of these receive renal replacement therapy. Kidney failure is associated with increased mortality and ICU and hospital length of stay, but renal recovery in survivors is generally good.

Literature search

Papers published between 1 January 2004 and 3 December 2018 were searched by a trained librarian (MSI) in PubMed, Cochrane Database of Systematic Reviews, UpToDate, and NICE (National Institute for Health and Care Excellence). Ongoing systematic reviews were identified by searching PROSPERO. In PubMed, Medical Subject Headings (MeSH) and text words including renal insufficiency, acute kidney injury, multiple trauma, nervous system trauma, wounds and injuries, penetrating wounds, accidents, trauma, traumatic, polytrauma, and multiple injuries were searched, alone or in combination. Adapted searches for the other databases, forward citation search using Google Scholar and Web of Science, and hand search of reference lists were conducted.

Inclusion was limited to studies in trauma patients admitted to an ICU, reporting on AKI occurring in the ICU and defined by full or modified RIFLE, AKIN, or KDIGO criteria. The search focused on study population irrespective of intervention, comparison, and outcome. It was limited to English, Swedish, Danish, or Norwegian language. See detailed literature search strategy (ESM2).

Study selection

Two collaborators (KMN and CKT) independently screened studies for eligibility according to predefined study selection criteria (ESM3). Titles, abstracts, and keywords from the search were examined, and full text was obtained for all potentially relevant records. Empirical studies comparing AKI and non-AKI patients were included; case reports were excluded. Studies on burns, drownings, and envenomation were excluded. Any disagreement was resolved through discussion with a senior author (SB).

Data extraction

Data was extracted in duplicate by two independent collaborators (KMN and CKT) and controlled by two others (SS and SB) according to a predefined data extraction form listing all outcomes (ESM4). In cases where data points were missing or ambiguously reported, the first and last author of the study were contacted by e-mail to

obtain the data. In case of no reply, one repeated e-mail was sent 1 month later.

We extracted data on AKI criteria used, incidence of AKI, AKI severity, days to AKI, patient age, gender, African American descent, body mass index (BMI), CKD, diabetes mellitus, chronic hypertension, trauma related risk factors (Injury Severity Score [ISS] [13], Glasgow Coma Scale score (GCS), blunt or penetrating trauma, abdominal injury, presence of shock, rhabdomyolysis), number of packed red blood cell (PRBC) transfusions, use of intravenous starch products and contrast agents, illness severity [Simplified Acute Physiology Score (SAPS II) [14], Acute Physiology And Chronic Health Evaluation (APACHE II and III) score [15, 16], mechanical ventilation, multiorgan failure, sepsis], RRT, renal recovery, ICU and hospital LOS, and ICU, hospital, and fixed-time mortality. Data was extracted as defined in the included studies, as absolute numbers and means or medians. Data distributions were extracted as standard deviation (SD), standard error (SE), 25th and 75th percentiles, interquartile range (IQR), or 95% confidence intervals (CI).

Quality assessment

Two authors (SS and SB) independently and in duplicate assessed the risk of bias of each included study using the Newcastle—Ottawa quality assessment scale [17]. Disagreements were resolved through discussion and by consulting a third author (TE).

Quantitative data synthesis

Statistical pooling

Meta-analyses and forest plots were prepared in R [18] using the meta [19] and the forestplot [20] packages. We expected heterogeneity between included studies, hence the meta-analyses were based on a random effect model using the DerSimonian–Laird estimator. Continuous and dichotomous outcomes were compared for patients with and without AKI by calculating mean differences (MD) and risk ratios (RR), respectively. Data primarily reported as medians with IQRs were re-expressed into means and SDs as suggested in the Cochrane handbook [21]. Studies reporting distribution of data only as ranges were not included in the meta-analyses. Meta-analyses of proportions were performed on arcsine-transformed data.

A number of risk factors potentially associated with the development of AKI were investigated. All risk factors reported in at least three primary studies were explored in pooled analyses. A forest plot containing summary estimates for multiple risk factors was generated. Estimates were presented on a common scale, i.e., odds ratio (OR). For dichotomous risk factors, ORs were calculated using the meta package in R. Continuous risk factors were expressed as standardized mean differences (SMDs) using the meta package in R and transformed to OR according to the formula suggested in the Cochrane handbook [22]. Descriptive data are reported as median (25–75% quartiles). For studies reporting mortality at several time points, the measure with longest observation time (up to 90 days) was used in pooled analyses.

Subgroup analyses

To assess if the results were robust, analyses were conducted in predefined subgroups with different severity levels of AKI, i.e., mild (RIFLE R, AKIN 1, KDIGO 1), moderate (RIFLE I, AKIN 2, KDIGO 2), and severe AKI (RIFLE F, AKIN 3, KDIGO 3). Patients with CKD prior to the trauma (RIFLE L and E) were outside the scope of this meta-analysis. Our protocol included subgroup analysis according to broadly defined trauma mechanisms. After inspecting the included studies we defined the following subgroups: mixed trauma, traumatic brain injury (TBI), and military casualties. No subgroup analysis according to level of study quality was planned.

Evaluation of heterogeneity

Statistical heterogeneity among studies was assessed with Cochran's Q test [23] and quantified by the I^2 statistic describing the proportion of total variation due to heterogeneity rather than chance [24, 25].

Results

Study selection

After removal of duplicates, 1106 studies were identified and their abstracts screened (Fig. 1). Of 278 studies considered potentially eligible, full-text assessment confirmed 34 studies fulfilling the inclusion criteria. In 12 of these publications data were not extractable. Enquiries to authors yielded data from two studies [26, 27], the remaining authors did not respond [28–37]. Thus, a total of 24 studies were included in the meta-analysis [1, 2, 26, 27, 38–57].

Study characteristics

All 24 included studies were observational. One was a pre-planned sub-study in patients recruited to a randomized controlled trial [55], the remaining had cohort design (Table 1). Median (25%–75% quartiles) study size was 407 (135–789) patients. Of the total 25,182 patients, 77% were males and 92% suffered blunt trauma. Age was 42 (34–51) years in AKI patients and 37 (30–42) years in non-AKI patients. Overall prevalence of diabetes mellitus and chronic hypertension was 5% [38, 42–44, 50, 52, 53] and 16% [38, 43, 44, 50, 52, 53], respectively. ISS was 26 (25–28) in AKI patients and 23 (19–25) in non-AKI patients [2, 26, 41, 42, 44–46, 49, 50, 52, 53, 55–57]. APACHE II score was 17 (17–18) in AKI patients and 14

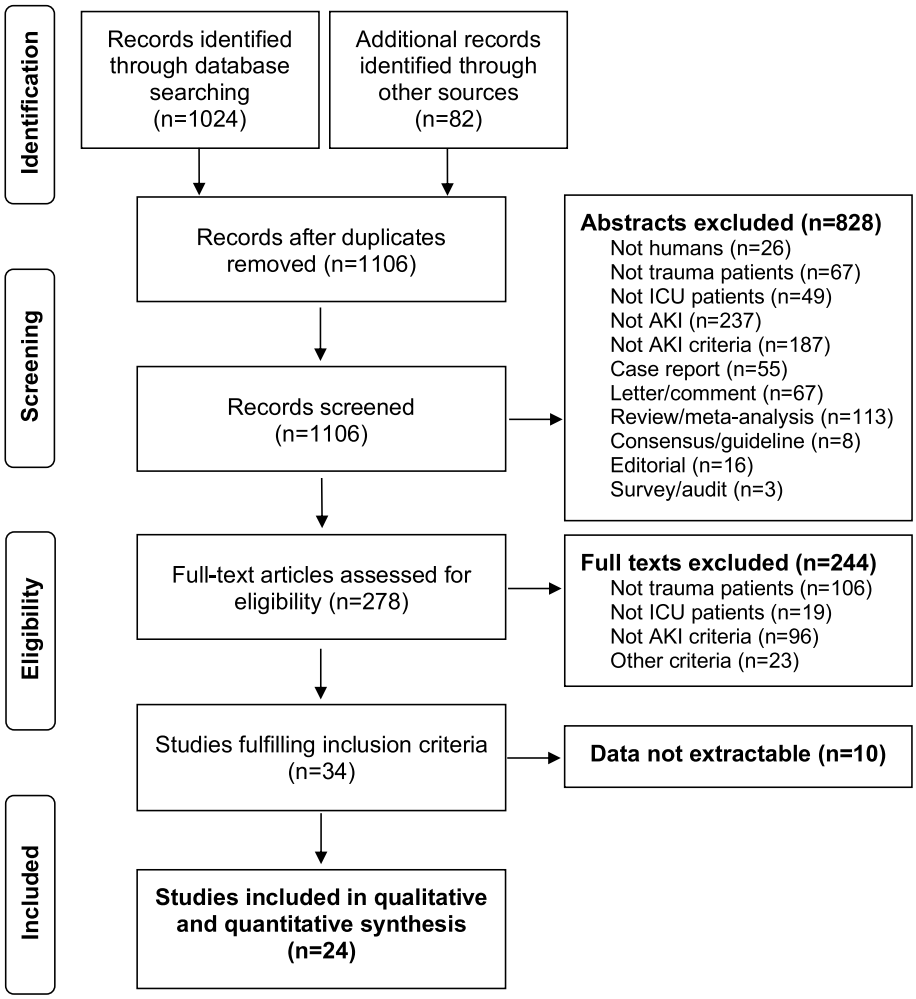

Fig. 1 Flowchart of search results according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA). *ICU* intensive care unit, *AKI* acute kidney injury

(11–15) in non-AKI patients [1, 27, 40, 44, 46, 49, 51, 55]. Three studies used APACHE III [40, 52, 53].

The numbers of studies with our defined trauma populations for subgroup analyses were 17 with mixed trauma, five with TBI, and two with military trauma (Table 1). RIFLE, AKIN, and KDIGO criteria were used in eight studies each. Only 13 of 24 studies used both creatinine and urine output to diagnose AKI; the remaining studies did not use urine output measurements.

Quality assessment

Overall study quality was moderate (Table 2). Eleven studies had generally representative study populations, i.e., unselected mixed trauma patients. All studies had internally representative control groups. Some uncertainty regarding diagnosis of AKI was prevalent: 11 of 24 studies used modified AKI criteria (Table 1) and pre-injury creatinine levels often were unknown; thus exclusion of patients with CKD pre-injury was not ensured. Two studies had short diagnostic windows [1, 50] and could have misclassified some patients. Multivariable analysis of risk factors for AKI was performed in 14 of 24 studies. Assessment of outcomes (AKI, RRT, LOS, mortality) was overall satisfactory, but only one study explicitly stated that no patients were lost to follow-up [42]. No study was excluded from quantitative analysis because of risk of bias.

Quantitative data synthesis

Incidence rates

All 24 studies (25,182 patients) reported incidence of AKI among trauma patients in the ICU [1, 2, 26, 27, 38–57]. Pooled analyses found an overall mean incidence of post-traumatic AKI of 24% (20–29) (Fig. 2). Time from trauma to AKI diagnosis was 3 days (range 1–6) [38, 43, 46, 56]. In 22 of 24 studies (24,630 patients) incidence rates were

Table 1 Included studies of acute kidney injury (AKI) in ICU trauma patients

First author (publication year)	AKI criteria	Criteria adherence	Population	Recruitment	AKI follow-up time	*N* total	*N* (%) with AKI
Bagshaw (2008) [1]	RIFLE	Modified[a]	Mixed trauma	RCS	24 h	9449	1711 (18)
Yuan (2009) [57]	RIFLE	Modified[a]	Mixed trauma	RCS	In-hospital	3945	423 (11)
Costantini (2009) [41]	AKIN	Original	Mixed trauma	RCS	Unspecified	571	170 (30)
Makris (2009) [49]	RIFLE	Original	Mixed trauma	PCS	5 days	31	11 (36)
Bihorac (2010) [40]	RIFLE	Modified	Mixed trauma	PCS	28 days	982	253 (26)
de Abreu (2010) [38]	RIFLE	Modified	Mixed trauma	RCS	Hospital stay	129	52 (40)
Fang (2010) [43]	RIFLE	Modified	TBI	RCS	Not specified	171	53 (31)
Gomes (2010) [45]	RIFLE	Original[a]	Mixed trauma	PCS	ICU stay	436	217 (50)
Li (2011) [47]	AKIN	Original	TBI	RCS	In-hospital	136	31 (23)
Shashaty (2012) [53]	AKIN	Modified	Mixed trauma	PCS	5 days	400	147 (37)
Li (2013) [48]	AKIN	Original	TBI	PCS	Hospital stay	55	13 (24)
Podoll (2013) [50]	AKIN	Modified	Mixed trauma	RCS	72 h	901	54 (6)
Skinner (2014) [2]	RIFLE	Modified	Mixed trauma	RCS	Hospital stay	666	102 (15)
Ahmed (2015) [39]	AKIN	Original	TBI	RCS	Hospital stay	95	11 (12)
Eriksson (2015) [42]	KDIGO	Modified[a]	Mixed trauma	PCS	1 year	413	103 (25)
Heegard (2015) [26]	KDIGO	Modified[a]	Military	PCS	14 days	134	46 (34)
Reilly (2015) [52]	AKIN	Modified	Mixed trauma	PCS	6 days	497	134 (27)
Stewart (2016) [56]	KDIGO	Modified[a]	Military	RCS	7 days	3807	474 (13)
Fujinaga (2017) [44]	KDIGO	Original[a]	Mixed trauma	PCS	ICU stay	333	66 (20)
Raju (2017) [51]	AKIN	Unknown	Mixed trauma	PCS	Not specified	90	14 (16)
Skinner (2017) [54]	KDIGO	Modified[a]	Mixed trauma	RCS	Not specified	310	46 (15)
Ülger (2017) [27]	KDIGO	Original[a]	Mixed trauma	RCS	Not specified	198	147 (74)
Haines (2018) [46]	KDIGO	Modified	Mixed trauma	RCS	7 days	830	163 (20)
Skrifvars (2018) [55]	KDIGO	Original	TBI	RCT	7 days	603	82 (14)

RIFLE Risk, Injury, Failure, Loss, End-stage, *AKIN* Acute Kidney Injury Network, *KDIGO* Kidney Disease: Improving Global Outcomes. *Modified* urine output not included, *TBI* traumatic brain injury, *RCT* randomized controlled trial, *PCS* prospective cohort study, *RCS* retrospective cohort study

[a] Baseline creatinine levels estimated by formulae if missing in patient records

also reported by AKI severity [1, 2, 26, 27, 38–47, 49–51, 53–57]. Among these, 13% (10–16), 5% (3–7), and 4% (3–6) had mild, moderate, and severe AKI, respectively.

Risk factors

Risk factors for AKI extracted from the various studies were patient age [1, 2, 26, 27, 38–50, 52–57], male gender [1, 2, 26, 27, 38–50, 52–57], African American descent [26, 40, 46, 52, 53, 56], BMI [40, 52], CKD [44, 52], diabetes mellitus [38, 42–44, 50, 52, 53], chronic hypertension [38, 43, 44, 50, 52, 53], ISS [2, 26, 41, 42, 44–46, 49, 50, 52, 53, 55–57], SAPS II score [45, 46], APACHE II or III score [1, 27, 40, 44, 46, 49, 51–53, 55], abdominal trauma [38, 45, 46, 57], number of transfused units of PRBC [40, 43, 44, 46, 49, 53], blunt and penetrating trauma [2, 41, 42, 44, 52, 53, 57], shock [38–40, 42, 44, 49, 56, 57], rhabdomyolysis [2, 57], sepsis [38, 42, 57], mechanical ventilation [1, 38, 45, 57], GCS [1, 39, 42, 43, 47, 48, 50, 55], acute surgery [43, 52], multiorgan failure [41, 42], and use of intravenous contrast agents [46, 52, 53] and hydroxyethyl starch [42] products.

Pooled analyses yielded effect estimates for the risk factors associated with increased incidence of post-traumatic AKI (Fig. 3). Abdominal injury and sepsis increased the odds ratio for AKI to more than 3. Presence of diabetes mellitus, high APACHE II score, low GCS score, shock, high ISS, and high age gave odds ratios above 2 for AKI. Chronic hypertension and African American descent were also associated with increased risk. Patients given intravenous contrast agents less often developed AKI [46, 52, 53].

Renal replacement therapy

Use of RRT was reported in 22 of 24 studies (15,702 patients) [2, 26, 27, 38–48, 50–57], revealing that it was used in 10% (6–15) of patients with AKI, corresponding to about 2% of the total trauma population. RRT modes were continuous RRT (CRRT) [42, 44, 46, 55], sustained

Table 2 Quality assessment of studies according to the Newcastle–Ottawa quality assessment scale

First author (publication year)	Representativeness[a]	Selection of non-exposed[b]	Ascertainment of exposure[c]	Incident disease[d]	Comparability[e]	Assessment of outcome[f]	Length of follow-up[g]	Adequacy of follow-up[h]
Bagshaw (2008) [1]	A	A	A	B	A	A	B	D
Yuan (2009) [57]	A	A	A	A	A	A	A	D
Costantini (2009) [41]	A	A	A	A	C	A	A	D
Makris (2009) [49]	B	A	A	A	C	A	A	D
Bihorac (2010) [40]	B	A	A	A	A	A	A	D
de Abreu (2010) [38]	C	A	A	B	C	A	A	D
Fang (2010) [43]	C	A	A	B[i]	A	A	A	D
Gomes (2010) [45]	A	A	A	A	C	A	A	D
Li (2011) [47]	C	A	A	A	C	A	A	D
Shashaty (2012) [53]	A	A	A	B[i]	A	A	A	D
Li (2013) [48]	C	A	A	A	C	A	A	D
Podoll (2013) [50]	A	A	A	A	A	A	A	D
Skinner (2014) [2]	C	A	A	B	A	A	A	D
Ahmed (2015) [39]	C	A	A	A	C	A	A	D
Eriksson (2015) [42]	A	A	A	A	A	A	A	A
Heegard (2015) [26]	C	A	A	B[j]	A	A	A	D
Reilly (2015) [52]	A	A	A	B[i]	A	A	A	D
Stewart (2016) [56]	C	A	A	B[j]	A	A	A	D
Fujinaga (2017) [44]	A	A	A	B[i]	A	A	A	D
Raju (2017) [51]	B	A	A	A	C	A	A	D
Skinner (2017) [54]	C	A	A	B	C	A	B	D
Ülger (2017) [27]	A	A	A	A	C	A	A	D
Haines (2018) [46]	A	A	A	A	A	A	A	D
Skrifvars (2018) [55]	C	A	A	A	A	A	A	D

[a] *A* truly representative, *B* somewhat representative, *C* selected group, *D* no description of the derivation of the cohort

[b] *A* drawn from the same community as the exposed, *B* drawn from a different source, *C* no description of the derivation of the non-exposed

[c] *A* secure record, *B* structured interview, *C* written self-report, *D* no description

[d] Demonstration that the outcome of interest was not present at start of study: *A* yes, *B* no

[e] *A* study controls for demographics/comorbidities, *B* study controls for any additional factor (e.g., age, severity of illness), *C* not done

[f] *A* independent or blind assessment, *B* record linkage, *C* self-report, *D* no description

[g] Long enough for outcomes to occur? *A* yes, (i.e., in-hospital or up to 30 days), *B* no

[h] *A* complete follow-up, *B* subjects lost to follow-up was unlikely to introduce bias, *C* follow-up rate 90% or lower, *D* no statement. Only one study explicitly stated complete follow-up. All studies reported complete numbers on mortality

[i] Only patients on chronic hemodialysis were excluded

[j] Not described; combat casualties who were unlikely to have chronic kidney disease

low efficiency dialysis (SLED) [2], mixed (61% intermittent hemodialysis (IHD); 39% CRRT) [57], or unspecified [26, 27, 38, 40, 41, 43, 47, 50–54, 56].

Length of stay

AKI patients had 6.0 (4.0–7.9) days longer ICU LOS (Fig. 4) [27, 38–42, 44–46, 51, 52, 55] and 5.8 (4.2–7.4) days longer hospital LOS [39–41, 44–46, 55] than non-AKI patients. Association between AKI and increased LOS applied to both the mixed trauma and the TBI subgroups.

Mortality

Mortality was evaluated at ICU discharge [2, 46, 49, 55], hospital discharge [1, 38–40, 45–48, 53, 55, 57], 28 days [44], 30 days [42, 50, 52], 90 days [56], 1 year [42], or was not specified [26, 41, 43, 51, 54]. Absolute mortality in AKI patients was 27% (20–35), but varied considerably (ESM5). Patients with AKI had markedly higher risk of mortality than non-AKI patients (RR 3.4 [2.1–5.7], Fig. 5).

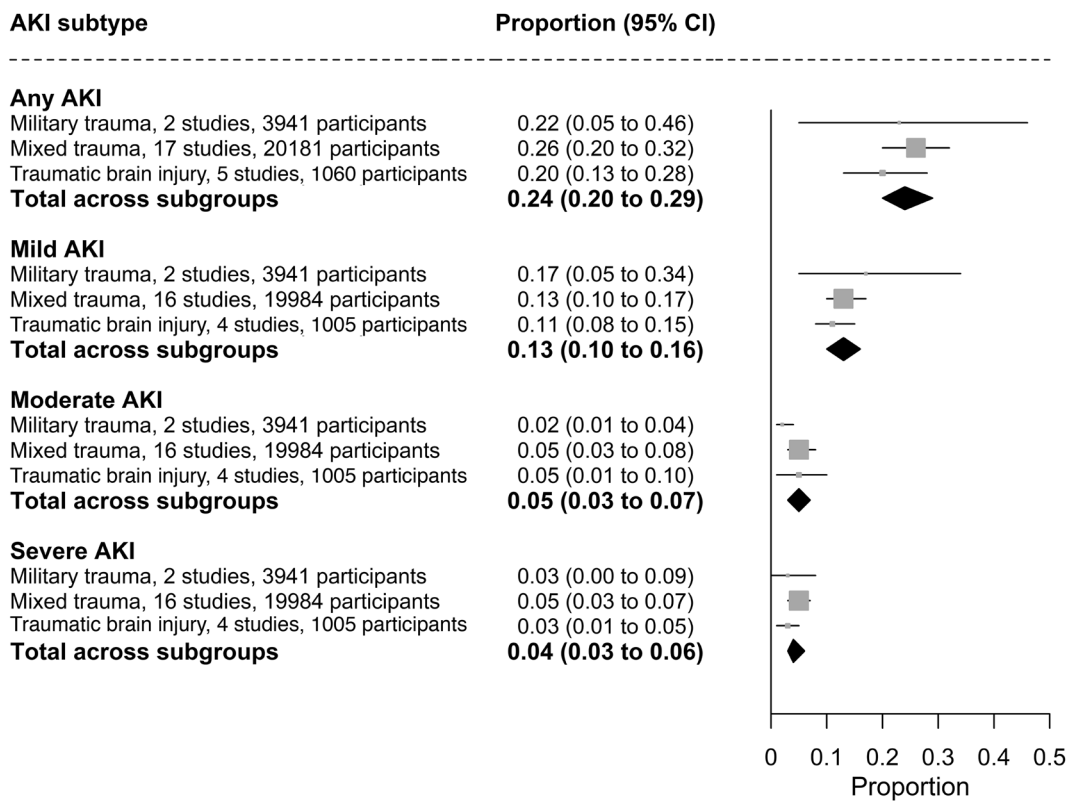

Fig. 2 Proportion of trauma patients admitted to the intensive care unit (ICU) developing acute kidney injury (AKI), overall and split by trauma mechanism. *Mild AKI* RIFLE R, AKIN 1, KDIGO 1; *Moderate AKI* RIFLE I, AKIN 2, KDIGO 2; *Severe AKI* RIFLE F, AKIN 3, KDIGO 3

Renal recovery

Renal recovery occurred in 96% (78–100) of patients [2, 39, 40, 42, 45, 47, 48, 55, 57] (ESM6). One study reported renal recovery as full or partial [40].

Health-care costs

None of the included studies reported health-care costs of post-traumatic AKI in the ICU.

Subgroup analyses

The risk ratio for mortality in AKI patients was 2.9 (1.7–5.1) in mixed trauma, 4.4 (3.1–6.2) in TBI, and 8.8 (6.2–12.4) in military trauma patients. Absolute mortality rates in patients with AKI were 29% (20–38) in mixed trauma, 27% (8–53) in TBI, and 16% (9–24) in military trauma.

Mortality data was reported according to AKI severity in 11 of 24 studies (21,191 patients) [1, 2, 26, 27, 40, 41, 45, 53, 55–57]. Pooled analyses showed that RR (95% CI) for death increased with severity of AKI, being 2.8 (1.7–4.6), 5.3 (2.6–10.6), and 6.9 (3.3–14.1) in mild, moderate, and severe AKI, respectively, compared to non-AKI patients. Effect of severity applied to both the mixed and military subgroups. Pooled absolute mortality rates in mild, moderate, and severe AKI were 20% (14–27), 38% (25–51), and 45% (31–59) (ESM7, ESM8, ESM9).

Heterogeneity

Considerable heterogeneity with I^2 above 90% was observed in some of the meta-analyses. This can be associated with clinical as well as methodological differences between studies. Caution is therefore advised when interpreting the results. Specifically, heterogeneity was demonstrated for mortality (Cochran's Q test $p<0.0001$; Higgins' $I^2=98\%$) and ICU LOS ($p<0.0001$; $I^2=85\%$), but not for hospital LOS ($p=0.38$, $I^2=7\%$).

Discussion

This systematic review and meta-analysis reveals that AKI occurs in approximately 24% of trauma patients admitted to the ICU, a population with a majority of relatively young male patients suffering blunt trauma.

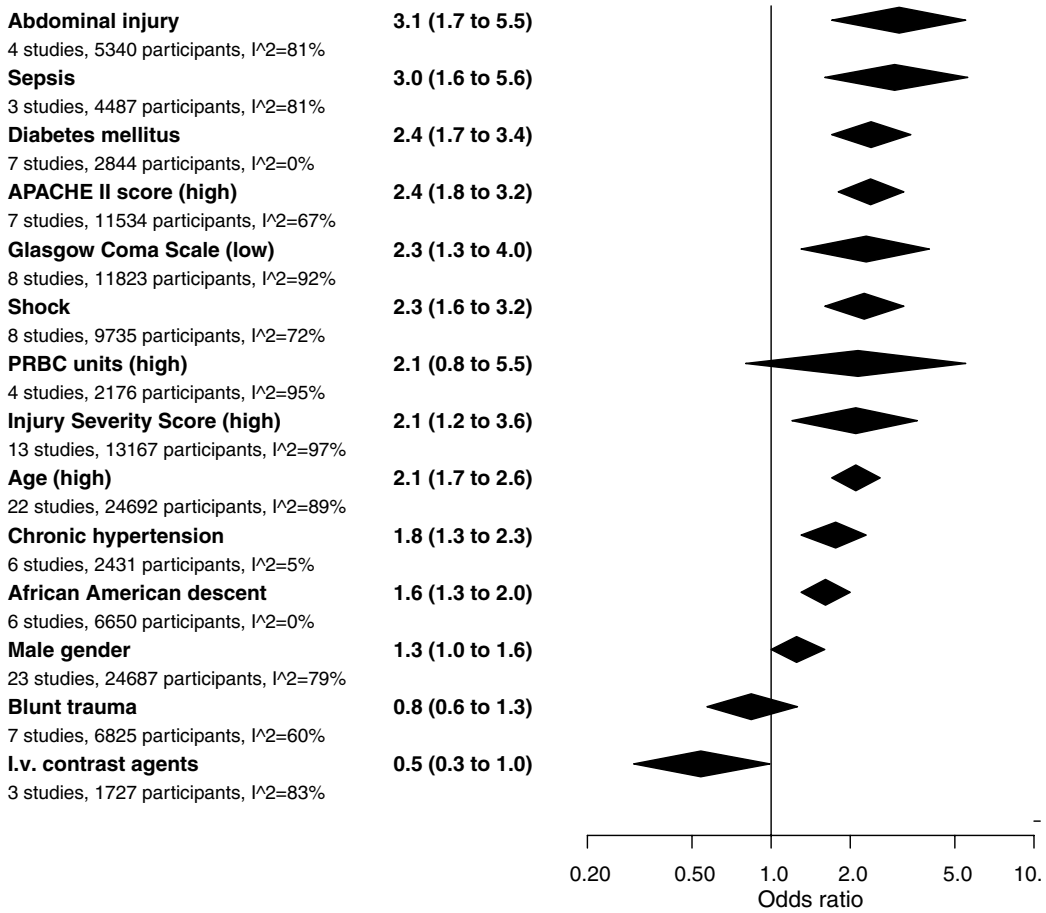

Fig. 3 Risk factors for acute kidney injury (AKI) in trauma patients admitted to the intensive care unit. The contributions from the various risk factors were statistically weighted and adjusted to a single scale. Odds ratios (OR) for continuous risk factors were derived from standardized mean differences. *CI* confidence interval, *PRBC* packed red blood cell, *APACHE* Acute Physiology And Chronic Health Evaluation

Among these, most patients have less severe AKI and only 4% have severe AKI. Altogether, less than 2% of all trauma patients are treated with RRT. Patient-related risk factors for post-traumatic AKI are African American descent, high age, chronic hypertension, and diabetes mellitus. Risk factors related to the anatomical injury and physiological response are high ISS, abdominal injury, shock, low GCS, high APACHE II score, and sepsis (Fig. 3). Presence of AKI is associated with substantially prolonged ICU and hospital LOS and increased mortality rate that is worsened with the severity of AKI. Kidney function seems to recover well in most trauma patients with AKI, but there is a lack of data on the risk of CKD and long-term mortality. Notably, none of the studies reported on the economic consequences of post-traumatic AKI. Study quality was moderate and heterogeneity was substantial for important outcomes. Our findings should be relevant for health-care providers, users, and policymakers.

A recent multinational study in a mixed ICU population found that 57% of patients experienced AKI according to the KDIGO criteria and that 13.5% were treated with RRT [58]. In contrast, in our systematic review in trauma patients only, about 24% developed AKI and less than 2% of the total population was treated with RRT. Post-traumatic AKI is known to represent only a small proportion of severe AKI in the ICU [59], and the subgroup of trauma patients likely differs from other groups of critically ill patients [1]. The trauma population in the present meta-analysis was young, and few had chronic hypertension or diabetes mellitus; this may have constituted a larger physiological reserve and reduced the incidence of AKI. However, the incidence of AKI in many of the studies in this systematic review was probably

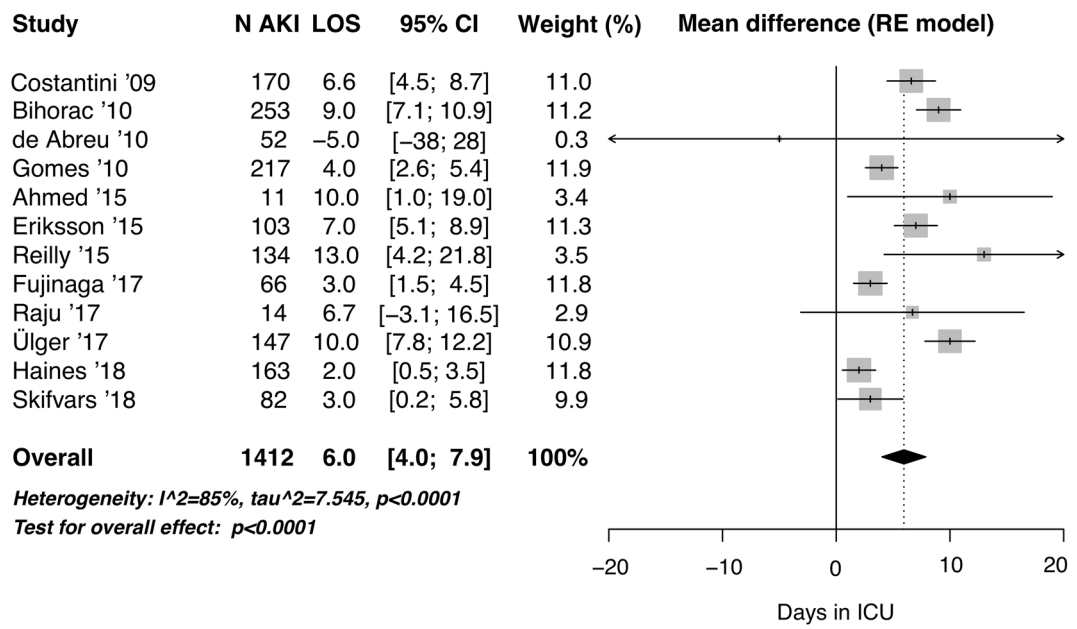

Fig. 4 Mean difference in intensive care unit length of stay (LOS, days) in trauma patients with acute kidney injury (AKI) relative to non-AKI trauma patients. *N AKI* number of AKI patients, *CI* confidence interval, *RE* random effects

underreported as a result of the use of modified AKI criteria.

We quantified the effects of many risk factors for post-traumatic AKI, some patient-related and some dependent on the anatomical injury and its physiological consequences (Fig. 3). From other patient groups it is known that high age, chronic hypertension, and diabetes mellitus are risk factors for AKI [58]. In trauma patients a high ISS is a marker of severity [13], while a low GCS score may be associated with hypoventilation and hypoxemia. Shock in trauma patients is usually due to severe bleeding, although other reasons may be present. In the studies reporting abdominal trauma it is unknown whether direct trauma to the kidneys and/or urinary tract affected kidney function. Packing of the abdomen during damage control surgery in severe intra-abdominal or retroperitoneal injuries may also affect kidney function. Sepsis in the ICU is known to be a major cause of AKI as it causes both hypoperfusion [60] and inflammatory insult. The APACHE score comprises markers of inflammation, respiratory and circulatory instability, and creatinine levels; a high APACHE II score was associated with AKI. Patients given intravenous contrast agents developed AKI less often [46, 52, 53], but several restrictions apply to this finding. Neither contrast type, dose, nor concurrent fluid treatment was specified. Also, contrast use may have been avoided in patients thought to be of higher risk of AKI [53].

Unfortunately, we were unable to quantify the impact of several relevant risk factors because they were reported in too few studies (BMI [40, 52], SAPS II [45, 46], multiorgan failure [41, 42], intravenous starch products [42]) or because several studies reported zero events in both groups (mechanical ventilation [1, 38, 45, 57]).

AKI in ICU patients is associated with high morbidity, and the condition is often part of multiorgan failure [61, 62]. Our observation that patients with AKI had longer ICU LOS and hospital LOS compared to non-AKI patients is therefore expected. The included studies varied widely regarding overall mortality rates and inclusion/exclusion of trauma patients treated in the ICU for less than 24–48 h. This likely affected the estimated effect on LOS. Although none of the studies in our analysis reported on economic consequences of post-traumatic AKI, it is evident that 6 days extra ICU LOS is associated with increased treatment costs. Use of RRT would add to these expenses as a result of the use of costly equipment and increased work load for the staff [63].

In concordance with previous studies in general ICU populations, we observed that post-traumatic AKI was associated with several-fold increased mortality, worsening with the severity of AKI. Notable exceptions were one study with greater than 95% overall mortality [38], one study where non-AKI patients had very high mortality during the initial 48 h post-injury [45], one study including only traumatic rhabdomyolysis patients [51], and studies with small [49] or elderly patient populations

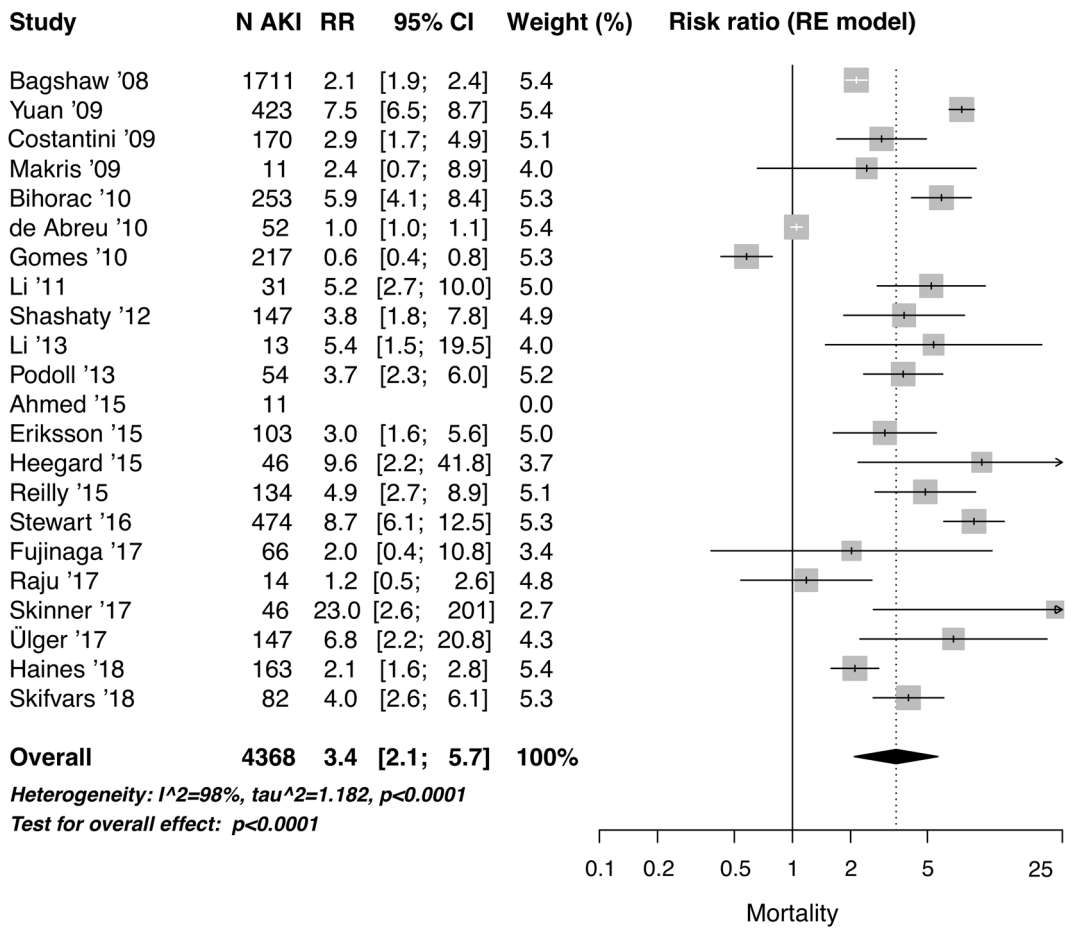

Fig. 5 Mortality in trauma patients with acute kidney injury (AKI) in the intensive care unit. Risk ratio (RR) of non-survival reported at any time point in patients with AKI, relative to non-AKI trauma patients. *N AKI* number of AKI patients, *CI* confidence interval, *RE* random effects

[44]. The increased mortality in trauma patients with AKI is probably multifactorial but is certainly associated with the severity of multiorgan failure. An overall mortality of 27% in post-traumatic AKI (ESM5) is comparable with what has been observed in a general ICU population [58].

Evaluation of renal recovery across populations is challenging because there is yet no consensus definition [64]; thus the definitions may vary from RRT independence via normalization of serum creatinine to full recovery of functional reserve. Despite varying definitions in the studies included in the present meta-analysis, renal recovery was reported to occur in 96% of patients with post-traumatic AKI. However, only one study followed kidney function over a prolonged period of time, and none evaluated the risk of CKD. In other groups of ICU patients it has become evident that an episode of AKI is associated with increased risk of CKD compared to a control group of critically ill patients without AKI [11].

There are important clinical limitations to the studies underlying this systematic review. The external validity of the presented results may be limited because included patient populations in the different studies varied widely with regard to age, comorbidities, and trauma mechanisms. None of the studies described their trauma system, in particular formal or informal patient selection processes determining hospital and ICU admission, transfer, and discharge. Thus, possible study bias could not be differentiated from true variation between populations. The estimated incidence of AKI may be confounded by a high overall mortality and high early mortality in some studies. Patients with pre-injury kidney disease were not uniformly excluded in all studies; thus some patients diagnosed with AKI might actually have had CKD. Conversely, most of the studies used modified AKI criteria resulting in systematic underestimation of AKI incidence. Variable and unspecified mortality definitions, especially the evaluation of survival status at administrative instead of fixed time points (e.g., ICU mortality instead of 30-day mortality), is an obvious source of bias since a substantial proportion of trauma deaths occur after transfer to other

ICUs, wards, hospitals, or institutions [65, 66]. Similarly, the effect of AKI on LOS likely was underestimated since no study reported time spent in other ICUs or hospitals after patient transfer. Use of RRT probably varied across sites as clinical practice depends on local treatment traditions and RRT availability [7]. Data on renal recovery should be interpreted with caution as definitions and assessment time points for this variable varied widely across studies. Unfortunately, we were unable to include data on economic costs because this was not reported in any of the studies.

Methodological limitations include that ten eligible studies could not be included because of unextractable data. As the included studies were observational, associations between risk factors and AKI do not imply a causal relationship. Some publications might have been missed as a result of the language limitation of our literature search. The strength of evidence varies since variables reported in a high number of primary studies yield better estimates than variables reported in few studies. No study reported rates of missing data; only one study reported no loss to follow-up. Possible bias introduced by use of means and SDs for variables that were probably skewed (e.g., durations) was not formally evaluated.

Strengths of this systematic review are the relatively large number of included studies and patients. Further, our literature search, study selection, and data extraction forms were predefined and published before study start. An experienced librarian (MSI) performed the literature search supervised by a consultant intensive care clinician (SB). Screening of studies for eligibility, systematic evaluation of study quality, and data extraction was performed in duplicate by two independent collaborators. For eligible studies without complete and extractable data we contacted authors twice by email in order to retrieve data.

Implications of the present systematic review for future research are the need of studies on post-traumatic AKI, exploring early resuscitative measures, use of RRT, long-term patient outcomes, and treatment costs. There is a clear need for development of uniform standards of reporting in AKI, addressing issues like incidence calculation in populations with high early mortality, definitions of renal recovery, and standardized time points for reporting clinical events such as AKI, renal recovery, and survival status.

In conclusion, the present meta-analysis shows that AKI occurs relatively frequently in trauma patients admitted to the ICU, although severe AKI with need of RRT is uncommon. AKI should be expected and prevention attempted especially in patients with high age, chronic hypertension, diabetes mellitus, severe anatomical injury, and/or marked physiological derangement. Development of post-traumatic AKI is closely associated with increased morbidity and mortality. There is a lack of data on long-term patient outcomes and economic consequences of post-traumatic AKI.

Electronic supplementary material
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Author details
[1] Department of Anaesthesia and Intensive Care, Akershus University Hospital, Lørenskog, Norway. [2] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. [3] Medical Library at Ullevål Hospital, University of Oslo Library, Oslo, Norway. [4] Department of Anaesthesiology, Division of Emergencies and Critical Care, Oslo University Hospital Ullevål, Oslo, Norway. [5] Division for Health Services, Norwegian Institute of Public Health, Oslo, Norway. [6] Center for Evidence Based Practice, Western Norway University of Applied Sciences, Bergen, Norway. [7] Renal Research Group Ullevål, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway.

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