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Incidence and mortality of acute kidney injury in patients undergoing hematopoietic stem cell transplantation: a systematic review and meta-analysis

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Summary

Background: While acute kidney injury (AKI) is commonly reported following hematopoietic stem cell transplant (HCT), the incidence and impact of AKI on mortality among patients undergoing HCT are not well described. We conducted this systematic review to assess the incidence and impact of AKI on mortality risk among patients undergoing HCT.
Methods: Ovid MEDLINE, EMBASE and the Cochrane Databases were searched from database inceptions through August 2019 to identify studies assessing the incidence of AKI and mortality risk among adult patients who developed AKI following HCT. Random-effects and generic inverse variance method of DerSimonian–Laird were used to combine the effect estimates obtained from individual studies.
Results: We included 36 cohort studies with a total of 5144 patients undergoing HCT. Overall, the pooled estimated incidence of AKI and severe AKI (AKI Stage III) were 55.1% (95% confidence interval (CI) 46.6–63.3%) and 8.3% (95% CI 6.0–11.4%), respectively. The pooled estimated incidence of AKI using contemporary AKI definitions (RIFLE, AKIN and KDIGO criteria) was 49.8% (95% CI 41.6–58.1%). There was no significant correlation between study year and the incidence of AKI ($P = 0.12$) or severe AKI ($P = 0.97$). The pooled odds ratios of 3-month mortality and 3-year mortality among patients undergoing HCT with AKI were 3.05 (95% CI 2.07–4.49) and 2.23 (95% CI 1.06–4.73), respectively.
Conclusion: The incidence of AKI among patients who undergo HCT remains high, and it has not changed over the years despite advances in medicine. AKI after HCT is associated with increased short- and long-term mortality.

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Introduction

Hematopoietic stem cell transplant (HCT) is being used for multiple malignant and non-malignant conditions.[1–4] In the current era, indications have been extended to metabolic, immune-related, autoimmune and other inflammatory disorders.[5] More than 50 000 patients undergo HCT every year, and its rate is increasing by 20–30% annually.[6] Despite the widespread use of preventive measures, acute kidney injury (AKI) remains a substantial problem after HCT. AKI is associated with significant cost burden, morbidity and mortality.[7,8] Survivors of AKI could sustain recurrent episodes of AKI, leading to multiple hospitalizations.[9] In long-term survivors after HCT, chronic kidney disease is prevalent in up to 20% of the patients.[10–12] They are at further risk for the development of hypertension, albuminuria and nephrotic range proteinuria.[13,14] Severe AKI requiring renal replacement therapy (RRT) is associated with significant mortality of about 80%.[15–18]

Multiple steps are involved in successful hematopoietic stem cell transplantation.[19] The process begins with the procurement of stem cells from the donor, while the recipient undergoes intensive chemotherapy (myeloablative)[3,20] vs. less intensive chemo (non-myeloablative)[21] depending on age and other comorbidities. The second stage includes the infusion of graft stem cells to the recipient (engraftment). Finally, the recipient receives immunosuppression to suppress rejection or graft vs. host disease. AKI can occur during any of the above-mentioned steps.[22] AKI following HCT is traditionally defined as 'Doubling of serum creatinine in the first hundred days'. However, in order to standardize AKI risk stratification, RIFLE, KDIGO and AKIN definitions were developed.[18,23–27] The reported incidence of AKI after HCT varies widely from 12% to 66%.[18,20,28–30] This wide variation is likely related to not using a standardized AKI definition, various conditioning regimens, allogeneic vs. autologous donor and retrospective nature of studies.[25,26] It is reported that the incidence of AKI after autologous stem cell transplant is 12–50%, non-myeloablative allogeneic 29–54% and myeloablative allogeneic at 19–66%.

Given the variability in the reported incidence of AKI post-HCT, we performed a systematic review and meta-analysis of the existing cohort studies up to August 2019 to assess the pooled incidence of AKI and its associated mortality.

Materials and methods

Search strategy

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement[31] was followed in conducting this systematic review. Ovid MEDLINE, EMBASE and the Cochrane Databases were systematically searched from database inceptions through August 2019 to identify studies fulfilled the following inclusion criteria: (i) clinical trials or observational studies published as original articles or conference abstracts; (ii) studies that assessed the incidence of AKI or AKI-associated mortality among patients undergoing HCT; (iii) adult patient population (age $\geq$ 18 years old). The primary outcome was AKI post-HCT. Mortality risk was also assessed among the studies that reported AKI-outcome. Two investigators (S.K. and K.K.) performed independent literature search using the search terms of (('bone morrow' OR 'stem cell') AND ('transplant' OR 'transplantation')) AND ('acute kidney injury' OR 'acute renal failure' OR 'renal replacement therapy'). Supplementary Data S1 provide information on the detailed search strategy. The data for this meta-analysis are publicly available through the Open Science Framework (URL: <seurld>https://osf.io/qfgj9/</seurld>). Language restriction was not applied. Potentially related studies were manually reviewed using the references. Gray literature was additionally searched for further relevant information.

Study selection

Observational studies and clinical trials providing 95% confidence intervals (CI) data on the incidence of AKI and mortality risk of AKI in adult patients undergoing HCT were included in the meta-analysis. Two investigators (S.K. and K.K.) independently reviewed retrieved articles for eligibility. A third reviewer (W.C.) solved inconsistencies by collective agreement. AKIN,[32] RIFLE[33] and KDIGO[34] definitions of AKI were used for subgroup analysis.

Data collection

The collected data from individual studies included title, name of authors, year of the study, publication year, the country where the study was conducted, patient characteristics, AKI definition, the incidence of AKI and severe AKI requiring RRT and finally reported death rate among patients with AKI following HCT.

Statistical analysis

Meta-analysis was performed using Comprehensive Meta-Analysis software version 3.3.070 (Biostat Inc., NJ, USA). Adjusted point estimates of included studies were incorporated by the generic inverse variance method of DerSimonian–Laird, which assigned the weight of individual study based on its variance.[35] Due to the probability of between-study variance, we applied a random-effects model to pool outcomes of interest, including the incidence of AKI and mortality risk. Cochran's Q test ($P < 0.05$ for a statistical significance) and I^2 statistic ($\leq$25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity and $\geq$75% represents high heterogeneity) were used to assess statistical heterogeneity.[36] Publication bias was assessed by funnel plot and the Egger test.[37]

Results

The search yielded a total of 1818 articles for initial screening. Four hundred seventy-eight duplicates were removed, and 1262 articles were excluded for the following reasons: *in vitro* studies, pediatric patient population, animal studies, case reports, correspondences or review articles. Full-length reviews of 90 studies were performed. Twenty-six studies were not observational studies and 28 studies were excluded due to not providing the outcome of interest; thus, 36 cohort studies[15–18,20,25,26,38–65] with a total of 5144 patients undergoing HCT were enrolled. Figure 1 outlines the flowchart of paper selection for inclusion. Table 1 provides details of the included studies.

Incidence of AKI among patients undergoing HCT

Overall, the pooled estimated incidence of AKI and severe AKI among patients undergoing HCT were 55.1% (95% CI 46.6–63.3%, $I^2 = 96\%$, Figure 2) and 8.3% (95% CI 6.0–11.4%, $I^2 = 92\%$, Figure 3), respectively. The pooled estimated incidence of AKI using

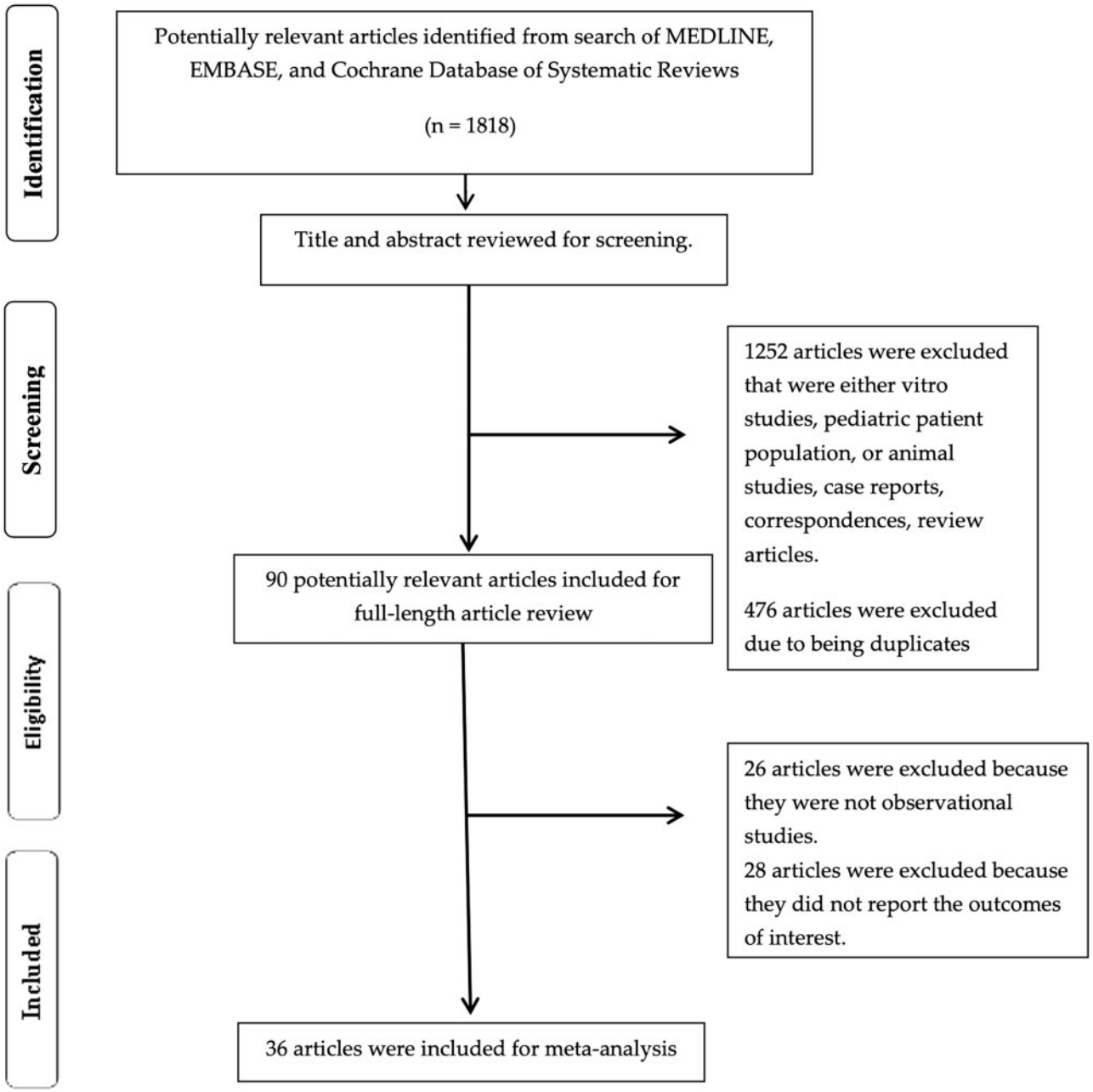

Figure 1. Outlines the flowchart of paper selection for inclusion.

standard AKI definitions was 49.8% (95% CI 41.6–58.1%, $I^2 = 93\%$, Supplementary Figure S1). The pooled estimated incidence of RRT among patients undergoing HCT was 7.2% (95% CI: 4.0–12.5%, $I^2 = 83\%$, Figure 3).

Subgroup analyses were performed according to AKI definitions. The pooled estimated incidence rates of AKI by RIFLE, AKIN and KDIGO criteria were 59.2% (95% CI 44.5–72.5%, $I^2 = 93\%$, Supplementary Figure S1), 48.2% (95% CI 37.4–59.1%, $I^2 = 86\%$, Supplementary Figure S1) and 34.1% (95% CI 16.7–57.2%, $I^2 = 96\%$, Supplementary Figure S1), respectively.

Meta-regression of all studies using standard AKI definitions showed that the year of the study did not significantly affect the incidence of AKI ($P = 0.12$, Supplementary Figure S2A) and severe AKI ($P = 0.97$, Supplementary Figure S2B).

Mortality risk of AKI in patients after HCT

Data on mortality risk from included studies are shown in Table 1. The pooled odds ratios (ORs) of 3-month mortality and 3-year mortality among patients undergoing HCT with AKI were 3.05 (95% CI 2.07–4.49, $I^2 = 19\%$, Figure 4A) and 2.23 (95% CI 1.06–4.73, $I^2 = 82\%$, Figure 4B), respectively.

Evaluation for publication bias

The funnel plot (Supplementary Figure S3) and Egger's regression asymmetry tests were performed to assess publication bias in analysis evaluating the 3-month mortality of AKI in patients undergoing HCT. We found no significant publication bias in the meta-analysis evaluating the mortality risk of patients after HCT with AKI ($P = 0.30$).

Table 1. The main characteristic of studies included in this meta-analysis of AKI incidence and mortality among patients with hematopoietic stem cell transplantation

Study	Year	Country	Patients	Indication for HCT	Number	AKI definition	AKI incidence	Mortality
Merouani *et al.*[38]	1995	Colorado, USA, 1991–1994	Autologous hemato-poietic cell transplant	Breast cancer	232	Grade 0: <25% decline in GFR, Grade 1: >25% decrease in GFR <2-fold rise in serum creatinine, Grade 2: >fold rise in creatinine, no HD Grade 3: need for dialysis	Overall AKI = 130/232 = (56%) Severe AKI/needing RRT = 7/232 = (3%)	60-day AKI mortality 12/130 (9%) Non-AKI mortality = 4/102(3.9%)
Gruss *et al.*[39]	1995	Madrid, Spain	Allogeneic and au-tologous BMT	AL, CML, AA, other	275	Doubling of serum creatinine or cre-atinine > 2 mg/dl or AKI requiring HD	Overall AKI—72/275 = (26%) AKI requiring HD = 17/275 = (6.18%)	90-day mortality AKI mortality = 33/72, (45.8%) Non-AKI mortality 36/203 = (17.7%)
Parikh *et al.*[40]	2002	Colorado, USA	Allogeneic hemato-poietic cell transplant	Hematological malignancy	88	Grade 0: <25% decline in GFR, Grade 1: > 25% decrease in GFR, <2-fold rise in serum creatinine, Grade 2: > fold rise in creatinine, no HD, Grade 3: need for dialysis	Overall AKI = 81/88 = (92%) Severe AKI = 29/88 = (32.9%)	Six-month AKI mortality = 48/81 (59%) Non-AKI mortality 3/7 = (42%)
Schrier *et al.*[53]	2005	New Haven, CT, USA	Autologous HCT	Breast cancer	232	Grade 0: <25% decline in GFR; Grade 1: >25% decrease in GFR, <2-fold rise in serum creatinine; Grade 2: > fold rise in creatinine, no HD Grade 3: need for dialysis	Overall AKI = 130/232 = (56%) Severe AKI = 17/232 (7%)	60-day mortality AKI mortality = 12/130 = (9%) Non-AKI mortality = 4/102 = (4%)
Lopes *et al.*[54]	2006	Portugal	Autologous and allo-geneic HCT	Hematological malignancy	140	RIFLE	Overall AKI = 53/140 = (38%) Severe AKI = 20/140 = (14.3%)	N/A
Parikh *et al.*[41]	2004	Colorado, USA, 1998–2001	Non-myeloablative HCT	CML ALL	253	Grade 0: <25% decline in GFR; Grade 1: >25% decrease in GFR, <2-fold rise in serum creatinine; Grade 2: >fold rise in creatinine, no HD; Grade 3: need for dialysis	Overall AKI = 228/253 = (90%) Severe AKI needing RRT = 11/253 = (4%)	N/A
Caliskan *et al.*[20]	2006	Turkey, 2001–2003	Myeloablative allo-geneic and autologous	Hematological malignancy	47	Grade 0: <25% decline in GFR; Grade 1: >25% decrease in GFR, <2-fold rise in serum creatinine; Grade 2: >fold rise in creatinine, no HD; Grade 3: need for dialysis	Overall AKI-33/47 = (70%) Severe AKI 7/47 = (14.8%)	100-day AKI mortality 8/33 = (24%) Non-AKI mortality = 1/14 = (7%)
Liu *et al.*[42]	2007	China, 2002–2005	Non-myeloablative peripheral blood stem cell transplant	CML	26	Grade 0: <25% decline in GFR; Grade 1: >25% decrease in GFR, <2-fold rise in serum creatinine; Grade 2: >2-fold rise in creatinine, no HD; Grade 3: need for dialysis	Overall AKI = 10/26 (38%) Severe AKI 1/26 = (3.8%)	100-day AKI mortality 4/10 = (40%) Non-AKI mortality = 1/16 = (6.25%)
Kersting *et al.*[43]	2008	Netherlands	Non-myeloablative HCT	CML, AA	150	Grade 1: decrease in glomerular filtra-tion rate > 25% and <doubling in serum creatinine; Grade 2: >doubling in serum creatinine; Grade 2 plus: tripling in serum creatinine.	Overall AKI = 141/150 = (94%) Severe AKI = 14/150 = (9.3%)	NA

(continued)

Table 1. (continued)

Study	Year	Country	Patients	Indication for HCT	Number	AKI definition	AKI incidence	Mortality
Kersting *et al.*[44]	2007	Netherlands, 1993–2004	Allogeneic myeloablative	AML, ALL, CML, OTHERS	363	Grade 0: <25% decline in GFR; Grade 1: >25% decrease in GFR, <2-fold rise in serum creatinine; Grade 2: >fold rise in creatinine, no HD; Grade 3: need for dialysis	90 days post-Tx Overall AKI = 339/363 = (93%) Severe AKI 4/363 = 1.1%	Six-month mortality AKI mortality 58/339 = 17%
Lopes *et al.*[17]	2008	Portugal, 1999–2005	Reduced-intensity conditioning, HCT	AML, CML	82	KDIGO	Overall AKI: 44/82 (53.6%) Severe AKI: 13/82 = (15.8%)	100-day AKI mortality = 17/44 (38%) Non-AKI mortality 1/38 = 2.6%
Yakushijin *et al.*[55]	2009	Tokyo, Japan	Reduced-intensity stem cell transplant	AML, ALL, CML, MDS	286	Grade 0: <25% decline in GFR; Grade 1: >25% decrease in GFR; <2-fold rise in serum creatinine, Grade 2: >fold rise in creatinine, no HD; Grade 3: need for dialysis	Overall AKI = 220/286 = (76.9%) Severe AKI = 9/286 = (3.14%)	N/A
Tokgoz *et al.*[56]	2009	Turkey, 2007–2008	Allogeneic myeloablative	AML, ALL	39	Grade 1: increase in creatinine >2 times Grade 2: increase in serum creatinine >3 times; Grade 3: Grade 2 along with needing dialysis	Overall AKI = 20/39 = (51.3)	100-day mortality AKI mortality = 2/20 = (10%) Non-AKI mortality = 1/19 = (5.2%)
Ando *et al.*[25]	2010	Japan, 2004–2007	Autologous and allogeneic HCT	Hematological malignancy	249	AKIN	Overall AKI = 116/249 (46%) Severe AKI: 25/249 (10%)	AKI mortality 60/116 = (51.7) Non-AKI mortality 32/133 = 24%
Lui *et al.*[18]	2010	China, 2002–2007	Non-myeloablative HCT	CML, ALL, CLL	62	AKIN	Overall AKI = 18/62 = 29% Severe AKI = 1/62 = 1.6%	OR = 3.3; 95% CI 1.0–11.1 AKI/mortality = 11/18 (61%) Non-AKI mortality = 6/44 (13.6%)
Yu *et al.*[66]	2010	China, 2003–2008	Allogeneic HCT	Hematological malignancy	96	Grade 0: <25% decline in GFR; Grade 1: >25% decrease in GFR, <2-fold rise in serum creatinine; Grade 2: >fold rise in creatinine, no HD; Grade 3: need for dialysis	Overall AKI = 28/96 = (29.2%) Severe AKI/RRT = 2/96 = (2.1%)	NA
Irazabal *et al.*[57]	2011	Rochester, USA, 1997–2009	Autologous stem cell transplant	Light chain amyloidosis	29	AKIN	Overall AKI = 28/29 = (96.5%) Severe AKI/RRT = 7/29 = 24.1%	100-day AKI mortality = 2/28 = (7.1%)
Helal *et al.*[45]	2011	France	Hematopoietic stem cell transplant	AML, ALL, CML, MM	101	Requiring RRT	AKI requiring RRT: 12/101 = (11.8%)	N/A
Morito *et al.*[47]	2011	Japan	Allogeneic HCT	Hematological malignancy	40	RIFLE	Overall AKI = 28/40 (70%) Severe AKI = 4/40 = 10%	100-day AKI mortality 4/28 = (14%)
Bao *et al.*[46]	2011	China, 2003–2008	Allogeneic hematopoietic stem cell transplant	CML, ALL, MDS, MM	143	RIFLE	Overall AKI = 70/143 (48.9%) Severe AKI = 12 /143 (8.4%)	100-day AKI mortality = OR: 6.984, 95% CI: 1.227–39.762 $P = 0.029$
Kagoya *et al.*[58]	2011	Tokyo	Autologous and allogeneic	Hematological malignancy	207	RIFLE	Overall AKI = 158/207 = (76.3%) Severe AKI = 92/207 = 44.4%	3-year AKI mortality, 24/158 (16.6%)
Durate *et al.*[59]	2012	Brazil, 2008–2011	Autologous BMT	Hodgkin lymphoma,	70	AKIN	Overall AKI = 7/20 = (35%) Severe AKI = 4/20 = (20%)	N/A

(continued)

Table 1. (continued)

Study	Year	Country	Patients	Indication for HCT	Number	AKI definition	AKI incidence	Mortality
				Non-Hodgkin's lymphoma, Multiple myeloma				
Mori *et al.*[48]	2012	Japan, 2004–2009	Allogeneic hemato-poietic stem cell transplant	ALL, CML, ATL, MDS, MM	289	AKIN	Overall AKI = 180/289 = (62.2%) Severe AKI = 46/289 (15.9%)	100 days AKI mortality = 82/180 = (45%) Non-AKI mortality = 28/109 (25%)
Canet *et al.*[60]	2014	Paris, France, 2007–2011	Allo—HCT	ALL, AML and lymphoma	75	KDIGO	Overall AKI = 49/75 = (65%) Severe AKI = 25/75 = (33%)	N/A
Chapchap *et al.*[61]	2016	Brazil, 2007–2014	Allogeneic HCT	Hematological malignancy	111	Requiring RRT	RRT = 20/111 = (18.3%)	N/A
Esposito *et al.*[62]	2016	Pavia, Italy, 2013–2015	Allogeneic HCT	Hematological malignancy	57	Grade 1: creatinine ≥ 2 times from the baseline; Grade 2: creatinine ≥3 times from the baseline; Grade 3: creatinine ≥ 4 times from the baseline.	Overall AKI = 18/57 = (31.6%) Severe AKI = 1/57 = (1.8%)	N/A
Liu *et al.*[26]	2017	China, May 2013–June 2014	Haplo stem cell transplantation AL, ALL, MDS	Leukemia (20%), lymphoma (36%), MM (28%)	353	Grade 0–3 Grade 1: <1.5-fold rise in baseline creatinine; Grade 2: ≥2-fold rise; Grade 3: ≥3-fold rise.	Overall AKI = 152/353 = 43% Severe AKI = 23/353 = 6.5%	N/A
Myhre *et al.*[63]	2017	Norway, 2004–2016	Non-myeloablative allogeneic	Lymphoma	108	RIFLE	Overall AKI = 75/108 = (69.4%)	N/A
Pinana *et al.*[52]	2017	Spain, 2008–2015	Allo- HCT	AML MDS	186	KDIGO	Overall AKI = 81/186 = 44% Severe AKI = 31/186 = 16.6%	Grade 2 KDIGO = HR 2.8; $P = 0.05$, Grade 3 KDIGO (HR 6.6; $P < 0.001$).
Sehgal *et al.*[49]	2017	India, 2008–2014	Hematopoietic stem cell transplant	MM, leukemia, lymphoma, aplastic anemia	65	RIFLE	Overall AKI = 49/65 = (75.4%) Severe AKI/needing dialysis = 4/65 (6.1%).	Three-month AKI mortality = 14/49 (28.5%) Non-AKI mortality 6/17 = (35%)
Deger *et al.*[50]	2017	Turkey, 2009–2011	Allogeneic HCT	Hematological malignancies	50	AKIN	Overall AKI = 19/50 (38%) Severe AKI = 2/50 (4%)	NA
Cekdemi *et al.*[64]	2018	Turkey, 2010–2017	Autologous and allogeneic	Hematological malignancy	155	AKIN	Overall AKI = 78/155 = (50.3%)	N/A
Khalil *et al.*[51]	2019	Jordan, 2002–2016	Hematopoietic stem cell transplant	CML, MM, ALL, AML, HL, NHL	60	RIFLE	Overall AKI = 19/60 = (31.6%) Severe AKI = 2/60 = (3.3%)	90-day AKI mortality = 8/19 = (42%) Non-AKI mortality = 7/41 = (17%)
Pereira *et al.*[65]	2018	Brazil, 2010–2014	Hematopoietic stem cell transplant	Multiple myeloma	132	Rise in serum creatinine >0.3 mg/dl	Overall AKI = 21/132 = (16%)	N/A
Andronesi *et al.*[15]	2019	Romania, 2016–2017	Autologous stem cell transplant	Multiple myeloma	185	KDIGO	One-month post-TX Overall AKI: 19/ 185 (10.3%) Severe AKI = 1/185 = (0.5%)	90-day mortality after AKI 1/19 = (5.2%) 90-day mortality in patients with no AKI 1/166 = (0.6%)
Mima *et al.*[16]	2019	Japan, 2006–2016	Hematopoietic stem cell transplant	AML, ALL, CML, MM, AA	108	KDIGO	Overall AKI (17/108 = 15.7%) Severe AKI = 4/108 = (3.7%)	N/A

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AKIN, acute kidney injury network; KDIGO, Kidney Disease Improving Global Outcomes; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; BMT, bone marrow transplant; HCT, hematopoietic stem cell transplantation; RRT, renal replacement therapy; GFR, glomerular filtration rate; HD, hemodialysis; CML, chronic myelogenous leukemia; CLL, chronic lymphocytic leukemia; AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; ATL, adult T-cell leukemia/lymphoma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; TX, transplant; NA, not applicable; USA, United States of America.

Table 2. Risk factors linked to incidence of AKI after HCT.

Risk factors linked to incidence of AKI after HCT
1. Diabetes mellitus[67]
2. Hypertension[44]
3. Chronic kidney disease[68]
4. Nephrotoxic agents
a. Amphotericin B[10]
b. Acyclovir[69]
c. Amino glycosides[70]
5. CaIcineurin inhibitor use for GVH prophylaxis[71]
6. Intravenous immunoglobulin[28]
7. Sepsis[18,28]
8. Intensive care unit stay[44]
9. Mechanical ventilation[41]
10. Preexisting lung toxicity[43]
11. HLA mismatch[18]
12. Female sex[44]
13. Weight gain >10%[18]
14. Cytomegalovirus infection[28]

Discussion

In this systematic review and meta-analysis, we found that the incidence of overall AKI and severe AKI requiring RRT after HCT is very high. Overall, the pooled estimated incidence of AKI and severe AKI among patients undergoing HCT are 55.1% and 8.3%, respectively. The pooled estimated incidence of AKI using standard AKI definition (KDIGO, RIFLE and AKIN) is 49.8%. Our findings showed significant increased short- and long-term mortality among patients with AKI after HCT. Meta-regression analyses showed that the year of the study did not significantly affect the incidence of AKI after HCT among included studies (published between years 1995 and 2019).

The etiology and mechanism of acute renal failure after HCT remain complex and multifactorial. Multiple risk factors are linked to the incidence of AKI after HCT. Major risk factors include diabetes,[67] hypertension,[44] preexisting chronic kidney disease,[68] nephrotoxic medications including amphotericin B,[10] acyclovir for viral prophylaxis,[69] aminoglycosides,[70] calcineurin

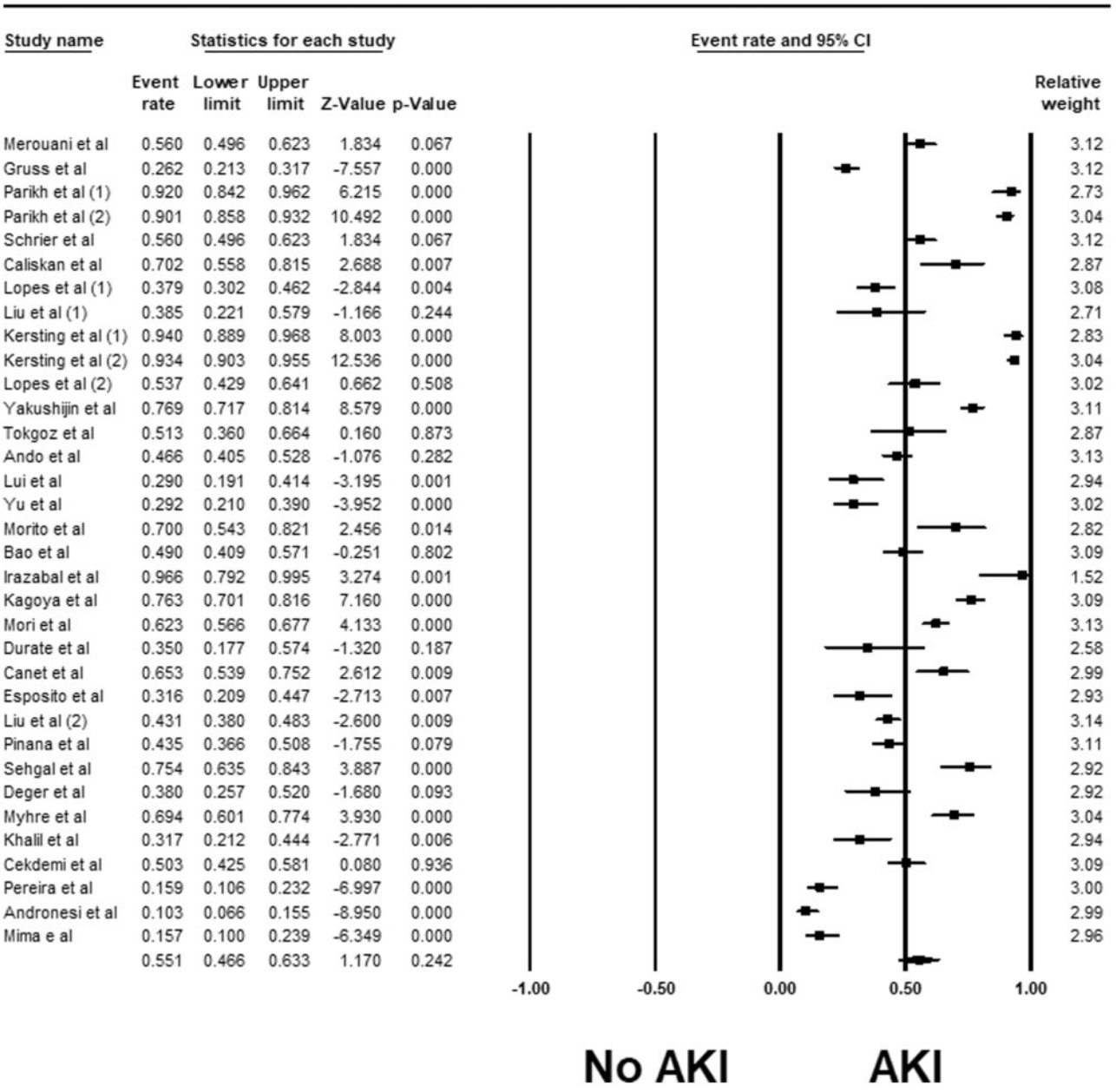

Figure 2. Forest plots of the included studies evaluating incidence rates of AKI among patients undergoing HCT.

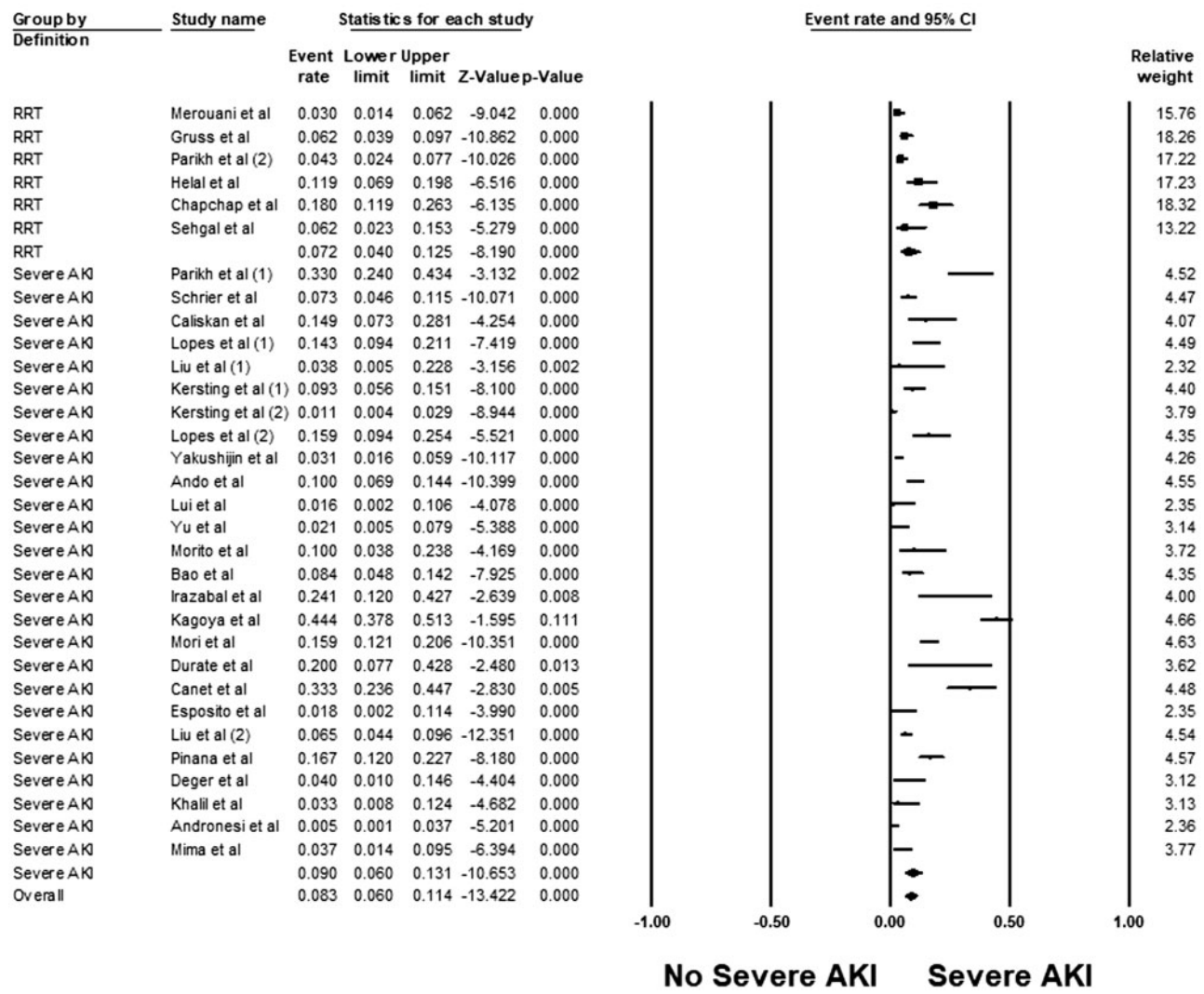

Figure 3. Forest plots of the included studies evaluating incidence rates of severe AKI among patients undergoing HCT.

inhibitors for prophylaxis of graft vs. host effect,[71] intravenous immune globulin,[28] underlying sepsis,[18] admission to intensive care unit,[44] use of mechanical ventilation,[41] preexisting lung toxicity,[43] incomplete human leukocyte antigen (HLA) matched transplant,[18] female sex, weight gain > 10% and cytomegalovirus infections (Table 2).[28]

In general, the etiology of AKI varies based on the different phases of HCT.[10,72–74] Tumor lysis syndrome and marrow intoxication syndrome manifest between 0–5 days of the preconditioning phase. Tumor lysis syndrome is rare in patients following HCT, as most are in the remission phase.[75–77] The incidence of tumor lysis is <1 in 400 patients.[5] Marrow intoxication syndrome is specifically seen in patients after HCT. Dimethyl sulfoxide (DMSO) is used as a freezing solvent to store stem cells and could contribute to RBC and granulocyte lysis.[76] With modified stem cell storing options and limiting the amount of DMSO, the incidence of marrow intoxication syndrome has reduced.[78]

In the early phase between 1 and 4 weeks, the etiology of AKI is attributed to chemo-induced volume loss, pre-renal AKI,[79], ischemic acute tubular necrosis (ATN), septic ATN,[80,81] engraftment syndrome,[82] hepatic veno-occlusive disease,[83–87] use of nephrotoxic medications including[69] aminoglycosides,[70,88] amphotericin[10] and acyclovir.[5,89] Acute graft vs. host disease (GVHD) can be seen first 100 days post-HCT. Acute GVHD post-HCT is associated with significant renal dysfunction and rejection episodes post-transplant.[6] Viral infections, including adenovirus and BK virus leading to AKI post-HCT, are worth mentioning. Calcineurin inhibitors play a significant role in causing renal vasoconstriction, tubular toxicity contributing to AKI post-HCT.[28,71] Transplant thrombotic microangiopathy, chronic calcineurin inhibitor nephrotoxicity and chronic GVHD are being noticed after 6–12 months post-transplant and could lead to chronic kidney disease.[1,19,78,79,90–94]

Our meta-analysis included some limitations. This systematic review was based on cohort studies. Thus, it is not identifying any causal relationship between AKI and death rate, but it reports associations. The missing data from the included studies related to the novel AKI biomarkers may be another limitation. Due to the presence of statistical heterogeneities among the studies, subgroup analyses were performed using standardized definitions of AKI (RIFLE, AKIN and KDIGO) to mitigate the risk of bias.

As demonstrated in our meta-analysis, AKI post-HCT is associated with increased risk of mortality especially if RRT is

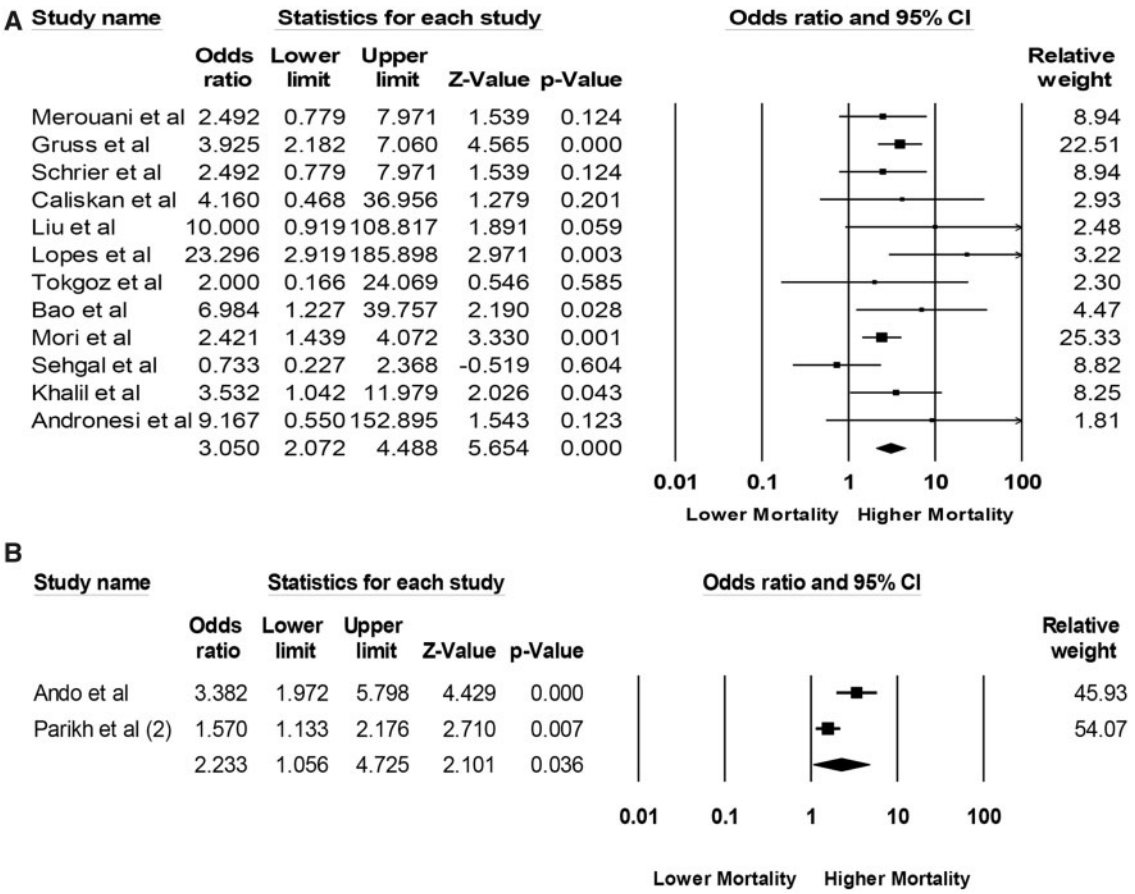

Figure 4. Forest plots of the included studies evaluating (**A**) mortality risk of AKI within 3 months and (**B**) mortality risk of AKI within 3 years after HCT.

needed. Despite medical advances, the overall incidence has not decreased since 1995. Our effort is to increase awareness about the continued high incidence of AKI in hopes that identifying at risk patients and implementing naive preventive measures through continued research might mitigate some AKI-associated poor outcomes.

Supplementary material

Supplementary material is available at *QJMED* online.

Conflict of interest: None declared.

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