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Original Article

Hospital readmissions after acute kidney injury: a systematic review and meta-analysis

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Abstract: Background and aims: Acute kidney injury (AKI) is a great burden not only during hospitalization but also after hospital discharge. The objective of this meta-analysis was to evaluate the hospital readmission rates and the mortality after survival of AKI. Methods: Pubmed, Web of Science, Cochrane Library, OVID and EMBASE databases through November 2015 were searched to identify studies reporting hospital readmission rates after AKI. The primary outcome were hospital readmission rates during 30-day, 60-day, 90-day and 1-year after discharge. And the mortality rates within 30-day and 1-year were also identified. Results: Eleven studies were eligible for inclusion. The pooled 30-day hospital readmission rates were 21.0% (95% confidence interval [CI], 16.3%-26.8%) in AKI group and 10.9% (95% CI, 9.7%-12.1%) in Non-AKI group, while the pooled 1-year rates were 48.0% (95% CI, 34.9%-61.3%) and 27.9% (95% CI, 16.3%-43.5%), respectively. The pooled unadjusted odds ratio (OR) for 30-day and 1-year hospital readmission in patients with AKI was 0.536 (95% CI, 0.443 to 0.649) and 0.453 (95% CI, 0.310 to 0.663), respectively, compared to patients without AKI (P = 0.000). The pooled 30-day post-discharge mortality was 10.7% in AKI group and 2.3% in Non-AKI group (P = 0.001), respectively, while the pooled 1-year mortality was 33.2% in AKI group and 13.8% in Non-AKI group (P = 0.000). Conclusions: There is a higher risk of short and long-term hospital readmission and death in patients who have survived the initial onset of AKI compared to Non-AKI patients. These patients deserve more attention after hospital discharge.

Keywords: Acute kidney injury, hospital readmission, meta-analysis

Introduction

Acute kidney injury (AKI) is a great burden in critically ill patients around the world. Approximately 30% to 60% of critically ill patients have AKI [1, 2], while the incidence is about 21.6% in hospitalized adults [3]. In intensive care units (ICU), the mortality of AKI patients can increase to as high as 60% to 70% [4, 5]. The mortality of hospitalized patients with AKI is approximately 20% to 40%, and among them, the patients with greater AKI severity tend to have higher mortality [6, 7]. The increased mortality of AKI was observed not only during hospitalization but also after hospital discharge. It is proved that survivors of episodes of AKI are at risk for the development or worsening of CKD [8]. In addition to this, there is growing evidence of an increased risk of myocardial infarction and heart failure in patients surviving AKI, especially in AKI patients without renal recovery at hospital discharge [9-11].

For patients, hospitalization can be stressful and even more so when it results in subsequent readmissions to the hospital. Researchers have found wide variation in hospital readmission rates [12] and a number of studies show that hospitals can engage in several activities to lower their rate of readmissions [13]. In USA, Medicare has started implementing incentives to reduce hospital readmissions, such as the Hospital Readmission Reduction Program (HRRP). Hospital readmissions contribute significantly to the cost of inpatient care and are targeted as a marker for quality of care [14].

Table 1. Characteristics of studies included in the meta-analysis

Source (Year)	Country	Clinical settings	Primary diseases	No. of patients	Female (%)		Age (y)		Definition of AKI
					Non-AKI	AKI	Non-AKI	AKI	
Wattad (2015) [19]	Israel	Cardiology	AHF	762	51	47	77	78	≥0.3 mg/dl increase in Scr above baseline
Koulouridis (2015) [20]	USA	Whole hospital	All-cause	22001	54	50	63	70	KDIGO
Horkan (2015) [15]	USA	ICU	All-cause	62096	40	43	57	57	RIFLE
Brown (2014) [25]	USA	Cardiac surgery	Cardiac surgery	2183	NR	NR	NR	NR	AKIN
Roy (2013) [27]	Ireland	HF service	AHF	637	18	45	65	64	KDIGO
Thakar (2012) [28]	USA	Internal Medicine	AHF	5635	NR	NR	NR	NR	≥0.3 mg/dl increase in Scr above baseline
Shirakabe (2012) [29]	Japan	ICU	AHF	500	15	40	69	72	RIFLE
Metra (2012) [30]	Italy	Cardiology	AHF	594	31	20	68	70	≥0.3 mg/dl increase in Scr above baseline
Eren (2012) [31]	Turkey	CCU	ACS	289	25	46	61	72	AKIN
Belziti (2010) [32]	Argentina	Coronary unit	AHF	200	40	52	71	81	≥0.3 mg/dl or 25% increase in Scr above baseline
Goldberg (2009) [23]	Israel	Cardiology	AMI	1957	20	26	59	67	AKIN

AKI = acute kidney injury, Scr = serum creatinine, AHF = acute heart failure, ACS = acute coronary syndrome, AMI = acute myocardial infarction, RIFLE = the risk, injury, failure, loss of kidney function and end stage criteria, AKIN = acute kidney injury network criteria, KDIGO = kidney disease: improving global outcomes classification systems, USA = United States of America, ICU = intensive care unit, CCU = coronary care unit, NR = not reported.

Recently, a study [15] included 62,096 adult survivors of critical illness and examined 30-day hospital readmission rate as the main outcome. Patients without AKI had a 30-day readmission risk of 12%, whereas patients with AKI had an admission risk of 19-21% depending on severity of AKI. But this was not the first study examining the association between AKI and readmission rate in survivors of AKI and this topic has not been systematically reviewed. So we conducted a meta-analysis to estimate the pooled hospital readmission rates and long-term mortality rates after discharge of AKI during various follow-up periods. By doing so, we hope to raise awareness of hospital readmissions after AKI and provide considerable healthcare resources after hospital discharge.

Methods

Search strategy and data sources

We performed a computerized search to identify relevant published original studies (1985 to november 2015). Pubmed, Web of Science, Cochrane Library, OVID and EMBASE databases were searched using medical subject headings (MeSH) or keywords. These search keywords were "acute kidney failure, acute kidney injury, acute kidney dysfunction, acute kidney insufficiency, acute tubular necrosis, acute renal failure, acute renal injury, acute renal dysfunction, acute renal insufficiency" and "re*hospital*, re*admission*". This search was not limited to English language or publication type. **Table 1** shows the number of studies found.

Selection criteria

An initial eligibility screening of all retrieved titles and abstracts was conducted, and only studies reporting AKI were selected for further review. The following inclusion criteria were used for final selection: (1) studies reporting the hospital readmissions after AKI, (2) studies providing detailed information about the re-hospitalization rates and (or) long-term mortality rates during follow-up periods (30-day, 60-day, 90-day, and 1-year), (3) studies showing clear definitions of AKI. We restricted our search to clinical studies performed in adult populations. Studies without clear re-hospitalization rates or experimental studies were excluded.

Data extraction and quality assessment

Two reviewers (Z.T. and H.J.C.) independently examined the studies, and disagreement was resolved by discussion. Data extraction included country of origin, year of publication, clinical settings, primary diseases, sample size, patient characteristics (age and sex), and definitions of AKI. The primary outcome were hospital readmission rates during 30-day, 60-day, 90-day and 1-year after discharge. The mortality rates within 30-day and 1-year were also identified. The study selection, data extraction, and reporting of results were all based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses checklist [16]. The quality of the cohort studies was assessed independently by pairs of two authors, using the

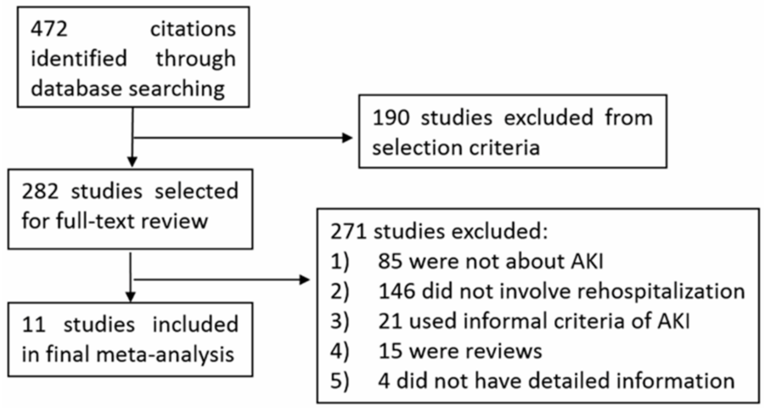


Figure 1. Flow Chart of Literature Search and Study Selection.

Newcastle-Ottawa scale (NOS) [17], which allocates a maximum of 9 points for quality of the selection, comparability, and outcome of study populations. Study quality scores were defined as poor (0-3), fair (4-6), or good (7-9).

Data synthesis and statistical analysis

Comprehensive Meta-Analysis (version 2.0; Biostat) was used to perform the meta-analysis. Heterogeneity across trials was evaluated using the I^2 index and the Q-test *p*-value. A *p*-value of less than 0.05 and an I^2 index of more than 25% indicated the presence of inter-study heterogeneity [18]. Random-effects model meta-analysis was conducted to generate pooled rates of hospital readmission and mortality rates after AKI and to compute pooled odds ratios (ORs) in patients with AKI compared to those without AKI. All pooled estimates are provided with 95% confidence intervals (CI). We also conducted subgroup meta-analysis of 30-day re-hospitalization rates by different primary diseases, and compared effects at different levels of subgroup within studies. Publication bias was assessed by constructing a funnel plot and Egger's regression test.

Results

Study selection

The article selection process is outlined in **Figure 1**. The electronic database searches identified 472 citations. After removal of duplicates, 282 articles were selected for full-text review for their relevance to this study and eleven were included in this systematic review. At the full-text review stage, 85 articles were not about AKI, 146 did not involve re-hospitalization and 21 used informal criteria of AKI. Fifteen reviews were also excluded. Four studies were excluded from the primary meta-analysis as they did not report the number of patients rehospitalizing during the follow-up periods, and the corresponding authors were unable to provide the requisite data. Agreement between investigators at the full-text review stage was excellent as indicated by a κ of 0.8.

Study description and quality assessment

A detailed description of the included studies is provided in **Table 1**. Most of the included studies were retrospective except of two studies [15, 19]. Four studies (n = 4) occurred in the United States of America, and the others scattered across the continents around the world. The patients were mostly admitted to the department of cardiology and acute heart failure was mostly discussed primary disease. Only one study [15] came from general ICU and observed all-cause AKI, while another study [20] discussing all-cause AKI was from the whole hospital. The total number of patients included in the primary meta-analysis was 96,854 with a median (interquartile range) of 762 (500-5,635) patients per study. The detailed information of age and gender was also listed in **Table 1**. The risk, injury, failure, loss of kidney function and end stage (RIFLE) criteria, acute kidney injury network (AKIN) criteria, and kidney disease: improving global outcomes classification systems (KDIGO) were mostly applied to define AKI, while four studies used the definition of more than 0.3 mg/dl or 25% increase in Scr above baseline, which is similar to the former criteria. Overall study quality was good with a mean NOS score of 8.2 out of a possible 9 (range, 6-9) and with 9 studies (82%) receiving a NOS greater than or equal to 7 (**Table 2**).

Hospital readmission rates after AKI

Six studies reported 30-day and 1-year post-discharge hospital readmission, while only two and three reported 60-day and 90-day re-hospitalization, respectively. The pooled 30-day

Table 2. Quality of the studies utilizing the Newcastle-Ottawa quality assessment scale (Cohort studies)

Reference (Year)	Selection				Comparability	Outcome			Total score
	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow up long enough	Adequacy of follow up of cohorts	
Wattad (2015) [19]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Koulouridis (2015) [20]	☆	☆	☆	☆	☆☆	☆	–	☆	8
Horkan (2015) [15]	☆	☆	☆	☆	☆☆	☆	–	☆	8
Brown (2014) [25]	☆	☆	☆	☆	–	☆	–	☆	6
Roy (2013) [27]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Thakar (2012) [28]	☆	☆	☆	☆	–	☆	–	☆	6
Shirakabe (2012) [29]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Metra (2012) [30]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Eren (2012) [31]	☆	☆	☆	☆	☆☆	☆	–	☆	8
Belziti (2010) [32]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Goldberg (2009) [23]	☆	☆	☆	☆	☆☆	☆	☆	☆	9

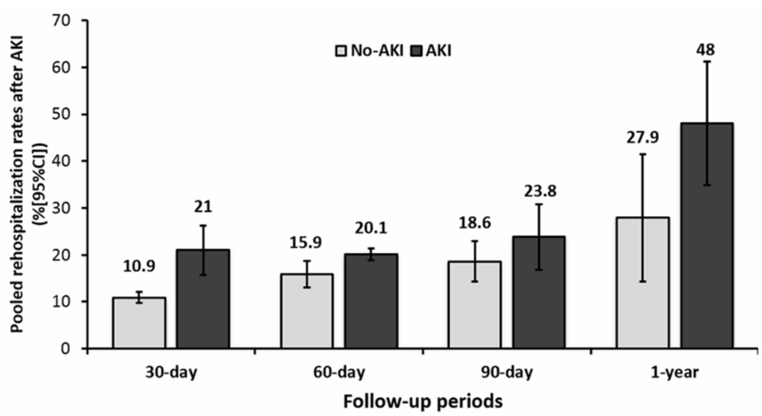


Figure 2. The pooled hospital readmission rates after acute kidney injury.

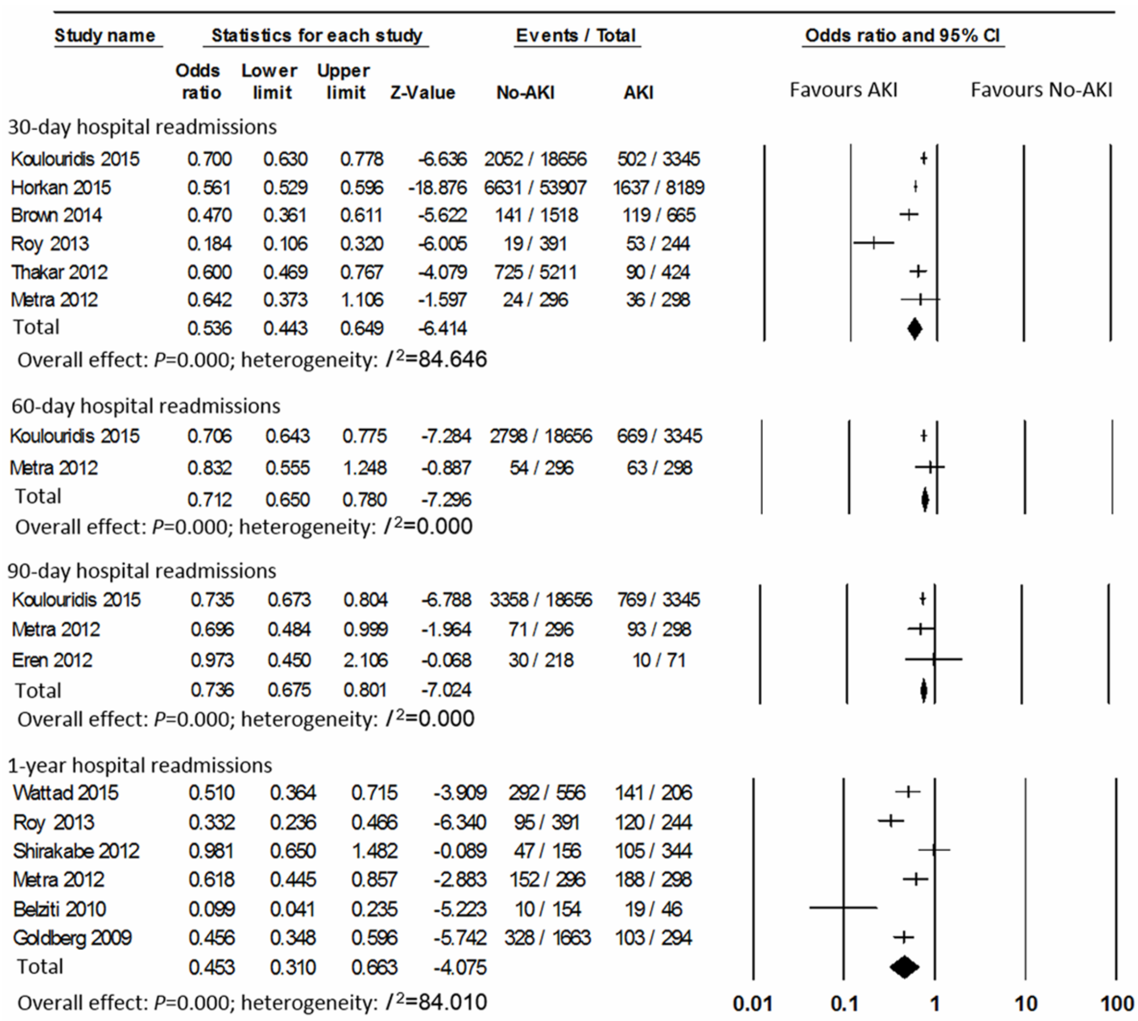
hospital readmission rate was 21.0% (95% CI, 16.3%-26.8%) in AKI group and 10.9% (95% CI, 9.7%-12.1%) in Non-AKI group, while the pooled 1-year rate was 48.0% (95% CI, 34.9%-61.3%) and 27.9% (95% CI, 16.3%-43.5%), respectively (**Figure 2**). The pooled unadjusted odds ratio (OR) for 30-day and 1-year hospital readmission in patients with AKI was 0.536 (95% CI, 0.443 to 0.649) and 0.453 (95% CI, 0.310 to 0.663), respectively, compared to patients without AKI (p = 0.000). The pooled 60-day and 90-day hospital readmission rates of the two groups and unadjusted OR for 60-day and 90-day hospital readmission in AKI group compared to Non-AKI group were also shown in **Figures 2** and **3**.

30-day and 1-year mortality after discharge of AKI

There were three and six studies reporting 30-day and 1-year mortality after discharge of AKI, respectively. The pooled 30-day post-discharge mortality was 10.7% (95% CI, 2.4%-36.9%) in AKI group and 2.3% (95% CI, 1.4%-3.8%) in Non-AKI group, while the pooled 1-year mortality were 33.2% (95% CI, 22.1%-46.6%) and 13.8% (95% CI, 6.2%-18.1%) in AKI group and Non-AKI group, respectively (**Figure 4**). The pooled unadjusted OR for 30-day and 1-year hospital readmission in patients with AKI was 0.381 (95% CI, 0.215 to 0.676, P = 0.001) and 0.337 (95% CI, 0.202 to 0.560, P = 0.000), respectively, compared to patients without AKI respectively (**Figure 5**).

Subgroup analyses

The results of subgroup analyses of 30-day hospital readmissions were presented in **Figure 6**. There were two studies reporting 30-day hospital readmission rate after all-cause AKI, and three studies reporting 30-day hospital readmission rate after acute heart failure (AHF) induced AKI. The pooled 30-day hospital readmission rate after all-cause AKI was 17.4% (95% CI, 13.0%-22.8%) and 11.6% (95% CI, 10.4%-13.0%) in Non-AKI group, respectively, while the rate after AKI induced by AHF were 18.1% (95% CI, 12.8%-24.9%) and 8.5% (95% CI, 4.3%-15.9%), respectively. The pooled unadjusted OR for 30-day hospital readmission in patients with all-cause and AHF induced AKI was 0.624 (95% CI, 0.503 to 0.774, P = 0.000)



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	No-AKI	AKI
30-day hospital readmissions						
Koulouridis 2015	0.700	0.630	0.778	-6.636	2052 / 18656	502 / 3345
Horkan 2015	0.561	0.529	0.596	-18.876	6631 / 53907	1637 / 8189
Brown 2014	0.470	0.361	0.611	-5.622	141 / 1518	119 / 665
Roy 2013	0.184	0.106	0.320	-6.005	19 / 391	53 / 244
Thakar 2012	0.600	0.469	0.767	-4.079	725 / 5211	90 / 424
Metra 2012	0.642	0.373	1.106	-1.597	24 / 296	36 / 298
Total	0.536	0.443	0.649	-6.414		
Overall effect: P=0.000; heterogeneity: I^2=84.646						
60-day hospital readmissions						
Koulouridis 2015	0.706	0.643	0.775	-7.284	2798 / 18656	669 / 3345
Metra 2012	0.832	0.555	1.248	-0.887	54 / 296	63 / 298
Total	0.712	0.650	0.780	-7.296		
Overall effect: P=0.000; heterogeneity: I^2=0.000						
90-day hospital readmissions						
Koulouridis 2015	0.735	0.673	0.804	-6.788	3358 / 18656	769 / 3345
Metra 2012	0.696	0.484	0.999	-1.964	71 / 296	93 / 298
Eren 2012	0.973	0.450	2.106	-0.068	30 / 218	10 / 71
Total	0.736	0.675	0.801	-7.024		
Overall effect: P=0.000; heterogeneity: I^2=0.000						
1-year hospital readmissions						
Wattad 2015	0.510	0.364	0.715	-3.909	292 / 556	141 / 206
Roy 2013	0.332	0.236	0.466	-6.340	95 / 391	120 / 244
Shirakabe 2012	0.981	0.650	1.482	-0.089	47 / 156	105 / 344
Metra 2012	0.618	0.445	0.857	-2.883	152 / 296	188 / 298
Belziti 2010	0.099	0.041	0.235	-5.223	10 / 154	19 / 46
Goldberg 2009	0.456	0.348	0.596	-5.742	328 / 1663	103 / 294
Total	0.453	0.310	0.663	-4.075		
Overall effect: P=0.000; heterogeneity: I^2=84.010						

Figure 3. Odds ratios of hospital readmissions after acute kidney injury. Closed diamonds indicate pooled result for all studies. Vertical lines indicate odds ratio for each study. Horizontal lines indicate CI.

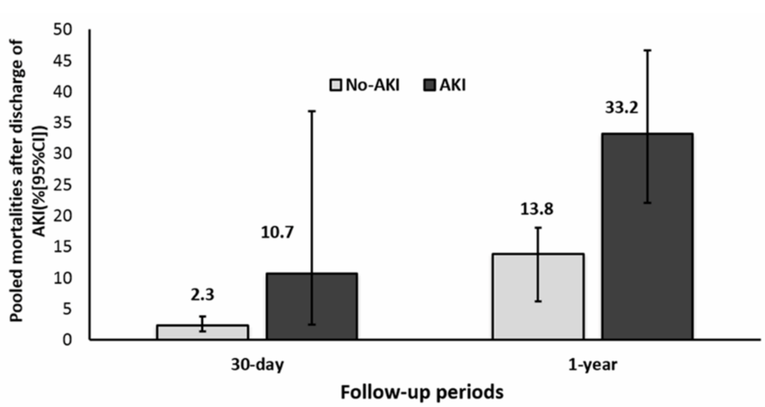


Figure 4. The pooled mortality rates after discharge of acute kidney injury.

and 0.423 (95% CI, 0.209 to 0.857, P = 0.000), respectively, compared to patients without AKI (**Figure 6**).

Publication bias

The funnel plots for **Figure 7A** and **7B** showed no evidence of publication bias. Egger's test for a regression intercept gave a *p*-value of 0.530 and 0.431 for 30-day and 1-year re-hospitalization rates after AKI, respectively, indicating no publication bias.

Discussion

In this study, we conducted a meta-analysis including 11 studies and 96,854 patients to assess the burden and significance of AKI and its impact on the hospital readmission rates and the mortal-

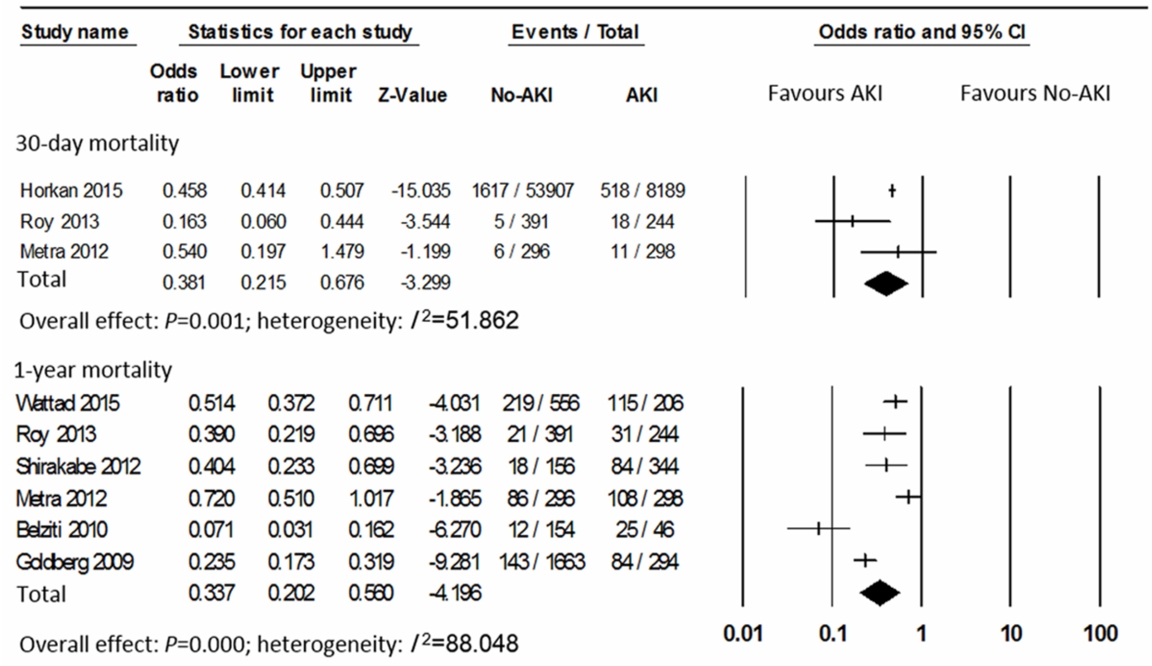


Figure 5. Odds ratios of death after discharge of acute kidney injury. Closed diamonds indicate pooled result for all studies. Vertical lines indicate odds ratio for each study. Horizontal lines indicate CI.

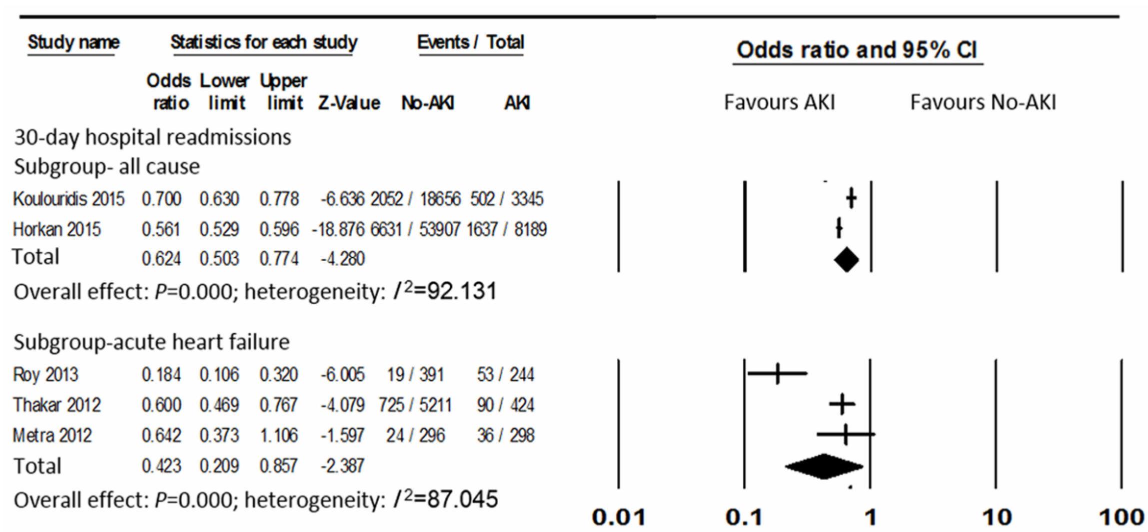


Figure 6. Subgroup analyses of 30-day hospital readmissions after acute kidney injury.

ity after hospital discharge. Overall, we concluded that AKI is associated with higher rehospitalization rates and post-discharge mortality. To our knowledge, this is the first meta-analysis to examine the risk of readmission or death following hospital discharge of AKI.

Patients who suffer AKI are at higher risk of early hospital readmissions, according to our meta-analysis. The 30-day time frame for hospital readmission, which is commonly used in outcomes research [15], has been demonstrated to be the statistically optimal choice for identifying readmission rates [21]. We found that the 30-day hospital readmission rates were 21.0% in AKI group and 10.9% in Non-AKI group (OR = 0.536, P = 0.000). In a cohort study of all hospitalized patients, AKI was asso-

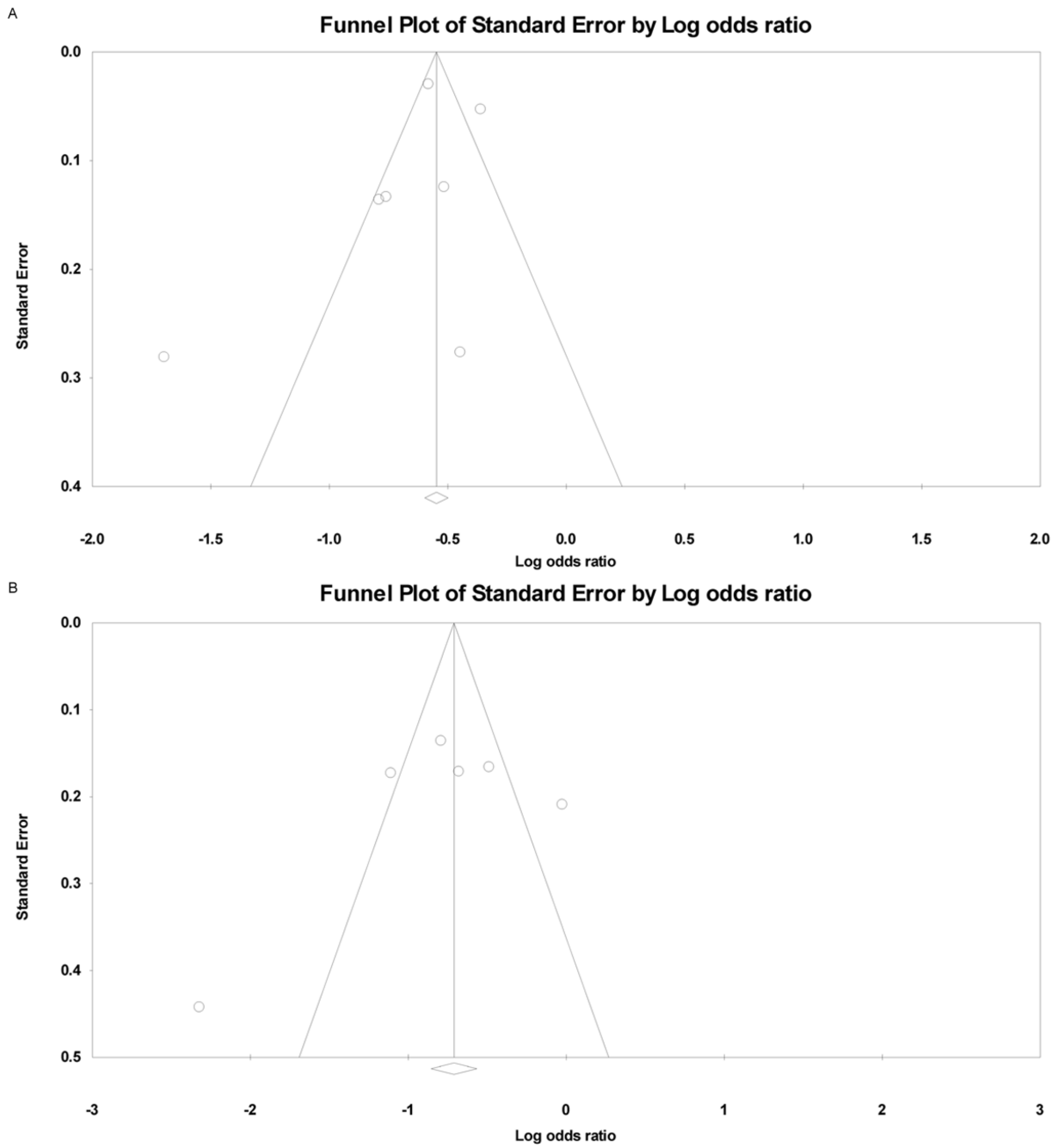


Figure 7. Funnel plots to evaluate for publication bias for 30-day (A) and 1-year (B) re-hospitalization rates after acute kidney injury.

ciated with a 16.2% readmission rate within 30 days after discharge compared with 8.7% in patients without AKI [22]. Another cohort study [15] of ICU patients demonstrated that the absolute risk of 30-day readmission was 12.3%, 19.0%, 21.2%, and 21.1% in patients with No AKI, Risk, Injury, Failure stages of RIFLE criteria respectively. In addition, we also found that patients with AKI are at higher risk of late hospital readmissions after discharge. The pooled 1-year hospital readmission rate was 48.0% in AKI group and 27.9% in Non-AKI group (OR = 0.453, P = 0.000), respectively. All these data indicate that patients survived from AKI will have higher risk of re-hospitalization compared to patients without AKI.

Hospital readmission rates after acute kidney injury might vary depending on the degree of recovery of renal function. There was only one study [23] reporting the AKI subgroups in accordance with the transient and persistent AKI classification during hospitalization. In each of the AKI subgroups, the patients experienced transient AKI had better outcomes than the patients with persistent AKI in terms of the long-term mortality and readmission after 5-year discharge. However, the adjusted hazard ratios of mortality and readmission rate due to heart failure and recurrent myocardial infarction in patients with transient mild AKI was similar to that of patients without AKI. Therefore, early detection of AKI and timely recovering of the patient's kidney function in the mild AKI might reduce long-term mortality and readmission rate.

Hospital readmission rates might vary depending on the primary diseases. But our subgroup meta-analysis found that the 30-day hospital readmission rate after AHF-induced AKI was similar to all-cause AKI (18.1% vs 17.4%). On the other hand, approximately 20% to 30% of patients admitted for AHF had worsening renal function (WRF), which further worsened the prognosis [24]. Besides AHF, patients with AKI after cardiac surgery were also at increased risk of 30-day readmission (16-29% depending on the severity of AKI vs 9% in non-AKI patients) [25]. Due to the limitation of the studies, we could not compare hospital readmission rates among more cause-specific AKI.

In addition, AKI is not only associated with higher in-hospital mortality, but also with increased long-term mortality. In a study in population of patients who survived at least 90 days after discharge, 17.4% died during follow-up with 29.8% being the patients with AKI and 16.1% being the patients without AKI. The adjusted mortality risk associated with AKI was 1.41 (95% CI 1.39 to 1.43) and increased with the increased AKI stage [26]. We found that the pooled 30-day post-discharge mortality was 10.7% in AKI group and 2.3% in Non-AKI group, while the pooled 1-year mortality were 33.2% and 13.8%, respectively.

Study limitations

The present study may have limitations. Although AKI is common in ICU, we only found one study discussing re-hospitalization after all-cause AKI in general ICU. Another study also observed all-cause AKI, but was from the whole hospital. Most of the included studies focused on cause-specific AKI, but mainly induced by cardiac diseases, such as acute heart failure or acute coronary syndrome. Although septic AKI accounts for nearly 50% of all cases of acute kidney injury in ICU and contrast medium-induced AKI has become the third most common cause for hospital-acquired AKI, there were limited studies evaluating the hospital readmission rates in these situations. The subgroup study concerning the recovery of renal function or the effect on re-hospitalization of AKI should be further strengthen. Further study on whether the degree of the recovery of the renal function at the time of hospital discharge has any effect on re-hospitalization of AKI is warranted.

In conclusion, results of our systematic review suggest that there is high risk of early and long term hospital readmission and death after survival of AKI. These patients deserve more attention after hospital discharge. Further large-scale, multicenter studies about various cause-specific AKI with careful matching and enough follow-up periods are needed for more convincing analysis.

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Disclosure of conflict of interest

None.

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