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Title Page

Effect of nephrology follow-up on long-term outcomes in patients with acute kidney injury: a systematic review and meta-analysis

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Running title: Nephrology follow-up for acute kidney injury

Title Page

Effect of nephrology follow-up on long-term outcomes in patients with acute kidney injury: a systematic review and meta-analysis

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Running title: Nephrology follow-up for acute kidney injury

Abstract

Aim Acute kidney injury (AKI) is associated with poor short-term and long-term clinical outcomes. The role of nephrology follow-up in post-AKI management remains uncertain.

Methods A systematic review and meta-analysis was performed examining all randomized controlled trials and observational studies assessing the effect of nephrology follow-up on patients' clinical outcomes. The primary outcome was all-cause mortality. The secondary outcomes were renal outcomes, which were defined as a composite of requirement of permanent dialysis and recurrent AKI. Pooled analysis was performed using a random-effect model.

Results We identified six studies (8972 patients, mean follow-up of 49 months). Five were retrospective cohort studies and one a prospective cohort study. Risk of bias was a concern with all studied. Only four studies reported primary and/or secondary

outcomes and were included. Compared with patients without nephrology follow-up, patients with nephrology follow-up had significantly reduced mortality by 22% (3 studies, 3240 patients, RR, 0.78; 95% CI 0.70-0.88; I^2=0.0%). Nephrology follow-up did not improve composite renal outcomes with high heterogeneity due to significant differences in reported renal outcomes and follow-up period (2 studies, 2537 patients, RR, 1.72; 95% CI, 0.49-6.05; I^2=90.1%).

Conclusion Current evidence from observational studies is biased. It suggests long-term survival benefits with post-discharge nephrology follow-up in AKI patients. However, due to its low quality, such evidence is only hypothesis generating. Nonetheless, it provides a rationale for future randomized controlled trials of nephrology follow-up in AKI patients.

Key words: acute kidney injury, follow-up studies, meta-analysis, nephrology, systematic review

Introduction

Acute kidney injury (AKI) is a common health problem worldwide. Its incidence is increasing globally. It occurs in 10 to 20% of hospitalized adults,[1-10] and 30 to 60% of intensive care units (ICU) patients.[3,11-13] AKI, especially in its severe form, is associated with increased risk of mortality,[10,12,14-19] progression to chronic kidney disease (CKD) or end-stage renal disease (ESRD),[5,9,20-23] recurrent AKI,[6,9,24,25] cardiovascular morbidity and mortality,[4,26-28] reduced quality of life, and increased socio-economic burdens.

Given the detrimental effects of AKI on short-term and long -erm clinical outcomes, nephrological follow-up of patients after AKI would appear desirable. However, a single-centre study in Scotland[29] involving AKI patients with a serum creatinine (SCr) $\geq$ 300 μmol/L over12-months found that only 22.6% were referred to a nephrologist. Nephrology referral was associated with reduced mortality. Moreover, two other cohort studies[30,31] also reported reduced mortality in patients with AKI who received nephrology referral. These observations suggest that nephrology follow-up may attenuate the adverse long-term consequences of AKI. However, a systematic assessment of current knowledge in this field is lacking.

Accordingly, we conducted a systematic review to assess current evidence from observational studies and randomized control trials of the impact of nephrology follow-

up on all-cause mortality and renal outcomes for patients with AKI.

Materials and Methods

Data Sources and Searches

Relevant bibliographic databases were searched to August 2019, including MEDLINE via OvidSP (1946-present), EMBASE via OvidSP (1947-present), and the Cochrane Library. In addition, hand searches of the reference lists of eligible studies were completed, and unpublished studies were sought in references of all selected studies, relevant conference abstracts, and from the ClinicalTrials.gov website. There were no language and publication period restrictions. Relevant text words and Medical Subject Headings were included in the search strategy (Figure S1).

Study Outcomes

The primary outcome was all-cause mortality among AKI survivors who received nephrology follow-up, compared with those without nephrology follow-up at final study endpoints. Secondary outcomes were renal endpoints in nature and were defined as a composite of requirement of permanent dialysis and recurrent AKI. Requirement of permanent dialysis and recurrent AKI were also analyzed separately.

Study Selection

We included observational studies with a cohort, case-control or nested case-control design and, if available, data from randomized controlled trials (RCTs) assessing the impact of nephrology care on adult patients following an episode of AKI. Study selection was independently completed by two reviewers (NY and YX). Any disagreements on the eligibility of a study were resolved by discussions with the third reviewer (AYW).

Data Extraction and Quality Assessment

Data were extracted independently by two reviewers (NY and YX) using a standardized data extraction form. Data extracted from each study included the study design, characteristics of study participants, follow-up duration, primary and secondary outcomes, criteria used for diagnosis of AKI, and elements for assessment of quality of included studies. Severe AKI was defined according to the authors as maximum SCr > 500μmol/L or stage 3 according to the Acute Kidney Injury Network (AKIN) criteria.[32] Khan index was also used to assess the severity of a patient's disease. Patients who are older, have more than one comorbidity, and have more severe comorbidities are defined as a high risk.[33]

The Cochrane risk-of-bias tool was used to assess risk of bias for RCTs. The Newcastle-Ottawa scale (NOS)[34] and quality assessment tool from National Heart, Lung, and Blood Institute (NHLBI)[35] were used to assess the risk of bias for observational studies.

The publication bias was assessed using a funnel plot and Egger's Test. The assessment was done at both the study and outcome level. Two reviewers (NY and YX) independently assessed each included study for the risk of bias. Any persistent disagreements were resolved by consensus or discussion with a third reviewer (AYW).

Data Synthesis and Analysis

The following data were synthesized if applicable: (1) all-cause mortality; (2) renal outcomes (composite of requirement of permanent dialysis and recurrent AKI); (3) requirement of permanent dialysis; (4) recurrent AKI; (5) characteristics of nephrology follow-up. The pooled analysis was performed using a random-effect model. Relative risks (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous variables. Standard mean differences (SMDs) and 95% CIs were calculated for continuous variables. Meta-regression analysis was planned to assess the effect of age and gender on clinical outcomes between nephrology and non-nephrology follow-up groups according to the mean study age and study population proportion of males. Statistical heterogeneity was assessed using I^2 for pooled results. Subgroup analysis was performed according to the severity of AKI to determine whether high-risk patients would be affect differently by nephrology follow-up. Statistical analyses were performed using Stata, version 15.0 and Review Manager, version 5.3. $P < 0.05$ was considered statistically significant for all analyses.

Results

Study Selection and Characteristics

The search identified 6 studies including 8972 participants with a mean follow-up of 49 months. The flow chart of the study selection was in Figure 1. Of these studies, five were retrospective cohort studies and one a prospective cohort study. Their key characteristics were presented in Table 1. The mean age of the participants ranged from 60.7 to 74.5 years, and a half of the studies had a mean age over 70 years. Patients were mostly, making up from 54.1% to 97.4% of study patients.

All-cause Mortality

All-cause mortality was reported in three studies.[29-31] Compared with patients without nephrology follow-up, patients with nephrology follow-up had significantly reduced mortality by 22% (three studies, 3240 patients, RR, 0.78; 95% CI 0.70-0.88; I^2=0.0%) (Figure 2). There was low heterogeneity. Furthermore, meta-regression analysis showed nephrology follow-up was not affected by age (coefficient 0.980, P = 0.751) and gender (coefficient 1.075, P = 0.597).

Renal Outcomes

Renal outcomes were reported in two studies. One study reported both requirement for

permanent dialysis and recurrent AKI,[36] while the other only reported the requirement for permanent dialysis.[31] Overall, nephrology follow-up did not improve composite renal outcomes. However, there was high heterogeneity due to significant differences in reported renal outcomes and study follow-up period (two studies, 2537 patients, RR, 1.72; 95% CI, 0.49-6.05; I^2=90.1%). Further analysis assessing individual renal outcomes showed that nephrology follow-up was associated with more frequent permanent dialysis requirements (two studies, 2537 patients, RR, 2.68; 95% CI, 1.82-3.96; I^2=0.0%). A trend towards a decreased incidence of recurrent AKI was seen with nephrology follow-up (169 patients, RR, 0.57; 95% CI, 0.33-1.01), but this outcome was only reported in one study (Figure 3).

Associations of baseline characteristics with nephrology referral/follow-up

In order to clarify which group of patients were more likely to be followed-up by nephrologists or referred to a nephrology service, additional analyses were conducted. They demonstrated that patients were more likely to be followed-up by nephrologists if they were younger (2 studies, 872 patients, OR, 0.28; 95% CI, 0.17-0.46; I^2=53.5%), had severe AKI (3 studies, 2614 patients, OR, 2.59; 95% CI, 1.55-4.35; I^2=56.5%), had previous CKD (3 studies, 6181 patients, OR, 2.02; 95% CI, 1.22-3.33; I^2=88.6%), or hypertension (3 studies, 6181 patients, OR, 1.21; 95% CI, 1.06-1.37; I^2=0.0%), had less severe conditions according to the Khan index (2 studies, 872 patients, OR, 0.32; 95%

CI, 0.23-0.44; I^2=0.0%), and were treated in hospitals equipped with a nephrology service (2 studies, 687 patients, OR, 2.42; 95% CI, 1.39-4.20; I^2=0.0%) (Figure 4).

An association between baseline renal function assessed as an estimated glomerular filtration rate (eGFR) and nephrology follow-up was also investigated.[18,36] Patients with lower eGFR were more likely to receive nephrology follow-up (two studies, 1911 patients, SMD, -0.18; 95% CI, -0.38,0.02; I^2=35.5%) (Figure S2). This result was consistent with the impact of previous CKD on nephrology referral.

Study Quality

The quality of the studies is summarized in Figure 5 and Figure S3. None of the studies were RCTs. Only 2 studies used AKIN or RIFLE criteria for AKI diagnosis.[18,30] Two out of six studies were single-centre studies.[29,36] Most had relatively small sample sizes.[29] None of the studies had blinded outcome assessment. All but one study[30] completed longer than one year follow up. Overall, most studies had a moderate or high risk of bias. The funnel plots for publication bias were shown in Figure S4 and Figure S5. No significant publication bias was seen for all-cause mortality (P = 0.143) and renal outcomes (P = 0.989).

Discussion

In a systematic review assessing the effect of nephrology follow-up on long-term

clinical outcomes in patients with AKI, we found a significant survival benefit associated with nephrology follow-up with a reduction in all-cause mortality of 22% but no significant effect on renal outcomes. Moreover, we found that patients were more likely to be followed-up by nephrologists if they were younger, had severe AKI, had previous CKD and hypertension, had less severe comorbidities, and were treated in hospitals equipped with a nephrology service. Finally, we found that the studies identified by our systematic search were few, of low quality, with no randomization and with substantial risk of bias.

In 2013, the International Society of Nephrology (ISN) launched a global initiative of 0 by 25 - zero death of patients with untreated AKI by 2025, with the purpose to increasing AKI awareness and improving outcomes.[37] Nephrology follow-up is considered as a potential strategy to improve short-term and long-term outcomes, because nephrologists appear more likely to recognize and manage CKD complications according to evidence-based guidelines than primary care providers.[9] Thus, the Kidney Disease: Improving Global Outcomes (KDIGO) recommends evaluating patients 3 months after AKI for resolution, new onset, or worsening of preexisting CKD.[1] However, the majority of patients after AKI, even those with the most severe forms, do not appear to receive follow up nephrology care after hospital discharge. For example, according to data from the United States Renal Data System (USRDS),[38] in 2015, 16%

of Medicare patients discharged alive from an AKI hospitalization had outpatient nephrology follow-up within the next six months.

Furthermore, the generalizability of nephrology follow-up may also be dependent on the healthcare setting. An AKI follow up clinic was implemented in Canada. For example, Silver et al[39] assessed the effect of establishment of an AKI Follow-Up Clinic in Canada on the proportion of AKI patients referral to nephrology service. They found that an AKI Follow-Up Clinic with an automatic referral process increased the 90-day follow-up rate. The majority of AKI survivors who saw a nephrologist post discharge received changes to their care plans. To our knowledge, the Prince of Wales Hospital in Australia also runs an AKI follow-up clinic aiming to improve the management of AKI post-discharge and the detection of non-renal recovery leading to development of chronic kidney disease or other AKI complications by providing advice and education to the General Practitioners. Whether or not nephrology follow-up is superior to a care bundle implemented by primary care providers needs to be further assessed by randomized controlled trials.

Our study found strong associations between baseline characteristics and nephrology follow up. In particular, patients with advanced CKD were more likely to be referred to a nephrology service, and had more opportunities of receiving dialysis therapy subsequently. Previous studies have identified risk factors for non-recovery of renal

function or CKD progression after AKI. These include, among others, the presence of diabetes mellitus, hypertension, heart failure, pre-existing CKD, and low levels of serum albumin.[5,14] Our finding suggest that some of these patients may be preferentially targeted for nephrology follow-up, creating a degree of selection bias. On the other hand, older patients and those with multiple comorbidities, who are also at greater risk, appear less likely referred to nephrology service, probably because such patients are more likely to be managed with supportive care in view of their less favorable prognosis.

The major strength of our study is that it is the first investigation to systematically assess the effect of nephrology follow-up on long-term clinical outcomes in patients with AKI. Other strengths include methodological rigor; consideration of multiple relevant outcomes and assessment of predictors of nephrology follow up. Based on the findings from this systematic review, there is a clear need for high quality RCTs to assess the impact of nephrology follow up of such patients.

Our study also has several limitations, which mostly derive form the poor quality of the available evidence. Firstly, all included studies were observational in design and some were retrospective. Therefore, the presence of potential confounders and biases may have an impact on the study. Secondly, most of the studies were of low quality and were underpowered, in particular with limited reporting on renal outcomes. Third, the number of studies was small and heterogeneity of renal outcomes was high.

Accordingly, the findings of this systematic review can only be considered hypothesis generating. A pilot multi-center randomized trial comparing nephrologist follow-up versus usual care after an AKI hospitalization (FUSION, ClinicalTrials.gov NCT02483039) is underway, which should provide more robust evidence on this issue.

In conclusion, current evidence from observational studies suggest long-term survival benefits with nephrology follow-up in AKI patients post discharge. However, due to multiple biases and the low quality of the available evidence, these findings are only hypothesis generating. Nonetheless, within the limitations of the available evidence, they provide the rationale for randomized trials of nephrology follow-up in AKI patients.

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Conflict of Interest Statement

None declared.

Author's Contributions

Research idea and study design: NY, AYW, RB, MG; study selection: NY, YX, AYW; data extraction: NY, YX, AYW; quality assessment: NY, YX, AYW; statistical analysis: NY, AYW; supervision: RB, MG, AYW.

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Figure Legends

Figure 1. Flow chart of studies considered for inclusion.

Figure 2. Impact of nephrology follow-up on all-cause mortality.

Abbreviations: RR, relative risk; CI, confidence interval.

Figure 3. Impact of nephrology follow-up on renal outcomes.

Abbreviations: AKI, acute kidney injury; RR, relative risk; CI, confidence interval.

Figure 4. Impact of baseline characteristics on nephrology referral/follow-up.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; DM, diabetes mellitus; CAD, coronary artery disease; PVD, peripheral vascular disease; OR, odds ratio; CI, confidence interval.

Figure 5. Risk of bias summary.

Review authors' judgements about each risk of bias item for each included study.

Table 1. Summary of included studies.

Study[a]	N	Intervention- vs Control	Study Design	Setting	Age (year)	Male	DM	Sepsis or infec-tion	Severe AKI	Required Dialysis in Hospital	Reported outcomes	Follow -up (year)[d]
Xie[36] (2014, CA)	169	Nephrologist follow-up vs Non nephrologist follow-up	Retrospec-tive cohort study	Single centre	67.7[b]	67.5%	37.9%	22.5%	NR	44.4%	Permanent dialysis; recurrent AKI;	5
Harel[31] (2013, CA)	3877[e]	Nephrologist follow-up vs Non nephrologist follow-up	Retrospec-tive matched cohort study	Multi-centre	60.7[b]	59.7%	43.0%	18.2%	NR	NR	All-cause mortality; permanent dialysis;	2
Siew[18] (2012, US)	3929[f]	Nephrology referral vs Non nephrology referral	Retrospec-tive cohort study	Multi-centre	73.0[c]	97.4%	57.8%	NR	4.1%	NR		1
Ali[30] (2011, UK)	562	Nephrologist follow-up vs Non	Retrospec-tive cohort	Multi-centre	74.5[b]	54.1%	NR	NR	10.9%	8.5%	All-cause mortality	0.5

nephrologist	study
follow-up	

(Continued)

Table 1 (Cont'd). Summary of included studies.

Study[a]	N	Intervention- vs Control	Study Design	Setting	Age (year)	Male	DM	Sepsis or infec-tion	Severe AKI	Required Dialysis in Hospital	Reported outcomes	Follow -up (year)[d]
Khan[29] (1997, UK)	310	Nephrologist follow-up vs Non nephrologist follow-up	Retrospec-tive cohort study	Single centre	68.6[b]	55.2%	NR	10.6%	16.5%	8.1%	All-cause Mortality	2
Feest[40] (1993, UK)	125	Nephrology referral vs Non nephrology referral	Prospec-tive cohort study	Multi-centre	72% patients were over 70 years	72.0%	NR	10.4%	100.0 %	12.8%		2

Abbreviations: AKI, acute kidney injury; CA, Canada; DM, diabetes mellitus; NR, not reported; UK, United Kingdom; US, United States of America.

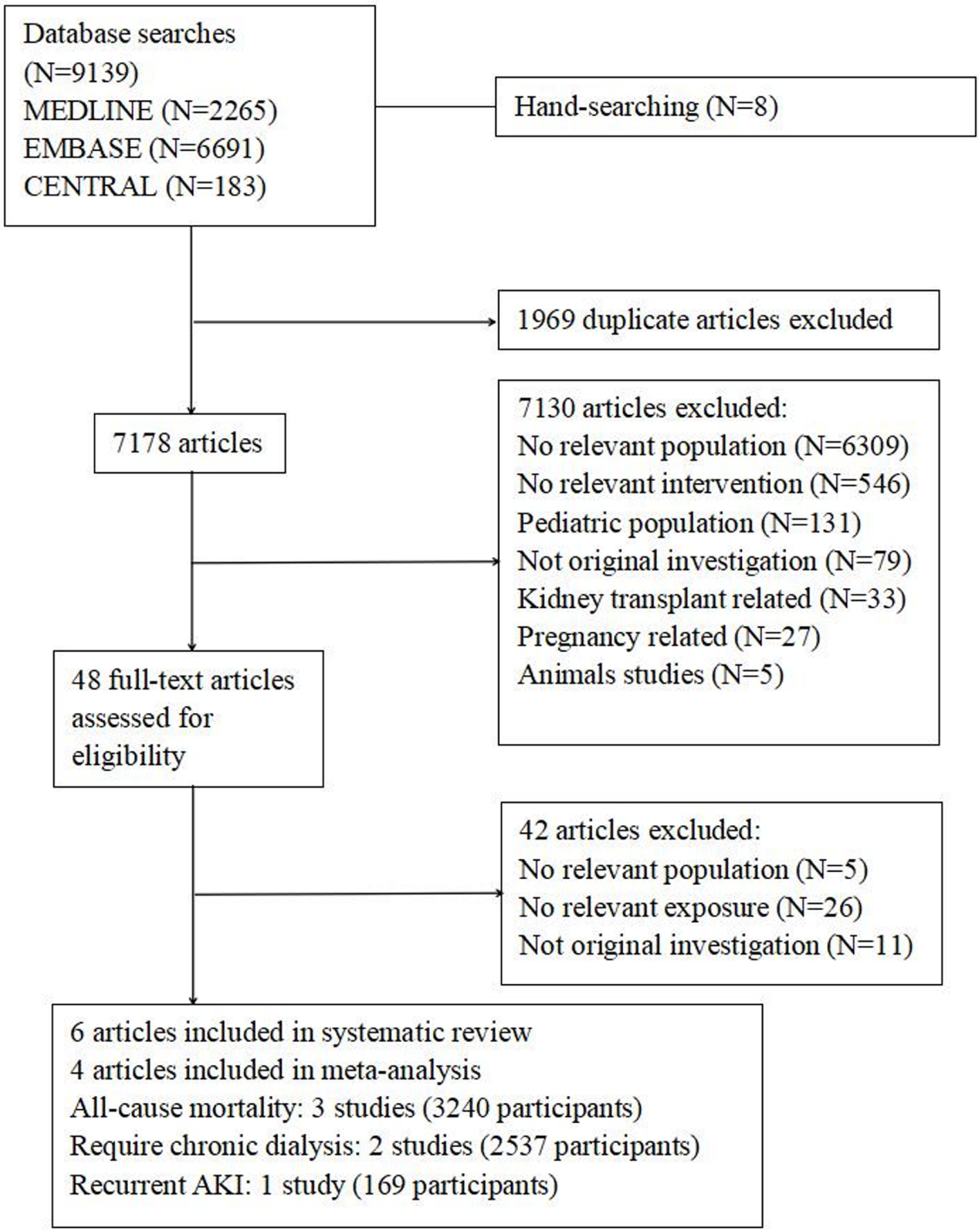
a. Year of publication and setting (country or region) provided in parentheses.

The average of the study was expressed by the b. mean value or c. Median value.

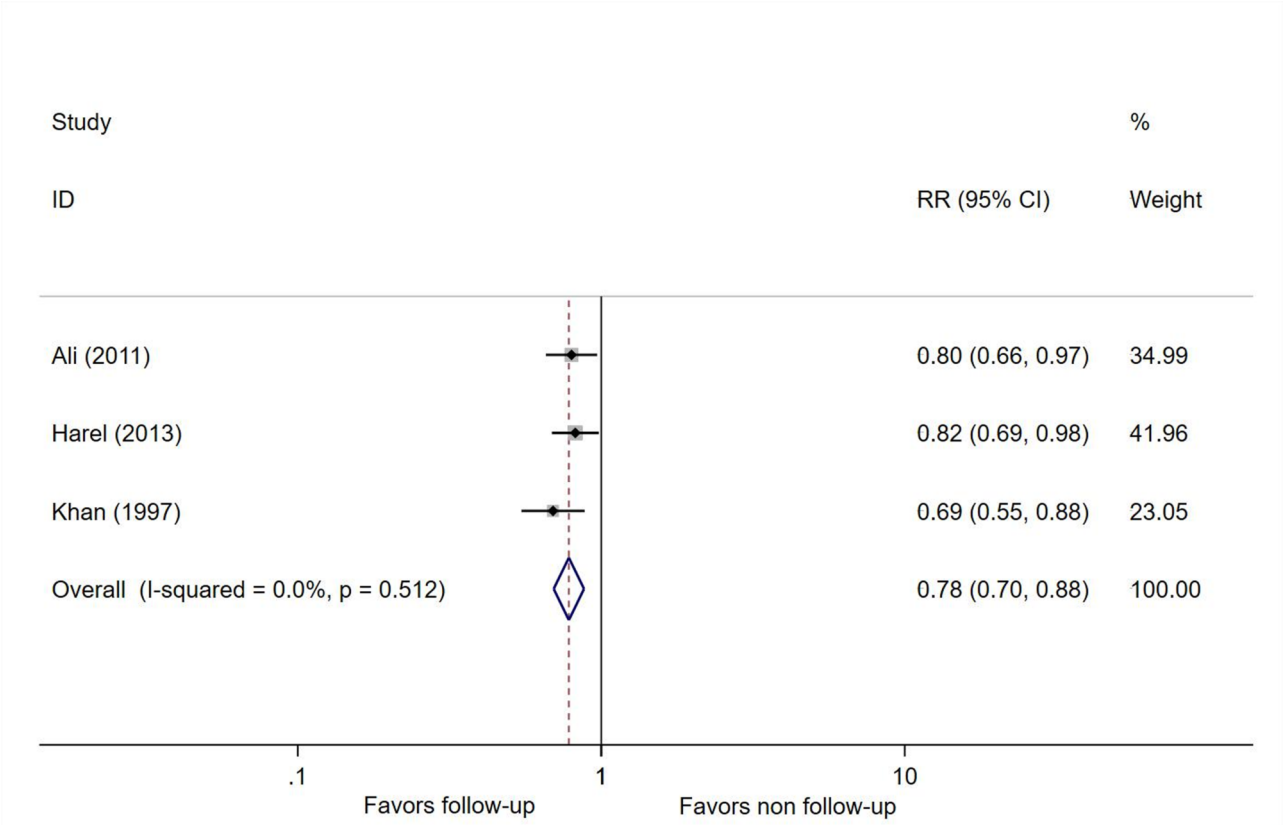
d. The follow-up period was defined as the longest follow-up period is presented.

e. There were total number of 3877 patients were recruited in this study but only 2368 patients were included in the meta-analysis for assessment of the primary and secondary outcomes after propensity score matching.

f. There were total number of 3929 patients were recruited in this study but only 1742 patients were included in the meta-analysis.



NEP_13698_Figure 1.tif



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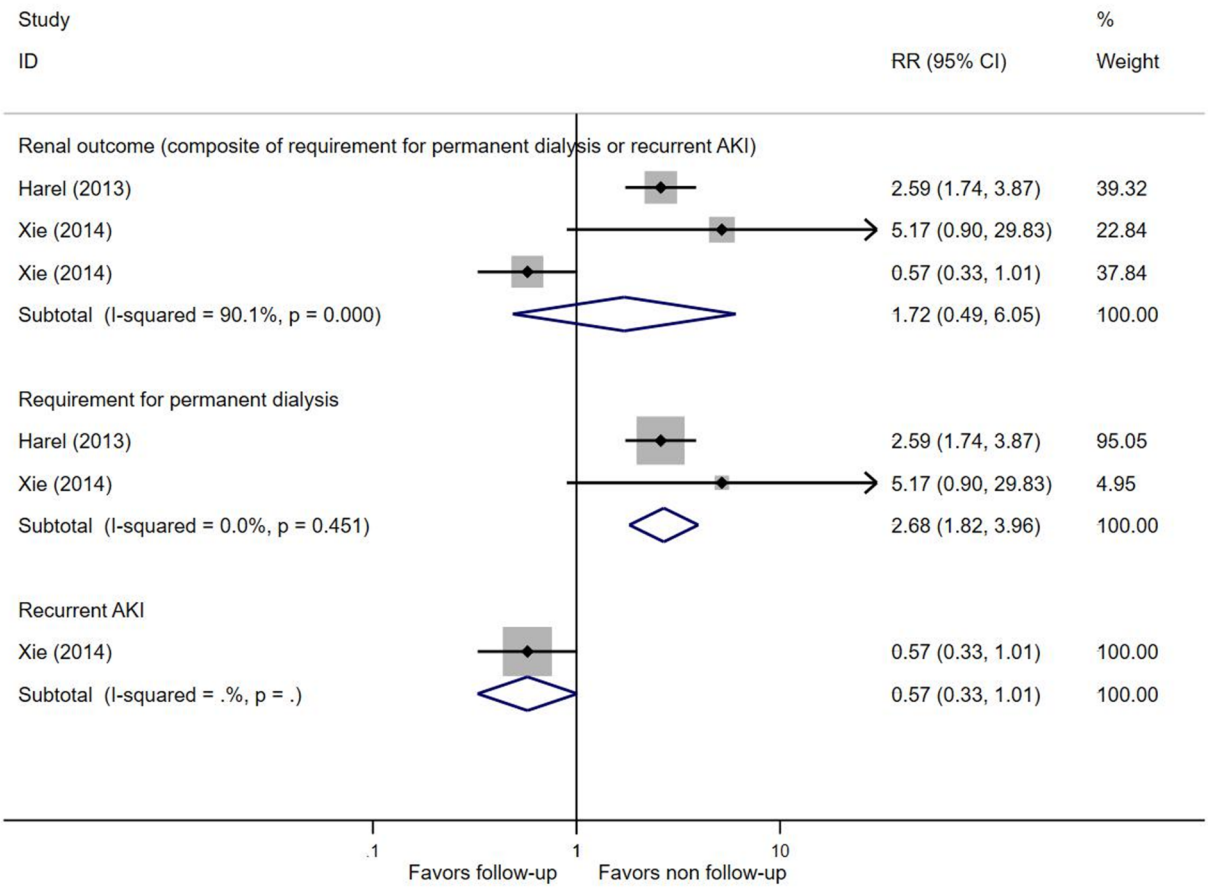

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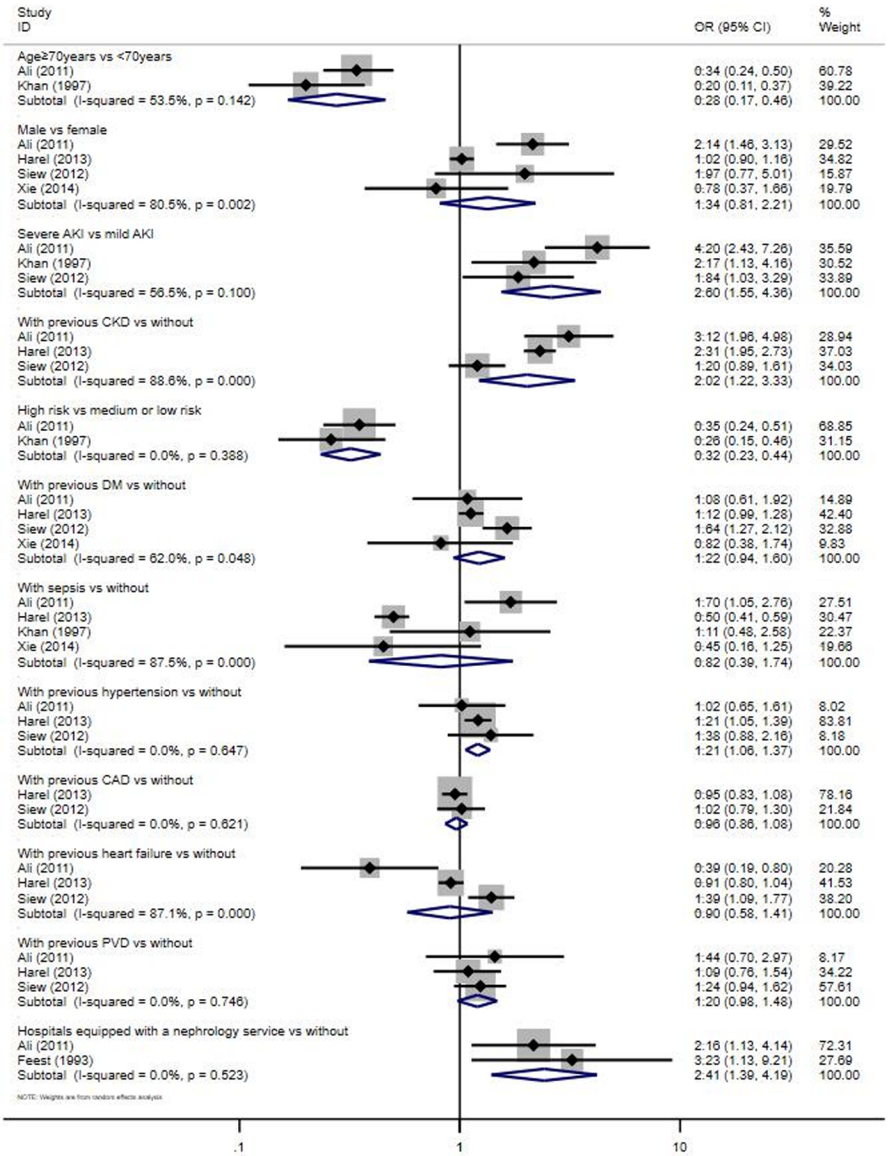
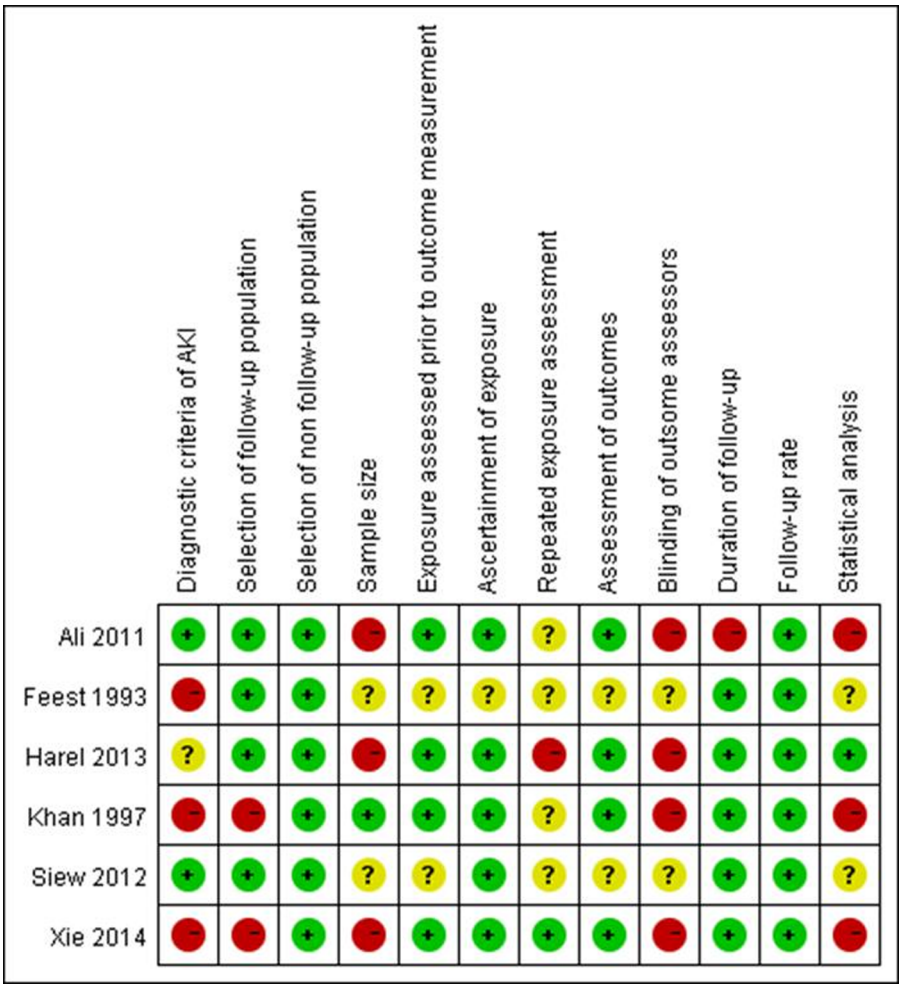


NEP_13698_Figure 4.tif



NEP_13698_Figure 5.tif

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