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ORIGINAL ARTICLE

Nephrologist follow-up care for the acute kidney injury-chronic kidney disease continuum and clinical outcomes: A systematic review and meta-analysis

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Abstract

Background: Acute kidney injury (AKI) to chronic kidney disease (CKD) continuum will increase patients' risk of mortality and long-term dialysis. The aim of the present meta-analysis is to explore the effectiveness of nephrologist care and focus on the follow-up in patients with AKI.

Methods: A systematic search of studies on nephrologist care for the AKI to CKD continuum has been conducted from PubMed and other different databases. Briefly, the primary outcome is the odds ratio of mortality as well as the secondary outcome is de novo renal replacement therapy.

Results: This research includes one randomized controlled trial (RCT) and four cohort studies comprised of 15 541 participants in total. The quantitative analysis displays a lower mortality rate with nephrologist care versus non-nephrologist care in patients' discharge after a hospitalization complicated by AKI (odds ratio: 0.768; 95% CI, 0.616-0.956). By means of Trial Sequential Analysis (TSA), we conclude that nephrologist care after an AKI episode declines 30% relative risks of all-cause mortality.

Conclusion: Nephrologist care for AKI patients after a hospitalization significantly has reduced mortality compared to those followed up by non-nephrologists. There is a trend toward a potentially superior survival rate with nephrologist care has been going well in the recent years.

Keywords: Acute kidney injury; Nephrology referral; Nephrologist care

1. INTRODUCTION

The acute kidney injury (AKI) to chronic kidney disease (CKD) continuum will increase the risk of mortality, early to long-term dialysis,[1–3] stroke,[4] and bone fracture.[5] AKI requiring dialysis therapy (AKI-D) incidence has been increasing around 10% per year in the United States, and the deaths related to dialysis require-AKI are more than doubled.[6] Patient survival of AKI has been increased by advance in renal replacement therapy (RRT) and critical care strategy. Therefore, an increasing number of hospitalized AKI patients who require RRT get to survive.[7] During index hospitalization in non-ICU patients, nephrology consultations can be as high as 78% when AKI is identified, but the follow-up rate after discharge demonstrates a significant gap.[8] Despite guidelines published by the "Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline" recommending that patients should be followed up by a nephrologist in survivors of AKI with acute kidney disease (AKD),[9] only 8.5% to 25% of all patients with severe AKI received nephrologist follow-up care after surviving to discharge.[10–12]

Moreover, there are no apparent differences in referral rates among different stages of AKD.[10] The consensus of the "16th Acute Disease Quality Initiative (ADQI)" highlights the importance of the clinical follow-up after AKI regarding the AKD period for resolutions, new-onset, or progressions of CKD.[13] However, the pros and cons of nephrologist care for patients' discharge after a hospitalization complicated by AKI remains inconclusive. Therefore, the aim of this medical research on the basis of meta-analysis is to explore the clinical outcome after nephrologist follow-up care after AKI discharge.

2. METHODS

2.1. Search strategy and selection criteria

The meta-analysis applied for this research has been accomplished on the basis of the "Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA)" statement[14] and made good use of Cochrane methods (Supplementary Appendix 1, http://links.lww.com/JCMA/A230).[15] We prospectively submit the systematic review protocol for registrations on

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PROSPERO (CRD42021225866) (Supplementary Appendix 2, http://links.lww.com/JCMA/A230).

2.2. Data sources and search strategy

On the top of that, there are no language limitations for us to search the published studies in PubMed, Embase, Cochrane, Medline, Collaboration Central Register of Controlled Clinical Trials, and Cnki.net (Supplementary Appendix 3, http://links.lww.com/JCMA/A230) from the inception to July 2021. That is to say, titles, abstracts, keywords, and related studies for further analyses have been screened. In addition, reference lists of associated studies, systematic reviews, and meta-analyses have been manually examined to identify any additional publications relevant to our researches.

Meanwhile, both abstracts and full papers have been selected for quality assessments and data syntheses. Only if it is available for us to contact the authors of the information we set for further analyses.

2.3. Inclusion criteria

Apparently, the randomized controlled trials (RCTs), cohort studies, or retrospective cohort studies are utilized but reviews, case series, and case reports are excluded in this research. More importantly, there are no language restrictions. Furthermore, in our essay, we define "nephrology care" as "nephrologist follow-up" in the out-patient department after hospital discharge.

The inclusion criteria for this research go as follows: (1) studies that clearly specified participants comprise at least two treatment arms, one of which is with nephrologist care and the other without nephrologist care; (2) literature search results using Medical Subject Headings (MeSH) terms or free-texts words with keywords AKI, AKD, nephrologist referral, and nephrologist care, as well as the words characterized with initiations; (3) participants included hospitalized patients with AKI who are at least 18 years of age; (4) patients assessed at least the outcome of mortality.

Full-text papers are selected for quality assessments and data syntheses.

2.4. Study selection and data extraction

Two investigators (C.-C. Hsieh; J.-Y. Chen) have searched the published studies independently. A third investigator (V.-C. Wu) has resolved the disagreements between one investigator and the other. All data have been independently extracted from the included studies by two investigators (C.-C. Hsieh; J.-Y. Chen) according to a standardized form. Namely, the extracted data includes study characteristics (the leading author, publication year, patient enrollments, sample size, events, duration of follow-up [weeks]) and participants' baseline (age [years], gender [%], comorbidities) (Table 1). The odds ratio and 95% CIs are extracted. In a word, the primary outcome is mortality in patients' discharge after a hospitalization complicated by AKI during the hospitalization period. The secondary outcome is subsequent RRT.

2.5.Quality assessment

The quality of the included studies is assessed independently by two investigators (C.-C. Hsieh; J.-Y. Chen) using the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) scoring system for comparative non-randomized studies corresponding to every study's designs (Supplementary Appendix 4, http://links.lww.com/JCMA/A230).[20] Studies with low risk of bias are comparable with RCTs; while, those with moderate risk of bias are reasonable for a non-randomized study. Again, two investigators (C.-C. Hsieh; J.-Y. Chen) independently have assessed the risk of bias from randomized controlled studies with the Cochrane Risk of Bias Tool version 1.0.[21] If there are discrepancies amongst reviewers, they will be solved through discussions under the supervision of the corresponding author. We use the GRADEpro app to rate evidence and present it in GRADE evidence profiles and summaries of findings tables (Supplementary Appendix 5, http://links.lww.com/JCMA/A230).[22] Finally, we formally assess the credibility of potential effect-modifiers by using GRADE guidance.[23]

2.6. Data syntheses and statistical analyses

Generally speaking, data syntheses are extracted from the mortality of patients' discharge after a hospitalization complicated by AKI within the index hospitalization (Table 2). In other word, all data are calculated with 95% CIs. Thus, the data from individual studies are pooled by using the random-effect model. What's more, inconsistencies across studies are assessed by using the I^2 statistics in which a value >50% indicated substantial heterogeneity. Moreover, that univariate randomly effects meta-regression is conducted to evaluate the possible effect on modifications of baseline characteristics, including age, sex, diabetic mellitus (DM), hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF), malignancy, and CKD. Similarly, publication bias is detected by funnel plots and an Egger test. Consequently, the statistical significance is defined as $p < 0.05$. The quantitative meta-analysis is conducted by using Comprehensive Meta-Analysis version 3.3.070 (BioSTAT, Englewood, NJ, USA).

Table 1

Characteristics of included comparative studies

Study	Subgroup	Population	Mortality	Age	Male (%)	DM (%)	HTN (%)	CAD (%)	CHF (%)	ACEI/ARB (%)
Khan et al[16]	N	70	36	NA	NA	NA	NA	NA	NA	NA
	C	240	178	NA	NA	NA	NA	NA	NA	NA
Harel et al[17]	N	1184	184	61	711 (60.1)	517 (43.7)	816 (68.9)	456 (38.5)	429 (36.2)	NA
	C	1184	224	61.4	710 (60)	510 (43.1)	839 (69.5)	443 (37.4)	430 (36.3)	NA
Karsanji et al[12]	N	500	35	64	339 (68)	236 (47)	69 (14)	62 (12)	113 (23)	NA
	C	1576	126	65	846 (54)	569 (36)	208 (13)	205 (13)	275 (17)	NA
Wu et al[18]	N	5358	2173	65.98	2996 (55.9)	3797 (70.9)	NA	358 (6.7)	1120 (20.9)	3204 (59.8)
	C	5358	2384	65.87	3006 (56.1)	3774 (70.4)	NA	380 (7.1)	1108 (20.7)	3186 (59.5)
Silver et al[19]	N	34	3	64	24 (71)	14 (41)	19 (56)	11 (32)	6 (18)	12 (35)
	C	37	1	67	12 (68)	17 (46)	29 (78)	9 (24)	11 (30)	18 (49)
Summary	N	7146	2431	64.99	4070 (57.5)	4564 (64.5)	904 (52.6)	887 (12.5)	2097 (29.6)	3216 (59.6)
	C	8395	2913	65.06	4574 (56.1)	4870 (59.7)	1076 (38.5)	1037 (12.7)	1824 (22.4)	3204 (59.4)
	Total	15 541	5344	65.03	8644 (56.8)	9434 (61.9)	1980 (49.8)	1924 (12.6)	3921 (25.7)	6420 (59.5)

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; C = control; CAD = coronary artery disease; CHF = congestive heart failure; DM = diabetes mellitus; HTN = hypertension; N = nephrologist care; NA = not available.

Table 2

Summary of included comparative studies for outcome evaluation

Author	Study duration	Follow-up (duration)	AKI definition	Primary outcome	Secondary outcome
Khan et al[16]	July 1, 1989-June 30, 1990	2 y	Rise in serum creatinine concentration for the first time >300 μmol/L	Mortality	NA
Harel et al[17]	April 1996-March 2008	2 y	Diagnosed code of AKI and claim for acute dialysis during hospitalization	All-cause mortality	NA
Karsanji et al[12]	May 1, 2005-March 31, 2014	9 y	KDIGO, stage 3 AKI	All-cause mortality	Dialysis dependence
Wu et al[18]	January 1991-December 2011	4.04±3.56 y	ICD-9: newly diagnosed AKI during admission, along with dialysis	All-cause mortality	ESRD, MACE, CHF, fracture, severe sepsis, readmission, malignancy
Silver et al[19]	July 2015-June 2017	1 y	KDIGO stage 2 AKI and above	Major adverse kidney event at 1 y (death, maintenance dialysis, or incident/progressive CKD)	Time to a major adverse kidney event, MACE, first rehospitalization; proportion with a major adverse cardiac event, number of rehospitalizations with AKI; and change in health-related quality of life

AKI = acute kidney injury; CHF = congestive heart failure; CKD = chronic kidney disease; ESRD = end-stage renal disease; KDIGO = Kidney Disease Improving Global Outcome; MACE = major adverse cardiac events; NA = not available.

To assess the effect of each article on the present studies temporally and cumulatively, we further have adopted trial sequential analysis (TSA) (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Denmark, software 0.9.5.10 Beta software) for the primary outcome. However, considering the heterogeneity among studies, which stem from the patient selection strategy, study design, methodological quality, and the duration of follow-up, we apply the random-effects model. Therefore, the conventional non-superiority boundaries have been set up at a significance level of 0.05 with a power of 90%, following as α-spending boundaries calculated by the O'Brien-Fleming multiple testing procedure.

3. RESULTS

3.1. Study search and characteristics of included patients

The study selection process is summarized in Supplementary Appendix 6, http://links.lww.com/JCMA/A230. A total of 590 articles are identified through a search of algorithm, after excluding duplicate articles and non-relevant articles, the titles and abstracts of the remaining 15 articles screened.[8,10,12,16–19,24–31] We exclude one study comparing the time that the nephrologist visited before initializing dialysis,[24] apart from two studies without reports of mortality,[10,29] two review articles,[26,31] and five studies comparing nephrology consultations during the hospitalization.[8,25,27,28,30] Therefore, the meta-analysis in this medical research is inclusive of one RCT[19] and four retrospective cohort studies.[12,16–18] The final quantitative analysis includes 15 541 participants, besides 46% of whom are followed up by nephrologists while 54% by non-nephrologists. Again, the patient's average age is 65.1 years in the nephrologist care group and 65.2 years in the control group. The study period is heterogenous, from 90 days to 9 years after hospital discharge.

3.2. Quality of enrolled trials

Generally speaking, the quality of enrolled trials has varied; earlier studies tended to lack sufficient information about participants or personnel blinding and the concealment process. Moreover, the studies have been published over 20 years and varied in sample sizes (71-10 716 patients). The ROBINS-I scoring system for assessing the risk of bias revealed moderate of risks in all nonrandomized study (Supplementary Appendix 4, http://links.lww.com/JCMA/A230). First of all, at the preintervention stage, bias due to confounding is mainly moderate except for one study without enough information in addition to the moderate in bias of selection of all inclusive studies due to lack of randomization. Second, at intervention stage, bias in the classification of intervention is low in all studies. Third, at postintervention stage, there is one study without enough information and the other is low risk of bias. As a result, we make good use of Cochrane Risk of Bias Tool version 1.0 for randomized controlled study (Supplementary Appendix 7, http://links.lww.com/JCMA/A230). Finally, it presents with low risk of bias in most domain, but high in blinding of participants and outcome assessments.

3.3. Publication bias

There are widely used funnel plots and Egger tests for detection of publication bias (Fig. 1A). However, there is a problem with poor power and sensitivity when studies' numbers are smaller than 10 studies behind. In response, we utilize the Doi plot and luis furuya–kanamori (LFK) index, a new graphical and quantitative method for detecting publication bias by MetaXL Version 5.3. Compared with Egger tests, the LFK index has higher sensitivity and specificity when they are fewer than 10 studies included (71.3%-72.1% vs 18.5%-28.6%).[32] The Doi plot is a quantile plot with a more objective appearance for the

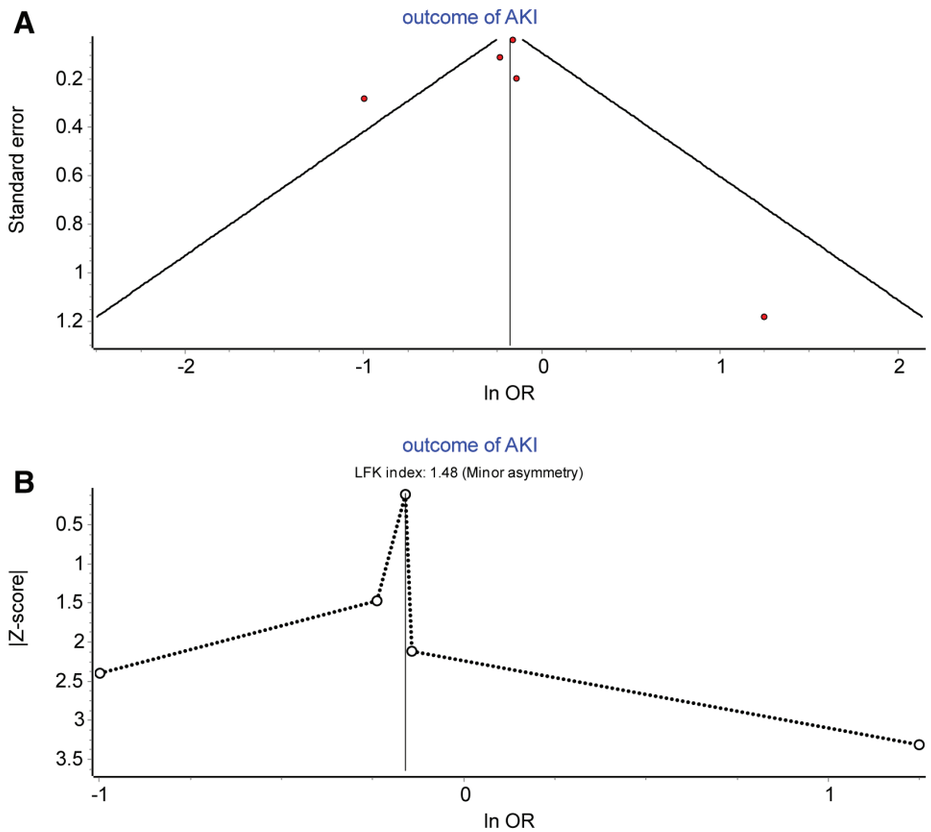

Fig. 1 A, Funnel plot depicts the publication bias for all-cause mortality. B, Doi plot depicts the publication bias for all-cause mortality. AKI = acute kidney injury; LFK = Luis Furuya-Kanamori; ln OR = natural logarithm of the Odds Ratio.

symmetrical detection. The LFK index is a value that quantifies the difference amongst each side of the area separated from the tip of the triangle. The closer the value of the LFK index to zero is, the more symmetrical the Doi plot can be, and zero represents complete symmetry. Besides, in view of our achievement based on meta-analysis, the Doi plot indicates mild asymmetry (Fig. 1B). It is a priori positive bias (positive effects of nephrologist care more likely to be published). There are equal studies making up each side of the limb but an unequal deviation of both limbs of the plot from the mid-point. The LFK index = 1.48 illustrates minor asymmetry (the LFK index >1 in a priori positive bias). According to the Doi plot and LFK index, it reveals mild publication bias in our research of meta-analysis.

3.4.Outcomes

The all-cause mortality after AKI diagnosis has comprised the main outcome which includes 15 541 patients with 5344 deaths. The pooled mortality rates are 34.02% (2431 of 7146) vs 34.7% (2913 of 8395) in the group of nephrologist care vs non-nephrologist

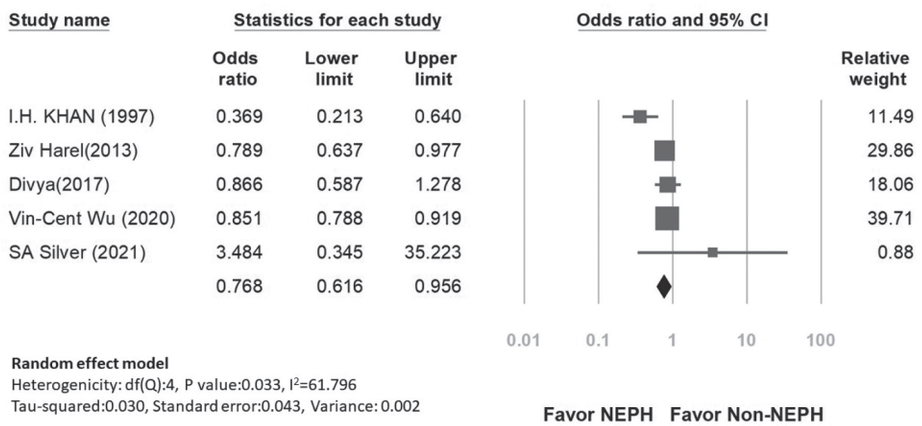

Fig. 2 Forest plots for all-cause mortality comparing NEPH vs non-NEPH in patient discharge after AKI in the random effects model. AKI = acute kidney injury; NEPH = nephrologist care.

care (odds ratio = 0.768; 95% CI, 0.616-0.956; $p = 0.033$) (Fig. 2). However, there is high heterogeneity among studies (random-effect model, I^2 value of 61.796%). Obviously, no significant values are found in the meta-regression of each baseline characteristic (age, sex, DM, HTN, CAD, CHF) in all included trials.

In regard to RRT, there are only three studies on our meta-analysis that reported data about de novo RRT. The pooled RRT rates are higher in nephrologist care than non-nephrology care (Table 3; 19.9% vs 7.2% [$p < 0.001$]).

3.5. Trial sequential analysis

We have applied TSA to evaluate the statistical reliability of enrolled studies and to overcome the limitation caused by relatively restricted sample sizes. Likewise, with an eye to calculating the required information size (RIS) and the trial sequential monitoring boundaries for detecting or rejecting an intervention effect of our primary outcome, we make some a priori assumptions and goals. The mortality rate of the control arm (non-nephrologist care) is assumed to be 18.9%, which presents the median event rate of all studies. Accordingly, we conclude a 30% relative risk reduction (RRR) in the intervention arm (nephrologist care) to be clinically reasonable. The significance level is set at 0.05 and power at 90%. Based on the factors, the RIS is calculated as 17 136 patients after being adjusted for heterogeneity.

With 15 541 patients accrued, before crossing the RIS, the cumulative Z-curve crosses the trial sequential monitoring boundary for benefits (Fig. 3), which displays a firm evidence for a 30% RRR of mortality in patients followed up by nephrologists. In addition, we demonstrate the temporally cumulative influence of included studies. What's more important, the consistently better performance has been found in the nephrologist care group on all-cause mortality during the last 20 years.

3.6. Assessment of evidence quality and summary of findings

Assessments of evidence quality is performed by using the GRADE system (Supplementary Appendix 8, http://links.lww.com/JCMA/A230). The RCT study in our meta-analysis

Table 3

Outcome about ESRD

Study	Subgroup	Population	ESRD/dialysis outcome (%)
Karsanji et al[12]	N	500	25 (5)
	C	1576	0 (0)
Wu et al[18]	N	5358	1150 (21.5)
	C	5358	501 (9.4)
Silver et al[19]	N	34	0 (0)
	C	37	0 (0)
Summary	N	5892	1175 (19.9)
	C	6971	501 (7.2)
	Total	12 863	1676 (13)

C = control; ESRD = end-stage renal disease; N = nephrologist care; NA: not available.

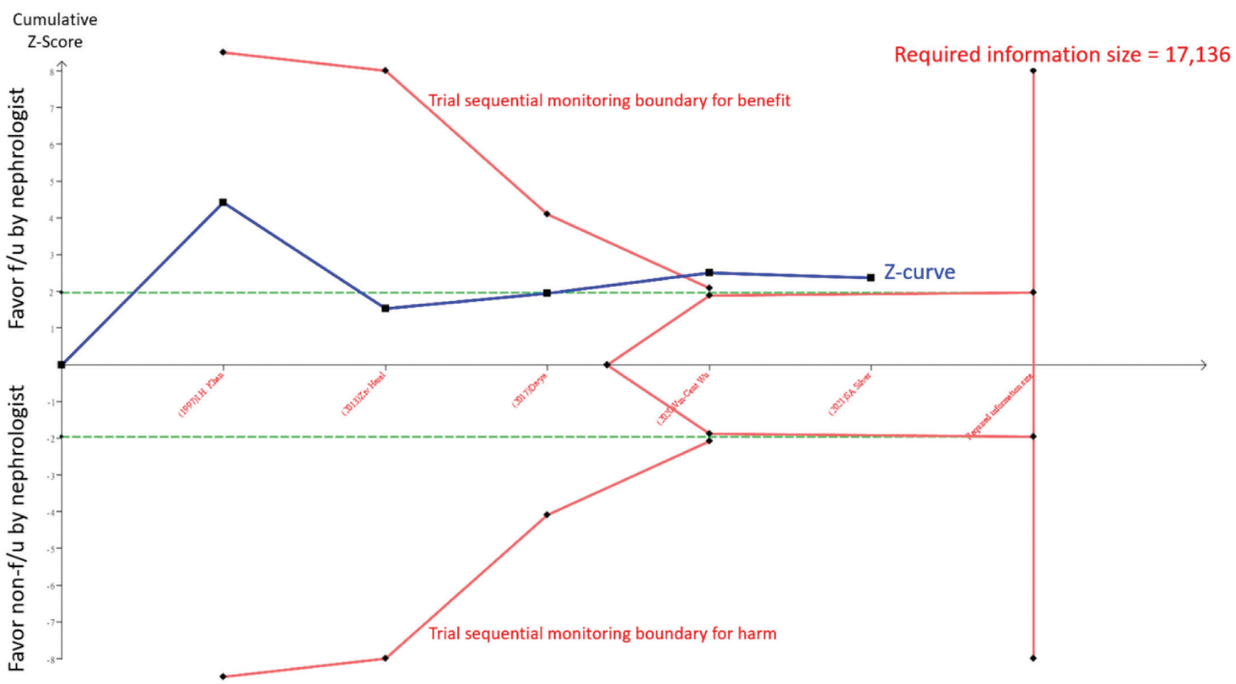

Fig. 3 Trial sequential analysis of 30% relative risk reduction comparing the impact on mortality of nephrologist care vs non-nephrologist care for patients discharged after acute kidney injury. The cumulative Z-curve crossed both the conventional boundary for statistical significance and the trial sequential monitoring boundary for benefit before reaching RIS. RIS = required information size.

illustrates the risk of bias due to lack of blinding. Among those four observation studies, there are incomplete follow-up events in two of four studies. Again, the inconsistency comes out with a significant value due to high heterogeneity. Consequently, there are no obvious indirectness, imprecision, or publication bias that demonstrates the result with low quality of evidence.

4. DISCUSSION

The findings of this systematic review of one RCT and four cohort studies (with comparative data on the controls) on all-cause mortality provide the best available evidence that collaboration with nephrologist care is associated with a survival benefit compared with non-nephrologist care for AKI patients after hospital discharge. What's significant, results from our TSA have reported a sustained superior performance of nephrologist care over the recent decades. Because the cumulative Z-curve crossed both the conventional boundary for the statistical significance and the trial sequential monitoring boundary for benefits before reaching RIS, we firmly have concluded that the follow-up by nephrologists after discharge will reduce the 30% relative risk of all-cause mortality.

4.1. Nephrologist follow-up care decreased mortality rate

In our meta-analysis, we focus on the nephrologist care for AKI patients after a hospitalization. Compared to other specialties, nephrologist care is associated with more frequent treatments of CKD complications and the use of angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) medications.[33] Besides, the good control of CKD and the use of ACEi/ARB can improve all-cause mortality, especially for patients with other morbidities such as DM or HTN, etc.[34] In view of a meta-analysis in 2017, Soares et al[35] found that early nephrology consultation results in a lower mortality rate in AKI patients. Due to a consequence that AKI is associated with higher mortality, morbidity, and cost,[36] we raise the important issue that the nephrology intervention after AKI or AKD period will decrease patient mortality.

4.2. Nephrologist care and the de novo RRT

RRT is also an important issue for nephrologist care. Despite a limited number of studies, the nephrologist follow-up group still has a higher de novo RRT than non-nephrologist care. This result indicates the competing bias by the high risk of mortality after AKI patients' discharge from the hospital. Namely, the patients with nephrologist care after hospital discharge are more likely to have severe kidney disease despite statistics adjustments. There are not enough data about patient's AKI stage and renal function after discharge from hospital in all included trials. There are also no significant values found about meta-regression for each characteristic. Again, more studies are needed for a further survey about de novo RRT rate in the future.

As the increasing burden of AKI, a better understanding of its related impacts on healthcare utilizations, policy implications, and optimal patient care capacities to meet this demand is also warranted. Improving care among AKD patients is essential to early recognitions of key modifiable risk factors, as well as timely and necessary monitoring/interventions.

4.3. Strength and study limitation

The large population size in the study strengthens the analyses of the attained risk factors and the associations among all comorbidities. To our knowledge, it's the first meta-analysis to discuss about the long-term effect of nephrologist care after AKI hospitalizations. In our study, we exclude patients who received the remained dialysis-dependent within 90 days after hospital discharge; the other study for those who remained RRT after discharge is excluded as well. Similarly, most studies also exclude death within 90 days after hospital discharge. Therefore, the treatment mentioned above can avoid survival bias and the acute illness effect of initial hospitalizations and focus on the long-term benefit of nephrologist care.

Furthermore, there are several study limitations for this meta-analysis. First of all, there are a limited number of articles about patients with AKI follow-up by nephrologists after hospital discharge. Second, no articles are mentioned about kidney functions after AKI, which makes it difficult to analyze at which stages of renal functions the nephrologist follow-up could be better. Third, the high heterogeneity is noted in our research, which could be different times to include patients and lengths of follow-up. We try to separate the study into two distinct subgroups, and follow-up time <2 years' odds ratio is 0.722 (CI, 0.592-0.881), follow-up time >2 years' odds ratio is 0.852 (CI, 0.790-0.918) (Supplementary Appendix 9, http://links.lww.com/JCMA/A230). Likewise, there is also mild publication bias noted from Doi plot and LFK index. Fourth, there will be indication bias where patients with a more severe AKD stage will seek nephrologist care, and those deemed at a higher risk of death (terminal cancer, potential hospice, etc.) are steered away from nephrologists. However, despite this unfavorable treatment of indication bias, the nephrologist care group is still associated with survival benefits compared to its counterparts. Apparently, the care under nephrologist is just a surrogate marker; the performance of a well-trained nephrologist is more homogeneous and predictable globally. Finally, the appropriate reasons for the lack of nephrology follow-up among these AKI-D survivors are not extensively understood.

In conclusion, generally believing, the present meta-analysis reveals that nephrologist care can lead to a lower mortality rate for AKI patients after a hospital discharge. Simultaneously, the accomplishment of our research also demonstrates the sustained superior performance of nephrologist care over the recent years in regard to attenuating mortality with the AKI-to-CKD continuum. To sum up, the meta-analysis for our research concludes that the nephrologist care is required when patients are discharged with a diagnosis of AKI.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A230.

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