The Association Between Chronic Kidney Disease and New Onset Renal Replacement Therapy on the Outcome of COVID-19 Patients: A Meta-analysis

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ABSTRACT

OBJECTIVE: The aim of the study was to evaluate the association between chronic kidney disease (CKD) and new onset renal replacement therapy (RRT) with the outcome of Coronavirus Disease 2019 (COVID-19) in patients.

METHODOLOGY: A systematic literature search from several databases was performed on studies that assessed CKD, use of RRT, and the outcome of COVID-19. The composite of poor outcome consisted of mortality, severe COVID-19, acute respiratory distress syndrome (ARDS), need for intensive care, and use of mechanical ventilator.

RESULTS: Nineteen studies with a total of 7216 patients were included. CKD was associated with increased composite poor outcome (RR 2.63 [1.33, 5.17], $P = .03$; $I^2 = 51\%$, $P = .01$) and its subgroup, consisting of mortality (RR 3.47 [1.36, 8.86], $P = .009$; $I^2 = 14\%$, $P = .32$) and severe COVID-19 (RR 2.89 [0.98, 8.46], $P = .05$; $I^2 = 57\%$, $P = .04$). RRT was associated with increased composite poor outcome (RR 18.04 [4.44, 73.25], $P < .001$; $I^2 = 87\%$, $P < .001$), including mortality (RR 26.02 [5.01, 135.13], $P < .001$; $I^2 = 60\%$, $P = .06$), severe COVID-19 (RR 12.95 [1.93, 86.82], $P = .008$; $I^2 = 81\%$, $P < .001$), intensive care (IC) (RR 14.22 [1.76, 114.62], $P < .01$; $I^2 = 0\%$, $P < .98$), and use of mechanical ventilator (RR 34.39 [4.63, 255.51], $P < .0005$).

CONCLUSION: CKD and new-onset RRT were associated with poor outcome in patients with COVID-19.

KEYWORDS: Chronic kidney disease, renal replacement therapy, Coronavirus, COVID-19, severity, mortality, SARS-CoV-2

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Introduction

Coronavirus Disease 2019 (COVID-19) is a global health concern requiring special attention. The cases of COVID-19 and deaths attributed to it are increasing every day; over 19 000 000 cases and 700 000 deaths have been documented as of 8 August 2020.[1] We may consider COVID-19 as a relatively benign illness since the majority of COVID-19 patients have only mild influenza-like symptoms; however, a minority of the patients may present with multi-organ failure, necessitating more advanced interventions such as the use of mechanical ventilator and renal replacement therapy (RRT).[2] Advanced age and several comorbidities were found to be associated with severe COVID-19.[3-8] Therefore, identifying all independent risk factors to predict COVID-19 severity is essential during this pandemic,[9] when intensive care may not be readily available.

Although chronic kidney disease (CKD) was apparently not as prevalent as other comorbidities in COVID-19 patients, it has been associated with increased risk of mortality and severe COVID-19 in a relatively small sample of patients (Bai, Tu and Wei, 2020).[10] It was hypothesized that increased angiotensin converting enzyme 2 (ACE2) levels in patients with CKD was associated with the increased risk of mortality and severe COVID-19. It was previously shown that CKD patients have increased levels of ACE2, which facilitates the entry of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) into human cells.[12]

The need for RRT in COVID-19 patients was also reportedly associated with poor outcome[11]; however, whether the risk of poor outcome was affected by the underlying CKD or other comorbidities is unknown. In the present study, a systematic review and meta-analysis was conducted to investigate the

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association between CKD, RRT, and poor outcome in patients with COVID-19.

Methodology

Eligibility criteria

Research articles on laboratory-confirmed COVID-19 patients with information on CKD, RRT, and outcome variables of interests, including severe COVID-19, acute respiratory distress syndrome (ARDS), mortality, intensive care (IC), and the use of mechanical ventilator, were considered eligible and included in our analysis. The following types of articles were excluded in our study: articles on pediatric population; articles not in English language; non-original research articles (ie, commentaries, non-research letters, or review articles); articles with population sizes below 20; and case reports.

Search strategy and study selection

Systematic literature search was performed through PubMed, SCOPUS, EuropePMC, and Cochrane Central Database with several search terms, including: (1) ("COVID-19" OR "SARS-CoV-2") AND "Characteristics" AND ("Mortality" OR "SEVERE"), (2) ("COVID-19" OR "SARS-CoV-2") AND "Characteristics", (3) ("COVID-19" OR "SARS-CoV-2") AND "Chronic Kidney Disease", (4) ("COVID-19" OR "SARS-CoV-2") AND "Renal Replacement Therapy." All duplicate results were then removed. The abstracts of the returned articles were screened and subsequently, the full texts of the potentially eligible articles were evaluated. The systematic search was completed on 23 April 2020. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data collection

A standardized criteria was used for data collection in this meta-analysis. The variables considered were: author, year, study design, sex, age, presence of comorbidities (including hypertension, diabetes, cardiovascular disease, respiratory comorbidities, CKD), baseline serum creatinine level, use of RRT, and the outcome of interest. The outcome of interest, which was composite poor outcome, included mortality, severe COVID-19, ARDS, need for intensive care, and the use of mechanical ventilator. Mortality was defined as death during hospitalization, while severe COVID-19 was defined according to the Report of the WHO-China Joint Mission on COVID-19 (respiratory rate $\geq$30 times per min, oxygen desaturation $\leq$93% without supplementation, ratio of partial pressure of arterial oxygen to fractional concentration of oxygen inspired air [PaO2/FiO2] ratio $\leq$300 mm Hg, or the presence of any of the following: respiratory failure, septic shock, or multi organ failure).[13] ARDS was defined according to the WHO interim guidance of severe acute respiratory infection (SARI) of COVID-19.[14] Intensive care and the use of mechanical ventilator were defined as admission to intensive care unit (ICU) regardless of the reasons and the use of mechanical ventilation, respectively.

Statistical analysis

All dichotomous variables were calculated using the Mantel-Haenszel method with random-effects model, irrespective of heterogeneity. Heterogeneity among the included studies was evaluated using the I^2 and chi square (χ^2) test. Significant heterogeneity was considered as I^2 test $>$50% with a χ^2 P-value $<$.05. Risk ratios (RRs) and mean differences (MD) with 95% confidence intervals (CIs) were used for dichotomous and continuous variables, respectively. The P-value was 2-tailed and values $\leq$.05 were considered statistically significant. Random effects meta-regression was performed using restricted-maximum likelihood for age, sex, cardiovascular disease, hypertension, respiratory comorbidities, and diabetes. Regression-based Harbord's test for binary outcome was used to measure small study effect, while the risk of publication bias was evaluated using Begg's funnel plot analysis. All statistical analyses were performed using Review Manager 5.3 (Cochrane Collaboration) and Stata® 16.

Results

Study identification and characteristics

The study flow chart used in this analysis is presented in Figure 1. Initially, 767 results were identified through all search engines. After the removal of duplicate results, 693 records remained. A total of 627 results were excluded after screening titles and abstracts. After assessing 66 full-text articles for eligibility, 47 articles were further excluded because: (1) no data on CKD patients or RRT were available (n = 30) and (2) the groups were not divided based on the outcome of interest (n = 17). Thus, 19 studies including a total of 7216 patients were included in the qualitative synthesis and meta-analysis (Table 1).[2,15-32]

Chronic kidney disease and poor outcome in COVID-19

Meta-analysis showed that CKD was associated with increased composite poor outcome (RR 2.63 [1.33, 5.17], P = .03; I^2: 51%, P = .01). Subgroup analysis in CKD patients also showed significantly increased risk for mortality, as shown in Figure 2(a) (RR 3.47 [1.36, 8.86], P = .009; I^2: 14%, P = .32) and severe COVID-19 (RR 2.89 [0.98, 8.46], P = .05; I^2: 57%, P = .04). Sensitivity analysis by removal of a single study did not reduce heterogeneity for severe COVID-19.

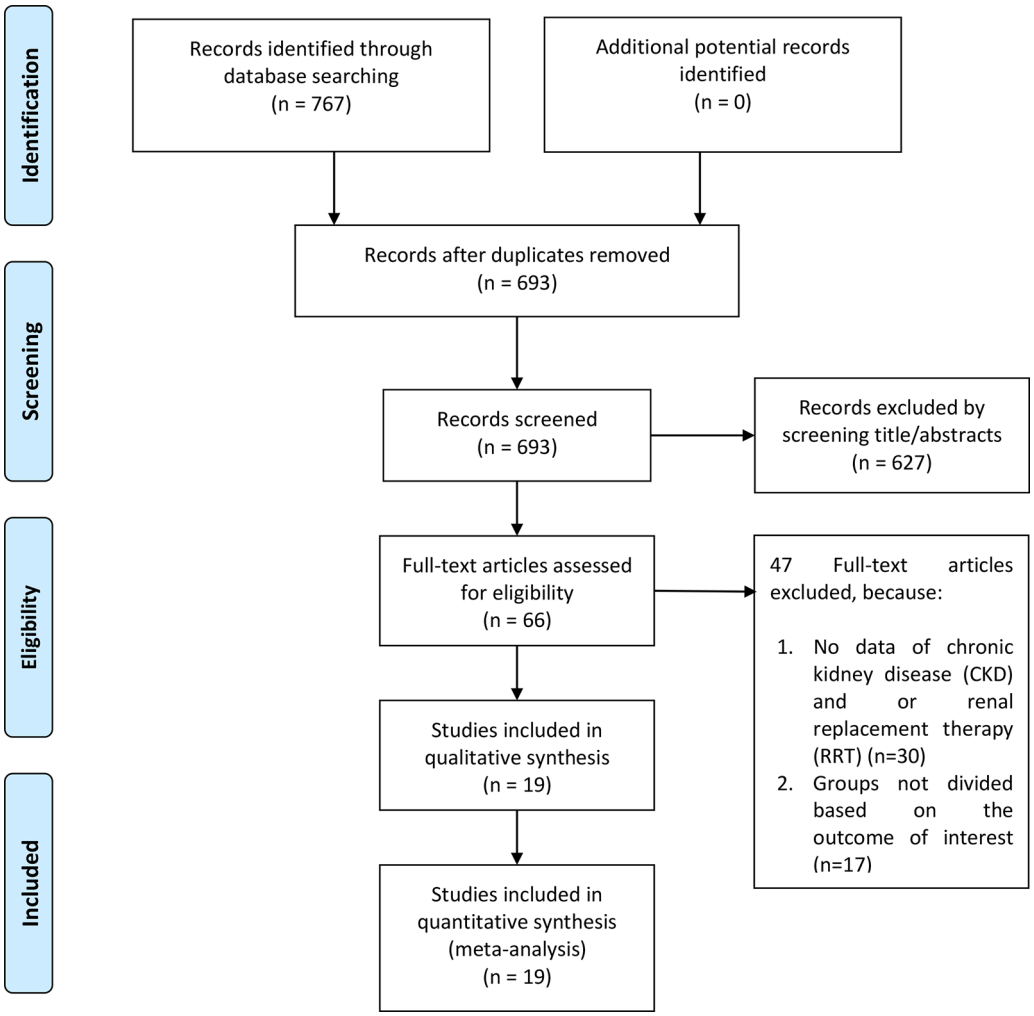


Figure 1. PRISMA flowchart.

Renal replacement therapy and poor outcome in COVID-19

The new onset RRT was associated with increased composite poor outcome (RR 18.04 [4.44, 73.25], $P < .001$; I^2: 87%, $P < .001$). Subgroup analysis also showed significantly increased risk for mortality (RR 26.02 [5.01, 135.13], $P < .001$; I^2: 60%, $P = .06$), severe COVID-19 (RR 12.95 [1.93, 86.82], $P = .008$; I^2: 81%, $P < .001$), intensive care (RR 14.22 [1.76, 114.62], $P < .01$; $I^2 = 0\%$, $P < .98$), and the need for mechanical ventilation (RR 34.39 [4.63, 255.51], $P < .0005$) (Figure 2(b)]. Leave-one-out sensitivity analysis by removing the study of Richardson et al resulted in 0% heterogeneity for mortality (RR 10.75 [2.58, 44.88], $P = .001$; I^2: 0%, $P = .39$), whereas removing the study of Hu et al resulted in an almost 2-fold increase in the risk of severe COVID-19 (RR 22.95 [6.74, 78.12], $P < .001$; I^2: 0%, $P = .44$) and composite poor outcome (RR 28.12 [13.69, 57.79], $P < .001$; I^2: 13%, $P = .32$).

Meta-regression

Meta-regression showed that the association between CKD and composite poor outcome was not influenced by sex ($P = .803$), respiratory comorbidities ($P = .104$), and RRT ($P = .164$), but was significantly affected by age ($P = .019$), hypertension ($P = .019$), cardiovascular diseases ($P = .041$), and diabetes ($P = .001$). In contrast, the meta-regression analysis on the association between RRT and composite poor outcome was not affected by any variables, including age ($P = .623$), sex ($P = .731$), cardiovascular diseases ($P = .170$), hypertension ($P = .551$), diabetes ($P = .375$), respiratory comorbidities ($P = .697$), and CKD ($P = .668$).

Publication bias

Funnel plots were asymmetrical for the association of both CKD (Figure 3(a)) and RRT (Figure 3(b)) with composite poor outcome. Regression-based Harbord's test showed a statistically

Table 1. Study characteristics.

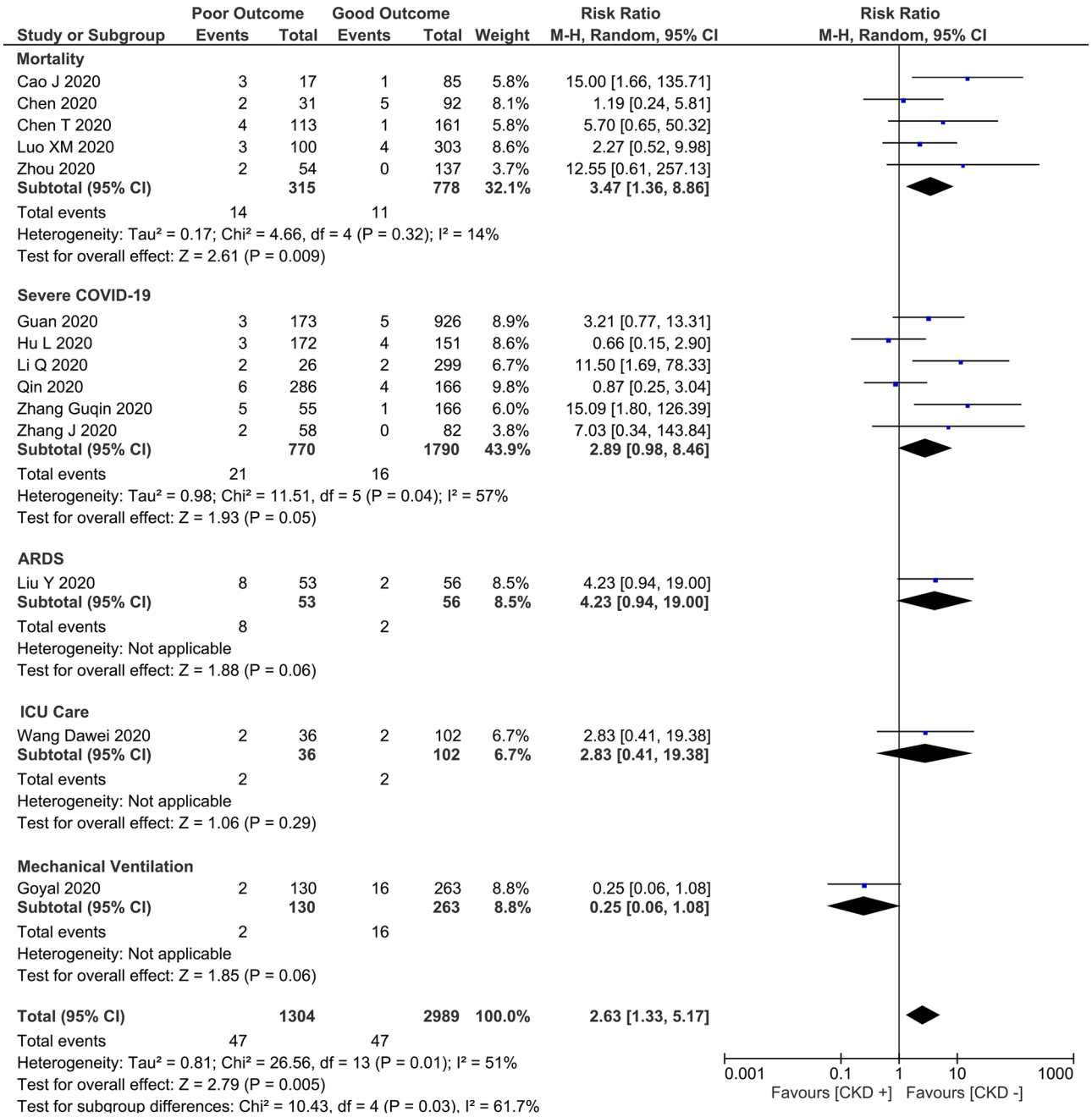
AUTHORS	STUDY DESIGN*	SAMPLES (POOR VS GOOD OUTCOME)	OUTCOME OF INTEREST	MALE (%)	AGE (MEAN/MEDIAN) (YEARS)	CKD (%)	BASELINE CREATININE (MEAN/MEDIAN) (μMOL/L)	RRT (%)
Cao[27] (Cao, Tu and Cheng, 2020)	Retrospective	102 (17 vs 85)	Mortality	76.5 vs 47.1	72 vs 53	17.6 vs 1.2	NR	NR
Chen[28] (Chen, Fan and Wu, 2020)	Retrospective	123 (31 vs 92)	Mortality	71.0 vs 42.0	72 vs 53	6.5 vs 5.4	150.0 vs 67.8	NR
Chen[26] (Chen, Wu and Chen, 2020)	Retrospective	274 (113 vs 161)	Mortality	73.0 vs 55.0	68 vs 51	3.5 vs 0.6	88.0 vs 66.0	3.0 vs 0
Luo[29] (Luo, Xia and Yang, 2020)	Retrospective	403 (100 vs 303)	Mortality	57.0 vs 44.9	71 vs 49	3.0 vs 1.3	82.0 vs 68.0	NR
Yang[30] (Yang, Yu and Xu,)	Retrospective	52 (32 vs 20)	Mortality	66.0 vs 70.0	64 vs 51	NR	80.7 vs 76.3	25.0 vs 5.0
Zhou[25] (Zhou, Yu and Du, 2020)	Retrospective	191 (54 vs 137)	Mortality	70.0 vs 59.0	69 vs 52	4.0 vs 0	NR	19.0 vs 0
Richardson[31] (Richardson, Hirsch and Narasimhan, 2020)	Retrospective	2634 (553 vs 2081)	Mortality	60.9 vs55.8	63 (Total)	NR	NR	14.1 vs 0.1
Guan[2] (Guan, Ni and Hu, 2020)	Retrospective	1099 (173 vs 926)	Severe COVID-19	57.8 vs 38.2	52 vs 45	1.7 vs 0.5	NR	5.2 vs 0
Hu[32] (Hu, Chen and Fu, 2020)	Retrospective	323 (172 vs 151)	Severe COVID-19	52.9 vs 49.7	65 vs 56	1.7 vs 2.6	NR	27.9 vs 17.2
Li[16] (Li, Ling and Zhang,)	Retrospective	325 (26 vs 299)	Severe COVID-19	76.9 vs 49.2	65 vs 49	7.7 vs 0.6	80.0 vs 62.0	11.5 vs 0
Liu[17] (Liu, Liu and Xiang, 2020)	Prospective	61 (17 vs 44)	Severe COVID-19	58.8 vs 47.7	56 vs 41	NR	64.0 vs 56.5	NR
Qin[18] (Qin, Zhou and Hu, 2020)	Retrospective	452 (286 vs 166)	Severe COVID-19	54.2 vs 48.2	61 vs 53	2.1 vs2.4	NR	NR
Wan[19] (Wan, Xiang and Fang, 2020)	Retrospective	135 (40 vs 135)	Severe COVID-19	52.5 vs 54.7	56 vs 44	NR	63.5 vs 66.0	10.0 vs 1.0
Zhang[20] (Zhang, Hu and Luo, 2020)	Retrospective	221 (55 vs 166)	Severe COVID-19	63.6 vs 44.0	62 vs 51	9.1 vs 0.6	75.0 vs 67.0	7.3 vs 0.6
Zhang[21] (Zhang, Dong and Cao, 2020)	Retrospective	140 (58 vs 82)	Severe COVID-19	56.9 vs 46.3	$<$30 (1.7 vs 4.9), 30-49 (15.5 vs 34.1), 50-69 (48.3 vs 50), $\geqslant$70 (34.5 vs 11.0)	3.4 vs 0	NR	NR
Liu[15] (Liu, Yang and Zhang, 2020)	Retrospective	109 (53 vs 56)	ARDS	52.8 vs 55.4	61 vs 49	15.1 vs 3.6	67.0 vs 64.0	NR
Huang[22] (Huang, Wang and Li, 2020)	Retrospective	41 (13 vs 28)	ICU Care	85.0 vs 68.0	49 vs 49	NR	79.0 vs 73.0	23.0 vs 0
Wang[23] (Wang, Hu and Hu, 2020)	Retrospective	138 (36 vs 102)	ICU Care	61.1 vs 52.0	66 vs 51	5.6 vs 2.0	80.0 vs 71.0	5.6 vs 0
Goyal[24] (Goyal, Choi and Pinheiro, 2020)	Retrospective	393 (130 vs 263)	Mechanical Ventilaton	70.8 vs 55.5	64 vs 61	1.5 vs 6.1	NR	13.3 vs 0.4

Data presentation: poor outcome vs good outcome.
Abbreviations: ARDS, acute respiratory distress syndrome; CKD, chronic kidney disease; COVID-19, Coronavirus disease 2019; ICU, intensive care unit; NR: not reported; RRT, renal replacement therapy.
*All the studies were observational.

significant small-study effect with CKD ($P<.001$) but not with RRT ($P=.359$).

Discussion

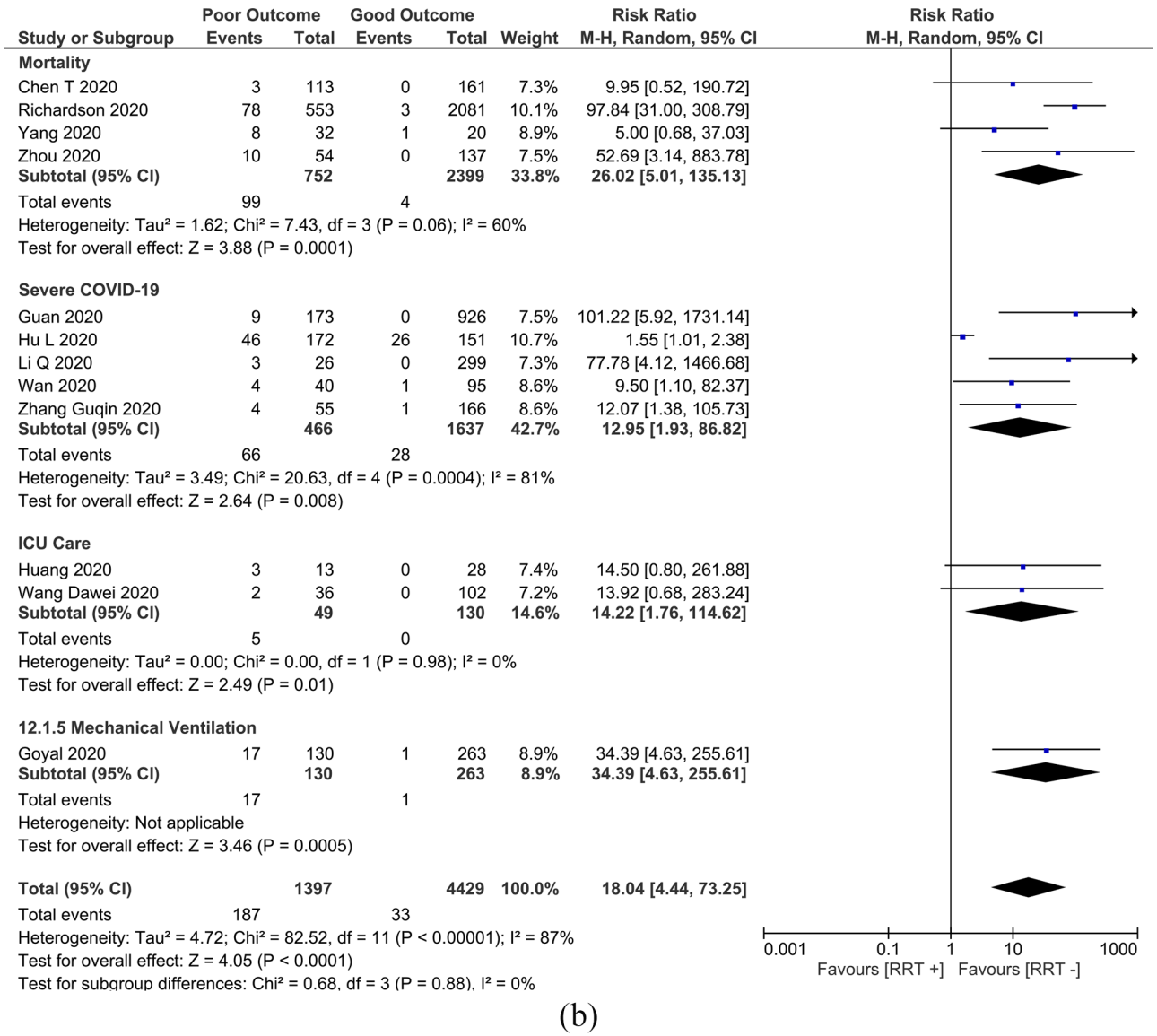
This meta-analysis showed that CKD was associated with and presents approximately 3-fold higher risk of mortality and severe COVID-19. Meta-regression analysis showed that the association between CKD and COVID-19 outcome was affected by age, hypertension, cardiovascular diseases, and diabetes. The results of this study reinforce our previous theory on the intertwined relationships of hypertension, diabetes, age, and CKD with the severe COVID-19,[3,4] culminating in the rationalization of renin-angiotensin system (RAS) signaling and angiotensin converting enzyme 2 (ACE2). It was demonstrated that individuals with CKD have increased levels of circulating ACE2,[12] which facilitates the entry of SARS-CoV-2 and may later be downregulated by the virus, leading to unregulated angiotensin-2 activity and multiple



(a)

(Continued)

Figure 2. (Continued)



(b)

Figure 2. Chronic kidney disease (CKD), renal replacement therapy (RRT), and poor outcome. The forest plot showed that CKD was associated with increased composite poor outcome and its subgroup, which consists of mortality and severe COVID-19 (a). The forest plot showed that RRT was associated with increased composite poor outcome and its subgroup, which consists of mortality, severe COVID-19, intensive care, and the use of mechanical ventilator in COVID-19 (b).
Abbreviations: ARDS: acute respiratory distress syndrome; CKD: chronic kidney disease; COVID-19: Coronavirus Disease 2019; IC: intensive care.

organ failure.[15,33,34] Moreover, the baseline serum creatinine levels of most patients included in this study were within the normal reference range. This might indicate that having early-stage CKD may increase the risk of poor outcome in COVID-19; however, further studies regarding the association between CKD stage and poor outcome must be sought. Other remarkable variables of interest that should be included in the analysis were the use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB) for hypertension, CKD, and cardiovascular disease. There have been speculations that these drug classes may reduce the severity of COVID-19; previous studies showed that the use of ACEI/ARB in hypertensive individuals was associated with a significant decrease in mortality of COVID-19 patients.[35,36] It was unfortunate that the data on these drug classes were lacking in all the included studies.

RRT is an advanced intervention in patients with kidney injury that is seldom reported in COVID-19 patients.[2,25,26] In this meta-analysis, we found that new-onset RRT was significantly associated with composite poor outcome, including mortality, severity, need for intensive care, ARDS, and the use of mechanical ventilator in patients with COVID-19. The increased risk for mortality was more than 25-fold compared to COVID-19 patients not receiving RRT. An interesting finding

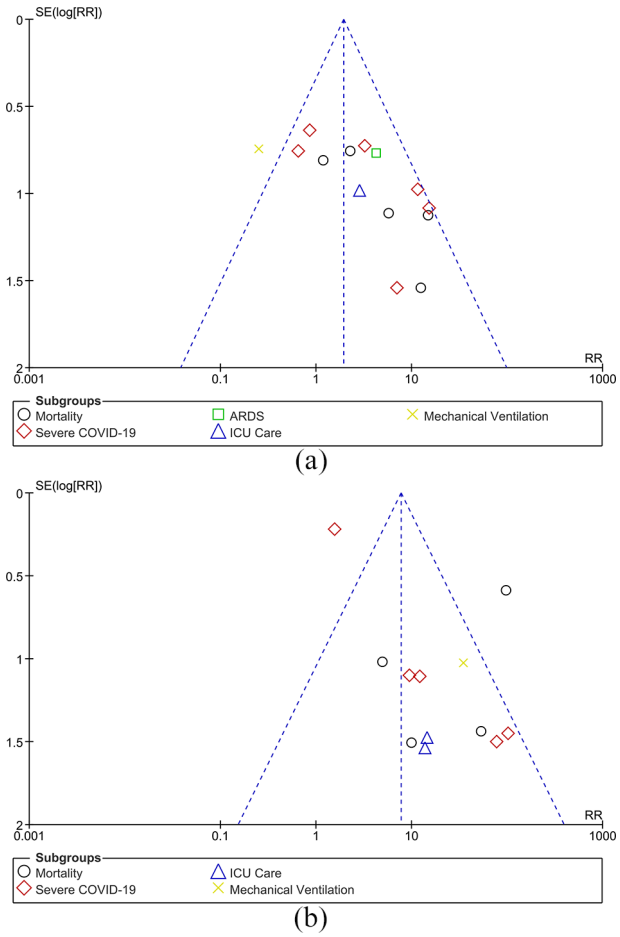


Figure 3. Funnel plots showed asymmetrical association of both chronic kidney disease (a) and renal replacement therapy (b) with composite poor outcome.

of this meta-regression analysis was that there were no variables that affected the association between RRT and poor outcome, including age, sex, cardiovascular diseases, hypertension, diabetes, respiratory comorbidities, and CKD.

A logical explanation for these findings is the direct effect of SARS-COV-2 on the kidney due to the abundant expression of ACE2 in tubular cells of the kidney.[37] Another possible explanation is that the hyper-inflammatory response caused by cytokine storms, rather than the direct invasion by SARS-CoV-2, is the primary causative of multi-organ failure including kidney injury.[38]

The impact of early versus late RRT initiation in critically ill patients with AKI is a contentious issue that is important to explore. Randomized controlled trial (RCT) in non-COVID-19 patients showed that early initiation of continuous renal replacement therapy (CRRT) within 8 hours following AKI stage II is associated with a significantly lower 90-days mortality rate compared to patients receiving CRRT within 12 hours after AKI Stage III diagnosis.[39] Conversely, another RCT reported no differences in terms of 90-days mortality between the approaches. Although a recent meta-analysis showed no mortality benefits between the 2 strategies, they note that the contradictory evidence is due to substantially heterogeneous definition of CRRT timing and dosing among the trials.[40] Unfortunately, all of the included studies in this meta-analysis did not report the timing of RRT initiation. Thus, the supposition whether the timing of RRT initiation might affect the outcome of COVID-19 patient cannot be explored by our study.

In the context of cytokine storm syndrome (CSS) with AKI and multi-organ failure in severe COVID-19,[41,42] there is a growing interest in using cytokine filtration through the extracorporeal techniques, including the high cutoff (HCO) membrane and CytoSorb.[43] Both blood purification strategies are considered effective in reducing inflammatory cytokines (especially IL-6),[44] but whether these approaches can effectively reduce mortality and severity in patients with COVID-19 is still unknown. In the absence of established treatment options for COVID-19, experts across the globe recommended these approaches to facilitate cytokine clearance.[44,45]

Other contentious issue concerning the RRT among patients with severe COVID-19 is the type of anticoagulation used during the process of RRT. Hypercoagulable state is considered as a hallmark of severe COVID-19 as depicted by the increased of serum D-dimer values and high rate of blood circuit failures in the process of RRT.[41,46,47] While regional citrate anticoagulation has been universally used in CRRT because of its efficacy in terms of prolonging the extracorporeal circuit lifespan and decreasing the risk of bleeding,[45] it has not been demonstrated to be as effective in COVID-19 as in other patients.[47] Furthermore, the discovery of the mortality benefits using heparin-based anticoagulation approach leads to a further question whether this citrate-based anticoagulation in CRRT is the best approach in patients with severe COVID-19.[48]

This current study reinforced previous meta-analyses concerning the association of renal impairment with severity of COVID-19.[49,50] Henry and Lippi reported in their meta-analysis that the presence of CKD are associated with severe COVID-19; however, they only included 4 studies with a total of 1389 COVID-19 patients.[49] Meanwhile, Ali et al showed that the presence of severe AKI is associated with high mortality among patients with COVID-19.[50] However, their meta-analysis only included 2 studies which required RRT. On the other hand, our meta-analysis included more studies with relatively higher samples and further meta-regression analysis which was not previously conducted. Thus, the evidence of the association between CKD and RRT with poor outcome is further strengthened by our findings.

The limitation of this meta-analysis was the presence of publication bias for both CKD and RRT on composite poor outcome, which was apparent in the asymmetrical funnel plot analysis. In addition, there were small-study effects for CKD. The inclusion of studies that were published in preprint servers and not yet peer-reviewed may be a limitation; nevertheless, we considered the studies as potential addition to the current literature. Moreover, the retrospective and observational nature of the included studies warrant careful interpretation in our findings.

Clinical implications

CKD and RRT were associated with composite poor outcome in patients with COVID-19. Although the risk for poor outcome was affected by other comorbidities associated with the RAS system, the presence of CKD should still be investigated when admitting patients with COVID-19, as it increases the risk of severe disease and mortality. Furthermore, the baseline serum creatinine level in most patients included in this study was within the normal reference range. This might possibly indicate that even early-stage CKD can increase the risk of poor outcome in patients with COVID-19. Furthermore, the presence of complications that necessitated RRT was associated with a more than 25-fold increased risk of mortality in COVID-19 patients.

Conclusion

CKD and RRT are associated with poor outcome in patients with COVID-19. The association between CKD and poor outcome in COVID-19 was influenced by other variables that might be interconnected with RAS.

Author Contributions

RP, RS, IH, and HP designed the study. RP and IH collected the data, drafted the manuscript, and accomplished data extraction and interpretation. AAL, RS, HP, IH, MAL, and EY performed extensive research. AAL, RS, HP, and NNMS critically reviewed and edited the manuscript. All authors contributed to the writing of the manuscript. RP performed the statistical analyses.

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