Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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The spatiotemporal trend of renal involvement in COVID-19: A pooled analysis of 17 134 patients

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ABSTRACT

Background: The spatiotemporal trend of renal involvement in coronavirus disease 2019 (COVID-19) patients is still unclear. Therefore, the aim of this study was to reveal the dynamics of renal involvement superimposed COVID-19 according to time and space.

Methods: COVID-19 patients reporting renal involvement were included in this study. The following information was collected from relevant articles: first author, patient demographics, patient enrollment period, location, definition of acute kidney injury (AKI), prevalence of AKI, and use of renal replacement therapy (RRT).

Results: A total of 17 134 patients were finally included. The overall prevalence of AKI in COVID-19 patients was 19%, with 7% of them undergoing RRT. The overall risk of AKI in patients enrolled before March 1, 2020 (9%) was significantly lower than that after March 1, 2020 (36%) ($P < 0.00001$). Moreover, the overall risk of AKI outside Asia (35%) was significantly higher than that in Asia (10%) ($P < 0.00001$). Additionally, similar to patients requiring RRT, AKI patients were more likely to become seriously ill or even to die ($P < 0.00001$).

Conclusions: This study found that renal involvement superimposed COVID-19, a comorbidity portending a poor prognosis, has become an increasingly serious problem over time and is more common outside Asia. Thus, more attention should be paid to the management of this specific group of patients.

Introduction

Coronavirus disease 2019 (COVID-19) is a novel respiratory infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has reopened the issue of the role and importance of coronaviruses in human pathology (World Health Organization, 2020a). In fact, only seven coronaviruses are known to be zoonotic, with the ability to jump from animals to humans. Four of them cause mild illnesses, such as the common cold, while the other three types have had more catastrophic consequences: severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and now SARS-CoV-2 (Čivljak et al., 2020).

Taking account of the alarming levels of spread and severity worldwide, COVID-19 has been declared as a pandemic by the World Health Organization (WHO), and no country could manage alone or stand aloof (World Health Organization, 2020b). The numbers of affected countries, cases, and deaths are climbing sharply, at an alarming rate. Up to June 30, 2020, more than 210 countries and territories had been affected by the crisis, with a total of 10 185 374 confirmed cases and 503 962 deaths (World Health Organization, 2020c). Moreover, COVID-19 has had a great impact on mental health, education, finance, transportation, the economy, and so on (Codagnone et al., 2020; Gautam and Sharma,

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2020; McKee and Stuckler, 2020; Sharma and Sharma, 2020a; Sharma et al., 2020b).

Early screening for clinical suspicion could effectively control this spread. In addition to the common symptoms of fever, fatigue, and an unproductive cough, the clinical manifestations in patients with COVID-19 include diarrhea, septic shock, and even multiple organ dysfunction syndromes (Wang et al., 2020a). Comorbidity superimposed COVID-19 is usually an indicator of more severe disability and a lower survival rate in affected patients. Although a recent study has suggested that renal involvement is uncommon in COVID-19 (Wang et al., 2020b), it may lead to a poor prognosis when acute kidney injury (AKI) develops in COVID-19 patients. Furthermore, few studies have focused on the spatiotemporal trends of renal involvement superimposed COVID-19. Therefore, the aim of this study was to conduct a pooled analysis of available studies reporting renal involvement in COVID-19 based on the space–time structure.

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

Search strategy

All studies reporting renal involvement in COVID-19 patients and published up to June 30, 2020 were identified in the PubMed, Scopus, and Web of Science databases. The search words were "COVID-19", "coronavirus disease 2019", "SARS-CoV-2", "severe acute respiratory syndrome coronavirus 2", "nCoV", "novel coronavirus", "corona virus", "kidney", "renal", and "nephrology". References cited in the retrieved original articles were also reviewed. There was no restriction on language. Two investigators (YFF and KPW) independently analyzed these publications by title and abstract. Full texts were reviewed to identify any potentially relevant studies.

Study selection and outcome measures

To be included in this study, the articles had to meet the following criteria: (1) study with an observational design; (2) study sample of more than 10 patients; (3) study patients with confirmed SARS-CoV-2 infection; (4) study reporting the prevalence of AKI in COVID-19 patients.

The following articles were excluded: (1) repeatedly published articles; (2) editorial, commentary, guidance, perspective, reply, review, and single case reports; (3) studies containing uncertain data; (4) studies lacking available data; and (5) studies on other coronavirus diseases, such as SARS and MERS.

The primary outcome in this study was the prevalence of AKI superimposed COVID-19. The requirement of renal replacement therapy (RRT) was the secondary outcome.

Data extraction and quality assessment

Two investigators (YFF and KPW) independently conducted the data extraction and quality assessment; any disagreement was settled by a third investigator (BY). The following information was retrieved from each article: first author, patient demographics, patient enrollment period, location, definition of AKI, prevalence of AKI, and requirement for RRT. If necessary, the corresponding authors of included studies were contacted directly for additional data. Disease severity and mortality were defined according to the studies. If the authors did not report the severity classification of COVID-19, the patients who developed acute respiratory distress syndrome, needed mechanical ventilation, or were admitted to the intensive care unit were classified as severe cases. The risk of bias was assessed using the quality assessment tool for case-series studies published by the National Institutes of Health, which poses nine questions, such as the study objective, study population, and study intervention (Mao et al., 2020).

Data analysis

Review Manager version 5.3 (Cochrane Collaboration) and Microsoft Excel (Microsoft Corporation) were used for the data analysis. Subgroup analyses were performed according to (1) the location of the study; (2) the patient enrollment period; (3) the severity of the disease; and (4) the mortality of the disease. To calculate the pooled estimated prevalence with 95% confidence intervals (CI) of AKI and RRT in COVID-19 patients, two simple formulas enumerated by Chen et al. to evaluate the probability and its standard error were employed (Chen et al., 2014). Risk ratios (RRs) with 95% CI of the outcome measures were used for the subgroup analyses based on disease severity and mortality. For the robustness of the pooled effects, the meta-analyses were conducted with the random-effects model by inverse variance method. Publication bias was examined by the symmetry of the funnel plot (Mao et al., 2020). Significant heterogeneity within and/or between studies was defined when $I^2 > 50\%$; otherwise, the heterogeneity was not considered substantial. $P < 0.05$ was considered statistically significant (Yi et al., 2020).

Results

Search results

Initially, 2751 records were retrieved, including 606 from PubMed, 1649 from Scopus, and 496 from Web of Science. After removing 809 duplicate records, 1849 records were also eliminated based on the title and abstract. Finally, following the full-text evaluation of 93 potentially relevant studies, a total of 30 eligible studies were identified for inclusion in this study (Aggarwal et al., 2020; Antinori et al., 2020; Argenziano et al., 2020; Bhargava et al., 2020; Cao et al., 2020a; Chen et al., 2020a,b; Cheng et al., 2020; Cummings et al., 2020; Deng et al., 2020; Hirsch et al., 2020; Hong et al., 2020; Li et al., 2020a,b,c; Malberti et al., 2020; Pei et al., 2020; Richardson et al., 2020; Shi et al., 2020a,b; Wang et al., 2020c; Yang et al., 2020a,b,c,d; Yu et al., 2020; Zhang et al., 2020a,c; Zhao et al., 2020; Zheng et al., 2020) (Figure 1).

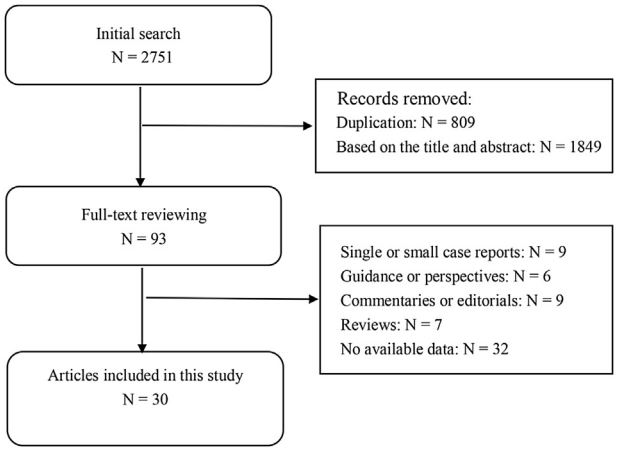

Figure 1. Flow diagram of the study selection.

Study characteristics

Overall, the 30 studies included 17 134 patients. Thirteen studies described the prevalence of AKI in patients with severe versus non-severe COVID-19 (Aggarwal et al., 2020; Antinori et al., 2020; Argenziano et al., 2020; Bhargava et al., 2020; Cao et al., 2020a; Chen et al., 2020a; Hirsch et al., 2020; Hong et al., 2020; Pei et al., 2020; Yang et al., 2020b; Zhang et al., 2020a; Zhao et al., 2020; Zheng et al., 2020) and five studies described the ratio of the probability of AKI in COVID-19 survivors versus non-survivors (Chen et al., 2020b; Deng et al., 2020; Richardson et al., 2020; Wang et al., 2020c; Yang et al., 2020d). In the majority of studies, AKI was defined according to the 'Kidney Disease: Improving Global Outcomes' (KDIGO) criteria (Yi et al., 2017).

The patients were enrolled during different periods in these studies: 20 studies enrolled patients before March 1, 2020 (Cao et al., 2020a; Chen et al., 2020a,b; Cheng et al., 2020; Deng et al., 2020; Li et al., 2020a,b,c; Pei et al., 2020; Shi et al., 2020a,b; Wang et al., 2020c; Yang et al., 2020a,b,c,d; Yu et al., 2020; Zhang et al., 2020a,c; Zhao et al., 2020) and six studies enrolled patients after March 1, 2020 (Aggarwal et al., 2020; Argenziano et al., 2020; Bhargava et al., 2020; Cummings et al., 2020; Hirsch et al., 2020; Richardson et al., 2020).

In addition, the locations differed across the 30 studies: one was from South Korea (Hong et al., 2020), two from Italy (Antinori et al., 2020; Malberti et al., 2020), six from the United States (Aggarwal et al., 2020; Argenziano et al., 2020; Bhargava et al., 2020; Cummings et al., 2020; Hirsch et al., 2020; Richardson et al., 2020), and the others were from China (Cao et al., 2020a; Chen et al., 2020a,b; Cheng et al., 2020; Deng et al., 2020; Li et al., 2020a,b,c; Pei et al., 2020; Shi et al., 2020a,b; Wang et al., 2020c; Yang et al., 2020a,b,c,d; Yu et al., 2020; Zhang et al., 2020a,c; Zhao et al., 2020; Zheng et al., 2020).

The quality score of all studies ranged from 5 to 6, representing a moderate risk of bias (Supplementary material Table S1). The main characteristics and quality assessment scores of these studies are summarized in Table 1.

Study outcomes

The prevalence of AKI in the 30 studies varied from 0.3% to 68.8%. AKI occurred in 4197 COVID-19 patients, with a pooled probability of 19% (95% CI 13–24%, I^2 = 99%) calculated in the analysis (Figure 2).

Due to the high heterogeneity, the possible confounders in these studies were explored. As reported in Table 1, the 30 studies were conducted over different periods. The subgroup analysis based on the cut-off time point of March 1, 2020 indicated that high heterogeneity existed before and after this time point (Chi-square = 46.29, df = 1, I^2 = 97.8%; Table 2). AKI occurred in 329 out of 4256 patients enrolled before March 1, 2020 among 20 studies (Cao et al., 2020a; Chen et al., 2020a,b; Cheng et al., 2020; Deng et al., 2020; Li et al., 2020a,b,c; Pei et al., 2020; Shi et al., 2020a,b; Wang et al., 2020c; Yang et al., 2020a,b,c,d; Yu et al., 2020; Zhang et al., 2020a,c; Zhao et al., 2020) and in 3824 out of 12 469 patients after March 1, 2020 among six studies (Aggarwal et al., 2020; Argenziano et al., 2020; Bhargava et al., 2020; Cummings et al., 2020; Hirsch et al., 2020; Richardson et al., 2020). Overall, there was a significant difference in the pooled risk of AKI between patients enrolled before March 1, 2020 (9%, 95% CI 7–12%) and those enrolled after that time point (36%, 95% CI 28–43%) (P < 0.00001).

During the analysis, it was observed that the 30 studies were from four countries: South Korea, Italy, the United States, and China. Given that South Korea and China are located in Asia, the subgroup analysis was conducted based on studies in and outside

Table 1
Characteristics of the included studies.

First author	Number of patients	Duration of enrolment	Location	Severity/survival reported	AKI definition	Quality score
A. Bhargava et al.	197	Mar 8, 2020–Apr 8, 2020	USA	Severity reported	KDIGO	5
D. Li et al.	163	Jan 31, 2020–Feb 18, 2020	China	NR	KDIGO	5
D. Wang et al.	107	Jan 2020–Feb 10, 2020	China	Survival reported	KDIGO	5
F. Malberti et al.	51	Feb 20, 2020–Apr 15, 2020	Italy	NR	KDIGO	5
F. Yang et al.	92	Jan 6, 2020–Feb 25, 2020	China	NR	Elevated SCr	5
G. Chen et al.	21	Late Dec 2019–Jan 27, 2020	China	Severity reported	KDIGO	5
G. Pei et al.	333	Jan 28, 2020–Feb 9, 2020	China	Severity reported	KDIGO	5
G. Zhang et al.	221	Jan 2, 2020–Feb 10, 2020	China	Severity reported	NR	5
J. Cao et al.	102	Jan 3, 2020–Feb 1, 2020	China	Severity reported	NR	5
J. Hirsch et al.	5449	Mar 1, 2020–Apr 5, 2020	USA	Severity reported	KDIGO	5
K. Hong et al.	98	Dec 2019– Mar 29, 2020	South Korea	Severity reported	KDIGO	6
M. Argenziano et al.	1000	Mar 1, 2020–Apr 5, 2020	USA	Severity reported	NR	6
M. Cummings et al.	257	Mar 2, 2020–Apr 1, 2020	USA	NR	Need for RRT	5
M. Shi et al.	161	Jan 1, 2020–Mar 1, 2020	China	NR	NR	6
Q. Yang et al.	136	Jan 28, 2020–Feb 12, 2020	China	Severity reported	NR	5
R. Yang et al.	212	Jan 11, 2020–Mar 16, 2020	China	NR	KDIGO	6
S. Aggarwal et al.	16	Mar 1, 2020–Apr 4, 2020	USA	Severity reported	Elevated SCr	5
S. Antinori et al.	35	Feb 23, 2020–Mar 20, 2020	Italy	Severity reported	Elevated SCr	6
S. Richardson et al.	5700	Mar 1, 2020–Apr 4, 2020	USA	Survival reported	Elevated SCr	6
S. Shi et al.	416	Jan 20, 2020–Feb 10, 2020	China	NR	KDIGO	6
T. Chen et al.	274	Jan 13, 2020–Feb 12, 2020	China	Survival reported	KDIGO	5
X. Li et al.	25	Jan 14, 2020–Feb 13, 2020	China	NR	Elevated SCr/BUN	5
X. Yang et al.	52	Dec 24, 2019–Jan 26, 2020	China	Survival reported	KDIGO	5
X. Zhang et al.	645	Jan 17, 2020–Feb 8, 2020	China	NR	NR	5
X. Zhao et al.	91	Jan 16, 2020–Feb 10, 2020	China	Severity reported	Elevated SCr/UA	5
Y. Cheng et al.	701	Jan 28, 2020–Feb 11, 2020	China	NR	KDIGO	6
Y. Deng et al.	225	Jan 1, 2020–Feb 21, 2020	China	Survival reported	NR	5
Y. Li et al.	54	Jan 28, 2020–Feb 11, 2020	China	NR	Reduced eGFR	5
Y. Yu et al.	226	Feb 26, 2020– Feb 27, 2020	China	NR	KDIGO	5
Y. Zheng et al.	34	Jan 22, 2020–Mar 5, 2020	China	Severity reported	KDIGO	5

AKI, acute kidney injury; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; NR, not reported; RRT, renal replacement therapy; SCr, serum creatinine; UA, uric acid.

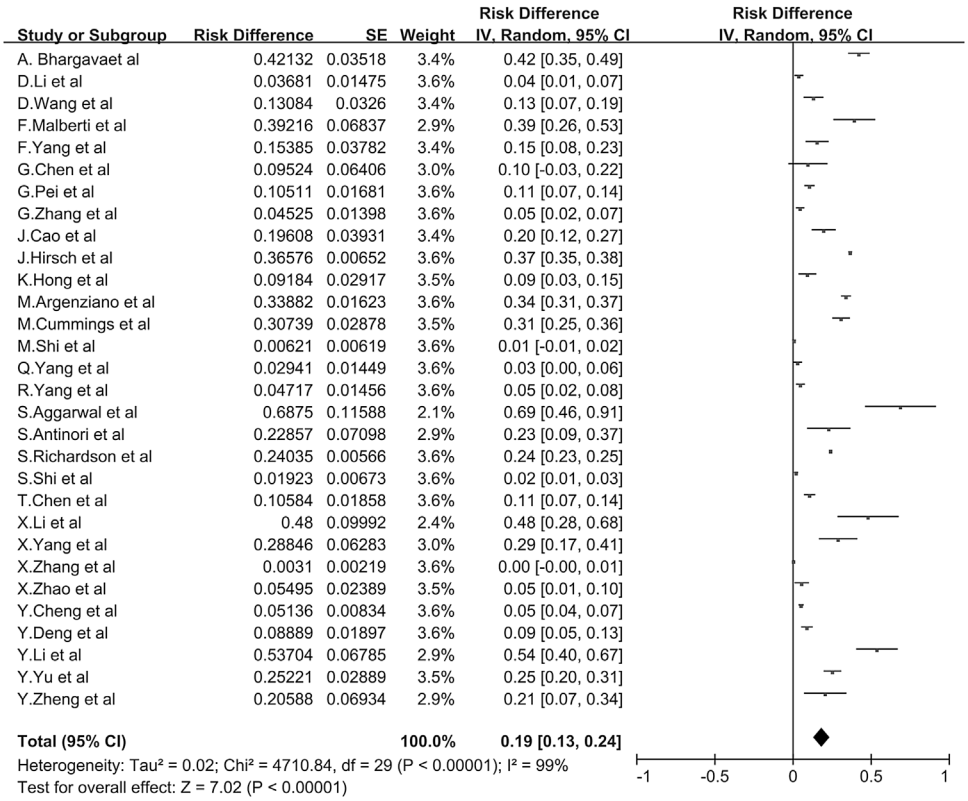

Figure 2. Forest plot of the overall risk of acute kidney injury. (Abbreviations: SE, standard error; IV, inverse variance method; CI, confidence interval).

Table 2
Subgroup analyses for the overall risk of AKI.

Subgroup	Number of studies	Number of patients	Cases of AKI	Pooled probability	95% CI	Subgroup difference	
						I^2 (%)	*P*-value
Enrolment duration						97.8	<0.00001
Before March 1, 2020	20	4256	329	0.09	0.07–0.12		
After March 1, 2020	6	12 469	3824	0.36	0.28–0.43		
Location						98.1	<0.00001
Asia	22	4388	345	0.10	0.07–0.12		
Non-Asia	8	12 555	3852	0.35	0.28–0.41		

AKI, acute kidney injury; CI, confidence interval.

Asia. The test for subgroup differences is shown in Table 2 (Chi-square = 40.29, df = 1, I^2 = 97.5%). AKI developed in 345 out of 4388 patients among 22 studies in Asia (Cao et al., 2020a; Chen et al., 2020a,b; Cheng et al., 2020; Deng et al., 2020; Hong et al., 2020; Li et al., 2020a,b,c; Pei et al., 2020; Shi et al., 2020a,b; Wang et al., 2020c; Yang et al., 2020a,b,c,d; Yu et al., 2020; Zhang et al., 2020a,c; Zhao et al., 2020; Zheng et al., 2020) and in 3852 out of 12 555 patients among eight studies outside Asia (Aggarwal et al., 2020; Antinori et al., 2020; Argenziano et al., 2020; Bhargava et al., 2020; Cummings et al., 2020; Hirsch et al., 2020; Hong et al., 2020; Malberti et al., 2020; Richardson et al., 2020). The pooled risk of AKI in Asia (10%, 95% CI 7–12%) was significantly lower than that outside Asia (35%, 95% CI 28–41%) (P < 0.00001).

Compared with those who had non-severe COVID-19, patients with severe COVID-19 showed a significantly higher risk of developing AKI (13 studies, 7583 patients: RR 3.72, 95% CI 2.65–5.32, P < 0.00001; I^2 = 79%; Figure 3A) (Aggarwal et al., 2020; Antinori et al., 2020; Argenziano et al., 2020; Bhargava et al., 2020; Cao et al., 2020a; Chen et al., 2020a; Hirsch et al., 2020; Hong et al., 2020; Pei et al., 2020; Yang et al., 2020b; Zhang et al., 2020a; Zhao et al., 2020; Zheng et al., 2020). Moreover, COVID non-survivors showed a statistically significant higher risk of developing AKI when compared to survivors (five studies, 6358 patients: RR 10.30, 95% CI 2.93–36.22, P < 0.00001; I^2 = 76%; Figure 3B) (Chen et al., 2020b; Deng et al., 2020; Richardson et al., 2020; Wang et al., 2020c; Yang et al., 2020d).

Overall, 792 of 13 982 COVID-19 patients in 15 studies needed RRT (Argenziano et al., 2020; Cao et al., 2020a; Chen et al., 2020b; Cummings et al., 2020; Hirsch et al., 2020; Hong et al., 2020; Malberti et al., 2020; Richardson et al., 2020; Shi et al., 2020a,b; Yang et al., 2020d; Yu et al., 2020; Zhang et al., 2020a; Zhao et al., 2020; Zheng et al., 2020), and the pooled requirement for RRT was 7% (95% CI 5–9%, I^2 = 96%) (Figure 4). Non-severe COVID-19 patients showed a significantly lower risk of RRT than severe COVID-19 patients (seven studies, 6845 patients: RR 0.06, 95% CI 0.02–0.25, P < 0.00001; I^2 = 89%; Figure 5A) (Argenziano et al., 2020; Cao et al., 2020a; Hirsch et al., 2020; Hong et al., 2020; Zhang et al., 2020a; Zhao et al., 2020; Zheng et al., 2020). In addition, RRT was less frequently required in COVID-19 survivors when compared to non-survivors (three studies, 6026 patients: RR 0.20, 95% CI 0.16–0.26, P

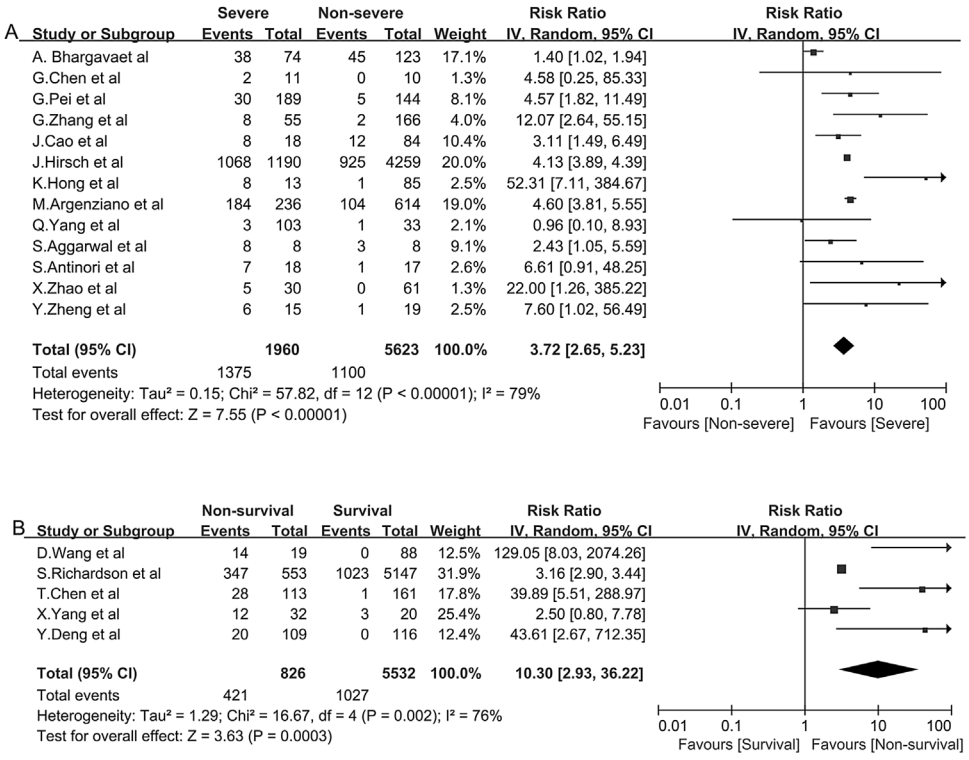

Figure 3. Forest plots for the comparison of the risk of acute kidney injury (AKI) between two groups. (A) Comparison between patients with severe disease and those with non-severe disease for the risk of AKI. (B) Comparison between survivors and non-survivors for the risk of AKI. (Abbreviations: IV, inverse variance method; CI, confidence interval).

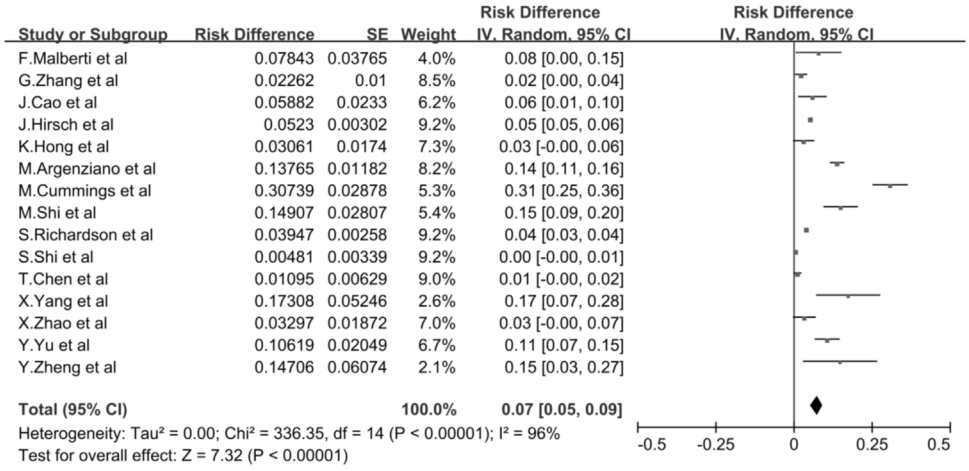

Figure 4. Forest plot of the overall requirement for renal replacement therapy. (Abbreviations: SE, standard error; IV, inverse variance method; CI, confidence interval).

< 0.00001; I^2 = 0%; Figure 5B) (Chen et al., 2020b; Richardson et al., 2020; Yang et al., 2020d).

Significant publication bias was noticed on the basis of the funnel plot for AKI (Supplementary material Figure S1) but not for RRT (Supplementary material Figure S2).

Discussion

Main findings

This study provides a comprehensive overview of the available evidence on the spatiotemporal trend of renal involvement in COVID-19. A total of 17 134 patients in 30 studies from four countries were included. The analysis revealed that the overall risk of AKI in COVID-19 patients was 19%, with a significant spatiotemporal difference. Moreover, patients with AKI, similar to patients who needed RRT, were found to be more likely to become seriously ill or even to die.

Interpretation

SARS-CoV-2 has caused the third coronavirus epidemic in the third millennium, after SARS-CoV and MERS-CoV (Čivljak et al., 2020). Coronaviruses, which belong to the family *Coronaviridae*, are a large group of RNA viruses named after their spiky structure that looks a bit like a corona, or crown (González et al., 2003). Like

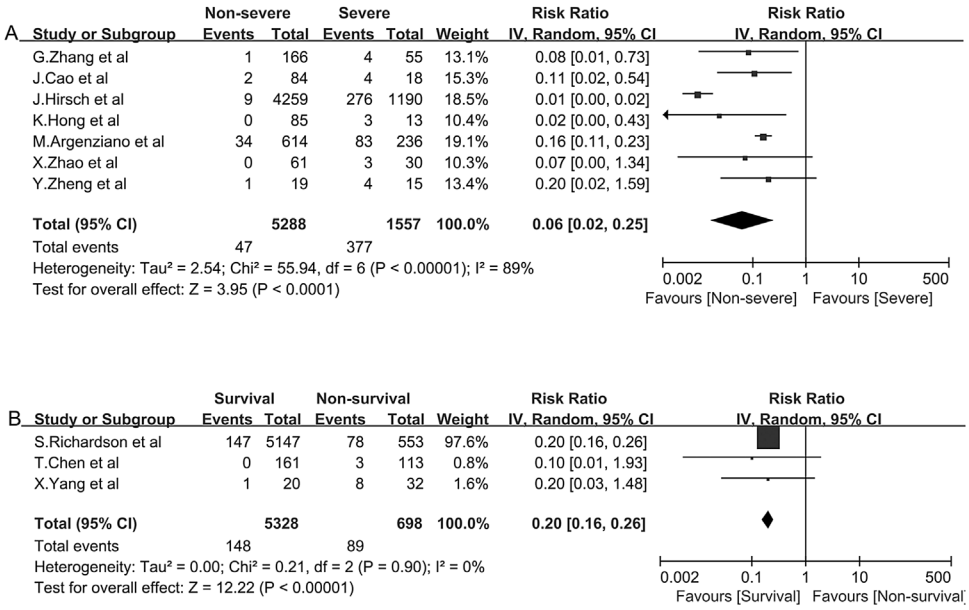

Figure 5. Forest plots for the comparison of the requirement for renal replacement therapy (RRT) between two groups. (A) Comparison between patients with severe disease and those with non-severe disease for the requirement for RRT. (B) Comparison between survivors and non-survivors for the requirement for RRT. (Abbreviations: IV, inverse variance method; CI, confidence interval).

other coronaviruses, SARS-CoV-2 is spherical with spike proteins, which allow the coronavirus to attach to cells that it can invade. Once a virus enters the human body through the eyes, mouth, or nose, it seeks cells with its favorite doorways—proteins called receptors. If the virus finds a compatible receptor, it can invade and start replicating itself. For SARS-CoV-2, this receptor is found across the entire body (Hirano and Murakami, 2020).

The attachment of SARS-CoV-2 spike protein to angiotensin-converting enzyme 2 (ACE2), the cellular receptor, can promote the invasion, replication, and intercellular transmission of the virus (Hirano and Murakami, 2020). Although there has been no evidence of glomerular involvement, immunohistochemistry has indicated that the SARS-CoV-2 nucleoprotein antigen is overexpressed in the tubular cells, and this is accompanied by severe acute tubular necrosis (Puelles et al., 2020). The biomolecular interactions between SARS-CoV-2 and ACE2 expressed in kidneys are considered to lead to the inevitable process of AKI in patients infected with this virus. On the other hand, immune-mediated disorders of the kidney could be one possible explanation for AKI in COVID-19. SARS-CoV-2 infection will result in disturbances of T1 and T2 immune responses (Hoiland et al., 2020), contributing to an increase in the levels of cytokines and chemokines including interleukin 4 (IL-4), interleukin 6 (IL-6), and interferon-inducible protein 10 (IP-10) (Hirano and Murakami, 2020). In addition, the toxicity of drugs might lead to AKI patients suffering from novel coronavirus pneumonia, based on the fact that pharmacotherapy is the key approach to manage it (Peng et al., 2020).

A surprising finding of this study was that the risk of AKI in patients with confirmed COVID-19 did not show a downward trend over time as expected. Instead, the subgroup analysis, according to the patient enrollment period, showed that the overall risk of AKI in patients enrolled after March 1, 2020 (36%) was higher than that in patients enrolled before March 1, 2020 (9%). The mutation of SARS-CoV-2 might have played a role in this finding. SARS-CoV-2 is an RNA virus with a high mutation rate, which can contribute to transmission and virulence. A recent study (Hu et al., 2020) that elaborated the dominant mutation of SARS-CoV-2 at position 614 of the spike protein (D614G mutation), reported that the proportion of the D614G strain in all SARS-CoV-2 increased from 0 in early 2020 to 70% in May 2020, indicating that the mutant strain had become the dominant strain globally. Moreover, Choe et al. found that the D614G mutation in SARS-CoV-2 could increase the number of spike proteins and facilitate viral invasion (Zhang et al., 2020b). During the present study, it was found that patients enrolled before March 1, 2020 were from Asia. Therefore, a further subgroup analysis based on location was performed.

Generally, there was less AKI in patients in Asia (10%) compared to patients outside Asia (35%). Given that the vast majority of the population in Italy and the United States are Caucasian, the study findings may be inextricably bound up with ethnic differences in the frequency of variants in ACE2, the cellular receptor of SARS-CoV-2. ACE2 variants, which are determined by genes, have been known to differ in frequency among populations (Cao et al., 2020b; Strafella et al., 2020). The virus might attach to receptors with higher affinity, if more ACE2 gene variants are expressed in the epithelial cells of the renal tubule among Caucasians. On the other hand, these ACE2 variants may be less expressed in Asians, who less frequently presented AKI among these COVID-19 patients. Moreover, it could be inferred that evident cultural differences also play an important role in the different risk between Caucasians and Asians, such as attitudes towards wearing a facemask, keeping a safe social distance, and strategies of containment.

Limitations

This study had some limitations. Firstly, as described above, the heterogeneity among the studies included was high, and publication bias was noticed for several outcomes. Therefore, caution should be taken when drawing conclusions, although heterogeneity was accounted for by using a random-effects model and performing subgroup analyses. Secondly, the definition of AKI was not uniform across all included studies; however, the KDIGO criteria were applied in most studies to define AKI. Nevertheless, we could not perform further investigations, due to the lack of information pertaining to the definition of AKI in some studies. Thirdly, the renal function indexes, including serum creatinine,

blood urea nitrogen, endogenous creatinine clearance rate, and estimated glomerular filtration rate, were not evaluated, as the raw data in the 30 studies were too scarce to conduct meta-analyses.

Conclusions

In conclusion, this study is novel in presenting an estimation of the spatiotemporal trend of renal involvement in COVID-19, which may act as a sign of deterioration. This study revealed that COVID-19 patients enrolled after March 1, 2020 had a higher risk of renal involvement than those enrolled before March 1, 2020. Also, compared to patients outside Asia, those in Asia had a lower risk of renal involvement. Constant vigilance and effort are required to manage these patients.

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Ethical approval and consent to participate

Not applicable.

Conflict of interest

The authors have no conflicts of interest to disclose.

Author contributions

YFF and KPW performed the literature search, screened for relevant studies, extracted data; JGM, YHX, LZW, and CJ analyzed the data, interpreted the results, and drafted the manuscript; XC and BY contributed equally as co-corresponding authors, conceived and designed the research, revised the manuscript, and offered suggestions. All authors approved the final version of the manuscript.

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Appendix A. Supplementary data

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References

Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): early report from the United States. Diagnosis 2020;7:91–6.

Antinori S, Cossu MV, Ridolfo AL, Rech R, Bonazzetti C, Pagani G, et al. Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and non-ICU patients: clinical outcome and differences in post-treatment hospitalisation status. Pharmacol Res 2020;158:104899.

Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ 2020;369:m1996.

Bhargava A, Fukushima EA, Levine M, Zhao W, Tanveer F, Szpunar SM, et al. Predictors for severe COVID-19 infection. Clin Infect Dis 2020;71:1962–8.

Cao J, Hu X, Cheng W, Yu L, Tu WJ, Liu Q. Clinical features and short-term outcomes of 18 patients with corona virus disease 2019 in intensive care unit. Intens Care Med 2020a;46:851–3.

Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 2020b;6:11.

Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest 2020a;130:2620–9.

Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020b;368.

Chen Y, Du L, Geng X, Liu G. Implement meta-analysis with non-comparative binary data in RevMan Sofware. Chin J Evid Based Med 2014;14:889–96.

Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020;97:829–38.

Čivljak R, Markotić A, Kuzman I. The third coronavirus epidemic in the third millennium: what's next?. Croat Med J 2020;61:1–4.

Codagnone C, Bogliacino F, Gomez C, Charris R, Montealegre F, Liva G, et al. Assessing concerns for the economic consequence of the COVID-19 response and mental health problems associated with economic vulnerability and negative economic shock in Italy, Spain, and the United Kingdom. PLoS One 2020;15:e240876.

Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet 2020;395:1763–70.

Deng Y, Liu W, Liu K, Fang Y, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chinese Med J-PEKING 2020;133:1261–7.

Gautam R, Sharma M. 2019-nCoV pandemic: a disruptive and stressful atmosphere for Indian academic fraternity. Brain Behav Immun 2020;88:948–9.

González JM, Gomez-Puertas P, Cavanagh D, Gorbalenya AE, Enjuanes LA. Comparative sequence analysis to revise the current taxonomy of the family Coronaviridae. Arch Virol 2003;148:2207–35.

Hirano T, Murakami M. COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. Immunity 2020;52:731–3.

Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int 2020;98:209–18.

Hoiland RL, Stukas S, Cooper J, Thiara S, Chen L, Biggs CM, et al. Amelioration of COVID-19 related cytokine storm syndrome: parallels to chimeric antigen receptor-T cell cytokine release syndrome. Br J Haematol 2020;190:e150–4.

Hong KS, Lee KH, Chung JH, Shin K, Choi EY, Jin HJ, et al. Clinical features and outcomes of 98 patients hospitalized with SARS-CoV-2 infection in Daegu, South Korea: a brief descriptive study. Yonsei Med J 2020;61:431–7.

Hu J, He C, Gao Q, Zhang G, Cao X, Long Q, et al. The D614G mutation of SARS-CoV-2 spike protein enhances viral infectivity and decreases neutralization sensitivity to individual convalescent sera. bioRxiv 2020;6:161323.

Li D, Chen Y, Liu H, Jia Y, Li F, Wang W, et al. Immune dysfunction leads to mortality and organ injury in patients with COVID-19 in China: insights from ERS-COVID-19 study. Signal Transduct Target Ther 2020a;5.

Li X, Wang L, Yan S, Yang F, Xiang L, Zhu J, et al. Clinical characteristics of 25 death cases with COVID-19: a retrospective review of medical records in a single medical center, Wuhan, China. Int J Infect Dis 2020b;94:128–32.

Li Y, Hu Y, Yu J, Ma T. Retrospective analysis of laboratory testing in 54 patients with severe- or critical-type 2019 novel coronavirus pneumonia. Lab Investig 2020c;100:794–800.

Malberti F, Pecchini P, Marchi G, Foramitti M. When a nephrology ward becomes a COVID-19 ward: the Cremona experience. J Nephrol 2020;33:625–8.

Mao R, Qiu Y, He J, Tan J, Li X, Liang J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:667–78.

McKee M, Stuckler D. If the world fails to protect the economy, COVID-19 will damage health not just now but also in the future. Nat Med 2020;26:640–2.

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.

Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. J Am Soc Nephrol 2020;31:1157–65.

Peng F, Tu L, Yang Y, Hu P, Wang R, Hu Q, et al. Management and treatment of COVID-19: the Chinese experience. Can J Cardiol 2020;36:915–30.

Puelles VG, Lutgehetmann M, Lindenmeyer MT, Sperhake JP, Wong MN, Allweiss L, et al. Multiorgan and renal tropism of SARS-CoV-2. N Engl J Med 2020;383:590–2.

Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323:2052–9.

Sharma M, Sharma S. The rising number of COVID-19 cases reflecting growing search trend and concern of people: a Google trend analysis of eight major countries. J Med Syst 2020a;44:117.

Sharma S, Sharma M, Singh G. A chaotic and stressed environment for 2019-nCoV suspected, infected and other people in India: fear of mass destruction and causality. Asian J Psychiatr 2020b;51:102049.

Shi M, Chen L, Yang Y, Zhang J, Xu J, Xu G, et al. Analysis of clinical features and outcomes of 161 patients with severe and critical COVID-19: a multicenter descriptive study. J Clin Lab Anal 2020a;e23415.

Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020b;5:802–10.

Strafella C, Caputo V, Termine A, Barati S, Gambardella S, Borgiani P, et al. Analysis of ACE2 genetic variability among populations highlights a possible link with COVID-19-related neurological complications. Genes (Basel) 2020;11.
Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020a;395:470–3.
Wang D, Yin Y, Hu C, Liu X, Zhang X, Zhou S, et al. Clinical course and outcome of 107 patients infected with the novel coronavirus, SARS-CoV-2, discharged from two hospitals in Wuhan, China. Crit Care 2020b;24.
Wang L, Li X, Chen H, Yan S, Li D, Li Y, et al. Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. Am J Nephrol 2020c;51:343–8.
World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. Geneva, Switzerland: World Health Organization; 2020.
World Health Organization. WHO declares COVID-19 a pandemic. Geneva, Switzerland: World Health Organization; 2020.
World Health Organization. Coronavirus disease (COVID-2019) situation reports-162. Geneva, Switzerland: World Health Organization; 2020.
Yang F, Shi S, Zhu J, Shi J, Dai K, Chen X. Analysis of 92 deceased patients with COVID-19. J Med Virol 2020a;92:2511–5.
Yang Q, Xie L, Zhang W, Zhao L, Wu H, Jiang J, et al. Analysis of the clinical characteristics, drug treatments and prognoses of 136 patients with coronavirus disease 2019. J Clin Pharm Ther 2020b;45:609–16.
Yang R, Gui X, Zhang Y, Xiong Y. The role of essential organ-based comorbidities in the prognosis of COVID-19 infection patients. Expert Rev Resp Med 2020c;14:835–8.
Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Resp Med 2020d;8:475–81.
Yi B, Chen X, Shi H, Lin T, Lin H, Xu Y, et al. Remote ischaemic preconditioning reduces acute kidney injury in adult patients undergoing cardiac surgery with cardiopulmonary bypass: a meta-analysis. Eur J Cardiothorac Surg 2017;51:616–23.
Yi B, Luo J, Jiang Y, Mo S, Xiao X, Chen X, et al. Nicorandil for periprocedural myocardial injury in elective percutaneous coronary intervention: a meta-analysis of 10 randomized controlled trials. Angiology 2020;71:609–15.
Yu Y, Xu D, Fu S, Zhang J, Yang X, Xu L, et al. Patients with COVID-19 in 19 ICUs in Wuhan, China: a cross-sectional study. Crit Care 2020;24:219.
Zhang G, Hu C, Luo L, Fang F, Chen Y, Li J, et al. Clinical features and short-term outcomes of 221 patients with COVID-19 in Wuhan, China. J Clin Virol 2020a;127.
Zhang L, Jackson CB, Mou H, Ojha A, Rangarajan ES, Izard T, et al. The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity. bioRxiv 2020b;6:148726.
Zhang X, Cai H, Hu J, Lian J, Gu J, Zhang S, et al. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. Int J Infect Dis 2020c;94:81–7.
Zhao X, Xu X, Yin H, Hu Q, Xiong T, Tang Y, et al. Clinical characteristics of patients with 2019 coronavirus disease in a non-Wuhan area of Hubei Province, China: a retrospective study. BMC Infect Dis 2020;20.
Zheng Y, Sun L, Xu M, Pan J, Zhang Y, Fang X, et al. Clinical characteristics of 34 COVID-19 patients admitted to intensive care unit in Hangzhou, China. J Zhejiang Univ Sci B 2020;21:378–87.