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Renal complications in COVID-19: A systematic review and meta-analysis

Running Head: Renal manifestations of COVID-19

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ABSTRACT

Purpose: Emerging data suggests coronavirus disease 2019 (COVID-19) has extrapulmonary manifestations but its renal manifestations are not clearly defined. We aimed to evaluaterenal complications of COVID-19 and their incidence using a systematic meta-analysis.

Design: Observational studies reporting renal complications in COVID-19 patients were sought from MEDLINE, Embase and the Cochrane Libraryfrom 2019 to June 2020. The nine-star Newcastle-Ottawa Scale was used to evaluate methodological quality.Incidence with 95% confidence intervals (CIs) were pooled using random-effects models. **Results:**We included 22observational cohort studies comprising of 17,391COVID-19 patients. Quality scores of studies ranged from 4-6.The pooled prevalence of pre-existing chronic kidney disease (CKD) and end-stage kidney disease was5.2% (2.8-8.1)and 2.3% (1.8-2.8) respectively. The pooled incidence over follow-up of 2-28 days was 12.5% (10.1-15.0) forelectrolyte disturbance (eg, hyperkalaemia), 11.0% (7.4-15.1) foracute kidney injury (AKI) and 6.8% (1.0-17.0) for renal replacement therapy (RRT).In subgroup analyses, there was a higher incidence of AKI inUS populations andgroups with higher prevalence of pre-existing CKD. **Conclusions:**Frequent renal complicationsreported among hospitalised COVID-19 patientsare electrolyte disturbance, AKI and RRT. Aggressive monitoring and management of these renal complications may help in the prediction of favourable outcomes.

Systematic review registration: PROSPERO 2020: CRD42020186873

Keywordsrenal complications; acute kidney injury; COVID-19; meta-analysis

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KEY MESSAGES

- COVID-19 affects multiple organs apart from the respiratory system; however, its renal manifestations are not clearly defined.
- In this systematic meta-analysis of 22 observational cohort studies, the prevalence of pre-existing chronic kidney disease (CKD) in COVID-19 patients was5.2%.
- The most frequent renal complication was electrolyte disturbance (particularly hyperkalaemia)with an incidence of 12.5% followed by acute kidney injury (AKI)with an incidence of 11.0%;US populations andgroups with higher prevalence of CKD had higher incidence of AKI.

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Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) was declared a global public health emergency on 30 January 2020. The COVID-19 pandemic has caused substantial morbidity and mortality worldwide(1)and poses the most significant modern-day public health challenge since the Spanish flu of 1918.Coronavirus disease 2019 predominantly affects the respiratory system, typically manifesting as acute respiratory distress syndrome (ARDS) and severe pneumonia in a few, whereas majority of patients are asymptomatic or present with mild symptoms.(2)The mostcommon symptoms of COVID-19 are fever, cough, myalgia or fatigue.(3)Older patients, males and those with pre-existing comorbidities such as cardiovascular disease (CVD), hypertension, chronic kidney disease, chronic liver disease and diabetes are reported to be more likely to be infected with SARS CoV-2(4) and are at highest risk for severe illness or death.(5, 6)Emerging data suggests that COVID-19 also affects multiple organs, leading to organ failure and eventually death.(7)Common cardiovascular complications reported to be associated with COVID-19 include myocardial injury and heart failure,(8)which have been shown to correlate with the severity of or mortality from COVID-19.(9)Further emerging data also suggests COVID-19 contributes to adverse renal manifestations such as acute kidney injury (AKI), which is also associated with severe COVID-19 or mortality.(10)Given the sparse data, the renal manifestations of COVID-19are not clearly defined. Despite the rapidly growing knowledge base on the clinical course of the disease, no effective therapeutic agents have been identified. Further data on the clinical course of the disease could help in the development of effective treatment strategies. Understanding the interplay between COVID-19and its renal manifestations could assist in the management of patients. In this context, wesought to address the following questions using a first systematic meta-analysisof published evidence: (i) what are the renal complications associated with COVID-19?(ii) what is the incidence of these complications? and (iii) are patients with pre-existing renal conditions more susceptible to these renal complications?

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Materials and methods

Data sources and search strategy

The review was based on a predefined protocol which was registered in the PROSPERO International prospective register of systematic reviews (CRD42020186873) and it was conducted in accordance with PRISMA and MOOSE guidelines(11, 12) (**Supplementary materials 1-2**).MEDLINE, Embase, and The Cochrane librarywere searched from 2019 to 13 June2020for published studies reporting on renal complications in patients with COVID-19. We combined search terms and key words related to the population (e.g., “COVID-19”, “SARS-CoV-2”) and outcomes (e.g., “kidney”, “renal”,“acute kidney injury”, “renal transplant therapy”, “albuminuria”) in humans, which was limited to only reportspublished in the English language given the potential for duplicate reporting using the same study participants.(13)The detailed search strategy can be foundin **Supplementary material 3**. Titles and abstracts were screened for potential eligible studies following retrieval of citations. Following initial screening, full texts of potentially eligible studies were acquired for detailedevaluation.Manual scanning of key articles and review papers was conducted to identify additional articles missed by the search strategy.

Study selection and eligibility criteria

The protocol was pre-specified to include observational studies (prospective and retrospective, nested case-control and case-control designs), non-randomised clinical studies and randomised controlled trials (RCTs) which reported renal complications in patients with COVID-19. Our protocol was pre-specified to include all renal complications anticipated to be reported by studies such asAKI, proteinuria, haematuria, albuminuria, electrolyte disturbance, renal acidosis and alkalosis, need for renal replacement therapy (RRT)and kidney transplantamong others.We also sought for studies reporting information on any pre-existing renal conditions (e.g., CKD, end-stage kidney disease); however, they were not included if they did not report on anyrenal complication.Patients must have had a period of follow-up prior to developing complications.

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Data extraction and quality assessment

Using a pre-designed data extraction form, the following data were extracted from the eligible studies: author and year of publication; study characteristics (design, locationand date of data collection); patient characteristics (average age, sex, percentage of males, total number of patients, pre-existing renal conditions and their counts and follow-up duration or hospital stay); and renal complications and their counts. Data were extracted and analysed as reported.However, hyperkalaemia was reported by one study and was classified as an electrolyte disturbance to enhance consistency and enable pooling.To minimise over- and under-reporting and maintain consistency, extraction of prevalence and incidence data employed an intention-to-treat principle. Methodological quality of studies was assessed using the nine-star Newcastle-Ottawa Scale (NOS),(14) a tool which has been validated for assessing the quality of non-randomised studies.

Statistical analysis

Pooled prevalence of pre-existing renal conditions(eg, CKD) with 95% confidence intervals (CIs) was calculated from the number of pre-existing renal conditions/total number of patients with COVID-19 in the study. Incidence of renal complications with 95% confidence intervals CIs was estimated from the number of patients experiencing the specific renal complication within period of follow-up (hospital stay)/total number of patients with COVID-19). Given that the data was binary with some low counts, the Freeman-Tukey variance stabilising double arcsine transformation (15) was used in calculating prevalence and incidence estimates as done in previous reports.(16-18)Heterogeneity was assessed and quantified usingCochrane $\chi^2$and I^2 statistics.(19) We also estimated 95% prediction intervals to determine the degree of heterogeneity, as they provide a region in which about 95% of the true effects of a new study are expected to be found.(20, 21)Pre-defined study-level characteristics such as location, age and comorbidities which may explain heterogeneity were explored using stratified analysis and random effects meta-regression.STATA release MP 16 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses.

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Results

Study identification and selection

The process of study selection is presented in **Figure 1**. Overall, atotal of 109articleswere identified from the search of major databases and manual scanning of reference lists of relevant articles.After initial screening based on titles and abstracts, full texts of 28 articles were retrieved for further evaluation. Six articles were excluded on the basis of (i) duplicates of the same study (n=4); (ii) outcome not relevant (n=1) and (iii) review article (n=1). This left a total of 22articles for inclusion in the review.(1, 3, 9, 22-40)

Study characteristics and quality

All 22 studies were based on observational cohort designs (21 retrospective cohorts and 1 prospective cohort), altogether comprising of 17,391 patientswith COVID-19(**Table 1**). Sixteen studies were based in China and six based in the United States.The average age at baseline ranged from 46 to 71 years, with a weighted mean (standard deviation, SD) of 60 (5) years.All studies enrolled both male and female patients.Hospital stay or follow-up duration ranged from 2 to 28 days with a weighted mean (SD) of 7.0 (4.0) days. The overall NOS methodological quality scores of studies ranged from 4 to 6.

Prevalence of pre-existing renal conditions

Across 20studiesproviding relevant data, the prevalence of pre-existingCKDin COVID-19 patients ranged from 0.7% to 47.6%, with a pooled random effects prevalence (95% CI) of5.2% (2.8-8.1;I^2 =98%; 95% CI 97, 98%; p for heterogeneity<0.01) (**Figure 2**). The 95% prediction interval for the summary prevalence was 0.0 to 23.1%, suggesting that the true prevalence of pre-existingCKD for any single new study will usually fall within this range. The prevalence of pre-existing end-stage kidney diseasebased on pooled analysis of two studies was 2.3% (1.8-2.8) (**Figure 2**).

Incidence of renal complications

Overhospital stays ranging from 2 to 28 days following admission, the pooled incidence for AKI (n=22 studies) was 11.0% (7.4-15.1; I^2 =97%; 95% CI 97, 98%; p for heterogeneity<0.01) (**Figure 3**). For 14 studies reporting data on the definition of AKI, 12 defined AKI according to Kidney Disease Improving Global

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Outcomes (KDIGO) criteria (**Appendix 4**).(41)The incidence of electrolyte disturbance (n=2 studies), need for RRT (n=3 studies)and acidosis (n=2 studies)were 12.5% (10.1-15.0), 6.8% (1.0-17.0)and 5.0 (3.2-7.2) respectively. (**Figure 3**). Based on the report by a single study, the incidence of alkalosis was 6.9 (4.5-10.6).

Given AKI was the outcome commonlyreported by studies(22 studies) and with the substantial heterogeneity between contributing studies, we explored for potential sources of heterogeneity using stratified analysis and random effects meta-regression.There was statistically significant evidence of effect modification on the incidence of AKI by location (*p*-value for meta-regression=0.03) and pre-existing CKD (*p*-value for meta-regression<0.001). There was no evidence of effect modification by age (**Figure 4**).

Discussion

In hospitalised patients with renal manifestations of COVID-19, the prevalence of pre-existing CKD was 5.2% and that for end-stage kidney disease was 2.3%.Over hospital stays ranging from 2 to 28 days,AKI was the common outcome reported by studies; howeverelectrolyte disturbance (hyperkalaemia)was the most frequent renal complication with an incidence of 12.5% followed by AKI and RRT at 11.0% and 6.8% respectively. Other reported complications included acidosis and alkalosis.Subgroup analyses suggested evidence of effect modification by location andpre-existing history of CKD on the incidence of AKI; incidence of AKI was higher in the US population (than the Chinese population) and among groups with higher prevalence of pre-existing CKD (than those with lower prevalence). However, AKI incidence was comparable in younger (<60 years) and older (≥60 years) individuals.

Though COVID-19 predominantly affects the respiratory system, there is involvement of multiple organs, such as the gastrointestinal system, the cardiovascular system, the liver as well as the kidneys. These multiple organ disturbances may then interact with each other, which correlates with the severity of the disease. The virusSARS-CoV-2is known to enter human lung cells by binding to angiotensin-converting enzyme 2 (ACE2).(42)The multiorgan involvement of SARS-CoV-2 has been linked to the wide distribution of ACE2 in the body; the highest expression of ACE2 is found in the ileum and kidneys.(43, 44)In the kidney, ACE2 is expressed on several cells including mesangial cells, podocytes, parietal epithelium of the Bowman's Capsule, and the collecting ducts.(45)Though the mechanisms for the renal manifestations of COVID-19 are still elusive, a complex multifactorial pathway has been proposed and it includes: (i) direct viral involvement

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and replication in the kidneys leading to dysfunction;(46) (ii) local disruption in renin-angiotensin-aldosteronesystem (RAAS) homeostasis;(44)(iii) lung protective fluid management strategy during treatment of ARDS(40)and (iv) as a result of a systemic inflammatory response “cytokine storm”.(44)

COVID-19 representsa great medical challengeand appears to have multisystem effects which include renal manifestations. The current data based on up-to-date evidence suggests that AKI is commonly reported as a complication among patients with COVID-19.In addition to pre-existing CKD being associated with severe illness or death in COVID-19,(5)it is also an independent risk factor for AKI.(47)Consistently, our study findings showed that groups with higher prevalence of pre-existing CKD might have higher incidence of AKI.Emerging evidence also suggests that renal manifestations of COVID-19 are also associated with increased risk of severe COVID-19 and fatal outcomes.(10, 30)Monitoring of markers of kidney function during hospitalization for COVID-19 could help in the identification of patients who at high risk for worse outcomes, to enable early and more aggressive intervention.The current evidence provides better insight on the extent of kidney damage by COVID-19. However, more work is needed to help us better understand the pathophysiology underlying renal manifestations of COVID-19, to help in the identification of effective management strategies.

We have provided up-to-date data on the different renal manifestations of COVID-19as well as their incidence rates. In addition, prevalence estimates of common renal comorbidities have also been presented. Other strengths of this study include ability to synthesise the data quantitatively as well as exploration for sources of heterogeneity. There were some limitations which were mostly inherent and included (i) inability to generalise the findings and the possibility of patient overlap, given that the majority of studies were based in China; (ii) the definition of CKD and classification into stages were not reportedby included studies; (iii) a number of studies did not report on the definition for AKI; however, the majority defined AKI according to KDIGO criteria; (iv) studies reporting on the complications of acidosis and alkalosis did not distinguish whether these outcomes were of renal or lung origin; (v) one study reported an outcome of electrolyte disturbance, but did not provide a definition of this; (vi)the potential fordifferences in the timing during hospitalisation with regards to assessment of complications; and (vii)the low sample sizes of some of the studies.

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Conclusion

Aggregate up-to-datesynthesis of the existing literature suggests that the most frequent renal complicationsamong patients hospitalised with COVID-19are electrolyte disturbance (particularly hyperkalaemia), AKI and the need for RRT.Aggressive monitoring and management of these renal complications may help in the prediction of more favourable outcomes.

Disclosure of interest

The authors report no conflicts of interest.

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Figure legends

Figure 1. Selection of studies included in the meta-analysis

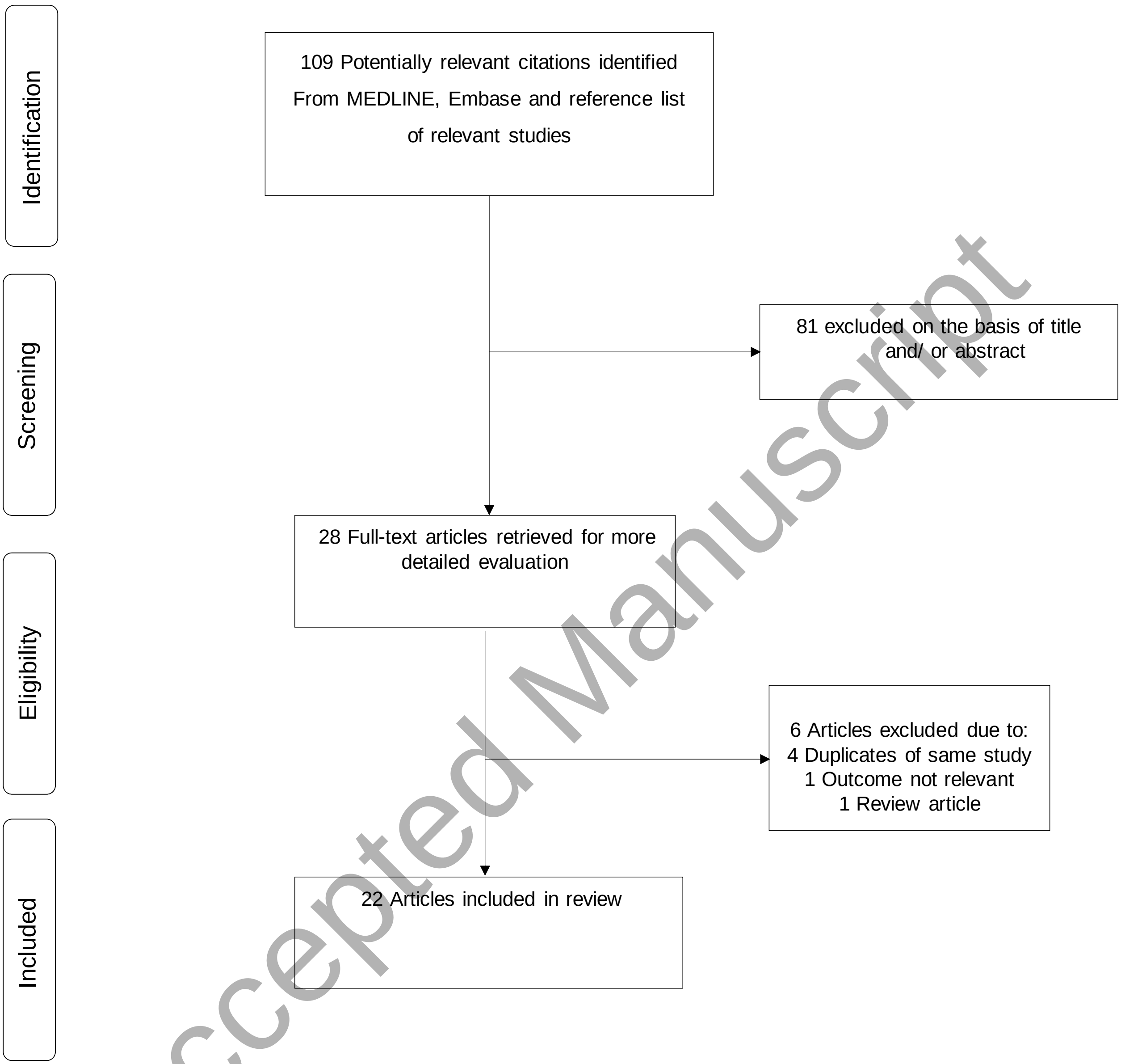

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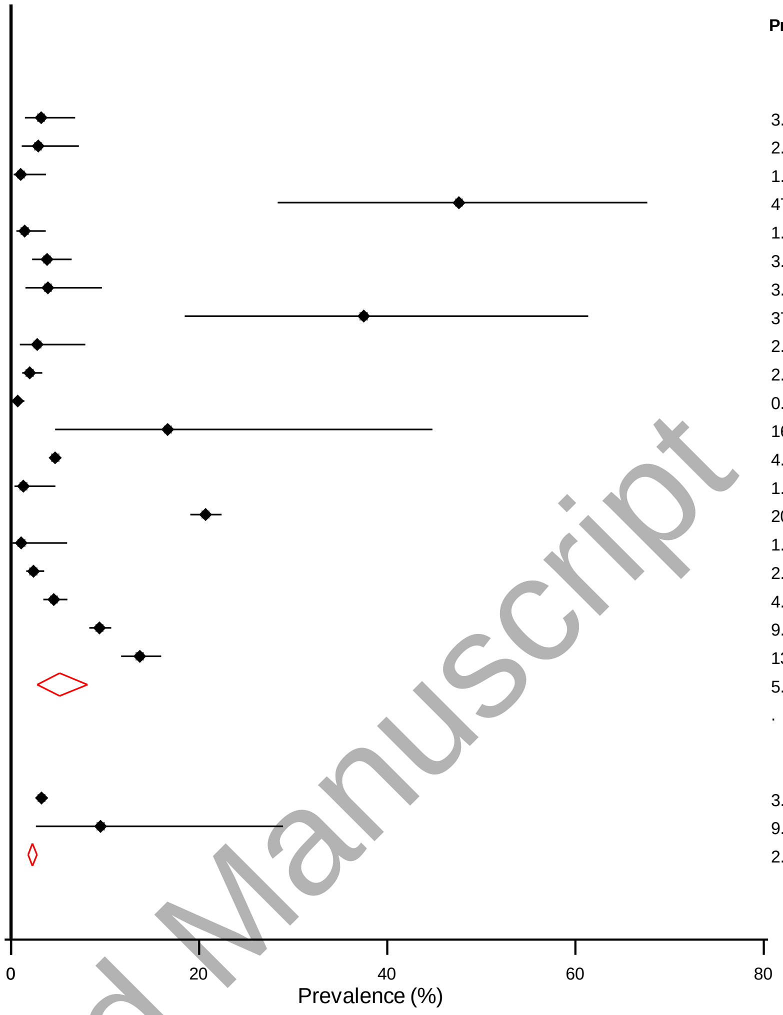
Figure 2. Prevalence of pre-existing renal conditions in COVID-19 patients

Author, year of publication	No. of cases	No. of patients	Prevalence (95% CI)
CKD			
Guo, 2020	6	187	3.2 (1.5, 6.8)
Wang, 2020	4	138	2.9 (1.1, 7.2)
Zhou, 2020	2	191	1.0 (0.3, 3.7)
Arentz, 2020	10	21	47.6 (28.3, 67.6)
Chen, 2020	4	274	1.5 (0.6, 3.7)
Wang, 2020b	13	339	3.8 (2.3, 6.4)
Cao, 2020	4	102	3.9 (1.5, 9.7)
Aggarwal, 2020	6	16	37.5 (18.5, 61.4)
Wang, 2020c	3	107	2.8 (1.0, 7.9)
Cheng, 2020	14	701	2.0 (1.2, 3.3)
Guan, 2020	8	1099	0.7 (0.4, 1.4)
Liu, 2020	2	12	16.7 (4.7, 44.8)
Richardson, 2020	268	5700	4.7 (4.2, 5.3)
Ruan, 2020	2	150	1.3 (0.4, 4.7)
Phipps, 2020	470	2273	20.7 (19.1, 22.4)
Zhao, 2020	1	91	1.1 (0.2, 6.0)
Zhao, 2020b	24	1000	2.4 (1.6, 3.5)
Price-Haywood, 2020 (W)	47	1030	4.6 (3.4, 6.0)
Price-Haywood, 2020 (B)	231	2451	9.4 (8.3, 10.6)
Argenziano, 2020	137	1000	13.7 (11.7, 16.0)
Subtotal			5.2 (2.8, 8.1)
95% prediction interval			. (0.0, 23.1)
End-stage kidney disease			
Richardson, 2020	186	5700	3.3 (2.8, 3.8)
Arentz, 2020	2	21	9.5 (2.7, 28.9)
Subtotal			2.3 (1.8, 2.8)



B, black; CI, confidence interval (bars); CKD, chronic kidney disease; W, white

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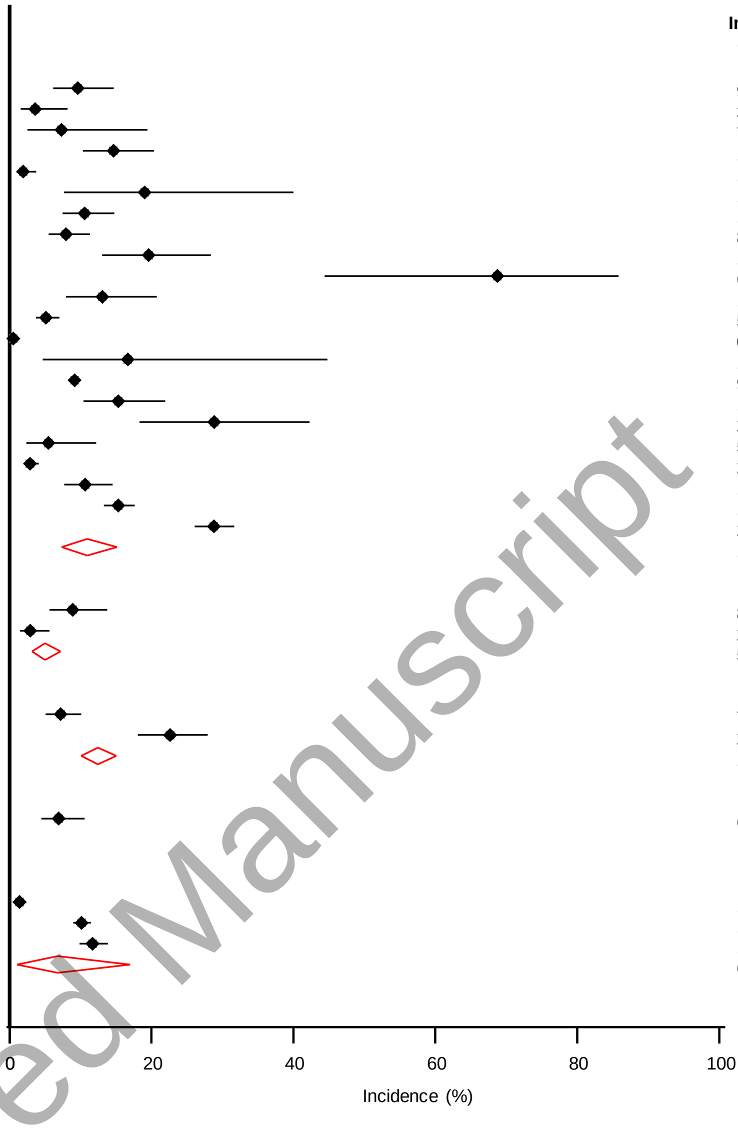
Figure 3. Incidence of renalcomplications in COVID-19 patients

Author, year of publication	No. of cases	No. of patients	Incidence (95% CI)
AKI			
Guo, 2020	18	187	9.6 (6.2, 14.7)
Wang, 2020	5	138	3.6 (1.6, 8.2)
Huang, 2020	3	41	7.3 (2.5, 19.4)
Zhou, 2020	28	191	14.7 (10.3, 20.4)
Shi,2020	8	416	1.9 (1.0, 3.7)
Arentz, 2020	4	21	19.0 (7.7, 40.0)
Chen, 2020	29	274	10.6 (7.5, 14.8)
Wang, 2020b	27	339	8.0 (5.5, 11.3)
Cao, 2020	20	102	19.6 (13.1, 28.4)
Aggarwal, 2020	11	16	68.8 (44.4, 85.8)
Wang, 2020c	14	107	13.1 (8.0, 20.8)
Cheng, 2020	36	701	5.1 (3.7, 7.0)
Guan, 2020	6	1099	0.5 (0.3, 1.2)
Liu, 2020	2	12	16.7 (4.7, 44.8)
Richardson, 2020	523	5700	9.2 (8.5, 10.0)
Ruan, 2020	23	150	15.3 (10.4, 22.0)
Yang, 2020	15	52	28.8 (18.3, 42.3)
Zhao, 2020	5	91	5.5 (2.4, 12.2)
Zhao, 2020b	29	1000	2.9 (2.0, 4.1)
Price-Haywood, 2020 (W)	34	319	10.7 (7.7, 14.5)
Price-Haywood, 2020 (B)	163	1063	15.3 (13.3, 17.6)
Argenziano, 2020	288	1000	28.8 (26.1, 31.7)
Subtotal			11.0 (7.4, 15.1)
Acidosis			
Zhou, 2020	17	191	8.9 (5.6, 13.8)
Chen, 2020	8	274	2.9 (1.5, 5.7)
Subtotal			5.0 (3.2, 7.2)
Electrolyte disturbance			
Shi,2020	30	416	7.2 (5.1, 10.1)
Chen, 2020	62	274	22.6 (18.1, 27.9)
Subtotal			12.5 (10.1, 15.0)
Alkalosis			
Chen, 2020	19	274	6.9 (4.5, 10.6)
Renal replacement therapy			
Richardson, 2020	81	5700	1.4 (1.1, 1.8)
Phipps, 2020	231	2273	10.2 (9.0, 11.5)
Argenziano, 2020	117	1000	11.7 (9.9, 13.8)
Subtotal			6.8 (1.0, 17.0)



AKI, acute kidney injury; CI, confidence interval (bars)

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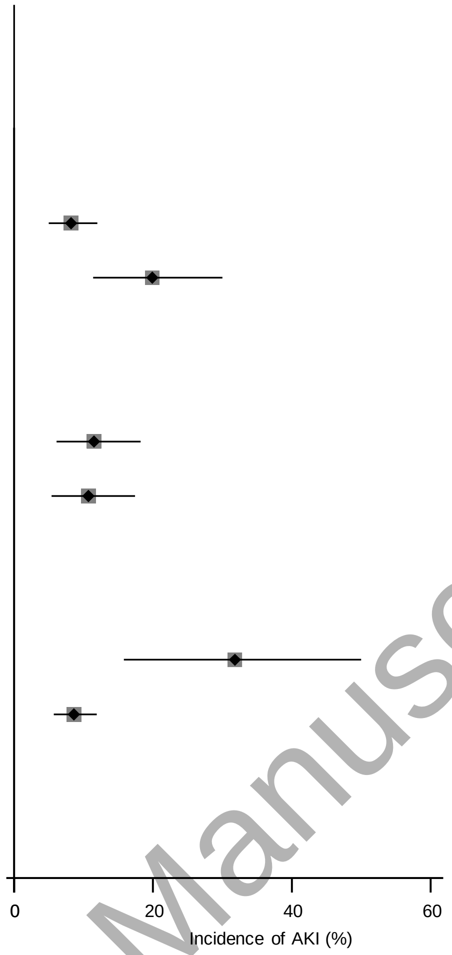
Figure 4. Incidence of acute kidney injury in COVID-19 patients, by clinically relevant characteristics

Subgroup	No. of AKI cases	No. of patients	Incidence (95% CI)	*p*-value*
Location				
China	268	4,900	8.2 (5.0, 12.0)	.03
USA	1,023	8,119	19.9 (11.4, 30.0)	
Average age (years)				
≥ 60	957	9,479	11.5 (6.1, 18.2)	.98
< 60	334	3,540	10.7 (5.4, 17.4)	
Pre-existing CKD				
High prevalence	305	1,049	31.8 (15.8, 50.0)	<0.001
Low prevalence	960	11,461	8.6 (5.7, 11.9)	



AKI, acute kidney injury; CI, confidence interval (bars); CKD, chronic kidney disease; *, p-value for meta-regression

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Table 1. Characteristics of included studies

Author, year of publication	Source of data	Country	Date of data collection	Mean/median age (years)	Males, %	Hospital stay/follow-up (days)	No. of patients	AKI cases	NOS score
Aggarwal, 2020	UnityPoint Clinic	USA	March - April 2020	67.0	75	2.0	16	11	4
Arentz, 2020	Evergreen Hospital in Kirkland, Washington	USA	Feb - March 2020	70.0	52	5.2	21	4	4
Cao, 2020	Zhongnan Hospital of Wuhan University	China	Jan - Feb 2020	54.0	52	11.0	102	20	4
Chen, 2020	Tongji Hospital in Wuhan	China	Jan - Feb 2020	62.0	62	13.0	274	29	4
Cheng, 2020	Tertiary teaching hospital	China	NR	63.0	52.4	10.0	701	36	6
Guan, 2020	National Health Commission	China	Dec - Jan 2020	47.0	58.1	12.0	1099	6	4
Guo, 2020	Seventh Hospital of Wuhan City	China	Jan - Feb 2020	58.5	48.7	16.3	187	18	5
Huang, 2020	Jin Yintan Hospital, Wuhan	China	Dec - Jan 2020	49.0	73	7.0	41	3	4
Liu, 2020	Shenzhen Third People's hospital	China	Dec - Jan 2020	NR	66.7	8.6	12	2	4
Phipps, 2020	New York-Presbyterian network	USA	March – April 2020	65.0	57.0	6.0	2,273	NR	6
Price-Haywood, 2020 (W)	Ochsner Health in Louisiana	USA	March – April 2020	55.5	45.7	7.0	1,030	34	6
Price-Haywood, 2020 (B)	Ochsner Health in Louisiana	USA	March – April 2020	53.6	37.7	6.0	2,451	163	6
Richardson, 2020	12 Hospitals in New York-Northwell Health system	USA	March - April 2020	63.0	60.3	4.5	5700	523	4
Ruan, 2020	Jin Yin-tan Hospital and Tongji Hospital	China	NR	57.7	68	10.1	150	23	4
Shi,2020	Renmin Hospital of Wuhan University	China	Jan - Feb 2020	64.0	49.3	NR	416	8	6
Wang, 2020	Zhongnan Hospital of Wuhan University	China	Jan, 2020	56.0	54.3	7.0	138	5	4
Wang, 2020b	Renmin Hospital of Wuhan University	China	Jan - Feb 2020	71.0	49	28.0	339	27	4
Wang, 2020c	Zhongnan Hospital of Wuhan University and Xishui People's Hospital	China	Up to Feb, 2020	51.0	53.3	11.0	107	14	5
Yang, 2020	Wuhan Jin Yin-tan hospital	China	Dec - Jan 2020	59.7	67	10.0	52	15	4
Zhao, 2020	Jingzhou Central Hospital	China	Jan - Feb 2020	46.0	53.8	NR	91	5	4
Zhao, 2020b	Shouyi and East districts of Renmin Hospital of Wuhan University	China	Jan – Feb 2020	61.0	46.6	7.0	1,000	29	4
Zhou, 2020	Jinyintan Hospital & Wuhan Pulmonary Hospital	China	Dec - Jan 2020	56.0	62	11.0	191	28	5

AKI, acute kidney injury; NOS, Newcastle-Ottawa Scale; NR, not reported

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