Incidence and Clinical Impacts of COVID-19 Infection in Patients with Hemodialysis: Systematic Review and Meta-Analysis of 396,062 Hemodialysis Patients

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Research

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Abstract

Background: Better understanding of incidence and clinical outcomes of COVID-19 infection in hemodialysis (HD) patients could assist healthcare providers to develop proper preventive strategies and optimal management. However, no published systematic review summarizes current epidemiological evidence regarding COVID-19 infection in HD patients.

Methods: This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We systematically searched PUBMED and EMBASE for articles published on incidence or mortality of COVID-19 infection in maintenance HD patients until September 2020, and conducted meta-analysis of proportions for incidence and mortality rate. Heterogeneity was measured by Cochran's Q and I^2 statistic. Publication bias was evaluated by Egger's test. The study protocol was registered in the PROSPERO database (CRD42020209134).

Results: In total, 29 articles with 3,261 confirmed COVID-19 cases from pooled 396,062 HD patients were identified. Overall COVID-19 incidence in these HD patients was 7.7% (95% CI: 5.0-10.9%), with significant heterogeneity among the studies (I^2 = 99.7%, p<0.001) and risk of publication bias (Egger's test, p<0.001). Overall mortality rate was 22.4% (95% CI: 17.9-27.1%) in HD patients with COVID-19, with significant heterogeneity among the studies (I^2 = 87.1%, p<0.001). Reported incidence and mortality varied by geographic area, being higher in non-Asian- than Asian countries.

Conclusions: Both incidence and mortality of COVID-19 infection were higher in HD patients. Available data may underestimate the real incidence of infection because screening and diagnosis differ between countries. International collaboration and standardized reporting of future epidemiologic studies is encouraged to improve clinical outcomes of COVID-19 infection in HD patients.

Introduction

The novel coronavirus, COVID-19, continues to generate a tremendous global burden with 54,301,156 confirmed cases and 1,316,994 deaths worldwide, as of November, 2020 [1]. The global incidence of COVID-19 is estimated at about 6,966 per million in population, and varies among different countries, depending on their screening strategies, study methodology and preventive measures. Many risk factors related to the incidence of COVID-19 infection have been identified; for example, advanced age, diabetes mellitus, hypertension and smoking [2, 3]. In addition, the mortality rate of COVID-19 infection varies from country to country, ranging from 33.2 per million population (South-east Asia) to 849.4 per million population (America) [1]. Higher risks of mortality caused by COVID-19 are found in patients with older age, more comorbidities and immune dysfunction [3, 4]. However, published literature with regard to the epidemiology in patients with renal dysfunction, infected by COVID-19, remains scarce.

The prevalence of chronic kidney disease (CKD) is about 9.1% worldwide [5], and end-stage renal disease (ESRD) is associated with higher comorbidity, mortality risks and socioeconomic impacts, affecting 2,859,750 patients globally [6]. In-center hemodialysis (HD) is the predominant renal replacement modality across different countries, except in Hong Kong, Mexico and Guatemala [7]. HD patients are immune-dysregulated patients on account of uremia, associated comorbidities and dialysis procedure-related bio-compatibility [8]. Furthermore, several aspects inherent to the treatment modality, including frequent contact with medical personnel, in-center facility treatment and grouped medical practice may hamper effective protective measures (such as social distancing, reducing personal contact, staying home) against COVID-19 infection. CKD has previously been associated with increased risk for COVID-19 infection [9], but the published observational studies have identified varying incidence and clinical impacts of COVID-19 in HD patients. To the best of our knowledge, there is no comprehensive understanding of incidence and clinical outcomes of COVID-19 in HD patients, but this information could be beneficial for future development of proper screening or preventive strategies against COVID-19 infection in this vulnerable population. The aim of the present study is to fill this knowledge gap, and systematically quantify the incidence and clinical impacts of COVID-19 infection in HD patients.

Materials And Methods

Search strategy

We conducted a systematic review and meta-analysis by including relevant observational studies in published literature. We searched PUBMED and EMBASE on September 9, 2020 to identify relevant studies. We used the following search terms with suitable MeSH or Emtree terms: COVID-19, hemodialysis, incidence, prevalence, mortality or prognosis **(Supplemental Table S1)**. Studies were required to provide data on either incidence of proven COVID-19 infection (nucleic acid testing by polymerase chain reaction, serology or image study) or related mortality of patients receiving maintenance HD therapy. The reference lists of included articles were also hand-searched. References were managed using EndNote X8. This study adhered to the reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [10] **(Supplemental Table S2)**, and it has been recorded in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020209134).

Literature selection

Two independent researchers (CYC and IWW) screened study titles and abstracts to identify potentially eligible studies related to incidence and mortality of COVID-19 infection in HD patients for full-text review. Full-text studies and data extractions were then reviewed for eligibility by the same researchers. We manually examined the cited references in all potentially eligible articles for additional studies, and only original articles and case series with over 2 cases in English language were included for review. We also excluded the articles incomplete data on incidence or mortality.

Data extraction and study quality

Data extraction was completed in duplicate by 2 independent reviewers (CYC, WIW) using a standardized data collection form. When multiple articles reporting data from the same study population were identified, the most comprehensive data were used. Information including country, study design, settings, age,

gender, presenting symptoms or signs, laboratory findings, treatment and preventive strategies were extracted. The raw number of total, infected and deceased cases were accurately recorded. Incidence rates were estimated by calculating the affected cases from the overall HD patients infected by COVID-19 during the reported period. Mortality was expressed as case fatality rate. We also contacted the study authors regarding possible incomplete data on incidence or mortality presented in selected publications.

Methodological quality of included studies was assessed independently by 2 authors (YTC, CKH) based on a 20-item critical appraisal checklist for case-series studies developed by the Institute of Health Economics (IHE) [11]. If we answered 'yes' on an item of the checklist, then the item scored 1 point. If we answered 'no' or 'unclear' on a checklist item then 0 points were scored. We considered studies scoring 14 or more points (≥ 70%) as "good quality" [12]. When the reviewers' assessments differed with regard to data extractions or study quality evaluations, the additional reviewer (SCS) were drawn in on a case by case basis to discuss and make the final judgments.

Data synthesis and analysis

We performed meta-analysis of the proportions (with 95%CI) for the incidence and mortality rates of COVID-19 infection in patients receiving HD. Statistical heterogeneity among the included studies was measured by Cochran's Q test with the p-value, and the extent of heterogeneity attributable to heterogeneity was measured by the I^2 statistic. We planned subgroup analyses based on geographic area (e.g., Asia or non-Asia) and quality of study (e.g., good or poor). We also used Egger's test to determine potential publication bias. Statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

Results

We identified 220 records form PUBMED (n = 144) and EMBASE (n = 76) databases for the initial assessment, and we excluded 205 of them due to 118 duplicates, 72 articles not related to HD patients, studies with case numbers less than 2 (n = 3), incomplete data on incidence or mortality (n = 4), unavailable full-text (n = 1), treatment consensus (n = 2), editorial comments (n = 3) or review articles (n = 2). Finally, 29 articles were included for full-text review. However, 22 articles reporting incidence (a further 7 from the 29 studies were excluded because either case number or HD pool could not be ascertained from the literature or through author queries) and 27 articles describing mortality (a further 2 from the 29 studies were excluded due to incomplete data) of COVID-19 infection in HD patients were included for systematic review and meta-analysis **(Fig. 1).**

This systematic review and meta-analysis evaluated 29 international studies with 3,261 confirmed COVID-19 cases from pooled 396,062 HD patients. The mean age of COVID-19 infected HD patients was 64.9 years and 64.5% were men. The characteristics of the included studies are described in **Table 1**. Due to emergency and uncertainty of this novel disease, articles were emerging into the literature after short observation periods. Out of all the articles, 25 publications reported an observation period for infection occurrence. The mean observation time was 46.6 days (ranging from 13 to 121). We identified 22 HD cohorts (Asian countries: 47.8%; good study quality: 43.5%) for assessment of incidence and 27 HD cohorts (Asian countries: 42.9%; good study quality: 35.7%) for analysis of mortality related to COVID-19 infection **(Table 2).**

We found that the incidence of COVID-19 infection in patients receiving HD therapy was 7.7% (95% CI: 5.0-10.9%), but there was evidence of statistical heterogeneity among the studies (I^2 = 99.7%, p < 0.001) (Fig. 2**)**. Egger's test (P < 0.001) indicated a high risk of publication bias in the studies reporting incidence of COVID-19 infection in patients receiving HD. Our meta-analysis also showed that the incidence of COVID-19 in HD patients was 5.0% (95% CI: 2.5–8.4%) and 10.5% (95% CI: 6.6–15.3%) in Asian and in non-Asian countries, respectively. In studies with good quality, the incidence was estimated at 5.2% (95% CI: 1.2–11.8%) of HD patients infected by COVID-19, lower than in those studies with poor quality (8.7%, 95% CI: 6.4–11.2%).

Fever was the most predominant clinical manifestation and was reported in 19 studies. Fever was observed in 889 patients out of 1448 COVID-19 infected HD patients (61.4%, 95% CI: 40.2–65.5%), followed by cough (19 studies, 654 of 1398 patients, 46.8%, 95% CI: 25.7–44.7%), dyspnea (16 studies, 438 of 1246 patients, 35.2%, 95% CI: 16.9–36.6%) and fatigue (12 studies, 136 of 471 patients, 35.2%, 95% CI: 14.6–49.9%). Eleven studies reported hematological parameters of infected patients; however, most of them had white blood cells, lymphocytes, neutrophils and platelet within normal ranges **(Table 1).**

The treatment regimen for COVID-19 infection in HD patients is largely empirical and has been incomplete in most of the studies. Eleven studies reported the use of antiviral agents and hydroxychloroquine, 7 studies reported the use of tocilizumab and 9 studies reported use of corticosteroid. Inpatient care was needed in 1045 (82.5%) of 1267 patients, from 19 studies pooled. Moreover, 11 of these 19 studies required absolute hospitalization (100.0%) of their infected patients. Admission to intensive care unit occurred in 84 (6.6%) of patients. Sixteen studies described presence of the acute respiratory distress syndrome (ARDS). The syndrome was found in 133 of 717 infected cases (18.5%, 95% CI 4.5–21.7%).

The overall mortality rate in HD patients with COVID-19 was 22.4% (95% CI: 17.9–27.1%), but significant statistical heterogeneity among the studies was also found (I^2 = 87.1%, p < 0.001) **(Fig. 3)**. However, based on the results of Egger's test (P = 0.197), there was no publication bias in this outcome. Compared with those in Asian countries (17.0%, 95% CI: 11.4–23.5%), COVID-19 infected HD patients in non-Asian countries had a higher mortality rate (26.7%, 95% CI: 22.5–31.0%). In the studies with good quality, mortality was estimated at 23.8% (95% CI: 20.2–27.6%) in COVID-19 patients receiving HD therapy, which was similar in those studies with poor quality (21.6%, 95% CI: 14.5–29.6%). The causes of mortality were unreported in most of the studies.

Twenty studies described the preventive strategies implemented for their HD patients. Ample alerts were observed in these studies regarding the use of protective measures. Masking was mandatory in the vast majority of HD facilities. Isolation in independent areas of treatment was instructed rather than social distancing. Other preventive methods included the use of gloves, face shields, disposable gowns, caps or alcohol sanitizer **(Table 2).**

Discussion

The COVID-19 infection has been declared a global emergency affecting 0.7% of the 7.8 billion worldwide human population, with the burden still growing [1]. The disease is causing revolutionary changes in personal lifestyle, health care systems and socio-economic distributions. In spite of universal precautions adopted to prevent this infection in the HD community, the incidence of this novel viral infection remains high among HD patients. This systematic review and meta-analysis of 29 international studies, including 3261 confirmed COVID-19 cases, drawn from a pool of 396,062 HD patients, found that the incidence of COVID-19 infection was 7.7% and the mortality rate was 22.4%, i.e. higher than in the general population. Understanding of incidence, clinical presentation and mortality related to COVID-19 in HD patients may help to design appropriate interventions for prevention, timely diagnosis and treatment of this global challenge in this vulnerable population.

HD patients are more susceptible to COVID-19 infection because of greater age, coexistence of multiple comorbidities, relatively immune-suppressed status and factors related to the scheduled renal replacement sessions constituting their lifelong treatment [13, 14]. Necessary, frequent visits to areas of high population density (public transportation or HD facilities) and close personal contacts (with medical-, nursing- or caregiver staff) make effective strategies to prevent viral infection, such as social distancing or stay-home orders, difficult to implement for this select population of patients [14]. Accordingly, a 15.4-fold increase was noted in the incidence of COVID-19 in our study, with patients also being older, compared to the general population [13]. The mean ages of patients were slightly greater (63.5 years) in patients of non-Asian studies than those of Asian studies (61.8 years). Variations in both criteria for viral screening and confirmatory methods of COVID-19 infection may also explain the difference in the incidence observed between studies of the two geographic areas. The difference in incidence observed between Asian and non-Asian populations may be greater than expected. Asian countries adopted universal screening using a nucleic acid test, serology or computed tomography. The serologic antibody response is detectable 7 to 10 days or later after the onset of symptoms of COVID-infection in the general population [15]; however, the humoral response may extend from 14 to 55 days in HD patients [16]. By contrast, non-Asian countries, except for Canada [17], conducted viral screening only in symptomatic patients or patients at high risk of exposure, using mainly nucleic acid test. The latter approach may mitigate the overwhelming burden on testing facilities; however, subclinical cases increase the difficulty of identifying COVID-19 infected HD patients and controlling outbreaks in the dialysis centers, and may lead to underestimation of the exact incidence of COVID-19 infection in asymptomatic HD patients. Manganos et al, at a very early stage of the disease outbreak, used radiographic signs suggestive of interstitial pneumonia as surrogate criteria for COVID-19 disease [18]. A nationwide serology screening involving 28,503 HD patients in the US found that seroprevalence was 8.3%, standardizing with the US dialysis population [19]; however, serology data were largely un-reported in non-Asian studies. All these differences may confer heterogeneity to the global incidence observed in the HD population.

COVID-19 related mortality estimates range from 1.4–8% in the general population and are higher (25.5–39%) in hospitalized patients [2, 3, 20–22]. The prognosis of HD patients with COVID-19 is still unclear. We found overall mortality of 22.4% in HD patients infected with COVID-19. Previous literature has indicated several risk factors for high mortality in HD, including greater age, male gender, underlying cardiac or pulmonary disease, diabetes and hypertension and the use of mechanical ventilation [13, 14, 23]. Cough was associated with risk of mortality in French and Italian HD patients [24, 25]. Fever also predicted mortality in an Italian HD cohort [14]. Other prognostic factors have included dialysis vintage, thrombocytopenia, lymphopenia and increased LDH or CRP level [14, 22, 24]. However, most studies have reported less severe clinical symptoms in HD patients compared with the general population [22, 26, 27, 28]. In a Chinese series, the most common symptoms were fever, cough and bilateral ground-glass or patchy opacity of the lungs [16]. However, a retrospective Chinese study comparing 49 HD vs 52 non-renal failure patients having similar baseline characteristics found that fever, fatigue and dry cough were more predominant in controls, but less frequent in HD infected patients. In this series, fatigue and anorexia were the most common symptoms among HD infected patients [29]. In addition, 25% of infected patients confirmed by nucleic acid test and 79% of those identified by serologic testing were asymptomatic during the whole clinical course [16]. Further large prospective studies, including different ethnicities, should be conducted to inform risk stratification with the ultimate goal of improving the outcome of HD patients with COVID-19 infection.

This viral infection can trigger severe immune cytokine storm and the respiratory failure secondary to ARDS represents the leading cause of mortality [30]. Increased serum concentration of interleukin (IL)-2, IL-6, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein 1-α, tumor necrosis factor (TNF)-α and ferritin have been observed in individuals infected with COVID-19 [30, 31]. This hyper-inflammatory storm may play an important role in the tissue damage and death of patients [4, 32]; however, this response is blunted in infected HD patients. Several studies have revealed leukopenia, lymphopenia, lower serum calcium concentration and elevated CRP levels in HD patients; however, several other researchers have failed to find changes in numbers of granulocytes or lymphocytes in infected HD patients [16, 26, 29, 33, 34]. Ma Y et al. found that the counts of T cells, CD4 T cells, CD8 T cells, natural killer cells, and B lymphocytes were reduced in the peripheral blood of infected HD patients compared with non-HD patients. In contrast, the serum levels of IL-4, IL-6, IL-10, interferon-γ and TNF-α were lowest in infected HD patients, compared to non-infected HD patients or COVID-19 infected patients with normal renal function [27]. Further evidence of attenuated cytokine reaction in HD patients could be manifest in the low proportion of ARDS reported in various studies. Our meta-analysis indicated an overall incidence of ARDS of 18.5%, significantly lower than the reported incidence from hospitalized patients (33%) [35]. It is unknown whether the immuno-compromised status *per se*, or the hemodiafiltration/hemoperfusion may have facilitated cytokine clearance. Although these findings may prove beneficial for patient survival they also imply protracted duration in eliminating the virus and hence persistent shedding in HD patients, which must be considered from a public health perspective. Studies investigating the dynamics of viral load in HD patients remain limited. Appropriate duration for quarantine or treatment course should be designed in future trials to avoid inadvertent transmission of COVID-19 among HD patients.

Again, studies among HD patients from Asian countries have reported lower mortality (17.0%) than from non- Asian countries (26.7%). Asian patients are more likely to be young and have milder clinical presentation than their non-Asian counterparts. The ubiquitous deployment of CT scan, especially in China, may have allowed better detection of severe lung condition feasible to timely intervention [33]. The optimal antiviral therapy for HD patients is largely unknown. Current consensus recommends the use of antiviral therapy in the first stage for viral clearance, followed up by immune-suppressive strategies (for example with glucocorticoids or anti-cytokine drugs) to ameliorate cytokine injury [36]. Combinations of antibiotics or Chinese herbal medicine administrations were

observed in Chinese studies [26, 29, 34]. Further randomized controlled trials comparing effectiveness and safety of different therapies should be undertaken in HD patients.

The findings of our study have several implications for clinical practice and also preventive medicine. The high incidence, with indolent or even asymptomatic clinical course may prevent timely identification of infected patients and may result in extensive spreading of virus in the crowded and highly-loaded medical area. Universal testing to stop the dissemination of COVID-19 should be leveraged with the appropriate testing capacity. For infected HD patients, cautions regarding prolonged viral shedding and prudence in the use of immuno-suppressive agents should be considered, taking into account the blunted immune reaction of HD patients. Ultimately, given the multiple coexistent high-risk conditions, vaccination, if proven safe, should be prioritized for HD patients.

The results of our study provide a panoramic understanding of COVID19 infection in HD patients. However, several limitations should be addressed. First, COVID-19 infection is unlikely to be eliminated in the near future, and more studies related to the epidemiology in HD patients with COVID-19 infection will be published after the presented work. Therefore, regularly updated systematic review and meta-analysis is suggested to confirm our findings. Second, all included studies report mortality with COVID-19 infection in HD patients after short follow-up periods, while the long-term outcomes in this population are yet to be determined. Third, we could not derive all the important information from the included studies, even if we did contact the study authors for those data. To reduce the effect of possible reporting bias on our result estimates, we conducted subgroup analyses using the study quality, which showed similar findings to the overall analyses. Finally, we included studies reporting data of patients receiving in-center HD treatment. Data of dialysis patients undergoing different modalities, such as home hemodialysis or peritoneal dialysis, remain unknown. We suggest the introduction of a standardized international registry of COVID-19 infected dialysis patients to collect detailed patient characteristics and prognosis data, which would be beneficial for the fight against the current pandemic and for the further development of optimal management for dialysis patients.

Conclusions

This systematic review and meta-analysis of international studies has demonstrated a higher incidence of COVID-19 infection and related mortality among HD patients, compared to the general population. Available data may underestimate the real incidence of infection since a substantial proportion of infected patients are asymptomatic at diagnosis. Absence of typical immune reactions presenting in infected HD patients may contribute to limited cytokine storm, less tissue damage but prolonged viral persistence. In spite of differences in incidence and mortality observed between Asian and non-Asian infected HD patients, the present data may provide insight for the design of surveillance and diagnosis strategies specific to HD patients. International collaboration for the comprehensive assessment of cases, with standardized reporting, should be urgently initiated to refine consensus on the optimal management of this novel infection in dialysis patients.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests: none to declare

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Authors' contributions: IWW and SCS designed the study; CYC, SCS, YTC and CKH carried out the study; CYC, SCS and IWW analyzed the data; SCS made the figures; IWW and SCS drafted the paper; HJK, CCL, CYS, YCC and MJH revised the paper. All authors approved the final version of the manuscript.

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Tables

Table 1: Characteristics of studies reporting COVID-19 infection in hemodialysis patients

First Author	Country	Total HD, n	COVID-19, n	Age (Covid-19)	Male, % (Covid-19)	Presenting Symptoms/Signs, n (%)						Laboratory findings, m SD), 10/L	
						Fever	Fatigue	Cough	Dyspnea	GI	Myalgia	WBC	Lymphocytes
Yau K	Canada	237	11	66 (63-72)	6 (55)	1 (9)	N/A	3 (27)	0 (0)	N/A	N/A	4.72 (3.1-21.8)	0.54 (0.05-1.38)
Wang H	China	230	37	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Su K	China	230	37	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Xiong F	China	7154	154	63.2 (13.1)	75 (57.3)	68 (52)a	59 (45)a	49 (37)a	34 (26)a	35 (27)a	NA	5.0 (3.8-7.3)	0.7 (0.5-1.1)
Wu J*	China	49	49	62 (54-71)	31 (63)	23 (47)	29 (59)	24 (49)	22 (45)	6 (12)	NA	5.6 (4.7-7.6)	0.8 (0.5–1.0)
Li J (1)	China	244	7	59 (39-66)	4 (57)	1 (14)	0 (0)	0 (0)	0	0	0	5.4 (2.6–6.4)	0.5 (0.4–0.9)
Li J (2)	China	6377	109	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wang R	China	201	5	57.6 (47-67)	3 (60)	3 (60)	3 (60)	1 (20)	2 (40)	2 (40)	0	7.50 (5.94-9.25)	0.80 (0.56-0.88)
Ma Y	China	230	42	64.57 (47-76)	25 (60)	4 (10)	3 (7)	3 (7)	N/A	2 (5)	N/A	N/A	1.42 (0.85–1.56)
Tang H^	China	1027	99	61.3±13.8	55 (56)	27 (27)	N/A	27 (27)	14 (14)	11 (11)	N/A	4.9 (4.04-6.51)	0.86 (0.66-1.15)
Wang R	China	202	7	59.43 (47-67)	4 (57)	5 (71)	5 (71)	3 (43)	4 (57)	6 (86)	NA	7.5 (5.03-8.02)	0.80 (0.49-0.92)
Tortonese S *	France	44	44	61 (51.5–72.5)	29 (66)	35 (80)	N/A	19 (43)	13 (30)	6 (14)	N/A	N/A	0.6 (0.46–1.04)
Alberici F*	Italy	21	21	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Manganaro M^	Italy	2893	98	70	58 (59.3)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Scarpioni R	Italy	257	41	73 (52-90)	31 (76)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Esposito P	Italy	260	17	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Alberici F	Italy	643	94	72 (62–79)	62 (66)	64 (68)	NA	22 (23)	24 (25)	6 (6)	16 (17)	5.08 (3.94-6.48)	0.75 (0.55-1.09)
Quintaliani G	Italy	30821	1093	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
La Milia V	Italy	209	55	72.26	N/A	21 (38)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Kikuchi K	Japan	339841	99	70-90	69 (70)	79 (95)b	N/A	47 (64)b	N/A	N/A	N/A	N/A	N/A
Cho JH	Korea	1175	11	57 (29–63)	7 (64)	6 (55)	0	2 (18)	0	0	0	N/A	N/A
Jung HY*	Korea	14	14	63.5 (40.0–88.0)	6 (43)	N/A	4 (29)	7 (50)	5 (36)	2 (14)	2 (14)	5.8 (4-10)	1.1 (1.0-4.5)
Sánchez-A JE*	Spain	548	548	71±15	359 (66)	416 (76)	N/A	372 (68)	236 (43)	13 (2.3)	N/A	N/A	N/A
Albalate M	Spain	90	37	67.79 (17-100)	23 (62)	16 (43)	N/A	10 (27)	3 (8)	0 (0)	3 (8)	N/A	0.919 (0.2-1.9)

Goicoechea M	Spain	282	36	71±12	23 (64)	24 (67)	9 (25)	16 (44)	N/A	6(17)	N/A	N/A	0.79±0.47
Sánchez-P P	Spain	478	16	79.5 [73.2-85]	11 (69)	16 (100)	11 (38)	11 (38)	3 (19)	5 (31)	11 (38)	N/A	8.4 (7,3-11,5)
Arslan H	Turkey	602	7	62 (25-79)	3 (43)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Corbett R.W.	UK	1530	300	67 (57–77)	180 (60)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Valeri AM*	USA	59	59	63 (56–78)	33 (56)	29 (49)	13 (22)	23 (39)	21 (36)	9 (15)	4 (7)	6 (4.5-7.8)	0.8 (0.58-1.23)
Fisher M*	USA	114	114			51 (45)	N/A	15 (13)	57 (50)	6 (5)	N/A	5.83	N/A

Abbreviation: HD: hemodialysis; GI: gastrointestinal symptoms; WBC: White blood cells; HCQ: hydroxychloroquine; CS: Corticosteroids; In: in-patient wards; Ou reported statistics of COVID-19 cases. Age was expressed in mean ± SD or median (ICQ).

The study of Li J et al. reported 2 independent cohorts that were analyzed separately for meta-analysis.

*Not included for incidence assessment because the denominator cannot be ascertained from literature or author queries. ^Not included for mortality assess

a. This study reported 154 confirmed covid-19 cases. Analyses were conducted from 131 cases because 23 patients did not provide consent. The percentage

b. This study reported 99 confirmed covid-19 cases. "Fever" recordings were missing in 16 cases (the percentages were calculated using 83 cases as denomi were calculated using 74 cases as denominator).

Antiviral therapy was reported as: c. not specified, used 115 patients as denominator; d. used 110 patients as denominator; e. lopinavir/ritonavir or remdesivi and 6 cases using lopinavir/ritonavir.

Table 2: Characteristics of studies related to COVID-19 infection in hemodialysis patients

Authors	Year	Journal	Date (M/D)	Country	City	Study Design	Setting	Duration	Confirmatory test	Preventive strategies	Qu sc
Yau K, et al	2020	Am J Kidney Dis	07/19	Canada	Toronto	Prospective	HD centers	15	RT-PCR	PPE, quarantine and isolation gowns	13
Wang H, et al	2020	Kidney Med	04/16	China	Wuhan	Retrospective	Hospital	34	RT-PCR + serology + CT	Timely upgrading of personal protection measures, quarantine and isolation	8
Su K, et al	2020	Infect Control Hosp Epidemiol	04/24	China	Wuhan	Retrospective	HD centers	26	RT-PCR + serology + CT	Isolation ward, quarantine	9
Xiong F, et al	2020	J Am Soc Nephrol	05/10	China	Wuhan	Retrospective	Hospital	69	RT-PCR	Medical mask, isolation	14
Wu J, et al	2020	Clin J Am Soc Nephrol	05/24	China	Wuhan	Retrospective	Hospital	40	RT-PCR	Isolation	13
Li J, et al (1)	2020	Kidney Disease	05/25	China	Wuhan	Retrospective	Hospital	17	RT-PCR + CT	Isolation in a dedicated area	12
Li J, et al (2)	2020	Kidney Disease	05/25	China	Wuhan	Retrospective	HD centers	13	RT-PCR + CT	N/A	12
Wang R, et al	2020	Am J Kidney Dis	05/31	China	Wuhan	Case series	HD centers	N/A	RT-PCR	Surgical or N95 masks	12
Ma Y, et al	2020	Kidney Int Rep	06/09	China	Wuhan	Retrospective	Hospital	58	RT-PCR+ CT	Patients: N95 mask, quarantine or Isolation. Staff: PPE	12
Tang H, et al	2020	Am J Kidney Dis	07/03	China	Wuhan	Retrospective	HD centers	121	RT-PCR, serology	N/A	15
Wang R, et al	2020	Clin Kidney J	07/23	China	Wuhan	Retrospective	Hospital	86	RT-PCR, RT-PCR+ CT	Patient: mask. Staff: Waterproof disposable gown, cap, gloves, face shield and N95 face mask	11
Tortonese S, et al	2020	Kidney Int Rep	07/18	France	Paris	Retrospective	Hospital	61	RT-PCR + CT	Mask	12
Alberici F, et al	2020	Kidney Int Rep	04/04	Italy	Brescia	Case series	Hospital	N/A	RT-PCR	N/A	11
Manganaro M, et al	2020	J Nephrol	04/12	Italy	Piedmont/ Aosta Valley	Retrospective	Hospital	35	CXR*	Surgical masks, hand disinfection	8
Scarpioni R, et al	2020	G Ital Nefrol	04/14	Italy	Piacenza	Retrospective	Hospital	N/A	RT-PCR, CT	Mask, alcohol-based sanitizer, changing clothes and shoes	3
Esposito P, et al	2020	Hemodial Int	05/05	Italy	Genoa	Retrospective	HD centers	N/A	RT-PCR	Handwashing, use of PPE	9
Alberici F, et al		Kidney Int	05/08	Italy	Brescia	Retrospective	HD centers	33	RT-PCR	N/A	14
Quintaliani G, et al	2020	J Nephrol	07/03	Italy	Nationwide	Retrospective	HD centers	59	RT-PCR	N/A	10
La Milia V,	2020	Kidney Int	07/10	Italy	Lombardy	Prospective	Hospital/	22	RT-PCR	Upgrade of	11

et al		Rep					HD centers			PPE	
Kikuchi K, et al	2020	Ther Apher Dial	06/09	Japan	Nationwide	Prospective	Hospital/ HD centers	89	RT-PCR, CT	Mask, sufficient distance	15
Cho JH, et al	2020	J Am Soc Nephrol	06/01	Korea	Daegu	Retrospective	HD centers	24	RT-PCR	Mask, hand sanitizer, cohort isolation, notify first	15
Jung HY, et al	2020	J Clin Med	06/02	Korea	Daegu	Prospective	Hospital	89	RT-PCR	Mask, isolation in negative pressure room	17
Sánchez-A JE, et al	2020	Nefrologia	04/06	Spain	Nationwide	Prospective	HD centers	24	RT-PCR	N/A	17
Albalate M, et al	2020	Nefrologia	04/30	Spain	Madrid	Retrospective	Hospital	35	RT-PCR	Mask, alcohol-based sanitizer	10
Goicoechea M, et al	2020	Kidney Int	05/11	Spain	Madrid	Retrospective	Hospital	29	RT-PCR	N/A	12
Sánchez-P P, et al	2020	Nefrologia	07/06	Spain	Valencia	Prospective	Hospital/HD centers	45	RT-PCR	PPE, isolation	17
Arslan H, et al	2020	Exp Clin Transplant	06/11	Turkey	Ankara	Retrospective	HD centers	N/A	RT-PCR+ CT	N/A	13
Corbett RW, et al	2020	J Am Soc Nephrol	06/19	UK	London	Prospective	HD centers	42	RT-PCR	Mask, isolation units	16
Valeri AM, et al	2020	J Am Soc Nephrol	05/28	USA	New York	Retrospective	Hospital	30	RT-PCR	Staff: Mask, PPE	15
Fisher M, et al	2020	Kidney360	06/17	USA	New York	Retrospective	Hospital	44	RT-PCR	N/A	14

Abbreviation: PPE: Personal protective equipment (including masking gloves, face shields, masks, disposable gowns, caps); RT-PCR, Reverse-transcriptase p reaction; CT: Chest computed tomography; CXR, chest X ray; Ref, reference. * COVID-19 infection was confirmed if signs of interstitial pneumonia presented o radiography.

The study of Li J et al. reported 2 independent cohorts which were analyzed separately for meta-analysis.

Duration: denoted observation period, expressed in days. Quality score indicates the number of positive answers in the case-series appraisal sheets.

Figures

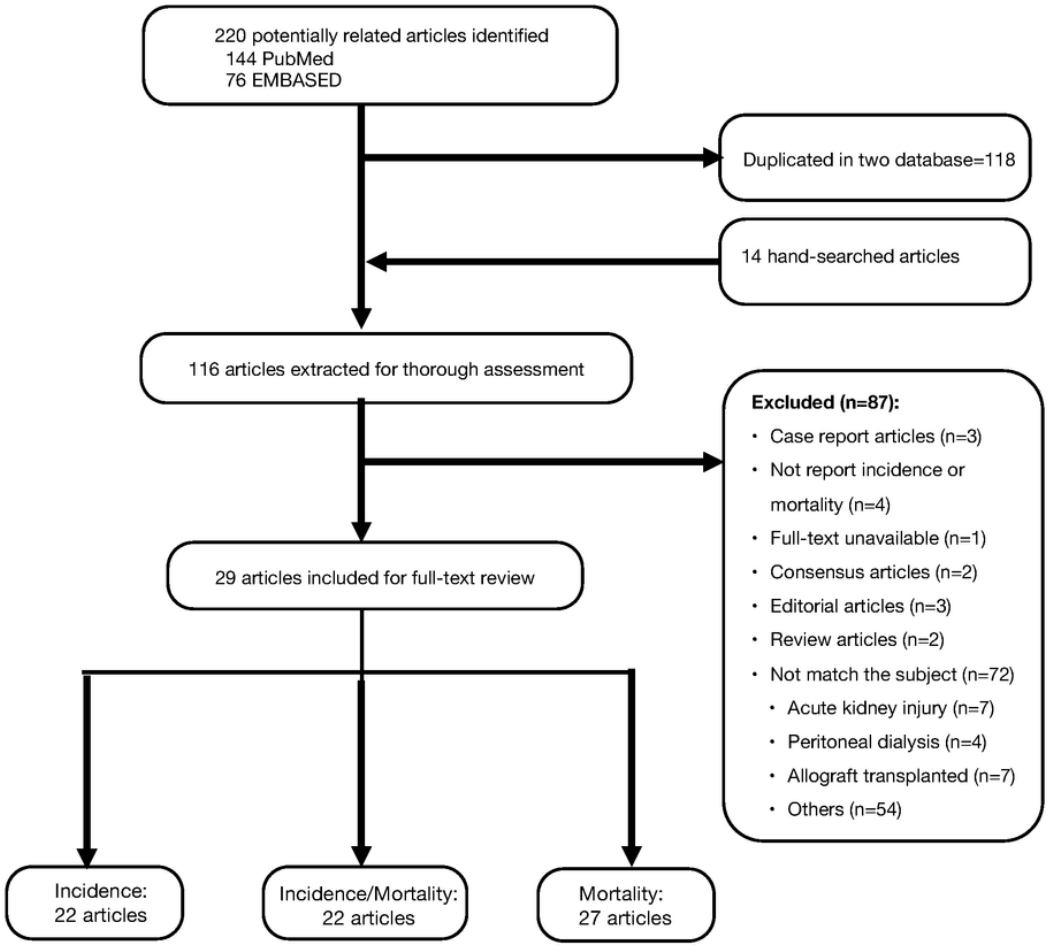
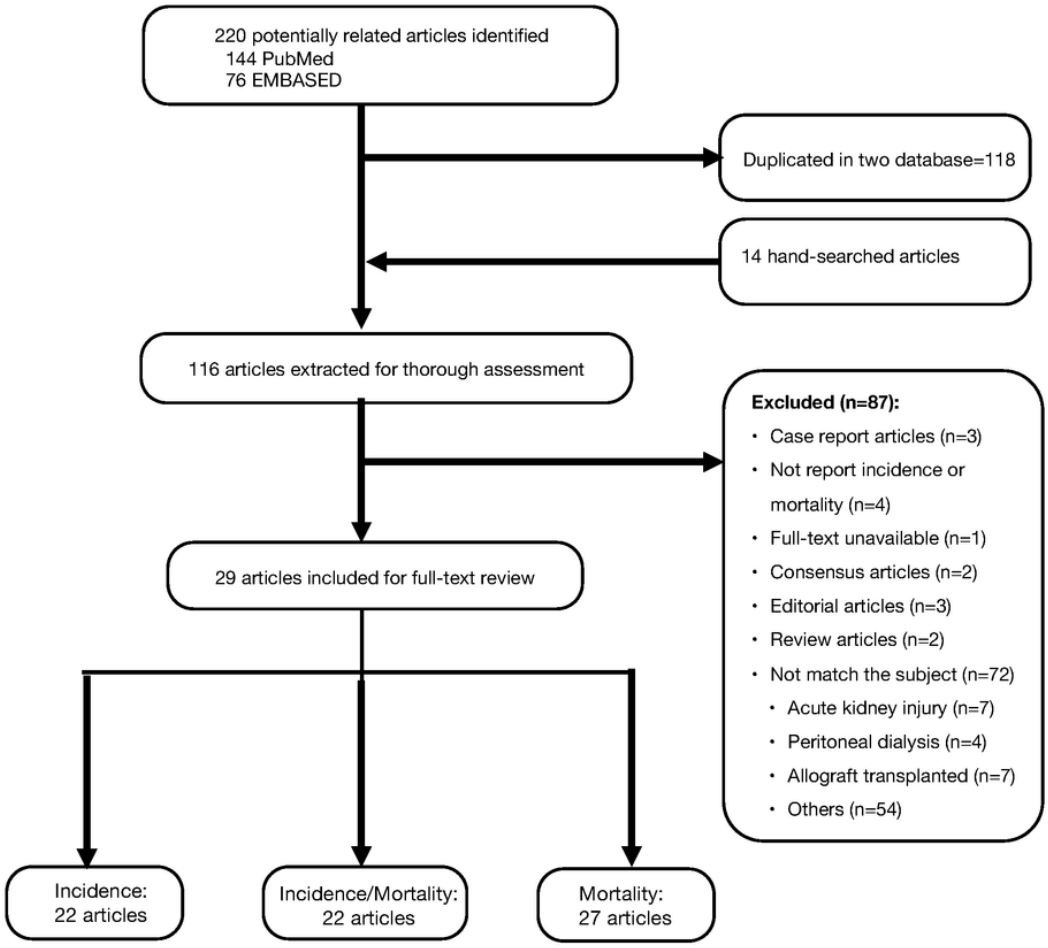


Figure 1

Flow chart of literature search and selection.



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Flow chart of literature search and selection.

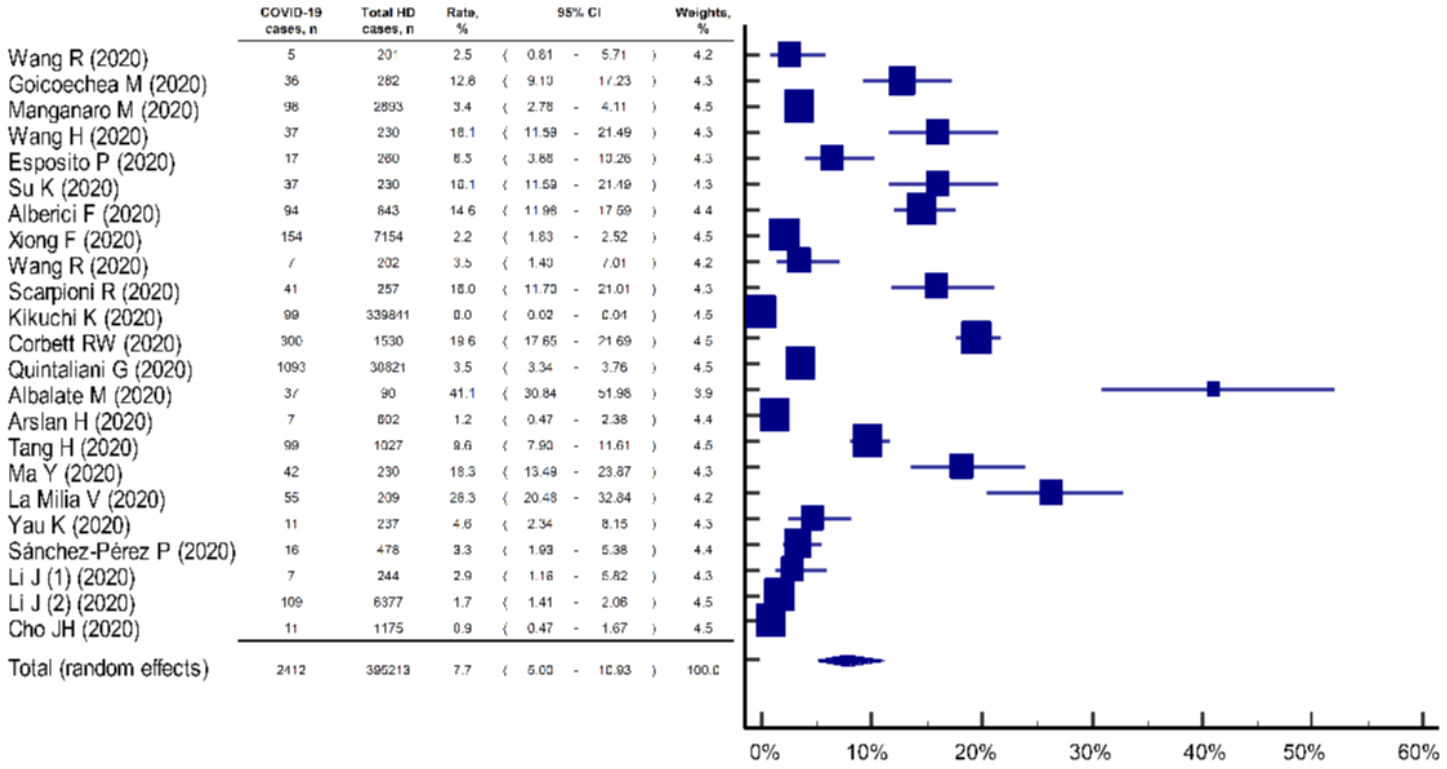
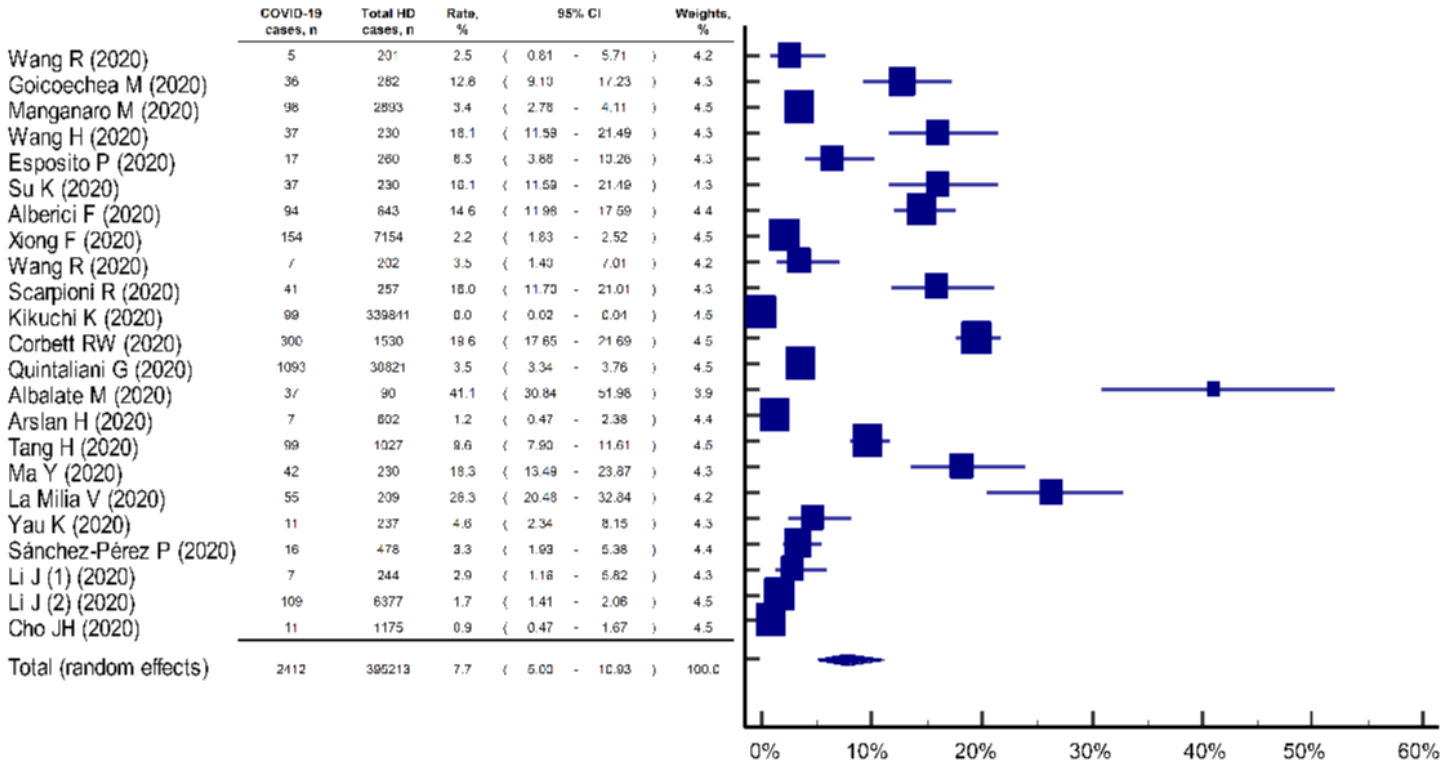


Figure 2

Incidence rate of COVID-19 infection in patients with hemodialysis. The study of Li J et al. reported 2 independent cohorts which were analyzed separately for meta-analysis. HD, hemodialysis; CI, confidential interval.



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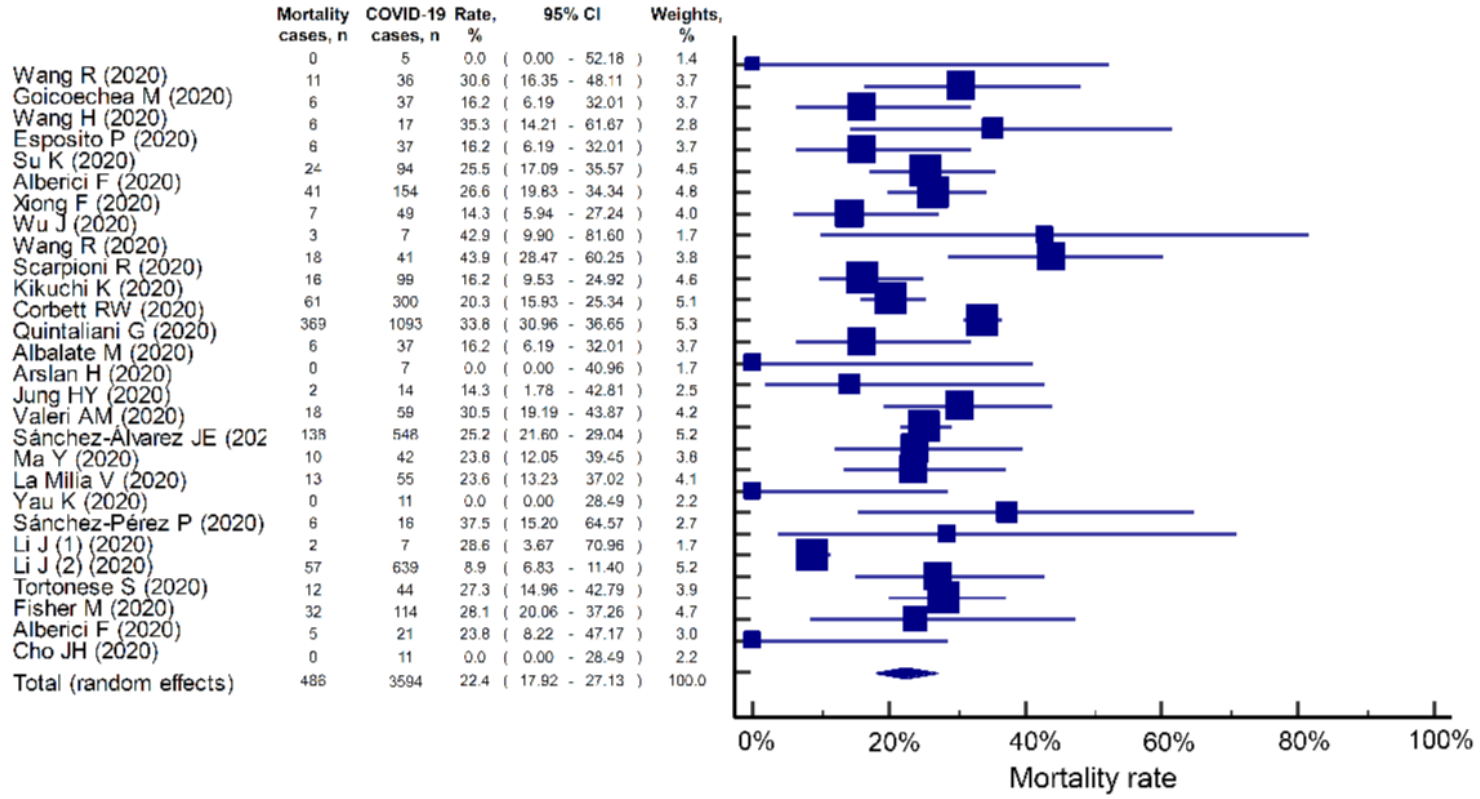
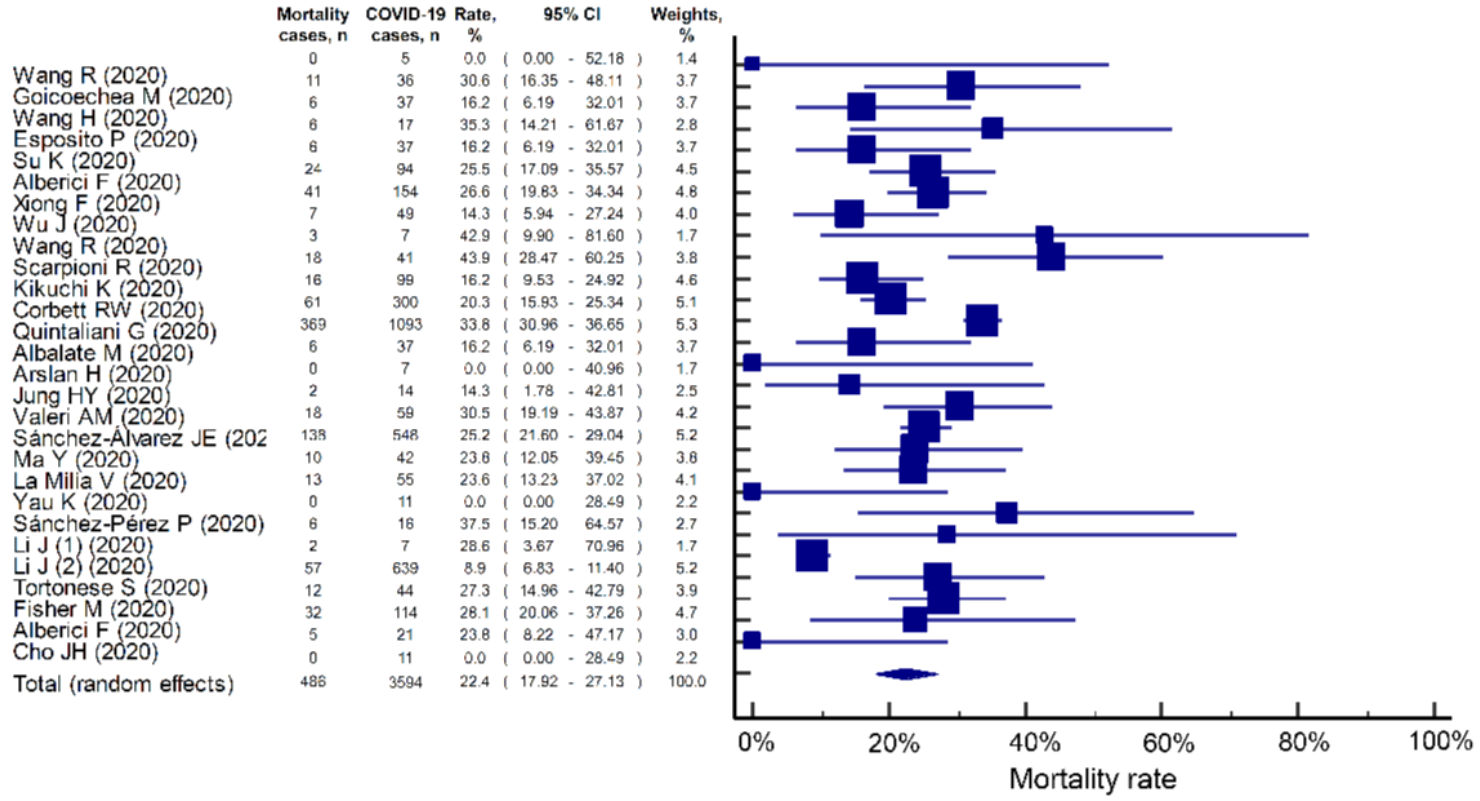


Figure 3

Mortality rate in hemodialysis patients with COVID-19 infection. The study of Li J et al. reported 2 independent cohorts which were analyzed separately for meta-analysis. The second cohort of Li J et al. reported mortality in 57 deaths from 639 COVID-19 cases (all cases showed feature of viral pneumonitis and 109 were further confirmed by nuclear acid testing). HD, hemodialysis; CI, confidential interval. HD, hemodialysis; CI, confidential interval.



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