Review Article

Systematic Review and Meta-Analysis of the Impact of COVID-19 on Dialysis Outcomes

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Abstract

Concerns have been raised regarding the impact of COVID-19, which is produced by the SARS-CoV-2 virus, on vulnerable groups, such as those receiving continuous dialysis for end-stage renal disease (ESRD). This systematic review and meta-analysis aim to comprehensively synthesize the existing evidence on the relationship between COVID-19 and dialysis outcomes. Following PRISMA and MOOSE guidelines, a systematic literature search was conducted across major databases to identify relevant studies published up to the date of the search initiation. Inclusion criteria encompassed studies reporting outcomes of COVID-19 in individuals undergoing chronic dialysis, and a standardized data extraction form was used to capture essential information.

In individuals with HD, the incidence of COVID-19 was 7.7% (95% CI: 5.0–10.9%), exhibiting notable heterogeneity ($I2 = 99.7\%$, $p < 0.001$). Clinical manifestations included fever (61.4%), cough (46.8%), dyspnea (35.2%), and fatigue (35.2%). Bilateral lung involvement with ground-glass opacities was prevalent radiologically, with 10–50% of patients showing negative results. Among the patients, the death rate was 22.4% (95% CI: 17.9-27.1%); nevertheless, there was a notable degree of heterogeneity among the trials ($I2=83.2\%$, $P=0.001$). Causes of mortality, often unreported, included respiratory failure (mainly due to ARDS), cardiac arrest, sepsis, and hyperkalemia. This study highlights the vulnerability of HD patients to COVID-19, with a notable incidence and mortality rate. The findings emphasize the importance of standardized treatment protocols and further research to guide evidence-based care for this high-risk population.

Keywords: COVID-19, Dialysis, ESRD, HD

Introduction

The global outbreak of the novel coronavirus infection (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in an unprecedented public health crisis, impacting millions of people globally [1, 2]. While the respiratory manifestations of COVID-19 have been extensively studied, there is a growing recognition of the virus's impact on individuals with pre-existing health conditions, particularly those undergoing dialysis for end-stage renal disease (ESRD) [3, 4]. This has prompted a surge in research efforts to understand the specific implications of COVID-19 on dialysis outcomes.

Patients with ESRD undergoing chronic dialysis face unique challenges, including compromised immune function and a higher burden of comorbidities [5-7]. These factors may increase susceptibility to severe complications if infected with SARS-CoV-2 [4, 8, 9]. Consequently, a comprehensive examination of the existing literature is imperative to elucidate the impact of COVID-19 on dialysis patients, with a particular focus on clinical outcomes, mortality rates, and other relevant health parameters.

This systematic review and meta-analysis aim to synthesize the current evidence regarding the association between COVID-19 and dialysis outcomes. By rigorously evaluating and synthesizing available data from diverse studies, including observational cohorts, case-control studies, and clinical trials, we seek to provide a comprehensive overview of the magnitude and patterns of the impact of COVID-19 on individuals undergoing dialysis.

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Understanding the nuanced relationship between COVID-19 and dialysis outcomes is crucial for informing clinical practice, guiding public health interventions, and shaping future research endeavors. Furthermore, insights derived from this review can contribute to developing targeted policies to mitigate the adverse effects of COVID-19 on dialysis patients, ultimately improving their overall health outcomes during the ongoing pandemic and future infectious disease challenges.

Materials and Methods

Study Design and Protocol Development

This systematic review and meta-analysis adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational-Studies in Epidemiology (MOOSE) guidelines. A priori, a comprehensive protocol was created that included the study's goals, inclusion/exclusion standards, and procedures for extracting data.

Search Strategy

Widespread literature searches were conducted in the Cochrane Library, Embase, Pub-Med/MEDLINE, and Scopus electronic databases. The search strategy combined terms related to COVID-19 (e.g., "SARS-CoV-2," "COVID-19") and dialysis outcomes (e.g., "dialysis," "end-stage renal disease"). Boolean operators and Medical Subject Headings (Mesh) terms were used to refine search precision. The search was limited to articles published up to the date of the search initiation.

Inclusion and Exclusion Criteria

Inclusion criteria encompassed studies reporting outcomes of COVID-19 in individuals undergoing chronic dialysis, including observational studies, case-control studies, and clinical trials. Exclusion criteria included studies with inadequate outcome data, duplicate publications, and those not written in English.

Study Selection

Two independent reviewers assessed Titles and abstracts for eligibility based on inclusion/exclusion criteria. Potentially pertinent study full-texts were evaluated before being included in the total. Conflicts were settled by agreement or by consulting a third reviewer.

Data Extraction

A standardized data extraction form was developed to capture relevant information, including study characteristics (author, publication year, study design), participant characteristics, dialysis modality, COVID-19 outcomes (mortality, hospitalization, complications), and other pertinent variables. Two reviewers independently extracted data, and any discrepancies were resolved through discussion.

Data Synthesis and Analysis

Meta-analysis was conducted for comparable outcomes across studies, employing random-effects or fixed-effects models as appropriate. The I2 statistic was used to measure heterogeneity, and subgroup studies were conducted to investigate its causes. Sensitivity analyses were performed to assess how reliable the findings were. Statistical tests (such as Egger's test) and funnel plots were used to evaluate publication bias.

Ethical Considerations

Ethical approval was not required as this study involves synthesizing existing data from published literature. We adhered to ethical standards, ensuring transparency and respecting the rights of study participants as reported in the original publications.

Reporting

The findings were reported following PRISMA guidelines, providing a detailed and transparent account of the review process, results, and potential limitations.

Results and Discussion

During the first evaluation, we found a total of 283 entries from the PUBMED (n = 148), Web of Science (n = 57), and EMBASE (n = 78) databases. As shown in **Figure 1**, 29 publications were chosen for full-text study after the filtering procedure. This systematic review and meta-analysis comprised data from 3,261 confirmed COVID-19 instances among 396,062 hemodialysis (HD) patients, spanning 29 international studies. 64.5% of HD patients with COVID-19 infection were male, with an average age of 64.9 years. **Tables 1 and 2** provide more information on the features of the included studies. Articles continued to appear with short observation times due to the unique disease's emergent character; as a consequence, 46.6 days was the average observation period (range: 13 to 121). **Table 3** lists the 22 HD cohorts (47.8% in Asian countries; 43.5% with high study quality) that we used to analyze mortality linked to COVID-19 infection and the 27 HD cohorts (42.9% in Asian countries; 35.7% with good research quality) that we used to estimate incidence.

The frequency of COVID-19 infection in patients receiving HD therapy was found to be 7.7% (95% CI: 5.0–10.9%), with significant statistical heterogeneity among the studies (I2 = 99.7%, $p < 0.001$) **(Figure 2)**. Egger's test revealed a substantial chance of publication bias ($p < 0.001$). The incidence was estimated to be 5.2% (95% CI: 1.2-118%) in high-quality research, compared to 8.7% (95% CI: 6.4-112%) in low-quality studies.

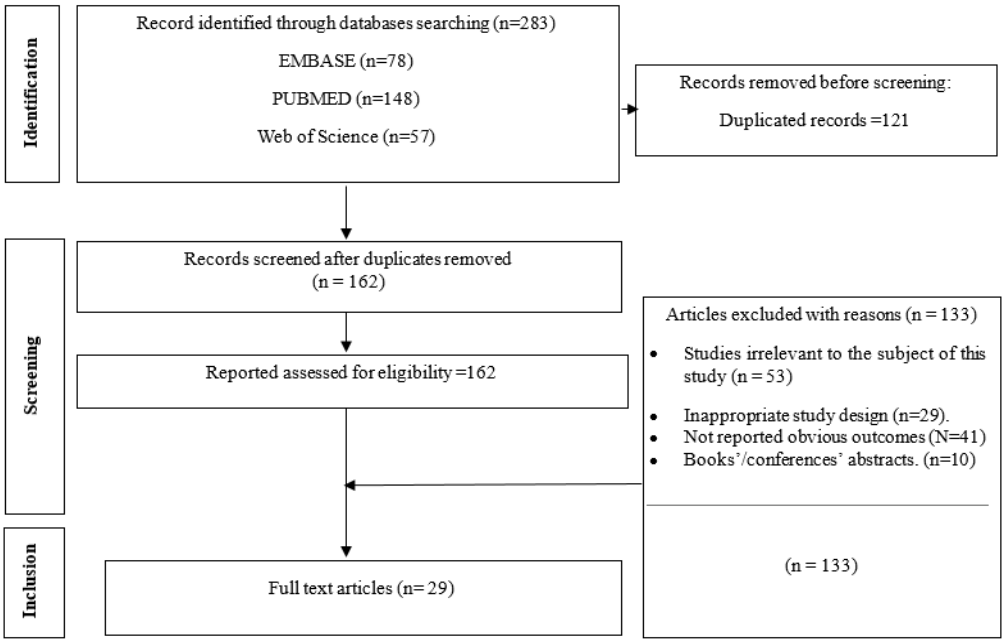

Figure 1. The PRISMA figures showing the steps to choose the studies for systematic review

Table 1. General characteristics of the study, population characteristics, and presenting symptoms/signs

First Author	Country	Total HD, *n*	COVID-19, *n*	Age (Covid-19)	Male, % (Covid-19)	Presenting Symptoms/Signs, *n* (%)					
						Fever	Fatigue	Cough	Dyspnea	Gastrointestinal symptoms	Myalgia
Albalate M, *et al.* [10]	Spain	90	37	67.79 (17–100)	23 (62)	16 (43)	N/A	10 (27)	3 (8)	0 (0)	3 (8)
Alberici F, *et al.* [11]	Italy	643	94	72 (62–79)	62 (66)	64 (68)	NA	22 (23)	24 (25)	6 (6)	16 (17)
Alberici F, *et al.* [12]	Italy	21	21	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Arslan H, *et al.* [13]	Turkey	602	7	62 (25–79)	3 (43)	N/A	N/A	N/A	N/A	N/A	N/A
Cho JH, *et al.* [14]	Korea	1175	11	57 (29–63)	7 (64)	6 (55)	0	2 (18)	0	0	0
Corbett RW, *et al.* [15]	UK	1530	300	67 (57–77)	180 (60)	N/A	N/A	N/A	N/A	N/A	N/A
Esposito P, *et al.* [16]	Italy	260	17	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fisher M, *et al.* [17]	USA	114	114	64.5	68 (61)	51 (45)	N/A	15 (13)	57 (50)	6 (5)	N/A
Goicoechea M, *et al.* [18]	Spain	282	36	71 ± 12	23 (64)	24 (67)	9 (25)	16 (44)	N/A	6(17)	N/A
Kikuchi K, *et al.* [19]	Japan	339,841	99	70–90	69 (70)	79 (95) b	N/A	47 (64) b	N/A	N/A	N/A
La Milia V, *et al.* [20]	Italy	209	55	72.26	N/A	21 (38)	N/A	N/A	N/A	N/A	N/A
Li J, *et al.* [21]	China	244	7	59 (39–66)	4 (57)	1 (14)	0 (0)	0 (0)	0	0	0
Li J, *et al.* [21]	China	6377	109	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ma Y, *et al.* [22]	China	230	42	64.57 (47–76)	25 (60)	4 (10)	3 (7)	3 (7)	N/A	2 (5)	N/A
Manganaro M, *et al.* [23]	Italy	2893	98	70	58 (59.3)	N/A	N/A	N/A	N/A	N/A	N/A
Quintaliani G, *et al.* [24]	Italy	30,821	1093	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sánchez-A JE, *et al.* [25]	Spain	548	548	71 ± 15	359 (66)	416 (76)	N/A	372 (68)	236 (43)	13 (2.3)	N/A
Sánchez-P P, *et al.* [26]	Spain	478	16	79.5 (73.2–85)	11 (69)	16 (100)	11 (38)	11 (38)	3 (19)	5 (31)	11 (38)

Scarpioni R, *et al.* [27]	Italy	257	41	73 (52–90)	31 (76)	N/A	N/A	N/A	N/A	N/A	N/A
Su K, *et al.* [28]	China	230	37	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tang H, *et al.* [29]	China	1027	99	61.3 ± 13.8	55 (56)	27 (27)	N/A	27 (27)	14 (14)	11 (11)	N/A
Tortonese S, *et al.* [30]	France	44	44	61 (51.5–72.5)	29 (66)	35 (80)	N/A	19 (43)	13 (30)	6 (14)	N/A
Valeri AM, *et al.* [31]	USA	59	59	63 (56–78)	33 (56)	29 (49)	13 (22)	23 (39)	21 (36)	9 (15)	4 (7)
Wang H, *et al.* [32]	China	230	37	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Wang R, *et al.* [33]	China	201	5	57.6 (47–67)	3 (60)	3 (60)	3 (60)	1 (20)	2 (40)	2 (40)	0
Wang R, *et al.* [34]	China	202	7	59.43 (47–67)	4 (57)	5 (71)	5 (71)	3 (43)	4 (57)	6 (86)	NA
Wu J, *et al.* [35]	China	49	49	62 (54–71)	31 (63)	23 (47)	29 (59)	24 (49)	22 (45)	6 (12)	NA
Xiong F, *et al.* [36]	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
Yau K, *et al.* [37]	Canada	237	11	66 (63–72)	6 (55)	1 (9)	N/A	3 (27)	0 (0)	N/A	N/A

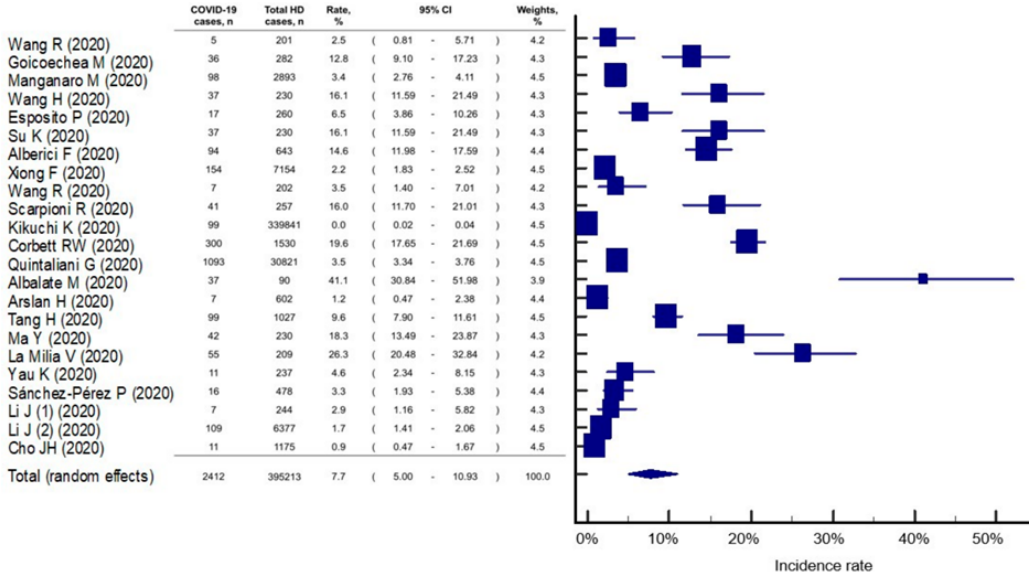

Figure 2. Incidence rate of COVID-19 infection in patients with hemodialysis.

The most common clinical symptom (found in 19 studies) among 61.4% of HD patients infected with COVID-19 (95% CI: 40.2–65.5%) was fever. Cough (46.8%, 95% CI: 25.7–44.7%), dyspnea (35.2%, 95% CI: 16.9–36.6%), and fatigue (35.2%, 95% CI: 14.6-49.9%) followed **(Table 1)**. Hematological parameters were reported in 11 studies, with most patients possessing platelets, neutrophils, lymphocytes, and white blood cells within typical ranges **(Table 2)**. The most common finding from studies documenting dyspnea or chest imaging was bilateral lung involvement with ground-glass opacities, whereas 10-50% of the patients had negative radiological findings.

For HD patients, the COVID-19 treatment plan was primarily empirical, and comparisons between different regimens were challenging due to limited information on dosing, duration, and prescription indications where antiviral agents and hydroxychloroquine were the most used medications, followed by tocilizumab and corticosteroids. Inpatient care was required for 82.5% of patients, with absolute hospitalization in 11 of 19 studies **(Table 2)**. It was discovered that there was a more significant mortality when these regimens were used less often. 6.6% of patients were admitted to the critical care unit. The average duration of stay in the hospital was 14.5 ± 8.8 days. In 18.5% of instances (95% CI 4.5–21.7%), acute respiratory distress syndrome (ARDS) was present, and 93% of patients in the trials required assistance.

In light of the COVID-19 results, it was discovered that the patient death rate was 22.4% (95 % CI: 17.9-27.1%); yet, there was a notable degree of heterogeneity among the trials (I2=83.2%, P=0.001) **(Figure 3)**. No significant difference was reported between good and poor-quality studies, considering the mortality rates of 23.8 % and 21.6 %, respectively. The leading cause of death was respiratory failure from ARDS, which was frequently undiagnosed.

Sepsis, cardiac arrest, and hyperkalemia were the next most common causes.

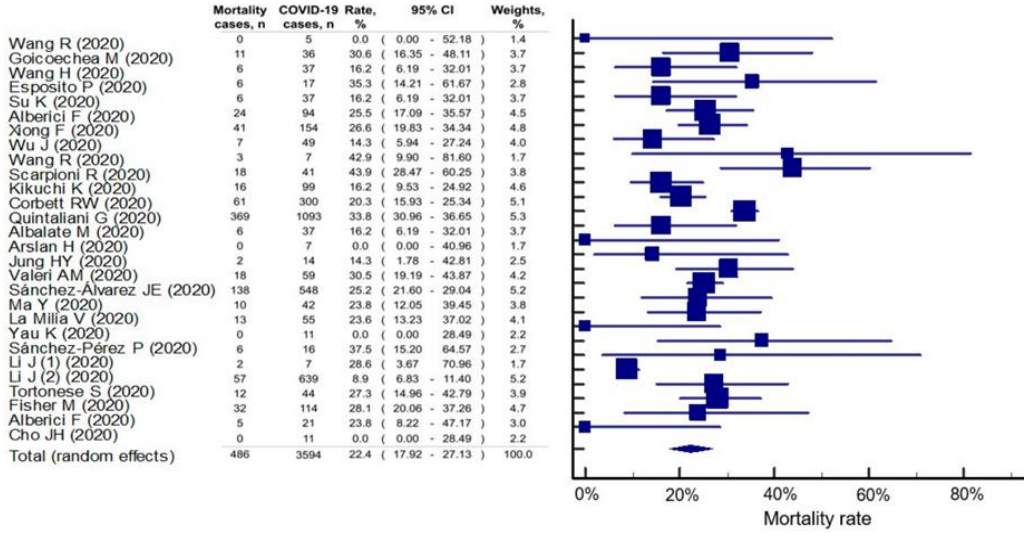

Figure 3. Mortality rate in hemodialysis patients with COVID-19 infection.

Table 2. The laboratory, treatment, location of treatment, and rate of ARDS among patients on dialysis and having COVID-19

First Author	Country	Laboratory Findings, Median (IQR) or Mean (± SD), 10^9/L				Treatment, *n* (%)				Location of Treatment, *n* (%)			ARDS
		WBC	Lymphocytes	Neutrophils	Platelet	Antiviral	Hydroxychloroquine	Tocilizumab	Corticosteroids	Inpatient wards	Out-patient clinic	ICU	*n*, %
Albalate M, *et al*. [10]	Spain	N/A	0.919 (0.2–1.9)	N/A	N/A	23 (62), Azithromycin	29 (78)	N/A	N/A	16 (43)	21 (57)	0 (0)	N/A
Alberici F, *et al*. [11]	Italy	5.08 (3.94–6.48)	0.75 (0.55–1.09)	3.51 (2.69–4.77)	162 (126–230)	60 (64), lopinavir/ritonavir or darunavir/ritonavir	72 (77)	19 (20)	N/A	57 (61)	37 (40)	N/A	57 (61)
Alberici F, *et al*. [12]	Italy	N/A	N/A	N/A	N/A	17 (81), lopinavir/ritonavir or remdesivir	17 (81)	1 (5)	4 (19)	21 (100)	0 (0)	0(0)	N/A
Arslan H, *et al*. [13]	Turkey	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0
Cho JH, *et al*. [14]	Korea	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	11 (100)	0 (0)	0(0)	0
Corbett RW, *et al*. [15]	UK	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Esposito P, *et al*. [16]	Italy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	6 (35)	11 (64)	1 (6)	N/A
Fisher M, *et al*. [17]	USA	5.83	N/A	N/A	N/A	0 (0)	87 (76)	0 (0)	0	114 (100)	0 (0)	15 (13)	14 (12)
Goicoechea M, *et al*. [18]	Spain	N/A	0.79 ± 0.47	NA	164 ± 66	2 (5), lopinavir/ritonavir	35 (97)	27 (75)	17 (47)	36 (100)	0	1 (2.7)	11 (31)
Kikuchi K, *et al*. [19]	Japan	N/A	N/A	N/A	N/A	31 (31), Favipiravir	N/A	N/A	15 (15)	99 (100)	0 (0)	N/A	N/A
La Milia V, *et al*. [20]	Italy	N/A	N/A	N/A	N/A	25 (46), lopinavir/ritonavir or remdesivir	25 (46)	0	0	25	30	8 (15)	

Li J, *et al*. [21]	China	5.4 (2.6–6.4)	0.5 (0.4–0.9)	4.4 (1.9–5.0)	134.0 (23.3)	0	0	0	0	7 (100)	0 (0)	N/A	N/A
Li J, *et al*. [21]	China	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Ma Y, *et al*. [22]	China	N/A	1.42 (0.85–1.56)	4.92 (4.23–7.06)	154 (140–200)	N/A	N/A	N/A	N/A	32 (76)	10 (24)	3 (7)	2 (5)
Manganaro M, *et al*. [23]	Italy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Quintaliani G, *et al*. [24]	Italy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sánchez-A JE, *et al*. [25]	Spain	N/A	N/A	N/A	N/A	176 (32), lopinavir/ritonavir or remdesivir	396 (72)	12 (2)	80 (14)	444 (81)	104 (19)	33 (6)	N/A
Sánchez-P P, *et al*. [26]	Spain	N/A	8.4 (7.3–11.5)	N/A	N/A	0 (0)	12 (75)	2 (13)	4 (33)	16 (100)	0 (0)	2 (13)	N/A
Scarpioni R, *et al*. [27]	Italy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Su K, *et al*. [28]	China	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0
Tang H, *et al*. [29]	China	4.9 (4.04–6.51)	0.86 (0.66–1.15)	3.45 (2.87–4.52)	161 (117–200)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tortonese S, *et al*. [30]	France	N/A	0.6 (0.46–1.04)	3.91 (2.39–6.00)	196.5 (136–249)	0 (0)	3 (7)	4 (9.1)	N/A	41 (93)	3(7)	15 (34)	12 (28)
Valeri AM, *et al*. [31]	USA	6 (4.5–7.8)	0.8 (0.58–1.23)	N/A	N/A	N/A	34 (58)	3 (5)	N/A	59 (100)	0 (0)	8 (14)	N/A
Wang H, *et al*. [32]	China	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	37 (100)	0	0	0
Wang R, *et al*. [33]	China	7.50 (5.94–9.25)	0.80 (0.56–0.88)	5.69 (4.97–7.76)	NA	N/A	N/A	N/A	N/A	5 (100)	0	0	0
Wang R, *et al*. [34]	China	7.5 (5.03–8.02)	0.80 (0.49–0.92)	5.65 (4.29–6.28)	141 (114–213)	5 (71), Not specific	N/A	N/A	3 (43)	N/A	N/A	N/A	1 (14)
Wu J, *et al*. [35]	China	5.6 (4.7–7.6)	0.8 (0.5–1.0)	4.0 (3.1–5.6)	169 (120–234)	47 (96), Not specific	N/A	N/A	8 (16)	N/A	N/A	N/A	10 (20)
Xiong F, *et al*. [36]	China	5.0 (3.8–7.3)	0.7 (0.5–1.1)	3.9 (3.0–6.1)	144.2 (107–186)	92 (80), Not specific	N/A	N/A	19 (17.3) d	N/A	N/A	N/A	16 (10)
Yau K, *et al*. [37]	Canada	4.72 (3.1–21.8)	0.54 (0.05–1.38)	N/A	N/A	N/A	N/A	N/A	N/A	5 (45)	6 (55)	2 (18)	0

Table 3. General characteristics of the studies

Authors	Year	Journal	Date (M/D)	Country	City	Study Design	Setting	Duration	Confirmatory Test	Preventive Strategies	Quality Score
Albalate M, *et al*. [10]	2020	Nefrologia	30-Apr	Spain	Madrid	Retrospective	Hospital	35	RT−PCR	Mask, alcohol-based sanitizer	10
Alberici F, *et al*. [11]	2020	Kidney Int Rep	4-Apr	Italy	Brescia	Case series	Hospital	N/A	RT−PCR	N/A	11
Alberici F, *et al*. [12]	2020	Kidney Int	8-May	Italy	Brescia	Retrospective	HD centers	33	RT−PCR	N/A	14

Arslan H, *et al*. [13]	2020	Exp Clin Transplant	11-Jun	Turkey	Ankara	Retrospective	HD centers	N/A	RT−PCR + CT	N/A	13
Cho JH, *et al*. [14]	2020	J Am Soc Nephrol	1-Jun	Korea	Daegu	Retrospective	HD centers	24	RT−PCR	Mask, hand sanitizer, cohort isolation, notify first	15
Corbett RW, *et al*. [15]	2020	J Am Soc Nephrol	19-Jun	UK	London	Prospective	HD centers	42	RT−PCR	Mask, isolation units	16
Esposito P, *et al*. [16]	2020	Hemodial Int	5-May	Italy	Genoa	Retrospective	HD centers	N/A	RT−PCR	Handwashing, use of PPE	9
Fisher M, *et al*. [17]	2020	Kidney360	17-Jun	USA	New York	Retrospective	Hospital	44	RT−PCR	N/A	14
Goicoechea M, *et al*. [18]	2020	Kidney Int	11-May	Spain	Madrid	Retrospective	Hospital	29	RT−PCR	N/A	12
Kikuchi K, *et al*. [19]	2020	Ther Apher Dial	9-Jun	Japan	Nationwide	Prospective	Hospital/ HD centers	89	RT−PCR, CT	Mask, sufficient distance	15
La Milia V, *et al*. [20]	2020	Kidney Int Rep	10-Jul	Italy	Lombardy	Prospective	Hospital/ HD centers	22	RT−PCR	Upgrade of PPE	11
Li J, *et al*. [21]	2020	Kidney Disease	25-May	China	Wuhan	Retrospective	Hospital	17	RT−PCR + CT	Isolation in a dedicated area	12
Li J, *et al*. [21]	2020	Kidney Disease	25-May	China	Wuhan	Retrospective	HD centers	13	RT−PCR + CT	N/A	12
Ma Y, *et al*. [22]	2020	Kidney Int Rep	9-Jun	China	Wuhan	Retrospective	Hospital	58	RT−PCR+ CT	Patients: N95 mask, quarantine, or Isolation. Staff: PPE	12
Manganaro M, *et al*. [23]	2020	J Nephrol	12-Apr	Italy	Piedmont/ Aosta Valley	Retrospective	Hospital	35	CXR *	Surgical masks, hand disinfection	8
Quintaliani G, *et al*. [24]	2020	J Nephrol	3-Jul	Italy	Nationwide	Retrospective	HD centers	59	RT−PCR	N/A	10
Sánchez-A JE, *et al*. [25]	2020	Nefrologia	6-Apr	Spain	Nationwide	Prospective	HD centers	24	RT−PCR	N/A	17
Sánchez-P P, *et al*. [26]	2020	Nefrologia	6-Jul	Spain	Valencia	Prospective	Hospital/HD centers	45	RT−PCR	PPE, isolation	17
Scarpioni R, *et al*. [27]	2020	G Ital Nefrol	14-Apr	Italy	Piacenza	Retrospective	Hospital	N/A	RT−PCR, CT	Mask, alcohol-based sanitizer, changing clothes and shoes	3
Su K, *et al*. [28]	2020	Infect Control Hosp Epidemiol	24-Apr	China	Wuhan	Retrospective	HD centers	26	RT-PCR + serology + CT	Isolation ward, quarantine	9
Tang H, *et al*. [29]	2020	Am J Kidney Dis	3-Jul	China	Wuhan	Retrospective	HD centers	121	RT−PCR, serology	N/A	15
Tortonese S, *et al*. [30]	2020	Kidney Int Rep	18-Jul	France	Paris	Retrospective	Hospital	61	RT−PCR + CT	Mask	12
Valeri AM, *et al*. [31]	2020	J Am Soc Nephrol	28-May	USA	New York	Retrospective	Hospital	30	RT−PCR	Staff: Mask, PPE	15
Wang H, *et al*. [32]	2020	Kidney Med	16-Apr	China	Wuhan	Retrospective	Hospital	34	RT-PCR + serology + CT	Timely upgrading of personal protection measures, quarantine and isolation	8
Wang R, *et al*. [33]	2020	Am J Kidney Dis	31-May	China	Wuhan	Case series	HD centers	N/A	RT−PCR	Surgical or N95 masks	12
Wang R *et al*. [34]	2020	Clin Kidney J	23-Jul	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
Wu J, *et al*. [35]	2020	Clin J Am Soc Nephrol	24-May	China	Wuhan	Retrospective	Hospital	40	RT−PCR	Isolation	13

Xiong F, *et al*. [36]	2020	J Am Soc Nephrol	10-May	China	Wuhan	Retrospective	Hospital	69	RT−PCR	Medical mask, isolation	14
Yau K *et al*. [37]	2020	Am J Kidney Dis	19-Jul	Canada	Toronto	Prospective	HD centers	15	RT−PCR	PPE, quarantine, and isolation gowns	13

Based on 29 worldwide studies with 3,261 confirmed instances among 396,062 HD patients, this systematic review and meta-analysis offers essential new information on the effects of COVID-19 on HD patients. Males comprised 64.5% of the infected HD patient population, with an average age of 64.9 years. The short observation durations of the included trials, averaging 46.6 days, clearly demonstrate the emerging character of the condition.

7.7% (95% CI: 5.0–10.9%) of patients undergoing HD treatment had COVID-19, with significant inter-study heterogeneity ($I2 = 99.7\%$, $p < 0.001$). According to quality evaluation, the prevalence of studies with high quality was lower (5.2%, 95% CI: 1.2–11.8%) than that of studies with poor quality (8.7%, 95% CI: 6.4–11.2%). Hemodialysis (HD) patients are particularly vulnerable, as evidenced by the incidence of COVID-19 that has been discovered in this community. Patients with HD have reduced immune systems, concurrent illnesses, and advanced age, making them more vulnerable to COVID-19 [28, 32]. It is challenging to successfully execute traditional preventative measures like social isolation and directives to stay at home due to the inherent challenges faced by HD patients, which include frequent visits to densely populated areas like public transportation or HD facilities, coupled with close interactions with healthcare professionals and caregivers [12]. Consequently, our study reveals a significant 15.4-fold elevation in the incidence of COVID-19 among HD patients, with the added factor of an older patient demographic compared to the general population [15].

Fever emerged as the predominant clinical manifestation, reported in 61.4% of cases, followed by cough (46.8%), dyspnea (35.2%), and fatigue (35.2%). Nonetheless, most studies have consistently reported milder clinical symptoms among hemodialysis (HD) patients than the general population [18, 21, 22, 33]. Frequent signs of COVID-19 were fever, coughing, and bilateral ground glass or patchy opacity in the lungs, according to a Chinese group of patients. [29]. A retrospective Chinese study, however, found that while HD-infected patients had a higher incidence of fatigue and anorexia, symptoms like fatigue, dry cough, and fever were more common in the non-renal failure group [35]. The study also compared 49 HD patients with 52 non-renal failure patients matched for baseline characteristics. Remarkably, a sizable fraction of patients with infection ascertained either serologic testing (79%) or nucleic acid testing (25%) and remained asymptomatic throughout their clinical care [29]. Eleven studies revealed that the hematological parameters of the majority of HD patients were within expected norms. Acute respiratory distress syndrome (ARDS) and respiratory failure can result from COVID-19-induced severe immune cytokine storm. However, the risk of death in infected HD patients seems to be reduced [38]. Elevated serum concentrations of interleukin (IL)-2, IL-6, IL-7, granulocyte-colony-stimulating-factor, tumor necrosis factor (TNF)-α, monocyte-chemoattractant protein-1, interferon-γ-inducible protein-10, macrophage-inflammatory protein 1-α, and ferritin are responsible for the hyper-inflammatory storm that has been linked to tissue damage and death in COVID-19 patients [38, 39]. However, this exaggerated response seems attenuated in infected HD patients. Several studies have reported variations in leukopenia, lymphopenia, lower serum calcium concentration, and elevated C-reactive protein (CRP) levels among HD patients infected with COVID-19 [29, 33-36]. Ma Y *et al*. discovered that compared to non-HD patients, infected HD patients had fewer T cells, CD4 T cells, CD8 T cells, natural killer cells, and B lymphocytes in their peripheral blood. Furthermore, blood levels of IL-4, IL-6, IL-10, interferon-γ, and TNF-α were considerably lower in HD patients with infection than in COVID-19-infected persons with adequate renal function and non-infected HD patients [22]. The very low prevalence of ARDS documented in many trials further supports the hypothesis of a muted cytokine response in HD patients. Compared to the reported incidence among hospitalized patients (33%) [40], our meta-analysis showed an overall ARDS incidence of 18.5%, which is much lower. These findings point to the possibility that HD patients' immune systems may react differently to COVID-19, which might explain why their clinical symptoms are less severe and why the risk of consequences like ARDS is reduced.

The COVID-19 treatment plan for HD patients seemed to be primarily empirical, and it was difficult to compare different regimens because there was little data available on dosage, duration, and prescription reasons. Tocilizumab and corticosteroids were the next most often utilized drugs, then antiviral drugs and hydroxychloroquine. Higher death rates were linked to the decreased usage of these regimens, as has been shown in other earlier research [41-43], of the 19 trials, 11 required total hospitalization, and 82.5% of the patients needed inpatient treatment. The critical care unit was accessed in 6.6% of cases, and patients spent an average of 14.5 ± 8.8 days in the hospital.

When compared to the general population, the death rate for COVID-19 patients ranged from 1.4% to 8%; however, it was much higher for hospitalized patients, reaching 25.5% to 39% [18, 44-47]. The prognosis for COVID-19-positive HD patients is yet uncertain. Overall mortality rate in HD patients with COVID-19 was 22.4% (95% CI: 17.9–27.1%), and study heterogeneity was significant ($I2 = 87.1\%$, $p < 0.001$). The leading cause of death was respiratory failure from ARDS, which was frequently undiagnosed. Sepsis, cardiac

arrest, and hyperkalemia were the next most common causes. Previous studies have revealed many risk factors associated with higher mortality in HD, such as advanced age, male gender, underlying cardiac or pulmonary disease, diabetes, hypertension, and the use of mechanical ventilation [23, 28]. This highlights the significance of customized therapies for this population, taking into account dialysis vintage, comorbidities, and other pertinent variables. More research is necessary to guide evidence-based clinical decision-making to determine the relationship between lower treatment regimen utilization and greater mortality.

Conclusion

To sum up, this thorough analysis provides an important new understanding of the difficulties HD patients have in the COVID-19 setting. The trends in incidence, clinical symptoms, treatment modalities, and results that have been found highlight the necessity of specialized techniques to improve the care of this susceptible group. For HD patients with COVID-19, further research—including prospective studies and randomized controlled trials—is necessary to improve our comprehension and guide the development of evidence-based therapies.

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