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SYSTEMATIC REVIEWS

The frail world of haemodialysis patients in the COVID-19 pandemic era: a systematic scoping review

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Abstract

Background Patients undergoing in-centre haemodialysis (HD) are particularly exposed to the dire consequences of COVID-19. The present systematic scoping review aims to identify the extent, range, and nature of articles related to COVID-19 and maintenance HD: it reports specifically the prevalence of the COVID-19 pandemic in the HD population, implementation of strategies for the prevention, mitigation and containment of the COVID-19 pandemic in HD centres, demographic and clinical characteristics, and outcomes of the pediatric and adult HD patients.

Methods A multi-step systematic search of the literature in Pubmed, Scopus, Ovid Medline, Embase and Web of Science, published between December 1, 2019, and January 30, 2021 was performed. Two authors separately screened the titles and abstracts of the documents and ruled out irrelevant articles. A report of the papers that met inclusion criteria was performed; then, a descriptive analysis of the characteristics of the included articles and a narrative synthesis of the results were performed.

Results The review process ended with the inclusion of 145 articles. Most of them were based on single-centre experiences, which spontaneously developed best practices. Most studies were conducted in high-income countries (69.7%) and a part of them (9.6%) were not in English. Prevalence of COVID-19 among dialysis patients accounted for 0%-37.6%. Preventive measures were reported in 54% of the included articles, with particular emphasis on education, triage, hygiene, and containment measures. Patients experienced a heterogeneous spectrum of symptoms that led 35%-88.2% of them to hospital admission. Median and mean hospital length of stay ranged from 8 to 28.5 and 16.2 to 22 days, respectively. Admission to intensive care units varied widely across studies (from 2.6% to 70.5%) and was associated with high mortality (42.8%–100%). Overall, prognosis was poor in 0%–47% of the hospitalized patients.

Conclusions This systematic scoping review provides an overview of the current knowledge on the impact of COVID-19 on the frail world of HD patients. Furthermore, it may help to implement the existing strategies of COVID-19 prevention and provide a list of unmet needs (safe transport, testing, shelter). Finally, it may be a stimulus for performing systematic reviews and meta-analyses which will form the basis for evidence-based guidelines.

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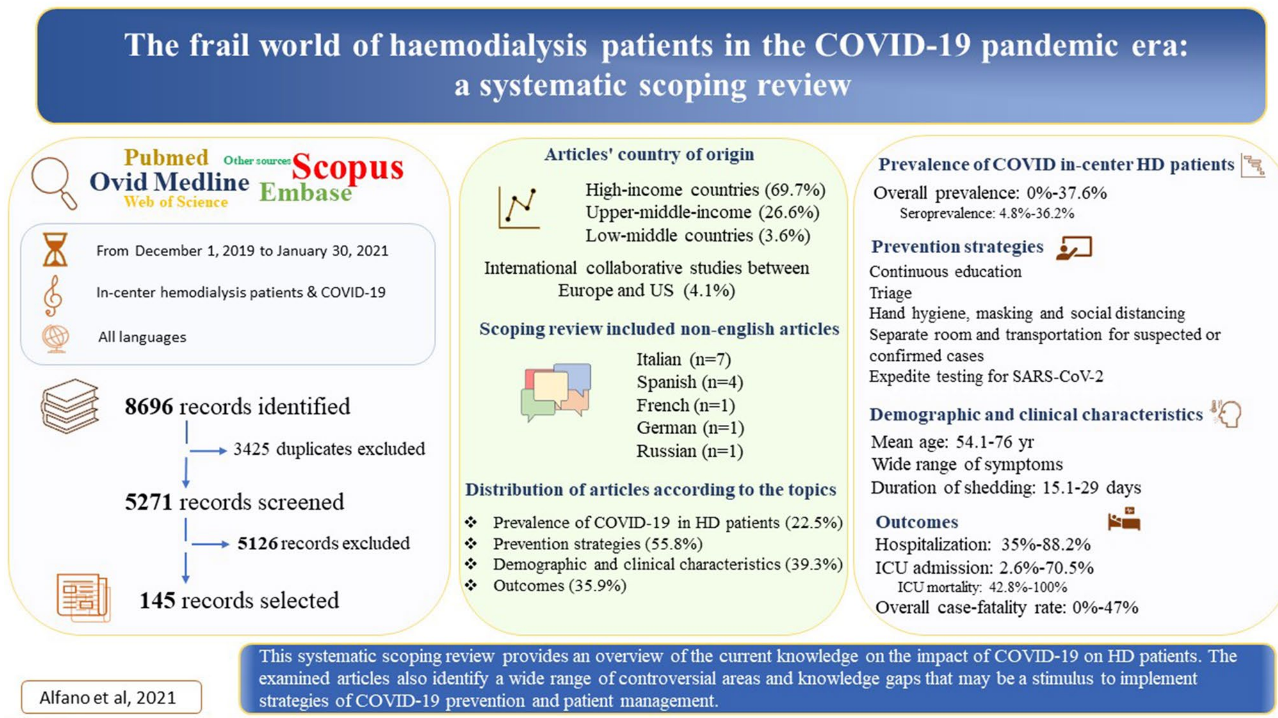
Graphic abstract



Keywords End-stage kidney disease · COVID-19 · SARS-CoV-2 · Haemodialysis

Introduction

Emerging evidence shows that patients with advanced chronic kidney disease (CKD) are susceptible to the detrimental effects of COVID-19 [1]. Patients on renal replacement therapy, especially haemodialysis (HD) patients, convey a higher risk of death compared to the general population [2–4]. Although age and the burden of accompanying comorbidities are associated with a poor outcome [5], dialysis condition is, per se, an independent factor for death after contracting COVID-19 [6]. Chronic maintenance dialysis is known to induce an immune system dysfunction that theoretically lessens responsiveness to SARS-CoV-2 infection. Furthermore, in-centre HD patients are more susceptible to COVID-19 because they lack the possibility to shelter at home during the outbreak. For their dependency on in-centre dialysis treatment, patients need to reach the dialysis unit thrice weekly and often travel to and from it with public or shared transport. This inevitably increases the risk of SARS-CoV-2 infection [7].

On this background, the deleterious association between COVID-19 and the high mortality rate in dialysis patients urged the nephrology community to adopt appropriate infection control measures to prevent viral infection spread. These interventions, rapidly implemented into clinical practice, have shaped the local and national guidelines to mitigate the risk factors associated with SARS-CoV-2 infection. However, the lack of international consensus guidelines on patient management and aggregate data on epidemiology and outcomes of COVID-19 has in part limited the effectiveness of these measures. Furthermore, the different containment strategies related to structural problems of some dialysis units and divergent national guidelines had the disadvantage of increasing heterogeneity across studies. In order to broaden our understanding of the effects of COVID-19 on HD patients and identify gaps in the current literature, we conducted a systematic scoping review with the aim of mapping and analyzing actual evidence on the prevalence, clinical manifestations and outcomes of the pediatric and adult HD patients during COVID-19 pandemic. A secondary objective of this scoping review was to help the nephrologist to navigate into the vast literature published on the COVID-19 and offer the opportunity to focus on knowledge gaps and/or controversial areas that need further investigations. However, given the evolving situation of COVID-19 worldwide, this review should be considered a "work in progress" project. Indeed, the map of the currently available evidence will evolve in parallel with the full understanding of COVID-19 pathogenesis in the general population as well as in patients on maintenance HD.

Methods

Search strategy

This systematic scoping review aimed to furnish an overview of the available literature on two research questions:

- Which has been the magnitude of the impact of the COVID-19 pandemic on the frail world of the HD patients?
- What strategies were implemented in the clinical practice for the prevention, mitigation and containment of the COVID-19 pandemic in HD centres?

To address this broad topic of interest, we followed published recommendations of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist and the PRISMA extension for scoping reviews [8, 9]. We also corresponded with experts in the field to sharpen search strategy and selection criteria. The review was not prospectively registered in any database of literature reviews (e.g., PROSPERO) as it was not applicable.

The search strategy was conducted after consultation with two librarians (C.P. and G.V) with expertise in the scientific literature. A literature search from December 1, 2019 to January 30, 2021 was conducted on the following 5 databases: PubMed, OVID Medline, Scopus, Embase, Web of Science and Google Scholar. Search in Cochrane Library did not furnish any results. The database results were uploaded on a reference manager software (Mendeley®).

We performed a multi-step search strategy (Fig. 1) [10] fully reported in the Supplementary Material. After identification of the literature, all duplicates were removed

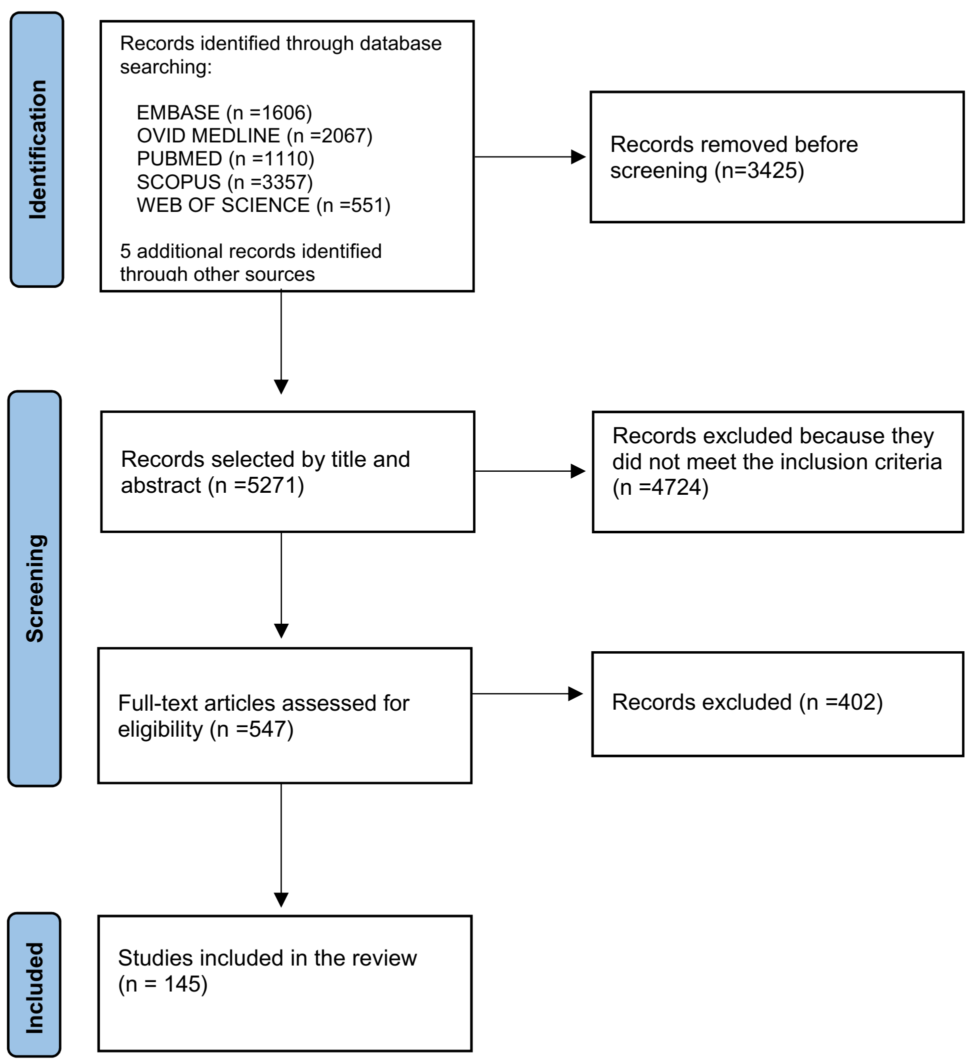


Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the study

automatically. The screening of the articles consisted of two stages: eligibility of references according to inclusion and exclusion criteria and selection of the articles. Selection of the articles was independently accomplished by two reviewers (G.A and A.F.) after the screening of titles and abstracts followed by the retrieval and screening of full-text articles. Disagreements were resolved through discussion between the two reviewers, or with the help of a third reviewer (R.M.), a researcher with 16 years of experience in the field of nephrology. Data charting from the selected studies included information on authorship, type of study, country, study population, modality of COVID-19 diagnosis, prevalence of the COVID-19 pandemic in the HD population, implementation of strategies for the prevention, mitigation and containment of the COVID-19 pandemic in HD centres, demographic and clinical characteristics, and outcomes of the pediatric and adult HD patients.

Results

Our search retrieved 8696 articles of which 5271 remained after the exclusion of duplicates (Fig. 1). After title and abstract screening, 4724 articles were further removed. The full texts of the remaining 547 articles were screened and 402 were excluded. The final review comprised 145 articles.

Most articles (69.7%) come from high-income countries whereas the remaining articles come from upper-middle-income (26.6%) and low-middle countries (3.6%) (Fig. 2). Six (4.1%) international collaborative studies were conducted in Europe and US. The review included articles that were translated into English from French (1), German (1), Italian (7), Russian (1) and Spanish (4). The arguments discussed in the review have been grouped into 4 domains: prevalence of the COVID-19 pandemic in the HD population, implementation of strategies for the prevention, mitigation and containment of the COVID-19 pandemic in HD centres, demographic and clinical characteristics, and outcomes of the COVID-19 HD patients.

Prevalence of the COVID-19 pandemic in the HD population

Prevalence of COVID-19 was reported in 22 (15.1%) studies, including 7 letters to the editor (31.8%). The population screened for COVID-19 consisted of 8338 patients (range 13–1542). Studies were conducted principally in China (31.8%) and Spain (27.2%). As detailed in Table 1S, different screening tests were used to estimate the prevalence of COVID-19. The screening was carried out using real-time polymerase chain reaction (RT-PCR) (45.5%) [11–21], serology (27.2%) [18, 20, 22–25], computed tomography (CT) scan (confirmed by SARS-CoV-2 RT-PCR) (13.6%)

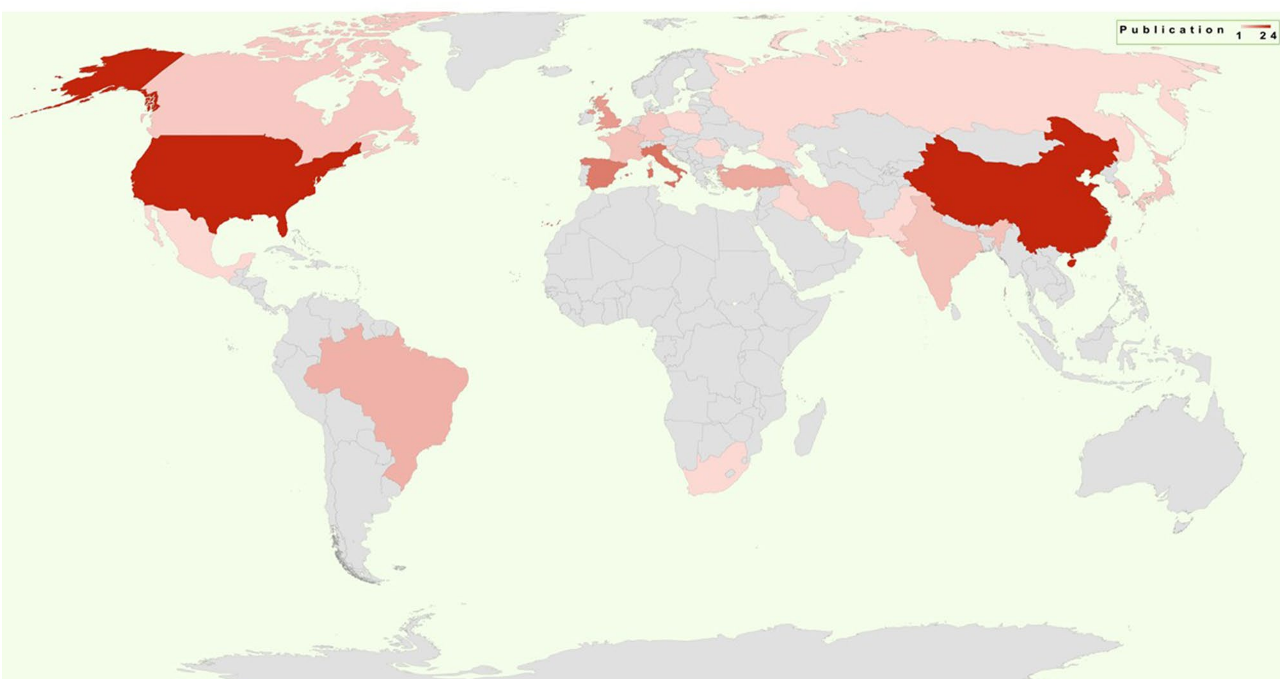


Fig. 2 World distribution of articles retrieved for the review (Singapore is not displayed on the world map but contributed with three publications)

[26–28] and combination of PCR and serology (13.6%) [29–31]. Considering all modalities of testing, prevalence of COVID-19 among HD patients ranged between 0 and 37.6% [11–32]. When COVID-19 was diagnosed by antibody testing, prevalence varied from 4.8 to 36.2% [23, 25]. A seroconversion of 97.5% was detected in PCR-positive patients [23], whereas it occurred in 4.4–19.0% [20, 23] of PCR-negative patients. Prevalence of COVID-19 in pediatric patients was assessed in only two studies reporting a seroprevalence of 23–38% (Fig. 1S) [22, 24]. The results of the epidemiology studies highlighted that asymptomatic patients accounted for about one-quarter of PCR-based screening of HD population (Fig. 2S).

Implementation of strategies for the prevention, mitigation and containment of the COVID-19 pandemic in HD centres

Surveillance and appropriate management of suspected or confirmed COVID-19 patients play a key role in the prevention, mitigation and containment of the COVID-19 pandemic in HD centres. Management of in-centre patients was reported in 81 (55.8%) publications, including 19 (23.4%) research articles. Most of the studies came from US (23.4%) followed by China (11.1%) and Italy (11.1%). A minority (5.4%) of the articles included an international authorship.

Education and recommendations

Given the evolving situation, continuous education on COVID-19 was considered essential for HD patients [33–44]. Dialysis staff provided patients with instructions (in appropriate languages) [41, 44–48] about respiratory hygiene, coughing and sneezing etiquette [39, 43, 45–52], how to use the masks [34, 39, 44, 46–48, 52–54] and how to practice self-quarantine at home and with family members after dialysis [50]. Signed posts or distribution of educational pamphlets in the patient's language were also part of the educational program on COVID-19 [12, 33, 38, 47, 50, 55, 56].

Particular emphasis was placed on hand hygiene, masking and social distancing. Handwashing [29, 33, 34, 40, 43, 57, 58] with alcohol-based solutions or soap [41, 42, 47, 51, 54, 56, 58–61] was advocated for patients presenting at triage [12, 21, 38, 47, 54, 56, 62–64], prior to departure from the dialysis unit [38, 47, 64] and if in contact with respiratory secretions [33, 47]. Fistula arm was washed before starting dialysis [16, 29, 60]. In the COVID area, patients implemented personal protective equipment (PPE) including gloves throughout the dialysis session [29, 65–67].

Patients were instructed to wear a surgical mask since leaving house [38] until hospital arrival [16, 35, 38, 43, 56, 63, 66, 68] and also during the ride [49, 54, 55]. To reduce the risk of infection within facilities, the use of the mask was recommended throughout the dialysis session [35, 36, 44, 49, 51, 54, 55, 57, 60, 61, 63, 69–73] unless it was made of textiles[54] or was worn by someone that was incapacitated to remove it without assistance [48]. Conversely, some recommendations supported the choice to wear a mask according to the epidemiology risk in the community principally for asymptomatic patients [38].

With regard to family relationships, HD patients needed to reduced contact with other people on their non-dialysis days [33, 47, 51, 65, 73]. Personal contacts, especially with younger relatives [33, 47, 65] were discouraged. A similar restriction was valid also for public, private or religious events or travels [47].

Transport

Use of individual transport to and from dialysis facilities—instead of public or shared transport—was proposed as a measure to prevent diffusion of COVID-19 [29, 33, 39, 40, 42, 47, 49, 68, 73]. Drivers were instructed to comply with infection control measures [29, 33, 38, 42, 57] including sanitization of the shuttle bus between rides [29, 33]. Drivers were invited to report any patient with symptoms to the dialysis facility and vice versa [33, 44]. Hand sanitizers needed to be accessible for patients and drivers on vehicle [33] and hand hygiene was required before and after entering the vehicle [38].

Public transport for suspected and/or confirmed COVID-19 patients was forbidden [29, 49–51, 53, 57, 62, 74]. In the absence of separate transportation, patients with confirmed COVID-19 were gathered in the same vehicle, providing them with a mask [38]. A possible solution for a patient who could not be provided with a separate transport was hospitalization [42].

Structural changes in the dialysis units

Different routes (including lift) for symptomatic and asymptomatic patients were designed to avoid cross-contamination among subjects [21, 29, 34, 60, 75].

Dispensers of hydro-alcoholic solutions [39, 41, 47, 50, 60] were installed in waiting rooms and, more generally, in the facility [43, 67]. Availability of tissue paper, masks [39, 50], easy access to PPE [33, 74] and a distance of at least 1–1.5 [61], 1.8–2 m [36, 48, 76] between patient beds needed to be ensured in the dialysis centre.

A separate room was reserved for testing [29, 38, 47, 67, 74] suspected or confirmed COVID-19 patients [16, 21, 29, 33, 36–38, 40, 43, 46–48, 50, 52, 56, 57, 62, 68, 77–79]. Although it was not a primary prerequisite [38, 46], a negative air pressure room was preferable for quarantine patients [37, 47, 49, 80]. In absence of a separated room, suspected or infected patients were courted on a separate shift [38], namely, during the last shift of the day, in a corner or at the end-of-row station [33, 35, 36, 38, 43, 44, 47, 48, 50, 52, 53, 72].

Cohorting suspected or confirmed COVID-19 patients together with asymptomatic subjects required droplet/contact precautions [38] and the maintenance of a distance longer than 1.8 m (6 feet) [44, 50, 52], 2 m [36, 40, 53, 55, 67] or as far as possible [36]. Another option was maintaining at least 2 m between patients using separating materials to provide spatial isolation [37, 38].

Peripheral dialysis centres, without the possibility of isolation and care of suspected or confirmed COVID-19 patients, needed to centralize patients towards referring hospitals [60].

Identifying toilet for suspected or infected cases [40], and maintaining good air conditioning and ventilation of dialysis rooms was suggested as preventive measures [36, 47, 51, 53, 67, 79].

Functional changes in the routine dialysis care

Patients were assigned to specific dialysis shifts [36, 49, 71] and patterns of patient flow were controlled by dialysis staff during the shift changes [49, 71]. Screening of the patients was required before shifting them to another unit [56].

Patients from different long-term care facilities or from other units were not cohorted together unless full droplet/contact precautions were respected [38]. Cohorting symptomatic patients with probable or suspected COVID-19 was forbidden [38, 47].

Among the series of containment measures patients had to enter the locker room one by one and left all their clothes inside the locker [29] or changing clothes and shoes before entry into the dialysis room [61].

Visitors were limited [44] or not allowed in the dialysis facilities [12, 21, 33, 39], even though a more permissive recommendation allowed the presence of visitors only if they facilitated the dialysis treatment of asymptomatic patients [38].

Number of dialysis per day was increased to reduce the number of patients per shift as well as in the waiting room [74]. Frequency of dialysis sessions was not shortened or paused to leave unaffected dialysis quality [36]. However, in a resource-constrained environment, a strategy could be taken into account shortening dialysis treatment time to 3 h in all stable patients [29] or reducing a three times weekly HD program to twice-weekly dialysis [81]. The latter solution should be considered provisional and be reserved for patients with preserved residual kidney function, minimal inter-dialytic weight gain and without hyperkalaemia or severe comorbidities [38]. For new dialysis patients, incremental twice-weekly dialysis could be taken into account to limit their time in the dialysis units [82].

The frequency of routine bloodwork and access flow measurement for stable patients was reduced to no more than 6 weeks unless clinically indicated [38]. Teleconsultation was implemented to decrease medical contact with patients [83].

Testing for COVID-19

Dialysis patients should be prioritized to have expeditious access to testing for COVID-19 [38]. Criteria for performing screening tests varied among studies. Two recommendations were released: universal screening for every dialysis patient [84] or reserving testing only for symptomatic patients [47, 48, 56, 85, 86]. However, despite the consistent implementation of SARS-CoV-2 testing, diagnosis of COVID-19 remained challenging in some dialysis units [87].

It was recommended to repeat a nasopharyngeal swab in case of a negative test for COVID-19 and a high clinical suspicion [38, 79, 80]. Infectious disease specialists consultation was required if more than 2 tests for a single patient resulted negative [38].

One study reported that CT scan once every 2 weeks was considered helpful to recognize and isolate patients as early as possible in the incubation period [80]. Conversely, other authors asserted that CT scan [38] as well as serology [48, 68, 79] (in the acute phase) were inappropriate for the diagnosis of COVID-19.

Pre-triage and waiting area

According to staff availability, dialysis staff phoned all patients before each dialysis shift to determine whether they had COVID-19 symptoms [17, 33, 45, 88]. Another strategy consisted of informing the facility of suspicious symptoms or contacts with COVID-19 subjects [38, 42–44, 49–53, 55, 57, 63, 65, 67, 72, 86, 88, 89] or in case of contact with COVID-19 patients [70].

Patients and transport companies were advised for progressive arrival and departure times to avoid overcrowded areas [29], and medically stable patients were suggested to wait outside the facility or in their vehicles [29, 38, 44, 47, 48, 52, 67, 90].

If the patients would wait in a communal area, sits needed to be separated by at least 1, [72] 1.5 [42, 49, 62] or about 2 m (6 feet) apart from each other [29, 33, 38, 42–45, 47–49].

Patients with confirmed COVID-19 were not allowed to wait in the common area [38, 48], unless (for special needs) they wore a mask and maintained > 2 m distance from others [38].

Triage

A pre-dialysis triage was based on the assessment of symptoms or signs suggestive for COVID-19 [29, 36–38, 41, 43–45, 47, 48, 50, 51, 58, 62, 66, 72, 79, 80, 86, 89, 91–93].

A questionnaire was provided regarding symptoms, exposure, contact and travel history for all the patients at every shift of dialysis [17, 33, 38, 52, 73]. This could be reserved even to visitors if they were allowed [38]. Atypical symptoms, including change from previous well-being and altered neurological status were considered suspect in the elderly and immune-compromised patients [38].

Body temperature was measured to all people prior entry to the dialysis centre [12, 29, 38, 41, 47, 53, 58, 61, 64, 66, 68–70, 73, 80, 92–95] using digital [12, 93] or infrared thermal devices [88].

An alert temperature was set at ≥ 37 °C [90], 37.3 °C, [35, 38, 96] ≥ 37.5 °C [29, 34, 66, 72, 93], 37.8 °C [48, 90], 38 °C [49, 89, 97] in different studies. A re-check of temperature with different types of thermometer was practiced [93]. After triage, some recommendations suggested a double-check of temperature and respiratory symptoms in the waiting room [96]. In some places patient's temperature measurement was performed before getting into shuttle bus headed to HD unit [97] or body temperature check was combined with a QRcode (dowloaded on the mobile phone) reporting the epidemiological risk of the patient [95].

During the dialysis session

Eating was not allowed during the dialysis session [16, 29, 36, 39, 66] to minimize time without mask [42, 90]. Special indications were released for diabetic patients after testing blood glucose [29]. If the patient manifested dyspnoea or any other clinical suspicious symptoms (temperature ≥ 37.5 °C) [97], HD session had to be stopped and the patient moved to a separate area for SARS-CoV-2 screening [16].

Screening and management of patients under investigation

According to local rules, the patients suspected of COVID-19 were sent to: (1) emergency room; [62, 66, 67] (2) hospital (e.g., COVID-19 referral hospital); [80] (3) dedicated isolated area in the dialysis ward [40, 66, 67]; (4) back home [62] or postponing HD session till the availability of the nasopharyngeal swab result [62, 74]. However, according to national recommendation, even asymptomatic patients could be hospitalized to control the spread of the infection [53].

From a clinical standpoint, physical examination and workup were suggested before dialysis [60, 66, 90]. Beyond SARS-CoV-2 PCR nasopharyngeal swab, [16, 62] examinations included lab blood tests, [16] arterial blood gas analysis, oxygen saturation, measurement of body weight, and chest X-rays [62]. Assessment of the patient's fluid status was essential to plan the next dialysis session [89].

Patients under investigation with negative tests were de-escalated back to their dialysis unit unless they remained symptomatic. In such patients, the plan was to continue cohort dialysis until the second swab came back as negative [57].

Recommendations for asymptomatic contacts consisted of a screening tests for COVID-19 and the referral to the HD cohort isolation adopting contact and droplet precautions [34, 48, 86]. In this setting, cohort isolation was discontinued after a negative result of nasopharyngeal swab on the thirteenth day after contact [34].

Management of the confirmed COVID-19 HD patients

According to the national guidelines, an outbreak of COVID-19 in dialysis units could be notified to the local public health department [38, 46, 48]. Confirmed COVID-19 patients were preferably managed in an outpatient setting [49, 74] if they were stable and there was the possibility to maintain home isolation and use dedicated transport. This strategy allowed to minimize the need for hospitalization beds [49].

High-efficiency dialyzers were used since many patients were considered in high catabolic states [98]. Heparin-free dialysis was avoided to reduce the need for frequent circuit flushing [92] and the risk of clotting [42]. One study underlined that despite some thromboembolic events (dialyzer clotting, arteriovenous fistula thrombosis) dose of heparin was not increased for all COVID-19 patients [21].

When the HD patient was admitted to a non-ICU ward, portable dialysis machines (including reverse osmosis machines) were used to keep COVID-19 patients in their rooms [36, 66, 81]. If the patient was being followed-up in the ICU, intermittent or continuous renal replacement therapy could be performed at the bedside [36]. Dialysis machines used for infected patients were generally restricted in COVID-19 areas [49, 62, 99].

Discontinuation of isolation

Isolation must have continued until the patient became asymptomatic, for a minimum of 14 days and until 2 negative tests were separated by at least 24 h [38, 42]. Another recommendation reported that asymptomatic patients could only be de-isolated after two consecutively negative results with a 24- [34, 58, 62, 80] or 48-h [42] interval regardless of the time elapsed from the diagnosis. However, if symptoms persisted, the patient continued HD treatment in an isolated room, even with a twice negative test [34]. Duration of isolation could be longer than 14 days for immune-compromised patients [38, 100]; therefore, a test-based strategy was suggested to avoid the risk of SARS-CoV-2 spreading [86]. Consultation with health authorities or local infectious disease experts on a case-by-case basis was suggested [38, 47].

Surgical operations

Surgical revision of malfunctioning vascular access [101] or the placement of vascular access remained an essential life-saving procedure [33, 44, 50, 101–104]. A local rule supposed to postpone the creation of arteriovenous fistulae for patients within six months of requiring HD [57].

Before vascular access surgery, patients underwent COVID-19 screening [47, 67, 105]. Operations on patients with confirmed or suspected COVID-19 infection were carried out in a designated room [47] if postponing the procedure was not advisable [101].

Disinfection

Dialysis stations and chairs were disinfected per protocol (using active product on SARS-CoV-2) [12, 38, 44, 46, 48–52, 66] including handrails on scales, waiting room seats, doorknobs and elevator buttons [46, 74]. Disinfection of hospital linens required soap and high temperature [65].

Ventilation [36, 40, 75] and terminal disinfection of the room including equipment and supplies was advised between two dialysis shifts [35, 38, 67, 75, 78, 94]. One percent diluted bleach (sodium hypochlorite) was used for floor and surface disinfection and 10% diluted bleach or 70% alcohol for areas contaminated with patient secretions [53, 56, 72, 73, 75]; instead, nebulizing hydrogen peroxide was used for room decontamination [12].

Pediatric patients on HD

Four articles reported the recommendations for pediatric patients on dialysis. Education about COVID-19 including hand, respiratory hygiene and use of PPE was provided for patients and caregivers [76, 106, 107]. Caregivers were instructed to advise the dialysis unit of Covid-19 symptoms before entry [76]. Private transportation [59, 106] or transportation provided by health authorities were suggested [106]. Children were accompanied by only one caregiver, preferably always the same [76, 106].

It was recommended to wear a mask [59, 76, 106, 107] (unless < 2 years old) [48], wash hands with alcohol-based hand rub [59, 76, 106] and maintain a social distance between other patients of at least 1 m. [59, 76] Screening of body temperature [59, 107] and respiratory symptoms[107] was required for patients and families before entry into dialysis facilities [76].

Dialysis beds needed to be spaced at a minimum distance of 1–2 m apart [76, 106, 107]; if these conditions could not be met, curtains were used to separate patients [107]. Unnecessary talking or eating was avoided during dialysis [106, 107].

Transfer of patients to different dialysis units was reduced as a control measure [106].

COVID-19 patients or suspected patients were dialyzed in a dedicated room at the last shift or with the same dialysis machine [59, 106, 107]. Patients with a COVID-19 positive caregiver performed dialysis in an isolated room [76, 107].

For all patients, dialysis was not reduced or shortened [59]. Suspected or confirmed COVID-19 patients were transferred to designated COVID-19 HD units if there was no space and/or a dedicated workforce [76].

Disinfection measures were applied between each shift using 1% bleach solution or 70% alcohol-based solution [76]. The dialysis machine was wiped with 70% ethyl alcohol or 0.05% chlorine solution [106].

Perspective

Only one report emphasized the need to construct appropriate numbers of isolation rooms, adequate spacing between dialysis beds and space in the waiting room for future dialysis units. [38]

Demographic and clinical characteristics of the confirmed COVID-19 HD patients

Clinical characteristics of in-centre HD patients with COVID-19 have been detailed in 57 (39.3%) studies including 7376 patients (range 1 to 2336) (Table 2S). The majority of studies were conducted in China (21%) followed by Spain (14%) and UK (10.5%); 1.7% of the articles included an international authorship.

Age of confirmed COVID-19 patients on HD was largely heterogeneous since principally tends to reflect national policy of access to dialysis treatment. Median and mean age of this large cohort of patients ranged between 48 and 79.5 years [11, 15, 17, 21, 23, 61, 82, 94, 108–122] and 54.1–76 years, [6, 19, 25, 31, 32, 69, 93, 123–135] respectively. The percentage of male was 37.5%-100% of the examined population [11, 13, 15, 17, 19, 21, 23, 25, 31, 32, 69, 82, 94, 108–131, 133–138].

In order to investigate the clinical manifestations of COVID-19 in HD patients, we collected information on COVID-19-related symptoms. Observation of the data led to the conclusion that COVID-19 HD patients showed a wide range of symptoms that reflected the pleiotropic manifestations of the infection. The worsening of symptoms led to the hospitalization in 35%-88.2% of cases. The prevalence of the main COVID-19-related symptoms is shown in Table 1.

Table 1 Prevalence of COVID-19-related symptoms in HD patients

Symptoms/signs	Prevalence
Adult population	
Fever	9–100% [6, 11, 13, 15–17, 21, 69, 93, 94, 108–110, 112, 114, 116, 119–125, 127, 130, 133, 135, 143]
Cough	7.1–83.9% [6, 13, 15–17, 21, 27, 69, 108–112, 114, 116, 119–125, 130, 132, 133, 135, 138]
Myalgia/fatigue	2.9–63% [6, 11, 15, 21, 27, 69, 108, 110–112, 114, 119–125, 130, 132, 135]
Anorexia	9.3–57% [27, 110, 112, 114, 121]
Dyspnea/gasping	0–56% [6, 11, 15–17, 21, 27, 69, 93, 108–112, 114, 119–122, 125, 127, 130, 132, 133, 138]
Nausea/vomit	4.7–43.6% [6, 13, 69, 110, 112, 121, 122, 143]
Gastrointestinal/diarrhea	0–40% [6, 11, 15, 16, 21, 69, 93, 108–111, 114, 116, 119–125, 132, 133, 135, 138]
Expectoration	21.4–33% [69, 121, 132]
Anosmia/dysgeusia	4–21.6% [113, 116, 133]
Sore throat	0–20% [6, 11, 16, 17, 21, 27, 69, 108, 111, 112, 114, 132]
Headache	6.25–8.1% [6, 111, 114, 121]
Altered mental status	5% [138]
Ageusia	3–13% [21, 116]
Chest pain	2.3–6.5% [21, 124]
Conjunctival congestion	7.6% [109]
Dizziness	14% [121]
Rhinorrhea/nasal congestion	0%–14.3% [109, 112, 132]
Abdominal pain	5.2% [135]
Ischemic stroke	20% [146]
Lymphocytopenia	50–100% [15–17, 21, 25, 93, 110, 111, 118, 130]
Weight loss*	40–100% [21, 143]
Chest X-ray abnormalities#	46–81% [6, 11, 108, 123, 129, 135, 136]
Computed tomography abnormalities#	27.5–100% [6, 15, 19, 25, 111, 112, 114, 120, 121, 125, 132, 133]
ICU Pediatric population	
Fever, fatigue, poor appetite, headache and lymphopenia at lab tests	Case-report [141]
Chest X-ray negative for COVID-19 lesions	
Fever, body aches, cough, fatigue and nasal congestion	Case-series (one out of three patients was symptomatic) [149]

*Mean weight loss of 2.4 kg [21, 154]

#Imaging abnormalities refer to COVID-19-related lesions

Shedding

Data on RNA shedding after COVID-19 diagnosis have been reported in 6 articles, including one case report. Nasal shedding of SARS-CoV-2 was detected in 41% of patients by day 15 following the initial positive swab [100]. On average shedding of viral particles lasted 15.1–29 days in infected patients on HD [135, 139]. Two studies reported that HD patients tested positive for SARS-CoV-2 RNA on repeated testing despite being negative on two prior consecutive nasopharyngeal swabs [138, 140]. Prolonged viral RNA shedding has been reported until 79 days in an adult HD patient [140] and 28 days in a pediatric patient [141]. Only one anecdotal case of reinfection has been reported in a dialysis patient [142].

Diagnosis

In research articles reporting clinical manifestation and outcome of COVID-19 patients (78[54.4%]) the diagnosis of SARS-CoV-2 infection relied principally on RT-PCR (52[63.4%]) [11–20, 32, 61, 62, 69, 93, 94, 100, 108–111, 113, 115–124, 126, 129, 132, 134, 135, 138–151], serology (4[6.3%]) [18, 20, 22–24, 86, 99], RT-PCR and serological assay (5[6.6%])[29–31, 85, 127, 152] or a combination of diagnostic tests including clinical evaluation [6, 13, 19, 21, 112, 114, 125, 128, 130, 131, 133, 136, 137, 153, 154].

Outcomes of the confirmed COVID-19 HD patients

Outcome of patients on in-centre HD was evaluated on 52 (35.9%) articles including 12,365 patients (range 11–3160) COVID-19 patients (Table 3S). Studies come principally from China (15.3%), Italy (15.3%) and Spain (11.5%); 3.8% of the studies included European authorship. Table 2 describes the timing of the main events occurring in the COVID-19 HD patients. All outcome measures were influenced by the sample size, the age of patients, length of follow-up and policy of healthcare delivery. Excluding studies reporting outcome of patient admitted to hospital as a preventive measure and regardless of symptoms, we found that hospitalization of HD patients varied from 35 to 88.2% [11–13, 17, 21, 32, 62, 82, 93, 109, 114, 116, 118, 120, 127, 129, 133, 136–138, 144, 145, 150, 154]. with a percentage of patients requiring ICU admission of 2.6–70.5% [6, 13, 17, 21, 32, 62, 109, 114, 116, 118, 119, 121, 125, 126, 129–134, 136, 138, 143, 154]. A nonlinear correlation between the rate of hospitalization and ICU admission was noticed (Fig. 3S). Case-fatality rate of HD patients was heterogeneus, ranging from 0 to 47% [11–13, 15, 17, 19, 21, 32, 62, 82, 93, 108, 109, 112–121, 123–138, 143–145, 147, 148, 150, 152, 154] and, as expected, outcome of patients who were admitted to ICU was poor with a mortality accounting for 42.8–100% of cases [13, 21, 82, 109, 114, 119, 125, 126, 129, 130, 154].

Discussion

Systematic scoping reviews are useful for examining emerging evidence when it is still unclear what other, more specific questions can be posed and valuably addressed by a more precise systematic review [8]. This is actually the case of COVID-19 pandemic. This systematic scoping review provides a synopsis of articles relating to COVID-19 and maintenance HD patients published in the time frame December 1, 2019–January 30, 2021. The areas investigated and analyzed by this scoping review range from the epidemiology to outcome and from clinical presentation to management of in-centre HD patients with suspected or confirmed COVID-19. The main results of this study underline a worldwide broad-based consensus for public health and clinical practice in the caring of HD patients (Table 3), a subset of the population severely affected by COVID-19. The nature of a semi-closed community has probably enhanced the rapid spread of the infection within HD facilities.Except for the Canary Island where zero cases were found after a dialysis-wide universal screening [31], about 15% of the screened HD population contracted the infection (Fig. 1S). Spread of COVID-19 was global and showed a highly heterogeneous distribution, changing significantly across the cities in the same country (China, Spain). A speculative explanation of this variable disease spreading pattern suggests that COVID-19 pandemic manifested with local outbreaks rather than reflecting national trends [155].

As already said, the results of the epidemiology studies highlighted that asymptomatic patients accounted for about one-quarter of PCR-based screening of HD population (Fig. 2S). The asymptomatic course of COVID-19, albeit favourable for the infected individuals, poses a threat for other patients, health workers as well as caregivers and drivers. Owing to the fact that COVID-19 can spread from asymptomatic carriers, surveillance and appropriate management of suspected or confirmed COVID-19 patients play a key role in the prevention of the infection. On this issue, a large amount of literature was published by the countries mostly hard-hit by the disease, namely, US, China, Italy, Brazil and UK [156].

Table 2 Timing of events in COVID-19 HD patients

Timing	Days	Statistical measure
Time elapsed from symptoms to diagnosis	1.5–8 [11, 94, 115, 120, 132–134, 157] 2.6–2.9 [133, 134]	(Median) (Mean)
Time elapsed from symptoms to hospitalization	2–9 [11, 110, 122, 124, 157] 3.0–3.5 [6, 133]	(Median) (Mean)
Length of hospital stay	8–25.5 [11, 15, 21, 82, 109, 110, 115, 119, 120, 122, 124, 130, 132, 153, 157] 16.2–22 [129, 131, 133]	(Median) (Mean)
Length of ICU stay	13–15 [21, 119, 130] 6–19 [131, 133, 134]	(Median) (Mean)
Time elapsed from diagnosis to death	5–31.5 [15, 110, 139] 8 [62]	(Median) (Mean)
Time elapsed from symptoms to death	7–17 [11, 21, 109, 119, 124, 157] 14–16 [134]	(Median) (Mean)
Time elapsed from hospital admission to death	6–14 [11, 109, 119, 124, 153] 12.3 [131]	(Median) (Mean)

Table 3 Areas of consensus and research bias of the selected studies

Area	Consensus	Research bias/study limitation
Epidemiology of COVID-19 within HD centers	Variability in the prevalence rate of COVID-19 among regions or countries Screening of contacts and suspected COVID-19 cases reduces the spread of the virus within the dialysis center	Prevalence of COVID-19 influenced by the country's exposure to the pandemic risk and timing of the screening Seroprevalence can be biased by the rate of seroconversion and antibody waning Use of different diagnostic tests
Management of HD patients	Continuous education of patients is a priority within HD centers Triage, hand hygiene, masking and social distancing are the cornerstone of COVID-19 containment measure Expedited testing for COVID-19 Separate transportation is required for suspected or confirmed COVID-19 patients An isolation room is required for testing and dialyzing suspected or confirmed COVID-19 Higher workload to dialyze COVID-19 HD patients in other rooms Time without mask (drinking and eating) was minimized	Recommendations are principally based on experts' opinion Lack of standardized management protocols to contain diffusion within dialysis centers Inadequate supply of PPE and molecular tests for COVID-19 Shortage of disposable HD material and reverse osmosis machines No consensus on the minimum distance between patients in the waiting room and dialysis room, threshold body temperature and device to measure body temperature
Demographic and clinical characteristics of HD patients	Age of COVID-19 patients is heterogeneous Variability in COVID-19 symptoms among HD patients Prolonged shedding in COVID-19 patients	Age of incident HD patients varies among countries Diagnosis of COVID-19 based on symptoms or chest imaging
Outcome	Wide variability in the hospitalization, ICU access and case-fatality rate	Hospitalization rate is influenced by national policy on the hospitalization of COVID-19 patients Mortality is influenced by bed capacity of the referring hospital Criteria for ICU access varies among countries

HD denotes hemodialysis; ICU, intensive care unit; PPE, personal protective equipment

Most of the current recommendations on the protection and control measures of HD patients derived from national guidelines, rapidly adapted to the dialysis setting to prevent the spread in the dialysis units. The analysis of the existing literature reported a common agreement on the cornerstones of the management of these patients. The principal clinical management decisions for apparently healthy individuals included education, patient collaboration (e.g., timely communication of information on contacts or variation of the clinical status), hygiene (e.g., handwashing), use of PPE (e.g., mask), social distancing and screening (e.g., triage, testing). For suspected or confirmed COVID-19 patients, the core principle of the management was based essentially on the maintenance of isolation from other patients. There was indeed a consensus to dedicate an isolated room (if any) for suspected or confirmed COVID-19 patients until the resolution of the infection. However, the map of the knowledge has brought to the light some divergences on the assessment of patients that may reflect the inter-country differences in resource availability, healthcare delivery (private or public), and the possibilities to isolate efficiently patients in their facility (hospital-based or satellite dialysis unit). For instance, a different approach has been proposed for the diagnostic pathway of SARS-CoV-2 infection. Although a routine universal screening provides an optimal and effective control measure, many authors suggested performing RT-PCR nasopharyngeal swab only in symptomatic patients. This solution, less time-consuming and more cost-effective than routine RT-PCR nasopharyngeal swab, has the main drawback of leaving undetected asymptomatic or pre-symptomatic patients.

Other differences in patient management concerned threshold of body temperature at triage, modality of COVID-19 screening, distance between patients and timing of patient de-isolation. Whereas the former two issues are of easy resolution, discontinuing transmission-based precautions for HD patients relies on more complex underpinnings. The immune-suppressed HD patients may shed the virus longer than previously recognized [139]. Given the evolving recommendations on the criteria for discontinuing isolation [157, 158], may be prudential to consider HD patients as immunocompromised and await the resolution of nasal shedding before de-isolating these patients.

The outcome of the patients was heterogeneous and showed a case-fatality rate that in some cases was up to 47% [93]. Similar to the general population, exceptional higher mortality was found in ICU, especially if the patients underwent mechanical ventilation [159]. As already said, a nonlinear correlation between the rate of hospitalization and ICU admission was noticed (Fig. 3S) and probably underscores a low ICU utilization among hospitalized HD patients. The causes of this event remain unanswered in the review. A lack of resource availability or a rapid worsening of clinical conditions in patients with multiple comorbidities probably discouraged from intensification of cures.

This review highlights the lack of information coming from low-income countries. Limited access to essential health services and SARS-CoV-2 testing probably justify poor reporting from these countries. A further alarming problem is that COVID-19 pandemic has disproportionately affected marginalized populations including patients with CKD [160, 161]. A study conducted across the US reported high seroprevalence of COVID-19 in younger patients, and patients living in poor and minority neighborhoods [162, 163]. Considering COVID-19 could have even more dire consequences in developing countries, the paucity of data must not falsely reassure on the absence of human basic needs in these patients.

This review has some limitations. During the COVID-19 pandemic, a consistent part (about one-third) of the published literature was based on opinion papers and small case series. To generalize the message of our review we have excluded from the research abstracts, posters or conference papers. Case reports or studies with a small sample size were selectively considered in case of a shortage of evidence. Conversely, we included (when present) knowledge on pediatric HD patients. An enormous gap concerning principally the clinical course of the disease remains for this subset of the dialysis population. The milder disease course would justify the paucity of information. No data have been reported on home-dialysis patients because they carry a different profile of risk than in-centre dialysis patients.

In conclusion, this systematic scoping review provides an overview of the current knowledge on the impact of COVID-19 on the frail world of HD patients. It underscores the need for extensive sharing of information between centres and within the healthcare community. A surrogate outcome of this review was the identification of knowledge gaps and areas for future research (Table 4), with the long-term goal of implementing the existing strategies of COVID-19 prevention and providing a list of unmet clinical needs (safe transport, testing, shelter) for this vulnerable group of patients. Finally, the mapping of information often by sparse and fragmented literature should be a stimulus for performing systematic reviews and meta-analyses which will form the basis for evidence-based guidelines.

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Declarations

Conflict of interest The authors have no conflicts of interest related to this manuscript.

Table 4 Controversies, knowledge gaps and areas for future research in the management of hemodialysis patients during COVID-19 pandemic

Definition of asymptomatic, paucisymptomatic and symptomatic COVID-19 patients
Sensitivity and specificity of the available diagnostic tests (molecular, antigen, serologic)
Regulations concerning the containment measures on public transport
Standardization of the triage process
Minimum distance to prevent the spread of COVID-19 within HD center
Modality and timing of screening of COVID-19 in asymptomatic HD patients
Examinations required in HD patients with a new diagnosis of COVID-19
Role of preventive hospitalization in asymptomatic COVID-19 patients
Use of PPE during COVID-19 pandemic in infected and non-infected patients
Regulations concerning eating and drinking and presence of visitors during dialysis treatment
Criteria for discontinuation of isolation in COVID-19 patients
Use of dedicated dialysis machine/room/pathway for COVID-19 patients
Effects of ventilation on the spread of COVID-19 within the HD center
Prognostic factors for severity and mortality of COVID-19 patients
Anticoagulation for hemodialysis in COVID-19 patients
Dialytic dose in COVID-19 patients
Priority-setting for arteriovenous fistula creation
Risk of reinfection in HD patients
Defining cleaning and disinfection protocol of room and tools

Ethical standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Research involving human participants or animals This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent is not required for this type of studies.

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