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NEPHROLOGY - REVIEW

Cardiovascular complications after COVID-19 in chronic kidney disease, dialysis and kidney transplant patients

Charalampos Loutradis[1,2] · Apostolos G. Pitoulias[2] · Eleni Pagkopoulou[3] · Georgios A. Pitoulias[2]

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Abstract

The coronavirus disease 2019 (COVID-19) is associated with increased mortality in patients with chronic kidney disease (CKD), dialysis patients and kidney transplant recipients (KTR). Cardiovascular complications, such as sudden arrhythmias, thromboembolic events, coronary events, cardiomyopathies and heart failure, may present in about 10–20% of patients with COVID-19. Patients with CKD, dialysis patients and KTR are all at increased cardiovascular risk and present with more cardiovascular complications after COVID-19 compared to the general population. During the pandemic, health care giving has rapidly changed by reducing elective outpatient reviews, which may refrain these high-risk patients from the appropriate management of their medical conditions, further increasing cardiovascular risk. Importantly, acute kidney injury (AKI) is another common complication of severe COVID-19 and associates with increased mortality. A large proportion of the AKI patients need renal replacement treatment, while 30% of them may not present renal function recovery and remain dialysis-dependent after discharge, thereby having potentially increased future cardiovascular risk. This review summarizes current knowledge regarding the cardiovascular events and mortality in patients with CKD or undergoing hemodialysis and in KTR.

Keywords COVID-19 · Hemodialysis · Chronic Kidney Disease · Renal Transplantation · Cardiovascular Disease

Introduction

The coronavirus disease 2019 (COVID-19), caused by a coronavirus strain known as acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a novel disease primarily affecting the respiratory system and causing from influenza-like symptoms to viral pneumonia, which may escalate to acute respiratory distress syndrome (ARDS) in some individuals [1, 2]. According to the World Health Organization, COVID-19 has evolved to a global pandemic, impacting > 250 million individuals and resulting in > 5.1 million deaths globally to date [3]. Mortality is higher in the elderly and in patients with existing comorbidities, such as hypertension, diabetes mellitus and cardiovascular disease [4]. In the general population, COVID-19 may also present a spectrum of atypical manifestations, such as gastrointestinal symptoms, acute kidney injury (AKI), neurological and upper respiratory symptoms, such as anosmia or taste loss [5]. However, COVID-19 can also lead to both onset of new, or the exacerbation of underlying, cardiovascular disease [6]. Importantly, COVID-19 has been tightly associated with severe cardiovascular complications including hypercoagulability, cardiac arrhythmias, acute coronary syndrome and decompensation of heart failure [7]. Whether potential long-term cardiovascular consequences, associated with COVID-19, exist is not yet known [8]. Moreover, the pandemic has introduced major problems in healthcare systems ranging from constraints on health care delivery to difficulties in accessing health services for patients with chronic diseases, which may further increase cardiovascular risk in the future [9].

The global burden of chronic kidney disease (CKD) is high, with prevalence being estimated at 9.1% and has increased by 29.3% during the past three decades [10]. Cardiovascular events are considered the main cause of mortality in these patients with infections being second [11].

✉ Charalampos Loutradis
loutradis_haris@hotmail.com

1 Evangelismos Private Hospital and Hemodialysis Unit, 59132 Veroia, Greece

2 Second Department of Surgery, Division of Vascular Surgery, G. Gennimatas Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

3 Fourth Department of Internal Medicine, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece

Mortality is even higher in patients with end-stage renal disease (ESRD) undergoing maintenance dialysis with cardiac and cerebrovascular events accounting for > 50%, while infections account for 15% of deaths from known causes [12]. CKD generates a high-risk phenotype with a clinical profile encompassing inflammation, protein-energy wasting, altered function of the autonomic and central nervous systems, cardiopulmonary, vascular and bone diseases [13]. Moreover, CKD is tightly associated with immune system dysfunction that contributes to the high prevalence of infections and more frequent infection-related complications among these individuals [14]. Observational data suggest that patients with CKD are at higher risk for severe COVID-19 disease and mortality during admission [15, 16]. Thus, a recent consensus document from the Working Group of the European Renal Association COVID-19 Database (ERACODA) delineated the greater vulnerability for severe COVID-19 infection and associated mortality in patients with CKD [17]. Possible cardiovascular involvement, related to the COVID-19, may further increase the cardiovascular risk in this compromised population both in the short and in the long term. Herein, we discuss all existing evidence on cardiovascular risk, complications and mortality associated with COVID-19 in patients with CKD or undergoing hemodialysis and in KTR.

Pathophysiology of cardiovascular involvement in COVID-19

COVID-19 is strongly associated with the occurrence of cardiovascular complications, such as sudden arrhythmias, thromboembolic events, coronary events, cardiomyopathies and a heart failure [18]. The mechanistic background of the cardiovascular involvement in patients with COVID-19 is complex (Fig. 1). The SARS-CoV-2 uses a structural protein, known as spike, to gain intracellular entry to the host cells, through binding to the cell-associated and soluble angiotensin-converting enzyme-2 (ACE2) receptor in synergy with the transmembrane serine protease 2 (TMPRSS2) [19–21]. ACE2 receptors are expressed in a variety of cells, such as the lung alveolar, nasal and oral mucosa epithelial cells, enterocytes, proximal tubular cells, endothelial cells, and the vascular smooth muscle cells [22]. After entry, the expression of ACE2 is downregulated, which minimizes the protective organ effects of the receptor [23]. This decrease in ACE2 receptors has a direct negative impact on the cardiovascular system by inducing myocardial inflammation, remodeling and injury, as well as contractility disorders [24]. It is also known that the downregulation of ACE2 in the heart, induced by coronavirus strains, also promotes macrophage infiltration in the myocardium leading to myocardial inflammation [25]. These changes also induce an imbalance between ACE2 and angiotensin-2 levels and a decrease in the cardioprotective effects of angiotensin-2 [26]. Animal studies have shown that loss of ACE2 causes severely impaired cardiac contractility and increases susceptibility to experimentally induced heart failure [27]. Importantly, patients with CKD have increased ACE2 activity compared to healthy individuals [28, 29].

In some patients, SARS-CoV-2 may provoke an acute systemic inflammatory response and cytokine storm, characterized by excessive increase in proinflammatory cytokines: interleukin (IL)-1b, IL-6, IL-8 and IL-10, tumor necrosis factor (TNF), and chemokines ligands (CCL)-2, CCL-3, and CCL-5 [30]. This reaction can result in endothelial cells damage and apoptosis leading to vascular leakage mainly in the lung, but also in several organs causing shock, acute cardiac injury and failure, as well as renal and hepatic failure [31]. In the heart, systemic inflammatory response and hypoxia increases cardiometabolic demands and causes

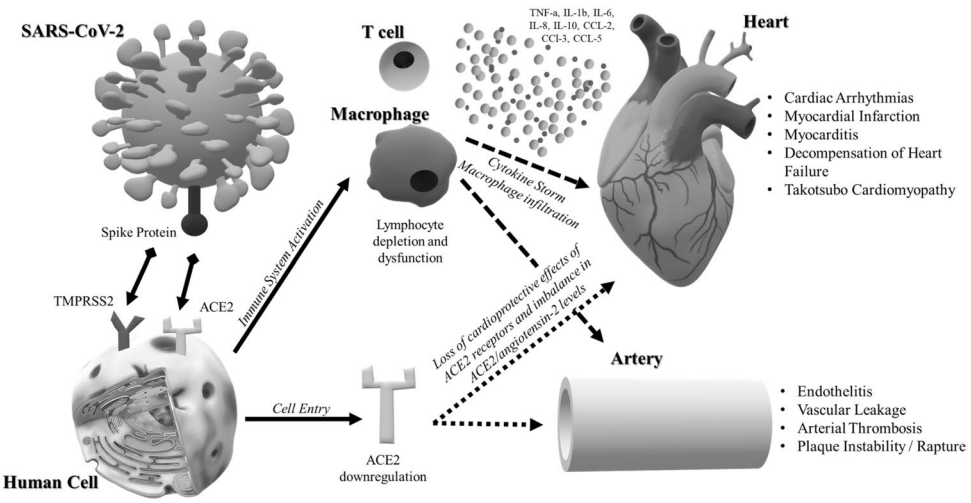

Fig. 1 Pathophysiologic mechanisms leading to cardiovascular complications in patients with COVID-19. *ACE2* angiotensin-converting enzyme-2 receptor; *CCL* chemokines ligands; *IL* interleukin; *SARS-CoV-2* acute respiratory syndrome coronavirus-2; *TMPRSS2* transmembrane serine protease 2; *TNF* tumor necrosis factor

an altered myocardial demand–supply ratio predisposing patients to cardiovascular events [24]. Systemic inflammation and increased shear stress, due to the hemodynamic changes associated with severe disease, can also cause atheromatous plaque rupture and destabilization, which may cause acute coronary syndrome and the formation of microthrombi from the release of foamy macrophages in the bloodstream [32]. Patients with COVID-19 present vascular inflammation and endothelial dysfunction which per se constitutes a hypercoagulable state [33]. In fact, evidence suggests the development of antiphospholipid antibodies, complement activation and deposition (C5-b9, C4d and mannose-binding lectin-associated serin protease) on the endothelial cells and microthrombi formation in some patients [34, 35]. These phenomena may be more pronounced in patients on dialysis, in whom endothelial cells have increased adhesiveness to leukocytes and platelets, as well as present increased synthesis of vasoactive molecules, cytokines and procoagulant factors [36].

Cardiovascular complications in CKD patients with COVID-19

So far, several studies showed that CKD is among the most common underlying diseases in patients with COVID-19, with prevalence ranging between 2% and 7% in unselected populations needing hospital admission [37, 38]. Importantly, the most common causal conditions of CKD, such as hypertension, diabetes mellitus and cardiovascular disease, have also been strongly associated with increased mortality risk after COVID-19 [39]. In one of the earlier studies in the field, patients with pre-existing CKD presented more severe COVID-19 infection (septic shock requiring vasoactive medications, or respiratory failure requiring mechanical ventilation) compared to those without CKD (38.1% vs. 15.7%; $P < 0.001$) [40]. Later observational data suggest that patients with CKD are at higher risk for severe COVID-19 disease and mortality during admission, ranging from 2.1-fold [95% confidence interval (CI): 1.36–3.26] higher for elevated serum creatinine, to 3.9-fold higher (95%CI: 2.57–6.14) for elevated blood urea nitrogen levels [15]. These observations have been confirmed in several subsequent studies [41–43]. In the largest study, including > 17 million primary care records from the United Kingdom (UK) and 10,926 COVID-19-related deaths, patients with estimated glomerular filtration rate (eGFR) 30–60 ml/min/1.73 m^2 [Hazard Ratio (HR): 1.33, 95%CI: 1.28–1.40] and < 30 ml/min/1.73 m^2 (HR: 2.52, 95%CI: 2.33–2.72) had higher mortality risk compared to those with eGFR > 60 ml/min/1.73 m^2, corresponding to mortality rates of 0.4% and 1.11%, respectively [16]. Results from another retrospective, observational study, including 289 CKD patients, 390 hemodialysis patients, 81 KTR and 450 controls, who were hospitalized due to COVID-19, showed increased mortality risk only in the CKD and hemodialysis groups and not for KTR (CKD, HR: 2.88, 95% CI: 1.52–5.44; hemodialysis: HR: 2.32, 95% CI: 1.21–4.46; KTR: HR: 1.87, 95%CI: 0.81–4.28, respectively) compared to controls [44].

Studies directly comparing cardiovascular events and mortality in patients with and without CKD are scarce. The results of the main studies directly comparing outcomes in patients with and without CKD are presented in Table 1. So far, most studies have included unselected populations, in whom CKD patients represent only a fraction of the patients included. Earlier case-series provided the first evidence on a possible association between CKD and increased cardiovascular complications due to SARS-CoV-2 infection, but results were contradictory [45–47]. Results from a later retrospective cohort study, including 4264 patients (12.2% with pre-existing CKD), who were admitted to intensive care units across the United States (US) with COVID-19, indicated that CKD patients had higher risk for 28-day in-hospital death (HR: 1.25, 95%CI: 1.08–1.44) compared to those with normal kidney function [48]. Among the secondary outcomes of this study, authors also evaluated the risk for ventricular arrhythmia or cardiac arrest (HR: 1.23, 95%CI: 0.99–1.53) and for thromboembolic events (HR: 0.90, 95%CI: 0.62–1.29), which was similar in patients with compared to those without CKD [48]. In another study, including 777 consecutively admitted patients with COVID-19 (29.6% with and 71.4% without CKD), results showed significantly higher all-cause mortality (59% vs. 26%; $P < 0.001$) and cardiovascular events rates (11% vs. 18%; $P = 0.010$) in patients with CKD compared to those with normal renal function, over a mean follow-up of 35 ± 22 days [49]. An observational study including a large population of 7341 patients with COVID-19, only a small fraction of whom had CKD (3.2%) or were undergoing maintenance dialysis (< 0.2%), showed a significant difference in the occurrence of cardiac arrest (0.5% vs 2.1% vs. 7.1%; $P < 0.001$), myocardial infraction (3.4% vs. 7.1% vs. 7.1%; $P = 0.006$) and acute heart failure (5.1 vs. 8.0 vs. 14.3%; $P = 0.046$) among patients without and those with CKD or on dialysis, respectively [50]. Despite the fact that hemodialysis patients represented a very small fraction of the population studied, these results further support a higher incidence of all cardiovascular end-points in CKD patients compared to those without CKD [50]. In the same context, results from an observational multi-ethnic multi-centre study in a UK cohort of 434 patients admitted across 6 hospitals and diagnosed COVID-19 positive indicated an independent association between CKD and myocardial injury (OR: 9.12, 95%CI: 4.24–19.64), defined as positive troponin during admission [51]. An observational study, including 4906 patients, showed that CKD was associated with increased risk (OR: 2.10, 95%CI: 1.47–3.0) for the primary outcome

Table 1 Studies comparing cardiovascular outcomes in patients with and without CKD

Study ID	Country	Design	*N*	Study groups	Mean/Median age (years)	Mean follow-up	Mortality	Cardiovascular events
Flythe JE. [48]	United States	Retrospective cohort study	4,264 COVID-19 patients admitted to ICUs	143 undergoing dialysis (3%) vs. 521 with CKD (21%) vs. 3600 without CKD (85%)	65 [56–71] vs. 69 [60–76] vs. 61 [51–70] ($P<0.05$)	28 days	50% vs 52% vs. 35% ($P<0.05$)	Ventricular arrhythmia or cardiac arrest: 21% vs 20% vs 15% ($P<0.05$) Thromboembolic event: 6% vs 7% vs 8% (p = N/S)
Russo E. [49]	Italy	Retrospective cohort study	777 consecutively admitted COVID-19 patients	222 with CKD (29%) vs. 555 without CKD (71%)	80 ± 12 vs. 66 ± 16 ($P<0.001$)	35 ± 22 days	59% vs 26% ($P<0.001$)	Cardiovascular events: 18% vs 11% ($P=0.010$)
Kang SH. [50]	Korea	Retrospective cohort study	7341 COVID-19 patients	8 undergoing dialysis (0.2%) vs. 122 with CKD (3%) vs. 7088 without CKD (97%)	59.6 ± 14.5 vs. 63.0 ± 14.8 vs. 46.5 ± 18.9	20.8 ± 13.1 days	28.6% vs. 9.6% vs. 2.8% ($P<0.001$)	Cardiac arrest: 7.1% vs. 2.1% vs. 0.5 ($P<0.001$) Myocardial infraction: 7.1% vs7.1% vs 3.4% ($P=0.006$) Acute heart failure: 14.3% vs 8.0% vs 5.1% ($P=0.046$)
Rao A. [54]	United States	Retrospective cohort study	8,574 COVID-19 patients	335 undergoing dialysis (3,9%) vs. 841 with CKD patients (9.8%) vs. 7416 without CKD (86.3%)	66 [53-74] vs. 74 [63–83] vs. 61 [48–73]	7.7 [3.9–13.1] vs. 6.7 [3.87–12.3] vs. 5.7 [3.5–10.7] days	28.7% vs. 30% vs. 16.6% ($P<0.001$)	Cardiac arrest: 9.9% vs. 7.9% vs 5.4% ($P<0.001$) Thrombotic events: 2.1% vs. 2.7% vs. 3.4% ($P=0.100$)
Ameri P. [56]	Italy	Retrospective cohort study	689 consecutively admitted COVID-19 patients	127 with CKD (19%)	37.3 ± 13.2 in the total cohort	15 (9–24) days	23.8% in the total cohort	Pulmonary embolism risk for CKD patients: HR: 0.45, 95%CI: 0.16–1.25
Waldman M. [61]	Worldwide Registry	Case–control	120 COVID-19 patients	40 glomerulonephritis patients with [median proteinuria: 1.0 (0.33–3.20) g/d] vs 80 COVID-19 controls (matched for infection time)	60.3 ± 17.7 vs 62.5 ± 15.6	17.0 (9.0–22.0) days	15% vs. 5%; ($P=0.026$)	Myocardial infarctions: 5.6% vs 0.0% ($P=0.12$) Cardiac arrhythmias 2.8% vs 7.9% ($P=0.034$)

of adjudicated venous or arterial thromboembolism or all-cause mortality [52]. In another analysis of outcomes in 8308 women from the US VA COVID-19 shared data repository, CKD was independently associated with increased risk for cardiovascular events within 60 days of testing positive for COVID-19 (OR: 2.24, 95%CI: 1.49–3.38) [53]. Similarly, results from another retrospective study including 8574 patients with COVID-19 from 88 US hospitals indicated that CKD and ESRD were associated with mortality or major adverse cardiac events compared to patients without CKD, but the association was rendered insignificant after multivariate adjustment for existing risk factors [54]. Results from a smaller retrospective study including 700 patients, 11% of whom had history of CKD, indicated no significant association between CKD and cardiac arrhythmias, such as atrial fibrillation, bradyarrhythmia and non-sustained ventricular tachycardia [55]. In the only study evaluating factors possibly associated with pulmonary embolism in 689 consecutive COVID-19 patients admitted to cardiology departments across Italy, CKD was not associated with increased risk for pulmonary embolism (HR: 0.45, 95%CI: 0.16–1.25) over 15 (9–24) days of follow-up [56].

Importantly, COVID-19 may itself result in glomerular injury, evidenced by de novo proteinuria associated with acute tubular injury, collapsing focal segmental glomerulosclerosis or post-AKI proteinuria in some cases [57, 58]. The severity of proteinuria is strongly associated with increasing COVID-19-related mortality risk for higher levels [59]. Evidence on cardiovascular mortality after COVID-19 in patients with proteinuric CKD is also scarce (Table 1). In one of the earlier studies in this field, including 168 Chinese patients admitted with mild-to-moderate COVID-19 symptoms, results showed that 18.4% of the patients had proteinuria and only 1 patient had AKI on admission, while proteinuria was associated with increased risk for development of severe COVID-19 infection [relative risk (RR): 7.37, 95%CI: 2.45–22.18] [60]. A case–control study included 40 patients with known glomerulonephritis and COVID-19 [median baseline proteinuria 1.0 (0.33–3.20) g/d], as well as 80 COVID-19 controls from the general population matched for the time of infections and results suggested significantly higher mortality rate (15% vs. 5%; $P=0.026$) and numerically higher myocardial infarctions (5.6% vs. 0.0%; $P=0.12$) for patients with glomerulonephritis, whereas controls presented more episodes of cardiac arrhythmias (2.8% vs. 7.9%; $P=0.034$) over a median follow-up of 17.0 (9.0–22.0) days [61]. In the study by Cheng et al., a total 43.9% of the patients had albuminuria on admission and results showed that mortality rates increased proportionally to the severity of albuminuria (measured semi-quantitatively by dipstick: 1^+, HR: 4.12, 95%CI: 1.97–8.62; $2–3^+$, HR: 10.92, 95%CI: 5.00–23.86) compared to those without albuminuria [15].

Cardiovascular complications in COVID-19 hemodialysis patients

During the pandemic of COVID-19, patients receiving hemodialysis are among the few populations with long-term conditions that continued their usual treatment by attending to their dialysis units, usually on a thrice weekly schedule, encountering other patients and medical staff in a limited space for several hours. Despite the implementation of preventative measures, such as social distancing and isolation of infected individuals, in-center transmission was not uncommon [62, 63]. Patients undergoing in-center hemodialysis present a high infection rate from SARS-CoV-2, ranging between 19.6% and 22.2% by real-time polymerase chain reaction (RT-PCR) and 36.2% by serologic testing, according to studies from the UK [64, 65]. The first case-series studies published since the COVID-19 outbreak, including patients undergoing maintenance hemodialysis in European countries and the United States, reported mortality rates between 31% and 41% [66–68]. Two studies, including COVID-19 hemodialysis patients across Europe, showed that mortality rate was about 20% at 28 days after diagnosis [69, 70]. In another large study from the US, being on dialysis was associated with higher mortality (31.7% vs. 25.4%, HR: 1.38, 95%CI: 1.12–1.70) compared to those without ESRD [71]. Results from a secondary analysis of the previously mentioned study by Williamson et al. showed a much lower mortality rate of 0.8% and a significantly higher mortality risk (HR 3.69, 95%CI:3.09–4.39) in patients with compared to those without history of hemodialysis or ESRD, but the former patient group represented only 2.3% of the population studied [16].

Limited data exist on cardiovascular events and mortality in patients undergoing dialysis. The studies evaluating the association of hemodialysis with cardiovascular events and mortality are presented in Table 2. In one of the first studies published in this field, including 49 hemodialysis and 52 patients without CKD who were hospitalized due to COVID-19 in Wuhan China, mortality rate (14% vs. 4%; $P<0.001$), incidence of arrhythmia (18% vs. 2%; $P<0.001$) and myocardial injury (29% vs. 8%; $P<0.001$) were higher in dialysis patients [72]. Similar were the results in other observational studies including Chinese hemodialysis patients, with results indicating cardiovascular events as the most common cause of death after COVID-19 [31, 73, 74]. A retrospective cohort study from the US in 7948 hemodialysis patients, among 5.5% of the population who developed COVID-19, 24.9% died in total, while pulmonary (51.9%), cardiac (9.3%) a combination of cardiac and pulmonary causes (7.4%) were the three most common causes of death during the 90-day follow-up period [75]. Results from a smaller study in a US population also showed a large number of in-hospital cardiac arrests in hemodialysis patients

Table 2 Studies evaluating cardiovascular events and mortality in patients undergoing hemodialysis

Study ID	Country	Design	*N*	Population Characteristics	Mean/median age (years)	Follow-up	Mortality	Cardiovascular Events
Wu J. [72]	China	Retrospective cohort study	101 admitted COVID-19 patients	49 hemodialysis vs. 52 patients without CKD	62 (54–71) vs. 62 (47–73)	38 days	14% vs. 4% ($P<0.001$)	Arrhythmia 18% vs. 2% ($P<0.001$) Myocardial injury 29% vs 8% ($P<0.001$)
Zou R. [74]	China	Prospective cohort study	602 hemodialysis patients	66 hemodialysis patients admitted with COVID-19 (11%)	64.5 (57.0, 72.0) in the total cohort	63 days	27% among COVID-19 cases	Acute cardiac injury: 18% Acute heart failure: 22%
Hsu CM. [75]	United States	Retrospective cohort study	7948 hemodialysis patients	438 (5.5%) COVID-19 cases	65.2 ± 13.2 in COVID-19 cases	90 days	24.9% among COVID-19 cases	Cardiovascular mortality: 9.3% Combination of cardiac and pulmonary causes: 7.4%
Fisher M. [76]	United States	Retrospective cohort study	114 hemodialysis patients	all patients hospitalized with COVID-19	64.5 (55–73) in the total cohort	20 days	28% among COVID-19 cases	Cardiac arrest: 44% among patients who died
Lano G. [77]	France	Prospective cohort study	2336 hemodialysis patients	129 (5.5%) COVID-19 cases	73.5 (64.2–81.2) in the total cohort	28 days	28% among COVID-19 cases	Cardiovascular mortality: 20% among patients who died
Stefan G et al. [78]	Romania	Case-Series	37 hemodialysis patients hospitalized with COVID-19	22 (59%) with mild/moderate and 15 (41%) with severe infection	64 (55–71) in the total cohort	12 weeks	19% died in total	Cardiovascular events: 13.5% Cardiac injury: 20% in patients with severe COVID-19
De Meester J. [79]	Belgium	Prospective cohort study	4297 hemodialysis patients	228 (2.5%) patients with vs 4069 (94.6%) without COVID-19	25–44: 2.2% vs. 4.6% 45–64: 16.7% vs. 17.2% 65–74: 19.3% vs. 21.5% 75–84: 36.0% vs. 35.3% ≥85: 25.9% vs. 87.2% ($P=0.26$)	12 weeks	29.6% vs. 19.9% ($P<0.001$)	Cardiovascular events: 4.7% vs. 13.2% ($P<0.001$) Sudden death: 3.1 vs. 16.7% ($P=0.006$)
Fontana F. [80]	Italy	Case-Series	14 dialysis patients hospitalized with COVID-19	12 hemodialysis and 2 peritoneal dialysis patients	75.96 ± 11.09 in the total cohort	5.5 days	40%	Cardiac ischemia: 1 patient

hospitalized due to COVID-19 [76]. In a multi-centre French cohort study, cardiovascular events (sudden death, heart failure, arterial or venous thrombosis, myocarditis) was again the second more common cause of death in 2336 hemodialysis patients enrolled, 5.5% of whom were COVID-19 cases [77]. A smaller single-center study evaluating clinical characteristics and outcomes in 37 hemodialysis patients in Romania hospitalized with COVID-19, 19% of whom died during follow-up, found that the main cause of death was cardiovascular events (13.5%) followed by respiratory distress syndrome (5.4%), while 20% of the patients with severe infection presented cardiac injury, defines as serum troponin-I levels above the 99th percentile upper reference levels [78].

In contrast, results from some studies, mainly in European populations, have not shown increased cardiovascular mortality during or after COVID-19. In a prospective, multicenter study from Belgium, including a total 4297 hemodialysis patients who were followed-up for 12 weeks (March 2–May 25, 2020), COVID-19 incidence was 2.54% (2.23–2.89%), mortality rate was similar to the mean rate during the same period of 2015–2019 (standardized mortality ratio: 51.02, 95%CI, 0.88 to 1.16; $P=0.82$) and the rates of cardiovascular events (4.7% vs. 13.2%) and sudden death (3.1 vs. 16.7%; $P=0.006$) were significantly lower in patients with compared to those without COVID-19 [79]. Importantly, the cause of death was identified as "infection" in 76.5% of the hemodialysis patients with COVID-19, which may limit the study's results regarding the true rates of death causes [79]. In the study by Flythe et al. analyzed above, 143 patients undergoing hemodialysis who represented 3.4% of the total population, presented a 28-day in-hospital mortality rate of 50% and had significantly higher mortality risk (HR: 1.41; 95%CI: 1.09–1.81), and insignificantly higher risk for cardiovascular and thromboembolic events compared to those with normal kidney function [48]. In another small study evaluating outcomes in 15 in-center dialysis patients with SARS-CoV-2 infection from Italy, 40% of whom died during a median follow-up of 5.5 days after diagnosis, but cardiac ischemia was identified as the cause of death only in 1 patient [80].

Cardiovascular complications in kidney transplant patients with COVID-19

Transplantation is the renal replacement modality of choice for patients with ESRD, as it confers improved survival, lower healthcare cost and higher quality of life compared to dialysis [81–83]. However, immunosuppression treatment results in increased susceptibility to infections and the expression of diminished signs and symptoms of the invasive infection [84]. With regards to COVID-19, organ transplantation was among the comorbidities associated with the highest mortality risk (HR: 3.53, 95%CI: 2.77–4.49) in the largest available study [16]. These results were also supported from the analyses performed in COVID-19 patients from the ERA-EDTA Registry, which showed that 28-day mortality was 19.9% (17.5%–22.5%) in KTR, while mortality risk was higher compared with age- and sex-matched dialysis patients (HR: 1.28, 95%CI 1.02–1.60) [69, 70]. Results from studies in the US were in same direction, further confirming that kidney transplantation was associated with increased mortality due to COVID-19 [85–87]. In KTR, the relevant rate of cardiovascular mortality is 20 times that of age- and sex-matched members of the general population [88]. In the study by De Meester et al. analyzed above, none of the six KTR with COVID-19 who died during follow-up experienced cardiovascular events [79]. Despite significant improvements over the past decades, cardiovascular disease still remains the leading cause of death among KTR during the first 10 years post-transplant period [89, 90]. So far, no study has evaluated whether KTR have higher risk for cardiovascular mortality after COVID-19 compared to the general population. In a case-report presenting the post-mortem findings of a 71-year old KTR who died due to COVID-19 showed the presence of viral elements within endothelial cells, diffuse endothelial inflammation and inflammatory cell death in several organs, including the kidney allograft [91].

Indirect cardiovascular consequences of the COVID-19 in patients with renal diseases

The COVID-19 pandemic has evolved in a serious challenge for all healthcare systems around the world. To cope with the pressure and to decrease the possibility of in-hospital transmission during COVID-19 waves, most of the healthcare systems worldwide postponed non-essential outpatient activities or elective operations and took measures to limit the number of inpatients for several months [92]. However, these infection control policies may have resulted in poor management of pre-existing CKD or many concomitant diseases such as diabetes, hypertension and cardiovascular disease, which in turn may further increase ESRD incidence and future cardiovascular risk in these patients [93].

Moreover, AKI is very common in severe COVID-19 cases (e.g., critically ill patients in the intensive care unit needing mechanical ventilation), a complication associated with increased mortality. Several studies showed that AKI occurs in 20–46% of patients with COVID-19, while 11–19% of these patients require renal replacement treatment during admission [94–96]. Importantly, 30–35% of the patients with COVID-19 and AKI remain dependent to renal replacement treatment at discharge [94–96]. Results from a previous metanalysis of 11 studies suggested that patients experiencing AKI present a significant risk for developing CKD (HR: 8.8, 95%CI 3.1–25.5) and ESRD (HR 3.1, 95%CI

1.9–5.0) [97] in the long term [97]. Occurrence of CKD after COVID-19 infection may indirectly increase cardiovascular events and further increase cardiovascular mortality in the future [98].

Unfortunately, patients with advanced CKD or ESRD have been excluded from many studies evaluating treatment options for COVID-19 [99, 100]. In contrast, most of the vaccination studies have not excluded patients with renal diseases from the populations studied, which may help in the prevention of COVID-19 in these patients [101–103]. Thus, patients with CKD and their treating physicians may have been left without an adequate evidence base from which to offer tested treatments to a group of patients known to be at increased risk of the worst outcomes from COVID-19 [104].

Conclusion

Patients with renal diseases present a high-risk phenotype that may result in increased susceptibility to cardiovascular complications after COVID-19. So far, several studies showed that these patients present higher all-cause mortality risk after SARS-CoV-2 infection compared to the general population. However, data on the possible association with cardiovascular mortality are scarce. Observational studies, including unselected populations, indicated a significant association between CKD and hemodialysis with cardiovascular events and mortality after COVID-19. Evidence associating cardiovascular events after COVID-19 in KTR is scarce. Importantly, most of the available studies in the field have not recorded a specific death cause, while in others, the cause of death has been identified as infection, possibly providing a false impression of the actual cardiovascular mortality rates in CKD and dialysis patients. Whether the association between renal dysfunction and cardiovascular events after SARS-CoV-2 infection can be attributed to the compromised cardiovascular background of these patients or to the cardiovascular manifestations of the COVID-19 is unsure.

COVID-19 is usually complicated by AKI in the general population, while a large proportion of these patients remain dialysis dependent after discharge, which in turn may further increase future cardiovascular risk. Moreover, management of CKD requires frequent outpatient reviews, particularly in those with advanced renal dysfunction, and health care measures implemented to reduce in-hospital transmissions of COVID-19 deprived proper follow-up during several months in the past few years. The same may be also applicable in patients with other diseases, such as hypertension, diabetes mellitus and cardiovascular disease, which all are among the most common causal conditions of CKD. Whether COVID-19 will potentially increase the demand for maintenance dialysis in the future or may escalate the long-term cardiovascular risk in patients with renal diseases is a matter requiring further investigation.

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