

Chronic Kidney Disease Major Risk Factor for COVID-19 Severity and Mortality, A Scoping Review

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A growing body of evidence points out at chronic kidney disease (CKD) as a major risk factor for severe COVID-19, increasing also the respective mortality risk. Preventive measures, rapid monitoring organ function and interventions capable of preventing multiorgan failures are of great importance to reduce adverse outcomes in COVID-19 patients with CKD. While efforts are underway to carry out indirect protection interventions and large-scale vaccination to achieve herd immunity in the general population, direct protection of patients with CKD through rapid vaccination trials are necessary since uraemia and immunosuppressive agents could have a negative impact on vaccination responses of CDK patients. More epidemiological data are needed for in-depth understanding of the course and outcome of COVID-19 in CKD patients, supporting clinical decision-making.

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INTRODUCTION

Chronic kidney disease (CKD) is a global public health issue, defined as kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73m² for at least 3 months, regardless the cause.¹ In several cases kidney damage can be established by the detection of an albumin-to-creatinine ratio > 30 mg/g in 2 out of 3 spot urine specimens. Kidney disease severity is classified into five stages according to the level of GFR:¹ 1) Kidney damage with normal or higher GFR (≥ 90 mL/min/1.73m²); 2) Kidney damage with mild GFR reduction (60 to 89 mL/min/1.73m²); 3) Moderate GFR reduction (30 to 59 mL/min/1.73m²); 4) Severe GFR reduction (15 to 29 mL/min/1.73m²); and 5) Kidney failure (GFR < 15 (or dialysis).

CKD is one of the main risk factors for severe COVID-19 and unfavourable outcome, according to various reports.²⁻⁹ The prevalence of CKD in COVID-19 patients is estimated to range from 0.09 to 47.05%.¹⁰ Understanding the epidemiology of

COVID-19 is therefore essential to determine its impact on CKD patients, manage such patients, design tailored health protection policies and deploy appropriate COVID-19 vaccination strategies.¹¹

In this scoping review, we examined the impact of COVID-19 in patients affected by CKD. PubMed, Scopus, Science Direct, and Google Scholar were selected to explore available data through the following keywords: COVID-19, SARS-CoV-2, chronic kidney disease (CKD), kidney diseases, kidney transplantation, dialysis, non-dialysis-dependent CKD patients and kidney replacement therapy.

CKD AND INCREASED VULNERABILITY TO COVID-19

Beyond acute respiratory distress syndrome (ARDS), COVID-19 also frequently involves the kidney with tissue inflammation, localized infiltration of immune cells, endothelial injuries and micro-vascular clots playing a key role in acute kidney injury (AKI).¹² The so called pro-

inflammatory cytokine storm syndrome and the oxidative stress determining lung inflammation likely explains the significantly higher risk of COVID-19 in CKD patients.¹³ In particular, CKD increases the mortality risk attributable to infections in general^{14,15}, including COVID-19.¹⁶ Hospital-diagnosed COVID-19 was significantly associated with renal failure (lower estimated GFR \leq 30 mL/min/1.73m²) in a case control study.¹⁷ Using OpenSAFELY platform from an electronic health record system, about 17 million CKD patients were stratified in three sub-groups by their mortality risk (HR = 2.52 for patients with eGFR < 30 mL/min/1.73m²). Severe forms of CKD were associated with higher risk of COVID-19 mortality as compared with other high-risk groups.^{18,19} The incidence of COVID-19 among patients with CKD reflects the circulation of SARS-CoV-2 in the community, as reported by the Emilia-Romagna Prevention of Progressive Renal Insufficiency (PIRP) project (Northern Italy), whereas the respective mortality risk was associated with the underlying renal condition and comorbidities of COVID-19 patients. In particular, COVID-19 increased 10 times the mortality risk from CDK in the latter Italian study.²⁰

The higher risk of severe COVID-19 and related death among CDK patients compared to non-CDK patients was confirmed in two systematic reviews and meta-analysis.^{21,22} The mortality rate of CDK patients due to COVID-19 is estimated to range between 0 to 34% according to various studies.²⁻⁹

CKD is the most relevant risk factor for AKI, requiring kidney replacement therapy in 3,099 critically ill patients affected by COVID-19.²³ Compared to patients without COVID-19 and without AKI, the mortality risk in-hospital was highest among COVID-19 patients with AKI (OR = 80.3, 95%CI: 27.3 to 235.6), followed by COVID-19 without AKI (OR = 16.3, 95%CI: 6.28 to 42.4), and by patients without COVID-19 and with AKI (OR = 10.2, 95%CI: 3.66 to 28.2).²⁴ A meta-analysis of 42 studies of moderate to high quality, enrolling 8,932 participants, reported significantly worse health outcomes due to COVID-19 in relation to CDK/AKI and AKI was found to be linked to higher risk of severity and mortality for COVID-19 in comparison with CKD.²⁵

Further factors contributing to enhance the mortality risk for COVID-19 in CKD patients are cardiovascular conditions, hypertension and

diabetes.² A meta-analysis of 73 studies reported the association of multi-organ dysfunction with severe forms of COVID-19.²⁶ In particular, hypertension (OR = 2.40, 95%CI: 2.08 to 2.78), cardiovascular disease (CVD) (OR = 3.54, 95%CI: 2.68 to 4.68), chronic obstructive pulmonary disease (COPD) (OR = 3.70, 95%CI: 2.93 to 4.68), chronic liver disease (CLD) (OR = 1.48, 95%CI: 1.09 to 2.01), CKD (OR = 1.84, 95%CI: 1.47 to 2.30), chronic cerebrovascular diseases (OR = 2.53; 95%CI: 1.84 to 3.49) and chronic gastrointestinal (GI) disease (OR = 2.13, 95%CI: 1.12 to 4.05) significantly increase the risk of severe COVID-19, aggravating acute multiorgan injury.²⁶

The European Renal Association COVID-19 Database (ERACODA) database provided clinical information on COVID-19 patients with end-stage renal disease receiving dialysis or kidney transplantation,²⁷ allowing rapid decision-making for their clinical management. In a systematic review on 348 studies (382,407 participants with COVID-19 as well as CKD, 1,139,979 total participants with CVD, with or without COVID-19). CDK patients in maintenance dialysis had a higher risk of COVID-19 than those without kidney replacement therapy requirement or those with kidney or pancreas-kidney transplantation.²⁸ However, the evidence of the role of kidney replacement therapy on risk of COVID-19 is conflicting. In a large study on 68 USA hospitals, for total 4,264 critically ill COVID-19 patients admitted to intensive care unit (ICU), CDK conditions significantly increased their mortality risk, irrespective of dialysis treatment.²⁹ In particular, in the latter study a 28-day in-hospital mortality rate of about 50% was reported for both non-dialysis-dependent CKD patients and kidney failure patients with maintenance dialysis.²⁹ By contrast, an Italian study reported higher vulnerability to COVID-19 among patients in non-dialytic stage of renal disease when compared with those with kidney replacement therapy (dialysis or kidney transplantation).²⁰

CONCLUSION

A growing body of evidence points out at CKD as a major risk factor for severe COVID-19, enhancing the respective mortality rate.

Preventive measures, rapid monitoring organ function and interventions capable of preventing multiorgan failures are of great importance to

reduce adverse outcomes in COVID-19 patients with CKD.^{10,21,28,30,31}

More epidemiological data are needed for in-depth understanding of the course and outcome of COVID-19 among CKD patients. Big data are of great importance for timely, statistically well-powered conclusions on outcomes and risk factors of COVID-19 in CKD patients, especially on health risk of kidney replacement therapy and decision-making on admission to dialysis in intensive care unit (ICU).

While efforts are underway to carry out indirect protection interventions and large-scale vaccination to achieve herd immunity in the general population, direct protection of patients with CKD through rapid vaccination trials are necessary since uraemia and immunosuppressive agents could have a negative impact on vaccination responses of CDK patients. Clinical trials involving patients with advanced stages of kidney disease and kidney transplantation are required for testing the efficacy of drugs and vaccine.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

FINANCIAL DISCLOSURES

None.

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