

This is the overview page

Chronic kidney disease is the key risk factor for severe COVID-19. A call to action by the European Renal Association.

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Response to the reviewer

Manuscript number: NDT-01849-2020
Manuscript title: Chronic kidney disease is the key risk factor for severe COVID-19.
A call to action by the European Renal Association.

We thank the editors and reviewers for careful reading of our manuscript and for the useful comments that we received. Please find a point-to-point response to these comments and recommendations below.

The paper is well written, timely and points to a major issue which is the neglect by the general community of the risk run by kidney patients (a problem that in se is not Covid-specific but general). I have a few minor remarks:

General:

An issue that is not mentioned at all is AKI. I can understand that this was considered out of the scope of the paper, which focuses on CKD, but still the two are linked (CKD is one of the major causes of AKI and AKI is one the major causes of CKD and mortality risk of AKI patients (any stage) is at least as high as that of CKD on dialysis. Since both diseases are considered as a continuum, I suggest the authors to devote at least a few sentences to this issue.

Indeed we felt that this was outside the scope of the present editorial that focuses on the association of CKD with COVID-19 severity. However, in response to your request we have added some lines and two references.

Another undiscussed issue is the potential confounding of CKD by age as a risk factor. Although briefly mentioned in the discussion of the risk run by dialysis patients, this might also be discussed for CKD. Is there any data to assess this potential for confounding, in other words, is there data on age-adjusted risk for CKD?

The data that we present in our manuscript on CKD as a risk factor is all age adjusted. We have added this information to the revised version of our manuscript.

Specific:

P 2, line 25, abstract: CKD-associated risk higher than that of DM – reading the rest of the abstract and looking at fig 2, this seems not entirely correct. This is only the case (at least as far as data is available) for advanced CKD (stage 4 or above).

We agree that this sentence is not entirely correct and have now formulated this more carefully: “The risk associated with CKD stages 4 and 5 is higher than... etc.”.

P 4, line 51-53: “Fast forward to September 2020 and Pubmed returns more ...” – I probably I miss something, but I don’t understand the sentence. Could you reformulate?

This sentence has been rephrased and we hope that it is more clear now: “Half a year later, in September 2020, a PubMed search for CKD and COVID-19 yielded more than 314 results and it

transpires that CKD is a key risk factor for severe COVID-19.”

P 5, line 20-24: “It was the most common ... 60-80 years (figure 4)” – this is a quite complex explanation which is more simply but also more tellingly explained in the caption of the figure as “at any age range”. To my opinion, that mortality of CKD and CVD is the same between age 60-80 (and only in that age window) is to my opinion of little relevance, and it cannot be deduced from fig 1. So, I would delete this and replace with “at any age”.

We have changed this sentence according to your suggestion.

P 7, line 37: few studies investigate risk factors within the wider CKD community – I don’t understand this reference to “wider CKD” in a section specifically devoted to ESKD.

We agree with your comment and have completely removed the first sentence of this section.

P 8, line 14: “the kidney community should take care that CKD patients are included in drug trials” – this is of course correct but only partially dependent on the kidney community; inclusion of kidney patients in studies depends on the general community, and as long as this problem is not recognized by the general community (with a few striking examples given in this review) this will remain difficult. So, one major point, is that the kidney community should also propagate the idea of kidney disease among general population and policy makers.

We fully agree with this statement and have changed the text accordingly. The following sentence has been added: “A first step in achieving this, is propagating awareness on the importance of CKD as key risk factor among the general community and policy makers, so that the problem is recognized.”

P 14, line 7: “most patients” – this could be anything in between 51 and 100%. Could this point be more precise?

It is difficult to specify here, because these numbers are different depending on the stage of CKD. We now state in Box 1 that at least 70-75% of the patients survive (in ESKD).

Minor:

P 6, line 11: “Despite having been widely ...”.

Thank you for noticing this error; we have added the word “having”.

Fig 4 is of low quality.

We have now submitted a high(er) quality version of Figure 4.

Chronic kidney disease is the key risk factor for severe COVID-19.

A call to action by the European Renal Association.

On behalf of The ERA-EDTA Council and the ERACODA Working Group*

*A list of members of the ERA-EDTA Council and the ERACODA Working Group can be found as

Supplementary Material

Contact address

Prof. Alberto ~~A.~~ Ortiz

Dept. Nephrology

Fundacion Jimenez Diaz

Av Reyes Catolicos 2

28040 Madrid, Spain

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Boxes 1

Figures 4

Abstract

Diabetes, hypertension, and cardiovascular disease have been listed as risk factors for severe COVID-19 since the first report of the disease in January 2020. However, this report did not mention chronic kidney disease (CKD), nor did it provide information on the relevance of estimated glomerular filtration rate (eGFR) or albuminuria. As the disease spread across the globe, information on larger populations with greater granularity on risk factors emerged.

The recently published OpenSAFELY project analyzed factors associated with COVID-19 death in 17 million patients. The picture that ~~emerged~~ arose differs significantly from initial reports. For example, hypertension is not an independent risk factor for COVID-19 death (adjusted hazard ratio [aHR] 0.89), but renal disease very much is. Dialysis (aHR 3.69), organ transplantation (aHR 3.53) and CKD (aHR 2.52 for patients with eGFR<30 ml/min/1.73 m²) represent three of the four comorbidities associated with the highest mortality risk from COVID-19. The ~~CKD-associated~~ risk associated with CKD stages 4 and 5 is higher than the risk associated with diabetes mellitus (aHR range 1.31-1.95, depending upon glycaemic control) or chronic heart disease (aHR 1.17). In another recent publication, the Global Burden of Disease collaboration identified that worldwide, CKD is the most prevalent risk factor for severe COVID-19. Moreover, the distribution of risk factors for COVID-19 mortality appears to be different in patients with CKD when compared to the general population.

The high prevalence of CKD in combination with the elevated risk of mortality from COVID-19 in CKD, necessitates urgent action for this group of patients. This article defines essential action points, among which advocating the inclusion of CKD patients in clinical trials testing the efficacy of drugs and vaccines to prevent severe COVID-19.

Key words

COVID-19; chronic kidney disease; renal replacement therapy; mortality; risk factor; prevalence.

Data availability statement

No new data were generated or analysed in support of this research.

Risk factors for severe COVID-19

By October 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus (COVID-19) pandemic has infected over 35 million people with over one million deaths.¹ An enigmatic and perilous feature of COVID-19 is the wide range of clinical manifestations from asymptomatic to multi-organ failure and death. The high frequency of asymptomatic infection has undoubtedly contributed to the rapid and worldwide spread of SARS-CoV-2.² A key unmet clinical need is the more precise and earlier identification of individuals at high risk of severe disease. These individuals may benefit from shielding and be a priority group for vaccination and for early antiviral therapy before clinical deterioration. Although age is the leading risk factor for severe disease, even the elderly may be asymptomatic or have mild disease. Notably, Spain's oldest woman, a survivor of the 1918 flu pandemic, survived mild COVID-19 which she probably acquired during her 113th birthday celebrations.³ Level of exposure to the virus and viral load most likely play a role, as well as poorly characterized genetic and immunological factors. Additionally, several co-morbidities are associated with more severe COVID-19, emphasizing the need to study the disease-associated drivers of the higher risk and the potential impact on COVID-19 of medications commonly used for these diseases. Recently, chronic kidney disease (CKD) emerged as the most common risk factor for severe COVID-19 and alarmingly it is also, after age, the strongest risk factor for severe COVID-19.^{4,5}

What is CKD?

CKD is defined as a decrease in kidney function measured by glomerular filtration rate (GFR) or evidence of kidney damage (even with normal GFR), such as increased albuminuria, abnormal urine sediment, or structural abnormalities persisting for longer than 3 months, with implications for health.⁶ The GFR and albuminuria thresholds thought to have implications for health are <60 mL/min/1.73 m² and >30 mg/g of urinary creatinine, respectively. Despite the consensus CKD definition dating back to 2012, there is still insufficient awareness of the concept and a diagnosis of CKD is frequently not recorded in patient medical records.⁷ The prevalence of CKD in the adult population has been estimated to be 10-15%, with 850 million people estimated to have CKD globally. CKD is projected to become the fifth cause of death by 2040 worldwide and one of the two top causes of death before the end of the century in some European countries, particularly in those countries where life expectancy is longest.⁸⁻¹¹ Indeed, patients with CKD, especially those with kidney failure, are at increased risk of premature death from

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3 many causes, including, but not limited to cardiovascular disease and infections.¹² Therapeutic nihilism
4 (e.g. withholding drugs or interventions shown to be effective in the general population) was identified by
5 multiple publications as a potential contributor to the high mortality.¹²
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10 **Diabetes, hypertension, and cardiovascular disease as risk factors for severe COVID-19**

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12 The first report of COVID-19 in PubMed is a January 24th, 2020 Lancet manuscript describing that
13 amongst patients admitted with the disease, 20% had diabetes mellitus (DM), 15% hypertension and 15%
14 cardiovascular disease (CVD) without any information on the prevalence of CKD, eGFR or
15 albuminuria.¹³ By late March 2020, another report, also from China, listed CKD status; finding it to be a
16 co-morbidity in only 1% of 274 COVID-19 patients (median age 62 years), thus likely significantly
17 underreporting the presence of CKD.¹⁴ Chronic hypertension and other cardiovascular comorbidities
18 occurred more frequently among deceased patients. A contemporary systematic review and meta-analysis
19 of 76,993 patients presented in 10 articles listed CKD among the seven most prevalent co-existing
20 diseases (alongside hypertension, CVD and DM), among hospitalized COVID-19 patients.¹⁵ Another
21 meta-analysis of four studies including 1389 COVID-19 patients, noted that although no study
22 individually found CKD to be significantly associated with severe COVID-19, in the combined analysis,
23 CKD was linked with severe COVID-19, without relevant heterogeneity (odds ratio 3.03 [95%
24 confidence interval 1.09–8.47], $I^2 = 0.0\%$, Cochran's Q, $p = 0.84$).¹⁶ Furthermore, in March 2020, UK
25 political and health authorities advised vulnerable persons, including those with CKD, to 'shield' i.e. to
26 minimize their social contacts.¹⁷ This statement drew criticism for not considering the fact that CKD can
27 vary from mild to severe, and that this could have consequences.¹⁸ Thus, early reports failed to adequately
28 assess the prevalence of CKD and to gauge its impact on COVID-19 disease severity and instead focused
29 on CKD associated conditions (e.g. hypertension, DM). This is despite acknowledgement of CKD as a
30 known risk factor for severity of several other bacterial and viral infections. As early as the end of March
31 some authors were calling for CKD to be recognized as a high-risk condition. [Fast forward to Half a year](#)
32 [later, in September 2020 and , a PubMed search for CKD and COVID-19 returns yielded](#) more than 314
33 [hits results in a search for CKD and COVID-19](#), and it transpires that CKD is a key risk factor for severe
34 COVID-19.
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CKD is the most prevalent risk factor for severe COVID-19 worldwide

The Global Burden of Disease (GBD) collaboration, that provides information on the health of populations worldwide annually, recently addressed the prevalence of risk factors for severe COVID-19 worldwide.^{5,18} The GBD produces age-, sex-, and country-specific health estimates using highly standardized, validated approaches applied to all available data sources and adjusting for major sources of bias. Using 2017 prevalence data and UN population estimates for 2020, the GBD estimated the number of individuals at increased risk of severe COVID-19 by age, sex, and country for 188 countries. This study estimated the global population at high risk for severe COVID-19 to be 1.7 billion people, comprising 22% of the global population, of whom 349 million would require hospital admission if infected. CKD was the most prevalent risk factor for severe COVID-19 worldwide.⁵ It was the most common risk factor in those aged under 60 years and over 80 years and as frequent as cardiovascular disease for ages 60 to 80 years at any age (Figure 1). Removal of CKD as a risk factor would decrease the percentage of the global population at increased risk of severe COVID-19 from 22% to 17%. Thus, CKD explains the increased risk of severe COVID-19 for around one in four high risk individuals worldwide (Supplementary Figure 1), equivalent to 5% of the global population, or 86,530,000 persons.

CKD is the disease condition conveying the highest risk for severe COVID-19

Williamson et al. recently published the largest analysis to date of risk factors for severe COVID-19 resulting in death.⁴ They analyzed data from over 17 million adults with almost 11,000 COVID-19-related deaths using OpenSAFELY, a health analytics platform that covers 40% of all patients in England. In the abstract, the authors state that COVID-19-related death was associated with male sex (adjusted hazard ratio [aHR] 1.59, 95% confidence interval 1.53–1.65), older age, deprivation, DM, severe asthma, Black and South Asian ethnicity and “various other medical conditions”. CKD is not mentioned in the abstract, yet from the full paper it is clear that advanced CKD (category G4 and G5) was among the conditions conveying the highest risk of death and notably higher than that conferred by all other factors mentioned in the abstract. Indeed, in a fully adjusted model including adjustment for age, patients with kidney disease e.g. dialysis patients (aHR 3.69), transplant recipients (aHR 3.53) and CKD (aHR 2.52 for patients with eGFR < 30 ml/min/1.73 m², CKD categories G4-G5), represented three of the top four risk categories. The risks in these subgroups were greater than the risk for COVID-19 death in diabetic patients (Adjusted HR range 1.31-1.95, depending upon glycaemic control) and in patients with chronic

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3 heart disease (Adjusted HR 1.17) (**Figure 2**). In sensitivity analyses with different populations (early
4 censoring, restricted to those with complete BMI/smoking data, adjusted for recorded or imputed
5 ethnicity), the risk conferred by CKD G4-G5 was consistently higher than the risk conveyed by poorly
6 controlled DM or severe asthma, which makes it all the more puzzling that CKD was not amongst the risk
7 factors detailed in the abstract.
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12 Data for hypertension are interesting. Despite **having** been widely mentioned as a risk factor for
13 severe COVID-19, in an analysis adjusted for age and sex, it was only weakly associated with the risk of
14 death (HR 1.09; 1.05–1.14). In a fully adjusted analysis the risk associated with hypertension was in fact
15 reversed (aHR 0.89; 0.85–0.93) thus suggesting that hypertension may be a surrogate for other conditions,
16 for example CKD, which convey the risk. A further explanation might be that the risk associated with
17 hypertension is influenced by the use of certain drugs e.g. renin-angiotensin system (RAS) blockers.
18 Although initially hypothesized that RAS blockade may increase the risk of severe COVID-19 by
19 increasing ACE2 expression (and subsequent virus entry into cells), or decrease the risk of severe
20 COVID-19 by promoting Ang1-7 synthesis, neither of these hypotheses has been proven thus far in
21 epidemiological studies which instead tend to show a neutral effect.^{18,19} The potential impact of RAS
22 blockade was not assessed in OpenSAFELY. Ultimately, even when CKD is clearly demonstrated to be
23 amongst co-morbidities which convey the highest risk of death in COVID-19, it is replaced in the paper
24 ‘headline’ i.e. the abstract by more “popular” conditions which somewhat ironically are actually
25 associated with a lower COVID-19 mortality risk than CKD.
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40 In a separate UK population-based cohort study undertaken in a general practice context, age and
41 eGFR were the variables that most strongly affected the adjusted hazard ratios for COVID-19-related
42 death in people with type 1 (T1DM, N=264390) and type 2 diabetes (T2DM, N=2874020) (**Figure 3**).²⁰
43 The increased risk was evident from eGFR 45–59 ml/min/1.73 m², but not with an eGFR above that
44 value, in both T1DM and T2DM, i.e. it was evident for patients with CKD as defined by eGFR
45 thresholds. Unfortunately, similarly as in the OpenSAFELY study, the effect of increased albuminuria
46 was not analyzed. Thus, the increased risk of persons with CKD G3-G5 was confirmed, but information
47 on CKD G1-G2 was lacking, as in other epidemiological studies. Of the different variables analyzed, an
48 eGFR <15 ml/min/1.73 m² conferred the highest risk of death after age, both in T1DM (aHR compared to
49 eGFR ≥90 ml/min/1.73 m² 8.35; 95%CI: 5.50–12.70) and in T2DM (aHR: 4.91; 95%CI: 4.34–5.56).
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51 Other variables analyzed included sex, socio-economic status or deprivation, ethnicity, HbA1c, BMI,
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3 blood pressure, antihypertensive drugs, smoking status and cardiovascular comorbidities. HRs for
4 impaired kidney function were consistent for males and females and were greater for people younger than
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7 70 years

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9 Results from the ERA-EDTA Registry further support the high mortality due to COVID-19 in
10 dialysis patients and kidney transplant recipients across Europe.²² The 28-day mortality was 20.0% (95%
11 confidence interval 18.7%-21.4%) in 3285 patients receiving dialysis, and 19.9% (17.5%-22.5%) in 1013
12 recipients of a kidney transplant. Mortality risk was 1.28 (1.02-1.60) times higher in transplant recipients
13 compared with [age and sex](#) matched dialysis patients. In both groups mortality is, for a large part, related
14 to age and in dialysis patients also to frailty status).²³ In addition frequent hospital attendance, as is
15 needed for in-centre dialysis, may increase the risk of infection for ESKD patients.²⁴

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17 A missing piece of information is quantification of the risk conveyed by pathological
18 albuminuria. This may be the sole criterion that can define CKD when eGFR is ≥ 60 ml/min/1.73 m² or
19 may further increase risk in CKD patients with a lower eGFR. Interestingly, COVID-19 itself may result
20 in glomerular injury, evidenced by the occurrence of proteinuria that can be associated with acute kidney
21 injury.²⁵ [In turn, acute kidney injury can lead to CKD, and when superimposed on CKD it increases the](#)
22 [risk for mortality conveyed by CKD even further \(REFS\).](#)^{26, 27} [These data also indicate that](#) ~~Apparently,~~
23 SARS-CoV-2 has multiorgan tropism that includes glomerular, but as it later showed, also tubular cells.^{28,}
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End-stage kidney disease and the need for specific studies

~~In contrast to other risk factors identified early in the course of the pandemic, e.g. DM, there are few well-~~
~~powered studies that investigate risk factors for severe COVID-19 within the wider CKD community.~~
~~However, e~~ Emerging data revealed risk factors for severe COVID-19 among patients on kidney
replacement therapy. The ERACODA cohort, established by the ERA-EDTA, showed that within dialysis
and kidney transplant populations the risk conferred by classical risk factors for severe COVID-19 is
completely different than in the general population.²³ For instance, in dialysis patients with COVID-19
(n=768, of which 192 (25%) died), the relative contribution of age to mortality is considerably less than
in subjects from the general population. In addition, in dialysis patients male sex, hypertension, coronary
artery disease and diabetes do not confer an independent increased risk of mortality (**Figure 4**).

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3 The mortality rates in dialysis and transplant cohorts clearly demonstrate that these are high risk
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5 populations,^{22,23} given the discrepancies between risk factors in this population as compared with the
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7 general population,²³ findings in the general population cannot and should not be extrapolated to end-
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9 stage kidney disease populations. There are other compelling reasons why the CKD population merits
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11 specific study. During the last two decades it has become clear that some drugs which are effective in
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13 patients with normal kidney function, have little or no efficacy in patients with impaired kidney function,
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15 especially in those on dialysis. This holds true for, amongst others, statins.^{28,30} Medications to be
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17 prescribed to lower COVID-19 morbidity and mortality must therefore be tested in patients with impaired
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19 kidney function to prove their efficacy in this patient category. Unfortunately, randomized clinical trials
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21 often exclude patients with impaired kidney function because of safety reasons.¹⁰ It is our
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23 recommendation that the kidney community should take great care to include CKD patients in COVID-19
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25 medication trials to avoid disparity in the treatment of this patient group. A first step in achieving this, is
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27 propagating awareness on the importance of CKD as key risk factor among the general community and
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29 policy makers, so that the problem is recognized. Furthermore, we know that because of the
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31 immunosuppressive nature of the uremic milieu in dialysis patients, and because of the use of
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33 immunosuppressants in transplantation patients, these patients respond poorly to vaccination.^{29,31} It is
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35 imperative, therefore, that CKD patients are included in trials testing the efficacy of vaccines against
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37 SARS-CoV-2 infection. It is very plausible that in such patients different vaccination schedules may be
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39 necessary (e.g. a higher dose or repeat vaccinations).

41 Conclusions

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43 Although not listed in initial reports as risk factor for severe COVID-19, CKD has emerged not only as
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45 the most prevalent comorbidity conveying an increased risk for severe COVID-19, but also as the
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47 comorbidity which conveys the highest risk for severe COVID-19. The increased risk is evident below
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49 the threshold of eGFR that defines CKD and the risk increases as the eGFR decreases, with the highest
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51 risk in patients on kidney replacement therapy. Although CKD patients are known to be at increased risk
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53 of death due to infectious diseases, the factors contributing to their higher vulnerability for severe
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55 COVID-19 should be explored, as they may provide valuable insight into therapeutic approaches to the
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57 disease in this patient group. It is presently unknown if earlier categories of CKD (G1/G2, i.e. patients
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59 with preserved kidney function but with increased albuminuria) are also at an increased risk of severe
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3 COVID-19 and this must be explored. Moreover, the recognition that CKD significantly contributes to
4 the severity of COVID-19 should now result in focused efforts to improve outcomes of the 850 million
5 global CKD patients.⁸ Paramount to this is the enrollment of patients representing all CKD stages,
6 including dialysis and transplantation, in clinical trials of vaccines to prevent, and drugs to treat COVID-
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13 Crucially, a CKD diagnosis should not be used as the sole criterion to deny intensive care
14 admission with severe COVID-19. Both scientific societies and patient associations should be vigilant in
15 this regard. Until better epidemiological data become available and the biological basis of the increased
16 risk of severe COVID-19 in CKD patients is ascertained, therapeutic nihilism may continue to play a role
17 and CKD patients may be denied vital support based on their increased risk of COVID-19-related death.
18 This becomes an unacceptable self-fulfilling prophecy. The threatening shortage of ICU capacity in some
19 parts of the world may have contributed to the high mortality of CKD patients in these areas. In those
20 with kidney disease, therapeutic nihilism has been repeatedly associated with adverse outcomes.¹¹ Facing
21 an ongoing pandemic of unquantifiable duration, this is not an acceptable strategy, particularly not
22 considering the high prevalence of CKD. We propose that those with CKD must be actively included in
23 research to ensure equitable access to effective vaccines and treatments in the future.
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35 **Author responsibility.**

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37 The present article was conceptualized by AAO and RTG, who also wrote the first draft of the
38 manuscript. All co-authors were involved with revising the work, and provided important intellectual
39 content. All authors have seen and approved the submitted version of the manuscript and can be hold
40 accountable for all aspects of the work.
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48
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51 al)²³ and the ERA-EDTA Registry (Jager)²².
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12 **Conflict of interest**
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14 None declared.
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For Peer Review

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Box 1. Background why Chronic Kidney Disease is important for the COVID-19 pandemic, resultant clinical and research consequences, and action points.

Background

- A. CKD is among the most prevalent conditions that increase the risk of severe COVID-19
- B. CKD is the condition that is most strongly associated with the risk of severe COVID-19.
- C. Particularly in advanced CKD, the normal risk factors for severe COVID-19 are less important.
- D. Patients with advanced CKD may be at additional increased risk of SARS-CoV-2 infection because of frequent hospital attendance.
- E. A CKD diagnosis may be missed by physicians, especially in environments in which eGFR is not calculated automatically from serum creatinine by clinical laboratories and where albuminuria is not routinely measured.

Clinical and research consequences, and related action points.

1. The study of the immune and inflammatory response to SARS-CoV-2 in CKD patients may provide clues to the pathogenesis of COVID-19 and successful treatments for CKD patients with COVID-19.

Action point: Research into the immune and inflammatory response to SARS-CoV-2 at different stages of CKD should be encouraged

2. The impact of increased albuminuria on COVID-19 severity in patients with eGFR categories G1 and G2 and also G3-G5 should be studied

Action point: Epidemiological research should be stimulated to clearly define the role of CKD, including elevated albuminuria, as a risk factor for severe COVID-19.

Action point: Consideration should be given to making testing for proteinuria/albuminuria mandatory for all individuals who test positive for COVID-19 and are admitted to hospital

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5 3. Patients with CKD have a high risk of COVID-19 related complications, including mortality.

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7 Notwithstanding, at least about 70-75% (in ESKD)most of the CKD patients survive.

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9 *Action point:* CKD diagnosis should not be used as sole criterion to deny vital supportive care
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11 to CKD patients with severe COVID-19

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13 *Action point:* Once CKD is identified, consider prompt transfer to a higher level of care
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16 4. Risk factors for COVID-19 mortality cannot be extrapolated from the general population to the CKD
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18 population.

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20 *Action point:* Epidemiological research should be encouraged to investigate which factors can
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22 be of help to triage which CKD patients will benefit most from more invasive treatment,
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24 including vital support care.
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27 5. Patients of all CKD categories should be represented in vaccine and drug trials, including patients on
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29 maintenance hemodialysis and those with a kidney transplant.

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31 *Action point:* Actively encourage the inclusion of CKD patients in vaccine and drug trials
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3 **Figures**
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9 **Figure 1. Global prevalence of key underlying conditions associated with severe COVID-19 if**
10 **infected.** Prevalence by age. The four most prevalent risk factors have been selected and ranked from left
11 to right according to highest global prevalence at any age range (bold black line). Grey lines represent
12 individual countries. Data from Clark et al.⁵
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20 **Figure 2. Risk factors for COVID-19 related death.** Graph shows the five medical conditions
21 associated with the highest Hazard Ratio of death, and, additionally, the risk associated with CKD G3 and
22 the risk associated with the risk factors recognized early in the pandemic as associated with severe
23 COVID-19 (diabetes, chronic heart disease and hypertension, in black). In red, conditions of
24 nephrological interest. Light blue represents non-kidney risk factors present in less than 100 individual.
25 Data derived from Williamson et al.⁴ Patients with CKD G4 G5 have an eGFR <30 ml/min/1.73 m² and
26 patients with CKD G3 an eGFR 30-60 ml/min/1.73 m².
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38 **Figure 3. CKD as a risk factor for COVID-19 related death in type 1 (T1DM) and type 2 (T2DM)**
39 **diabetic patients in general practice. A)** Adjusted hazard ratios (HR) for COVID-19-related death
40 according to type of diabetes and eGFR range. **B)** Adjusted hazard ratios (HR) for COVID-19-related
41 death according to type of diabetes, age and eGFR range. eGFR ≥ 90 ml/min/1.73m² was the reference for
42 both graphs and was considered to be 1 in each of the categories (T1DM, T2DM and age categories
43 within) assessed. * p<0.0001 vs eGFR ≥ 90 ml/min/1.73m²; + non-overlapping 95% CI vs eGFR ≥ 90
44 ml/min/1.73m² (Data derived from Holman et al.²¹).
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56 **Figure 4. Risk factors for COVID-19 related death.** Left graph shows the situation in subjects of the
57 general population (as derived from the Open Safely study, data from Williamson) and the right graph the
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3 situation in patients with end-stage kidney disease treated by maintenance hemodialysis (as derived from
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5 the ERACODA cohort), data derived from Hilbrands et al.²³
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For Peer Review

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3 **Supplementary material**
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9 **Supplementary File 1.** List of collaborative authors on behalf of the Council of the European Renal
10 Association (ERA) and the Working Group of the European Renal Association CCOVID-19 Database
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12 (ERACODA)
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18 **Supplementary Figure 1.** Distribution of risk factors for severe COVID-19 in the world.
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For Peer Review

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7 **Chronic kidney disease is the key risk factor for severe COVID-19.**

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10 **A call to action by the European Renal Association.**

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16 ERA-EDTA Council and the ERACODA Working Group*

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20 *A list of members of the ERA-EDTA Council and the ERACODA Working Group can be found as

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22 Supplementary Material

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33 **Contact address**

34 Prof. Alberto Ortiz

35 Dept. Nephrology

36 Fundacion Jimenez Diaz

37 Av Reyes Catolicos 2

38
39
40
41
42
43 28040 Madrid, Spain

44
45
46
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Abstract

Diabetes, hypertension, and cardiovascular disease have been listed as risk factors for severe COVID-19 since the first report of the disease in January 2020. However, this report did not mention chronic kidney disease (CKD), nor did it provide information on the relevance of estimated glomerular filtration rate (eGFR) or albuminuria. As the disease spread across the globe, information on larger populations with greater granularity on risk factors emerged.

The recently published OpenSAFELY project analyzed factors associated with COVID-19 death in 17 million patients. The picture that arose differs significantly from initial reports. For example, hypertension is not an independent risk factor for COVID-19 death (adjusted hazard ratio [aHR] 0.89), but renal disease very much is. Dialysis (aHR 3.69), organ transplantation (aHR 3.53) and CKD (aHR 2.52 for patients with eGFR<30 ml/min/1.73 m²) represent three of the four comorbidities associated with the highest mortality risk from COVID-19. The risk associated with CKD stages 4 and 5 is higher than the risk associated with diabetes mellitus (aHR range 1.31-1.95, depending upon glycaemic control) or chronic heart disease (aHR 1.17). In another recent publication, the Global Burden of Disease collaboration identified that worldwide, CKD is the most prevalent risk factor for severe COVID-19. Moreover, the distribution of risk factors for COVID-19 mortality appears to be different in patients with CKD when compared to the general population.

The high prevalence of CKD in combination with the elevated risk of mortality from COVID-19 in CKD, necessitates urgent action for this group of patients. This article defines essential action points, among which advocating the inclusion of CKD patients in clinical trials testing the efficacy of drugs and vaccines to prevent severe COVID-19.

Key words

COVID-19; chronic kidney disease; renal replacement therapy; mortality; risk factor; prevalence.

Data availability statement

No new data were generated or analysed in support of this research.

Risk factors for severe COVID-19

By October 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus (COVID-19) pandemic has infected over 35 million people with over one million deaths.¹ An enigmatic and perilous feature of COVID-19 is the wide range of clinical manifestations from asymptomatic to multi-organ failure and death. The high frequency of asymptomatic infection has undoubtedly contributed to the rapid and worldwide spread of SARS-CoV-2.² A key unmet clinical need is the more precise and earlier identification of individuals at high risk of severe disease. These individuals may benefit from shielding and be a priority group for vaccination and for early antiviral therapy before clinical deterioration. Although age is the leading risk factor for severe disease, even the elderly may be asymptomatic or have mild disease. Notably, Spain's oldest woman, a survivor of the 1918 flu pandemic, survived mild COVID-19 which she probably acquired during her 113th birthday celebrations.³ Level of exposure to the virus and viral load most likely play a role, as well as poorly characterized genetic and immunological factors. Additionally, several co-morbidities are associated with more severe COVID-19, emphasizing the need to study the disease-associated drivers of the higher risk and the potential impact on COVID-19 of medications commonly used for these diseases. Recently, chronic kidney disease (CKD) emerged as the most common risk factor for severe COVID-19 and alarmingly it is also, after age, the strongest risk factor for severe COVID-19.^{4,5}

What is CKD?

CKD is defined as a decrease in kidney function measured by glomerular filtration rate (GFR) or evidence of kidney damage (even with normal GFR), such as increased albuminuria, abnormal urine sediment, or structural abnormalities persisting for longer than 3 months, with implications for health.⁶ The GFR and albuminuria thresholds thought to have implications for health are <60 mL/min/1.73 m² and >30 mg/g of urinary creatinine, respectively. Despite the consensus CKD definition dating back to 2012, there is still insufficient awareness of the concept and a diagnosis of CKD is frequently not recorded in patient medical records.⁷ The prevalence of CKD in the adult population has been estimated to be 10-15%, with 850 million people estimated to have CKD globally. CKD is projected to become the fifth cause of death by 2040 worldwide and one of the two top causes of death before the end of the century in some European countries, particularly in those countries where life expectancy is longest.⁸⁻¹¹ Indeed, patients with CKD, especially those with kidney failure, are at increased risk of premature death from

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3 many causes, including, but not limited to cardiovascular disease and infections.¹² Therapeutic nihilism
4 (e.g. withholding drugs or interventions shown to be effective in the general population) was identified by
5 multiple publications as a potential contributor to the high mortality.¹²
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10 **Diabetes, hypertension, and cardiovascular disease as risk factors for severe COVID-19**

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12 The first report of COVID-19 in PubMed is a January 24th, 2020 Lancet manuscript describing that
13 amongst patients admitted with the disease, 20% had diabetes mellitus (DM), 15% hypertension and 15%
14 cardiovascular disease (CVD) without any information on the prevalence of CKD, eGFR or
15 albuminuria.¹³ By late March 2020, another report, also from China, listed CKD status; finding it to be a
16 co-morbidity in only 1% of 274 COVID-19 patients (median age 62 years), thus likely significantly
17 underreporting the presence of CKD.¹⁴ Chronic hypertension and other cardiovascular comorbidities
18 occurred more frequently among deceased patients. A contemporary systematic review and meta-analysis
19 of 76,993 patients presented in 10 articles listed CKD among the seven most prevalent co-existing
20 diseases (alongside hypertension, CVD and DM), among hospitalized COVID-19 patients.¹⁵ Another
21 meta-analysis of four studies including 1389 COVID-19 patients, noted that although no study
22 individually found CKD to be significantly associated with severe COVID-19, in the combined analysis,
23 CKD was linked with severe COVID-19, without relevant heterogeneity (odds ratio 3.03 [95%
24 confidence interval 1.09–8.47], $I^2 = 0.0\%$, Cochran's Q, $p = 0.84$).¹⁶ Furthermore, in March 2020, UK
25 political and health authorities advised vulnerable persons, including those with CKD, to 'shield' i.e. to
26 minimize their social contacts.¹⁷ This statement drew criticism for not considering the fact that CKD can
27 vary from mild to severe, and that this could have consequences.¹⁸ Thus, early reports failed to adequately
28 assess the prevalence of CKD and to gauge its impact on COVID-19 disease severity and instead focused
29 on CKD associated conditions (e.g. hypertension, DM). This is despite acknowledgement of CKD as a
30 known risk factor for severity of several other bacterial and viral infections. As early as the end of March
31 some authors were calling for CKD to be recognized as a high-risk condition. Half a year later, in
32 September 2020, a PubMed search for CKD and COVID-19 yielded more than 314 results and it
33 transpires that CKD is a key risk factor for severe COVID-19.
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CKD is the most prevalent risk factor for severe COVID-19 worldwide

The Global Burden of Disease (GBD) collaboration, that provides information on the health of populations worldwide annually, recently addressed the prevalence of risk factors for severe COVID-19 worldwide.^{5,18} The GBD produces age-, sex-, and country-specific health estimates using highly standardized, validated approaches applied to all available data sources and adjusting for major sources of bias. Using 2017 prevalence data and UN population estimates for 2020, the GBD estimated the number of individuals at increased risk of severe COVID-19 by age, sex, and country for 188 countries. This study estimated the global population at high risk for severe COVID-19 to be 1.7 billion people, comprising 22% of the global population, of whom 349 million would require hospital admission if infected. CKD was the most prevalent risk factor for severe COVID-19 worldwide.⁵ It was the most common risk factor and as frequent as cardiovascular disease at any age (**Figure 1**). Removal of CKD as a risk factor would decrease the percentage of the global population at increased risk of severe COVID-19 from 22% to 17%. Thus, CKD explains the increased risk of severe COVID-19 for around one in four high risk individuals worldwide (**Supplementary Figure 1**), equivalent to 5% of the global population, or 86,530,000 persons.

CKD is the disease condition conveying the highest risk for severe COVID-19

Williamson et al. recently published the largest analysis to date of risk factors for severe COVID-19 resulting in death.⁴ They analyzed data from over 17 million adults with almost 11,000 COVID-19-related deaths using OpenSAFELY, a health analytics platform that covers 40% of all patients in England. In the abstract, the authors state that COVID-19-related death was associated with male sex (adjusted hazard ratio [aHR] 1.59, 95% confidence interval 1.53–1.65), older age, deprivation, DM, severe asthma, Black and South Asian ethnicity and “various other medical conditions”. CKD is not mentioned in the abstract, yet from the full paper it is clear that advanced CKD (category G4 and G5) was among the conditions conveying the highest risk of death and notably higher than that conferred by all other factors mentioned in the abstract. Indeed, in a fully adjusted model including adjustment for age, patients with kidney disease e.g. dialysis patients (aHR 3.69), transplant recipients (aHR 3.53) and CKD (aHR 2.52 for patients with eGFR < 30 ml/min/1.73 m², CKD categories G4-G5), represented three of the top four risk categories. The risks in these subgroups were greater than the risk for COVID-19 death in diabetic patients (Adjusted HR range 1.31-1.95, depending upon glycaemic control) and in patients with chronic

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3 heart disease (Adjusted HR 1.17) (**Figure 2**). In sensitivity analyses with different populations (early
4 censoring, restricted to those with complete BMI/smoking data, adjusted for recorded or imputed
5 ethnicity), the risk conferred by CKD G4-G5 was consistently higher than the risk conveyed by poorly
6 controlled DM or severe asthma, which makes it all the more puzzling that CKD was not amongst the risk
7 factors detailed in the abstract.
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12 Data for hypertension are interesting. Despite having been widely mentioned as a risk factor for
13 severe COVID-19, in an analysis adjusted for age and sex, it was only weakly associated with the risk of
14 death (HR 1.09; 1.05–1.14). In a fully adjusted analysis the risk associated with hypertension was in fact
15 reversed (aHR 0.89; 0.85–0.93) thus suggesting that hypertension may be a surrogate for other conditions,
16 for example CKD, which convey the risk. A further explanation might be that the risk associated with
17 hypertension is influenced by the use of certain drugs e.g. renin-angiotensin system (RAS) blockers.
18 Although initially hypothesized that RAS blockade may increase the risk of severe COVID-19 by
19 increasing ACE2 expression (and subsequent virus entry into cells), or decrease the risk of severe
20 COVID-19 by promoting Ang1-7 synthesis, neither of these hypotheses has been proven thus far in
21 epidemiological studies which instead tend to show a neutral effect.^{18,19} The potential impact of RAS
22 blockade was not assessed in OpenSAFELY. Ultimately, even when CKD is clearly demonstrated to be
23 amongst co-morbidities which convey the highest risk of death in COVID-19, it is replaced in the paper
24 ‘headline’ i.e. the abstract by more “popular” conditions which somewhat ironically are actually
25 associated with a lower COVID-19 mortality risk than CKD.
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40 In a separate UK population-based cohort study undertaken in a general practice context, age and
41 eGFR were the variables that most strongly affected the adjusted hazard ratios for COVID-19-related
42 death in people with type 1 (T1DM, N=264390) and type 2 diabetes (T2DM, N=2874020) (**Figure 3**).²⁰
43 The increased risk was evident from eGFR 45–59 ml/min/1.73 m², but not with an eGFR above that
44 value, in both T1DM and T2DM, i.e. it was evident for patients with CKD as defined by eGFR
45 thresholds. Unfortunately, similarly as in the OpenSAFELY study, the effect of increased albuminuria
46 was not analyzed. Thus, the increased risk of persons with CKD G3-G5 was confirmed, but information
47 on CKD G1-G2 was lacking, as in other epidemiological studies. Of the different variables analyzed, an
48 eGFR <15 ml/min/1.73 m² conferred the highest risk of death after age, both in T1DM (aHR compared to
49 eGFR ≥90 ml/min/1.73 m² 8.35; 95%CI: 5.50–12.70) and in T2DM (aHR: 4.91; 95%CI: 4.34–5.56).
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60 Other variables analyzed included sex, socio-economic status or deprivation, ethnicity, HbA1c, BMI,

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3 blood pressure, antihypertensive drugs, smoking status and cardiovascular comorbidities. HRs for
4 impaired kidney function were consistent for males and females and were greater for people younger than
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7 70 years

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9 Results from the ERA-EDTA Registry further support the high mortality due to COVID-19 in
10 dialysis patients and kidney transplant recipients across Europe.²² The 28-day mortality was 20.0% (95%
11 confidence interval 18.7%-21.4%) in 3285 patients receiving dialysis, and 19.9% (17.5%-22.5%) in 1013
12 recipients of a kidney transplant. Mortality risk was 1.28 (1.02-1.60) times higher in transplant recipients
13 compared with age and sex matched dialysis patients. In both groups mortality is, for a large part, related
14 to age and in dialysis patients also to frailty status).²³ In addition frequent hospital attendance, as is
15 needed for in-centre dialysis, may increase the risk of infection for ESKD patients.²⁴

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18 A missing piece of information is quantification of the risk conveyed by pathological
19 albuminuria. This may be the sole criterion that can define CKD when eGFR is ≥ 60 ml/min/1.73 m² or
20 may further increase risk in CKD patients with a lower eGFR. Interestingly, COVID-19 itself may result
21 in glomerular injury, evidenced by the occurrence of proteinuria that can be associated with acute kidney
22 injury.²⁵ In turn, acute kidney injury can lead to CKD, and when superimposed on CKD it increases the
23 risk for mortality conveyed by CKD even further (REFS).^{26, 27} These data also indicate that SARS-CoV-2
24 has multiorgan tropism that includes glomerular, but as it later showed, also tubular cells.^{28, 29}

35 36 37 **End-stage kidney disease and the need for specific studies**

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39 Emerging data revealed risk factors for severe COVID-19 among patients on kidney replacement therapy.
40 The ERACODA cohort, established by the ERA-EDTA, showed that within dialysis and kidney
41 transplant populations the risk conferred by classical risk factors for severe COVID-19 is completely
42 different than in the general population.²³ For instance, in dialysis patients with COVID-19 (n=768, of
43 which 192 (25%) died), the relative contribution of age to mortality is considerably less than in subjects
44 from the general population. In addition, in dialysis patients male sex, hypertension, coronary artery
45 disease and diabetes do not confer an independent increased risk of mortality (**Figure 4**).

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48 The mortality rates in dialysis and transplant cohorts clearly demonstrate that these are high risk
49 populations;^{22,23} given the discrepancies between risk factors in this population as compared with the
50 general population,²³ findings in the general population cannot and should not be extrapolated to end-
51 stage kidney disease populations. There are other compelling reasons why the CKD population merits
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3 specific study. During the last two decades it has become clear that some drugs which are effective in
4 patients with normal kidney function, have little or no efficacy in patients with impaired kidney function,
5 especially in those on dialysis. This holds true for, amongst others, statins.³⁰ Medications to be prescribed
6 to lower COVID-19 morbidity and mortality must therefore be tested in patients with impaired kidney
7 function to prove their efficacy in this patient category. Unfortunately, randomized clinical trials often
8 exclude patients with impaired kidney function because of safety reasons.¹⁰ It is our recommendation that
9 the kidney community should take great care to include CKD patients in COVID-19 medication trials to
10 avoid disparity in the treatment of this patient group. A first step in achieving this, is propagating
11 awareness on the importance of CKD as key risk factor among the general community and policy makers,
12 so that the problem is recognized. Furthermore, we know that because of the immunosuppressive nature
13 of the uremic milieu in dialysis patients, and because of the use of immunosuppressants in transplantation
14 patients, these patients respond poorly to vaccination.³¹ It is imperative, therefore, that CKD patients are
15 included in trials testing the efficacy of vaccines against SARS-CoV-2 infection. It is very plausible that
16 in such patients different vaccination schedules may be necessary (e.g. a higher dose or repeat
17 vaccinations).

33 **Conclusions**

34 Although not listed in initial reports as risk factor for severe COVID-19, CKD has emerged not only as
35 the most prevalent comorbidity conveying an increased risk for severe COVID-19, but also as the
36 comorbidity which conveys the highest risk for severe COVID-19. The increased risk is evident below
37 the threshold of eGFR that defines CKD and the risk increases as the eGFR decreases, with the highest
38 risk in patients on kidney replacement therapy. Although CKD patients are known to be at increased risk
39 of death due to infectious diseases, the factors contributing to their higher vulnerability for severe
40 COVID-19 should be explored, as they may provide valuable insight into therapeutic approaches to the
41 disease in this patient group. It is presently unknown if earlier categories of CKD (G1/G2, i.e. patients
42 with preserved kidney function but with increased albuminuria) are also at an increased risk of severe
43 COVID-19 and this must be explored. Moreover, the recognition that CKD significantly contributes to
44 the severity of COVID-19 should now result in focused efforts to improve outcomes of the 850 million
45 global CKD patients.⁸ Paramount to this is the enrollment of patients representing all CKD stages,
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3 including dialysis and transplantation, in clinical trials of vaccines to prevent, and drugs to treat COVID-
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7 Crucially, a CKD diagnosis should not be used as the sole criterion to deny intensive care
8 admission with severe COVID-19. Both scientific societies and patient associations should be vigilant in
9 this regard. Until better epidemiological data become available and the biological basis of the increased
10 risk of severe COVID-19 in CKD patients is ascertained, therapeutic nihilism may continue to play a role
11 and CKD patients may be denied vital support based on their increased risk of COVID-19-related death.
12 This becomes an unacceptable self-fulfilling prophecy. The threatening shortage of ICU capacity in some
13 parts of the world may have contributed to the high mortality of CKD patients in these areas. In those
14 with kidney disease, therapeutic nihilism has been repeatedly associated with adverse outcomes.¹¹ Facing
15 an ongoing pandemic of unquantifiable duration, this is not an acceptable strategy, particularly not
16 considering the high prevalence of CKD. We propose that those with CKD must be actively included in
17 research to ensure equitable access to effective vaccines and treatments in the future.
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30 **Author responsibility.**

31 The present article was conceptualized by AO and RTG, who also wrote the first draft of the manuscript.
32 All co-authors were involved with revising the work, and provided important intellectual content. All
33 authors have seen and approved the submitted version of the manuscript and can be hold accountable for
34 all aspects of the work.
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41 **Acknowledgments**

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43 for providing data on COVID-19 mortality for analyses by the ERACODA collaboration (Hilbrands et
44 al)²³ and the ERA-EDTA Registry (Jager)²².
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Conflict of interest

None declared.

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Box 1. Background why Chronic Kidney Disease is important for the COVID-19 pandemic, resultant clinical and research consequences, and action points.

Background

- A. CKD is among the most prevalent conditions that increase the risk of severe COVID-19
- B. CKD is the condition that is most strongly associated with the risk of severe COVID-19.
- C. Particularly in advanced CKD, the normal risk factors for severe COVID-19 are less important.
- D. Patients with advanced CKD may be at additional increased risk of SARS-CoV-2 infection because of frequent hospital attendance.
- E. A CKD diagnosis may be missed by physicians, especially in environments in which eGFR is not calculated automatically from serum creatinine by clinical laboratories and where albuminuria is not routinely measured.

Clinical and research consequences, and related action points.

1. The study of the immune and inflammatory response to SARS-CoV-2 in CKD patients may provide clues to the pathogenesis of COVID-19 and successful treatments for CKD patients with COVID-19.

Action point: Research into the immune and inflammatory response to SARS-CoV-2 at different stages of CKD should be encouraged

2. The impact of increased albuminuria on COVID-19 severity in patients with eGFR categories G1 and G2 and also G3-G5 should be studied

Action point: Epidemiological research should be stimulated to clearly define the role of CKD, including elevated albuminuria, as a risk factor for severe COVID-19.

Action point: Consideration should be given to making testing for proteinuria/albuminuria mandatory for all individuals who test positive for COVID-19 and are admitted to hospital

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5 3. Patients with CKD have a high risk of COVID-19 related complications, including mortality.
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7 Notwithstanding, at least about 70-75% (in ESKD) of the CKD patients survive.
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9 *Action point:* CKD diagnosis should not be used as sole criterion to deny vital supportive care
10 to CKD patients with severe COVID-19
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12 *Action point:* Once CKD is identified, consider prompt transfer to a higher level of care
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16 4. Risk factors for COVID-19 mortality cannot be extrapolated from the general population to the CKD
17 population.
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19 *Action point:* Epidemiological research should be encouraged to investigate which factors can
20 be of help to triage which CKD patients will benefit most from more invasive treatment,
21 including vital support care.
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27 5. Patients of all CKD categories should be represented in vaccine and drug trials, including patients on
28 maintenance hemodialysis and those with a kidney transplant.
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30 *Action point:* Actively encourage the inclusion of CKD patients in vaccine and drug trials
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Figures

Figure 1. Global prevalence of key underlying conditions associated with severe COVID-19 if infected. Prevalence by age. The four most prevalent risk factors have been selected and ranked from left to right according to highest global prevalence at any age range (bold black line). Grey lines represent individual countries. Data from Clark et al.⁵

Figure 2. Risk factors for COVID-19 related death. Graph shows the five medical conditions associated with the highest Hazard Ratio of death, and, additionally, the risk associated with CKD G3 and the risk associated with the risk factors recognized early in the pandemic as associated with severe COVID-19 (diabetes, chronic heart disease and hypertension, in black). In red, conditions of nephrological interest. Light blue represents non-kidney risk factors present in less than 100 individual. Data derived from Williamson et al.⁴ Patients with CKD G4 G5 have an eGFR <30 ml/min/1.73 m² and patients with CKD G3 an eGFR 30-60 ml/min/1.73 m².

Figure 3. CKD as a risk factor for COVID-19 related death in type 1 (T1DM) and type 2 (T2DM) diabetic patients in general practice. A) Adjusted hazard ratios (HR) for COVID-19-related death according to type of diabetes and eGFR range. **B)** Adjusted hazard ratios (HR) for COVID-19-related death according to type of diabetes, age and eGFR range. eGFR ≥ 90 ml/min/1.73m² was the reference for both graphs and was considered to be 1 in each of the categories (T1DM, T2DM and age categories within) assessed. * p<0.0001 vs eGFR ≥ 90 ml/min/1.73m²; + non-overlapping 95% CI vs eGFR ≥ 90 ml/min/1.73m² (Data derived from Holman et al.²¹).

Figure 4. Risk factors for COVID-19 related death. Left graph shows the situation in subjects of the general population (as derived from the Open Safely study, data from Williamson) and the right graph the

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3 situation in patients with end-stage kidney disease treated by maintenance hemodialysis (as derived from
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5 the ERACODA cohort), data derived from Hilbrands et al.²³
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For Peer Review

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3 **Supplementary material**
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9 **Supplementary File 1.** List of collaborative authors on behalf of the Council of the European Renal
10 Association (ERA) and the Working Group of the European Renal Association CCOVID-19 Database
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12 (ERACODA)
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18 **Supplementary Figure 1.** Distribution of risk factors for severe COVID-19 in the world.
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Figure

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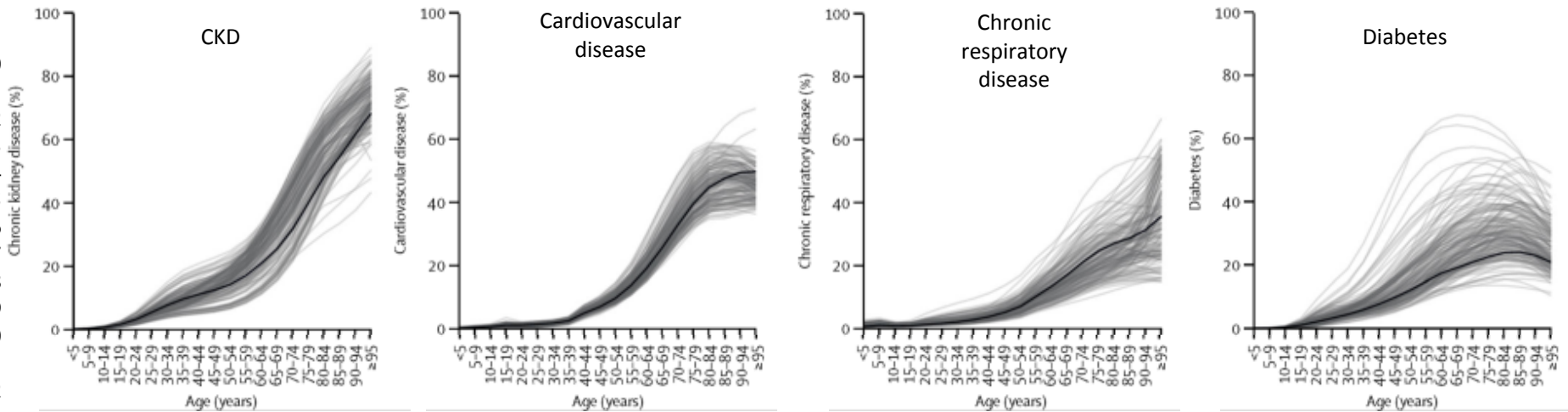
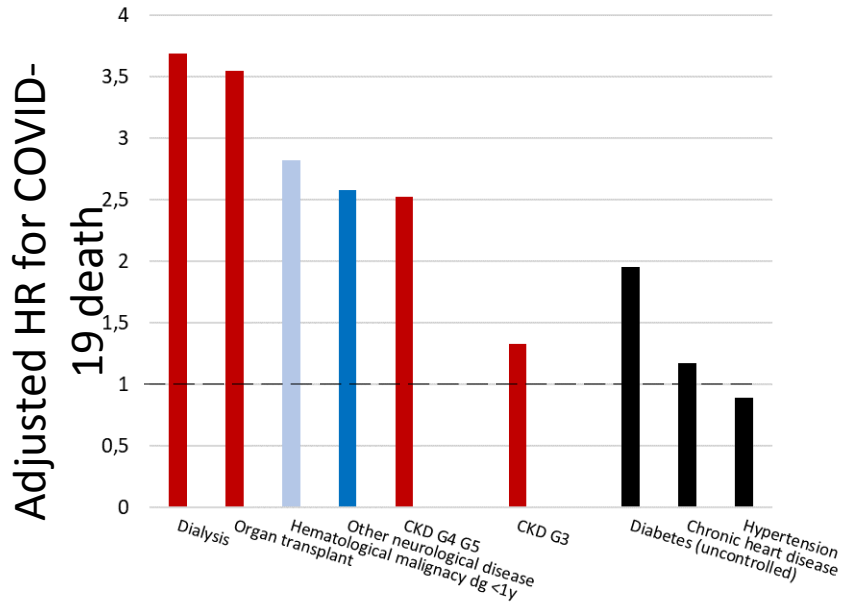


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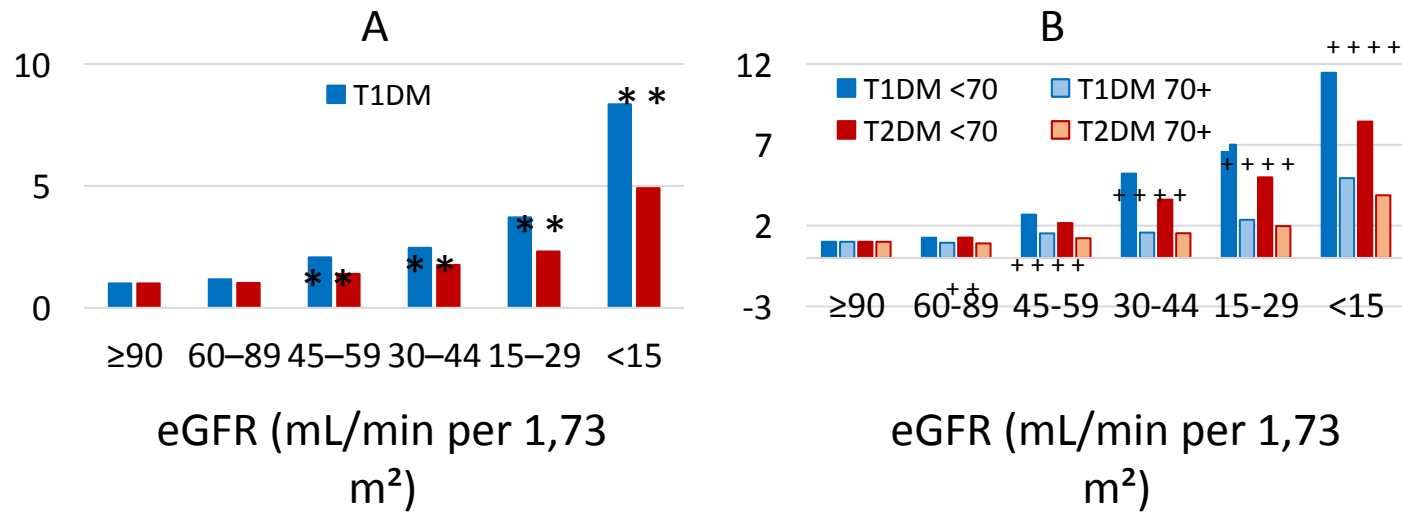
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27 **Figure 2. Risk factors for COVID-19 death.** Graph shows the five medical conditions associated with the highest Hazard Rate of death, and, additionally, the risk
28 associated with CKD G3 and the risk associated with the risk factors recognized early in the pandemic as associated with severe COVID-19 (diabetes, chronic heart
29 disease and hypertension, in black). In red, conditions of nephrological interest. Light blue represents non-kidney risk factors present in less than 100 individual.
30 Data derived from Williamson et al⁵. Patients with CKD G4 G5 have an eGFR<30 ml/min/1.73 m² and patients with CKD G3 an eGFR 30-60 ml/min/1.73 m².

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28 **Figure 3. CKD as a risk factor for COVID-19-related death in type 1 (T1DM) and type 2 (T2DM) diabetic patients in general practice. A)** Adjusted hazard
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32 derived from Holman et al.²¹
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Figure 4

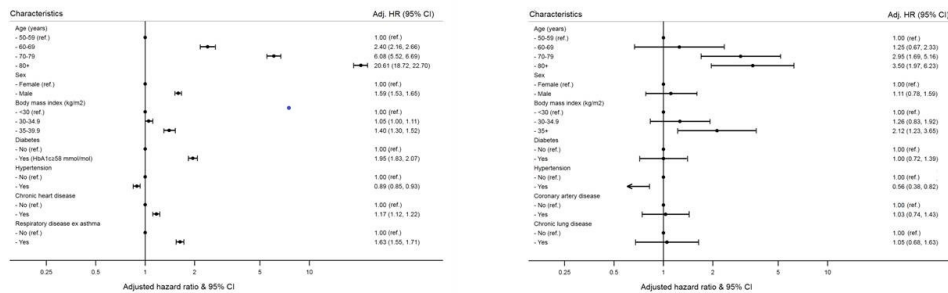


Figure 4. Risk factors for COVID-19 death. Graph shows on the left the situation in subjects of the general population (as derived from the Open Safely study, data from Williamson et al.⁵) and on the right the situation in patients with end-stage kidney disease treated by maintenance hemodialysis (as derived from the ERACODA cohort, data from Hilbrands et al.²³).

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338x190mm (96 x 96 DPI)