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Emilie J. Lambourg, Peter J. Gallacher, Robert W. Hunter, Moneeza Siddiqui, Eve Miller-Hodges, James Chalmers, Dan Pugh, Neeraj Dhaun, Samira Bell

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ORIGINAL INVESTIGATION

Cardiovascular outcomes in patients with chronic kidney disease and COVID-19: a multi-regional data-linkage study

Emilie J. Lambourg*, PharmD,[1] Peter J. Gallacher*, MBChB MPH,[2] Robert W. Hunter, MBChB PhD,[2,3] Moneeza Siddiqui, PhD,[1] Eve Miller-Hodges, MBChB PhD,[2,3] James Chalmers, MBChB PhD,[4] Dan Pugh, MBChB,[3] Neeraj Dhaun†, MBChB PhD,[2,3] Samira Bell†, MBChB MD[1]

[1] Division of Population Health and Genomics, University of Dundee, Dundee, UK

[2] BHF/University Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

[3] Department of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK

[4] Department of Molecular and Clinical Medicine, University of Dundee, Dundee, UK

*These authors contributed equally

†These authors contributed equally

Corresponding author:

Dr. Neeraj Dhaun *(Bean)*

BHF/University Centre for Cardiovascular Science

University of Edinburgh

Edinburgh EH16 4SA

United Kingdom

E-mail: bean.dhaun@ed.ac.uk

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Abstract

Background: Data describing cardiovascular outcomes in patients with COVID-19 and chronic kidney disease (CKD) are lacking. We compared cardiovascular outcomes of patients with and without COVID-19, stratified by CKD status.

Methods: This retrospective, multi-regional data-linkage study utilised individual patient-level data from two Scottish cohorts. All patients tested for SARS-CoV-2 in Cohort 1 between 01/02/2020 and 31/03/2021, and in Cohort 2 between 28/02/2020 and 08/02/2021, were included.

Results: Overall, 86,964 patients were tested for SARS-CoV-2. There were 36,904 patients (61±21 years, 58.1% women, 15.9% CKD, 10.1% COVID-19 positive) in Cohort 1 and 50,060 patients (63±20 years, 62.0% women, 16.4% CKD, 9.1% COVID-19 positive) in Cohort 2. In CKD patients, COVID-19 increased the risk of cardiovascular death by more than two-fold within 30 days (cause-specific hazard ratio [csHR] meta-estimate 2.34, 95% confidence interval [CI] 1.83-2.99), and by 57% at the end of follow-up (csHR meta-estimate 1.57, 95% CI 1.31-1.89). Similarly, the risk of all-cause death in COVID-19 positive *versus* negative CKD patients was greatest within 30 days (HR 4.53, 95% CI 3.97-5.16). Compared to patients without CKD, those with CKD had a higher risk of testing positive (11.5% *versus* 9.3%). Following a positive test, CKD patients had higher rates of cardiovascular death (11.1% *versus* 2.7%), cardiovascular complications, and cardiovascular hospitalisations (7.1% *versus* 3.3%) than those without CKD.

Conclusions: COVID-19 increases the risk of cardiovascular and all-cause death in CKD patients, especially in the short-term. CKD patients with COVID-19 are also at a disproportionate risk of cardiovascular complications than those without CKD.

Introduction

Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),[1] has had an unprecedented public health, societal and economic impact. Disease severity in patients with COVID-19 can vary markedly, from no symptoms or a mild respiratory illness, to life-threatening pulmonary and extra-pulmonary complications and death.[2] Several factors have been identified that increase disease severity. These include older age, male sex, social deprivation, obesity, and comorbidities such as cardiovascular disease and chronic kidney disease (CKD).[3-8] The risk of critical illness and death following COVID-19 increases as kidney function declines, such that patients with the most advanced CKD have the poorest outcomes.[4, 9-11]

The commonest complication of CKD is cardiovascular disease.[12] As estimated glomerular filtration rate (eGFR) declines, the risk of cardiovascular disease and major adverse cardiovascular events increases.[13] Whilst pre-existing cardiovascular disease is a risk factor for COVID-19 severity, several studies have also suggested that myocardial injury and cardiovascular complications are common following COVID-19 and associated with worse outcomes for these patients.[14-16] However, data describing the nature and frequency of cardiovascular outcomes in patients with CKD and COVID-19 are lacking. Specifically, it is unclear how COVID-19 modifies the existing cardiovascular risk in patients with CKD in the short- and medium-term. In this unique multi-regional data-linkage study, we evaluated the clinical characteristics and cardiovascular outcomes of patients with and without COVID-19, stratified by the presence or absence of CKD.

Methods

Patient population and study design

We conducted a retrospective, multi-regional study utilising linked individual patient-level data from two cohorts in Scotland, United Kingdom. All SARS-CoV-2 polymerase chain reaction tests performed during the relevant time periods described for each cohort were included, regardless of whether they were from a hospital or community setting, and irrespective of their indication (e.g. clinical, screening, or research). Each patient's index COVID-19 status was defined as follows: *1)* **COVID-19 positive** – where a patient first recorded a positive SARS-CoV-2 test result, they were included as an index positive episode occurring on that date. In this sub-population, prior or subsequent negative SARS-CoV-2 test results within the study period were excluded, as were subsequent positive SARS-CoV-2 test results. *2)* **COVID-19 negative** – where a patient first recorded a negative SARS-CoV-2 test result, but in the *absence* of any prior or subsequent positive test result, they were included as an index negative episode occurring on that date. In this sub-population, subsequent negative SARS-CoV-2 test results were also excluded. The date of each index positive or negative episode was assigned as the index date.

Study cohorts

Cohort 1

All patients who had a SARS-CoV-2 test in the NHS Lothian Health Board between 02/01/2020 and 03/31/2021 were identified. Positive and negative COVID-19 episodes were linked with regional electronic patient and biochemistry records and national hospitalisation, dispensed community prescription and death records within the DataLoch Repository and Safe Haven (*University of Edinburgh*/NHS Lothian, Scotland) (**Appendix**).

Cohort 2

All patients who had had a measure of serum creatinine in the NHS Fife or Tayside Health Boards since 04/01/2009, and subsequently had a SARS-CoV-2 test between 02/28/2020, and 02/08/2021, were identified. Positive and negative COVID-19 episodes were defined as for Cohort 1 before being linked with national hospitalisation, dispensed community prescription, and death

records within the Health Informatics Centre Safe Haven (*University of Dundee*/NHS Fife and Tayside, Scotland) (**Appendix**).[17]

Determination of patient demographics, CKD status, comorbidities and causes of death

Patient age, sex and socio-economic status were determined from linked hospitalisation records. Socio-economic status was defined according to the Scottish Index of Multiple Deprivation – a validated measure of social deprivation determined by factors related to residential address (zip code) (**Appendix**).[18] CKD status was determined at the time of index SARS-CoV-2 test utilising the same, previously validated criteria for both study cohorts.[19] eGFRs were calculated for all serum creatinine results using the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation.[20] CKD was defined when a patient's most recent eGFR was <60 ml/min/1.73m^2 and at least one value obtained >90 days prior was also <60 ml/min/1.73m^2. Using the eGFR value closest to the index date for each patient, CKD stage was classified according to '*Kidney Disease: Improving Global Outcomes*' guidelines.[21] Patients with kidney failure requiring kidney replacement therapy (i.e. haemodialysis, peritoneal dialysis or kidney transplantation) were identified from record linkage with regional or national renal registries (Cohort 1 – VitalData; Cohort 2 – Scottish Renal Registry). Those patients with only a single measure of eGFR <60 ml/min/1.73m^2 prior to their index test were excluded (**Supplementary Figure 1**).

Patient comorbidities (i.e. angina, atrial fibrillation, cancer, chronic liver disease, chronic lower respiratory disease, heart failure, myocardial infarction, and stroke) were defined from International Classification of Diseases (ICD) codes associated with hospitalisations during a 5-year 'lookback' period prior to the index SARS-CoV-2 test (**Appendix**). Diabetes status was obtained *via* record linkage with a national diabetes registry (Scottish Care Information – Diabetes Collaboration).[22] History of prescribed medications was determined from the community prescribing records of individual patients during the 6 months preceding their index SARS-CoV-2 test. Causes of death were determined following the identification of relevant ICD codes in linked National Records of Scotland death records (**Appendix**).

Study follow-up and outcomes

Patients were followed-up from the index date until either their date of death or April 30, 2021 (Cohort 1) or May 20, 2021 (Cohort 2), whichever came first. For both study cohorts, information relating to primary and secondary causes of death was obtained *via* record linkage with the National Records of Scotland death registry (**Appendix**). Primary outcomes included cardiovascular, COVID-19-related, and all-cause death. Secondary outcomes included subsequent fatal and non-fatal myocardial infarction, heart failure or stroke, hospitalisation for cardiovascular diagnoses, hospitalisation for any reason and length of hospital stay. For each cohort, outcomes were reported at 30 days, 90 days and to the end of follow-up.

Statistical analysis

Summary statistics

Baseline clinical characteristics and crude outcomes for all index SARS-CoV-2 tests included in each cohort were summarised according to CKD and COVID-19 status. Continuous variables were presented as medians and interquartile ranges and categorical variables were presented as percentages. Where appropriate, groupwise comparisons were performed using Chi-square tests.

Covariate-balanced propensity scoring and regression modelling

With the aim of obtaining unconfounded estimates, we utilised a 'doubly-robust' estimator with bootstrapped standard errors and 95% confidence intervals in our evaluation of the primary outcomes (**Appendix**).[23] This approach combines a multivariable outcome regression model with weighting by the covariate-balanced propensity score (CBPS). For the primary analysis, Cox regression was used to explore the association between COVID-19 status (the primary exposure) and cardiovascular and all-cause death (the primary outcomes). For the secondary analysis, Cox regression was used to explore the association between CKD status (the primary exposure) and cardiovascular, COVID-19 and all-cause death (the primary outcomes). Confounders were specified *a priori* and included age, sex, socio-economic status, comorbidities (i.e. angina, myocardial infarction, heart failure, stroke, diabetes, cancer, chronic respiratory disease, chronic liver disease) and selected current medication (ACE-inhibitors/ARBs, immunosuppressant therapy)

based on their potential relevance to COVID-19 outcomes.[24, 25] For each primary outcome, hazard ratios derived from CBPS-weighted, adjusted multivariable models in individual cohorts were pooled using a fixed-effects model to obtain an overall meta-estimate (**Appendix**). Finally, a sensitivity analysis was also performed to evaluate the effect of restricting the cohorts to those patients not hospitalised either in the week before or in the two weeks following their index COVID-19 test. All data were analysed using the R statistical programming language (Version 3.6.2, Vienna, Austria).

Ethical approval

The study was performed with the approvals of local Research Ethics Committees and delegated Caldicott Guardians for the NHS Fife, Lothian, and Tayside Health Boards, in accordance with the Declaration of Helsinki (**Appendix**). Data provision and linkage were carried out by the DataLoch (University of Edinburgh/NHS Lothian, https://www.dataloch.org/) and University of Dundee Health Informatics Centre (HIC, https://www.dundee.ac.uk/hic) within ISO27001 and Scottish Government accredited secure Safe Havens for Cohorts 1 and 2, respectively. Patient consent was not sought as the study utilised fully-anonymised data. Our analysis code is publicly available here.

Results

Study cohorts

In total, 86,964 of 102,894 (84.5%) patients tested for SARS-CoV-2 were included in the study (**Supplementary Figure 1**). There were 36,904 patients (61±21 years; 58.1% women) in Cohort 1 and 50,060 patients (63±20 years; 62.0% women) in Cohort 2. Overall, the distribution of patient demographics and clinical characteristics between each cohort was similar. CKD was present in 15.9% (5,853/36,904) of patients in Cohort 1 and 16.4% (8,201/50,060) of patients in Cohort 2 (**Supplementary Table 1**), whilst a positive SARS-CoV-2 test was recorded in 10.1% (3,731/36,904) and 9.1% (4,556/50,060) of patients in Cohorts 1 and 2, respectively (**Supplementary Table 2**). In both cohorts, CKD was commoner in patients with COVID-19 than in those without (Cohort 1: 19.7% *versus* 15.4%; Cohort 2: 19.0% *versus* 16.1%).

Baseline characteristics of patients with CKD according to COVID-19 status

In patients with CKD, those with COVID-19 were older and more socially deprived than those without COVID-19 (**Table 1**). Although SARS-CoV-2 testing was performed more frequently in women than in men with CKD (Cohort 1: 53.8% *versus* 46.2%; Cohort 2: 59.5% *versus* 40.5%) (**Supplementary Table 3**), the proportion of women testing positive and negative was similar (Cohort 1: 52.3% *versus* 54.0%; Cohort 2: 58.0% *versus* 59.7%) (**Table 1**). Patients with CKD who tested positive had higher rates of cardiovascular comorbidity but similar eGFR compared to patients who tested negative. Despite this, across both cohorts, patients with CKD who tested positive were less likely to be prescribed an ACE-inhibitor or ARB at the time of their index SARS-CoV-2 test than those who tested negative (Cohort 1: 35.8% *versus* 41.5%; Cohort 2: 25.2% *versus* 36.7%) (**Table 1**). The baseline characteristics of patients without CKD summarised according to COVID-19 status (**Table 1**), and of patients with and without COVID-19 summarised according to CKD status (**Supplementary Table 4**), are described in the **Supplementary Results**.

Outcomes of patients with CKD according to COVID-19 status

In patients with CKD, the crude rate of cardiovascular death at 30 days in those with COVID-19 was double that of patients without COVID-19 (Cohort 1: 7.8% *versus* 3.4%; Cohort 2: 7.2% *versus*

3.5%) (**Table 2; Figure 1a; Supplementary Table 5**). After balancing differences in covariates between positive and negative patients (**Supplementary Figure 2**) – and following adjustment for confounders – this increase in short-term cardiovascular risk persisted and was more than two-fold higher in positive than in negative patients at 30 days (cause-specific hazard ratio [csHR] meta-estimate 2.34, 95% confidence interval [CI] 1.83 to 2.99) (**Figure 2a**). By the end of study follow-up, the difference in cardiovascular risk between positive and negative patients with CKD had narrowed (csHR meta-estimate 1.57, 95% CI 1.31 to 1.89) (**Figures 1a & 2a**).

In patients with CKD, the risk of all-cause death at 30 days in those with COVID-19 was substantially higher than in those without COVID-19 (Cohort 1: 35.4% *versus* 8.6%; Cohort 2: 34.9% *versus* 8.8%) (**Table 2; Figure 1b; Supplementary Table 5**). In the fully adjusted models, the risk of all-cause death in patients with CKD and COVID-19 was increased more than four-fold at 30 days (HR meta-estimate 4.53, 95% CI 3.97 to 5.16), and by more than two-fold overall (HR meta-estimate 2.41, 95% CI 2.17 to 2.64) compared to those with CKD testing negative. In contrast, cardiovascular complications and subsequent hospitalisations were lower in positive than in negative patients with CKD at 30 days, 90 days and to the end of study follow-up (**Table 2**).

In a sensitivity analysis restricted to patients with CKD not hospitalised either in the week before or in the two weeks following their index COVID-19 test, overall rates of cardiovascular and all-cause death were lower than those reported in the primary analysis (**Supplementary Table 6**). However, COVID-19 was associated with a significantly increased risk of cardiovascular and all-cause death at all time points, especially in the short-term – a pattern which was comparable to the primary analysis (**Supplementary Table 7**).

Outcomes of patients with COVID-19 according to CKD status and eGFR

In patients with COVID-19, those with CKD had a higher risk of cardiovascular death than those without CKD (csHR meta-estimate 1.64, 95% CI 1.29 to 2.10) (**Supplementary Table 8; Supplementary Figures 3 & 4**). Similarly, CKD was associated with a significantly increased risk of all-cause death in patients testing positive (csHR meta-estimate 1.25, 95% CI 1.12 to 1.41) (**Supplementary Table 8; Supplementary Figures 3 & 4**). When eGFR was analysed as a

continuous variable, the risk of both cardiovascular and all-cause death increased as kidney function declined (**Supplementary Figure 5**).

In patients with COVID-19, CKD was associated with an increased risk of COVID-19-related death (csHR meta-estimate 1.27, 95% CI 1.12 to 1.43) (**Supplementary Table 8 & Supplementary Figure 6**). Again, the risk of COVID-19-related death increased significantly as eGFR declined, even after adjustment for confounders (**Supplementary Figure 7**). Rates of cardiovascular complications and subsequent hospitalisations were also higher in COVID-19 positive patients with CKD than without (**Supplementary Table 8**).

The outcomes of patients without CKD summarised according to COVID-19 status (**Table 2; Figures 1a & 2a**), and of patients without COVID-19 summarised according to CKD status and eGFR (**Supplementary Table 8; Supplementary Figures 3 & 4**), are described in the **Supplementary Results**.

Discussion

In this multi-regional data-linkage study, we utilised a robust statistical approach combining multivariable outcome regression with propensity score weighting to evaluate the outcomes of ~87,000 patients with and without CKD tested for SARS-CoV-2. Overall, one-in-ten patients had a positive SARS-CoV-2 test. In patients with CKD, those with COVID-19 had a higher risk of cardiovascular and all-cause death than those without COVID-19 throughout follow-up, but especially within 30 days of SARS-CoV-2 testing. During this early period, patients with CKD and COVID-19 had a more than two-fold increased risk of cardiovascular death – and a more than four-fold increased risk of all-cause death – than CKD patients testing negative. Compared to patients without CKD, those with CKD were also more likely to test positive. Following a positive test, CKD patients had higher rates of cardiovascular complications, including hospitalisations, and cardiovascular death than those without CKD. Moreover, the risks of cardiovascular, COVID-19-related, and all-cause death increased as kidney function declined.

Our study has several strengths. First, its multi-regional design combined high-fidelity, high-quality Scottish linked healthcare data from patients undergoing community *and* hospital-based SARS-CoV-2 testing in three large NHS Health Boards (which together provide care for ~1.7 million people), irrespective of age, sex, socio-economic, kidney function, or hospitalisation status. Thus, the influence of case selection bias on our patient cohorts was minimised. Moreover, the accuracy and completion rates of the data sources used in this study were recently reported as 96%[26] and 99%,[27] respectively. Second, we utilised routinely-collected biochemistry data and criteria previously validated in electronic health records[19] to determine baseline kidney function, reducing the potential for misclassification of CKD status. Third, our inclusion of control populations – COVID-19 negative patients and patients without CKD – alongside our use of a 'doubly-robust' estimator (concomitant multivariable outcome regression and weighting by the propensity score), limited the influence of confounding bias in our analyses.[23, 28]

Whilst the majority of patients with COVID-19 are considered to have increased cardiovascular risk,[29] few studies have examined the nature or extent of this risk in patients with CKD.[30] This is

important given the well-recognised association between cardiovascular disease and CKD.[12, 13] Here, in ~14,000 non-hospitalised and hospitalised patients with CKD tested for SARS-CoV-2, we found that COVID-19 more than doubled the risk of cardiovascular death within 30 days, and by 57% overall. Our secondary analysis showed that patients with COVID-19 and CKD had an increased risk of fatal and non-fatal myocardial infarction, heart failure and stroke compared to patients with COVID-19 but no CKD. In an adjusted model, CKD was also associated with a 64% increased risk of cardiovascular death in patients with COVID-19. In contrast, Rao and colleagues investigated the risk of cardiovascular complications in patients with COVID-19 but found no increase in risk in patients with CKD compared to those without CKD.[31] However, this study excluded non-hospitalised patients and patients who had tested negative for SARS-CoV-2, and relied on manual case note review to determine CKD status.

Our data add to the literature on COVID-19 outcomes in high-risk populations. However, a novel aspect of our approach is the inclusion of patients with CKD who tested negative for SARS-CoV-2. Of the few studies that have included such patients, all have identified COVID-19 as being strongly associated with a poor prognosis. Indeed, a recent meta-analysis found that COVID-19 increased the odds of death approximately six-fold in patients with CKD.[32] This is more in-line with the risk of all-cause death we report in patients with CKD and COVID-19 at 30 days post-index test, consistent with the fact that most studies included in this meta-analysis reported in-hospital mortality only. Thus, our study is unique in reporting both short- *and* medium-term patient outcomes. Our study is also less biased towards severe COVID-19 as we included both non-hospitalised and hospitalised patients, making our results more accurate, representative, and informative for patients with all severities of CKD and COVID-19.

We found that, compared to patients without CKD, those with CKD were more likely to test positive for COVID-19. Thereafter, patients with COVID-19 and CKD had higher rates of fatal and non-fatal myocardial infarction, heart failure and stroke, cardiovascular hospitalisations, and cardiovascular, COVID-19-related, and all-cause death than patients with COVID-19 but no CKD. Few studies have reported on all these aspects. Our data are consistent with reports of an increasing incidence

of COVID-19 as kidney function declines.[33, 34] A number of factors likely contribute to this increased risk of COVID-19 in CKD, including case ascertainment bias (i.e. patients with CKD are more likely to be tested for SARS-CoV-2), greater viral exposure secondary to more frequent healthcare encounters (e.g. in-centre haemodialysis),[11] and an underlying increased predisposition to infection due to altered immune response.[35]

We recognise some limitations. First, our inability to account for selected variables (e.g. body mass index, smoking status, type of atrial fibrillation [i.e. paroxysmal *versus* permanent; non-valvular or valvular]) means that we cannot exclude the potential for residual confounding. In addition, selected data relating to co-existing atrial fibrillation and prescribed cardiovascular medications were not available for patients included in Cohort 1. Second, rates of non-fatal cardiovascular complications, including atrial fibrillation and cardiovascular hospitalisations, may have been under-reported due to the competing risk of death in patients with COVID-19. Given the crude rates of non-fatal cardiovascular complications were generally higher in patients without COVID-19 suggests that this might be the case. We overcame this when evaluating cardiovascular and COVID-19-related death by calculating cause-specific hazard ratios from our regression models. Third, we excluded patients with no record of kidney function and those with only a single eGFR <60 ml/min/1.73 m^2 during the biochemistry 'lookback' period. Consequently, young or less comorbid patients – who are less likely to have had their kidney function tested – may be relatively under-represented. Finally, those patients with CKD who tested negative for SARS-CoV-2 were a relatively 'sick' control group; their all-cause mortality was substantially higher than might be expected for the CKD population in general.[36] One explanation for this is that SARS-CoV-2 PCR testing was largely restricted to the in-hospital setting for much of the early phase of the COVID-19 pandemic in the UK.[37] To address this issue – and to illustrate the effect of including a more widely representative control group – we performed a sensitivity analysis restricted to those patients not hospitalised either in the week before or in the two weeks following their index COVID-19 test, and demonstrated a similar pattern of increased risk of cardiovascular and all-cause death in patients with COVID-19 compared to those without.

Conclusions

Our unique and comprehensive analysis suggests that COVID-19 significantly increases the risk of cardiovascular complications and death in patients with CKD, especially in the short-term. There is an urgent need to prioritise COVID-19 vaccination and cardiovascular risk reduction strategies in all patients with CKD.

Acknowledgements

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Conflicts of Interest

The authors have nothing to disclose.

Author contributions

EL, PJG, RWH, ND and SB conceived the study. PJG, RWH and ND contributed to the design and collection of data relating to Cohort 1; EL and SB contributed to the design and collection of data relating to Cohort 2. Data analysis was completed by EL and PJG. Interpretation and drafting of the manuscript were conducted by EL, PJG, ND and SB. All authors critically reviewed the manuscript and approved the final version.

Table Legends

Table 1. Clinical characteristics of patients included in Cohorts 1 and 2, grouped according to CKD and COVID-19 status.

Table 2. Outcomes of patients included in Cohorts 1 and 2, grouped according to CKD and COVID-19 status.

Figure Legends

Figure 1. Survival curves for cardiovascular **(a)** and all-cause **(b)** death according to COVID-19 status (i.e. positive *versus* negative) for patients with CKD (**Panel A**: Cohort 1; **Panel C**: Cohort 2) and patients without CKD (**Panel B**: Cohort 1; **Panel D**: Cohort 2). Note: y-axis scales are different for cardiovascular and all-cause death plots.

Figure 2. Forest plot summarising adjusted hazard ratios (HR) from Cohorts 1 and 2 and associated pooled meta-estimates for cardiovascular (**a**) and all-cause death (**b**) according to COVID-19 status (i.e. positive *versus* negative) for patients with CKD (**red**) and patients without CKD (**blue**) at 30 days (**top panel**), 90 days (**middle panel**) and to the end of study follow-up (**bottom panel**).

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Table 1. Clinical characteristics of patients included in Cohorts 1 and 2, grouped according to CKD and COVID-19 status.

	COHORT 1				COHORT 2			
	CKD		No CKD		CKD		No CKD	
	COVID-19 positive	COVID-19 negative	COVID-19 positive	COVID-19 negative	COVID-19 positive	COVID-19 negative	COVID-19 positive	COVID-19 negative
Number of patients, n	**734**	**5,119**	**2,997**	**28,054**	**865**	**7,336**	**3,691**	**38,168**
Age, years	81 (11)	79 (12)	59 (21)	57 (20)	84 (10)	82 (10)	59 (20)	59 (19)
Sex								
Women	384 (52.3)	2,764 (54.0)	1,726 (57.6)	16,584 (59.1)	502 (58.0)	4,377 (59.7)	2,453 (66.5)	23,696 (62.1)
Men	350 (47.7)	2,355 (46.0)	1,271 (42.4)	11,470 (40.9)	363 (42.0)	2,959 (40.3)	1,238 (33.5)	14,472 (37.9)
SIMD quintile								
1 (most deprived)	103 (14.0)	616 (12.0)	476 (15.9)	4,263 (15.2)	162 (18.7)	1,160 (15.8)	831 (22.5)	7,522 (19.7)
2	207 (28.2)	1,280 (25.0)	795 (26.5)	6,872 (24.5)	185 (21.4)	1,391 (19.0)	747 (20.2)	7,264 (19.0)
3	113 (15.4)	920 (18.0)	532 (17.8)	4,945 (17.6)	182 (21.0)	1,491 (20.3)	665 (18.0)	7,187 (18.8)
4	112 (15.3)	889 (17.4)	519 (17.3)	4,873 (17.4)	216 (25.0)	1,977 (26.9)	905 (24.5)	9,932 (26.0)
5 (least deprived)	198 (27.0)	1,404 (27.4)	675 (22.0)	6,883 (24.5)	120 (13.9)	1,317 (18.0)	543 (14.7)	6,262 (16.4)
Co-existing medical conditions								
Angina	91 (12.4)	571 (11.2)	125 (4.2)	1,130 (4.0)	69 (8.0)	533 (7.3)	98 (2.7)	960 (2.5)
Atrial fibrillation*	-	-	-	-	207 (23.9)	1,444 (19.7)	215 (5.8)	2,003 (5.2)
Myocardial infarction	124 (16.9)	807 (15.8)	178 (5.9)	1,765 (6.3)	91 (10.5)	744 (10.1)	96 (2.6)	1,239 (3.2)
Heart failure	196 (26.7)	1,152 (22.5)	135 (4.5)	1,268 (4.5)	133 (15.4)	847 (11.5)	84 (2.3)	740 (1.9)
Stroke	127 (17.3)	704 (13.8)	257 (8.6)	1,729 (6.2)	123 (14.2)	671 (9.1)	237 (6.4)	1,454 (3.8)
Diabetes	275 (37.5)	1,819 (35.5)	491 (16.4)	3,592 (12.8)	277 (32.0)	2,388 (32.6)	589 (16.0)	5,831 (15.3)
Cancer	159 (21.7)	1,372 (26.8)	384 (12.8)	5,373 (19.2)	98 (11.3)	858 (11.7)	154 (4.2)	2,415 (6.3)
Chronic lower respiratory disease	223 (30.4)	1,418 (27.7)	809 (27.0)	7,411 (26.4)	232 (26.8)	1,877 (25.6)	634 (17.2)	7,797 (20.4)
Chronic liver disease	27 (3.7)	213 (4.2)	77 (2.6)	984 (3.5)	21 (2.4)	171 (2.3)	40 (1.1)	590 (1.5)
Renal history								
Kidney failure	35 (4.8)	302 (5.9)	-	-	29 (3.4)	211 (2.9)	-	-
Baseline eGFR	40 (14)	42 (14)	90 (19)	91 (18)	43 (12)	44 (12)	93 (18)	94 (19)
Baseline eGFR category								
≥90	-	-	1,396 (46.6)	14,090 (50.2)	-	-	2,020 (54.7)	20,764 (54.4)
60 – 89	-	-	1,601 (53.4)	13,964 (49.8)	-	-	1,671 (45.3)	17,404 (45.6)
45 – 59	314 (42.8)	2,394 (46.8)	-	-	436 (50.4)	3,828 (52.2)	-	-
30 – 44	236 (32.2)	1,632 (31.9)	-	-	270 (31.2)	2,279 (31.1)	-	-
15 – 29	118 (16.1)	669 (13.1)	-	-	105 (12.1)	809 (11.0)	-	-

≤15	66 (9.0)	424 (8.3)	-	-	54 (6.2)	420 (5.7)	-	-
Current medication								
ACE-inhibitor or ARB	263 (35.8)	2,126 (41.5)	674 (22.5)	5,959 (21.2)	218 (25.2)	2,695 (36.7)	589 (16.0)	7,171 (18.8)
Aspirin*	-	-	-	-	157 (18.1)	1,599 (21.8)	299 (8.1)	3,437 (9.0)
Other antiplatelet agent*	-	-	-	-	128 (14.8)	861 (11.7)	247 (6.7)	2,099 (5.5)
Beta-blockers*	-	-	-	-	300 (34.7)	2,655 (36.2)	497 (13.5)	5,862 (15.4)
Immunosuppressants	27 (3.7)	201 (3.9)	66 (2.2)	566 (2.0)	11 (1.3)	151 (2.1)	13 (0.4)	246 (0.6)
Loop diuretic*	-	-	-	-	303 (35.0)	2,312 (31.5)	264 (7.1)	2,553 (6.7)
Mineralocorticoid receptor antagonist*	-	-	-	-	66 (7.6)	558 (7.6)	64 (1.7)	644 (1.7)
Novel oral anticoagulant*	-	-	-	-	142 (16.4)	1,136 (15.5)	154 (4.2)	2,018 (5.3)
Warfarin*	-	-	-	-	43 (5.0)	499 (6.8)	45 (1.2)	651 (1.7)

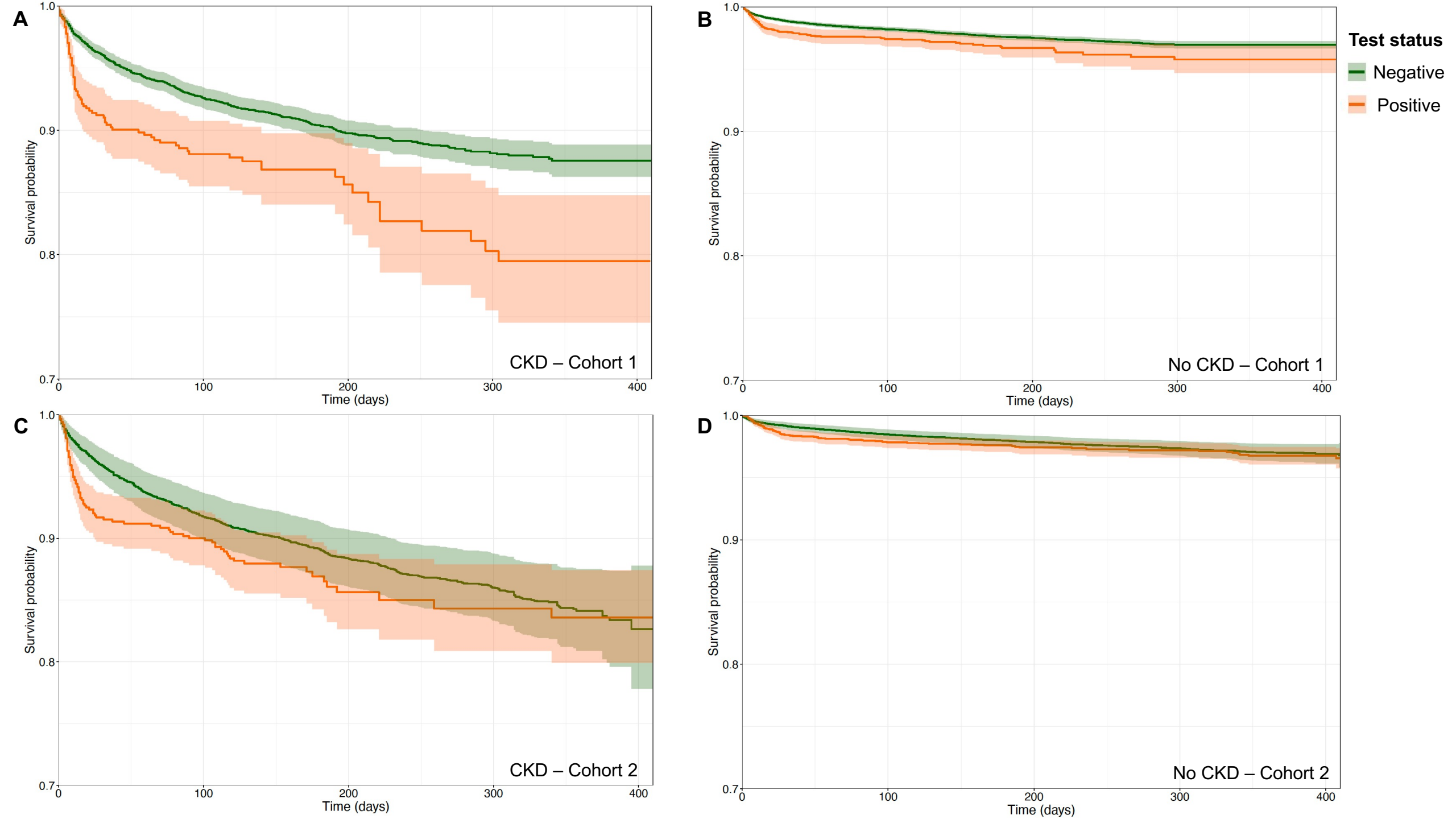
Values are mean ± SD, n (%), or median [interquartile range]. Abbreviations: ACE – angiotensin converting enzyme; ARB – angiotensin receptor blocker; CKD – chronic kidney disease (please refer to Methods section for definition of CKD status); eGFR – estimated glomerular filtration rate (ml/min/1.73 m^2); SIMD – Scottish index of multiple deprivation. *data not available for Cohort 1.

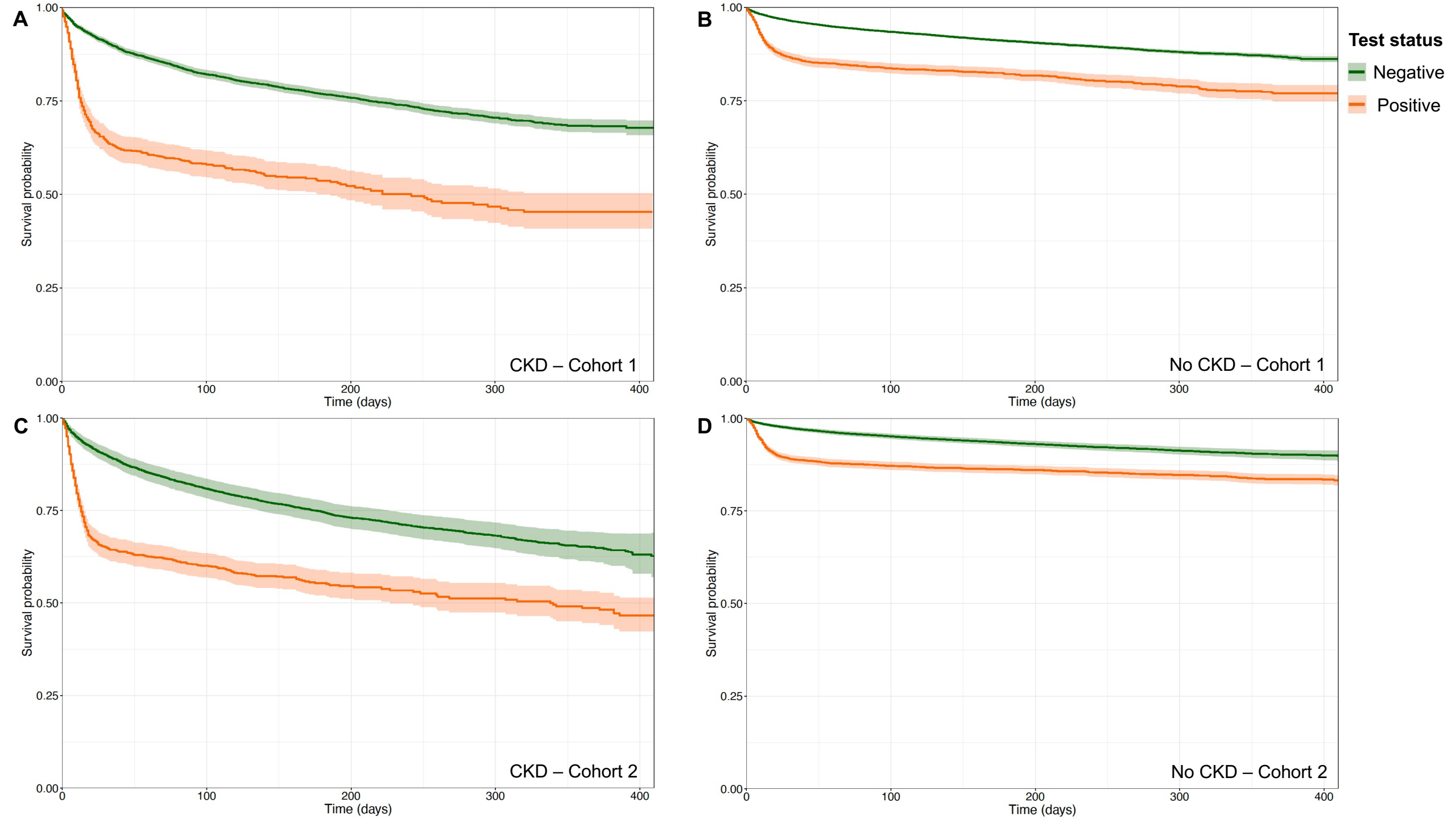
Table 2. Outcomes of patients included in Cohorts 1 and 2, grouped according to CKD and COVID-19 status.

	COHORT 1				COHORT 2			
	CKD		No CKD		CKD		No CKD	
	COVID-19 positive	COVID-19 negative	COVID-19 positive	COVID-19 negative	COVID-19 positive	COVID-19 negative	COVID-19 positive	COVID-19 negative
Number of patients, n	**734**	**5,119**	**2,997**	**28,054**	**865**	**7,336**	**3,691**	**38,168**
Primary outcomes								
Cardiovascular death								
30 days	57 (7.8)	172 (3.4)	57 (1.9)	254 (0.9)	62 (7.2)	254 (3.5)	55 (1.5)	316 (0.8)
90 days	72 (9.8)	290 (5.7)	68 (2.3)	377 (1.3)	72 (8.3)	453 (6.2)	70 (1.9)	515 (1.3)
End of study follow-up	86 (11.7)	426 (8.3)	86 (2.9)	542 (1.9)	92 (10.6)	730 (10.0)	94 (2.5)	840 (2.2)
COVID-19-related death								
30 days	250 (34.1)	-	377 (12.6)	-	295 (34.1)	-	397 (10.8)	-
90 days	267 (36.4)	-	404 (13.5)	-	313 (36.2)	-	423 (11.5)	-
End of study follow-up	270 (36.8)	-	407 (13.6)	-	318 (36.8)	-	427 (11.6)	-
All-cause death								
30 days	260 (35.4)	442 (8.6)	399 (13.3)	974 (3.5)	302 (34.9)	642 (8.8)	405 (11.0)	1,025 (2.7)
90 days	304 (41.4)	803 (15.7)	473 (15.8)	1,702 (6.1)	342 (39.5)	1,157 (15.8)	466 (12.6)	1,782 (4.7)
End of study follow-up	346 (47.1)	1,246 (24.3)	541 (18.1)	2,688 (9.6)	397 (45.9)	1,880 (25.6)	547 (14.8)	3,007 (7.9)
Secondary outcomes								
Fatal/non-fatal myocardial infarction								
30 days	7 (1.0)	132 (2.6)	8 (0.3)	254 (0.9)	9 (1.0)	154 (2.1)	NA	386 (1.0)
90 days	8 (1.1)	155 (3.0)	9 (0.3)	293 (1.0)	9 (1.0)	193 (2.6)	9 (0.2)	428 (1.1)
End of study follow-up	11 (1.5)	190 (3.7)	15 (0.5)	351 (1.3)	13 (1.5)	248 (3.4)	11 (0.3)	505 (1.3)
Fatal myocardial infarction								
End of study follow-up	NA	62 (1.2)	NA	74 (0.3)	7 (0.8)	113 (1.5)	10 (0.3)	142 (0.4)
Fatal/non-fatal heart failure								
30 days	16 (2.2)	117 (2.3)	NA	133 (0.5)	21 (2.4)	348 (4.7)	6 (0.2)	362 (0.9)
90 days	21 (2.9)	168 (3.3)	8 (0.3)	166 (0.6)	23 (2.7)	423 (5.8)	8 (0.2)	414 (1.1)
End of study follow-up	24 (3.3)	226 (4.4)	10 (0.3)	212 (0.8)	28 (3.2)	496 (6.8)	14 (0.4)	478 (1.3)
Fatal heart failure								
End of study follow-up	18 (2.5)	88 (1.7)	NA	60 (0.2)	20 (2.3)	182 (2.5)	11 (0.3)	93 (0.2)
Fatal/non-fatal stroke								
30 days	10 (1.4)	96 (1.9)	18 (0.6)	348 (1.2)	15 (1.7)	249 (3.4)	31 (0.8)	574 (1.5)
90 days	13 (1.8)	121 (2.4)	23 (0.8)	415 (1.5)	19 (2.2)	294 (4.0)	38 (1.0)	648 (1.7)

End of study follow-up	16 (2.2)	158 (3.1)	28 (0.9)	487 (1.7)	25 (2.9)	348 (4.7)	44 (1.2)	744 (1.9)
Fatal stroke								
End of study follow-up	6 (0.8)	57 (1.1)	14 (0.5)	135 (0.5)	NA	263 (3.6)	NA	410 (1.1)
Fatal/non-fatal pulmonary embolism								
End of study follow-up	NA	60 (1.2)	15 (0.5)	286 (1.0)	7 (0.8)	87 (1.2)	17 (0.5)	370 (1.0)
Fatal pulmonary embolism								
End of study follow-up	NA	11 (0.2)	NA	20 (0.1)	NA	11 (0.1)	NA	41 (0.1)
Atrial fibrillation hospitalisations								
30 days	NA	189 (3.7)	7 (0.2)	461 (1.6)	7 (0.8)	259 (3.5)	10 (0.3)	626 (1.6)
90 days	12 (1.6)	225 (4.4)	13 (0.4)	557 (2.0)	12 (1.4)	303 (4.1)	13 (0.3)	714 (1.9)
End of study follow-up	15 (2.0)	292 (5.7)	18 (0.6)	676 (2.4)	24 (2.8)	435 (5.9)	24 (0.6)	939 (2.5)
Cardiovascular hospitalisations								
30 days	28 (3.8)	630 (12.3)	53 (1.8)	1,847 (6.6)	41 (4.7)	1,311 (17.9)	80 (2.2)	3,076 (8.1)
90 days	41 (5.6)	765 (14.9)	82 (2.7)	2,175 (7.8)	49 (5.7)	1,483 (20.2)	100 (2.7)	3,381 (8.9)
End of follow-up	54 (7.4)	958 (18.7)	105 (3.5)	2,549 (9.1)	60 (6.9)	1,636 (22.3)	119 (3.2)	3,685 (9.7)
All hospitalisations								
30 days	274 (37.3)	2,928 (57.2)	896 (29.9)	13,361 (47.6)	359 (41.5)	5,063 (69.0)	899 (24.4)	18,562 (48.6)
90 days	335 (45.6)	3,408 (66.6)	1,128 (37.6)	15,767 (56.2)	388 (44.9)	5,267 (71.8)	970 (26.3)	19,242 (50.4)
End of follow-up	386 (52.6)	3,887 (75.9)	1,311 (43.7)	17,952 (64.0)	411 (47.5)	5,429 (74.0)	1,043 (28.3)	19,911 (52.2)
Length of stay	12 [5, 24]	5 [2, 12]	7 [3, 18]	3 [1, 7]	9 [4, 17]	6 [2, 16]	5 [2, 15]	2 [0, 7]

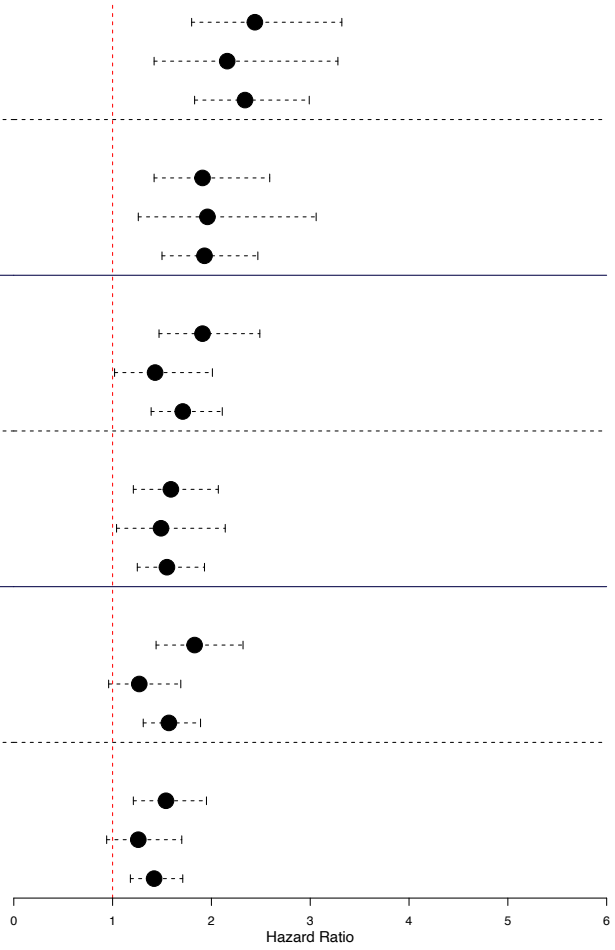
Values are median [interquartile range] or n (%). NAs represent potentially identifiable or count data <5, redacted in order to protect patient confidentiality.


A
B
C
D
Test status
Negative
Positive
Survival probability
Time (days)
1.0
0.9
0.8
0.7
0
100
200
300
400
CKD – Cohort 1
No CKD – Cohort 1
CKD – Cohort 2
No CKD – Cohort 2


A
B
C
D
Test status
Negative
Positive
Survival probability
Time (days)
1.00
0.75
0.50
0.25
0.00
0
100
200
300
400
CKD – Cohort 1
No CKD – Cohort 1
CKD – Cohort 2
No CKD – Cohort 2

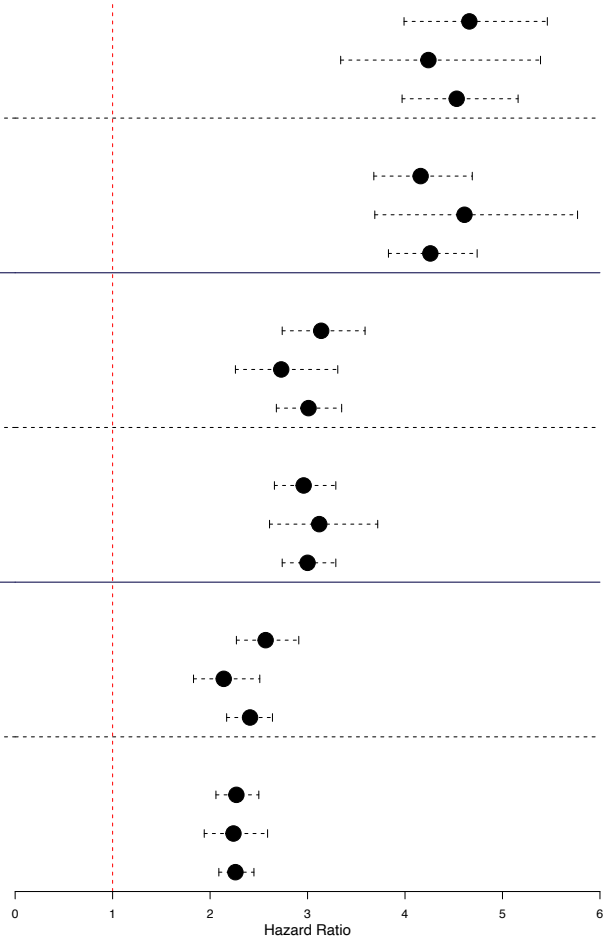
A – Cardiovascular death

	HR	lower	upper
CKD – 30 days			
Cohort 1	2.44	1.80	3.32
Cohort 2	2.16	1.42	3.28
Summary	2.34	1.83	2.99
Non–CKD – 30 days			
Cohort 1	1.91	1.42	2.59
Cohort 2	1.96	1.26	3.06
Summary	1.93	1.50	2.47
CKD – 90 days			
Cohort 1	1.91	1.47	2.49
Cohort 2	1.43	1.02	2.01
Summary	1.71	1.39	2.11
Non–CKD – 90 days			
Cohort 1	1.59	1.21	2.07
Cohort 2	1.49	1.04	2.14
Summary	1.55	1.25	1.93
CKD – study end			
Cohort 1	1.83	1.44	2.32
Cohort 2	1.27	0.96	1.69
Summary	1.57	1.31	1.89
Non–CKD – study end			
Cohort 1	1.54	1.21	1.95
Cohort 2	1.26	0.94	1.70
Summary	1.42	1.18	1.71



B – All-cause death

	HR	lower	upper
CKD – 30 days			
Cohort 1	4.66	3.99	5.46
Cohort 2	4.24	3.34	5.39
Summary	4.53	3.97	5.16
Non–CKD – 30 days			
Cohort 1	4.16	3.68	4.69
Cohort 2	4.61	3.69	5.77
Summary	4.26	3.83	4.74
CKD – 90 days			
Cohort 1	3.14	2.74	3.59
Cohort 2	2.73	2.26	3.31
Summary	3.01	2.68	3.35
Non–CKD – 90 days			
Cohort 1	2.96	2.66	3.29
Cohort 2	3.12	2.61	3.72
Summary	3.00	2.74	3.29
CKD – study end			
Cohort 1	2.57	2.27	2.91
Cohort 2	2.14	1.83	2.51
Summary	2.41	2.17	2.64
Non–CKD – study end			
Cohort 1	2.27	2.06	2.50
Cohort 2	2.24	1.94	2.59
Summary	2.26	2.09	2.45



APPENDIX

Cardiovascular outcomes in patients with chronic kidney disease and COVID-19: a multi-regional data-linkage study

Emilie J. Lambourg*, PharmD,[1] Peter J. Gallacher*, MBChB MPH,[2] Robert W. Hunter, MBChB PhD,[2,3] Moneeza Siddiqui, PhD,[1] James Chalmers, MBChB PhD,[4] Dan Pugh, MBChB,[3] Neeraj Dhaun†, MBChB PhD,[2,3] Samira Bell†, MBChB MD[1,]

[1] Division of Population Health and Genomics, University of Dundee, Dundee, UK

[2] BHF/University Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

[3] Department of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK

[4] Department of Molecular and Clinical Medicine, University of Dundee, Dundee, UK

[5] Scottish Renal Registry, Scottish Health Audits, Public Health & Intelligence, Glasgow, UK

*These authors contributed equally

†These authors contributed equally

Non-standard abbreviations

CHI – Community Health Index (number)

ICD – International Classification of Diseases

NRS – National Records for Scotland

SIMD – Scottish Index of Multiple Deprivation

SMR01 – Scottish Morbidity Record 01

Supplementary Methods

Study cohorts

Cohort 1

All patients who had a SARS-CoV-2 test in the NHS Lothian Health Board between February 1, 2020, and March 31, 2021 were identified. Positive and negative COVID-19 episodes were linked with regional electronic patient and biochemistry records (TrakCare software application, InterSystems Corporation, Cambridge, MA, USA) and national hospitalisation (Scottish Morbidity Record 01, Information Services Division, Scotland), dispensed community prescription (Prescribing Information System, Information Services Division, Scotland) and death records (National Records of Scotland, Scotland) within the DataLoch Repository and Safe Haven (University of Edinburgh/NHS Lothian, Edinburgh, Scotland).

Cohort 2

All patients who had had a measure of serum creatinine in the NHS Fife or Tayside Health Boards since April 1, 2009, and subsequently had a SARS-CoV-2 test between February 28, 2020, and February 8, 2021, were identified. Positive and negative COVID-19 episodes were defined as for Cohort 1 before being linked with national hospitalisation (Scottish Morbidity Record 01, Information Services Division, Scotland), dispensed community prescription (Prescribing Information System, Information Services Division, Scotland), and death records (National Records of Scotland, Scotland) within the Health Informatics Centre Safe Haven (University of Dundee/NHS Fife and Tayside, Dundee, Scotland).[17]

Data sources

Scottish Morbidity Record 01 (SMR01)

The Scottish Morbidity Record 01 (SMR01) general / acute inpatient and day case is an episode-based hospitalisation record, indexed by community health index (CHI) number, capturing all hospitalisations from non-obstetric and non-psychiatric specialties from all residents in Scotland. SMR01 are routinely collected healthcare data of high-quality in terms of consistency and national coverage. To ensure its quality, a set of validation rules is applied to all SMR01 data before release.(1) Across all SMR01

records, estimated completion and accuracy rates are 99% and 89%, respectively. For SMR01 records relating to cardiovascular diagnoses, the accuracy rate is 94.2%.(2)

Information contained in SMR01 data includes: date of admission and discharge date, admission type and where the episode took place, patient's conditions (ICD-10 coded) and interventions received (OPCS-4 coded). Up to 6 diagnoses are available to describe patients' conditions (main and five additional reasons for admission). All 6 positions were searched for presence of at least one relevant ICD-10 code over a 5-year look-back period prior to the index date to assess patient's baseline comorbidities. However, only the first 2 positions were searched to characterise cardiovascular hospitalisations occurring on or after the index date. Previously conducted sensitivity analyses validated the accuracy of restricting diagnosis coding to the first 2 out of 6 positions to ensure an optimal balance of diagnostic coding specificity and sensitivity.(3) Further information regarding SMR01 data is available on the website of the Information Services Division (National Services Scotland, NHS Scotland): https://www.ndc.scot.nhs.uk/National-Datasets/data.asp?SubID=5

National Records of Scotland (NRS) Death Records

The NRS is a CHI-indexed dataset covering all deaths in Scotland. Information on the death status, date of death, and causes of death were extracted and linked to the other records of patients tested for SARS-CoV-2 *via* their unique CHI number. Up to eleven different causes of death (the underlying cause and up to 10 additional causes) based on the amended cause of death text are recorded in the NRS data and coded using the ICD-10 classification. Besides the underlying cause, the additional causes of death are factors, diseases or injury that have contributed in some way to the occurrence of the death.(4) All positions were searched for relevant ICD-codes to identify COVID-19 related deaths whilst only the first two positions were considered to assess cardiovascular mortality. More information on the NRS data is

available on the website of the Information Services Division (National Services Scotland, NHS Scotland): https://www.ndc.scot.nhs.uk/National-Datasets/data.asp?SubID=13

The Scottish Renal Registry (SRR)

For the Tayside/Fife cohort, patients on chronic renal replacement therapy (RRT) were identified from the SRR. The SRR was established in 1991 with data backfilled to 1960 from European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). It is a national registry of all patients receiving RRT (haemodialysis, peritoneal dialysis or kidney transplant) for end-stage kidney disease in Scotland, indexed by CHI number. The SRR has 100% unit and patient coverage. Data held by the registry include patient demographics, full RRT history, primary renal diagnosis (using ERA-EDTA codes) and monthly linkage with National Health Service Blood and Transplant (NHS BT) for transplant status. More information is available on the SRR website: https://www.srr.scot.nhs.uk/

The Scottish Care Information – Diabetes (SCI-D) database

The SCI-D is a CHI-indexed high-quality integrated database containing clinical information on over 99% of people with diagnosed diabetes in Scotland.(5) It is automatically updated from primary and secondary care systems, with almost all practices in Scotland participating to data collection. The dataset was used here as a population-based diabetes register since only the diagnosis date was extracted to identify all patients with a diagnosis of diabetes made prior to their index date.

Community prescribing

Medications prescribed over the 6-month period prior to the index date were used to determine presence of a baseline exposure to ACE-inhibitor/ARB, immunosuppressants or presence of a chronic respiratory disease in patients included in the cohort. The identification of a single relevant BNF code (see **Supplementary Text 1**) was necessary and sufficient to identify the comorbidity or drug exposure.

Determination of patient demographics, CKD status, comorbidities, causes of death and history of prescribed medications

Patient demographics

For both study cohorts, patient age, sex and social deprivation status were determined from linked hospitalisation records. Social deprivation status was defined according to the Scottish Index of Multiple Deprivation (SIMD) – a validated measure of social deprivation determined by factors related to residential address (zip code) (**Appendix**).(6) Patients were assigned an individual SIMD rank at the time of their index SARS-CoV-2 test. Based on these ranks, patients were assigned a SIMD quintile, where the first and fifth quintiles were considered the most and least deprived, respectively.(7)

Chronic kidney disease

Both study cohorts utilised the same criteria – validated in electronic health records and based on the timing and nature of prior serum creatinine results – to determine CKD status at the time of index SARS-CoV-2 test.(8) For patients included in Cohort 1, two years of prior serum creatinine data were used to inform CKD status using these criteria. For patients included in Cohort 2, all historic serum creatinine results dating back to April 1, 2009, were available for analysis.

In brief, eGFRs were calculated for all assay-corrected serum creatinine results using the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation.(9) CKD was defined when a patient's most recent eGFR was <60 ml/min/1.73m^2 and at least one value obtained >90 days prior was also calculated as <60 ml/min/1.73m^2. Using the eGFR value closest to the index date for each patient, CKD stage was classified according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.(10) Patients with kidney failure requiring kidney replacement therapy (i.e. haemodialysis, peritoneal dialysis or kidney transplantation) were identified from record linkage with regional or national renal registries (Cohort 1 – VitalData; Cohort 2 – Scottish Renal Registry). Those patients with only a single measure of eGFR <60 ml/min/1.73m^2 prior to their index test were excluded from further analysis (**Supplementary Figure 1**).

Comorbidities and causes of death

Patient comorbidities were defined from International Classification of Diseases (ICD) codes associated with hospitalisations during a 5-year 'lookback' period prior to the index SARS-CoV-2 test. For every

index COVID-19 episode identified in Cohorts 1 and 2, the following comorbidity data were extracted from linked hospitalisation records: (history of) angina, cancer, chronic liver disease, chronic lower respiratory disease, heart failure, myocardial infarction, and stroke. For Cohort 2, data relating to co-existing atrial fibrillation were also available. In addition, diabetes status was obtained *via* record linkage with a national diabetes registry (Scottish Care Information – Diabetes Collaboration).(11) Causes of death were determined following the identification of relevant ICD codes in linked National Records of Scotland death records.

History of prescribed medications

Anatomical Therapeutic Chemical (ATC) and British National Formulary (BNF) codes were used to identify dispensed prescriptions of angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACE-inhibitors/ARBs) and immunosuppressants in the community prescribing records of individual patients during the 6 months preceding their index SARS-CoV-2 test. For patients included in Cohort 2, prescription data relating to common cardiovascular medications (i.e. ACE-inhibitor, angiotensin receptor blockers, aspirin, antiplatelet agents, beta-blockers, loop diuretics, mineralocorticoid receptor antagonists, novel oral anticoagulants and warfarin) dispensed during the 6 months preceding each index SARS-CoV-2 test were also available.

Statistical analysis

Covariate-balanced propensity scoring and regression modelling

For our primary analysis, we sought to estimate the causal effect of COVID-19 on outcomes in patients with and without CKD, whilst for our secondary analysis, we sought to estimate the causal effect of CKD on outcomes in patients with and without COVID-19. With the aim of obtaining an unconfounded estimate, we utilised a 'doubly-robust' estimator with bootstrapped standard errors and 95% confidence intervals for the primary outcome analyses (**Appendix**).[12] This approach combines a multivariable outcome regression model with weighting by the covariate-balanced propensity score (CBPS). A key

strength of this method is that an unbiased effect estimate can still be obtained, even if one of the component models (either the outcome regression or CBPS model) has been mis-specified.[12, 13]

For the primary analysis, Cox regression was used to explore the association between COVID-19 status (the primary exposure) and cardiovascular and all-cause death (the primary outcomes). For the secondary analysis, Cox regression was used to explore the association between CKD status (the primary exposure) and cardiovascular, COVID-19 and all-cause death (the primary outcomes). For cardiovascular and COVID-19-related death, cause-specific hazard ratios were calculated to account for the competing risks of death from non-cardiovascular causes and death from non-COVID-19 causes, respectively.

For each analysis, we initially ran an unadjusted model before combining CBPS weighting and adjustment for several known confounders in a fully adjusted model. Using CBPS, covariates were balanced between exposure groups (COVID-19 and CKD status) in patients with and without CKD, and in patients with and without COVID-19 for the primary and secondary analyses, respectively.[14] Confounders were specified *a priori* and included age, sex, social demographic status, comorbidities (history of angina, myocardial infarction, heart failure, stroke, diabetes, cancer, chronic respiratory disease, chronic liver disease) and selected current medication (ACE-inhibitors/ARBs, immunosuppressant therapy) based on their potential relevance to COVID-19 outcomes.[15, 16]

For each primary outcome, hazard ratios derived from CBPS-weighted, fully-adjusted multivariable models in individual cohorts were pooled to obtain an overall meta-estimate. Both cohorts utilised similar patient populations based in the same country, whilst the design, definitions and overall methodology employed in each study cohort were also similar. Consequently, meta-estimates were computed using a fixed-effects model.

Thereafter, Cox regression models adjusting for the same confounders as before but with no CBPS-weighting were used to estimate the association between eGFR (primary exposure) and the risk of

cardiovascular, all-cause, and COVID-19-related death in patients with and without COVID-19. For this analysis, eGFR was modelled as a continuous variable with restricted cubic splines using knots placed at the 5th, 25th, 50th and 75th centiles of eGFR measures in each cohort, as described previously.[17]

Unadjusted and CBPS-weighted, multivariable Cox models were generated and fitted using the *cobalt*, *rms*, *survival*, and *WeightIt* packages, whilst meta-estimates were obtained using the *meta* package. All data were analysed using the R statistical programming language (Version 3.6.2, Vienna, Austria).

Missing data

Age, sex, comorbidity, prescribing, and outcome data were complete for all patients in both study cohorts. In Cohort 1, data relating to kidney function and social deprivation status were missing in 13.2% and 0.7% of all patient records, respectively. These were excluded from further analysis. In Cohort 2, data relating to social deprivation status were missing in 5.1%. For these records, hot deck imputation was implemented, with missing SIMD quintiles replaced by the observed value of another individual randomly chosen from all patients sharing a similar zip code.

Ethical (IRB) approval and statement of data transparency

The study was performed with the approvals of local Research Ethics Committees and delegated Caldicott Guardians for the NHS Fife, Lothian, and Tayside Health Boards, in accordance with the Declaration of Helsinki. All study methods and results were described and reported according to STROBE guidelines.(18) Data provision and linkage were carried out by the DataLoch (University of Edinburgh/NHS Lothian, https://www.dataloch.org/) and University of Dundee Health Informatics Centre (HIC, https://www.dundee.ac.uk/hic) within ISO27001 and Scottish Government accredited secure Safe Havens for Cohorts 1 and 2, respectively. HIC Standard Operating Procedures have been reviewed and approved by the NHS East of Scotland Research Ethics Service and consent was obtained from the NHS Fife Caldicott Guardian. Patient consent was not sought as the study utilised fully-anonymised data. To minimise the risk of disclosure, only summary data were extracted from each Safe Haven.

Individual-level data are available *via* application to the DataLoch and Health Informatics Centre. Our analysis code is publicly available here.

Supplementary Results

Baseline characteristics of patients without CKD according to COVID-19 status

In patients without CKD, differences in baseline characteristics according to COVID-19 status were less marked across both cohorts (**Table 1**). In patients who tested positive and negative, the proportion of women, rates of cardiovascular comorbidity and drug prescriptions, and eGFR were all similar.

Baseline characteristics of patients with COVID-19 according to CKD status

A positive SARS-CoV-2 test was more likely in patients with CKD than in those without CKD (Cohort 1: 12.5% *versus* 9.7%; Cohort 2: 10.5% *versus* 8.8%). In patients with COVID-19, those with CKD were older and had a greater burden of cardiovascular comorbidity than patients without CKD (**Supplementary Table 4**). The differences between patients with and without CKD were as marked in those without COVID-19.

Outcomes of patients without CKD according to COVID-19 status

In patients without CKD, the adjusted risk of cardiovascular death at 30 days was increased two-fold in patients with COVID-19 compared to patients testing negative (csHR meta-estimate 1.94, 95% CI 1.52 to 2.47) (**Table 2; Figures 1a & 2a**). By the end of study follow-up, the adjusted risk of cardiovascular death in positive *versus* negative patients without CKD had reduced (csHR meta-estimate 1.42, 95% CI 1.19 to 1.70). A similar pattern was evident for the risk of all-cause death in these patients (**Table 2; Figures 1b & 2b**).

Outcomes of patients without COVID-19 according to CKD status and eGFR

Across both cohorts, significant differences in outcomes between those with and without CKD were also evident in patients without COVID-19. CKD was associated with an increased risk of cardiovascular death (csHR meta-estimate 1.46, 95% CI 1.33 to 1.60) and all-cause death (csHR meta-estimate 1.24, 95% CI 1.18 to 1.31) (**Supplementary Table 6; Supplementary Figures 3 & 4**). Finally, CKD was also

associated with higher rates of cardiovascular complications and subsequent hospitalisations in these patients.

Supplementary Text 1. List of International Classification of Diseases and BNF codes employed in study.

Condition	ICD-10 Code
Cancer	
ICD-10	Any "C" code
Chronic liver disease	
ICD-10	B18, K70, K74.3, K74.4, K74.5, K74.6, I85.0, I85.9, I98.2, I98.3, K76, R18, Z94.4, K72.1, K71.3, K71.4, K71.5, K71.7
Chronic respiratory disease*	
ICD-10	I27.8, I27.9 J40-45, J46, J47, J60-67, J68.4, J70.1, J70.3
BNF	030101, 030102, 030104, 0302, 030302
COVID-19	
ICD-10	U071, U072
Cardiovascular diagnoses	**ICD-10 Code**
Angina	
ICD-10	I201, I208, I209
Heart failure	
ICD-10	I11.0, I13.0, I13.2, I50
Myocardial infarction	
ICD-10	I21, I22, I23, I241, I252
Stroke	
ICD-10	G45, G46, I60-69
Pulmonary embolism	
ICD-10	I26.0, I26.9
Community prescription data	**ATC Code**
Exposure to ACE-inhibitor/ARB	
ATC	C09AA, C09CA
Exposure to immunosuppressants	
ATC	L04

Abbreviations: ACE-inhibitor – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; ATC – anatomical therapeutic classification, BNF – British National Formulary, ICD – international classification of diseases. *For chronic respiratory disease, the presence of a single ICD-10 code in SMR01 data **OR** a single BNF code in community prescription data was necessary and sufficient to assess the presence of the comorbidity.

Supplementary Tables

Supplementary Table 1. Clinical characteristics of patients included in Cohorts 1 and 2.

	COHORT 1	COHORT 2
Number of patients, n	**36,904**	**50,060**
Age, years	61 (21)	63 (20)
Sex		
Women	21,458 (58.1)	31,028 (62.0)
Men	15,446 (41.9)	19,032 (38.0)
SIMD quintile		
1 (most deprived)	5,458 (14.8)	9,675 (19.3)
2	9,154 (24.8)	9,587 (19.2)
3	6,510 (17.6)	9,525 (19.0)
4	6,393 (17.3)	13,030 (26.0)
5 (least deprived)	9,145 (24.8)	8,242 (16.5)
Co-existing medical conditions		
Angina	1,917 (5.2)	1,660 (3.3)
Atrial fibrillation*	-	3,869 (7.7)
Myocardial infarction	2,874 (7.8)	2,170 (4.3)
Heart failure	2,751 (7.5)	1,804 (3.6)
Stroke	2,817 (7.6)	2,485 (5.0)
Diabetes	6,177 (16.7)	9,085 (18.1)
Cancer	7,288 (19.7)	3,525 (7.0)
Chronic lower respiratory disease	9,861 (26.7)	10,540 (21.1)
Chronic liver disease	1,301 (3.5)	822 (1.6)
Renal history		
CKD	5,853 (15.9)	8,201 (16.4)
End-stage kidney disease	337 (0.9)	240 (0.5)
Baseline eGFR	83 (25)	86 (26)
Baseline eGFR category		
≥90	15,486 (42.0)	22,784 (45.5)
60 – 89	15,565 (42.2)	19,075 (38.1)
45 – 59	2,708 (7.3)	4,264 (8.5)
30 – 44	1,868 (5.1)	2,549 (5.1)
15 – 29	787 (2.1)	914 (1.8)
≤15	490 (1.3)	474 (0.9)
Current medication		
ACE-inhibitor or ARB	9,022 (24.4)	10,673 (21.3)
Aspirin*	-	5,492 (11.0)
Other antiplatelet agent*	-	3,335 (6.7)
Beta-blockers*	-	9,314 (18.6)
Immunosuppressants	860 (2.3)	421 (0.8)
Loop diuretic*	-	5,432 (10.9)
Mineralocorticoid receptor antagonist*	-	1,332 (2.7)
Novel oral anticoagulant*	-	3,450 (6.9)
Warfarin*	-	1,238 (2.5)

Values are mean ± SD, n (%), or median (interquartile range). Abbreviations: ACE-inhibitor – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate (ml/min/1.73 m^2); SIMD – Scottish index of multiple deprivation. *data not available for Cohort 1.

Supplementary Table 2. Clinical characteristics of patients included in Cohorts 1 and 2, grouped by COVID-19 status.

	COHORT 1		COHORT 2	
	COVID-19 positive	**COVID-19 negative**	**COVID-19 positive**	**COVID-19 negative**
Number of patients, n	**3,731**	**33,173**	**4,556**	**45,504**
Age, years	63 (22)	61 (20)	64 (21)	63 (20)
Sex				
Women	2,110 (56.6)	19,348 (58.3)	2,955 (64.9)	28,073 (61.7)
Men	1,621 (43.4)	13,825 (41.7)	1,601 (35.1)	17,431 (38.3)
SIMD quintile				
1 (most deprived)	579 (15.5)	4,879 (14.7)	993 (21.8)	8,682 (19.1)
2	1,002 (26.9)	8,152 (24.6)	932 (20.5)	8,655 (19.0)
3	645 (17.3)	5,865 (17.7)	847 (18.6)	8,678 (19.1)
4	631 (16.9)	5,762 (17.4)	1,121 (24.6)	11,909 (26.2)
5 (least deprived)	858 (23.0)	8,287 (25.0)	663 (14.6)	7,579 (16.7)
Co-existing medical conditions				
Angina	216 (5.8)	1,701 (5.1)	167 (3.7)	1,493 (3.3)
Atrial fibrillation*	-	-	422 (9.3)	3,447 (7.6)
Myocardial infarction	302 (8.1)	2,572 (7.8)	187 (4.1)	1,983 (4.4)
Heart failure	331 (8.9)	2,420 (7.3)	217 (4.8)	1,587 (3.5)
Stroke	384 (10.3)	2,433 (7.3)	360 (7.9)	2,125 (4.7)
Diabetes	766 (20.5)	5,411 (16.3)	866 (19.0)	8,219 (18.1)
Cancer	543 (14.6)	6,745 (20.3)	252 (5.5)	3,273 (7.2)
Chronic lower respiratory disease	1,032 (27.7)	8,829 (26.6)	866 (19.0)	9,674 (21.3)
Chronic liver disease	104 (2.8)	1,197 (3.6)	61 (1.3)	761 (1.7)
Renal history				
CKD	734 (19.7)	5,119 (15.4)	865 (19.0)	7,336 (16.1)
End-stage kidney disease	35 (0.9)	302 (0.8)	29 (0.6)	211 (0.5)
Baseline eGFR	80 (27)	84 (25)	84 (26)	86 (26)
Baseline eGFR category				
≥90	1,396 (37.4)	14,090 (42.5)	2,020 (44.3)	20,764 (45.6)
60 – 89	1,601 (42.9)	13,964 (42.1)	1,671 (36.7)	17,404 (38.2)
45 – 59	314 (8.4)	2,394 (7.2)	436 (9.6)	3,828 (8.4)
30 – 44	236 (6.3)	1,632 (4.9)	270 (5.9)	2,279 (5.0)
15 – 29	118 (3.2)	669 (2.0)	105 (2.3)	809 (1.8)
≤15	66 (1.8)	424 (1.3)	54 (1.2)	420 (0.9)
Current medication				
ACE-inhibitor or ARB	937 (25.1)	8,085 (24.4)	807 (17.7)	9,866 (21.7)
Aspirin*	-	-	456 (10.0)	5,036 (11.1)
Other antiplatelet agent*	-	-	375 (8.2)	2,960 (6.5)
Beta-blockers*	-	-	797 (17.5)	8,517 (18.7)
Immunosuppressants	93 (2.5)	767 (2.3)	24 (0.5)	397 (0.9)
Loop diuretic*	-	-	567 (12.4)	4,865 (10.7)
Mineralocorticoid receptor antagonist*	-	-	130 (2.9)	1,202 (2.6)
Novel oral anticoagulant*	-	-	296 (6.5)	3,154 (6.9)
Warfarin*	-	-	88 (1.9)	1,150 (2.5)

Values are mean ± SD, n (%), or median (interquartile range). Abbreviations: ACE-inhibitor – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate (ml/min/1.73 m^2); SIMD – Scottish index of multiple deprivation. *data not available for Cohort 1.

Supplementary Table 3. Clinical characteristics of patients included in Cohorts 1 and 2, grouped by CKD status.

	COHORT 1		COHORT 2	
	CKD	**No CKD**	**CKD**	**No CKD**
Number of patients, n	**5,853**	**31,051**	**8,201**	**41,859**
Age, years	79 (12)	58 (20)	82 (10)	59 (19)
Sex				
Women	3,148 (53.8)	18,310 (59.0)	4,879 (59.5)	26,149 (62.5)
Men	2,705 (46.2)	12,741 (41.0)	3,322 (40.5)	15,710 (37.5)
SIMD quintile				
1 (most deprived)	719 (12.3)	4,739 (15.3)	1,322 (16.1)	8,353 (20.0)
2	1,487 (25.4)	7,667 (24.7)	1,576 (19.2)	8,011 (19.1)
3	1,033 (17.6)	5,477 (17.6)	1,673 (20.4)	7,852 (18.8)
4	1,001 (17.1)	5,392 (17.4)	2,193 (26.7)	10,837 (25.9)
5 (least deprived)	1,602 (27.4)	7,558 (24.3)	1,437 (17.5)	6,805 (16.3)
Co-existing medical conditions				
Angina	662 (11.3)	1,255 (4.0)	602 (7.3)	1,058 (2.5)
Atrial fibrillation*	-	-	1,651 (20.1)	2,218 (5.3)
Myocardial infarction	931 (15.9)	1,943 (6.3)	835 (10.2)	1,335 (3.2)
Heart failure	1,348 (23.0)	1,403 (4.5)	980 (11.9)	824 (2.0)
Stroke	831 (14.2)	1,986 (6.4)	794 (9.7)	1,691 (4.0)
Diabetes	2,094 (35.8)	4,083 (13.1)	2,665 (32.5)	6,420 (15.3)
Cancer	1,531 (26.2)	5,757 (18.5)	956 (11.7)	2,569 (6.1)
Chronic lower respiratory disease	1,641 (28.0)	8,220 (26.5)	2,109 (25.7)	8,431 (20.1)
Chronic liver disease	240 (4.1)	1,061 (3.4)	192 (2.3)	630 (1.5)
Renal history				
End-stage kidney disease	337 (5.8)	-	240 (2.9)	-
Baseline eGFR	42 (14)	91 (18)	44 (12)	94 (19)
Baseline eGFR category				
≥90	-	15,486 (49.9)	-	22,784 (54.4)
60 – 89	-	15,565 (50.1)	-	19,075 (45.6)
45 – 59	2,708 (46.3)	-	4,264 (52.0)	-
30 – 44	1,868 (31.9)	-	2,549 (31.1)	-
15 – 29	787 (13.4)	-	914 (11.1)	-
≤15	490 (8.4)	-	474 (5.8)	-
Current medication				
ACE-inhibitor or ARB	2,389 (40.8)	6,633 (21.4)	2,913 (35.5)	7,760 (18.5)
Aspirin*	-	-	1,756 (21.4)	3,736 (8.9)
Other antiplatelet agent*	-	-	989 (12.1)	2,346 (5.6)
Beta-blockers*	-	-	2,955 (36.0)	6,359 (15.2)
Immunosuppressants	228 (3.9)	632 (2.0)	162 (2.0)	259 (0.6)
Loop diuretic*	-	-	2,615 (31.9)	2,817 (6.7)
Mineralocorticoid receptor antagonist*	-	-	624 (7.6)	708 (1.7)
Novel oral anticoagulant*	-	-	1,278 (15.6)	2,172 (5.2)
Warfarin*	-	-	542 (6.6)	696 (1.7)

Values are mean ± SD, n (%), or median (interquartile range). Abbreviations: ACE-inhibitor – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate (ml/min/1.73 m^2); SIMD – Scottish index of multiple deprivation. *data not available for Cohort 1.

Supplementary Table 4. Clinical characteristics of patients included in Cohorts 1 and 2, grouped according to COVID-19 and CKD status.

	COHORT 1				COHORT 2			
	COVID-19 positive		COVID-19 negative		COVID-19 positive		COVID-19 negative	
	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD
Number of patients, n	**734**	**2,997**	**5,119**	**28,054**	**865**	**3,691**	**7,336**	**38,168**
Age, years	81 (11)	59 (21)	79 (12)	57 (20)	84 (10)	59 (20)	82 (10)	59 (19)
Sex								
Women	384 (52.3)	1,726 (57.6)	2,764 (54.0)	16,584 (59.1)	502 (58.0)	2,453 (66.5)	4,377 (59.7)	23,696 (62.1)
Men	350 (47.7)	1,271 (42.4)	2,355 (46.0)	11,470 (40.9)	363 (42.0)	1,238 (33.5)	2,959 (40.3)	14,472 (37.9)
SIMD quintile								
1 (most deprived)	103 (14.0)	476 (15.9)	616 (12.0)	4,263 (15.2)	162 (18.7)	831 (22.5)	1,160 (15.8)	7,522 (19.7)
2	207 (28.2)	795 (26.5)	1,280 (25.0)	6,872 (24.5)	185 (21.4)	747 (20.2)	1,391 (19.0)	7,264 (19.0)
3	113 (15.4)	532 (17.8)	920 (18.0)	4,945 (17.6)	182 (21.0)	665 (18.0)	1,491 (20.3)	7,187 (18.8)
4	112 (15.3)	519 (17.3)	889 (17.4)	4,873 (17.4)	216 (25.0)	905 (24.5)	1,977 (26.9)	9,932 (26.0)
5 (least deprived)	198 (27.0)	675 (22.0)	1,404 (27.4)	6,883 (24.5)	120 (13.9)	543 (14.7)	1,317 (18.0)	6,262 (16.4)
Co-existing medical conditions								
Angina	91 (12.4)	125 (4.2)	571 (11.2)	1,130 (4.0)	69 (8.0)	98 (2.7)	533 (7.3)	960 (2.5)
Atrial fibrillation*	-	-	-	-	207 (23.9)	215 (5.8)	1,444 (19.7)	2,003 (5.2)
Myocardial infarction	124 (16.9)	178 (5.9)	807 (15.8)	1,765 (6.3)	91 (10.5)	96 (2.6)	744 (10.1)	1,239 (3.2)
Heart failure	196 (26.7)	135 (4.5)	1,152 (22.5)	1,268 (4.5)	133 (15.4)	84 (2.3)	847 (11.5)	740 (1.9)
Stroke	127 (17.3)	257 (8.6)	704 (13.8)	1,729 (6.2)	123 (14.2)	237 (6.4)	671 (9.1)	1,454 (3.8)
Diabetes	275 (37.5)	491 (16.4)	1,819 (35.5)	3,592 (12.8)	277 (32.0)	589 (16.0)	2,388 (32.6)	5,831 (15.3)
Cancer	159 (21.7)	384 (12.8)	1,372 (26.8)	5,373 (19.2)	98 (11.3)	154 (4.2)	858 (11.7)	2,415 (6.3)
Chronic lower respiratory disease	223 (30.4)	809 (27.0)	1,418 (27.7)	7,411 (26.4)	232 (26.8)	634 (17.2)	1,877 (25.6)	7,797 (20.4)
Chronic liver disease	27 (3.7)	77 (2.6)	213 (4.2)	984 (3.5)	21 (2.4)	40 (1.1)	171 (2.3)	590 (1.5)
Renal history								
End-stage kidney disease	35 (4.8)	-	302 (5.9)	-	29 (3.4)	-	211 (2.9)	-
Baseline eGFR	40 (14)	90 (19)	42 (14)	91 (18)	43 (12)	93 (18)	44 (12)	94 (19)
Baseline eGFR category								
≥90	-	1,396 (46.6)	-	14,090 (50.2)	-	2,020 (54.7)	-	20,764 (54.4)
60 – 89	-	1,601 (53.4)	-	13,964 (49.8)	-	1,671 (45.3)	-	17,404 (45.6)
45 – 59	314 (42.8)	-	2,394 (46.8)	-	436 (50.4)	-	3,828 (52.2)	-
30 – 44	236 (32.2)	-	1,632 (31.9)	-	270 (31.2)	-	2,279 (31.1)	-
15 – 29	118 (16.1)	-	669 (13.1)	-	105 (12.1)	-	809 (11.0)	-
≤15	66 (9.0)	-	424 (8.3)	-	54 (6.2)	-	420 (5.7)	-
Current medication								
ACE-inhibitor or ARB	263 (35.8)	674 (22.5)	2,126 (41.5)	5,959 (21.2)	218 (25.2)	589 (16.0)	2,695 (36.7)	7,171 (18.8)
Aspirin*	-	-	-	-	157 (18.1)	299 (8.1)	1,599 (21.8)	3,437 (9.0)
Other antiplatelet agent*	-	-	-	-	128 (14.8)	247 (6.7)	861 (11.7)	2,099 (5.5)
Beta-blockers*	-	-	-	-	300 (34.7)	497 (13.5)	2,655 (36.2)	5,862 (15.4)

Immunosuppressants	27 (3.7)	66 (2.2)	201 (3.9)	566 (2.0)	11 (1.3)	13 (0.4)	151 (2.1)	246 (0.6)
Loop diuretic*	-	-	-	-	303 (35.0)	264 (7.1)	2,312 (31.5)	2,553 (6.7)
Mineralocorticoid receptor antagonist*	-	-	-	-	66 (7.6)	64 (1.7)	558 (7.6)	644 (1.7)
Novel oral anticoagulant*	-	-	-	-	142 (16.4)	154 (4.2)	1,136 (15.5)	2,018 (5.3)
Warfarin*	-	-	-	-	43 (5.0)	45 (1.2)	499 (6.8)	651 (1.7)

Values are mean ± SD, n (%), or median (interquartile range). Abbreviations: ACE-inhibitor – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate (ml/min/1.73 m^2); SIMD – Scottish index of multiple deprivation.
*data not available for Cohort 1.

Supplementary Table 5. Summary of unadjusted hazard ratios and 95% confidence intervals relating to cardiovascular, all-cause, and COVID-19-related death for primary (**A**) and secondary (**B**) analyses.

		COHORT 1			COHORT 2		
		Unadjusted Hazard Ratio	**Lower 95% CI**	**Upper 95% CI**	**Unadjusted Hazard Ratio**	**Lower 95% CI**	**Upper 95% CI**
A) COVID-19 positive *versus* negative	**CKD**						
	Cardiovascular death*						
	30 days	2.65	1.97	3.58	2.42	1.83	3.20
	90 days	2.15	1.66	2.78	1.69	1.31	2.16
	End of study follow-up	1.99	1.58	2.51	1.50	1.21	1.87
	All-cause death						
	30 days	4.81	4.13	5.61	4.71	4.10	5.40
	90 days	3.33	2.92	3.80	3.14	2.78	3.54
	End of study follow-up	2.79	2.48	3.15	2.51	2.25	2.80
	No CKD						
	Cardiovascular death*						
	30 days	2.20	1.65	2.94	1.86	1.40	2.48
	90 days	1.81	1.40	2.34	1.48	1.16	1.91
	End of study follow-up	1.76	1.40	2.21	1.24	1.00	1.53
	All-cause death						
	30 days	4.05	3.60	4.55	4.26	3.80	4.78
	90 days	2.81	2.54	3.11	2.87	2.59	3.18
	End of study follow-up	2.25	2.05	2.46	2.03	1.85	2.22
B) CKD *versus* no CKD	**COVID-19 positive**						
	Cardiovascular death*						
	30 days	4.53	3.14	6.54	5.62	3.91	8.08
	90 days	4.97	3.56	6.92	5.29	3.81	7.36
	End of study follow-up	4.80	3.56	6.47	5.60	4.19	7.47
	All-cause death						
	30 days	3.03	2.59	3.54	3.70	3.19	4.30
	90 days	3.06	2.65	3.53	3.73	3.24	4.29
	End of study follow-up	3.09	2.70	3.53	3.95	3.47	4.50
	COVID-19-related death*						
	30 days	3.07	2.62	3.61	3.67	3.16	4.27
	90 days	3.10	2.65	3.61	3.69	3.19	4.27
	End of study follow-up	3.11	2.67	3.63	3.75	3.24	4.33
	COVID-19 negative						
	Cardiovascular death*						
	30 days	3.81	3.14	4.62	4.30	3.64	5.07

	90 days	4.36	3.74	5.08	4.83	4.26	5.48
	End of study follow-up	4.39	3.87	4.99	4.95	4.49	5.47
	All-cause death						
	30 days	2.54	2.27	2.85	3.36	3.04	3.71
	90 days	2.67	2.46	2.91	3.58	3.32	3.85
	End of study follow-up	2.58	2.41	2.76	3.57	3.37	3.78

Abbreviations: CKD – chronic kidney disease; CI – confidence interval. *Hazard ratios for cardiovascular and COVID-19-related death are cause-specific.

Supplementary Table 6. Outcomes of patients included in sensitivity analysis, in which study cohorts were restricted to patients not hospitalised either in the week before or in the two weeks following their index COVID-19 test. Patients are grouped according to COVID-19 and CKD status.

	COHORT 1				COHORT 2			
	COVID-19 positive		COVID-19 negative		COVID-19 positive		COVID-19 negative	
	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD
Number of patients, n	**314**	**574**	**1,786**	**9,575**	**460**	**1,877**	**2,717**	**18,526**
Primary outcomes								
Cardiovascular death								
30 days	18 (5.7)	6 (1.0)	22 (1.2)	12 (0.1)	21 (4.6)	35 (1.9)	20 (0.7)	46 (0.2)
90 days	23 (7.3)	17 (3.0)	28 (1.6)	27 (0.3)	25 (5.4)	67 (3.6)	27 (1.0)	90 (0.5)
End of study follow-up	29 (9.2)	41 (7.1)	37 (2.1)	57 (0.6)	37 (8.0)	131 (7.0)	44 (1.6)	181 (1.0)
All-cause death								
30 days	99 (31.5)	29 (5.1)	144 (8.1)	112 (1.2)	141 (30.6)	95 (5.1)	193 (7.1)	156 (0.8)
90 days	120 (38.2)	61 (10.6)	182 (10.2)	208 (2.2)	161 (35.0)	200 (10.6)	220 (8.1)	306 (1.6)
End of study follow-up	138 (43.9)	125 (21.8)	215 (12.0)	371 (3.9)	192 (41.7)	401 (21.4)	274 (10.1)	673 (3.6)

Supplementary Table 7. Summary of adjusted hazard ratios and 95% confidence intervals from sensitivity analysis, in which study cohorts were restricted to patients not hospitalised either in the week before or in the two weeks following their index COVID-19 test.

		COHORT 1			COHORT 2		
		Adjusted Hazard Ratio	**Lower 95% CI**	**Upper 95% CI**	**Adjusted Hazard Ratio**	**Lower 95% CI**	**Upper 95% CI**
COVID-19 positive *versus* negative	**CKD**						
	Cardiovascular death*						
	30 days	6.70	2.19	20.51	2.30	1.10	4.81
	90 days	2.62	1.26	5.45	1.46	0.81	2.62
	End of study follow-up	2.02	1.17	3.47	1.37	0.87	2.16
	All-cause death						
	30 days	7.48	4.69	11.93	5.93	3.97	8.84
	90 days	4.04	2.87	5.69	3.37	2.50	4.53
	End of study follow-up	2.63	2.03	3.41	2.36	1.87	2.98
	No CKD						
	Cardiovascular death*						
	30 days	3.43	1.55	7.58	2.30	1.06	5.00
	90 days	2.35	1.32	4.16	1.50	0.84	2.69
	End of study follow-up	1.66	1.09	2.54	1.35	0.87	2.09
	All-cause death						
	30 days	3.93	2.94	5.25	6.69	4.58	9.77
	90 days	2.68	2.14	3.35	3.91	2.95	5.18
	End of study follow-up	1.82	1.52	2.19	2.41	1.96	2.97

Abbreviations: CKD – chronic kidney disease; CI – confidence interval. *Hazard ratios for cardiovascular death are cause-specific.

Supplementary Table 8. Outcomes of patients included in Cohorts 1 and 2, grouped according to COVID-19 and CKD status.

	COHORT 1				COHORT 2			
	COVID-19 positive		COVID-19 negative		COVID-19 positive		COVID-19 negative	
	CKD	No CKD	CKD	No CKD	CKD	No CKD	CKD	No CKD
Number of patients, n	**734**	**2,997**	**5,119**	**28,054**	**865**	**3,691**	**7,336**	**38,168**
Primary outcomes								
Cardiovascular death								
30 days	57 (7.8)	57 (1.9)	172 (3.4)	254 (0.9)	62 (7.2)	55 (1.5)	254 (3.5)	316 (0.8)
90 days	72 (9.8)	68 (2.3)	290 (5.7)	377 (1.3)	72 (8.3)	70 (1.9)	453 (6.2)	515 (1.3)
End of follow-up	86 (11.7)	86 (2.9)	426 (8.3)	542 (1.9)	92 (10.6)	94 (2.5)	730 (10.0)	840 (2.2)
COVID-19-related death								
30 days	250 (34.1)	377 (12.6)	-	-	295 (34.1)	397 (10.8)	-	-
90 days	267 (36.4)	404 (13.5)	-	-	313 (36.2)	423 (11.5)	-	-
End of follow-up	270 (36.8)	407 (13.6)	-	-	318 (36.8)	427 (11.6)	-	-
All-cause death								
30 days	260 (35.4)	399 (13.3)	442 (8.6)	974 (3.5)	302 (34.9)	405 (11.0)	642 (8.8)	1,025 (2.7)
90 days	304 (41.4)	473 (15.8)	803 (15.7)	1,702 (6.1)	342 (39.5)	466 (12.6)	1,157 (15.8)	1,782 (4.7)
End of follow-up	346 (47.1)	541 (18.1)	1,246 (24.3)	2,688 (9.6)	397 (45.9)	547 (14.8)	1,880 (25.6)	3,007 (7.9)
Secondary outcomes								
Fatal/non-fatal myocardial infarction								
30 days	7 (1.0)	8 (0.3)	132 (2.6)	254 (0.9)	9 (1.0)	NA	154 (2.1)	386 (1.0)
90 days	8 (1.1)	9 (0.3)	155 (3.0)	293 (1.0)	9 (1.0)	9 (0.2)	193 (2.6)	428 (1.1)
End of follow-up	11 (1.5)	15 (0.5)	190 (3.7)	351 (1.3)	13 (1.5)	11 (0.3)	248 (3.4)	505 (1.3)
Fatal myocardial infarction								
End of follow-up	NA	NA	62 (1.2)	74 (0.3)	7 (0.8)	10 (0.3)	113 (1.5)	142 (0.4)
Fatal/non-fatal heart failure								
30 days	16 (2.2)	NA	117 (2.3)	133 (0.5)	21 (2.4)	6 (0.2)	348 (4.7)	362 (0.9)
90 days	21 (2.9)	8 (0.3)	168 (3.3)	166 (0.6)	23 (2.7)	8 (0.2)	423 (5.8)	414 (1.1)
End of follow-up	24 (3.3)	10 (0.3)	226 (4.4)	212 (0.8)	28 (3.2)	14 (0.4)	496 (6.8)	478 (1.3)
Fatal heart failure								
End of follow-up	18 (2.5)	NA	88 (1.7)	60 (0.2)	20 (2.3)	11 (0.3)	182 (2.5)	93 (0.2)
Fatal/non-fatal stroke								

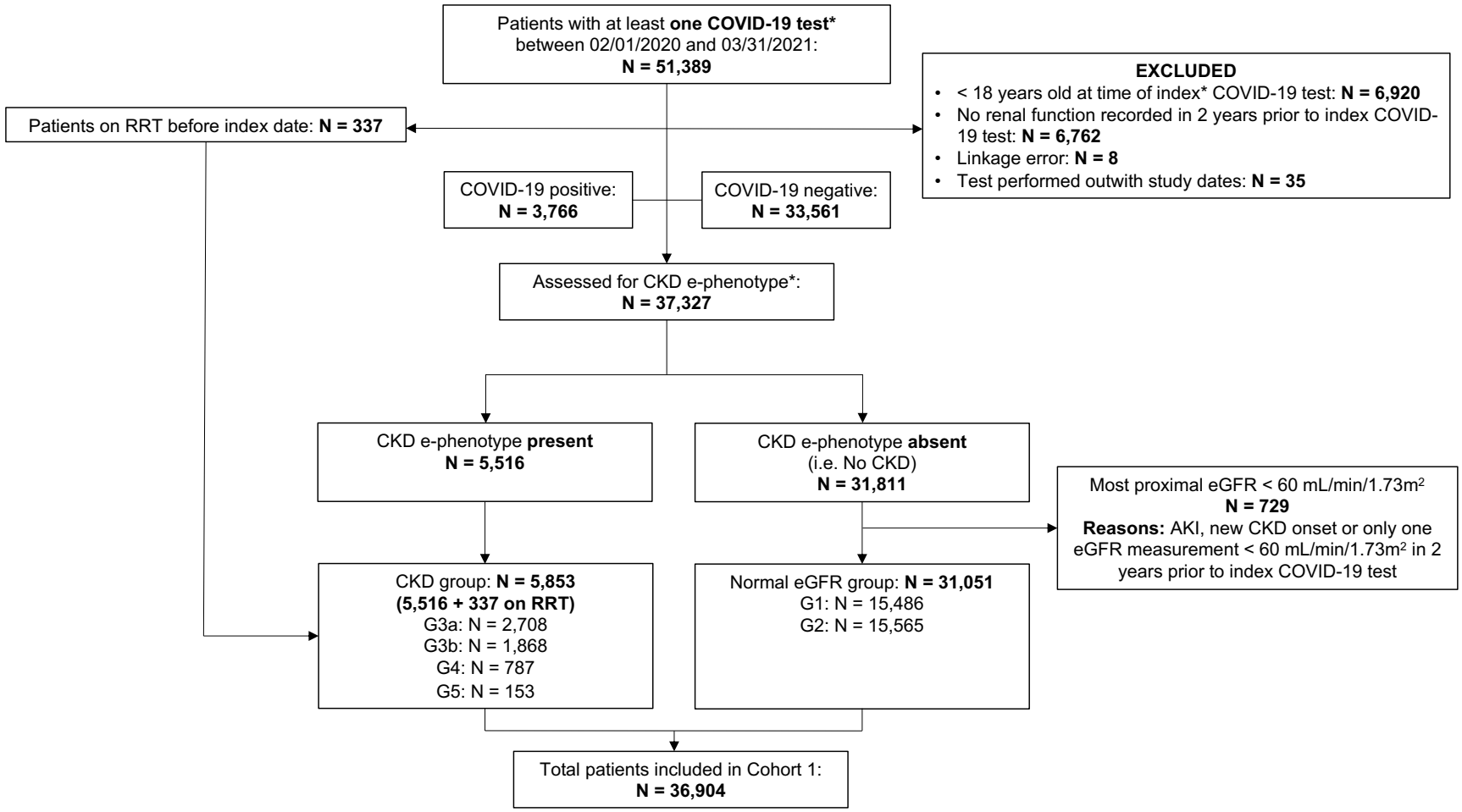
30 days	10 (1.4)	18 (0.6)	96 (1.9)	348 (1.2)	15 (1.7)	31 (0.8)	249 (3.4)	574 (1.5)
90 days	13 (1.8)	23 (0.8)	121 (2.4)	415 (1.5)	19 (2.2)	38 (1.0)	294 (4.0)	648 (1.7)
End of follow-up	16 (2.2)	28 (0.9)	158 (3.1)	487 (1.7)	25 (2.9)	44 (1.2)	348 (4.7)	744 (1.9)
Fatal stroke								
End of follow-up	6 (0.8)	14 (0.5)	57 (1.1)	135 (0.5)	NA	NA	263 (3.6)	410 (1.1)
Fatal/non-fatal pulmonary embolism								
End of follow-up	NA	15 (0.5)	60 (1.2)	286 (1.0)	7 (0.8)	17 (0.5)	87 (1.2)	370 (1.0)
Fatal pulmonary embolism								
End of follow-up	NA	NA	11 (0.2)	20 (0.1)	NA	NA	11 (0.1)	41 (0.1)
Atrial fibrillation hospitalisations								
30 days	NA	7 (0.2)	189 (3.7)	461 (1.6)	7 (0.8)	10 (0.3)	259 (3.5)	626 (1.6)
90 days	12 (1.6)	13 (0.4)	225 (4.4)	557 (2.0)	12 (1.4)	13 (0.3)	303 (4.1)	714 (1.9)
End of follow-up	15 (2.0)	18 (0.6)	292 (5.7)	676 (2.4)	24 (2.8)	24 (0.6)	435 (5.9)	939 (2.5)
Cardiovascular hospitalisations								
30 days	28 (3.8)	53 (1.8)	630 (12.3)	1,847 (6.6)	41 (4.7)	80 (2.2)	1,311 (17.9)	3,076 (8.1)
90 days	41 (5.6)	82 (2.7)	765 (14.9)	2,175 (7.8)	49 (5.7)	100 (2.7)	1,483 (20.2)	3,381 (8.9)
End of follow-up	54 (7.4)	105 (3.5)	958 (18.7)	2,549 (9.1)	60 (6.9)	119 (3.2)	1,636 (22.3)	3,685 (9.7)
All hospitalisations								
30 days	274 (37.3)	896 (29.9)	2,928 (57.2)	13,361 (47.6)	359 (41.5)	899 (24.4)	5,063 (69.0)	18,562 (48.6)
90 days	335 (45.6)	1,128 (37.6)	3,408 (66.6)	15,767 (56.2)	388 (44.9)	970 (26.3)	5,267 (71.8)	19,242 (50.4)
End of follow-up	386 (52.6)	1,311 (43.7)	3,887 (75.9)	17,952 (64.0)	411 (47.5)	1,043 (28.3)	5,429 (74.0)	19,911 (52.2)
Length of stay, median [IQR]	12 [5, 24]	7 [3, 18]	5 [2, 12]	3 [1, 7]	9 [4, 17]	5 [2, 15]	6 [2, 16]	2 [0, 7]

Values are mean ± SD, n (%), or median (interquartile range). NAs represent redacted count data <5.

Supplementary Figures

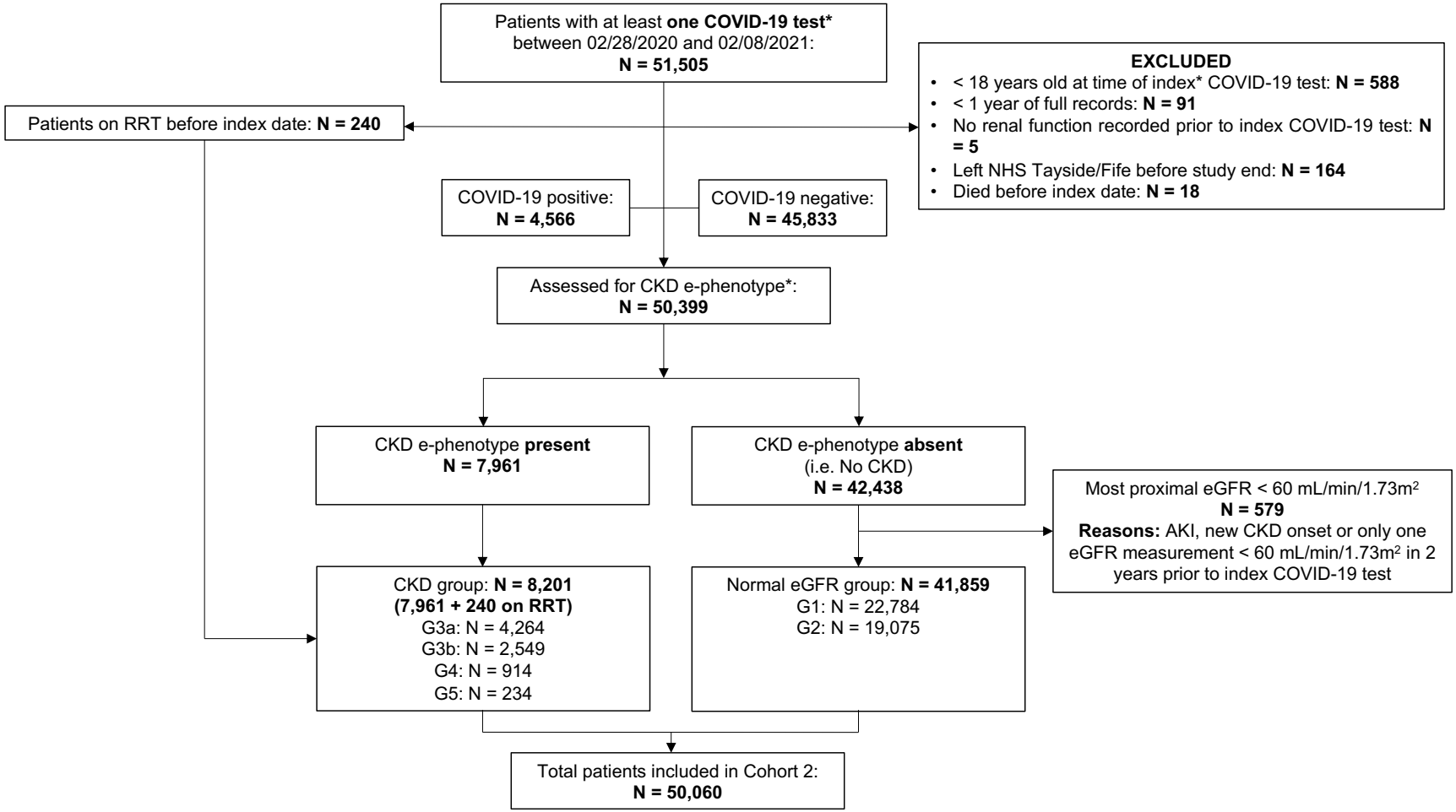
Supplementary Figure 1. Flow diagrams for Cohorts 1 (**a**) and 2 (**b**). Abbreviations: AKI – acute kidney injury; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate (ml/min/1.73 m^2); KTx – kidney transplant; HD – haemodialysis; PD – peritoneal dialysis; RRT – renal replacement therapy.

a) Cohort 1



*See **Methods** for definitions. Abbreviations: AKI – acute kidney injury CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; KTx – kidney transplant; HD – hemodialysis; PD – peritoneal dialysis; RRT – renal replacement therapy;

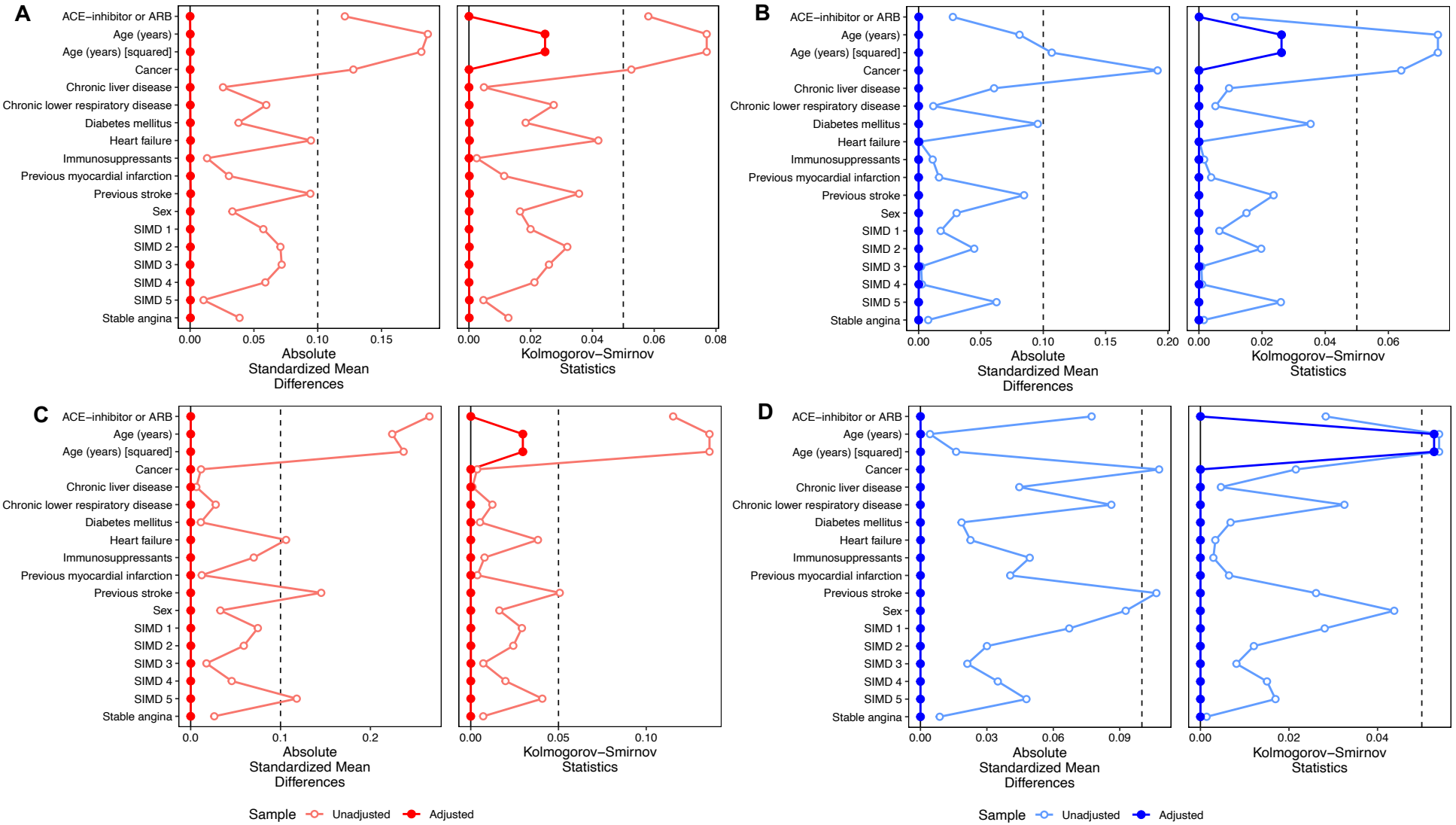
b) Cohort 2



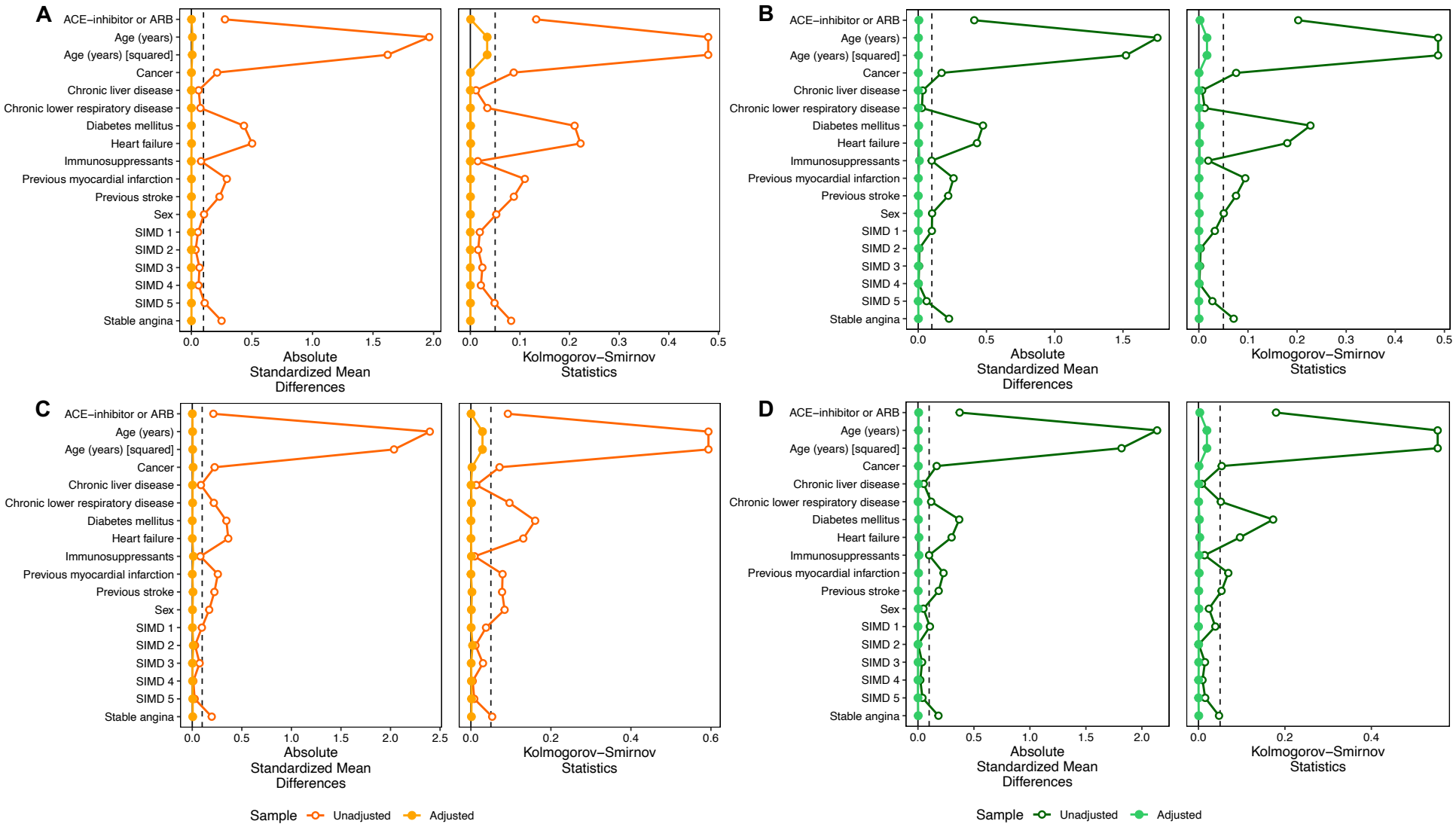
*See **Methods** for definitions. Abbreviations: AKI – acute kidney injury CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; KTx – kidney transplant; HD – hemodialysis; PD – peritoneal dialysis; RRT – renal replacement therapy;

Supplementary Figure 2. Love plots summarising the effect of covariate balancing according to COVID-19 status (i.e. positive *versus* negative) (**a**) in patients with CKD (**Panel A**: Cohort 1; **Panel C**: Cohort 2) and in patients without CKD (**Panel B**: Cohort 1; **Panel D**: Cohort 2), and the effect of covariate balancing according to CKD status (i.e. CKD *versus* no CKD) (**b**) in patients with COVID-19 (**Panel A**: Cohort 1; **Panel C**: Cohort 2) and in patients without COVID-19 (**Panel B**: Cohort 1; **Panel D**: Cohort 2). Abbreviations: ACE-inhibitor – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; SIMD – Scottish index of multiple deprivation.

a) Covariate balancing according to COVID-19 status

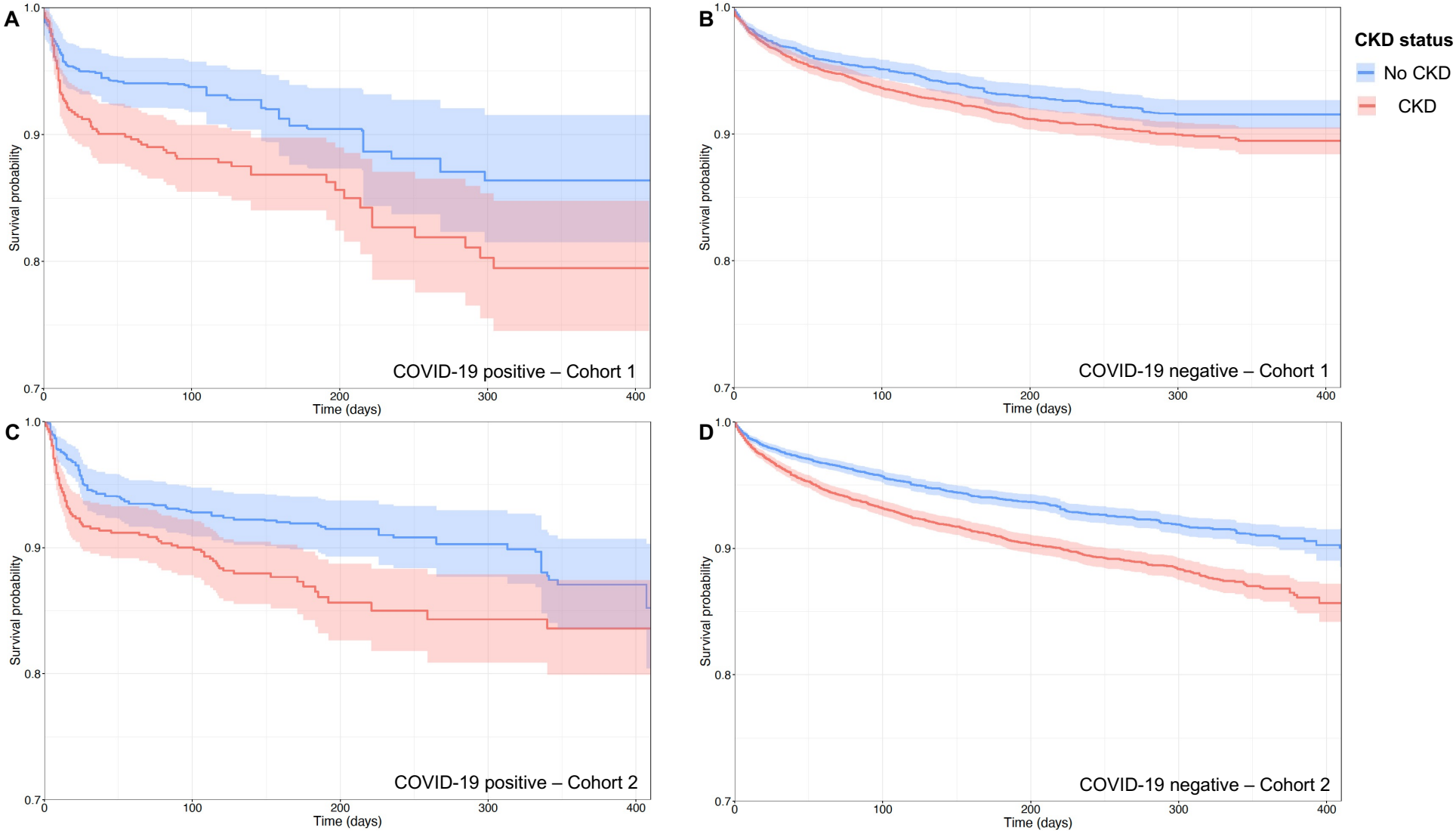


b) Covariate balancing according to CKD status

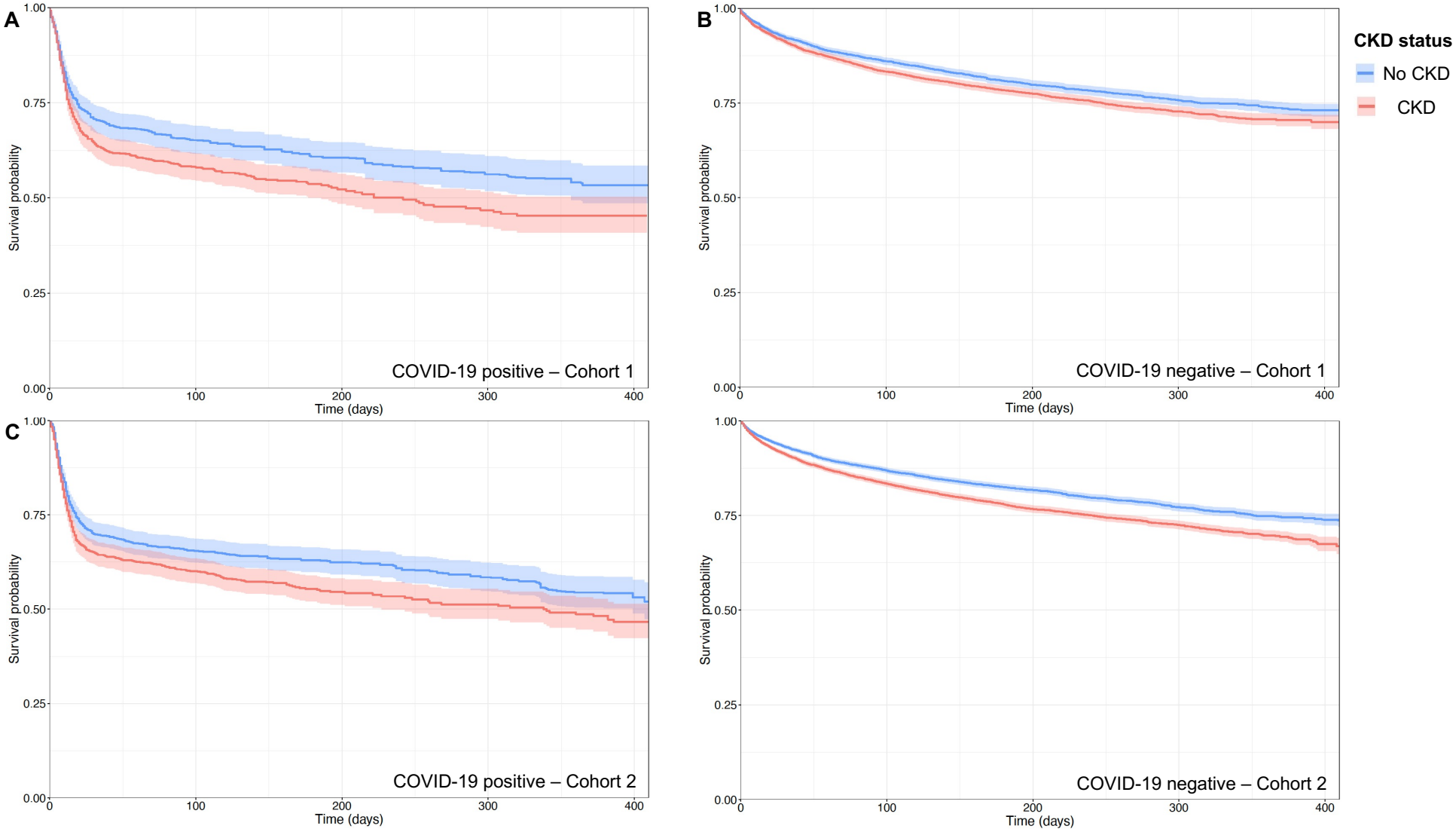


Supplementary Figure 3. Survival curves for cardiovascular (**a**) and all-cause death (**b**) according to CKD status (i.e. CKD *versus* no CKD) for patients with COVID-19 (**Panel A**: Cohort 1; **Panel C**: Cohort 2) and patients without COVID-19 (**Panel B**: Cohort 1; **Panel D**: Cohort 2).

a) Cardiovascular death



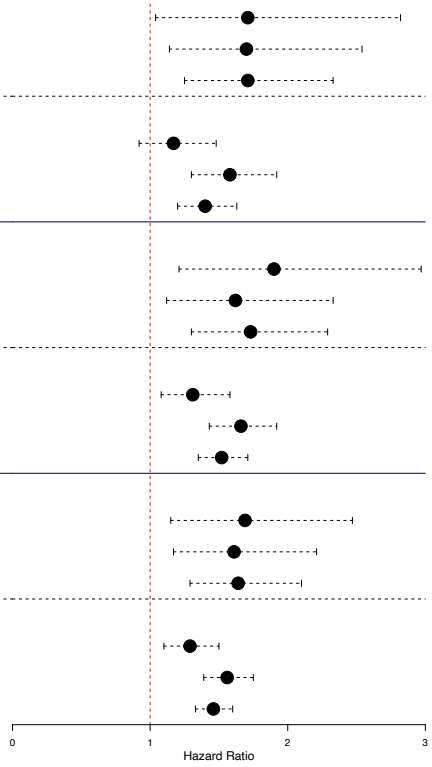
b) All-cause death



Supplementary Figure 4. Forest plot summarising adjusted hazard ratios (HR) from Cohorts 1 and 2 and associated pooled meta-estimates for cardiovascular (**a**) and all-cause death (**b**) according to CKD status (i.e. CKD *versus* No CKD) for patients with COVID-19 (**red**) and for patients without COVID-19 (**blue**) at 30 days (**top panel**), 90 days (**middle panel**) and to the end of study follow-up (**bottom panel**).

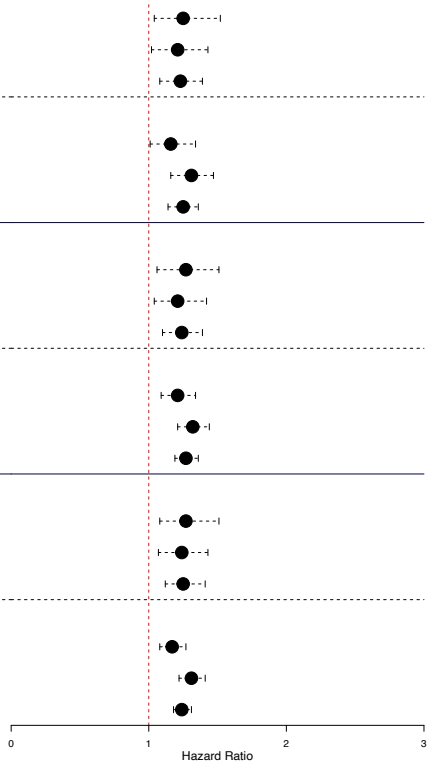
a) Cardiovascular death

	HR	lower	upper
COVID positive – 30 days			
Cohort 1	1.71	1.04	2.82
Cohort 2	1.70	1.14	2.54
Summary	1.71	1.25	2.33
COVID negative – 30 days			
Cohort 1	1.17	0.92	1.48
Cohort 2	1.58	1.30	1.92
Summary	1.40	1.20	1.63
COVID positive – 90 days			
Cohort 1	1.90	1.21	2.97
Cohort 2	1.62	1.12	2.33
Summary	1.73	1.30	2.29
COVID negative – 90 days			
Cohort 1	1.31	1.08	1.58
Cohort 2	1.66	1.43	1.92
Summary	1.52	1.35	1.71
COVID positive – study end			
Cohort 1	1.69	1.15	2.47
Cohort 2	1.61	1.17	2.21
Summary	1.64	1.29	2.10
COVID negative – study end			
Cohort 1	1.29	1.10	1.50
Cohort 2	1.56	1.39	1.75
Summary	1.46	1.33	1.60



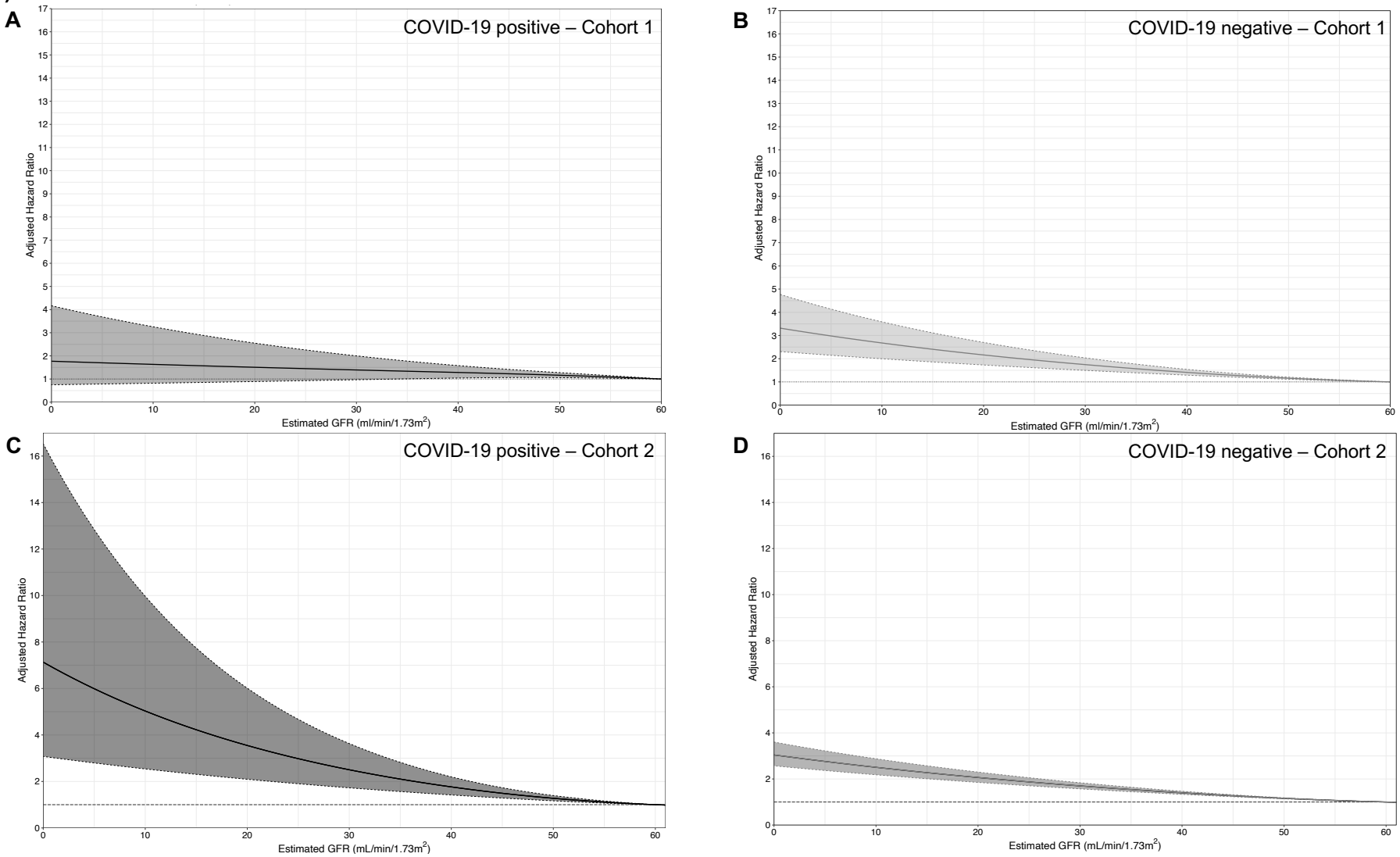
b) All-cause death

	HR	lower	upper
COVID positive – 30 days			
Cohort 1	1.25	1.04	1.52
Cohort 2	1.21	1.02	1.43
Summary	1.23	1.08	1.39
COVID negative – 30 days			
Cohort 1	1.16	1.01	1.34
Cohort 2	1.31	1.16	1.47
Summary	1.25	1.14	1.36
COVID positive – 90 days			
Cohort 1	1.27	1.06	1.51
Cohort 2	1.21	1.04	1.42
Summary	1.24	1.10	1.39
COVID negative – 90 days			
Cohort 1	1.21	1.09	1.34
Cohort 2	1.32	1.21	1.44
Summary	1.27	1.19	1.36
COVID positive – study end			
Cohort 1	1.27	1.08	1.51
Cohort 2	1.24	1.07	1.43
Summary	1.25	1.12	1.41
COVID negative – study end			
Cohort 1	1.17	1.08	1.27
Cohort 2	1.31	1.22	1.41
Summary	1.24	1.18	1.31

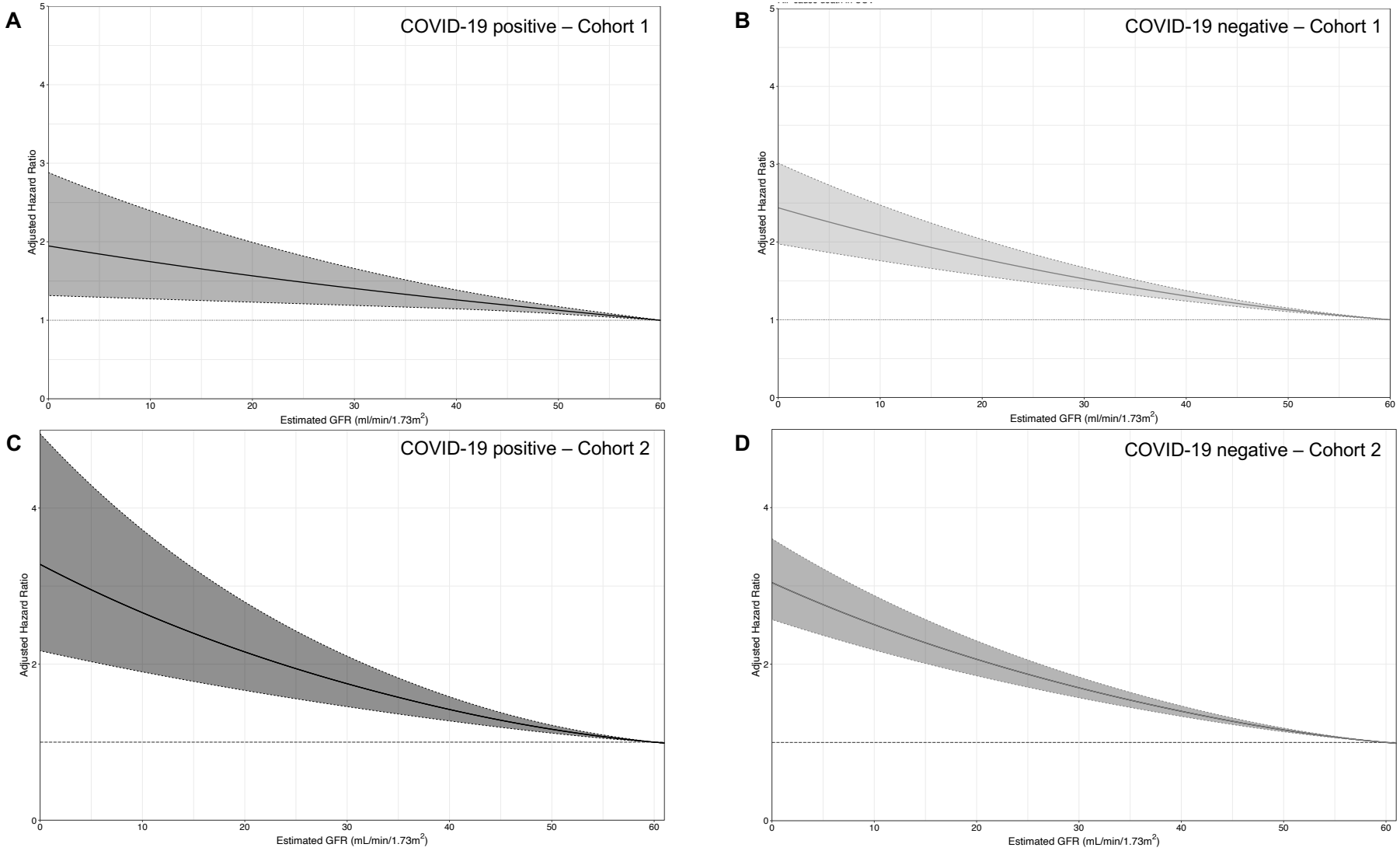


Supplementary Figure 5. Adjusted hazard ratios of cardiovascular (**a**) and all-cause death (**b**) according to eGFR (ml/min/1.73 m^2), in patients with COVID-19 (**Panel A**: Cohort 1; **Panel C**: Cohort 2) and in patients without COVID-19 (**Panel B**: Cohort 1; **Panel D**: Cohort 2).

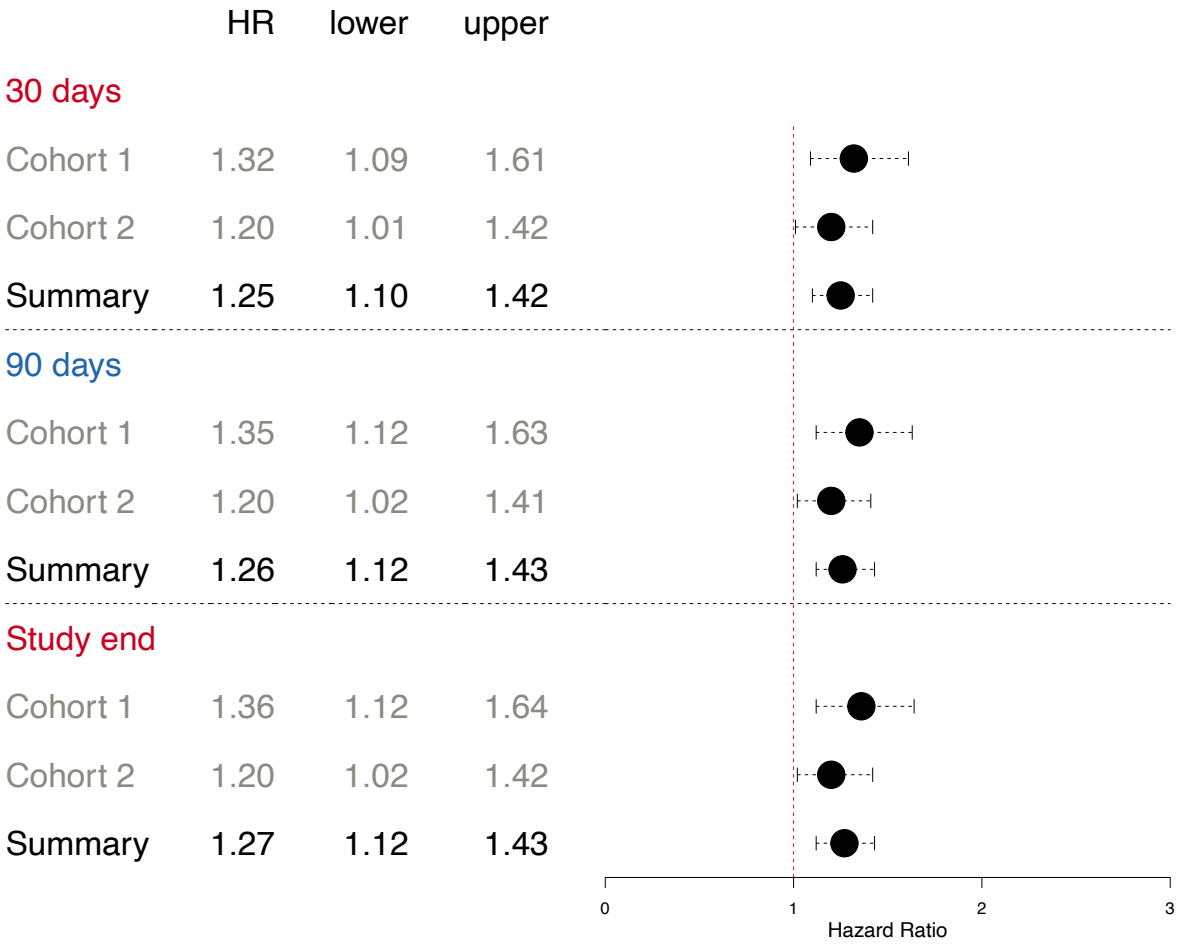
a) Cardiovascular death



b) All-cause death

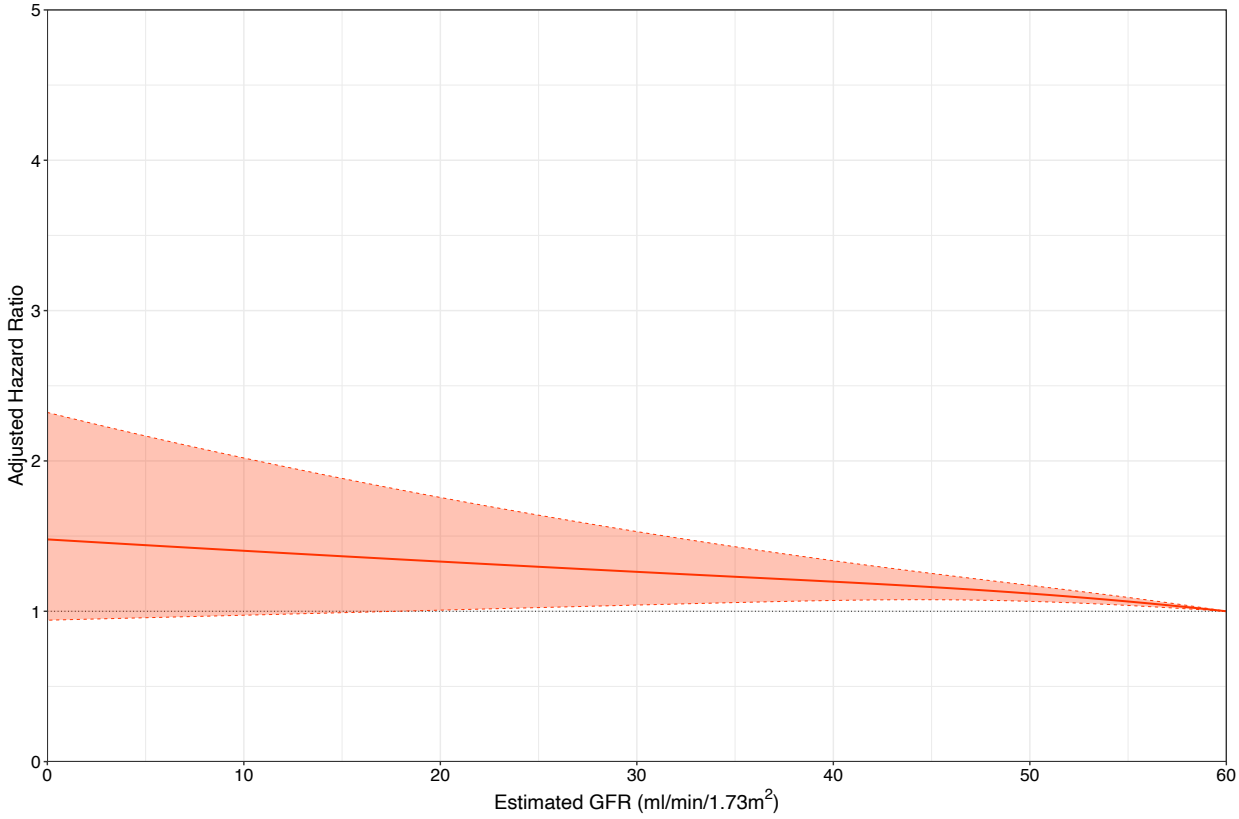


Supplementary Figure 6. Forest plot summarising adjusted hazard ratios (HR) from Cohorts 1 and 2 and associated pooled meta-estimates for COVID-19-related death according to CKD status (i.e. CKD *versus* no CKD) at 30 days (**top panel**), 90 days (**middle panel**) and to the end of study follow-up (**bottom panel**).

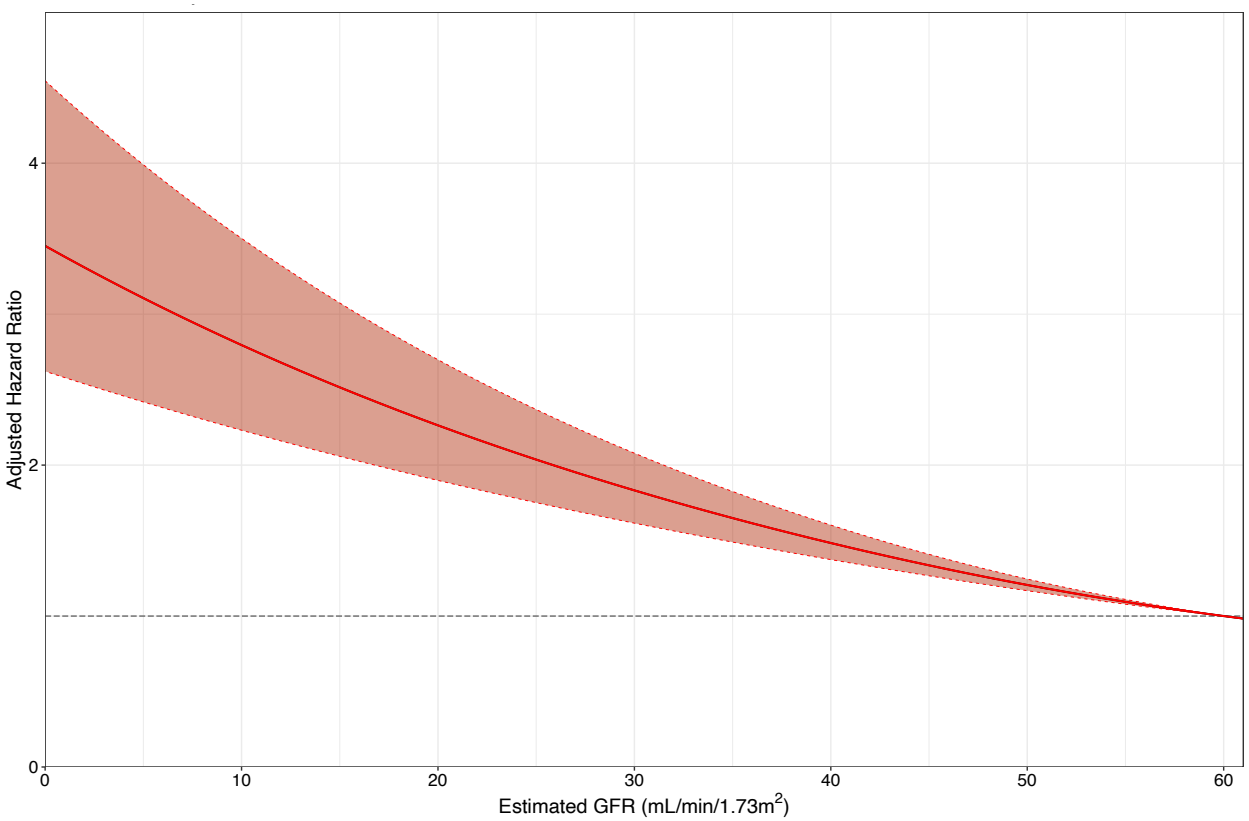


Supplementary Figure 7. Adjusted hazard ratios of COVID-19-related death according to estimated glomerular filtration rate (ml/min/1.73 m^2) in Cohort 1 (**a**) and Cohort 2 (**b**).

a) Cohort 1



b) Cohort 2



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Cardiovascular outcomes in patients with chronic kidney disease & COVID-19: a multi-regional data-linkage study

Lambourg & Gallacher *et al*, 2021

Methods

SARS-CoV-2 PCR

86,964 patients
with prior measures of serum creatinine tested in Scotland, UK

Cohort 1: N = 36,904
CKD = 15.9%

Cohort 2: N = 50,060
CKD = 16.4%

Primary outcomes
- Cardiovascular death
- All-cause death

Covariate Balancing Propensity Score
Weighted comparison by test status

SARS-CoV-2 ⊕ / ⊖

in CKD

in non-CKD

Results

CKD
- SARS-CoV-2 ⊕ : **11.4%**
- Outcomes in patients with COVID-19:
  - Cardiovascular death: **11.1%**
  - COVID-19 death: **36.8%**
  - All-cause death: **46.5%**

No CKD
- SARS-CoV-2 ⊕ : **9.2%**
- Outcomes in patients with COVID-19:
  - Cardiovascular death: **2.7%**
  - COVID-19 death: **12.5%**
  - All-cause death: **16.3%**

COVID-19 ⊕ *vs* ⊖ → EXCESS RISK in PATIENTS WITH CKD

Adjusted meta-estimates combining both cohorts for cardiovascular and all-cause death

	Hazard ratio	Lower 95% CI	Upper 95% CI
30 days	2.34	1.83	2.99
90 days	1.71	1.39	2.11
Study end	1.57	1.31	1.89
30 days	4.53	3.97	5.16
90 days	3.01	2.68	3.35
Study end	2.41	2.17	2.64