JIM Original Article

doi: 10.1111/joim.13239

Increased vulnerability to COVID-19 in chronic kidney disease

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Abstract. Carlson N, Nelveg-Kristensen K-E, Freese Ballegaard E, Feldt-Rasmussen B, Hornum M, Kamper A-L, Gislason G, Torp-Pedersen C (Copenhagen University Hospital Rigshospitalet, Kobenhavn; The Danish Heart Foundation, Copenhagen; Copenhagen University Hospital Gentofte, Hellerup and North Zealand Hospital, Hilleroed, Denmark). Increased vulnerability to COVID-19 in chronic kidney disease. *J Intern Med* 2021; **290**: 166–178. https://doi.org/10.1111/joim.13239

Background. The significance of chronic kidney disease on susceptibility to COVID-19 and subsequent outcomes remains unaddressed.

Objective. To investigate the association of estimated glomerular filtration rate (eGFR) on risk of contracting COVID-19 and subsequent adverse outcomes.

Methods. Rates of hospital-diagnosed COVID-19 were compared across strata of eGFR based on conditional logistic regression using a nested case–control framework with 1:4 matching of patients diagnosed with COVID-19 with controls from the Danish general population on age, gender, diabetes and hypertension. Risk of subsequent severe COVID-19 or death was assessed in a cohort study with comparisons across strata of eGFR based on adjusted Cox regression models with G-computation of results to determine 60-day risk standardized to the distribution of risk factors in the sample.

Results. Estimated glomerular filtration rate was inversely associated with rate of hospital-diagnosed COVID-19: eGFR 61–90 mL/min/1.73m^2 HR 1.13 (95% CI 1.03–1.25), $P = 0.011$; eGFR 46–60 mL/min/1.73m^2 HR 1.26 (95% CI 1.06–1.50), $P = 0.008$; eGFR 31–45 mL/min/1.73m^2 HR 1.68 (95% CI 1.34–2.11), $P < 0.001$; and eGFR ≤ 30 mL/min/1.73m^2 3.33 (95% CI 2.50–4.42), $P < 0.001$ (eGFR > 90 mL/min/1.73m^2 as reference), and renal impairment was associated with progressive increase in standardized 60-day risk of death or severe COVID-19; eGFR > 90 mL/min/1.73m^2 13.9% (95% CI 9.7–15.0); eGFR 90–61 mL/min/1.73m^2 16.1% (95% CI 14.5–17.7); eGFR 46–60 mL/min/1.73m^2 17.8% (95% CI 14.7–21.2); eGFR 31–45 mL/min/1.73m^2 22.6% (95% CI 18.2–26.2); and eGFR ≤ 30 mL/min/1.73m^2 23.6% (95% CI 18.1–29.1).

Conclusions. Renal insufficiency was associated with progressive increase in both rate of hospital-diagnosed COVID-19 and subsequent risk of adverse outcomes. Results underscore a possible vulnerability associated with impaired renal function in relation to COVID-19.

Keywords: COVID-19, estimated glomerular filtration rate, renal insufficiency.

Abbreviations: AKI, acute kidney injury; ATC, Anatomical Therapeutic Chemical Classification System; CI, confidence interval; CKD, chronic kidney disease; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ICD-10, 10th edition of the International Classification of Diseases; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has had devastating health-related consequences worldwide [1, 2]. Accordingly, there is an extraordinary and immediate need for better understanding of

factors associated with disease susceptibility and outcomes, to improve risk stratification and subsequent protection of potentially vulnerable individuals. Renal dysfunction, specifically renal replacement therapy, is associated with an increased risk of infection due to advanced comorbidity, uraemia-associated immune dysfunction and frequent disruptions of the natural skin barrier [3–6], and outcomes subsequent to infection are worse as compared to general populations [7, 8].

Acute kidney injury (AKI), chronic kidney disease (CKD) and end-stage renal disease have recently been identified as possible risk factors for death in patients infected with SARS-CoV-2 [9–13], and although renal insufficiency in hospitalized patients with COVID-19 has been shown to be associated with both disease severity and outcome [13, 14], interpretation remains uncertain due to limitations with regard to effective discrimination between COVID-19-associated AKI and pre-existing CKD. Based on data from multiple nationwide Danish healthcare registers, we investigated the association between renal function and risk of COVID-19 and subsequent adverse outcomes.

Methods

Data sources

The Danish healthcare system provides tax-funded healthcare services for all Danish residents. Cross-referencing of data from differing administrative healthcare registers is possible through individual-level linkage via the unique central person number afforded all Danish residents at birth or immigration [15]. A multitude of administrative and clinical healthcare registers exist, enabling access to divergent healthcare information from numerous data sources. Laboratory work-up from four of five administrative regions was retrieved from the nationwide Register of Laboratory Results [16]. Comorbidities, specific diagnoses and prescription medication were identified through the Danish National Patient Register and Danish National Database of Reimbursed Prescriptions based on administrative code registered in accordance with the 10th edition of the International Classification of Diseases (ICD-10), Nordic Medico-Statistical Committee Classification of Surgical Procedures and Anatomical Therapeutic Chemical Classification System (ATC) code [17–20]. Of note, ICD-10 codes identifying SARS-CoV-2/COVID-19 have previously been validated with a positive predicative value of 98% [21]. An overview of all employed administrative codes is provided in Table S1a–c.

Study design

Two distinct study designs were employed:

1 Susceptibility for COVID-19 was assessed in a nested case–control framework. All Danish residents with available plasma creatinine work-up were followed until either incident hospital-diagnosed COVID-19, death or end of follow-up (24th July 2020). Cases were identified based on incident hospital-diagnosed COVID-19 and subsequently matched with four controls without hospital-diagnosed COVID-19 on age, gender, diabetes and hypertension.

2 Outcomes following hospital-diagnosed COVID-19 were assessed in a retrospective cohort design with inclusion of all Danish residents with available plasma creatinine and confirmed hospital-diagnosed COVID-19. Index was defined as the date of hospital-diagnosed COVID-19, with follow-up until either admission to intensive care, death or end of follow-up (24th July 2020).

Study exposures and covariates

Patient demographics, pre-existing comorbidities and concomitant medications were identified in national health care registers. Identified comorbidities included hypertension, diabetes, ischaemic heart disease, obstructive pulmonary disease, stroke and cancer. Identification of hypertension and diabetes was augmented through employment of data pertaining to prescription medication. All baseline medication was identified based on redeemed prescriptions within six months prior to index and consisted of antihypertensives and antidiabetics. Estimated glomerular filtration rate (eGFR) was computed based on the last plasma creatinine recorded until one week prior to index using the EPI-CKD equation [22]. Assessment of eGFR based on the last recorded plasma creatinine recorded until 7 days before index in data clusters has previously been adjudicated with an intraclass correlation coefficient of 0.88 [95% confidence interval (CI) 0.85–0.91] [23].

Study outcomes

The association of renal function with rate of hospital-diagnosed COVID-19 was analysed using a nested case–control framework with primary

outcome defined as any hospital diagnosis of SARS-CoV-2/COVID-19. Hazard rate was compared across five eGFR strata using eGFR > 90 mL/min/1.73m^2 as reference.

The association of renal function with outcomes following hospital-diagnosed COVID-19 was analysed in a retrospective cohort for a primary composite outcome of severe COVID-19 illness, as defined by requirement of intensive care including mechanical ventilation, or death. Secondary outcomes were defined as (i) death and (ii) severe COVID-19.

Statistical analyses

Patient characteristics were summarized as means with standard deviations or medians with interquartile range (IQR) for continuous variables, and as percentages for categorical variables. Differences were compared using Wilcoxon or chi-square tests, respectively. The association of renal function with study end-points was evaluated across strata of eGFR (>90 mL/min/1.73m^2; 90–61 mL/min/1.73m^2; 60–46 mL/min/1.73m^2; 45–30 mL/min/1.73m^2; and ≤30 mL/min/1.73m^2).

Evaluation of COVID-19 susceptibility was computed in a conditional logistic regression model comparing rate of diagnosis with stratification of baseline hazard rate by age, gender, diabetes and hypertension. Model fitting was accomplished using a nested case–control design with 1 : 4 risk-set matching of cases with age-, gender-, diabetes- and hypertension-matched controls [24]. Cases, that is patients with a hospital diagnosis confirming COVID-19 and controls, were identified from a nationwide Danish population with available laboratory work-up enabling estimation of renal function. All cases were matched with four controls from the overall cohort providing controls remained 'at-risk', that is alive and without hospital-diagnosed COVID-19 at index. Since the partial likelihood is mathematically equivalent to the conditional logistic likelihood used for matched case–control studies, one can maximize the proposed likelihood by 'tricking' statistical software written for conditional logistic regression. The approach is accomplished through the inclusion of multiple inputs for subjects selected multiple times by converting all randomly selected failures to non-failures. Consequently, linear coefficients are to be interpreted as log hazard ratios and not as log odds-ratios [25–27].

Outcomes following COVID-19 diagnosis were compared using the Kaplan–Meier method with adjusted comparison based on Cox regression. Models were adjusted for age, gender, comorbidities (ischaemic heart disease, diabetes, pulmonary disease, heart failure, stroke, malignancy and hypertension) and concomitant medication (renin–angiotensin inhibition, diuretics and insulin). Based on the reported hazard ratios, 60-day risks of outcomes were computed standardized to the distribution of risk factors of all patients in the sample [28]. Subgroup analyses by gender and age-strata were performed, and differences in hazard ratios between subgroups were compared using Wald tests for interaction.

All statistical analyses were performed using the SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA) and R [Version 4.0.1; R Core Team (2019)]. The level of statistical significance was set at 5%, and all statistical tests were 2-tailed.

Sensitivity analyses

To assess possible Berkson's bias, that is admission bias leading to the potential spurious association between SARS-CoV-2/COVID-19 and renal dysfunction, a sensitivity analysis was performed evaluating susceptibility based on rate of positive SARS-CoV-2 swab and risk of subsequent outcomes in two of four administrative regions in Denmark encompassing 2.6 million Danish citizens (46.1% of the Danish general population). Evaluation of susceptibility adjudged by rate of positive swab for SARS-CoV-2 and risk of subsequent outcome as defined by hospitalization due to COVID-19 or death were evaluated in accordance with methods describe in principal analyses.

Due to possible risk of misclassification bias due to case mix, that is misclassification of AKI as CKD, principal results pertaining to rates of hospital-diagnosed COVID-19 and risk of subsequent outcomes were re-analysed in sensitivity analyses with computation of eGFR based on plasma creatinine recorded >90 days prior to time of diagnosis only.

The principal model employed a complete case approach with exclusion of cases and controls without pre-existing information related to renal function. To estimate possible bias related to

Table 1. *Nested case–control: Baseline characteristics of patients with hospital-diagnosed COVID-19 and matched controls*

Variables	Patients with COVID-19 n = 3647	Matched controls n = 14 458	All patients n = 18 105
Gender, male, n (%)	1682 (46.1)	6667 (46.1)	8349 (46.1)
Age, median years (IQR)	57.6 (43.8, 74.6]	57.9 (43.6, 74.]	57.9 (43.6, 74.5]
eGFR strata			
≤30 mL/min/1.73m^2	97 (2.7)	153 (1.1)	250 (1.4)
31–45 mL/min/1.73m^2	142 (3.9)	434 (3.0)	576 (3.2)
46–60 mL/min/1.73m^2	278 (7.6)	1084 (7.5)	1362 (7.5)
61–90 mL/min/1.73m^2	1,481 (40.6)	5944 (41.1)	7425 (41.0)
>90 mL/min/1.73m^2	1649 (45.2)	6843 (47.3)	8492 (46.9)
Hypertension, n (%)	698 (19.1)	2867 (19.8)	3565 (19.7)
Diabetes, n (%)	518 (14.2)	2026 (14.0)	2544 (14.1)
Heart failure, n (%)	224 (6.1)	516 (3.6)	740 (4.1)
Ischaemic heart disease, n (%)	484 (13.3)	1524 (10.5)	2008 (11.1)
Prior stroke, n (%)	228 (6.3)	641 (4.4)	869 (4.8)
Pulmonary disease, n (%)	279 (7.7)	662 (4.6)	941 (5.2)
Prior cancer, n (%)	435 (11.9)	1522 (10.2)	1957 (10.8)
ACEi/ARB, n (%)	843 (23.1)	3388 (23.4)	4231 (23.4)
Betablocker, n (%)	509 (14.0)	1827 (12.6)	2336 (12.9)
Calcium channel blocker, n (%)	456 (12.5)	1940 (13.4)	2396 (13.2)
Diuretics, n (%)	477 (13.1)	1939 (13.4)	2416 (13.3)
Metformin, n (%)	281 (7.7)	1218 (8.4)	1499 (8.3)
Insulin, n (%)	170 (4.7)	537 (3.7)	707 (3.9)

differences between incomplete and complete cases, main results were re-analysed in sensitivity analyses following imputation of eGFR in individuals without pre-existent measurement of plasma creatinine under an assumption of random missingness, based on a multiple linear regression model adjusted for sex, age, history of hypertension, ischaemic heart disease and heart failure, and prescriptions of renin-angiotensin inhibitors, diuretics and insulin.

Ethics

Register-based studies do not require pre-existing ethical approval in Denmark. The use of study data was approved through the Danish Data Protection Agency (ref. P-2019-191). All pseudo-anonymized data were linked, stored and analysed securely within a research platform administered through Statistics Denmark. All code is shared openly for review and re-use under the Statistics Denmark licence. As detailed patient data holds potential for re-identification, full data sharing is not possible.

Results

Hospital-diagnosed COVID-19 was confirmed in a total of 4658 patients in the Danish National Patient register between 22nd February and 24th July 2020. Pre-existing plasma creatinine permitting estimation of renal function was recorded in 3647 (78.3%) patients. A comparison of baseline demographics in all patients and patients with pre-existing plasma creatinine is provided in the supplemental materials (Table S2). In the subset of patients with pre-existing plasma creatinine, gender distribution was 46.1% male, median age was 57.6 [IQR 42.8–74.6] years, median eGFR was 88 [IQR 72–103] mL/min/1.73m^2 with an eGFR ≤ 60 mL/min/1.73m^2 in 14.2% of patients, and a prevalence of hypertension and diabetes of 19.1% and 14.2%, respectively. End-stage renal

Table 2. *Nested case–control: Hazard ratios for strata of eGFR for rate of hospital-diagnosed COVID-19*

All patients		
eGFR Strata	Hazard ratio	*P*-value
>90 mL/min/1.73m^2	REF	
61–90 mL/min/1.73m^2	1.13 (1.03–1.25)	0.011
46–60 mL/min/1.73m^2	1.26 (1.06–1.50)	0.008
31–45 mL/min/1.73m^2	1.68 (1.34–2.11)	<0.001
≤30 mL/min/1.73m^2	3.33 (2.50–4.42)	<0.001

Gender-specific strata	Male		Female	
eGFR strata	Hazard ratio	*P*-value	Hazard ratio	*P*-value
>90 mL/min/1.73m^2	REF		REF	
61–90 mL/min/1.73m^2	1.18 (1.02–1.36)	0.025	1.10 (0.96–1.26)	0.165
46–60 mL/min/1.73m^2	1.62 (1.28–2.06)	<0.001	0.97 (0.76–1.24)	0.816
31–45 mL/min/1.73m^2	1.83 (1.32–2.52)	<0.001	1.54 (1.12–2.11)	0.008
≤30 mL/min/1.73m^2	4.12 (2.79–6.08)	<0.001	2.61 (1.71–3.97)	<0.001

Age-specific strata	Patient age ≤60 years		Patient age 61–70 years		Patient age >70 years	
eGFR strata	Hazard ratio	*P*-value	Hazard ratio	*P*-value	Hazard ratio	*P*-value
>90 mL/min/1.73m^2	REF		REF		REF	
61–90 mL/min/1.73m^2	1.16 (1.03–1.32)	0.016	1.17 (0.92–1.50)	0.208	0.73 (0.54–0.99)	0.040
46–60 mL/min/1.73m^2	1.41 (0.83–2.41)	0.207	1.48 (0.83–2.64)	0.188	0.84 (0.60–1.16)	0.292
31–45 mL/min/1.73m^2	2.84 (0.92–8.77)	0.070	2.72 (1.13–6.52)	0.025	1.04 (0.73–1.49)	0.831
≤30 mL/min/1.73m^2	3.35 (1.27–8.81)	0.015	9.10 (3.02–22.75)	<0.001	2.00 (1.31–3.05)	0.034

disease was identified in a total of 17 patients based on pre-existing dialysis requirement.

Nested case–control study

A total of 3647 patients with hospital-diagnosed COVID-19 and known eGFR were matched 1 : 4 with a total of 14 458 controls with known eGFR without SARS-CoV-2/COVID-19. Baseline characteristics are shown in Table 1. Median eGFR was 88 [IQR 72–103] mL/min/1.73m^2 and 89 [IQR 73–103] mL/min/1.73m^2 in cases and controls, respectively; however, the prevalence of eGFR ≤ 60 mL/min/1.73m^2 was substantially greater in cases compared with controls (14.2% vs. 11.6%, $P < 0.001$). Median time between creatinine sample and index was 229 [IQR 75–686] days (60.9% recorded within one year, and 76.6% within two years). Characteristics of the Danish general population with recorded plasma creatinine are provided in the supplemental materials (Table S3).

Renal insufficiency was associated with a progressive increase in rate of hospital-diagnosed COVID-19. Overall and stratified results are shown in Table 2. Prior renal transplantation and dialysis-treated end-stage renal disease were associated with increased rate of hospital-diagnosed COVID-19, HR 2.69 (95% CI 1.11–6.55), $P = 0.029$ and HR 14.67 (95% CI 4.09–52.57), $P < 0.001$, respectively, and overall results remain unchanged in sensitivity analyses on patients with and without hypertension, and with and without diabetes, respectively, and in data augmented by imputation of eGFR in patients without creatinine measurement prior to hospital admission (Tables S7 and S8).

Retrospective cohort study

For assessment of outcomes following COVID-19 diagnosis, the 3647 patients with confirmed hospital-diagnosed COVID-19 and known eGFR were followed for a median 110 [IQR 79–121] days.

Table 3. *Retrospective cohort of patients with COVID-19: Baseline characteristics of patients with hospital-diagnosed COVID-19*

	eGFR (mL/min/1.73m^2)					
	≤30	31–45	46–60	61–90	>90	All
Variables	*n* = 97	*n* = 142	*n* = 278	*n* = 1481	*n* = 1649	*n* = 3647
Gender, male, *n* (%)	54 (55.7)	75 (52.8)	156 (56.1)	716 (48.3)	689 (41.8)	1682 (46.1)
Age, median years (IQR]	78.2 (69.4, 85.6]	83.1 (77.0, 87.2]	80.8 (73.8, 85.8]	66.5 (55.2, 77.7]	44.9 (33.3, 54.7]	57.6 (43.8, 74.6]
Hypertension *n* (%)	49 (50.5)	60 (42.3)	115 (41.4)	371 (25.1)	103 (6.2)	698 (19.1)
Diabetes, *n* (%)	44 (45.4)	43 (30.3)	67 (24.1)	192 (13.0)	172 (10.4)	518 (14.2)
Heart failure, *n* (%)	30 (30.9)	34 (23.9)	49 (17.6)	88 (5.9)	23 (1.4)	224 (6.1)
Ischaemic heart disease, *n* (%)	35 (36.1)	44 (31.0)	83 (29.9)	241 (16.3)	81 (4.9)	484 (13.3)
Prior stroke, *n* (%)	15 (15.5)	25 (17.6)	52 (18.7)	109 (7.4)	27 (1.6)	228 (6.3)
Pulmonary disease	17 (17.5)	23 (16.2)	44 (15.8)	145 (9.8)	50 (3.0)	279 (7.7)
Prior cancer, *n* (%)	26 (26.8)	31 (21.8)	62 (22.3)	236 (15.9)	80 (4.9)	435 (11.9)
ACEi/ARB, *n* (%)	48 (49.5)	70 (49.3)	130 (46.8)	428 (28.9)	167 (10.1)	843 (23.1)
Betablocker, *n* (%)	49 (50.5)	59 (41.6)	89 (32.0)	253 (17.1)	59 (3.6)	509 (14.0)
Calcium channel blocker, *n* (%)	30 (30.9)	33 (23.2)	58 (20.9)	246 (16.6)	89 (5.4)	456 (12.5)
Diuretics, *n* (%)	20 (20.6)	35 (24.6)	76 (27.3)	272 (18.4)	74 (4.5)	477 (13.1)
Metformin, *n* (%)	7 (7.2)	19 (13.4)	39 (14.0)	126 (8.5)	90 (5.5)	281 (7.7)
Insulin, *n* (%)	28 (28.9)	21 (14.8)	30 (10.8)	53 (3.6)	38 (2.3)	170 (4.7)

Table 4. *Retrospective cohort study: Hazard ratios and standardized 60-day risk of outcomes following hospital-diagnosed COVID-19*

	Unadjusted model		Age- and sex-adjusted model		Fully adjusted model		
eGFR (mL/min/1.73 m^2)	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Standardized 60-day risk % (95% CI)
Severe COVID-19							
>90	Ref.		Ref.		Ref.		5.5 (4.1–7.2)
61–90	2.67 (1.98–3.61)	<0.001	1.44 (1.03–2.01)	0.031	1.44 (1.03–2.02)	0.032	7.5 (0.4–11.8)
46–60	3.17 (2.05–4.91)	0.003	1.65 (1.01–2.68)	0.045	1.53 (0.94–2.51)	0.089	7.8 (6.5–9.1)
31–45	2.55 (1.38–4.74)	<0.001	1.46 (0.75–2.81)	0.264	1.39 (0.71–2.70)	0.333	8.3 (5.6–11.4)
≤30	4.05 (2.23–7.38)	<0.001	1.89 (1.01–3.55)	0.048	1.67 (0.88–3.19)	0.118	8.9 (4.1–14.0)
Death							
>90	Ref.		Ref.		Ref.		9.6 (7.2–12.0)
61–90	5.38 (3.96–7.31)	<0.001	1.24 (0.90–1.73)	0.194	1.26 (0.91–1.75)	0.170	11.8 (10.5–13.0)
46–60	13.15 (9.30–18.58)	<0.001	1.58 (1.08–2.31)	0.020	1.50 (1.02–2.21)	0.040	13.6 (11.2–16.2)
31–45	20.11 (13.88–29.12)	<0.001	2.33 (1.55–3.50)	<0.001	2.26 (1.50–3.41)	<0.001	18.7 (15.6–23.2)
≤30	19.49 (12.99–29.23)	<0.001	2.69 (1.75–4.14)	<0.001	2.33 (1.49–3.63)	<0.001	19.1 (14.0–24.6)
Severe COVID-19 or death							
>90	Ref.		Ref.		Ref.		12.3 (10.1–14.9)
61–90	3.99 (3.16–5.03)	<0.001	1.36 (1.05–1.76)	0.019	1.36 (1.05–1.77)	0.019	16.1 (14.5–17.7)
46–60	7.99 (6.05–10.57)	<0.001	1.64 (1.19–2.26)	0.003	1.54 (1.11–2.13)	0.009	17.8 (14.8–20.8)
31–45	10.94 (8.00–14.96)	<0.001	2.22 (1.56–3.16)	<0.001	2.09 (1.46–2.98)	<0.001	22.6 (18.2–27.9)
≤30	11.23 (7.94–15.88)	<0.001	2.55 (1.75–3.72)	<0.001	2.20 (1.50–3.24)	<0.001	23.6 (17.9–28.8)

Baseline characteristics stratified by eGFR are provided in Table 3. Median time from creatinine sample to index was 181 [IQR 51–568] days (65.8% within one year and 80.2% within 2 years). Unadjusted 60-day mortality was 12.4% (n = 452), and the combined end-point of either death or requirement of intensive care was recorded in a total of 16.6% (n = 606) of patients.

Renal function was associated with crude 60-day risk of death or requirement of intensive care: eGFR > 90 mL/min/1.73m^2 5.3%; eGFR 90–61 mL/min/1.73m^2 20.1%; eGFR 46–60 mL/min/1.73m^2 37.4%; eGFR 31–45 mL/min/1.73m^2 48.0%; and eGFR ≤ 30 mL/min/1.73m^2 49.6%. Amongst patients with end-stage renal disease, 60-day risks of death or requirement of

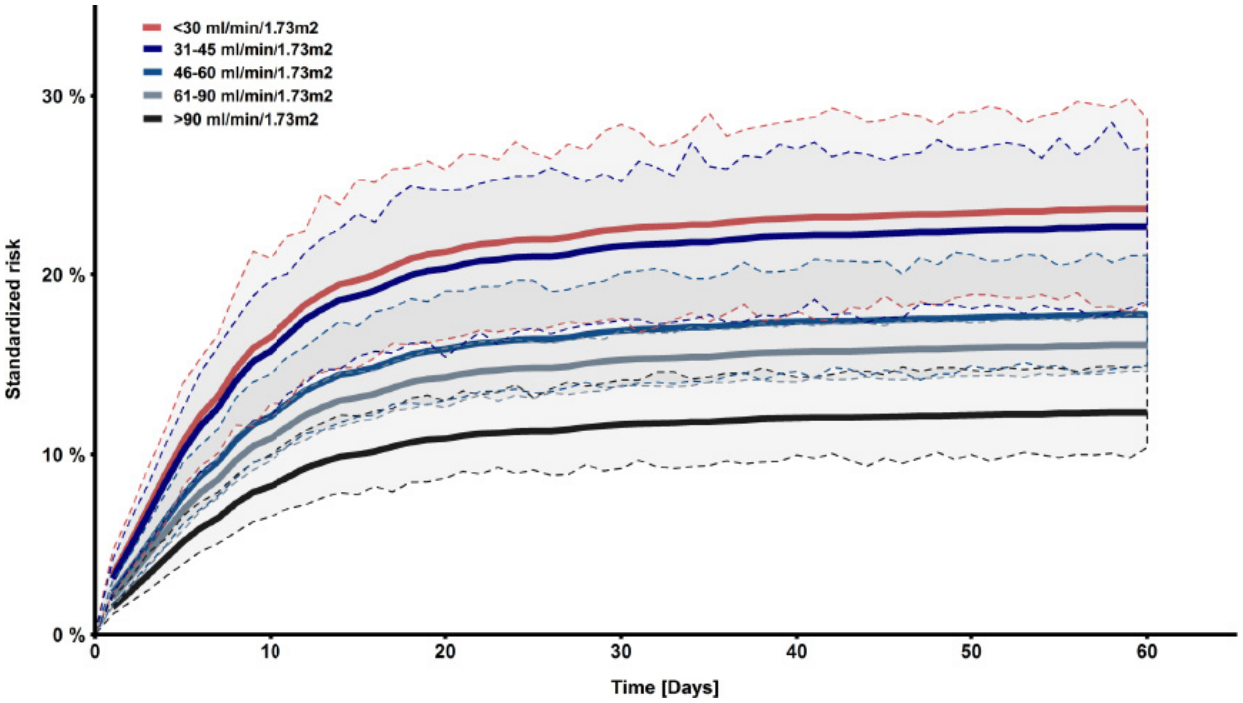

Fig. 1 *Cohort study: Standardized risk of severe COVID-19 or death stratified by eGFR in patients with hospital-diagnosed COVID-19.*

intensive care, and death were 64.7% and 52.9%, respectively.

Renal insufficiency was associated with progressive risk of all designated outcomes. Unadjusted and adjusted results from the Cox proportional hazards regression models, and standardized 60-day risks for severe COVID-19, death, and severe COVID-19 or death are provided in Table 4. Risk of severe COVID-19 or death stratified by eGFR is illustrated in Fig. 1. Gender- and age-stratified standardized 60-day risks, and risk differences and ratios of outcomes in all patients are provided in the supplemental materials (Tables S4 and S5). Standardized 60-day risk for severe COVID-19 or death was 30.5% (95% CI 14.8–48.9%) and 22.4% (95% CI 0.0–42.1%) in end-stage renal disease and renal transplantation, respectively. Results remained unchanged in stratified analyses on patients with and without hypertension, with and without diabetes, in patients diagnosed in- and outpatient, respectively, in sensitivity analyses limited to patients with eGFR defined based on plasma creatinine recorded >90 days before time of diagnosis, and in sensitivity analyses based on data augmented by imputation of eGFR in patients without creatinine measurement prior to hospital admission. Results from sensitivity analyses are shown in the supplemental materials (Tables S6, S9 and S10, respectively).

Sensitivity analysis: Susceptibility and risk of subsequent outcomes based on SARS-CoV-2 swab

A positive swab for SARS-CoV-2 was confirmed in a total of 9652 patients in the Capital Region and Region Zealand between 22 February and 24 July 2020. Pre-existing plasma creatinine permitting estimation of renal function was recorded in 7509 (77.8%) patients. Median age was 51.0 [IQR 36.2–65.4] years, gender distribution was 39.6% male, median eGFR was 97 [IQR 79–110] mL/min/1.73m^2 with an eGFR $\leq$ 60 mL/min/1.73m^2 in 9.1% of patients, and a prevalence of hypertension and diabetes of 14.0% and 11.4%, respectively. The prevalence of dialysis requirement due to end-stage renal disease and prior renal transplantation was 0.1% and 0.2%, respectively.

For assessment of susceptibility of SARS-CoV-2/COVID-19, the 7509 patients with confirmed positive SARS-CoV-2 swabs and known eGFR were matched 1:4 with a total of 29 724 controls with known eGFR without a confirmed positive SARS-CoV-2 swab in a nested case–control study. Baseline characteristics of cases and controls are provided in the supplemental materials (Table S11). Renal function was inversely associated with progressive increase in rate of positive SARS-CoV-2 swab: eGFR 61–90 mL/min/1.73m^2 HR 1.01 (95% CI 0.94–1.08), $P = 0.860$; eGFR 46–60 mL/min/1.73m^2 HR 1.14 (95% CI 0.99–1.31), $P = 0.075$; eGFR 31–45 mL/min/1.73m^2 HR 1.44 (95% CI 1.19–1.73), $P = 0.001$; and eGFR ≤ 30 mL/min/1.73m^2 HR 2.29 (95% CI 1.79–2.92), $P < 0.001$ (eGFR > 90 mL/min/1.73m^2 as reference). Prior renal transplantation and dialysis-treated end-stage renal disease were both associated with increased rate of positive SARS-CoV-2 swab, HR 1.77 (95% CI 0.88–357), $P = 0.111$ and HR 3.50 (95% CI 1.27–9.65), $P = 0.016$, respectively.

For assessment of outcomes, the 7509 patients with confirmed SARS-CoV-2 and known eGFR were followed for a median 70 (IQR 2–101) days to assess risk of hospitalization due to COVID-19 or death. Baseline characteristics are provided in the supplemental materials (Table S12). Renal insufficiency was associated with progressive 60-day risk of hospitalization due to COVID-19 or death. Specifically, 60-day risk of hospitalization due to COVID-19 or death increased by eGFR strata: eGFR > 90 mL/min/1.73m^2 33.3% (95% CI 31.7–35.2%); eGFR 90–61 mL/min/1.73m^2 38.5% (95% CI 36.4–40.4%); eGFR 46–60 mL/min/1.73m^2 42.5% (95% CI 38.1–47.3%); eGFR 31–45 mL/min/1.73m^2 43.8% (95% CI 37.8–50.3%); eGFR ≤ 30 mL/min/1.73m^2 50.8% (95% CI 44.4–57.5%); end-stage renal disease 64.3% (95% CI 43.0–83.7%); and renal transplantation 52.0% (95% CI 25.6–77.3%). Adjusted results from the Cox proportional hazards regression models are provided in the supplemental materials (Table S13).

Discussion

In a nationwide general population sample, impairment of renal function was independently associated with progressive increase in both susceptibility to SARS-CoV-2/COVID-19 and subsequent risk of adverse outcomes. Specifically, results demonstrated a >3-fold increased rate of infection with SARS-CoV-2/COVID-19 amongst patients with eGFR < 30 mL/min/1.73m^2, with a subsequent 60-day risk of death or requirement of intensive care of >20%.

Renal dysfunction as defined by either albuminuria or reduced GFR has been shown to be a risk factor for both community-acquired bacteremia and infection, and related adverse outcomes, including influenza-associated mortality [7, 29–34]. Notably, risk of bacteremia has previously been demonstrated to be proportional to renal function [32], and our results also demonstrated an independent association between progressive renal insufficiency and rate of both positive SARS-CoV-2 swab and hospital-diagnosed COVID-19. CKD infers substantial modifications to the immune system relative to renal insufficiency including B- and T-cell phagocytic dysfunction, increased and persistent systemic inflammation leading to increase in pro-inflammatory cytokines and monocytes, loss of neutrophil function, and increased rate of B-lymphocyte apoptosis [35–39]. Furthermore, evidence-based treatment of a multitude of divergent kidney diseases necessitates long-term immunosuppression for mitigation of risk of disease progression. As such, evidence exists to support a possible mediation of infection susceptibility due to immunological dysfunction caused by renal insufficiency.

The prevalence of CKD in patients with COVID-19 has been reported from 0.7% to 47.6% dependent on patient selection [2, 40, 41]; overall, prevalence is estimated to be 5.2% (95% CI 2.8–8.1) with incidence of end-stage renal disease purported to be 2.3% (95% CI 1.8–2.8) [42]. Our understanding is, however, predominantly based on administrative billing codes as opposed to laboratory work-up with computation of eGFR. Nonetheless, the prevalences of CKD as defined by eGFR < 60 mL/min/1.73m^2 and end-stage renal disease were reported to be 6.4% and 0.1%, respectively, in >17 million primary care patients with COVID-19 in the British OpenSafely cohort [13]. Comparably, the prevalences of CKD in the current study as defined by eGFR < 60 mL/min/1.73m^2 and end-stage renal disease were 14.2% and 0.5%, respectively, differences plausibly attributable to patient demographics; that is 68.4% of patients in the OpenSafely cohort were younger than 60 years as opposed to only 53.2% in the present cohort.

The impact of CKD on risk associated with COVID-19 has also previously been tentatively evaluated

in the Danish general population [43]. Based on pre-existent administrative billing code, CKD was associated with increased odds of both hospitalization due to COVID-19 and subsequent death in analyses adjusting for age and gender; however, the associated odds decreased substantially when adjusting for competing comorbidities.

Our results demonstrated a progressive increase in risk of severe COVID-19 or death associated with renal insufficiency as defined by eGFR computed from pre-admission plasma creatinine. Notably, principal results remained unchanged in sensitivity analyses censoring plasma creatinine recorded within 90 days of time of diagnosis, and in subgroup analyses stratified on age, gender and specific risk factors. Furthermore, principal results were also confirmed in sensitivity analyses evaluating susceptibility and subsequent outcomes based on patients with confirmed positive SARS-CoV-2 swabs.

Chronic kidney disease is known to be a potent and independent risk factor for AKI [44], and current evidence supports an association of renal insufficiency with severity of COVID-19 illness and risk of adverse outcomes [9, 11, 45]. A number of studies have reported on an association of CKD with mortality in COVID-19 [40, 41, 46], and results from the OpenSafely cohort demonstrated a progressive increase in risk of death following COVID-19 for patients with eGFR 30–60 mL/min/1.73m^2 and eGFR < 30 mL/min/1.73m^2. However, the OpenSafely cohort employed a broad non-specific exploratory scope; that is, the interaction of renal function with specific confounders was not addressed, outcome definition included clinically suspected (non-laboratory-confirmed) cases of COVID-19 leading to risk of misclassification bias, and, importantly, renal function was assessed with risk of bias due to case mix, that is misclassification of AKI as CKD [13]. Overall, numerous studies have reported on the association of renal insufficiency at diagnosis with adverse outcomes [9, 47]; causality, however, remains unaddressed due to a general inability in discrimination between pre-existent CKD and COVID-19-associated AKI.

Although all models adjust for multiple confounders, and the nationwide scope of the study effectively minimized selection biases due to geographical demographic variation, the impact of unmeasured residual confounding cannot be excluded. As such, details related to proteinuria, obesity, lifestyle, smoking and alcohol remain, and no details were available pertaining to clinical parameters. Furthermore, the inherently observational nature of the study precludes causal inference whereby conclusions remain exploratory. Additionally, confirmation of SARS-CoV-2/COVID-19 was limited to administrative diagnostic code in principal analyses. The accuracy of employing billing codes for identification of SARS-CoV-2/COVID-19 in Denmark has been previously assessed with a positive predicative value of 98% [21]; that is misclassification of false negatives remains negligible; however, requirement of hospitalization remains limited to 20% of SARS-CoV-2 PCR-positive cases overall [43]. Although renal insufficiency could be associated with greater preponderance for hospital admission due to COVID-19, principal results remained unchanged in sensitivity analyses based on verification of COVID-19 by positive SARS-CoV-2 swab alone. Nonetheless, consequent to the frequent in- and outpatient assessment associated with renal insufficiency, results remain susceptible to possible ascertainment biases. However, testing propensity, as adjudged by the percentage of positive SARS-CoV-2 PCR swabs, remained comparable, with positive rates of 2.7% and 3.3% in individuals with no known comorbidity and patients with hospital-diagnosed kidney disease, respectively [43]. Although subject to interpretation, the observed positivity rates plausibly preclude an increased likelihood for testing in patients with renal insufficiency, particularly in light of the perceived greater risk of infection related to poor renal function. Furthermore, the majority of tested individuals had no recent history of hospitalization or pre-existent comorbidity.

Conclusions

Renal insufficiency is associated with a progressive increase in both susceptibility to SARS-CoV-2/COVID-19 and subsequent risk of adverse outcomes. Results underscore a possible independent vulnerability associated with poor renal function in relation to SARS-CoV-2 infection; particularly for patients with eGFR ≤30 mL/min/1.73m^2.

Conflicts of interest

The results presented in this paper have not been published previously in whole or part. The authors have no conflicts of interest to declare.

Author Contributions

Nicholas Carlson: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Methodology (lead); Software (lead); Writing-original draft (lead); Writing-review & editing (equal). **Karl-Emil Nelveg-Kristensen:** Conceptualization (supporting); Formal analysis (supporting); Methodology (supporting); Supervision (supporting); Writing-review & editing (supporting). **Ellen Linnea Freese Ballegaard:** Writing-review & editing (supporting). **Bo Feldt-Rasmussen:** Conceptualization (supporting); Supervision (supporting); Writing-review & editing (supporting). **Mads Hornum:** Conceptualization (supporting); Methodology (supporting); Supervision (supporting); Writing-review & editing (supporting). **Anne-Lise Kamper:** Conceptualization (supporting); Methodology (supporting); Supervision (supporting); Writing-review & editing (supporting). **Gunnar Hilmar Gislason:** Conceptualization (supporting); Data curation (supporting); Project administration (supporting); Supervision (supporting); Writing-review & editing (supporting). **Christian Torp-Pedersen:** Conceptualization (supporting); Data curation (supporting); Methodology (equal); Project administration (supporting); Supervision (supporting); Writing-review & editing (supporting).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Applied administrative billing codes related to hospitalization, procedures, and prescription medication.

Table S2. Baseline characteristics of all patients with hospital-diagnosed COVID-19, and patients with hospital-diagnosed COVID-19 and preexistent plasma creatinine only.

Table S3. Characteristics of the Danish general population with preexistent registration of plasma creatinine on February 1st 2020.

Table S4. Gender- and age-stratified standardized 60-day risk of severe COVID-19 or death in patients with hospital-diagnosed COVID-19.

Table S5. Cohort study: standardized 60-day risk differences and ratios for outcomes following hospitaldiagnosed COVID-19.

Table S6. Sensitivity analysis: standardized 60-day risk of severe COVID-19 or death following hospitaldiagnosed COVID-19 in patients with eGFR computed based on plasma creatinine recorded >90 days before diagnosis only.

Table S7. Sensitivity analysis – imputed dataset: nested case-control – baseline characteristics of patients with hospital-diagnosed COVID-19 and matched controls.

Table S8. Sensitivity analysis – imputed dataset: nested-case-control – hazard ratios for strata of eGFR for rate of hospital-diagnosed COVID-19.

Table S9. Sensitivity analysis – imputed dataset: baseline characteristics of patients with hospital-diagnosed COVID-19.

Table S10. Sensitivity analysis – imputed dataset: hazard ratios and standardized 60-day risk of severe COVID-19 or death following hospital-diagnosed COVID-19.

Table S11. Sensitivity analysis based on SARS-COV-2 swab – nested case-control: baseline characteristics.

Table S12. Sensitivity analysis – retrospective cohort of patients with positive SARS-COV-2 swab.

Table S13. Sensitivity analyses – retrospective cohort study of patients with positive SARS-COV-2 swab: hazard ratios for hospitalization due to COVID-19 or death.

