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ORIGINAL ARTICLE

# Impaired kidney function biomarkers and risk of severe COVID-19: Analysis of population-based cohort data

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## Abstract

**Background:** Patients with impaired kidney function were found at a high risk of COVID-19 hospitalization and mortality in many observational, cross-sectional, and hospital-based studies, but evidence from large-scale prospective cohorts has been lacking. We aimed to examine the association of kidney function-related biomarkers and their genetic predisposition with the risk of developing severe COVID-19 in population-based data.

**Methods:** We analyzed data from UK Biobank to examine the prospective association of abnormal kidney function biomarkers with severe COVID-19, defined by laboratory-confirmed COVID-19 hospitalizations. Using genotype data, we constructed polygenic risk scores (PRS) to represent an individual's overall genetic risk for these biomarkers. We also identified tipping points where the risk of severe COVID-19 began to increase significantly for each biomarker.

**Results:** Of the 502,506 adults, 1650 (0.32%) were identified as severe COVID-19, before August 12, 2020. High levels of cystatin C (OR: 1.3; 95% CI: 1.2–1.5; FDR $= 1.5\times10^{-5}$), serum creatinine (OR: 1.7; 95% CI: 1.3–2.1; $p = 3.5\times10^{-4}$; FDR $= 3.5\times10^{-4}$), microalbuminuria (OR: 1.4; 95% CI: 1.2–1.6; FDR $= 4\times10^{-4}$), and UACR (urinary albumin creatinine ratio; OR: 1.4; 95% CI: 1.2–1.6; $p = 3.5\times10^{-4}$; FDR $= 3.5\times10^{-4}$) were found significantly associated with severe COVID-19. Individuals with top 10% of PRS for elevated cystatin C, urate, and microalbuminuria had 28% to 43% higher risks of severe COVID-19 than individuals with bottom 30% PRS ($p<0.05$). Tipping-point analyses further supported that severe COVID-19 could occur even when the values of cystatin C, urate (male), and microalbuminuria were within their normal value ranges (OR >1.1, $p<0.05$).

**Conclusions:** Findings from this study might point to new directions for clinicians and policymakers in optimizing risk-stratification among patients based on polygenic risk estimation and tipping points of kidney function markers. Our results call for further investigation to develop a better strategy to prevent severe COVID-19 outcomes among patients with genetic predisposition to impaired kidney function. These findings could provide a new tool for clinicians

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and policymakers in the future especially if we need to live with COVID-19 for a long time.

**KEYWORDS**

COVID-19, cystatin C, GWAS, kidney function, polygenic risk score, SARS-CoV-2, UK Biobank, urate

## 1 | BACKGROUND

Coronavirus disease 2019 (COVID-19) global pandemic has already had an unprecedented impact on populations all over the world. The etiologic agent of COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), brings about a particularly severe illness, especially for those with various coexisting conditions, including cardiovascular disease, diabetes, non-allergy asthma, chronic obstructive pulmonary disease (COPD), obesity, and chronic kidney disease (CKD) (Deng et al., 2020; Zhu et al., 2020a, 2020b). With promising news that several vaccines in various countries were highly efficient against COVID-19 (Polack et al., 2020; Voysey et al., 2021), the optimization of the vaccine allocation and distribution has aroused a rather heated debate. The question- who to vaccinate first? – has become the most urgent for COVID-19 pandemic control through public health strategies, especially when the Delta variant of COVID-19 brought about a growing threat to world recovery (Matrajt et al., 2021; Usher, 2020).

As people without comorbidities could also be susceptible to severe COVID-19, we hope to find the potential risk factors of severe COVID-19 in the population. On the one hand, accumulating recent evidences from clinical observational studies detected that individuals with long-term kidney function impairment had a higher risk of COVID-19 hospitalization and higher mortality (D'Marco et al., 2020; Gansevoort & Hilbrands, 2020; Williamson et al., 2020). However, due to the fact that early damage to kidney function is asymptomatic, kidney health tends to be given far less attention both by public health authorities and the general population (Baumgarten & Gehr, 2011; GBD Chronic Kidney Disease Collaboration, 2020). Since various kidney function biomarkers, including serum creatinine and cystatin C, are closely related to kidney health, there might be unnoticeable changes in kidney function biomarkers that can predict the potential relationship between kidney function and the risk of COVID-19.

On the other hand, given most studies only explored the clinical significance with cross-sectional or hospital-based design for limited biomarkers, very few studies could elucidate the association of kidney function with the risk of COVID-19, using diverse kidney function biomarkers and a large prospective cohort (Wang et al., 2021; Williamson et al., 2020; Zhao & Schooling, 2021). Existed observational studies were subject to residual confounding, therefore using genetics as an instrument could help establish the robust association between kidney function and COVID-19.

In the present study, we analyzed the data of ~500,000 individuals, from UK Biobank (UKB), to investigate the prospective relationship of biomarkers of kidney function with severe COVID-19, defined as laboratory-confirmed COVID-19 hospitalizations. We then developed the polygenic risk score (PRS) and identified the correlations of the genetic predisposition for kidney function biomarkers with the risk of developing severe COVID-19. Finally, we hoped to explore the tipping points and critical thresholds for different kidney function biomarkers, which are associated with an elevated risk for severe COVID-19.

## 2 | METHODS

### 2.1 | Design, setting, and participants

The overall study design is shown in Figure 1. The current study is an analysis of data from the UKB, a population-based cohort study. The complete description of the design, settings, participants, and methods of data measurements in the UKB are described elsewhere (Sudlow et al., 2015). The UKB enrolled more than 500,000 adults (aged 40–69 years at enrollment) across the United Kingdom in 2006–2010, with an overall aim of permitting detailed investigations of nongenetic and genetic determinants of multiple diseases (Sudlow et al., 2015). According to standardized protocols, the study has collected baseline assessment consisting of detailed characterization of socio-demographics, lifestyle, health, a series of physical measures, and blood biochemistry via linkages to national datasets. All participants provided informed consent to the UKB. The institutional review board of Harvard University approved the current study.

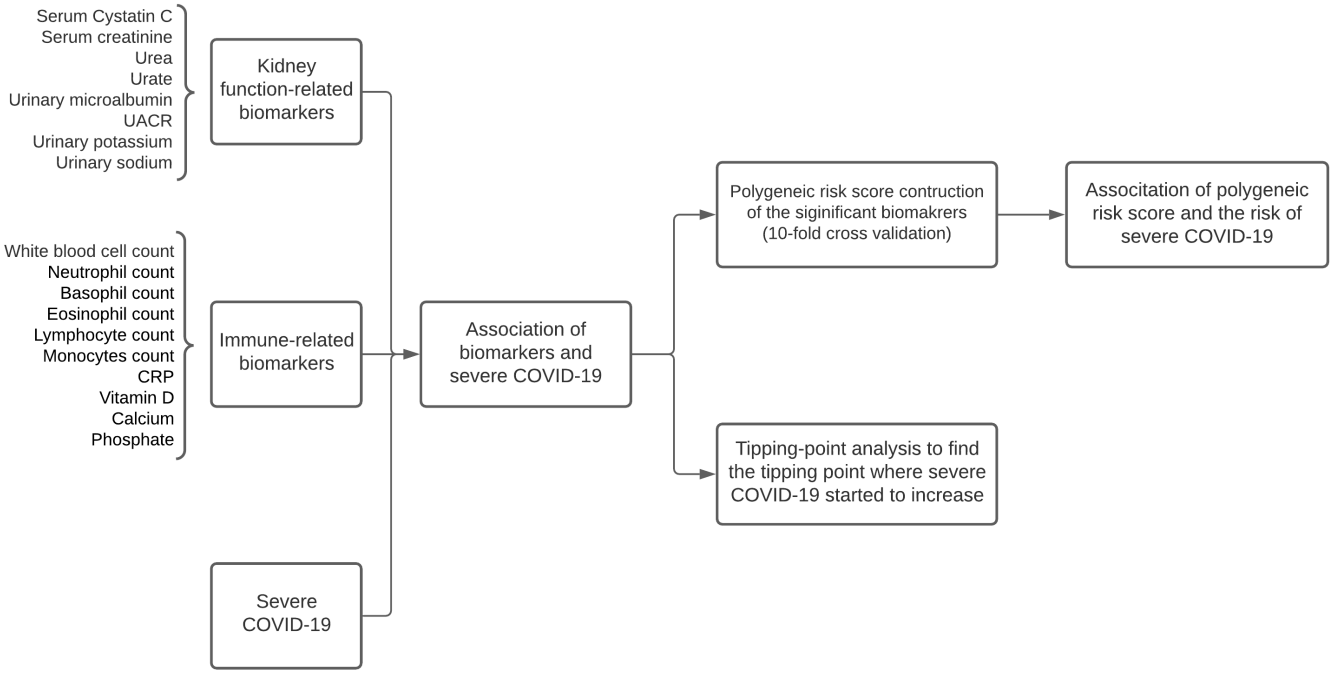



FIGURE 1 Overall study design.

## 2.2 | Exposures

The primary exposures were the kidney function biomarker phenotypes in UKB, including blood biochemistry test (cystatin C, serum creatinine, urea, urate), urine biochemistry test (potassium, sodium, creatinine, microalbumin, UACR). All biomarker test results were acquired years before the patients' COVID-19 admission to the hospital (blood: 2006–2010; urine: 2014–2016) on 3 Beckman Coulter AU5400 clinical chemistry analyzer, and 2 Siemens Advia 1800 (detail methods, quality control, and standardization process could be found at https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/serum_biochemistry.pdf & https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/urine_assay.pdf). Based on the reference ranges defined by an international guide (Pagana et al., 2019), we classified the participants into low, normal, and high (Table S1). The secondary exposures were immune-related biomarkers including white blood biomarker phenotypes and infection biomarker phenotypes in UKB, that is, white blood cell count, neutrophil count, basophil count, eosinophil count, lymphocyte count, monocytes count, CRP, vitamin D, calcium, and phosphate (Table S1). These traits were also included in the analyses to help support the underlying immune mechanism between COVID-19 infection and kidney function.

## 2.3 | Outcome measure

In the current study, we analyzed the first and second releases of the UKB with laboratory-confirmed COVID-19 status, which were released on August 12, 2020. The data contained the SARS-CoV-2 polymerase chain reaction results in hospitalized participants from March 16, 2020, onwards. A total of 1650 hospitalized patients with SARS-CoV-2 infection were defined as "severe COVID-19," compared to the rest of the UKB sample (i.e., test negative and untested samples). The time-to-event outcome was considered as the time for the diagnosis of severe COVID-19. The detailed information on released COVID-19 data can be found elsewhere (https://biobank.ndph.ox.ac.uk/showcase/exinfo.cgi?src=COVID19) and were acquired through UKB application #45052.

## 2.4 | Statistical analysis

We first described the baseline characteristics by the status of kidney function using summary statistics. We used both cystatin C and serum creatinine to reflect kidney function based on international guide (Pagana et al., 2019), as they were considered to capture a better association of preclinical impairments of kidney function than eGFR and most current equations to eGFR had their own drawbacks (Delanaye et al., 2017; Inker et al., 2012; Singh et al., 2007). One-way ANOVA analysis was performed to test the difference among different groups. To investigate the association between kidney function biomarkers and risk of severe COVID-19, we carried out unadjusted and adjusted logistic regression models, using the normal value group as the reference, adjusting for potential confounders, including age, sex, race/ethnicity, and BMI based on

clinical plausibility and a priori knowledge from previous studies (Kang et al., 2019; Upadhyay et al., 2009; Wu & McGoogan, 2020). We further adjusted hypertension and diabetes as additional confounders and quantitative values of these biomarkers were also applied in the logistic regression as sensitivity analysis. Moreover, multivariable Cox regression analyses were performed to validate the results by assessing the hazard ratio (HR) with time to severe COVID-19, adjusting for same covariates. The false discovery rate (FDR) was estimated using the Benjamini-Hochberg approach (Benjamini & Hochberg, 1995) with p. adjust package (R Core Team, 2019). We use FDR less than 5% to determine significant biomarkers in relation to severe COVID-19.

Next, to explore the genetic predisposition for kidney function biomarker phenotypes, we calculated polygenic risk score (PRS) for each significant biomarker phenotype in adjusted logistic regression, using both LDpred (Vilhjalmsson et al., 2015) and LassoSum (Mak et al., 2017). Only genetically white British individuals were used and the details of methods used in computation of the PRSs may be found in the Supplemental Methods. We reported the results of PRS based on the PRS reporting standard. (Wand et al., 2021).

Then, we investigated the association between the derived PRSs and severe COVID-19 using logistic regression models, adjusting for age, sex, BMI, 20 ancestry principal components (which account for population stratification), assessment center, and genotyping array. Individuals within the top 20% and bottom 80% of PRS were first considered as high and low genetic risk, respectively. In order to explore the relationship between the gradient of the genetic score for kidney functions and severe COVID-19, we classified the population into 10 equal bins according to the distribution of PRS (Figures S25–S34). Participants within the bottom 30% were considered as the reference, and we compared it with the other seven genetic risk bins (from 30%–40% to 90%–100%).

To further investigate the tipping point for kidney functions in relation to the diagnosis of severe COVID-19, we identified the tipping point where the risk for severe COVID-19 began to increase significantly (OR >1.1 & $p<0.05$). For those biomarkers with sex differences, we also stratified our analyses based on males and females and identified sex-specific tipping points for the corresponding kidney function biomarker.

# 3 | RESULTS

## 3.1 | Patient baseline characteristics

Our analysis included 502,506 adults in UKB and we summarized the baseline characteristics based on the participants who were considered low, normal, or high levels of cystatin C or serum creatinine (Table 1). Among all the participants, 32.66% were reported with high cystatin C and 2.4% were with high serum creatinine. Specifically, the UKB identified 1650 patients (August 12, 2020, release) diagnosed with severe COVID-19, who were hospitalized with laboratory-confirmed positive status. Among them, 645 (0.39%) patients were with high baseline level of cystatin C while 862 (0.28%) had normal baseline cystatin C ($p<0.001$). The mean ages in low, normal, and high cystatin C group were $54.11\pm8.16$, $54.75\pm8.09$, and $59.89\pm6.98$ years, respectively ($p<0.001$). And 59.94%, 46.21%, and 54.56% were female in low, normal, and high groups, respectively ($p<0.001$). For serum creatinine, the results were similar and other baseline characteristics including kidney function-related biochemistry results were also summarized in Table 1.

## 3.2 | Association of severe COVID-19 with baseline kidney function biomarkers and other biomarkers

We tried to explore the association of severe COVID-19 with kidney function and other immune-related biomarkers. All the associations of categorial biomarker variables (high, normal, low based on international guide; Pagana et al., 2019) with COVID-19 were showed in Figure 2 and Table S3. For kidney function-related biomarkers, comparing to the normal range based on the international guide (Pagana et al., 2019), high cystatin C (OR: 1.3; 95% CI: 1.2–1.5; $p = 4.2\times10^{-7}$; FDR $= 1.5\times10^{-5}$), high serum creatinine (OR: 1.7; 95% CI: 1.3–2.1; $p = 3\times10^{-5}$; FDR $= 3.5\times10^{-4}$), high microalbuminuria (OR: 1.4; 95% CI: 1.2–1.6; $p = 4.6\times10^{-5}$; FDR $= 4.0\times10^{-4}$), and high UACR (OR: 1.4; 95% CI: 1.2–1.6; $p = 2.60\times10^{-5}$; FDR $= 3.5\times10^{-4}$) were significantly associated with severe COVID-19, whether or not adjusted for potential confounders, including age, sex, race/ethnicity, and BMI (all $p<0.05$). In addition, marginal significant association with severe COVID-19 was shown for high urate in blood (OR: 1.3; 95% CI: 1–1.7; $p = 0.049$; FDR $= 0.17$) and low potassium in urine (OR: 1.2; 95% CI: 1–1.4; $p = 0.023$; FDR $= 0.1$), only after adjusting for potential confounders.

Adjusted model also showed other immune-related biomarkers had marginal significantly positive association with severe COVID-19, including high white blood cell count (OR: 1.2; 95% CI: 1–1.5; $p = 0.03$; FDR $= 0.12$). We further adjusted hypertension and diabetes as additional confounders for sensitivity analysis and most of the results of the analysis were consistent (Table S2). Moreover, similar results were shown either using original quantitative values or through multivariable Cox regression analyses (Tables S3 and S4).

**TABLE 1** Baseline characteristics in 502,506 UKB participants stratified by either cystatin C level or serum creatinine level[a]

| | Cystatin C | | | | | | | Serum creatinine | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low ($n$ = 322; 0.06%) | | Normal ($n$ = 305,134; 60.72%) | | High ($n$ = 164,104; 32.66%) | | $p$-value | Low ($n$ = 3999; 0.79%) | | Normal ($n$ = 453,296; 90.21%) | | High ($n$ = 12,064; 2.4%) | | $p$-value |
| | *N* | % | *N* | % | *N* | % | | *N* | % | *N* | % | *N* | % | |
| Age (year)), Mean, SD | 54.11 | 8.16 | 54.75 | 8.09 | 59.86 | 6.98 | <0.001 | 56.27 | 7.96 | 56.44 | 8.09 | 60.07 | 7.58 | <0.001 |
| Female | 193 | 59.94 | 159,555 | 52.29 | 94,864 | 57.81 | <0.001 | 2857 | 71.44 | 248,833 | 54.89 | 2817 | 23.35 | <0.001 |
| Race/ethnicity | | | | | | | <0.001 | | | | | | | <0.001 |
| White | 311 | 96.88 | 286,684 | 94.04 | 155,565 | 94.91 | | 3579 | 89.95 | 427,840 | 94.48 | 10,954 | 90.92 | |
| Asian /Asian British | 4 | 1.25 | 5195 | 1.70 | 3907 | 2.38 | | 199 | 5.00 | 8617 | 1.90 | 287 | 2.38 | |
| Black /Black British | 2 | 0.62 | 5575 | 1.83 | 1726 | 1.05 | | 23 | 0.58 | 6722 | 1.48 | 556 | 4.61 | |
| Chinese | 0 | 0 | 1261 | 0.41 | 184 | 0.11 | | 51 | 1.28 | 1371 | 0.30 | 21 | 0.17 | |
| Mix | 0 | 0 | 2048 | 0.67 | 708 | 0.43 | | 29 | 0.73 | 2668 | 0.59 | 56 | 0.46 | |
| Other | 4 | 1.25 | 4078 | 1.34 | 1818 | 1.11 | | 98 | 2.46 | 5624 | 1.24 | 174 | 1.44 | |
| BMI (kg/m$^2$), Mean, SD | 26.73 | 4.72 | 26.55 | 4.21 | 29.04 | 5.32 | <0.001 | 27.06 | 6.03 | 27.38 | 4.76 | 29.07 | 4.92 | <0.001 |
| Hypertension | 47 | 14.60 | 52,416 | 17.18 | 55,377 | 33.75 | <0.001 | 1212 | 30.31 | 100,447 | 22.16 | 6141 | 50.90 | <0.001 |
| Diabetes | 12 | 3.73 | 13,681 | 4.48 | 15,401 | 9.38 | <0.001 | 638 | 15.95 | 26,418 | 5.83 | 2030 | 16.82 | <0.001 |
| Kidney function-related blood test | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | |
| Serum creatinine (μmol/L) | 67.09 | 14.37 | 69.17 | 13.01 | 78.10 | 24.13 | <0.001 | 43.32 | 5.05 | 71.13 | 12.79 | 125.94 | 63.42 | <0.001 |
| Cystatin C (mg/L) | 0.48 | 0.04 | 0.82 | 0.08 | 1.06 | 0.20 | <0.001 | 0.78 | 0.13 | 0.90 | 0.14 | 1.31 | 0.55 | <0.001 |
| Urate (μmol/L) | 286.66 | 75.99 | 295.83 | 76.72 | 334.11 | 81.24 | <0.001 | 254.87 | 74.01 | 307.12 | 78.42 | 405.53 | 91.47 | <0.001 |
| Urea (mmol/L) | 5.11 | 1.22 | 5.16 | 1.19 | 5.85 | 1.63 | <0.001 | 4.27 | 1.23 | 5.34 | 1.25 | 8.03 | 3.12 | <0.001 |

(Continues)

TABLE 1 (Continued)

| | Cystatin C | | | | | | | Serum creatinine | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low ($n$ = 322; 0.06%) | | Normal ($n$ = 305,134; 60.72%) | | High ($n$ = 164,104; 32.66%) | | $p$-value | Low ($n$ = 3999; 0.79%) | | Normal ($n$ = 453,296; 90.21%) | | High ($n$ = 12,064; 2.4%) | | $p$-value |
| | *N* | % | *N* | % | *N* | % | | *N* | % | *N* | % | *N* | % | |
| *Kidney function-related urine test* | | | | | | | | | | | | | | |
| Potassium in urine (mmol/L) | 60.01 | 31.55 | 62.39 | 33.96 | 64.48 | 33.61 | <0.001 | 54.68 | 31.92 | 63.12 | 33.89 | 65.83 | 32.84 | <0.001 |
| Sodium in urine (mmol/L) | 76.49 | 47.28 | 77.88 | 45.32 | 76.71 | 42.73 | <0.001 | 75.55 | 47.06 | 77.49 | 44.51 | 77.55 | 41.07 | 0.03 |
| Creatinine in urine (μmol/L) | 8017.46 | 5287.42 | 8573.82 | 5622.19 | 9477.76 | 6141.85 | <0.001 | 6024.22 | 4364.76 | 8830.99 | 5767.83 | 11998.52 | 7134.72 | <0.001 |
| Microalbumin in urine (mg/L) | 11.19 | 28.38 | 11.25 | 39.58 | 20.15 | 109.74 | <0.001 | 21.56 | 90.48 | 12.81 | 55.13 | 69.98 | 290.02 | <0.001 |
| UACR (mg/μmol) | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | <0.001 | 0.00 | 0.02 | 0.00 | 0.01 | 0.01 | 0.04 | <0.001 |
| *Other lab tests* | | | | | | | | | | | | | | |
| White blood cell count ($10^9$ cells/L) | 6.75 | 1.63 | 6.68 | 2.02 | 7.25 | 2.28 | <0.001 | 7.17 | 2.41 | 6.87 | 2.10 | 7.34 | 2.57 | <0.001 |
| Neutrophil count ($10^9$ cells/L) | 4.12 | 1.24 | 4.10 | 1.35 | 4.46 | 1.50 | <0.001 | 4.47 | 1.69 | 4.21 | 1.41 | 4.64 | 1.59 | <0.001 |
| Basophil count ($10^9$ cells/L) | 0.04 | 0.04 | 0.03 | 0.05 | 0.04 | 0.06 | <0.001 | 0.04 | 0.06 | 0.03 | 0.05 | 0.03 | 0.05 | <0.001 |
| Eosinophil count ($10^9$ cells/L) | 0.17 | 0.13 | 0.17 | 0.13 | 0.19 | 0.15 | <0.001 | 0.17 | 0.13 | 0.17 | 0.14 | 0.20 | 0.16 | <0.001 |

**TABLE 1** (Continued)

| | Cystatin C | | | | | | | Serum creatinine | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low ($n$ = 322; 0.06%) | | Normal ($n$ = 305,134; 60.72%) | | High ($n$ = 164,104; 32.66%) | | $p$-value | Low ($n$ = 3999; 0.79%) | | Normal ($n$ = 453,296; 90.21%) | | High ($n$ = 12,064; 2.4%) | | $p$-value |
| | *N* | % | *N* | % | *N* | % | | *N* | % | *N* | % | *N* | % | |
| Lymphocyte count ($10^9$ cells/L) | 1.95 | 0.59 | 1.92 | 1.06 | 2.05 | 1.40 | <0.001 | 2.01 | 1.32 | 1.97 | 1.14 | 1.93 | 1.79 | <0.001 |
| Monocyte count ($10^9$ cells/L) | 0.47 | 0.15 | 0.46 | 0.29 | 0.50 | 0.25 | <0.001 | 0.48 | 0.21 | 0.47 | 0.27 | 0.53 | 0.29 | <0.001 |
| CRP (mg/L) | 2.65 | 5.65 | 2.09 | 3.70 | 3.54 | 5.25 | <0.001 | 3.79 | 6.44 | 2.56 | 4.28 | 3.63 | 6.03 | <0.001 |
| Vitamin D (nmol/L) | 49.24 | 21.02 | 49.06 | 21.1 | 47.78 | 21.12 | <0.001 | 41.69 | 21.44 | 48.65 | 21.06 | 49.23 | 22.31 | <0.001 |
| Calcium (mmol/L) | 2.38 | 0.10 | 2.38 | 0.09 | 2.39 | 0.10 | <0.001 | 2.36 | 0.11 | 2.38 | 0.09 | 2.38 | 0.11 | <0.001 |
| Phosphate (mmol/L) | 1.16 | 0.17 | 1.15 | 0.16 | 1.17 | 0.16 | <0.001 | 1.17 | 0.16 | 1.16 | 0.16 | 1.16 | 0.18 | 0.008 |

Abbreviations: CRP, C-reactive protein; SD, standard deviation; UACR, urinary albumin creatinine ratio.

[a]Low, medium, and high values were based on international reference: Cystatin C: male: 0.56–0.98 mg/L; female: 0.52–0.9 mg/L; Serum creatinine: male: 53–106 μmol/L; female: 44-97 μmol/L.

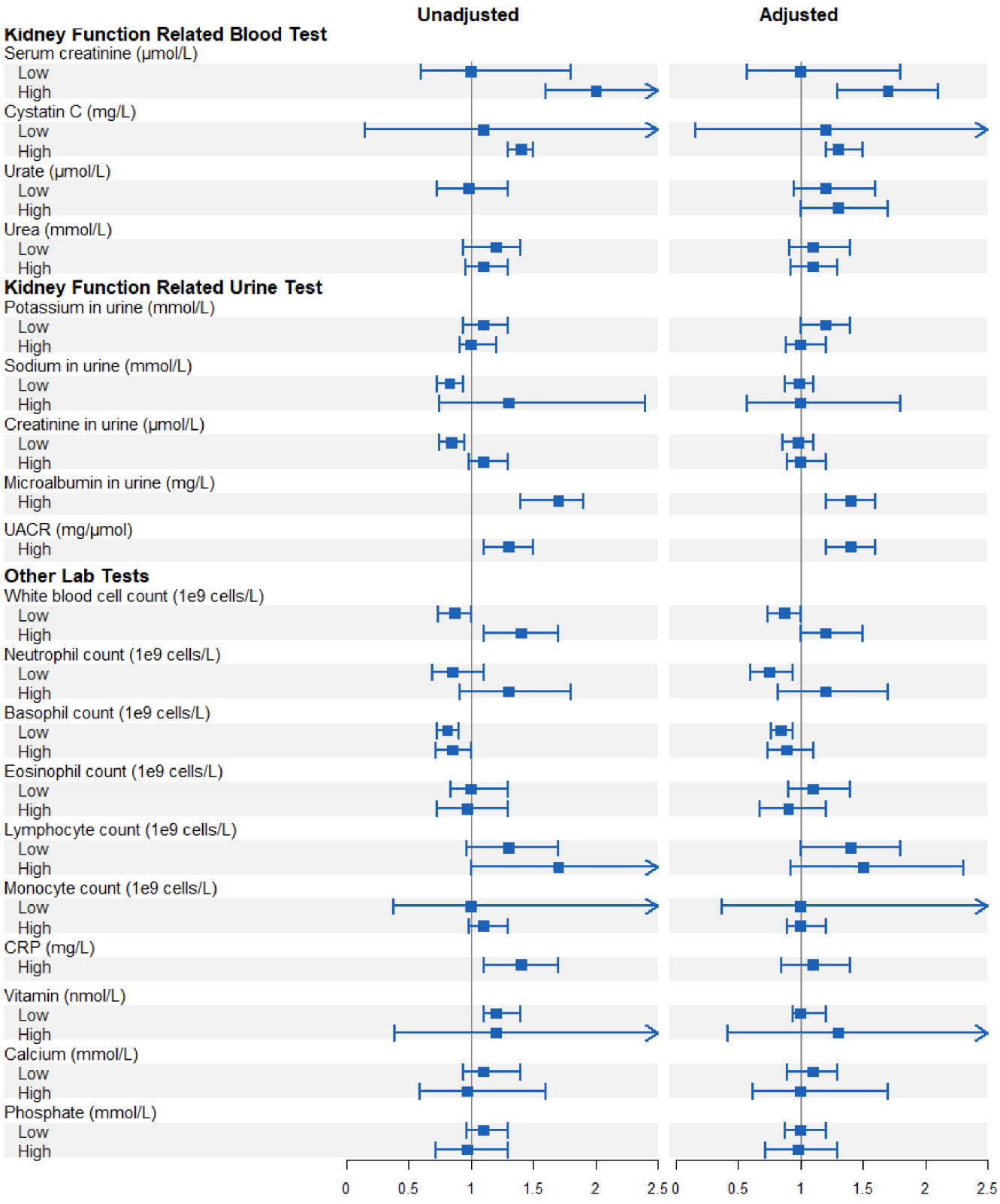



FIGURE 2 Association of kidney function-related traits with severe COVID-19 in unadjusted and adjusted model.

## 3.3 | PRS construction and the evaluation for risk of severe COVID-19

We first calculated GWAS of different kidney function biomarkers based on UKB genotype and imputation data. Then in regard to biomarkers with significant association with severe COVID-19, we computed their PRS using the LassoSum method (Mak et al., 2017), and the number of participants included in the GWAS and PRS calculation were shown in Table S1. Comparing participants in the

top 20% vs. bottom 80% of corresponding PRS (Table 2), high value of cystatin C (OR: 1.16; 95% CI: 1.02–1.33; $p = 0.025$; FDR = 0.083), urate (OR: 1.23; 95% CI: 1.07–1.4; $p = 0.003$; FDR = 0.025), microalbuminuria (OR: 1.18; 95% CI: 1.04–1.35; $p = 0.013$; FDR = 0.065), and neutrophil count (OR: 1.16; 95% CI: 1.01–1.32; $p = 0.034$; FDR = 0.085) were marginal significantly associated with severe COVID-19.

To show the risk of severe COVID-19 with the trend of polygenic risk for the above biomarkers, we used the bottom 30% PRS as reference and showed the number of severe COVID-19 cases per 10,000 participants for each of 10% PRS bin (Figure 3, Figures S1–S7, Tables S5–S14). Individuals with higher genetic risk grades of cystatin C, urate, white blood cell count, and neutrophil count were significantly associated with developing severe COVID-19. Specifically, compared to individuals with bottom 30% PRS, participants started to show a significant increase in severe COVID-19 (34.9 vs. 25.3 severe COVID-19 patients per 10,000 individuals) at 70%–80% of high polygenic risk of elevated cystatin C (OR: 1.32, 95% CI: 1.08 to 1.61; $p = 6.4\times10^{-3}$) (Figure 3a, Table S5). In terms of urate, participants started to show a significant increase in severe COVID-19 (32.5 vs. 24.8 severe COVID-19 patients per 10,000 individuals) at 50%–60% of high polygenic risk of elevated urate, compared with the bottom 30% PRS (OR: 1.25, 95% CI: 1.02 to 1.54; $p = 0.03$) (Figure 3b, Table S7). As for microalbuminuria, only the participants with top 10% of high polygenic risk of elevated microalbuminuria (90%–100%) had a relatively higher risk of developing severe COVID-19 (37.2 vs. 27.9 severe COVID-19 patients per 10,000 individuals) than the individuals with bottom 30% PRS (OR: 1.29, 95% CI: 1.06 to 1.56; $p = 0.01$) (Figure 3c, Table S8).

**TABLE 2** Adjusted associations between kidney function polygenic risk scores and risks of severe COVID-19 in UK Biobank: Low risk (reference) 0%–80% vs. high risk 20%

| PRS models | OR | 95% CI | *p* | FDR |
|---|---|---|---|---|
| Serum creatinine | 1.05 | 0.91–1.2 | 0.520 | 0.58 |
| Cystatin C | 1.16 | 1.02–1.33 | 0.025 | 0.083 |
| Urate | 1.23 | 1.07–1.4 | 0.003 | 0.025 |
| Microalbumin in urine | 1.18 | 1.04–1.35 | 0.013 | 0.065 |
| UACR | 0.91 | 0.79–1.05 | 0.210 | 0.300 |
| Potassium in urine | 1.1 | 0.96–1.26 | 0.190 | 0.300 |
| White blood cell counts | 1.14 | 1–1.31 | 0.056 | 0.110 |
| Neutrophil count | 1.16 | 1.01–1.32 | 0.034 | 0.085 |
| Lymphocytes | 0.95 | 0.82–1.09 | 0.440 | 0.550 |
| Basophils | 0.99 | 0.86–1.13 | 0.840 | 0.840 |

Abbreviations: FDR, false discover rate; OR, odds ratio; UACR, urinary albumin creatinine ratio.

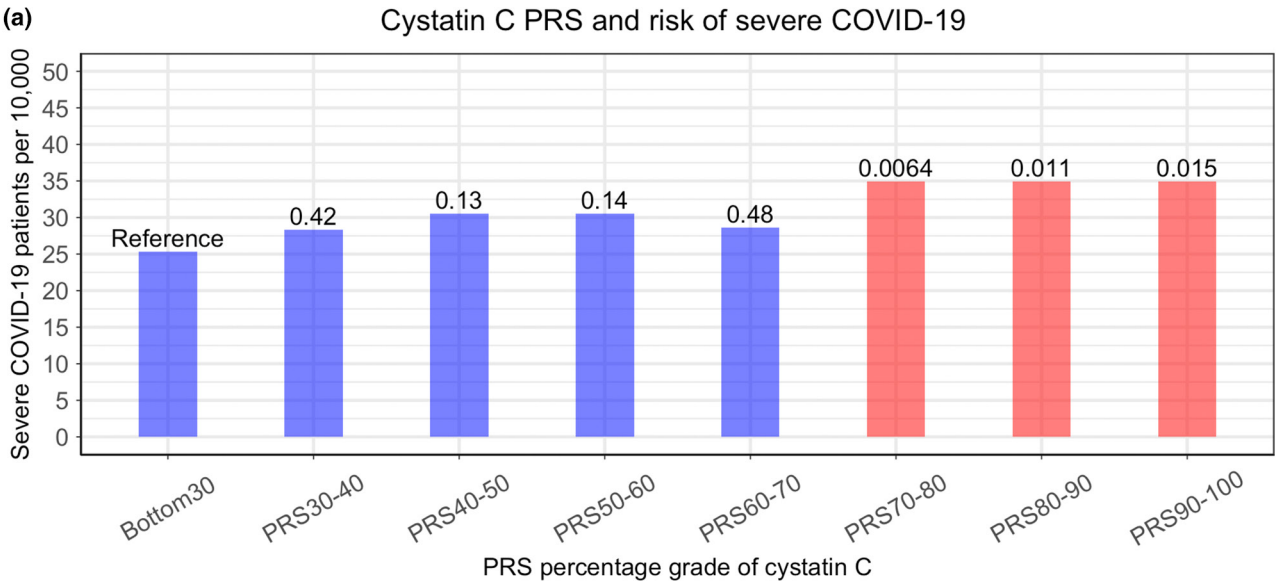
Besides, individuals in top 10 percentile of elevated PRS for cystatin C, urate, and microalbuminuria had 28% to 43% higher risks of developing severe COVID-19 than individuals with bottom 30% PRS of each biomarker ($p < 0.05$, Figure 2 and Tables S6, S8, and S9). Further, PRS using LDpred method (Vilhjalmsson et al., 2015), as sensitivity analyses, had consistent results (Figures S8–S17 and Tables S5, S15–S25) and prediction performance of both PRS methods were shown in Tables S26 and S27.

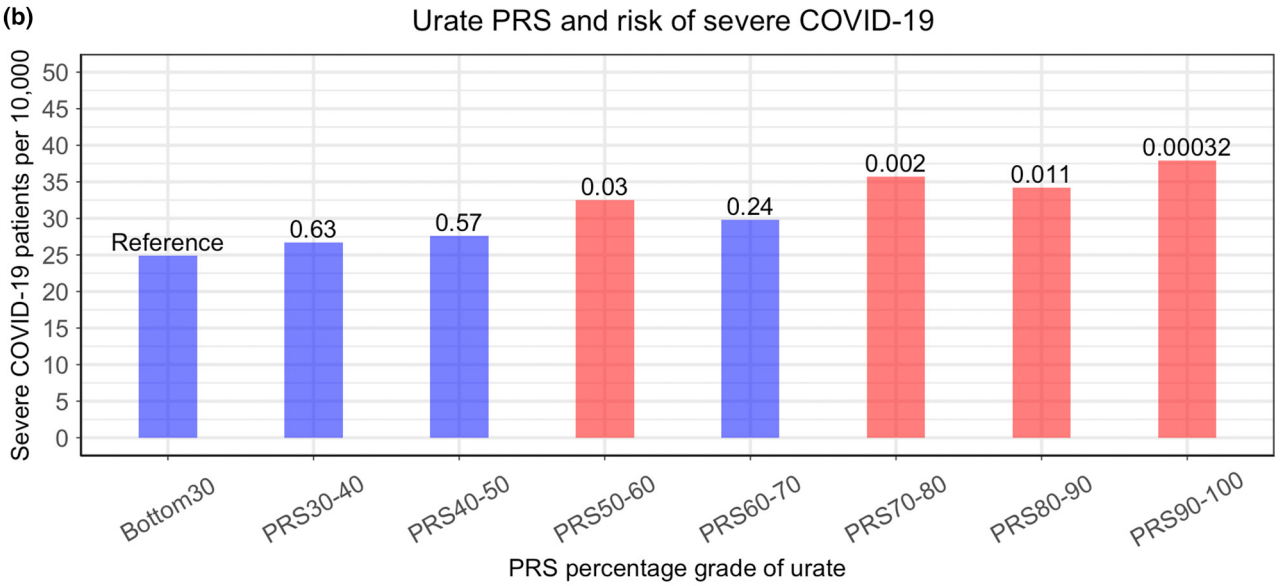
## 3.4 | The tipping points of biomarkers showed the risk of severe COVID-19 started to increase significantly

Since our PRS analysis revealed the underlying robust association between genetic predisposition for kidney function biomarkers and the risk of severe COVID-19, we performed tipping-point analyses to identify the tipping point of the significant kidney function biomarker, where the elevated risk for severe COVID-19 started to be significant (Figure 4, Figures S18–S24, and Table S28). Tipping-point analyses were stratified by sex when clinically normal ranges were different between sexes (Pagana et al., 2019).

According to our results, biomarkers whose tipping points were lower than the clinically defined normal limit (Pagana et al., 2019) included cystatin C (Figure 4a; male: 0.56 to 0.98 mg/L, female: 0.52 to 0.9 mg/L), microalbuminuria (Figure S22; 0 to 20 mg/L), UACR (Figure S23; 0 to 3 mg/mmol), male serum creatinine (Figure S18; 53 to 106 μmol/L), and male urate (Figure S20; 0.24–0.51 mmol/L). Specifically, for blood test, the tipping point of cystatin C for men were found at 0.81 mg/L (OR: 1.3; 95% CI: 1.03–1.62; $p = 0.022$), which were about 0.17 mg/L lower than the male normal upper limit (0.98 mg/L); and for women was 0.82 mg/L (OR: 1.2; 95% CI: 1.008–1.42; $p = 0.04$), which was 0.08 lower than the female normal upper limit (0.9 mg/L) (Figure 4b, Table S25). The tipping point of male serum creatinine was 103 μmol/L (OR: 1.3; 95% CI: 1.005–1.67; $p = 0.046$) which was only 3 μmol/L lower than the normal upper limit (106 μmol/L). Moreover, the tipping point of male urate was 0.46 mmol/L (OR: 1.3; 95% CI: 1.002–1.59; $p = 0.047$) which was 0.05 mmol/L lower than the normal upper limit (0.51 mmol/L).

As for urine test, the tipping point of microalbumin was 7 mg/L (Figure S22), which was just 0.3 higher than the lowest value of analytical range of the instrument (https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/urine_assay.pdf) and 13 mg/L (OR: 1.2; 95% CI: 1.09–1.34; $p = 4.7\times10^{-4}$) lower than the normal upper limit (20 mg/L); the tipping point of UACR was 0.9 mg/mmol (Figure S23, OR: 1.1; 95% CI: 1.02–1.26; $p = 0.018$),


(a)
Cystatin C PRS and risk of severe COVID-19
Severe COVID-19 patients per 10,000
Reference
0.42
0.13
0.14
0.48
0.0064
0.011
0.015
Bottom30
PRS30-40
PRS40-50
PRS50-60
PRS60-70
PRS70-80
PRS80-90
PRS90-100
PRS percentage grade of cystatin C


(b)
Urate PRS and risk of severe COVID-19
Severe COVID-19 patients per 10,000
Reference
0.63
0.57
0.03
0.24
0.002
0.011
0.00032
Bottom30
PRS30-40
PRS40-50
PRS50-60
PRS60-70
PRS70-80
PRS80-90
PRS90-100
PRS percentage grade of urate

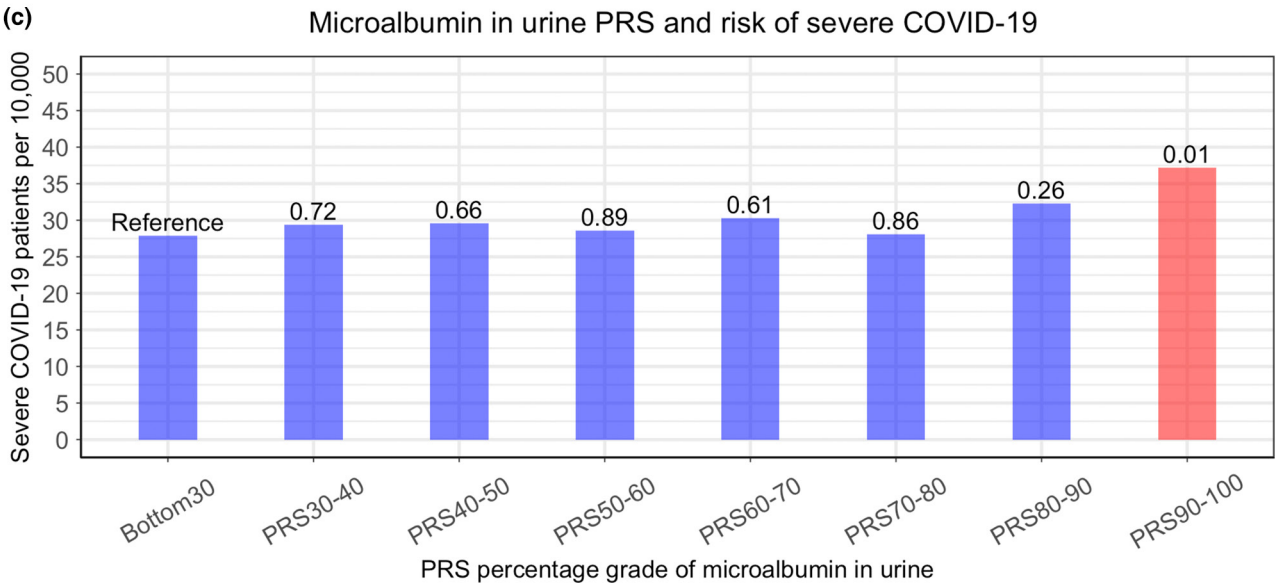

(c)
Microalbumin in urine PRS and risk of severe COVID-19
Severe COVID-19 patients per 10,000
Reference
0.72
0.66
0.89
0.61
0.86
0.26
0.01
Bottom30
PRS30-40
PRS40-50
PRS50-60
PRS60-70
PRS70-80
PRS80-90
PRS90-100
PRS percentage grade of microalbumin in urine

**FIGURE 3** Association of severe COVID-19 patients (per 10,000) and PRS of kidney function biomarkers. All P values were above the bins. Red bins were the significant PRS subgroups of the biomarkers ($p < 0.05$). (a) Association of severe COVID-19 patients (per 10,000) and different PRS subgroups of cystatin C. (b) Association of severe COVID-19 patients (per 10,000) and different PRS subgroups of urate. (c) Association of severe COVID-19 patients (per 10,000) and different PRS subgroups of microalbumin in urine.

which was 2.1 mg/mmol lower than the upper limit (3 mg/mmol). All the tipping points were summarized in Table S26.

At last, the other biomarkers, including serum creatinine (female) and potassium in urine, had the same boundary tipping points as the limits of normal range (Figures S21 and S24). However, in terms of the cut-off points of female urate trait, no significant association was found with COVID-19 and the trend of the ORs showed no obvious relation with severe COVID-19.

## 4 | DISCUSSION

Based on the large-scale prospective cohort of UKB, this study demonstrated significant correlations between kidney function biomarkers and severe COVID-19 based on both phenotypic and genetic associations. In our analysis, the development of severe COVID-19 was significantly associated with GWAS-derived PRS of kidney function traits, including cystatin C and urate in blood as well as potassium and microalbuminuria. Our tipping-point analyses further indicated that severe COVID-19 could occur even when the value of serum cystatin C, microalbuminuria, and potassium was in normal range in both genders. To our knowledge, this is the first analysis based on large-scale prospective cohort that has examined the relationship between kidney function biomarkers, and their genetic predisposition to the risk of developing severe COVID-19. The discovery of relevant kidney function markers, their polygenic risk score, and their tipping points for significant risk increment in the process of developing severe COVID-19 could be bases for further investigation for decision reference and evidence for clinical practice.

As kidney function insufficiency was one of the most serious extrapulmonary organ dysfunctions that COVID-19 might encounter, many current clinical observational studies focused on the relationship between kidney function biomarkers and COVID-19. For example, Li et al retrospectively analyzed 101 severe and critically ill COVID-19 patients in Wuhan, China, and found serum cystatin C could be a more sensitive biomarker for early renal impairment than serum creatinine (Li et al., 2020). In addition, a prospective observational cohort study found that 87% of patients with COVID-19 who were admitted to two hospitals in New York City, USA, had proteinuria, indicating the fact that microalbuminuria, as a crucial biomarker for kidney function impairment, should also attract enough attention for COVID-19 prognosis (Cummings et al., 2020). Interestingly, a multi-centered retrospective cohort study, with 12,413 COVID-19 patients included, found dynamic changes in blood urea, urate, and creatinine during admission, suggesting these biomarkers had potential associations with COVID-19 mortality (Liu et al., 2021). Despite that these prior studies from different populations explored the roles of various kidney function biomarkers in COVID-19, most tests of the biomarkers were only carried out upon admission to the hospital (Ponti et al., 2020). Since very few studies reported these biomarkers before or at earlier stages of the COVID-19 infection, let alone patients baseline kidney function biomarkers years before SARS-CoV-2 infection, evidences from large-scale prospective cohorts have been lacking.

Previous researches investigated the long-term mild-to-moderate impairment of participants' kidney health along with many other relevant subclinical status, including high blood glucose, high blood pressure, and obesity (Blonde et al., 2017; Sheppard et al., 2018; Zhang et al., 2020; Zhu et al., 2020b). We additionally found the mechanism linking kidney health with severe COVID-19 may be multifactorial. First, angiotensin-converting enzyme 2 (ACE2) can be one of the main driving causes. It has been shown to contribute to the pathogenesis of CKD (Williams & Scholey, 2018), and was implicated in a role as a functional host cell-surface membrane receptor for SARS-CoV-2 (Hoffmann et al., 2020; Maksimowski et al., 2020). Additionally, CKD or long-term kidney function impairment may cause marked alterations in the immune system, including persistent systemic inflammation and acquired immunosuppression (Vaziri, 2012), which will predispose the patients to any infection. Furthermore, as RNA of COVID-19 was not detected in the urine (Wölfel et al., 2020), other indirect mechanisms could also explain the potential link, including cytokine storm (Pan et al., 2020) or white blood cell disorders, which were also implicated by our results.

The observed relationship between PRSs for kidney function biomarkers and risks of severe COVID-19 might suggest potential clinical implications. To better interpret that, tipping-point analyses were performed to help us reclassify the damage level of cystatin C (male and female, separately), serum creatinine (male), urate (male), microalbuminuria, and UACR for better prevention of severe COVID-19.

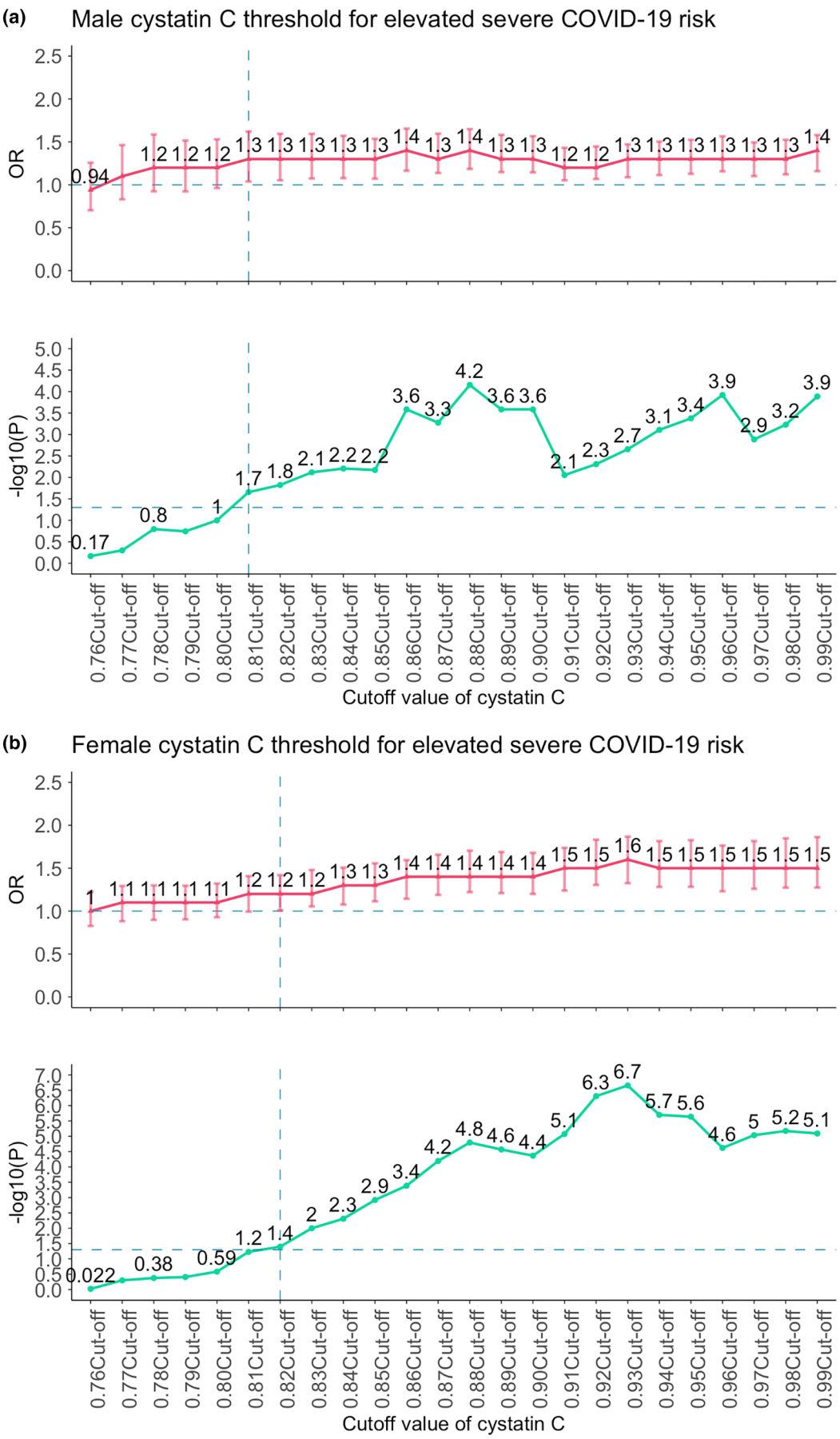



**FIGURE 4** Tipping-point analyses of severe COVID-19 patients and cystatin C stratified by sex. Horizontal dash line stands for the OR = 1 and $p = 0.05$ (−log10[P] = 1.30). (a) For male, the tipping point is 0.81 mg/L (OR: 1.3; 95% CI: 1.03–1.62; $p = 0.022$); (b) for female, the tipping point is 0.82 mg/L (OR: 1.2; 95% CI: 1.008–1.42; $p = 0.04$).

First and foremost, as cystatin C and serum creatinine were considered to capture a better association of pre-clinical impairments of kidney function than eGFR that is sometimes biased (Delanaye et al., 2017; Inker et al., 2012; Singh et al., 2007), our results also indicated that they both were strongly associated with severe COVID-19 in our phenotypic association analysis. Nevertheless, only cystatin C suggested a significant association of higher genetic risk with positive severe COVID-19 patients. This might also be the reason why increased cystatin C level during COVID-19 hospitalization might increase the risk of severe complications, namely diabetes or death (Yang et al., 2021). Tipping-point analyses further discovered that risk of severe COVID-19 patients was substantially increased when the level of cystatin was in a critical state (Figure 2: 0.81–0.98 mg/L for men; 0.81–0.9 mg/L for women), which was still within generally used normal range. As a result, COVID-19 can progress together with deterioration of kidney function from critical state to real severe state. This could explain the phenomenon that patients with underlying kidney disease had higher in-hospital mortality than patients without preexisting kidney disease (Flythe et al., 2021).

In addition, high level of urate and its PRS were both associated with severe COVID-19 prospectively. Participants with a higher genetic risk of urate had 29% to 43% increased risk of developing severe COVID-19 patients, comparing to the participants with low risk (bottom 30% PRS). Tipping-point analyses suggested, in the male population, the tipping point of urate level was 0.05 mmol/L lower than the upper limit of normal range (0.24–0.51 mmol/L). In contrast, the relationship between the tipping point for female urate and severe COVID-19 was not clear. The reason might be that in females, estrogen could help excrete serum urate (Yahyaoui et al., 2008) and protect them from developing urate-associated comorbidities (Halperin Kuhns & Woodward, 2020).

Moreover, for urine test, severe COVID-19 was associated with increased microalbuminuria, UACR, and decreased urinary potassium. By measuring PRS for these three biomarkers, only higher genetic risk grades of microalbuminuria (top 10%) showed significant association with positive severe COVID-19, indicating that microalbuminuria might be more predictive for severe COVID-19 than UACR. Noticeably, albeit the normal range for microalbuminuria is 0–20 mg/L, the tipping point of significant association with severe COVID-19 was 7 mg/L, or 0.3 mg/L higher than the lowest value of analytical range of the instrument by UKB (https://biobank.ndph.ox.ac.uk/showcase/ showcase/docs/urine_assay.pdf), indicating that the critical state of microalbuminuria for severe COVID-19 could be regarded as almost the entire normal range.

Despite the analysis for kidney function biomarkers, our analysis also suggested that the baseline level, as well as the genetic risk, of white blood cell count and neutrophil count were associated with severe COVID-19, consistent with previous researches (Cellina et al., 2020; Huang et al., 2020; Wang et al., 2020). However, we did not observe the correlation with C-reaction Protein (CRP), as many studies believed CRP could be used for early diagnosis of COVID-19 (Chen et al., 2020; Wang, 2020). The reason might be that these studies focused on CRP alteration only during admission to the hospital rather than the baseline before the infection. Plus, baseline CRP values, measured more than 10 years ago, may not be predictive to the risk of the severe COVID-19.

While knowing the current level of kidney dysfunction markers is important to know the health status of the subject, genetic risk can be assessed well ahead of time to facilitate effective prevention. And genetic markers could be assessed using a non-invasive method (e.g., by collecting saliva) comparing to an invasive method for kidney markers (e.g., serum creatine or cystatin C level in blood). The experimental cost of genetic testing might still be more expensive than some of these kidney dysfunction markers, but the decreasing cost of genotyping, the total burden to patient starting from data collection, and the advantage of making prediction ahead of time, together could outweigh its relatively expensive cost in near future. This could provide a new tool for clinicians and policymakers in the future especially if we need to live with COVID-19 for a long time.

This study comprehensively investigated the phenotypic and genetic-based association of kidney function biomarkers with severe COVID-19. The main strengths of the study included large-scale prospective observational and genetic data (sample size up to 408,885), the use of PRS, and clinical implication based on the tipping-point analysis. Of note, we would like to highlight the critical state of kidney function biomarkers. It was a pre-kidney disease status where severe COVID-19 started to occur significantly and this state was between the significant tipping point and the range limit of impaired kidney function. Even if the levels of serum cystatin C, urate, urinary potassium, and microalbumin were within typical normal ranges, patients could still have substantially higher risk for severe COVID-19. Our results also agreed with the recent follow-up study that 13% of patients with normal eGFR at the acute phase had decreased eGFR at follow-up of discharged patients with COVID-19 (Huang et al., 2021). We believed it could help better reclassify the risk for COVID-19, so as to optimize medical resources and vaccine allocation for prevention.

Yet, the present study has several limitations. First, participants of UKB were not a population-representative cohort for the United Kingdom, and testing practices and capacity changed over time in the United Kingdom, so the earlier data (data before August 12, 2020) represented a limited subset of COVID-19 infections in the United Kingdom, and selection bias may affect the results (Sudlow et al., 2015). However, since genetic variants remain stable during a lifetime, our study might provide insights from a lifetime of genetically altered biomarker levels. By contrast, early data also have advantages, as in the initial part of 2020, patients were admitted either based on their comorbid conditions, affordability, or availability. Thus, only the severe ones could be hospitalized, while hospitalized patients later time might not be with severe COVID-19. Second, despite that there may have been some misclassification of the exposure and outcome of interest, all the biomarkers and diseases were identified using standardized methods and protocols in the UKB (Sudlow et al., 2015). However, the study focused on severe COVID-19 requiring inpatient management, without mild and moderate COVID-19 infection, thus partially narrowing the effect of the above issues. As there is currently no existing large prospective cohort to test all their participants, our study compared severe COVID-19 with general population which might be more interested to clinicians and policymakers as these are the patients who should be cared for the most among all people exposed to COVID-19. Third, there were overlapping samples between training and validation dataset for PRS, but we applied 10-fold cross-validation to avoid overfitting. Finally, since we only included severe COVID-19 cases in European ancestry for the study, cautious interpretation is warranted if applied to other populations, especially for those with mild-to-moderate COVID-19. Regardless, our data are highly relevant for hundreds of thousands of patients hospitalized for COVID-19.

## 5 | CONCLUSION

Based on the data from a large prospective cohort of 502,506 individuals, we found that adults with impaired kidney function have a significantly higher risk of severe COVID-19. Additionally, we demonstrated a significant positive relationship between the PRS for kidney function biomarkers and the risk of developing severe COVID-19, including cystatin C and urate in blood, as well as microalbumin and potassium in urine. Finally, we highlighted cases of COVID-19 that could occur even when the levels of serum cystatin C, microalbuminuria, and urinary potassium were in normal range. Findings from this study might point to new directions for clinicians and policymakers in optimizing risk-stratification among patients based on polygenic risk estimation and tipping points of kidney function markers. Our results call for further investigation to develop a better strategy to prevent severe COVID-19 outcomes among patients with genetic predisposition to impaired kidney function. These findings could provide a new tool for clinicians and policymakers in the future especially if we need to live with COVID-19 for a long time.

### AUTHOR CONTRIBUTIONS

YL: Conceive and design the study, carried out most analyses, and write the first draft. YY: PRS development and edit the manuscript. BM: PRS development and edit the manuscript. YC: contribute to analysis and edit the manuscript. XY, JH, and WL: Interpret the results and edit the manuscript. LL: Conceive and design the study, supervise analyses, interpret the results, and edit manuscript. All authors contributed to revising the manuscript critically for important intellectual content and gave their final approval for the version of the manuscript being published.

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### CONFLICT OF INTEREST

The authors declare no competing interests.

### DATA AVAILABILITY STATEMENT

Data sets related to this article are available at UKB resource (https://www.ukbiobank.ac.uk/).

### CONSENT FOR PUBLICATION

Not applicable.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The institutional review board of Harvard University approved the current study.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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