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# Increased Estimated GFR Is Negatively Associated With the Risk of SARS-CoV-2 Infection and Severe COVID-19 Within Normal to Mildly Decreased Levels: Nested Case-Control Study

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## ABSTRACT

**Background:** While accumulating evidence indicates chronic kidney disease as a risk factor for coronavirus disease 2019 (COVID-19), the association between normal or mildly decreased kidney function and COVID-19 is unaddressed. Here, we have examined the association of an increase in estimated glomerular filtration rate (eGFR) with the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe COVID-19 outcomes among patients within normal to mildly decreased kidney function.
**Methods:** The patients who participated in both health screenings from period I (2017–2018) to II (2019–2020) were enrolled to our study. All participants were categorized into four groups according to the changes in eGFR stage from period I to II: 1) persistently stage G1, 2) from stage G2 to G1, 3) from stage G1 to G2, 4) persistently stage G2. In addition, the changes in eGFR value were defined by subtracting its value of period I from II. Patients were followed up for SARS-CoV-2 infection from January 1, 2021 to any diagnosis of COVID-19 or December 31, 2021, whichever happened first. In addition, those with SARS-CoV-2 infection were followed-up for one month after diagnosis to analyze severe COVID-19. Adjusted odds ratio (aOR) was calculated using multivariable-adjusted logistic regression.
**Results:** We identified 159,427 patients with and 1,804,798 patients without SARS-CoV-2 infection. The risk of SARS-CoV-2 infection decreased when eGFR stage changed from G2 to G1 (aOR, 0.957; 95% confidence interval [CI], 0.938–0.977) and persistently maintained at G1 (aOR, 0.966; 95% CI, 0.943–0.990), compared with the persistently stage G2 group. In addition, the risk showed an inverse relationship with changes in eGFR value, which was depicted by restricted cubic spline curves. For the overall risk of severe COVID-19, the persistently stage G1 showed the lowest risk (aOR, 0.897; 95% CI, 0.827–0.972), followed by those from stage G1 to G2 (aOR, 0.900; 95% CI, 0.828–0.978) and those from stage G2 to G1 (aOR, 0.931; 95% CI, 0.871–0.995), compared with the persistently stage G2 group.
**Conclusion:** An increase in eGFR was negatively associated with the risk of SARS-CoV-2 infection and severe COVID-19 among normal or mildly decreased kidney function. For severe COVID-19, maintaining higher baseline eGFR may act as a protective factor against its risk.

**Keywords:** eGFR; SARS-CoV-2; COVID-19; Nested Case-Control Study

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**Disclosure**
The authors have no potential conflicts of interest to disclose.

**Data Sharing Statement**
The data are only granted for authorized researchers of National Health Insurance Service (NHIS).

**Author Contributions**
Conceptualization: Lim Y, Jeong S. Data curation: Lim Y, Lee MH, Jeong S. Formal analysis: Lim Y, Jeong S. Methodology: Lim Y, Jeong S. Supervision: Han HW. Writing - original draft: Lim Y, Jeong S. Writing - review & editing: Lim Y, Lee MH, Lee SK, Jeong S, Han HW.

## INTRODUCTION

A novel coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been threatening global health at an unprecedented level. Many researchers investigated the risk factors of COVID-19-related outcomes to find determinants of promising or poor prognosis. Age and sex are proven to play an important role in the incidence and severity of COVID-19.[1,2] Currently, chronic kidney disease (CKD) has emerged as the most prevalent risk factor for COVID-19-related outcomes.[3-5]

As reported by Clark et al.,[1] the risk of COVID-19-related outcomes decreased from 22% to 17% by removing CKD, emphasizing the need to understand the underlying mechanisms with COVID-19. Dysfunction in the kidney causes uremia-associated changes in innate and adaptive immunity, predisposing patients to an increased risk of infection.[6,7] Indeed, the progression of renal insufficiency correlated well with an increase in the risk of SARS-CoV-2 infection and severe COVID-19. A retrospective cohort study of 18,105 patients showed that estimated glomerular filtration rate (eGFR) was inversely associated with severe COVID-19.[8] In addition, a study using OpenSafely cohort reported that CKD with eGFR < 30 mL/min/1.73 $m^2$ showed the highest risk among other CKD stages.[9]

As accumulating evidence indicates an advanced CKD as a risk factor for increased susceptibility to SARS-CoV-2 infection and severe COVID-19, the association between increased kidney function and COVID-19 also needs to be investigated. Although Carlson et al.[8] reported a higher risk of severe COVID-19 with eGFR 61–90 mL/min/1.73 $m^2$ compared with eGFR > 90 mL/min/1.73 $m^2$, the observed association was based on a single measurement which is vulnerable to misclassification or measurement bias. Therefore, we investigated the association of an increase in eGFR among normal to mildly decreased kidney function based on two consecutive health screening tests (2017–2018 and 2019–2020) with the risk of SARS-CoV-2 infection and severe clinical events of COVID-19 to investigate the prognostic implications of COVID-19 with improved kidney function.

## METHODS

### Data source

Approximately 97.2% of the Korean population is enrolled in the Korean National Health Insurance Service (NHIS).[10] Through the medical records of the biennial health screening, qualification, and treatment claims collected by the NHIS, researchers can investigate many population-based epidemiologic studies. Other details of NHIS data are described elsewhere.[11] To establish the scientific basis for the quarantine policy and to investigate the risk factors of COVID-19, the NHIS and the Korea Disease Control and Prevention Agency (KDCA) have generated the K-COV-N cohort by matching patients with COVID-19 at 1:10 ratio based on age and sex propensity score. Therefore, the cohort dataset is comprised of 6.3 million participants with the following variables: 1) socio-demographic information, diagnosis statements by International Classifications of Diseases, 10th revision (ICD-10), prescriptions records, serological data, and biennial health screening data between January 1, 2009 and December 31, 2021; 2) COVID-19 vaccination data including inoculation date, series, types of vaccines and confirmation date, death and transmission route of SARS-CoV-2 infection accumulated at the KDCA and Ministry of Health and Welfare from October 9, 2020 to December 31, 2021.

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## Study population

The participants who were aged 20 years or older were selected as a candidate for the biennial health screening from period I (2017–2018) to period II (2019–2020; n = 2,128,608). Next, those who died without SARS-CoV-2 infection before January 1, 2022 (n = 6,234), who were infected with SARS-CoV-2 before January 1, 2021 (n = 12,871), had missing information for eGFR (n = 9,732), had missing information for other covariates (n= 2,026), had an eGFR < 60 mL/min/1.73 $m^2$ at both health screenings (n = 122,130), or were diagnosed with any history of chronic kidney disease or acute kidney injury (ICD-10 code; N17–N19) before study enrollment (n = 11,390) were excluded from the study. Finally, 1,964,225 participants were included for the first analytic cohort for examining the risk of COVID-19. To confirm the association of changes in eGFR with severe clinical outcomes of COVID-19, we generated a second analytic cohort comprising 159,427 patients with SARS-CoV-2 infection. If diagnosed with SARS-CoV-2 infection after December 1, 2021 (n = 54,840), they were excluded from the cohort due to a relatively short follow-up period. Therefore, 104,587 patients were included in the second analytic cohort for examining the risk of severe clinical outcomes of COVID-19 (**Fig. 1**).

## Exposures

Serum creatinine (mg/dL) was measured by traceable isotope dilution mass spectrometry during both health screenings. Based on the laboratory results, eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: eGFR = 141 × $\min(S_{cr}/\kappa, 1)^{\alpha}$ × $\max(S_{cr}/\kappa, 1)^{-1.209}$ × $0.993^{Age}$ × 1.018 [if female]. $S_{cr}$ is serum creatinine in

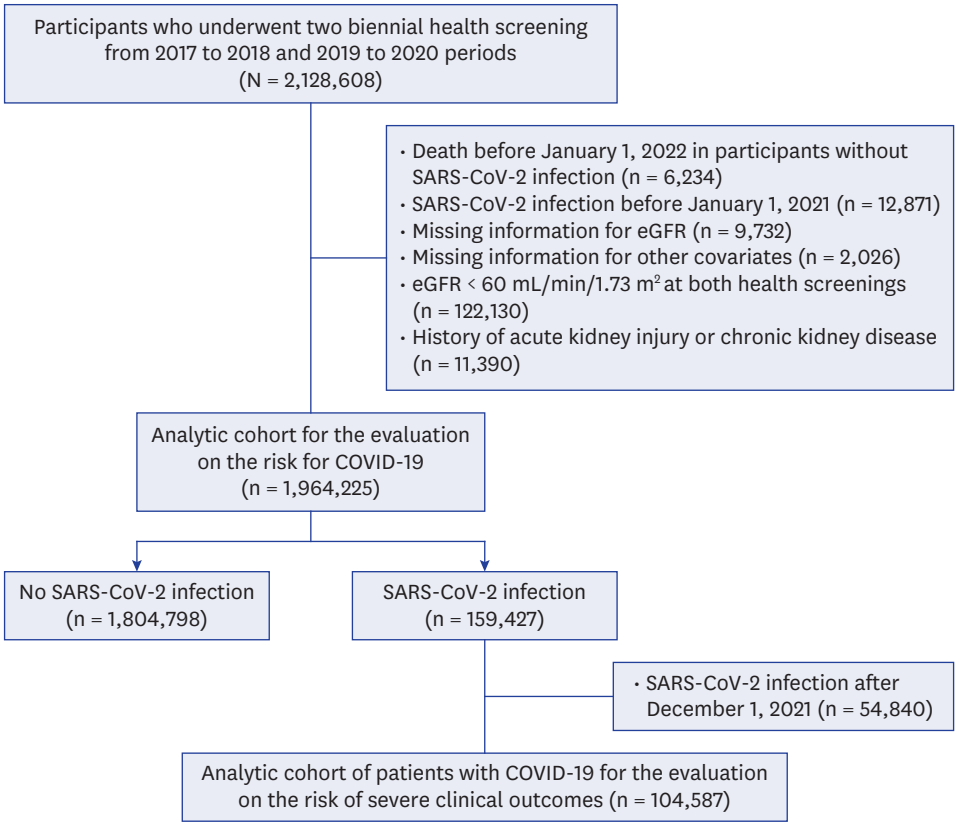


**Fig. 1.** Flow diagram for the inclusion of study populations.
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, eGFR = estimated glomerular filtration rate, COVID-19 = coronavirus disease 2019.


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mg/dL, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males. According to the calculated eGFR, the kidney function status was categorized in two stages according to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline: stage G1 and G2.[12] Stage G1 was defined as an eGFR level of 90 mL/min/1.73 $m^2$ or higher. Stage G2 was defined as an eGFR level between 60 and 89 mL/min/1.73 $m^2$. By the stages of eGFR in two consecutive health screenings, all participants were categorized into 4 levels as follows: 1) persistently stage G1, 2) from stage G2 to G1, 3) from stage G1 to G2, 4) persistently stage G2. In addition, for the change in eGFR, it was defined by subtracting its value of period I from period II.

### Outcomes

The main outcome was a positive diagnosis of SARS-CoV-2 infection (based on the laboratory result of real-time reverse transcription polymerase chain reaction assays using either nasopharyngeal or oropharyngeal swabs) after January 1, 2021. The secondary outcome was a composite term of severe clinical outcome of COVID-19 including requirement of conventional oxygen therapy (COT), high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), admission to intensive care unit (ICU), requirement of mechanical ventilation (MV), extracorporeal membrane oxygenation (ECMO), and death within following month after the diagnosis of SARS-CoV-2 infection. If the same clinical event occurred one or more times, it was counted as one for each patient.

### Key variables

Age, sex, household income, moderate-to-vigorous physical activity (MVPA), body mass index (BMI), alcohol consumption, smoking status, history of hypertension, diabetes mellitus, dyslipidemia, comorbidities, COVID-19 vaccination status, and baseline eGFR value (period I) were included for the adjusting covariates. Vaccination status was evaluated based on the number of inoculated COVID-19 vaccines that were available in South Korea as follows: BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), ChAdOx1 nCoV-19 (AstraZeneca), NVX-CoV2373 (Novavax), and Ad26.COV2.S (Janssen/Johnson & Johnson). Because the additional dose of Ad26.COV2.S vaccine was not approved, a single vaccination of Ad26.COV2.S was considered as two. Therefore, the vaccination status was categorized as 0, 1, 2, and ≥ 3. Those who were diagnosed with SARS-CoV-2 infection within 2 weeks after the vaccination were considered as non-vaccinated and were not counted in the vaccination status. MVPA was calculated by adding the frequency (times/week) of each moderate and vigorous physical activity reported by self-questionnaires in the health screening. Household income was evaluated by the insurance premium and classified by quartiles. Smoking status was classified as ever smoker if smoked more than 100 cigarettes in their lifetime or never smoker if not. Alcohol consumption was classified as a drinker or a non-drinker. Comorbidities were calculated by Charlson Comorbidity Index (CCI) score using accumulated medical records through NHIS, which was validated in a previous study.[13] After calculating the CCI score, we categorized it as 0, 1, and ≥ 2. The history of hypertension, diabetes, and dyslipidemia was confirmed by the physician records which were reported through the health screening.

### Statistical analysis

We analyzed the association of eGFR with the risk of COVID-19 stratified by the change in eGFR stage from period I (2017–2018) to II (2019–2020). The participants were followed-up from January 1, 2021 to any diagnosis of COVID-19 or December 31, 2021, whichever happened first. Values of continuous variables for each group were presented as mean (standard

deviation; SD) and categorical variables as number (%). Baseline characteristics were defined with the values measured in period II. The effect size by one-way ANOVA (> 0.01 = small; > 0.06 = medium; > 0.14 = large) for continuous and Cramer's V (> 0.1 = small; > 0.3 = medium; > 0.5 = large) for categorical variables were calculated to assess the mean differences between groups.[14] For the main analysis, we estimated the odds ratio using logistic regression. Age, sex-adjusted logistic regression and multivariate-adjusted logistic regression by age, sex, household income, MVPA, BMI, CCI, alcohol consumption, smoking status, history of diabetes mellitus, hypertension, dyslipidemia, dose of COVID-19 vaccinations, and baseline eGFR value (period I) were calculated to examine the association. The adjusted odds ratio (aOR) was rounded off to 3 decimal places. In addition, when analyzing the association with an increase in eGFR, it was calculated per 5 mL/min/1.73 $m^2$. Restricted cubic spline curves were drawn to depict the non-linear association of change in eGFR with adjusted odds ratio by 3 knots and 0 mL/min/1.73 $m^2$ (no change in eGFR) was set as a reference. For the subgroup analysis, we analyzed stage G1 and G2 of period I with 5 mL/min/1.73 $m^2$ increase of eGFR by age (≥ 65 or < 65), sex (men or women), CCI (0, 1, or ≥ 2), COVID-19 vaccination (none, 1st, 2nd, or ≥ 3rd dose), history of hypertension (yes or no), diabetes (yes or no), and dyslipidemia (yes or no), and tested the interaction to examine the subgroup differences. Two-sided *P* values of < 0.05 were regarded as statistically significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA), R (version 3.6.2) and R Studio (version 1.3.959) software (R Foundation for Statistical Computing, Vienna, Austria).

### Ethics statement

This study was approved by the Institutional Review Board of CHA University Hospital (No. CHAMC 2022-05-052) and was conducted in accordance with the STROBE guidelines.[15] The requirement for informed consent was waived because of anonymous data retrieved from the K-COV-N cohort.

## RESULTS

### Baseline characteristics

We identified 159,427 patients with and 1,804,798 patients without SARS-CoV-2 infection in the first analytic cohort. For the second analytic cohort, there were 14,016 patients with severe clinical events among 104,587 patients with COVID-19. The mean ± SD serum creatinine (mg/dL) was 0.75 ± 0.15, 0.96 ± 0.14, 0.78 ± 0.15, 0.98 ± 0.16 at health screening period I (2017–2018) and 0.75 ± 0.15, 0.77 ± 0.15, 0.96 ± 0.15, 0.98 ± 0.16 at health screening period II (2019–2020) among patients with persistently stage G1, from stage G2 to G1, from stage G1 to G2, and persistently stage G2, respectively. In addition, the mean ± SD eGFR (mL/min/1.73 $m^2$) was 105.8 ± 10.6, 80.8 ± 6.7, 100.0 ± 8.8, 77.5 ± 8.0 at period I and 105.2 ± 10.4, 99.8 ± 8.3, 80.8 ± 6.9, 77.1 ± 8.0 at period II among the same groups, respectively. Age differed the most between the groups (effect size = 0.42), followed by the history of hypertension (effect size = 0.17). However, the effect size of the baseline comorbidities between groups was small, indicating low practical significance (**Supplementary Table 1**). Other baseline characteristics are described in **Table 1**.

### Association of eGFR with risk of SARS-CoV-2 infection

There were 159,427 COVID-19 patients during the follow-up. The number of SARS-CoV-2 infections according to the eGFR stages are shown in **Table 2**. The risk of SARS-CoV-2 infection showed a decrease when eGFR stage changed from stage G2 to G1 (aOR, 0.957;


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**Table 1.** Descriptive characteristics of the study participants by eGFR stages

| Characteristics | Persistently stage G1 (n = 863,060) | From stage G2 to G1 (n = 263,604) | From stage G1 to G2 (n = 282,165) | Persistently stage G2 (n = 555,396) | Effect size[a] |
|---|---|---|---|---|---|
| Health screening period I (2017–2018) | | | | | |
| Serum creatinine, mg/dL | 0.75 ± 0.15 | 0.96 ± 0.14 | 0.78 ± 0.15 | 0.98 ± 0.16 | 0.71 |
| eGFR, mL/min/1.73 m$^2$ | 105.8 ± 10.6 | 80.8 ± 6.7 | 100.0 ± 8.8 | 77.5 ± 8.0 | > 1.00 |
| Health screening period II (2019–2020) | | | | | |
| Serum creatinine, mg/dL | 0.75 ± 0.15 | 0.77 ± 0.15 | 0.96 ± 0.15 | 0.98 ± 0.16 | 0.72 |
| eGFR, mL/min/1.73 m$^2$ | 105.2 ± 10.4 | 99.8 ± 8.3 | 80.8 ± 6.9 | 77.1 ± 8.0 | > 1.00 |
| Age, yr | 45.3 ± 12.7 | 51.5 ± 12.0 | 51.3 ± 12.7 | 57.9 ± 12.7 | 0.42 |
| Sex | | | | | 0.09 |
| Men | 414,856 (48.1) | 132,344 (50.2) | 146,822 (52.0) | 325,737 (58.7) | |
| Women | 448,204 (51.9) | 131,260 (49.8) | 135,343 (48.0) | 229,659 (41.4) | |
| Household income | | | | | 0.05 |
| First quartile | 174,291 (20.2) | 55,526 (21.1) | 59,017 (20.9) | 114,337 (20.6) | |
| Second quartile | 188,786 (21.9) | 52,411 (19.9) | 56,457 (20.0) | 100,376 (18.1) | |
| Third quartile | 248,124 (28.8) | 69,053 (26.2) | 75,256 (26.7) | 133,169 (24.0) | |
| Fourth quartile (highest) | 251,859 ± 29.2 | 86,614 ± 32.9 | 91,435 ± 32.4 | 207,514 ± 37.4 | |
| Systolic blood pressure, mmHg | 123.0 ± 14.3 | 124.8 ± 14.4 | 124.6 ± 14.4 | 126.8 ± 14.5 | 0.11 |
| Diastolic blood pressure, mmHg | 76.5 ± 10.1 | 77.3 ± 10.0 | 77.4 ± 10.0 | 77.8 ± 9.9 | 0.06 |
| Body mass index, kg/m$^2$ | 24.2 ± 3.8 | 24.5 ± 3.5 | 24.5 ± 3.5 | 24.7 ± 3.3 | 0.06 |
| Triglyceride, mg/dL | 133.3 ± 106.1 | 136.1 ± 100.6 | 131.9 ± 98.2 | 135.0 ± 94.6 | 0.01 |
| Cigarette smoking | | | | | 0.04 |
| Non-smoker | 555,656 (64.4) | 167,783 (63.7) | 176,164 (62.4) | 332,889 (59.9) | |
| Smoker | 307,404 (35.6) | 95,821 (36.4) | 106,001 (37.6) | 222,507 (40.1) | |
| Alcohol consumption | | | | | 0.10 |
| Yes | 583,615 (67.6) | 163,195 (61.9) | 174,567 (61.9) | 309,590 (55.7) | |
| No | 279,445 (32.4) | 100,409 (38.1) | 107,598 (38.1) | 245,806 (44.3) | |
| MVPA | | | | < 0.001 | 0.03 |
| 0 time/wk | 231,259 (26.8) | 70,570 (26.8) | 70,225 (24.9) | 140,156 (25.2) | |
| 1–2 time/wk | 158,686 (18.4) | 45,352 (17.2) | 47,146 (16.7) | 83,364 (15.0) | |
| 3–4 time/wk | 172,756 (20.0) | 52,196 (19.8) | 56,169 (19.9) | 108,597 (19.6) | |
| ≥ 5 time/wk | 300,359 (34.8) | 95,486 (36.2) | 108,625 (38.5) | 223,279 (40.2) | |
| Hypertension | 128,412 (14.9) | 57,262 (21.7) | 62,400 (22.1) | 174,521 (31.4) | 0.17 |
| Diabetes | 57,528 (6.7) | 22,211 (8.4) | 24,730 (8.8) | 64,671 (11.6) | 0.07 |
| Dyslipidemia | 75,369 (8.7) | 33,265 (12.6) | 35,263 (12.5) | 91,259 (16.4) | 0.10 |
| Charlson comorbidity index | | | | | 0.09 |
| 0 | 399,946 (46.3) | 106,522 (40.4) | 115,673 (41.0) | 194,321 (35.0) | |
| 1 | 278,647 (32.3) | 85,065 (32.3) | 89,368 (31.7) | 171,769 (30.9) | |
| ≥ 2 | 184,467 (21.4) | 72,017 (27.3) | 77,124 (27.3) | 189,306 (34.1) | |
| COVID-19 vaccination | | | | | 0.10 |
| None | 64,973 (7.5) | 16,664 (6.3) | 17,492 (6.2) | 28,372 (5.1) | |
| 1st dose | 23,523 (2.7) | 5,839 (2.2) | 6,313 (2.2) | 9,583 (1.7) | |
| 2nd dose | 437,086 (50.6) | 112,416 (42.7) | 122,155 (43.3) | 187,256 (33.7) | |
| ≥ 3rd dose | 337,478 (39.1) | 128,685 (48.8) | 136,205 (48.3) | 330,185 (59.5) | |

Data shown are mean ± standard deviation or number (%). Baseline was defined as the NHIS health screening period II (2019–2020). According to the calculated eGFR, the kidney function status was categorized in two stages according to the KDIGO clinical practice guideline: 1) stage G1 was defined as an eGFR level of 90 mL/min/1.73 m$^2$ or higher; 2) stage G2 was defined as an eGFR level between 60 and 89 mL/min/1.73 m$^2$. By the eGFR stages in two consecutive health screenings (period I [2017–2018] and period II [2019-2020]), all participants were categorized into 4 levels as follows: 1) persistently stage G1, 2) from stage G2 to G1, 3) from stage G1 to G2, 4) persistently stage G2.

eGFR = estimated glomerular filtration rate, MVPA = moderate-to-vigorous physical activity, COVID-19 = coronavirus disease 2019, NHIS = National Health Insurance Service, KDIGO = Kidney Disease Improving Global Outcomes, ANOVA = analysis of variance.

[a]The effect size was calculated by one-way ANOVA (> 0.01 = small; > 0.06 = medium; > 0.14 = large) for continuous or Cramer's V (> 0.1 = small; > 0.3 = medium; > 0.5 = large) for categorical variables, respectively.[15]

95% confidence interval [CI], 0.938–0.977) and with persistently stage G1 (aOR, 0.966; 95% CI, 0.943–0.990) (**Table 2**). In addition, the change in eGFR was inversely associated with the risk of SARS-CoV-2 infection in both stages at period I (**Fig. 2**). When analyzing the association by an increase in eGFR between each period, the odds per 5 mL/min/1.73 m$^2$ increase in eGFR showed a decrease for both stages at period I (aOR in stage G1, 0.994; 95% CI, 0.990–0.997; aOR in stage G2, 0.995; 95% CI, 0.991–0.999) (**Supplementary Table 2**).


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**Table 2.** Association of change in eGFR stage with risk of SARS-CoV-2 infection between period I (2017–2018) and II (2019–2020)

| Variables | Change in eGFR stage from period I to II | | | | *P* for trend |
|---|---|---|---|---|---|
| | Persistently stage G2 (n = 555,396) | From stage G1 to G2 (n = 282,165) | From stage G2 to G1 (n = 263,604) | Persistently stage G1 (n = 863,060) | |
| Event number | 44,595 | 23,298 | 21,517 | 70,017 | |
| Age, sex-adjusted OR (95% CI) | 1.000 (Reference) | 1.037 (1.020–1.055)*** | 1.024 (1.006–1.041)** | 1.024 (1.010–1.037)*** | < 0.001 |
| Multivariable-adjusted OR (95% CI)[a] | 1.000 (Reference) | 0.981 (0.957–1.006) | 0.957 (0.938–0.977)*** | 0.966 (0.943–0.990)** | < 0.001 |

The staging of eGFR was classified as G1 (eGFR ≥ 90 mL/min/1.73 m²) or G2 (eGFR 60–89 mL/min/1.73 m²) based on the measurement for each period using CKD-EPI formula. OR was calculated using logistic regression.
eGFR = estimated glomerular filtration rate, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, OR = odds ratio, CI = confidence interval, COVID-19 = coronavirus disease 2019.
[a]OR was adjusted for age, sex, household income, body mass index, hypertension, diabetes, dyslipidemia, Charlson comorbidity index, smoking, alcohol consumption, dose of COVID-19 vaccination, and baseline eGFR value (period I).
*$P$ < 0.05, **$P$ < 0.01, ***$P$ < 0.001.

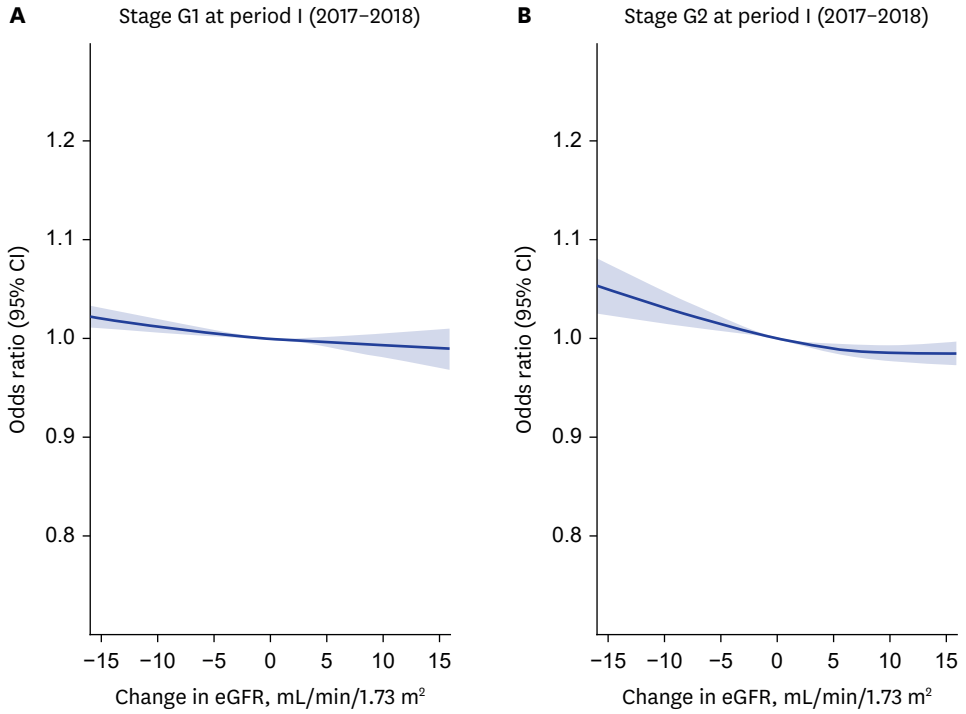


**Fig. 2.** Graphical visualization of the association of change in eGFR with risk of SARS-CoV-2 infection. Odds ratio was calculated after adjustments for age, sex, household income, body mass index, hypertension, diabetes, dyslipidemia, Charlson comorbidity index, smoking, alcohol consumption, dose of COVID-19 vaccination, and baseline eGFR value (period I). Restricted cubic spline curves were drawn by 3 knots with 0 mL/min/1.73 m² (no change in eGFR) set as a reference. The blue line represents the adjusted odds ratio and shaded area represents the 95% CI. (**A**) Association of change in eGFR from health screening period I (2017–2018) to period II (2019–2020) in patients with eGFR stage G1 at period I (2017–2018). (**B**) Association of change in eGFR from health screening period I (2017–2018) to period II (2019–2020) in patients with eGFR stage G2 at period I (2017–2018).
eGFR = estimated glomerular filtration rate, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, COVID-19 = coronavirus disease 2019, CI = confidence interval.

## Association of eGFR with risk of severe clinical events of COVID-19

There were 14,016 severe clinical events that occurred within the following month after the diagnosis of SARS-CoV-2 infection. The requirement of COT happened the most (n = 13,515), while the requirement of CPAP happened the least (n = 59). Compared with those who were persistently stage G2, the overall risk of severe COVID-19 was lowest among those with persistently stage G1 (aOR, 0.897; 95% CI, 0.827–0.972), followed by those from stage G1 to G2 (aOR, 0.900; 95% CI, 0.828–0.978) and those from stage G2 to G1 (aOR 0.931; 95% CI, 0.871–0.995). Moreover, those who were persistently stage G1 showed a lower risk compared with those who were persistently stage G2 in COT (aOR, 0.911; 95% CI, 0.840–0.988), HFNC (aOR, 0.819; 95% CI, 0.690–0.972), ICU (aOR, 0.752; 95% CI, 0.593–0.952) (**Table 3**).


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**Table 3.** aORs for severe clinical outcomes of COVID-19 according to the change in eGFR stages among participants with SARS-CoV-2 infection

| Variables | From period I (2017–2018) to II (2019–2020) | | | | |
|---|---|---|---|---|---|
| | Persistently stage G2 (n = 44,595) | From stage G1 to G2 (n = 23,298) | From stage G2 to G1 (n = 21,517) | Persistently stage G1 (n = 70,017) | *P* for trend |
| Overall | | | | | |
| Event number | 5,325 | 2,029 | 1,887 | 4,775 | |
| aOR (95% CI) | 1.000 (reference) | 0.900 (0.828–0.978)* | 0.931 (0.871–0.995)* | 0.897 (0.827–0.972)** | 0.024 |
| COT | | | | | |
| Event number | 5,092 | 1,955 | 1,809 | 4,659 | |
| aOR (95% CI) | 1.000 (reference) | 0.913 (0.840–0.993)* | 0.934 (0.874–0.999)* | 0.911 (0.840–0.988)* | 0.064 |
| HFNC | | | | | |
| Event number | 1,231 | 414 | 359 | 762 | |
| aOR (95% CI) | 1.000 (reference) | 0.936 (0.788–1.112) | 0.922 (0.802–1.060) | 0.819 (0.690–0.972)* | 0.085 |
| CPAP | | | | | |
| Event number | 29 | 8 | 12 | 10 | |
| aOR (95% CI) | 1.000 (reference) | 1.271 (0.354–4.568) | 1.487 (0.657–3.365) | 1.340 (0.393–4.566) | 0.819 |
| MV | | | | | |
| Event number | 471 | 139 | 121 | 210 | |
| aOR (95% CI) | 1.000 (reference) | 0.944 (0.707–1.263) | 0.892 (0.697–1.142) | 0.803 (0.599–1.076) | 0.394 |
| ICU | | | | | |
| Event number | 605 | 188 | 178 | 342 | |
| aOR (95% CI) | 1.000 (reference) | 0.831 (0.654–1.057) | 0.912 (0.750–1.108) | 0.752 (0.593–0.952)* | 0.13 |
| ECMO | | | | | |
| Event number | 72 | 18 | 20 | 42 | |
| aOR (95% CI) | 1.000 (reference) | 0.562 (0.281–1.124) | 0.850 (0.502–1.441) | 0.546 (0.283–1.052) | 0.294 |
| Death | | | | | |
| Event number | 366 | 84 | 78 | 91 | |
| aOR (95% CI) | 1.000 (reference) | 1.222 (0.803–1.859) | 1.257 (0.882–1.791) | 0.937 (0.597–1.470) | 0.331 |

The staging of eGFR was classified as G1 (eGFR ≥ 90 mL/min/1.73 m$^2$) or G2 (eGFR 60–89 mL/min/1.73 m$^2$) based on the measurement for each period using CKD-EPI formula. aOR was calculated using logistic regression after adjustments for age, sex, household income, body mass index, hypertension, diabetes, dyslipidemia, Charlson comorbidity index, smoking, alcohol consumption, dose of COVID-19 vaccination, and baseline eGFR value (period I).
aOR = adjusted odds ratio, COVID-19 = coronavirus disease 2019, eGFR = estimated glomerular filtration rate, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, CI = confidence interval, COT = conventional oxygen therapy, HFNC = high-flow nasal cannula, CPAP = continuous positive airway pressure, ICU = intensive care unit, MV = mechanical ventilation, ECMO = extracorporeal membrane oxygenation, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration.
*$P$ < 0.05, **$P$ < 0.01.

However, the odds per 5 mL/min/1.73 m$^2$ increase in eGFR did not reveal to have any association with severe clinical events (**Supplementary Table 3**).

### Subgroup analyses

Subgroup analyses were conducted by stratifying age, sex, CCI, COVID-19 vaccination, hypertension, diabetes, and dyslipidemia with aOR calculated by 5 mL/min/1.73 m$^2$ increase of eGFR. For those who were stage G1 at period I, patients who were age < 65, with 0 CCI, without hypertension, diabetes, and dyslipidemia showed a lower risk of SARS-CoV-2 infection (**Supplementary Table 4**). The association was consistent for those who were stage G2 at period I (**Supplementary Table 5**). For both stages, the increase in eGFR level did not have any association with COVID-19 when vaccinated for ≥ 2nd dose of COVID-19. In contrast, when analyzing the risk of severe COVID-19, only age below 65 years showed lower risk when eGFR increased in both stages at period I (**Supplementary Tables 6** and **7**).

## DISCUSSION

To the best of our knowledge, this is the first large-scale study to investigate the changes in eGFR with the risk of COVID-19. Our study demonstrated that an increase in eGFR within normal to mildly decreased levels is negatively associated with the risk of SARS-CoV-2 infection. For the risk of severe clinical events of COVID-19, those who were persistently stage


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G1 showed a lower risk compared with those who were persistently stage G2. However, the increase in eGFR showed a limited association with severe COVID-19.

The inverse association between eGFR and the risk of COVID-19-related outcomes was shown by some previous studies. In a retrospective analysis of 231 patients with SARS-CoV-2 infection, eGFR increase per 10 mL/min/1.73 $m^2$ showed a 7% risk-lowering effect with severe outcomes including ICU admission or death.[16] However, the eGFR measurement was held at the admission for suspected SARS-CoV-2 infection, which is different from our study that we measured it before the infection occurred. In addition, the previous study included those with eGFR < 60 mL/min/1.73 $m^2$, which was comprised of 38% acute kidney injury patients. Therefore, the association with the baseline eGFR and the severe outcomes of COVID-19 may have been underestimated.

Using the Danish healthcare system, Carlson et al.[8] reported that eGFR was inversely associated with the risk of SARS-CoV-2 infection and severe COVID-19 (ICU admission or requirement of MV), which was similar to the results of our study. In a retrospective cohort study of 18,105 patients, the authors reported that those with stage G2 showed a 13% higher risk of SARS-CoV-2 infection and 44% higher risk of severe COVID-19 compared with stage G1. In addition, the standardized risk of severe COVID-19 was 2.0% higher from stage G2 to G1, and thereby we could assume that an increase in eGFR lowers the risk of severe COVID-19. Our results showed a lower risk-lowering effect (10%) when comparing those with persistently stage G1 to persistently stage G2. The explanation for the difference in observed risks can be accounted for by the measurement of eGFR based on its trajectory with two consecutive health screening tests, which allows tracking the change in eGFR and examining the true association.

Even though we could not provide any interventions for eGFR restoration, our subgroup analyses suggest that participants who are younger and healthier (no comorbidities) may benefit from improved eGFR value. Those who are already considered as low-risk group for COVID-19 could also mildly benefit by improving their kidney function. As many studies focused on the impact of decreased kidney function and its related outcomes, focusing on the improved state and its contributing factor could also be important on understanding the nature of COVID-19 with kidney function. Although renal function improvement and COVID-19 is mostly unknown, homeostasis of the immune system by improved renal function may influence the susceptibility of COVID-19, which is mostly influenced by age and comorbidity.[17,18]

The possible mechanisms for reduced risk of COVID-19-related outcomes by increased eGFR include an immunoprotective effect due to decreased angiotensin-converting enzyme (ACE)/ACE2 ratio. Higher ACE/ACE2 ratio induced via the ACE-Ang II-AT1 axis is detected in various disease conditions and is inversely correlated with GFR levels.[19,20] After the virus enters the cell, it downregulates ACE2 and causes an imbalance in the ACE/ACE2 ratio.[21] Therefore, higher ACE/ACE2 ratio induced by impaired baseline condition could be detrimental in SARS-CoV-2 infection that could accelerate the dysregulated systemic inflammatory response, causing severe COVID-19.[22] Conversely, lower ACE/ACE2 ratio, which is associated with exercise and high GFR levels, could reduce the risk of worsening SARS-CoV-2 infection as the subsequent inflammatory reaction is determined by the predisposing ACE/ACE2 ratio which is responsible for modulating reactive oxygen and cytokine.[22] In addition, higher ACE/ACE2 ratio are also observed in early chronic kidney disease or mild renal dysfunction,


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which may be crucial in severe COVID-19.[20,23] Even though there are no direct studies that compared the renal function and ACE/ACE2 ratio between stage G1 and G2, Wang et al.[24] showed the inverse correlation by eGFR ranging from 20 to 140 mL/min/1.73 $m^2$, which may partially explain our results.

The present study has several limitations. First, eGFR could not be calculated by other filtration markers (e.g., cystatin C) that could validate our results. However, eGFR measurement using CKD-EPI formula is suggested for general use and has less bias when measuring eGFR > 60 mL/min/1.73 $m^2$, which is recommended by KDIGO.[25,26] Second, the patients were not categorized by CKD stage that has higher clinical applicability. Although there are some studies that defined CKD stages using only eGFR, it is hard to trust due to the lack of other biomarkers that show kidney damage (e.g., urine albumin-creatinine ratio). However, only 5% of Korean patients with eGFR G1-G2 were reported to have urine albumin-to-creatinine ratio ≥ 30 mg/g, which is classified as CKD.[27] Therefore, further studies are needed to adjust the association of eGFR and the risk of COVID-19-related outcomes using other biomarkers to define CKD progression. Third, there is a lack of evidence that therapeutic interventions for increasing eGFR could prevent or lower the risk of COVID-19. However, there are many longitudinal studies that reported the non-linear trajectory of kidney function[28,29] and need further investigation associated with its trajectory and the effect on the susceptibility of COVID-19.[30,31] Finally, our dataset could not fully explain the association by ACE inhibitors and angiotensin II receptor blockers (ARB), which is known to affect the ACE/ACE2 ratio. Our dataset consists of anonymized hypertension medication data (includes not only ACE inhibitors and ARB but also calcium channel blocker, diuretics, etc.) following the policy of the NHIS to reduce the likelihood of exposure to certain pharmaceutical companies.

An increase in eGFR was negatively associated with the risk of SARS-CoV-2 infection but not with severe clinical events of COVID-19 among those with normal to mildly decreased kidney function. For the risk of severe COVID-19, maintaining higher baseline eGFR (> 90 mL/min/1.73 $m^2$) was associated with a lower risk and thereby suggests higher baseline eGFR within normal range as a protective factor against severe COVID-19.

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## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Baseline comorbidities of the study participants

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**Supplementary Table 2**

Association of change in eGFR with risk of SARS-CoV-2 infection between period I (2017–2018) and II (2019–2020)

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**Supplementary Table 3**

aORs with 95% CI for severe clinical outcomes of COVID-19 according to the increase in eGFR per 5 mL/min/1.73 $m^2$ among participants with SARS-CoV-2 infection stratified by eGFR stage

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**Supplementary Table 4**

Stratified analyses on the association of the increase in eGFR with risk of COVID-19 infection among participants with stage G1 at period I (2017–2018)

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**Supplementary Table 5**

Stratified analyses on the association of increase in eGFR with risk of COVID-19 infection among participants with stage G2 at period I (2017–2018)

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**Supplementary Table 6**

Stratified analyses on the association of increase in eGFR with risk of severe COVID-19 among participants with stage G1 at period I (2017–2018)

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**Supplementary Table 7**

Stratified analyses on the association of increase in eGFR with risk of severe COVID-19 among participants with stage G2 at period I (2017–2018)

Click here to view

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