# Risk factors for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections: a nationwide population-based study

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**Background:** The coronavirus disease 2019 (COVID-19) has rapidly turned into a public health emergency worldwide; however, the risk factors for infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have not been well-described. We aimed to identify the clinical risk factors for SARS-CoV-2 infections in Korea, where social distancing and face masks have been strongly recommended.

**Methods:** The data of individuals who underwent the reverse transcription polymerase chain reaction test for SARS-CoV-2 between January 3 and May 31, 2020 were retrieved from the Health Insurance Review and Assessment Service dataset. We used multivariable logistic regression models to identify the risk factors for SARS-CoV-2 infections in the population.

**Results:** We retrieved the results of 219,729 SARS-CoV-2 tests, of which 7,333 were positive results. In the multivariable analysis, female sex was associated with a higher risk of testing positive for SARS-CoV-2 [odds ratio (OR) =1.30, 95% confidence interval (CI): 1.24–1.37, P<0.0001]. Additionally, populations living in areas that had large outbreaks of COVID-19 were at an increased risk of testing positive for SARS-CoV-2 (OR =6.87, 95% CI: 6.55–7.21, P<0.0001). The odds of a positive test were greater for the Medical Aid beneficiaries (OR =1.99, 95% CI: 1.82–2.18, P<0.0001) than for the National Health Insurance beneficiaries. Individuals with diabetes mellitus (DM) were more likely to test positive (OR =1.15, 95% CI: 1.07–1.24, P=0.0002).

**Conclusions:** Women, individuals living in areas with large outbreaks of COVID-19, Medical Aid beneficiaries, and individuals with DM might have greater risks of contracting SARS-CoV-2 infections despite practicing social distancing and using face masks.

**Keywords:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); coronavirus disease 2019 (COVID-19); risk factors

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## Introduction

The coronavirus disease 2019 (COVID-19) is an infectious respiratory syndrome that displays a wide spectrum of clinical presentations and outcomes (1,2). It is caused by a newly identified betacoronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Subsequently, the Director-General of the World Health Organization (WHO) declared this virus outbreak to constitute a public health emergency of international concern on January 30, 2020. Since there is no effective antiviral pharmacological treatment or vaccine that will be available in the immediate future, reducing the infection rate is the immediate priority, and prevention of infection is the best approach. Therefore, it is necessary to identify the risk factors for SARS-CoV-2 infection in the general population to enhance patient awareness, help the public health care system in disease management, and provide customized advice to the patients.

Many studies have reported risk factors for poor outcomes [age above 65 years, male sex, hypertension, diabetes mellitus (DM), and cardiovascular diseases] in patients with COVID-19 admitted to the hospital (3-5). However, few studies have evaluated the risk factors for SARS-CoV-2 infection. A study conducted in the UK showed that similar risk factors were associated with a positive SARS-CoV-2 test in the primary care cohort (6). Recently, practicing social distancing and wearing face masks have been reported to be effective in preventing the person-to-person transmission of SARS-CoV-2 (7). Like other countries, South Korea has experienced the COVID-19 outbreak since the first case was reported on January 3, 2020. Social distancing practices and wearing masks have been strongly advised since the beginning of the outbreak, and most people have followed these recommendations well. Therefore, we aimed to identify the clinical risk factors for SARS-CoV-2 infections in the population despite following social distancing and using facial masks.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-5958).

## Methods

### *Data collection*

The Ministry of Health and Welfare and the Health Insurance Review and Assessment Service (HIRA) of Korea have shared the nationwide data of SARS-CoV-2 infections for global research collaboration on SARS-CoV-2. The HIRA dataset was based on insurance benefit claims and comprised data on all cases tested for SARS-CoV-2 in Korea. This dataset contained various health-related variables such as socio-demographic information and information on health care utilization including diagnosis, medications, and survival status. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the National Health Insurance Service of Ilsan Hospital (NHIMC 2020-05-002). The need for written informed consent was waived as patient identification data were removed from the database used.

### *Outcome definition*

Patients with SARS-CoV-2 infections were defined by the following diagnostic codes using the HIRA dataset: coronavirus infection (B342), coronavirus as the cause of diseases classified to other chapters (B972), domestic temporary designation or emergency use of new diseases (B18), novel coronavirus infection (U181), and coronavirus disease 2019 (U071). All diagnoses were confirmed by reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2.

### *RT-PCR*

Currently, all reagents that have been approved for emergency use in Korea to diagnose COVID-19 are based on a gene detection method that amplifies the specific gene of SARS-CoV-2. In Korea, on January 17, 2020, the RNA-dependent RNA polymerase (*RdRp*) gene and envelope protein (*E*) gene of SARS-CoV-2 were targeted for gene amplification according to the test method published by WHO (8). For RT-PCR tests, upper respiratory samples including nasopharyngeal and oropharyngeal swabs and lower respiratory samples including sputum, bronchoalveolar lavage, and tracheal aspirates are used (9).

### *Assessment of related variables*

The clinical characteristics of the population were obtained when the diagnosis of SARS-CoV-2 infection was confirmed. The Charlson Comorbidity Index (CCI), which is the most widely used index for calculating the adjusted risk of mortality or the use of resources for patients based on comorbidities, was utilized as previously described (10).

**Table 1** Baseline characteristics of the population tested for SARS-CoV-2

| Variables | Overall (N=219,729) |
|---|---|
| Age, years, median [min, max] | 48.0 [19, 117] |
| 18< and ≤35, n (%) | 65,159 (29.7) |
| 35< and ≤50, n (%) | 52,896 (24.1) |
| 50< and ≤65, n (%) | 46,870 (21.3) |
| >65, n (%) | 54,804 (24.9) |
| Female, n (%) | 115,519 (52.6) |
| Daegu and Gyeonsangbuk-do province, n (%) | 35,258 (16.0) |
| Medical Aid beneficiaries, n (%) | 12,654 (5.8) |
| CCI, n (%) | |
| 0 | 5,2083 (23.7) |
| 1 | 5,4123 (24.6) |
| 2 | 3,4147 (15.5) |
| ≥3 | 7,9376 (36.1) |
| Hypertension, n (%) | 75,299 (34.3) |
| DM, n (%) | 62,423 (28.4) |
| Asthma, n (%) | 64,515 (29.4) |
| COPD, n (%) | 16,978 (7.7) |
| IHD, n (%) | 30,048 (13.7) |
| CHF, n (%) | 20,469 (9.3) |
| Cancer, n (%) | 29,766 (13.5) |
| Liver cirrhosis, n (%) | 8,096 (3.7) |
| ESRD with dialysis, n (%) | 4086 (1.9) |
| IBD, n (%) | 1,454 (0.7) |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; IHD; ischemic heart disease; CHF, congestive heart failure; ESRD, end-stage renal disease; IBD, inflammatory bowel disease.

Data about the underlying diseases in three years preceding the diagnosis of SARS-CoV-2 infection were retrieved. According to the International Classification of Diseases, 10th Revision (ICD-10), the comorbidities were categorized as heart disease [ischemic heart disease (IHD), I20–25, except I20.1; congestive heart failure (CHF), I50], respiratory disease [asthma, J45–46; chronic obstructive pulmonary disease (COPD), J43–44], cancer (C00–97), hypertension (I10), and DM (E10–14). Liver cirrhosis was defined using ICD-10 codes K702, K703, K704, K717, K720, K721, K729, K740–K746, K761, K766–K767, R18, I850, I859, I864, I868, I982, and I983 among the category of liver diseases (K70–K77). Inflammatory bowel disease (IBD), including Crohn disease (CD) and ulcerative colitis (UC), was defined using ICD-10 codes and registration codes from the rare/intractable disease patient support program (CD: K50 and V130, UC: K51 and V131) as previously described (11). Patients with end-stage renal disease (ESRD) on dialysis were defined as those who submitted claims for any procedure or material associated with either hemodialysis or peritoneal dialysis, as revealed by the Korean electronic interchange codes (special dialysis claim codes V001 and V003; treatment codes of O7020 for hemodialysis and O7061 for peritoneal dialysis) combined with the ICD-10 code for chronic kidney disease and end-stage kidney disease (N18).

### *Statistical analysis*

Descriptive statistics were performed for all variables. Differences between the two groups were assessed using the chi-squared test for categorical variables. Additionally, a multiple logistic regression analysis was performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for factors independently related to SARS-CoV-2 infections. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

## Results

### *Baseline characteristics of the population tested for SARS-CoV-2*

Between January 3 and May 31, 2020, a total of 219,729 individuals underwent RT-PCR testing for SARS-CoV-2, of whom 115,519 (52.6%) were women (*Table 1*). The median age of the population was 48.0 years (min, max; 19, 117). The most common age group that underwent was 18–35 years, and 75.1% of the tests were obtained in individuals under 65 years of age. Of the study population, the number of individuals living in Daegu and Gyeongsangbuk-do province, which experienced a large outbreak of COVID-19, was 35,258 (16.0%), and the number of Medical Aid beneficiaries tested was 12,654 (5.8%). A total of 52,083 (23.7%) patients had CCI =0 and 79,376 (36.1%) had CCI ≥3. Among the

**Table 2** Comparison between groups that tested for positive and negative for SARS-CoV-2

| Variables | Positive for SARS-CoV-2 (N=7,333) | Negative for SARS-CoV-2 (N=212,396) | P value |
|---|---|---|---|
| Age, years, median [min, max] | 48.0 [19, 98] | 49.0 [19, 117] | <0.0001 |
| Age, years, n (%) | | | <0.0001 |
| >18 and ≤35 | 2,436 (33.2) | 62,723 (29.5) | |
| >35 and ≤50 | 1,406 (19.2) | 51,490 (24.2) | |
| >50 and ≤65 | 2,151 (29.3) | 44,719 (21.1) | |
| >65 | 1,340 (18.3) | 53,464 (25.2) | |
| Female, n (%) | 4,367 (59.6) | 111,152 (52.3) | <0.0001 |
| Daegu and Gyeonsangbuk-do province, n (%) | 4,025 (54.9) | 31,233 (14.7) | <0.0001 |
| Medical Aid beneficiaries, n (%) | 619 (8.4) | 12,035 (5.7) | <0.0001 |
| CCI, n (%) | | | <0.0001 |
| 0 | 2472 (33.7) | 49,611 (23.4) | |
| 1 | 1,958 (26.7) | 52,165 (24.6) | |
| 2 | 1,104 (15.1) | 33,043 (15.6) | |
| ≥3 | 1799 (24.5) | 77,577 (36.5) | |
| Hypertension, n (%) | 1,910 (26.0) | 73,389 (34.6) | <0.0001 |
| DM, n (%) | 1,687 (23.0) | 60,736 (28.6) | <0.0001 |
| Asthma, n (%) | 1,562 (21.3) | 62,953 (29.6) | <0.0001 |
| COPD, n (%) | 222 (3.0) | 16,756 (7.9) | <0.0001 |
| IHD, n (%) | 541 (7.4) | 29,507 (13.9) | <0.0001 |
| CHF, n (%) | 329 (4.5) | 20,140 (9.5) | <0.0001 |
| Cancer, n (%) | 425 (5.8) | 29,341 (13.8) | <0.0001 |
| Liver cirrhosis, n (%) | 96 (1.3) | 8,000 (3.8) | <0.0001 |
| ESRD with dialysis, n (%) | 19 (0.3) | 4,067 (1.9) | <0.0001 |
| IBD, n (%) | 21 (0.3) | 1,433 (0.7) | <0.0001 |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; CHF, congestive heart failure; ESRD, end-stage renal disease; IBD, inflammatory bowel disease.

underlying diseases, the most commonly reported medical history in the study population was hypertension (34.3%), followed by asthma (29.4%) and DM (28.4%).

### *Comparison between the SARS-CoV-2-positive and SARS-CoV-2-negative groups*

The comparison of socio-demographic and clinical factors between those who tested positive and negative for SARS-CoV-2 is shown in *Table 2*. Overall, 7,333 individuals tested positive for SARS-CoV-2 whereas 212,396 tested negative. The positive group showed a younger age, had a higher percentage of females, included a greater number of subjects living in Daegu and Gyeongsangbuk-do province, and had a greater number of Medical Aid beneficiaries (P<0.0001) as compared to the negative group. The positive group also had a lower CCI score than the negative group (P<0.0001). All the underlying diseases were less common in the positive group (all P<0.0001).

### *Risk factors for obtaining a positive test for SARS-CoV-2*

**Table 3** Association between potential risk factors and SARS-CoV-2 infection

| Variable | Multivariate logistic analysis | |
|---|---|---|
| | OR (95% CI) | P value |
| Female | 1.30 (1.24–1.37) | <0.0001 |
| Age >65 years | 1.01 (0.93–1.09) | 0.8676 |
| Daegu and Gyeonsangbuk-do province | 6.87 (6.55–7.21) | <0.0001 |
| Medical Aid beneficiaries | 1.99 (1.82–2.18) | <0.0001 |
| CCI (ref.: CCI =0) | | |
| 1 | 0.79 (0.74–0.84) | <0.0001 |
| 2 | 0.70 (0.65–0.76) | <0.0001 |
| ≥3 | 0.61 (0.56–0.67) | <0.0001 |
| Essential hypertension | 0.98 (0.92–1.05) | 0.6005 |
| DM | 1.15 (1.01–1.24) | 0.0002 |
| Asthma | 0.86 (0.81–0.92) | <0.0001 |
| COPD | 0.56 (0.49–0.65) | <0.0001 |
| IHD | 0.77 (0.70–0.85) | <0.0001 |
| CHF | 0.72 (0.63–0.81) | <0.0001 |
| Cancer | 0.60 (0.53–0.67) | <0.0001 |
| Liver cirrhosis | 0.53 (0.43–0.65) | <0.0001 |
| ESRD with dialysis | 0.18 (0.11–0.29) | <0.0001 |
| IBD | 0.51 (0.33–0.80) | 0.0028 |

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CCI, Charlson Comorbidity Index; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; CHF, congestive heart failure; ESRD, end-stage renal disease; IBD, inflammatory bowel disease; OR, odds ratio; CI, confidence interval.

A multivariate logistic regression analysis was performed to identify the risk factors for an individual testing positive for SARS-CoV-2 (*Table 3*). A higher number of women tested positive for SARS-CoV-2 compared to men (OR =1.30, 95% CI: 1.24–1.37, P<0.0001). Residence in an area that experienced a large outbreak (Daegu and Gyeongsangbuk-do province) was associated with higher ORs for positive results for SARS-CoV-2 testing (OR =6.87, 95% CI: 6.55–7.21, P<0.0001). Compared with National Health Insurance beneficiaries, Medical Aid beneficiaries remained at an increased risk of testing positive for SARS-CoV-2 (OR =1.99, 95% CI: 1.82–2.18, P<0.0001). Furthermore, the presence of DM increased the risk of testing positive for SARS-CoV-2 (OR =1.15, 95% CI: 1.01–1.24, P=0.0002).

An increase in the CCI scores was associated with a sequential decrease in the odds of a positive SARS-CoV-2 test (CCI =1: OR =0.79, 95% CI: 0.74–0.84, P<0.0001; CCI =2: OR =0.70, 95% CI: 0.65–0.76, P<0.001; CCI ≥3: OR =0.61, 95% CI: 0.56–0.67, P<0.0001). Moreover, underlying diseases such as asthma, COPD, IHD, CHF, cancer, liver cirrhosis, ESRD with dialysis, and IBD were also significantly associated with a decreased odds of a positive SARS-CoV-2 test (asthma: OR =0.86, 95% CI: 0.81–0.92, P<0.0001; COPD: OR =0.56, 95% CI: 0.49–0.65, P<0.0001; IHD: OR =0.77, 95% CI: 0.70–0.85, P<0.0001; CHF: OR =0.72, 95% CI: 0.63–0.81, P<0.0001; cancer: OR =0.60, 95% CI: 0.53–0.67, P<0.0001; liver cirrhosis: OR =0.53, 95% CI: 0.43–0.65, P<0.0001; ESRD with dialysis: OR =0.18, 95% CI: 0.11–0.29, P<0.0001; IBD: OR =0.51, 95% CI: 0.33–0.80, P=0.0028).

## Discussion

 

This was a large cross-sectional analysis of a nationwide study using the Korean HIRA database to assess the risk factors for SARS-CoV-2 infections despite following the recommendations for social distancing and the use of face masks. This study showed that underlying diseases such as asthma, COPD, IHD, CHF, cancer, liver cirrhosis, ESRD on dialysis, and IBD were associated with a reduced risk for SARS-CoV-2 infection. It also confirmed that, compared to the normal healthy population, the risk of SARS-CoV-2 infections decreased as the CCI increased in patients with comorbidities. Some of the underlying diseases mentioned above are known potential risk factors for severe illness and death from COVID-19 (3-5). Conversely, in our study, these factors were not observed to be risk factors for SARS-CoV-2 infection; rather a decreased risk for SARS-CoV-2 infections was observed in their presence. There could be several reasons for this result. For instance, active diagnostic tests, contact tracing, and quarantine were implemented in Korea since the initial outbreak of COVID-19 based on the previous experience of the Middle East Respiratory Syndrome outbreak. The Korean Centers for Disease Control and Prevention recommended social distancing practices and the use of masks to prevent transmission, and the majority of the population voluntarily followed these recommendations. Additionally, the healthy population was advised to avoid crowded social gatherings when there was a short supply of masks. Moreover, individuals with underlying diseases and immunocompromised individuals were strongly recommended to avoid social gatherings and to wear masks in situations where social gatherings are inevitable, such as during visits to the hospital. In a recent meta-analysis, it was reported that social distancing and face mask usage prevented SARS-CoV-2 transmission in the population (7). Another study emphasized that wearing masks in public is the most effective way to prevent person-to-person transmission, in conjunction with social distancing, contact tracing, and quarantine (12). Thus, people with underlying diseases might not necessarily be less susceptible to the SARS-CoV-2 infection, but social distancing practices and the use of masks may reduce their risks of infection.

Individuals of the female sex, those residing in areas with large COVID-19 outbreaks (Daegu and Gyeongsangbuk-do province), Medical Aid beneficiaries, and those having comorbidity with DM had increased ORs for a positive SARS-CoV-2 result in this study. Sex-based difference was noted in SARS-CoV-2 infection and mortality from COVID-19 (13,14). Females express robust innate and adaptive immune response to viral infections (15). Elevated transcriptional activation of immune response genes on the X-chromosome and sex-specific hormones help to promote clearance of viral load (16). So, many studies suggest that men appear at higher risk of mortality from COVID-19 with SARS-CoV-2 than women (4,5,17). However, few studies have evaluated the risk factors for SARS-CoV-2 infection. Our study shows an increased risk of SARS-CoV-2 infection in women. Women might be at a higher risk because they have traditionally played roles of caregivers (13). The closure of schools to control COVID-19 transmission in Korea might have had a negative effect on females because they tend to provide most of the care within their families. Moreover, due to their predominant roles in the family as well as in the healthcare workplace, women were more susceptible to the viral infection. This observation was also noted during the Ebola outbreak in West Africa (18). Daegu and Gyeongsangbuk-do province had the first large outbreak of COVID-19 in Korea (19). During this time, shortages of personal protective equipment, inpatient beds, and healthcare workers caused higher infection rates in these areas than in other parts of Korea. Furthermore, Medical Aid beneficiaries are socially and economically vulnerable; therefore, they are likely to be in a more serious affected than National Health Insurance beneficiaries (20). A previous study underlined that poor health possibly resulted in household poverty among Medical Aid beneficiaries in Korea (21). Such deprivation might be associated with an increased risk of SARS-CoV-2 infections. While the risk factors investigated in the study expose individuals to frequently come in close contact with infected populations, among the underlying diseases, DM was found to be the only risk factor for SARS-CoV-2 infections. On March 28, 2020, preliminary data from the United States Centers for Disease Control and Prevention showed that DM was the most prevalent underlying disease in populations infected with SARS-CoV-2 (22). The underlying potential mechanism for the increased risk of SARS-CoV-2 infections in people with DM is not completely understood; however, some hypotheses have been suggested. For instance, patients with DM are more susceptible to a wide range of infections (23). Such immune vulnerability is influenced by multiple factors including hyperglycemia, altered cytokine production, impaired phagocytosis and chemotaxis, non-effective microbial clearance, and the expression of angiotensin-converting enzyme 2 receptor (24-27). Further studies about the relationship between these immune responses in DM and SARS-CoV-2 infection should be conducted to better understand the current phenomenon.

This study had several limitations. First, our study had a risk of selection bias because certain groups in Korea might have undergone testing for SARS-CoV-2 based on the guidelines, regardless of symptoms. If the threshold of a certain group of individuals with underlying diseases is low and the group shows mild symptoms or is asymptomatic, the test result is more likely to be a negative result. Second, due to the retrospective nature of study design that used the Korean HIRA database, all clinical data (laboratory test, height, weight, smoking status, etc.) were not available. In addition, the severity of comorbidities at the time of SARS-CoV-2 testing could not be evaluated. Third, our study is the geographical features of the infection, so the generalization of the results or external validity is undermined.

In conclusion, this study provided important insights that females, Medical Aid beneficiaries, individuals residing in areas with large outbreaks of COVID-19, and individuals with DM as the underlying disease might be at greater risk of contracting SARS-CoV-2 infections. Since there is no definite treatment or vaccine available for COVID-19, careful attention to those groups that are the most vulnerable to SARS-CoV-2 infections could be helpful in preparing for the global health crisis and in employing prevention practices in the time of COVID-19.

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## Footnote

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-5958). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the National Health Insurance Service of Ilsan Hospital (NHIMC 2020-05-002). The need for written informed consent was waived as patient identification data were removed from the database used.



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