Effect of Underlying Comorbidities on the Infection and Severity of COVID-19 in Korea: a Nationwide Case-Control Study

Wonjun Ji, Kyungmin Huh, Minsun Kang, Jinwook Hong, Gi Hwan Bae, Rugyeom Lee, Yewon Na, Hyoseon Choi, Seon Yeong Gong, Yoon-Hyeong Choi, Kwang-Pil Ko, Jeong-Soo Im, and Jaehun Jung

1Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
2Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
3Artificial Intelligence and Big-Data Convergence Center, Gil Medical Center, Gachon University College of Medicine, Incheon, Korea
4Department of Preventive Medicine, Gachon University College of Medicine, Incheon, Korea

ABSTRACT

Background: The coronavirus disease 2019 (COVID-19) pandemic is an emerging threat worldwide. It remains unclear how comorbidities affect the risk of infection and severity of COVID-19.

Methods: This is a nationwide retrospective case-control study of 219,961 individuals, aged 18 years or older, whose medical costs for COVID-19 testing were claimed until May 15, 2020. COVID-19 diagnosis and infection severity were identified from reimbursement data using diagnosis codes and on the basis of respiratory support use, respectively. Odds ratios (ORs) were estimated using multiple logistic regression, after adjusting for age, sex, region, healthcare utilization, and insurance status.

Results: The COVID-19 group (7,341 of 219,961) was young and had a high proportion of female. Overall, 13.0% (954 of 7,341) of the cases were severe. The severe COVID-19 group had older patients and a proportion of male ratio than did the non-severe group. Diabetes (odds ratio range [ORR], 1.206–1.254), osteoporosis (ORR, 1.128–1.157), rheumatoid arthritis (ORR, 1.207–1.244), substance use (ORR, 1.321–1.381), and schizophrenia (ORR, 1.614–1.721) showed significant association with COVID-19. In terms of severity, diabetes (OR, 1.247; 95% confidential interval, 1.009–1.543), hypertension (OR, 1.245–1.317), chronic lower respiratory disease (ORR, 1.216–1.233), chronic renal failure, and end-stage renal disease (ORR, 2.052–2.178) were associated with severe COVID-19.

Conclusion: We identified several comorbidities associated with COVID-19. Health care workers should be more careful while diagnosing and treating COVID-19 when patients have the abovementioned comorbidities.

Keywords: COVID-19; SARS-CoV-2; Comorbidity; Risk Factor; Severity
INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has rapidly emerged since December 2019. As of May 24, 2020, a total of 5,204,508 confirmed cases, including 337,687 deaths, have been reported worldwide. Despite the introduction of social distancing to slow the spread in many countries, the outbreak of COVID-19 has overwhelmed healthcare systems in several countries. Inadequate medical resources have warranted the identification of risk factors for the diagnosis and severity of COVID-19. Although early epidemiological studies from China reported the prevalence of comorbidities, and its association with disease severity, the host factors that increase the risk of COVID-19 infection or its severity still need to be identified.

The national health insurance service of Korea registered approximately all COVID-19 patients and test negative controls within the national insurance system. Recently, the Health Insurance Review & Assessment Service (HIRA) of Korea agreed to the share invaluable national health insurance claims data related to COVID-19 for public health purposes. This data is useful for the identification of underlying comorbidities which are associated with the diagnosis and severity of COVID-19.

We conducted a retrospective case-control study, examining the effect of various underlying comorbidities on the risk of infection and severity of COVID-19 using data from the nationwide medical insurance claim database in Korea.

METHODS

Data source

We extracted data from the insurance claims database of the HIRA of Korea. The claims (Fig. 1) are made with a special “public crisis” code (MT043) under the national insurance coverage for every suspected case. The reimbursement for confirmed cases is claimed with the Korean Standard Classification of Diseases and Causes of Death, 7th edition (KCD-7) codes, which is a modified version of the International Classification of Diseases and Related Health Problems, 10th edition (ICD-10), designated for COVID-19. Thus, we identified all tested individuals within the national health insurance coverage using the code MT043. All subjects with KCD-7 codes for COVID-19 were categorized as reverse transcription polymerase...
chain reaction (RT-PCR) test-positive cases when the diagnosis was confirmed using RT-PCR with respiratory tract specimens, all RT-PCR positive subjects were identified as a confirmed cases using the database of Korean Center for Disease Control (KCDC); the remaining subjects were categorized as controls (“RT-PCR test-negative” controls). Moreover, severe cases were defined as patients with a diagnosis confirmed by an RT-PCR test, who had claim data for oxygen therapy, mechanical ventilator, extracorporeal membrane oxygenation, and cardiopulmonary resuscitation. The remaining laboratory confirmed subjects were categorized as non-severe cases (Fig. 2).

**Study design and definitions**
This was a two-staged retrospective case-control study that evaluated the underlying comorbidities associated with the diagnosis and severity of COVID-19. First, we examined the underlying comorbidities associated with the diagnosis of COVID-19 between laboratory confirmed cases and test-negative controls. In addition, the underlying comorbidities associated with the severity of COVID-19 were evaluated and compared between the severe and non-severe confirmed cases. Underlying comorbidities were defined as the reimbursement for ≥ 2 times of KCD-7 code of study diseases, within 3 years prior to the test for COVID-19. The disease of interest was selected from the list of ICD-10 mapping tree, with reports of possible association with SARS-CoV-2 in previous epidemiologic studies, and those with theoretical concerns for increased risk (Supplementary Table 1). Two authors reviewed the literature and selected the diseases of interest, and disagreement was arbitrated by the third author. There were 56 categories in the disease group (Supplementary Table 2). The location of the medical institution where the patients were treated was identified to control a
substantially higher risk of community acquired infection. Daegu city and Gyeongsangbuk-
do province (DG) had large regional outbreaks, and many cases did not have any identifiable contact trace.\textsuperscript{7} A subgroup analysis was conducted for DG area and outside of DG area to identify the risk factors related to community outbreaks. Also, Charlson comorbidity index (CCI) was calculated as previously described (Supplementary Table 3).\textsuperscript{8} Healthcare utilization was evaluated by the number of hospitalizations, number of outpatient visits, and number of emergency room visits within one year prior to tests for COVID-19. The analysis codes for this study was presented in Supplementary Data 1.

**Statistical analysis**

The baseline characteristics of cases and controls were compared using the $\chi^2$ test and Student’s \textit{t}-test, as appropriate. The prevalence of comorbidities was compared using logistic regression models adjusted for sex, age, residence, CCI, and healthcare utilization as covariates. To mitigate the risk of quasi-separation and overfitting, we performed two different types of multivariate analysis. The multivariate model 1 included one comorbidity at a time with all other covariates, constructing individual models for each comorbidity; the multivariate model 2, included all comorbidities and other covariates in a single model. We used the significance threshold of $P < 0.05$, and all tests were two-tailed. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the analyses.

**Ethics statement**

This study was approved by the Institutional Review Board (IRB) of the Gil Medical Center, Gachon University College of Medicine which provided a waiver of consent (GFIRB2020-134). The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

**RESULTS**

**Baseline demographics between case- and test-negative controls**

At the data cutoff time on May 15, 2020, a total of 219,961 individuals aged $\geq$ 18 years, who underwent laboratory tests for COVID-19 in Korea were identified and analyzed. The proportion of female was slightly higher (4,371 of 7,341; 59.5%) than that of male in the case group. More than half of COVID-19 patients (4,027 of 7,341; 54.9%) were treated in medical facilities in the DG area, while 45.1% of confirmed cases, treated outside of the DG area. The control group showed higher healthcare utilization within 1 year before undergoing laboratory tests for COVID-19. Overall, the case group showed a lower prevalence than that of the control group, except for schizophrenia, mental retardation, and developmental disorders (Table 1).

**Comorbidities associated with diagnosis of COVID-19**

**Result of overall analysis**

Fig. 3 and Supplementary Table 4 represent the odds ratios (ORs) for the diagnosis of COVID-19 according to the 56 categories of comorbidities. Schizophrenia, mental retardation, and developmental disorders were associated with an increased risk of COVID-19 in univariate analysis. In terms of multivariate analysis, diabetes (odds ratio range [ORR], 1.206–1.254), osteoporosis (ORR, 1.128–1.157), rheumatoid arthritis (ORR, 1.207–1.244), substance use (ORR, 1.321–1.381), and schizophrenia (ORR, 1.614–1.721) showed an increased risk in the whole study population (Supplementary Table 4). Non-insulin dependent
diabetes mellitus (NIDDM) (ORR, 1.182–1.278), mental retardation and developmental disorder (OR, 1.511; 95% confidential interval [CI], 1.051–2.173) showed an increased risk only in multivariate analysis with single disease category. Ischemic heart disease (ORR, 0.789–0.803), chronic lower respiratory disease (ORR, 0.772–0.778), interstitial lung disease

Table 1. Baseline demographics and prevalence of comorbidities between case and test negative controls

| Variables                                      | Cases (n = 7,341) | Controls (n = 212,620) | P value |
|------------------------------------------------|-------------------|------------------------|---------|
| Demographic characteristics                    |                   |                        |         |
| Sex, male                                      | 2,970 (40.5)      | 101,361 (47.7)         | < 0.001 |
| Age, yr                                        | 47.05 ± 19.0      | 49.48 ± 19.9           | < 0.001 |
| 18–49                                          | 3,819 (52.0)      | 113,734 (53.5)         |         |
| 50–64                                          | 2,159 (29.4)      | 44,652 (21.0)          |         |
| 65–79                                          | 992 (13.5)        | 34,080 (16.0)          |         |
| ≥ 80                                           | 373 (5.1)         | 20,154 (9.5)           |         |
| Residence                                      |                   |                        |         |
| DG area                                        | 4,027 (54.9)      | 31,259 (14.7)          | < 0.001 |
| Except DG                                      | 3,314 (45.1)      | 181,361 (85.3)         |         |
| Charlson comorbidity index                     | 1.23 ± 1.6        | 1.94 ± 2.4             | < 0.001 |
| Healthcare utilization within 1 years before diagnosis of COVID-19 |                   |                        |         |
| No. of hospitalization                         | 0.25 ± 0.9        | 0.83 ± 2.1             | < 0.001 |
| No. of outpatient visit                        | 17.19 ± 21.4      | 25.46 ± 31.9           | < 0.001 |
| No. of ED visit                                | 0.12 ± 0.5        | 0.44 ± 1.6             | < 0.001 |
| Medical aids                                   | 619 (8.4)         | 12,031 (5.7)           | < 0.001 |
| Underlying diseases                            |                   |                        |         |
| Endocrinopathy                                 |                   |                        |         |
| Diabetes                                       | 1,043 (14.2)      | 39,037 (18.4)          | < 0.001 |
| Thyroid disease                                | 434 (5.9)         | 13,491 (6.4)           | 0.134   |
| Cushing syndrome                               | 2 (0.03)          | 215 (0.1)              | 0.047   |
| Osteoporosis                                   | 633 (8.6)         | 20,467 (9.6)           | 0.004   |
| Cardiac disease                                |                   |                        |         |
| Isolated hypertension                         | 1,628 (22.2)      | 64,412 (30.3)          | < 0.001 |
| Ischemic heart disease                         | 306 (4.2)         | 18,971 (8.9)           |         |
| Heart failure and cardiomyopathy              | 266 (3.62)        | 13,881 (6.5)           | < 0.001 |
| Valvular heart disease                         | 28 (0.4)          | 1,960 (0.9)            | < 0.001 |
| Cardiac arrhythmia                             | 201 (2.7)         | 11,517 (5.4)           | < 0.001 |
| Chronic respiratory disease                    |                   |                        |         |
| Chronic upper respiratory disease              | 4,430 (60.4)      | 140,924 (66.3)         | < 0.001 |
| Chronic lower respiratory disease              | 1,639 (22.3)      | 72,058 (33.9)          | < 0.001 |
| Environmental lung disease                     | 11 (0.2)          | 1,267 (0.6)            | < 0.001 |
| Interstitial lung disease                      | 12 (0.2)          | 1,580 (0.7)            | < 0.001 |
| Chronic respiratory failure and diaphragm palsy| 1 (0.01)          | 261 (0.1)              | 0.008   |
| Pulmonary vascular disease                     | 11 (0.2)          | 1,279 (0.6)            | < 0.001 |
| Renal disease and ESRD                         |                   |                        |         |
| Hypertensive renal disease                     | 19 (0.3)          | 1,611 (0.8)            | < 0.001 |
| Glomerular disease                             | 76 (1.0)          | 3,690 (1.7)            | < 0.001 |
| Renal tubule-interstitial disease              | 37 (0.5)          | 1,811 (0.9)            | 0.001   |
| History of acute renal failure                 | 6 (0.1)           | 2,282 (1.1)            | < 0.001 |
| Chronic renal failure and ESRD                 | 72 (1.0)          | 9,149 (4.3)            | < 0.001 |
| Urolithiasis                                   | 85 (1.2)          | 3,814 (1.8)            | < 0.001 |
| Viral hepatitis and chronic liver disease       |                   |                        |         |
| HBV, acute and chronic                         | 115 (1.6)         | 4,387 (2.1)            | 0.003   |
| HCV, acute and chronic                         | 17 (0.2)          | 954 (0.5)              | 0.006   |
| Non-B, non-C hepatitis                         | 612 (8.3)         | 22,196 (10.4)          | < 0.001 |
| Liver cirrhosis                                | 44 (0.6)          | 3,833 (1.8)            | < 0.001 |
| Hepatic failure                                | 6 (0.1)           | 751 (0.4)              | < 0.001 |
| Disease of digestive system                    |                   |                        |         |
| Non-infectious disease of upper digestive system| 6,388 (87.0)      | 196,527 (92.4)         | < 0.001 |
| Non-infectious disease of lower digestive system| 2,013 (27.4)      | 80,096 (37.7)          | < 0.001 |
| Pancreatic disease                             | 40 (0.5)          | 4,933 (2.3)            | < 0.001 |
| Biliary disease                                | 129 (1.8)         | 9,813 (4.6)            | < 0.001 |

(continued to the next page)
Underlying Comorbidities and COVID-19

### Table 1. (Continued) Baseline demographics and prevalence of comorbidities between case and test negative controls

| Variables                                      | Cases (n = 7,341) | Controls (n = 212,620) | P value |
|------------------------------------------------|-------------------|------------------------|---------|
| Chronic neurologic disease                     |                   |                        |         |
| Systemic atrophy                               | 3 (0.04)          | 320 (0.2)              | 0.016   |
| Parkinsonism and movement disorder             | 265 (3.6)         | 8,890 (4.2)            | 0.016   |
| Alzheimer and degenerative disease             | 207 (2.8)         | 9,266 (4.4)            | < 0.001 |
| Multiple sclerosis                             | 6 (0.08)          | 190 (0.09)             | 0.830   |
| Epilepsy                                       | 131 (1.8)         | 6,776 (3.2)            | < 0.001 |
| Transient cerebral ischemia, stroke, cerebral hemorrhage | 487 (6.6)       | 22,223 (10.5)          | < 0.001 |
| Dementia                                       | 368 (5.0)         | 13,809 (6.5)           | < 0.001 |
| Malignancy                                     |                   |                        |         |
| Solid organ, except respiratory, thyroid       | 223 (3.0)         | 18,556 (8.7)           | < 0.001 |
| Respiratory tract                              | 28 (0.4)          | 3,822 (1.8)            | < 0.001 |
| Thyroid cancer                                 | 80 (1.1)          | 2,473 (1.2)            | 0.564   |
| Hematologic                                    | 8 (0.1)           | 1,731 (0.8)            | < 0.001 |
| Rheumatologic disease                          |                   |                        |         |
| Rheumatoid arthritis                           | 186 (2.5)         | 5,853 (2.8)            | 0.259   |
| SLE                                            | 0 (0.0)           | 0 (0.0)                |         |
| Systemic connective tissue disease             | 39 (0.5)          | 2,410 (1.1)            | < 0.001 |
| Hematologic disease                            |                   |                        |         |
| Anemia                                         | 505 (6.9)         | 26,462 (12.5)          | < 0.001 |
| Coagulopathy                                   | 35 (0.5)          | 2,839 (1.3)            | < 0.001 |
| Bone marrow dysfunction                        | 24 (0.3)          | 2,298 (1.1)            | < 0.001 |
| Obesity                                        | 3 (0.04)          | 339 (0.2)              | 0.011   |
| Nutritional deficiency                         | 287 (3.9)         | 15,128 (7.1)           | < 0.001 |
| Mental and Behavioral disorders                |                   |                        |         |
| Substance use                                  | 86 (1.2)          | 2,504 (1.2)            | 0.962   |
| Schizophrenia                                  | 263 (3.6)         | 4,777 (2.2)            | < 0.001 |
| Mood disorder                                  | 769 (10.8)        | 31,575 (14.9)          | < 0.001 |
| Neurosis                                       | 931 (12.7)        | 36,488 (17.2)          | < 0.001 |
| Personality disorder                           | 13 (0.2)          | 415 (0.2)              | 0.729   |
| Mental retardation, development disorder       | 37 (0.5)          | 542 (0.3)              | < 0.001 |
| Immune deficiency, HIV infection               | 4 (0.1)           | 320 (0.2)              | 0.035   |

Data are presented as mean ± standard deviation or number (%).
DG = Daegu city and Gyeongsangbuk-do province area, COVID-19 = coronavirus disease 2019, ED = emergency department, ESRD = end-stage renal disease, HBV = hepatitis B virus, HCV = hepatitis C virus, SLE = systemic lupus erythematosus, HIV = human immunodeficiency virus.

(O RR, 0.494–0.547), history of acute renal failure (ARF) (ORR, 0.222–0.284), chronic renal failure (CRF) and end-stage renal disease (ESRD) (ORR, 0.503–0.505), liver cirrhosis (ORR, 0.633–0.656), non-infectious upper digestive system disease (ORR, 0.683–0.720), non-infectious lower digestive system diseases (ORR, 0.841–0.884), pancreatic disease (ORR, 0.473–0.531), biliary disease (ORR, 0.611–0.669), epilepsy (ORR, 0.738–0.786), transient cerebral ischemia, stroke, hemorrhage (ORR, 0.821–0.853), solid organ malignancy (ORR, 0.682–0.748), hematologic malignancy (ORR, 0.353–0.393), systemic connective tissue disease (ORR, 0.647–0.679), anemia (ORR, 0.789–0.854), and neurosis (ORR, 0.894–0.919) showed a decreased risk of COVID-19 in whole multivariate analysis.

Analysis of subgroup which excluded high regional outbreak area (DG area)

The case group showed a lower prevalence than that of the control group in most disease categories (Supplementary Table 5). NIDDM without complication (OR, 1.170; 95% CI, 1.005–1.362) showed an increased risk only in multivariate analysis with single disease category, while rheumatoid arthritis (ORR, 1.335–1.400) showed an increased risk in whole multivariate analysis (Fig. 3). Cardiac arrhythmia (ORR, 0.536–0.590), chronic upper respiratory diseases (ORR, 0.793–0.903), dementia (ORR, 0.621–0.734), and mood disorder (ORR, 0.760–0.824) additionally showed a decreased risk of COVID-19 in multivariate analysis of this subgroup. The other overall pattern of association was consistent with the
### Underlying Comorbidities and COVID-19

#### Other region
- **Daegu and Gyeongsangbuk-do (high regional outbreak)**
  - Diabetes: 0.737, 0.426, 1.254, 1.314, 1.206, 1.255, 1.216, 1.308
  - IDDM: 0.491, 0.168, 1.175
  - NIDDM with complication: 0.650, 0.334, 1.182, 1.258
  - Osteoporosis: 0.886, 0.505, 1.128, 1.157, 1.145
  - Isolated hypertension: 0.656, 0.400, 0.915, 0.855
  - Uremic heart disease: 0.444, 0.275, 0.684, 0.789, 0.750, 0.806, 0.800, 0.842, 0.789, 0.829
  - Heart failure and cardiomyopathy: 0.538, 0.287, 0.822
  - Cardiac arrhythmia: 0.492, 0.230, 0.820, 0.815, 0.536, 0.590
  - Chronic upper respiratory disease: 0.774, 0.689, 0.935, 0.703, 0.903, 1.166, 0.903, 1.162
  - Chronic lower respiratory disease: 0.561, 0.450, 0.734, 0.762, 0.717, 0.782, 0.772, 0.747, 0.750, 0.806, 0.728, 0.747, 0.672, 0.656, 0.750, 0.728, 0.728, 0.728
  - Environmental lung disease: 0.250, 0.099, 0.407, 0.822
  - Interstitial lung disease: 0.219, 0.076, 0.400, 0.490, 0.223, 0.547, 0.547, 0.221
  - Glomerular disease: 0.886, 0.505, 1.128, 1.157, 1.145
  - History of acute renal failure: 0.675, 0.053, 0.144, 0.222, 0.220, 0.243, 0.284, 0.390, 0.271, 0.299
  - Chronic renal failure and ESRD: 0.550, 0.450, 0.734, 0.762, 0.717, 0.782, 0.772, 0.747, 0.750, 0.806, 0.728, 0.747, 0.672, 0.656, 0.750, 0.728, 0.728, 0.728
  - Pancreatic disease: 0.231, 0.196, 0.335, 0.473, 0.515, 0.477, 0.547, 0.547, 0.221
  - Biliary disease: 0.370, 0.248, 0.521, 0.611, 0.557, 0.645, 0.666, 0.600, 0.705, 0.669, 0.586, 0.708
  - Alzheimer and degenerative disease: 0.592, 0.371, 0.914, 0.708
  - Epilepsy: 0.552, 0.342, 0.786, 0.701, 0.742, 0.750, 0.738, 0.758, 0.758
  - Transient cerebral ischemia, Stroke, Hemorrhage: 0.609, 0.269, 0.813, 0.853, 0.667, 0.857, 0.847, 0.715, 0.843, 0.882, 0.843, 0.908, 0.884, 0.842, 0.894, 0.816, 0.842, 0.816
  - Dementia: 0.760, 0.285, 0.621, 0.701, 0.742, 0.750, 0.738, 0.758, 0.758
  - Solid organ malignancy (except respiratory and thyroid): 0.328, 0.232, 0.532, 0.734, 0.754, 0.682, 0.675, 0.742, 0.699, 0.644, 0.742
  - Respiratory tract malignancy: 0.209, 0.172, 0.345, 0.651, 0.624, 0.645, 0.634
  - Hematologic malignancy: 0.123, 0.069, 0.318, 0.392, 0.359, 0.226, 0.375, 0.224
  - Rheumatoid arthritis: 0.687, 1.207, 1.361, 1.238, 1.400, 1.244, 1.335
  - Systemic connective tissue diseases: 0.466, 0.413, 0.587, 0.679, 0.647, 0.648
  - Anemia: 0.520, 0.324, 0.643, 0.789, 0.774, 0.774, 0.85, 0.798, 0.854, 0.835, 0.801
  - Mental disorder of substance use: 0.358, 0.149, 1.321, 1.756, 1.381, 1.698, 1.346, 1.688
  - Schizophrenia: 1.638, 0.725, 2.458, 4.164, 2.178, 1.721, 2.285, 1.692, 2.205
  - Mood disorder: 0.697, 0.420, 0.760, 0.824, 0.824
  - Neurosis: 0.701, 0.484, 0.814, 0.894, 0.872, 0.882, 0.919, 0.852, 0.895, 0.855
  - Mental retardation and development disorder: 3.983, 2.372, 1.511, 1.843, 1.772, 1.662

Fig. 3. Analysis of relationship between comorbidities and infection of COVID-19.

COVID-19 = coronavirus disease 2019, N/A = not applicable, IDDN = insulin-dependent diabetes mellitus, NIDDM = non-insulin dependent diabetes mellitus, ESRD = end-stage renal disease, OR = odds ratio.

whole group analysis except ischemic heart disease, history of ARF, liver cirrhosis, epilepsy, systemic connective tissue diseases, and neurosis.
Analysis of subpopulation in high regional outbreak area (DG area)
This subpopulation analysis was conducted to identify the risk factors for high regional outbreak areas. Substance use, schizophrenia, mental retardation, and developmental disorder were associated with an increased risk of COVID-19 in univariate analysis. Diabetes (ORR, 1.255–1.750), substance use (ORR, 1.680–1.750), schizophrenia (ORR, 2.178–2.245), mental retardation and developmental disorder (ORR, 1.668–1.943) were associated with an increased risk of COVID-19 outbreak in whole multivariate analysis, while chronic upper respiratory diseases (ORR, 1.160–1.162), glomerular diseases (ORR, 1.372–1.381) was associated with an increased risk of COVID-19 only in multivariate analysis with all comorbidities (Fig. 3 and Supplementary Table 6). The disease categories which showed a decreased risk of COVID-19 were consistent with whole group analysis except interstitial lung diseases, respiratory malignancy, hematologic malignancy, and systemic connective tissue diseases.

Baseline demographics between severe and non-severe confirmed COVID-19
Severe cases accounted for 13.0% (954 of 7,341) of the laboratory confirmed cases. The mean age was 67.01 (standard deviation, 15.1), and 48.0% (458 of 954) of the patients in the severe group were male. The severe group had relatively older patients, The proportion of Daegu/Gyeongbuk area (DG area, 74.4%, 710 of 954), median CCI, the number of healthcare utilization, and the prevalence of comorbidities were higher in the severe group than in the non-severe group (Table 2).

Table 2. Baseline demographics and prevalence of comorbidities between severe and non-severe laboratory confirmed COVID-19

| Variables                        | Severe (n = 954) | Non-severe (n = 6,387) | P value |
|----------------------------------|------------------|------------------------|---------|
| **Demographic characteristics**  |                  |                        |         |
| Sex, male                        | 458 (48.1)       | 2,512 (39.3)           | < 0.001 |
| Age, yr                          | 67.01 ± 15.1     | 44.07 ± 17.7           | < 0.001 |
| 18–49                            | 99 (10.4)        | 3,730 (58.2)           |         |
| 50–64                            | 295 (30.9)       | 1,862 (29.2)           |         |
| 65–79                            | 350 (36.7)       | 642 (10.3)             |         |
| ≥ 80                             | 210 (22.0)       | 163 (2.6)              |         |
| Residence                        |                  |                        |         |
| DG area                          | 710 (74.4)       | 3,317 (51.9)           | < 0.001 |
| Except DG                        | 244 (25.6)       | 3,070 (48.1)           |         |
| Charlson comorbidity index       | 2.68 ± 2.2       | 1.01 ± 1.4             | < 0.001 |
| **Healthcare utilization within 1 years before diagnosis of COVID-19** |                  |                        |         |
| No. of hospitalization           | 0.67 ± 1.5       | 0.19 ± 0.8             | < 0.001 |
| No. of outpatient visit          | 29.44 ± 35.3     | 15.36 ± 17.7           | < 0.001 |
| No. of ED visit                  | 0.25 ± 0.7       | 0.10 ± 0.4             | < 0.001 |
| Medical aids                     | 120 (12.6)       | 499 (7.8)              | < 0.001 |
| **Underlying diseases**          |                  |                        |         |
| Endocrinopathy                   |                  |                        |         |
| Diabetes                         | 346 (36.3)       | 697 (10.9)             | < 0.001 |
| Thyroid disease                  | 89 (9.3)         | 345 (5.4)              | < 0.001 |
| Cushing syndrome                 | 1 (0.1)          | 1 (0.02)               | 0.120   |
| Osteoporosis                     | 184 (19.3)       | 449 (7.0)              | < 0.001 |
| Cardiac disease                  |                  |                        |         |
| Isolated hypertension            | 531 (55.7)       | 1,097 (17.2)           | < 0.001 |
| Ischemic heart disease           | 115 (12.1)       | 191 (3.0)              | < 0.001 |
| Heart failure and cardiomyopathy | 131 (13.7)       | 135 (2.1)              | < 0.001 |
| Valvular heart disease           | 9 (0.9)          | 19 (0.3)               | 0.007   |
| Cardiac arrhythmia               | 84 (8.8)         | 117 (1.8)              | < 0.001 |

(continued to the next page)
Table 2. (Continued) Baseline demographics and prevalence of comorbidities between severe and non-severe laboratory confirmed COVID-19

| Variables | Severe (n = 954) | Non-severe (n = 6,387) | P value |
|-----------|-----------------|------------------------|---------|
| Chronic respiratory disease | | | |
| Chronic upper respiratory disease | 589 (61.7) | 3,841 (60.1) | 0.345 |
| Chronic lower respiratory disease | 364 (38.2) | 1,275 (20.0) | < 0.001 |
| Environmental lung disease | 7 (0.7) | 4 (0.1) | < 0.001 |
| Interstitial lung disease | 10 (1.1) | 2 (0.3) | < 0.001 |
| Chronic respiratory failure and diaphragm palsy | 0 (0.0) | 1 (0.02) | 1.000 |
| Pulmonary vascular disease | 4 (0.4) | 7 (0.1) | 0.044 |
| Renal disease and ESRD | | | |
| Hypertensive renal disease | 7 (0.7) | 12 (0.2) | 0.008 |
| Glomerular disease | 22 (2.3) | 54 (0.9) | < 0.001 |
| Renal tubule-interstitial disease | 12 (1.3) | 25 (0.4) | 0.002 |
| History of acute renal failure | 0 (0.0) | 6 (0.1) | 1.000 |
| Chronic renal failure and ESRD | 39 (4.1) | 33 (0.5) | < 0.001 |
| Urolithiasis | 19 (2.0) | 66 (1.0) | 0.010 |
| Viral hepatitis and chronic liver disease | | | |
| HBV, acute and chronic | 26 (2.7) | 89 (1.4) | 0.002 |
| HCV, acute and chronic | 4 (0.4) | 13 (0.2) | 0.264 |
| Non-B, non-C hepatitis | 129 (13.5) | 483 (7.6) | < 0.001 |
| Liver cirrhosis | 14 (1.5) | 30 (0.5) | < 0.001 |
| Hepatic failure | 2 (0.2) | 4 (0.1) | 0.778 |
| Disease of digestive system | | | |
| Non-infectious disease of upper digestive system | 879 (92.1) | 5,509 (86.3) | < 0.001 |
| Non-infectious disease of lower digestive system | 418 (43.8) | 1,595 (25.0) | < 0.001 |
| Pancreatic disease | 6 (0.6) | 34 (0.5) | 0.705 |
| Biliary disease | 42 (4.4) | 87 (1.4) | < 0.001 |
| Chronic neurologic disease | | | |
| Systemic atrophy | 0 (0.0) | 3 (0.1) | 1.000 |
| Parkinsonism and movement disorder | 72 (7.6) | 193 (3.0) | < 0.001 |
| Alzheimer and degenerative disease | 70 (7.3) | 137 (2.1) | < 0.001 |
| Multiple sclerosis | 2 (0.2) | 4 (0.1) | 0.778 |
| Epilepsy | 35 (3.7) | 96 (1.5) | < 0.001 |
| Transient cerebral ischemia, stroke, cerebral hemorrhage | 184 (19.3) | 303 (4.7) | < 0.001 |
| Dementia | 186 (19.5) | 182 (2.9) | < 0.001 |
| Malignancy | | | |
| Solid organ, except respiratory, thyroid | 70 (7.3) | 153 (2.4) | < 0.001 |
| Respiratory tract | 15 (1.6) | 13 (0.2) | < 0.001 |
| Thyroid cancer | 12 (1.3) | 68 (1.1) | 0.592 |
| Hematologic | 2 (0.2) | 6 (0.1) | 0.279 |
| Rheumatologic disease | | | |
| Rheumatoid arthritis | 33 (3.5) | 153 (2.4) | 0.051 |
| SLE | 0 (0.0) | 0 (0.0) | 0.000 |
| Systemic connective tissue disease | 7 (0.7) | 32 (0.5) | 0.356 |
| Hematologic disease | | | |
| Anemia | 140 (14.7) | 365 (5.7) | < 0.001 |
| Coagulopathy | 9 (0.9) | 26 (0.4) | 0.039 |
| Bone marrow dysfunction | 7 (0.7) | 17 (0.3) | 0.029 |
| Obesity | 0 (0.0) | 3 (0.1) | 1.000 |
| Nutritional deficiency | 69 (7.2) | 218 (3.4) | < 0.001 |
| Mental and behavioral disorders | | | |
| Substance use | 15 (1.6) | 71 (1.0) | 0.217 |
| Schizophrenia | 51 (5.4) | 212 (3.3) | 0.002 |
| Mood disorder | 203 (21.3) | 593 (9.3) | < 0.001 |
| Neurosis | 228 (23.8) | 703 (11.0) | < 0.001 |
| Personality disorder | 5 (0.5) | 8 (0.1) | 0.019 |
| Mental retardation, development disorder | 4 (0.4) | 33 (0.5) | 1.000 |
| Immune deficiency, HIV infection | 1 (0.1) | 3 (0.1) | 0.427 |

Data are presented as mean ± standard deviation or number (%).

DG = Daegu city and Gyeongsangbuk-do province area, COVID-19 = coronavirus disease 2019, ED = emergency department, ESRD = end-stage renal disease, HBV = hepatitis B virus, HCV = hepatitis C virus, SLE = systemic lupus erythematosus, HIV = human immunodeficiency virus.
Comorbidities associated with severity of COVID-19

Result of overall analysis

The ORs for the severity of COVID-19 according to the 56 categories of comorbidities are shown in Fig. 4 and Supplementary Table 7. Most disease categories except Cushing syndrome, chronic upper respiratory diseases, hepatitis C, hepatic failure, pancreatic diseases, multiple sclerosis, thyroid cancer, hematologic malignancy, rheumatoid arthritis, systemic connective tissue disease, substance use, mental retardation, and immune deficiency were associated with an increased risk of severe COVID-19 in univariate analysis. Isolated hypertension (ORR, 1.245–1.317), CRF and ESRD (ORR, 2.052–2.178) were significantly associated with an increased risk of severe COVID-19, while pancreatic diseases (ORR, 0.258–0.296), Alzheimer’s and degenerative diseases (ORR, 0.693–0.701) were associated with a decreased risk of severe COVID-19 in all multivariate analysis. NIDDM without complication (ORR, 1.353–1.371), heart failure, and cardiomyopathy (ORR, 1.464–1.465) and cardiac arrhythmia (ORR, 1.400–1.405) showed an increased risk of severe COVID-19 in multivariate analysis with single disease category, while diabetes (OR, 1.247; 95% CI, 1.009–1.543), chronic respiratory diseases (OR, 1.216–1.233) showed an increased risk of COVID-19 in multivariate analysis with all comorbidities.

Analysis of subpopulation which excluded high regional outbreak area (DG area)

In multivariate analysis, dementia (ORR, 2.440–3.471) was significantly associated with severe COVID-19 in all multivariate analysis, while diabetes (ORR, 1.522–1.620), bone marrow dysfunction (ORR, 6.748–9.259) showed an increased risk of severe disease only in multivariate analysis with all comorbidities (Supplementary Table 8).

Analysis of subpopulation in high regional outbreak area (DG area)

In multivariate analysis, the overall pattern of association was consistent with the whole group analysis except diabetes, heart failure and cardiomyopathy, and chronic lower respiratory disease (Supplementary Table 9).

| Model | Other diseases as covariables | Univariate | Multivariate |
|-------|-------------------------------|------------|--------------|
| Variable selection | N/A | All | No | Backward Selection | All | No | Backward Selection |
| Subpopulation | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| Other region | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No | Yes | No |
| Daegu and Gyeonsangbuk-do (high regional outbreak) | Diabetes | 4.646 | 4.433 | 3.838 | 1.247 | 1.420 | 1.522 |
| | IDDM | 4.803 | 4.453 | 3.244 |
| | NIDDM without complication | 4.077 | 4.224 | 3.599 |
| | NIDDM with complication | 5.625 | 6.681 | 4.466 | 1.571 | 1.333 | 1.353 |
| | Isolated hypertension | 6.054 | 5.665 | 5.344 | 1.513 | 1.298 | 1.312 | 1.298 | 1.245 | 1.317 | 1.272 |
| | Heart failure and cardiomyopathy | 7.372 | 8.872 | 5.888 | 1.405 | 1.600 | 1.600 | 1.600 | 1.516 | 1.378 |
| | Cardiac arrhythmia | 5.177 | 2.857 | 4.736 | 1.405 | 1.600 | 1.600 | 1.600 | 1.600 | 1.600 | 1.600 | 1.600 | 1.600 |
| | Chronic lower respiratory disease | 2.474 | 2.324 | 2.255 | 1.235 | 1.235 | 1.235 |
| | Chronic renal failure and ESRD | 3.064 | 12.939 | 5.871 | 1.373 | 1.373 | 1.373 | 1.373 | 1.373 | 1.373 | 1.373 |
| | Pancreatic disease | 3.403 | 6.168 | 2.539 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 |
| | Alzheimer and degenerative disease | 3.633 | 6.168 | 2.539 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 | 1.327 |
| | Dementia | 6.523 | 15.332 | 5.779 | 1.268 | 1.268 | 1.268 | 1.268 | 1.268 | 1.268 | 1.268 | 1.268 | 1.268 |
| | Bone marrow dysfunction | 2.707 | 2.631 | 2.513 | 1.255 | 1.255 | 1.255 | 1.255 | 1.255 | 1.255 | 1.255 | 1.255 | 1.255 | 1.255 |
| | Mental disorder of substance use | 0.523 |

Fig. 4. Analysis of relationship between comorbidities on severity of COVID-19.

COVID-19 = coronavirus disease 2019, N/A = not applicable, IDDM = insulin-dependent diabetes mellitus, NIDDM = non-insulin dependent diabetes mellitus, ESRD = end-stage renal disease, OR = odds ratio.
DISCUSSION

In this study, we identified the possible comorbidities that might be associated with the risk of COVID-19 infection and its severity. Diabetes, osteoporosis, rheumatoid arthritis, substance use, and schizophrenia showed significant associations with the diagnosis of COVID-19. The patterns of comorbidities associated with the occurrence of COVID-19 might be different between high and non-high regional outbreak areas. Diabetes, chronic upper respiratory diseases, glomerular disease, substance use, schizophrenia, mental retardation, and developmental disorders were associated with community outbreak (DG area), whereas rheumatoid arthritis was associated with containment area (e.g., institutional outbreak). Diabetes, isolated hypertension, chronic lower respiratory disease, CRF, and ESRD were associated with severe COVID-19. Moreover, diabetes was strongly associated with the diagnosis and severity of COVID-19.

When interpreting the results of this study, it is necessary to consider the demographic differences between the case and control groups. Most diseases, except schizophrenia, mental retardation, and developmental disorders, showed a higher prevalence in the control group than in the case group (Table 1). This suggested that more tests for COVID-19 were performed in people at a risk of febrile respiratory illness, regardless of the COVID-19 pandemic. Therefore, we presumed that the negative association in univariate analysis related to COVID-19 occurrence was based on biased baseline demographics and found that this selection bias was alleviated in the multivariate analysis (Fig. 3). Moreover, we compared the laboratory confirmed cases to the RT-PCR-negative control groups and conducted subgroup analysis according to high regional outbreak areas where this bias would have been less affected. As a result, the comorbidities that increased the risk of diagnosis of COVID-19 were more meaningful. Therefore, we found that diabetes, osteoporosis, and rheumatoid arthritis might be risk factors for the diagnosis of COVID-19.

In the case of psychological disorders including substance use, schizophrenia, mental retardation, and developmental disorders, consideration as risk factors for COVID-19 was unjustifiable because this might be correlated with the large clustered outbreak in hospitalized patients who were admitted in closed wards for psychological treatment. Even considering these epidemiological characteristics, some early case reports on the COVID-19 outbreak suggested that differences in socioeconomic levels may influence SARS-CoV-2 infection. It might be suggested that the accompanying low socioeconomic status might increase the risk of developing COVID-19 rather than schizophrenia or a psychological disorder itself. This study also found that rheumatoid was associated with the diagnosis of COVID-19. Although the impact of immunosuppression on the diagnosis of COVID-19 remains unclear, it is suggested that the long-term use of steroids or immunosuppressants may increase susceptibility to COVID-19.

In spite of a potential selection bias, the result suggested the possibility of chronic illness including ischemic heart disease, cardiac arrhythmia, chronic upper and lower respiratory disease, chronic renal disease, liver cirrhosis, non-infectious upper and lower digestive disease, pancreatic disease, biliary disease, epilepsy, cerebrovascular disease, dementia, malignancy, systemic connective tissue, anemia, and neurosis being associated with a decreased risk of COVID-19. Patients with these conditions might have reduced social activity, which may reduce the possible risk of exposure to SARS-CoV-2. However, this is not clear, and more precise research is needed.
In early epidemiological studies of COVID-19, it was reported that comorbidities including diabetes, hypertension, and chronic respiratory disease, except for malignancy, were related to disease severity or death as observed in this study. We also found that CRF and ESRD were significant risk factors for severe COVID-19. In addition, heart failure, cardiomyopathy, and cardiac arrhythmia might be associated with the severity of COVID-19. Human angiotensin-converting enzyme 2 (ACE2) is a functional receptor of SARS-CoV-2, and the heart is a tissue rich in ACE receptors along with the lungs. Cases of COVID-19 related to myocarditis were reported in China and Korea, and myocarditis was also reported as a risk factor for severe COVID-19.

In this study, pancreatic disease, Alzheimer’s disease, and degenerative diseases were associated with a decreased risk of severe COVID-19. Although the detailed mechanism of this protective effect remains unclear, it is suggested that the possible protective effect may be attributable to drugs used to treat these diseases. For example, camostat mesylate which is widely used protease inhibitor in chronic pancreatic disease might have protective role in COVID-19. TMPRSS2 is a serine protease that primes the spike protein of human coronaviruses and facilitates its entry into the host cell. Camostat mesylate was effective in SARS-CoV infected mouse model, and it is suggested as a potential therapeutic option in COVID-19.

This study has a few limitations. First, this study was limited to data from the nationwide claims database of subjects who underwent laboratory testing for COVID-19. Thus, the data of patients who were tested via “Drive Through” or local health centers and were treated at non-medical facilities was not included in this study. Therefore, the actual population affected by the disease was different from that of the analyzed population, which was used in this study. Despite this limitation, this study was conducted only for those who underwent the laboratory test for COVID-19 as per the insurance claims database. Therefore, the negative control group had a confirmed a negative result of SARS-CoV-2 infection. Thus, the comparison between this negative control group and case group helped in proper evaluation of the risk factors for COVID-19 occurrence. Another limitation was the inability of the data source to provide information on the severity of the comorbidities. Finally, we could not evaluate the detailed mechanism underlying the relationship between comorbidities and the diagnosis or severity of COVID-19. However, most comorbidities identified in each individual’s health insurance claims data could be used for this study. It may be possible to discover previously unknown or unexpected risk factors based on a data driven approach.

In this retrospective case control study, we suggest that diabetes, osteoporosis, rheumatoid arthritis, disorder owing to substance use, and schizophrenia might be risk factors for COVID-19. Besides, hypertension, chronic lower respiratory disease, CRF, and ESRD are associated with severe COVID-19. In addition, diabetes is associated with the occurrence and severity of COVID-19.

ACKNOWLEDGMENTS

The authors appreciate healthcare professionals dedicated to treating COVID-19 patients in Korea, and the Ministry of Health and Welfare and the Health Insurance Review & Assessment Service of Korea for sharing invaluable national health insurance claims data in a prompt manner.
SUPPLEMENTARY MATERIALS

Supplementary Table 1
Variables in the Korean National Health Insurance claim data
Click here to view

Supplementary Table 2
ICD 10 codes for disease category
Click here to view

Supplementary Table 3
ICD-10 mapping for Charlson Comorbidity Index
Click here to view

Supplementary Table 4
Analysis of relationship between comorbidities and presence of COVID-19 in whole study participants
Click here to view

Supplementary Table 5
Subpopulation analysis of relationship between comorbidities and presence of COVID-19 except the DG region
Click here to view

Supplementary Table 6
Subpopulation analysis of relationship between comorbidities and presence of COVID-19 in the DG region
Click here to view

Supplementary Table 7
Analysis of relationship between comorbidities and severity of COVID-19 in whole study participants
Click here to view

Supplementary Table 8
Subpopulation analysis of relationship between comorbidities and severity of COVID-19 except the DG region
Click here to view
Supplementary Table 9
Subpopulation analysis of relationship between comorbidities and severity of COVID-19 in the DG region

Click here to view

Supplementary Data 1
Analytic codes for diagnosis and severity of COVID-19 in Claim data.

Click here to view

REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Updated 2020. Accessed May 24, 2020.

2. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med 2020;8(1):e55. PMID

3. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91-5. PMID | CROSSREF

4. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020;55(5):2000547. PMID

5. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. Forthcoming 2020. DOI: 10.1016/j.jaci.2020.04.006. PMID | CROSSREF

6. Jung J, Im JH, Ko YJ, Huh K, Yoon CG, Rhee C, et al. Complementing conventional infectious disease surveillance with national health insurance claims data in the Republic of Korea. Sci Rep 2019;9(1):8750. PMID | CROSSREF

7. Korea Centers for Disease Control & Prevention. Coronavirus disease-19 in South Korea. http://ncov.mohw.go.kr/. Updated 2020. Accessed April 21, 2020.

8. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373-83. PMID | CROSSREF

9. Kim I, Lee J, Lee J, Shin E, Chu C, Lee SK. KCDC risk assessments on the initial phase of the COVID-19 outbreak in Korea. Osong Public Health Res Perspect 2020;11(2):67-73. PMID | CROSSREF

10. COVID-19 National Emergency Response Center, Epidemiology & Case Management Team, Korea Centers for Disease Control & Prevention. Contact transmission of COVID-19 in South Korea: novel investigation techniques for tracing contacts. Osong Public Health Res Perspect 2020;11(1):60-3. PMID | CROSSREF

11. Her M. How is COVID-19 affecting South Korea? What is our current strategy? Disaster Med Public Health Prep. Forthcoming 2020. DOI: 10.1017/dmp.2020.69. PMID | CROSSREF

12. Chung RV, Dong D, Li MM. Socioeconomic gradient in health and the covid-19 outbreak. BMJ 2020;369:m1329. PMID | CROSSREF

13. Luo Y, Zhang L, He P, Pang L, Guo C, Zheng X. Individual-level and area-level socioeconomic status (SES) and schizophrenia: cross-sectional analyses using the evidence from 1.9 million Chinese adults. BMJ Open 2019;9(9):e026532. PMID | CROSSREF

14. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. Forthcoming 2020. DOI: 10.1002/dmrr.3319. PMID | CROSSREF
15. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in critically ill patients in the Seattle region - case series. *N Engl J Med* 2020;382(21):2012-22.

16. Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. *Crit Care* 2020;24(1):108.

17. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579(7798):270-3.

18. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. *Infection*. Forthcoming 2020. DOI: 10.1007/s15010-020-01424-5.

19. Kim IC, Kim JY, Kim HA, Han S. COVID-19-related myocarditis in a 21-year-old female patient. *Eur Heart J* 2020;41(19):1859.

20. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181(2):271-280.e8.

21. Zhou Y, Vedantham P, Lu K, Agudelo J, Carrion R Jr, Nunneley JW, et al. Protease inhibitors targeting coronavirus and filovirus entry. *Antiviral Res* 2015;116:76-84.

22. McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. Candidate drugs against SARS-CoV-2 and COVID-19. *Pharmacol Res* 2020;157:104859.

23. Bittmann S, Weissenstein A, Villalon G, Moschuring-Alieva E, Luchter E. Simultaneous treatment of COVID-19 with serine protease inhibitor camostat and/or cathepsin L inhibitor? *J Clin Med Res* 2020;12(5):320-2.