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

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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 (ORR, 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

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

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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.[1] 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,[2,3] and its association with disease severity,[4,5] 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**)[6] 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

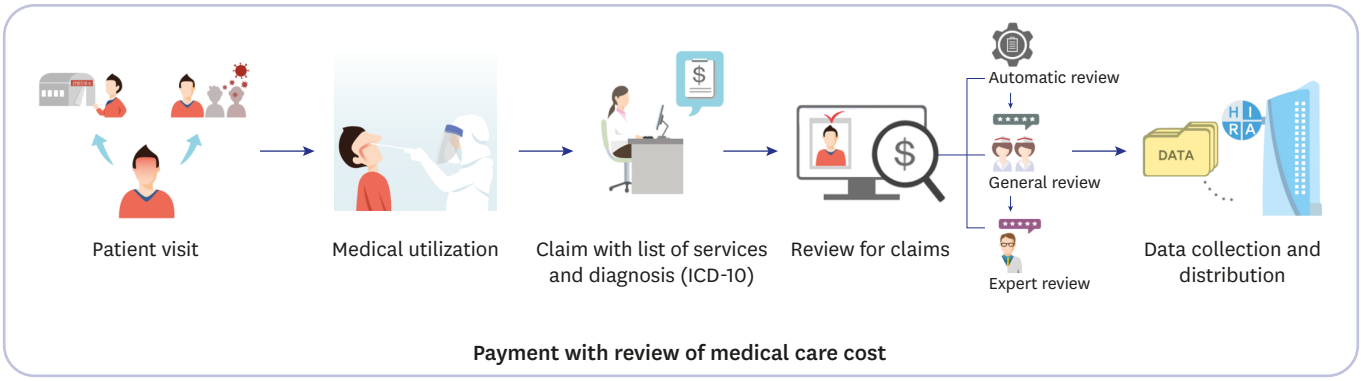

Fig. 1. Overview of national health insurance claims data from Health Insurance Review & Assessment Service of Korea (Redrawn from Jung et al. *Sci Rep* 2019;19(1):8750).[6]

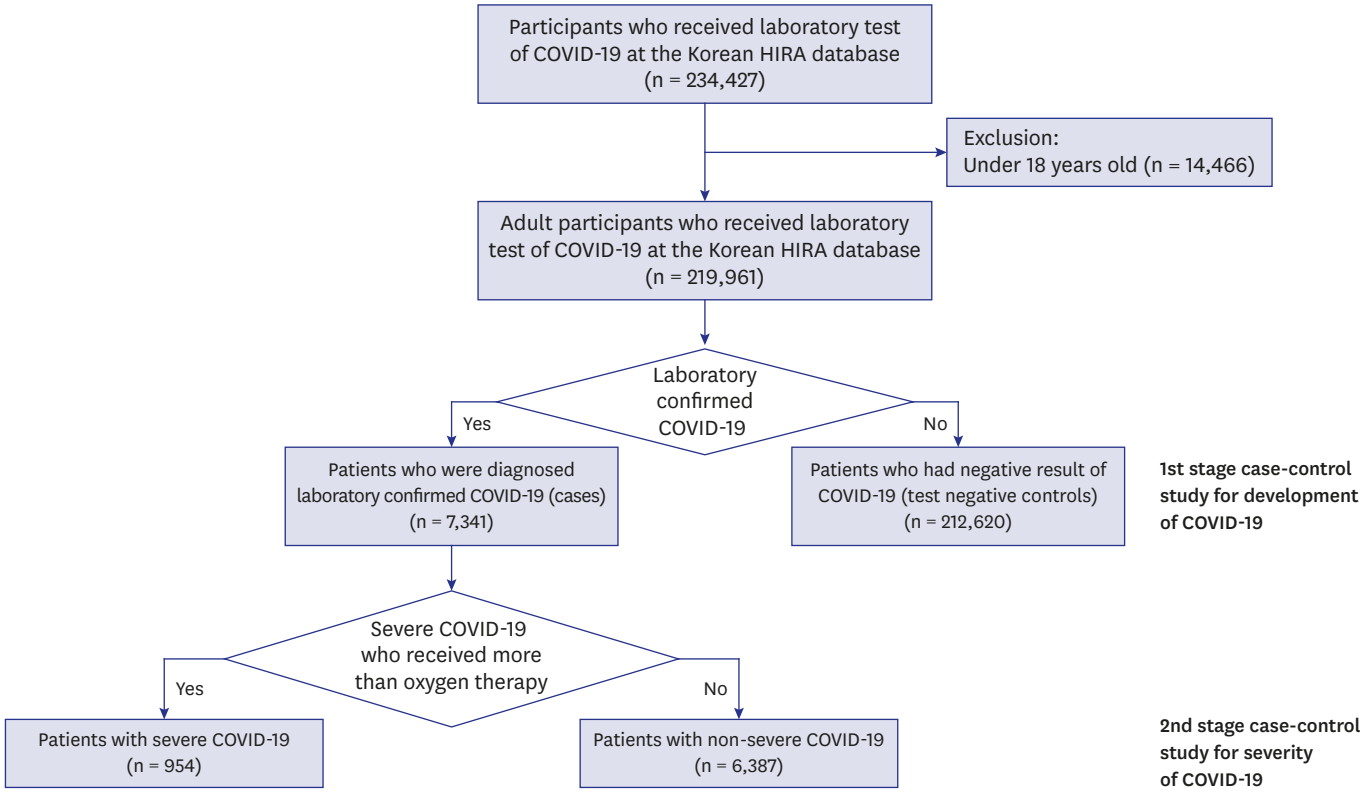

Fig. 2. Flow chart of selecting process for study participants.
COVID-19 = coronavirus disease 2019, HIRA = Health Insurance Review & Assessment Service.

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.[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**).[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 χ^2 test and Student's *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 ≥ 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

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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)	< 0.001
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)

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. (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)	4,717 (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.

(ORR, 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

Color	OR
	No significant
	< 1.0
	1.0 ≤, < 1.5
	1.5 ≤, < 2.0
	2.0 ≤, < 2.5
	2.5 ≤, < 3.0
	3.0 ≤

Model	Univariate			Multivariable								
Other diseases as covariates	N/A			No			Yes					
Variable selection	N/A			All			All			Backward Selection		
Subpopulation	1	2	3	1	2	3	1	2	3	1	2	3
Other region	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Daegu and Gyeonsangbuk-do (high regioinal outbreak)	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes
Diabetes	0.737	0.426		1.254		1.314	1.206		1.255	1.216		1.300
IDDM	0.491	0.168				1.175						
NIDDM without complication	0.745	0.428		1.278	1.170	1.343						
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		0.885							
Ischemic heart disease	0.444	0.275	0.684	0.780	0.750	0.806	0.803		0.842	0.789		0.829
Heart failure and cardiomyopathy	0.538	0.287	0.686			0.822						
Cardiac arrhythmia	0.492	0.230	0.820	0.815	0.536			0.590			0.571	
Chronic upper respiratory disease	0.774	0.689		0.905	0.793			0.903	1.160		0.903	1.162
Chronic lower respiratory disease	0.561	0.450	0.734	0.762	0.717	0.812	0.772	0.747	0.790	0.778	0.738	0.800
Environmental lung disease	0.250	0.099	0.407	0.536								
Interstitial lung disease	0.219	0.076	0.490	0.494	0.223		0.547	0.233		0.547	0.221	
Glomerular disease	0.592	0.271							1.381			1.372
History of acute renal failure	0.075	0.053	0.144	0.222	0.220	0.243	0.284		0.303	0.277		0.298
Chronic renal failure and ESRD	0.220	0.093	0.344	0.532	0.413	0.547	0.503	0.393	0.549	0.505	0.346	0.554
Liver cirrhosis	0.329	0.208	0.523	0.655		0.685	0.633		0.647	0.656		0.765
Non-infectious upper digestive system diseases	0.549	0.427	0.681	0.683	0.639	0.791	0.710	0.699	0.780	0.720	0.695	0.784
Non-infectious lower digestive system diseases	0.625	0.464	0.801	0.841	0.773	0.895	0.883	0.843	0.908	0.884	0.842	0.916
Pancreatic disease	0.231	0.196	0.335	0.473	0.515	0.477	0.525	0.582	0.527	0.531	0.573	0.525
Biliary disease	0.370	0.248	0.521	0.611	0.557	0.645	0.666	0.600	0.705	0.669	0.586	0.700
Alzheimer and degenerative disease		0.296			0.708							
Epilepsy	0.552	0.345		0.786	0.701		0.742		0.758	0.738		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	0.821	0.676	0.871
Dementia	0.760	0.286			0.621			0.734			0.694	
Solid organ malignancy (except respiratory and thyroid)	0.328	0.232	0.532	0.748		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			0.634		
Hematologic malignancy	0.133	0.069	0.319	0.393			0.353	0.236		0.375	0.234	
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	0.775	0.774	0.851		0.798	0.854	0.835	0.801
Mental disorder of substance use		0.358	1.489	1.321		1.750	1.381		1.696	1.346		1.680
Schizophrenia	1.638	0.728	2.458	1.614		2.178	1.721		2.245	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		0.854
Mental retardation and development disorder	1.983		2.372	1.511		1.943			1.717			1.668

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.

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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, 1.255–1.314), 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)	3,720 (58.2)	
50–64	295 (30.9)	1,862 (29.2)	
65–79	350 (36.7)	642 (10.1)	
≥ 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 (0.03)	< 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)	0.178
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)	0.178
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)	
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 (23.9)	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.

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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 (ORR, 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	Univariate			Multivariable												
Other diseases as covariates	N/A			No						Yes						
Variable selection	N/A			All			Backward Selection			All			Backward Selection			
Subpopulation	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	
Other region	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	
Daegu and Gyeonsangbuk-do (high regional outbreak)	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	
Diabetes	4.646	4.833	3.883							1.247	1.620			1.522		
IDDM	4.631	8.453	3.247													
NIDDM without complication	4.077	4.224	3.398													
NIDDM with complication	5.625	6.681	4.464	1.371		1.333	1.353									
Isolated hypertension	6.054	5.665	5.342	1.313		1.298	1.312		1.298	1.245			1.317		1.272	
Heart failure and cardiomyopathy	7.372	8.872	5.888	1.465			1.464				2.359					
Cardiac arrhythmia	5.177	2.857	4.789	1.405		1.601	1.400		1.601			1.516			1.578	
Chronic lower respiratory disease	2.474	2.324	2.251							1.216			1.233			
Chronic renal failure and ESRD	8.204	12.939	5.971	2.052		2.015	2.178		1.994	2.110		2.141	2.095		2.124	
Pancreatic disease				0.274		0.229	0.290		0.240	0.258		0.183	0.296		0.261	
Alzheimer and degenerative disease	3.613	6.168	2.569	0.693		0.601	0.701		0.602	0.699		0.633	0.693		0.612	
Dementia	8.257	15.332	5.759		2.665			2.440			3.471			2.870		
Bone marrow dysfunction	2.770	7.631									9.259			6.748		
Mental disorder of substance use										0.521						

Color	OR
	No significant
	< 1.0
	1.0 ≤, < 1.5
	1.5 ≤, < 2.0
	2.0 ≤, < 2.5
	2.5 ≤, < 3.0
	3.0 ≤

Fig. 4. Analysis of relationship between comorbidities on severity 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.

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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.[9-11] 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.[12] 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.[13] 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.

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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[4,5,14-16] 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,[17] 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[18] and Korea,[19] and myocarditis was also reported as a risk factor for severe COVID-19.[3]

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.[20] Camostat mesylate was effective in SARS-CoV infected mouse model,[21] and it is suggested as a potential therapeutic option in COVID-19.[22,23]

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.

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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

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Supplementary Table 3
ICD-10 mapping for Charlson Comorbidity Index

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

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

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

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

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Supplementary Table 8
Subpopulation analysis of relationship between comorbidities and severity of COVID-19 except the DG region

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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.

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