Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Impact of obesity, fasting plasma glucose level, blood pressure, and renal function on the severity of COVID-19: A matter of sexual dimorphism?

Kyungmin Huh [a,1], *Rugyeom Lee* [b,1], *Wonjun Ji* [c], *Minsun Kang* [b], *In Cheol Hwang* [d], *Dae Ho Lee* [e,*], *Jaehun Jung* [b,f,*]

[a] *Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*
[b] *Artificial Intelligence and Big-Data Convergence Center, Gil Medical Center, Gachon University College of Medicine, Incheon, South Korea*
[c] *Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*
[d] *Department of Family Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, South Korea*
[e] *Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, South Korea*
[f] *Department of Preventive Medicine, Gachon University College of Medicine, Incheon, South Korea*

ARTICLE INFO

Article history:
Received 7 September 2020
Received in revised form
6 October 2020
Accepted 9 October 2020
Available online 21 October 2020

Keywords:
COVID-19
Hypertension
Diabetes
Dyslipidemia
Obesity
Outcome

ABSTRACT

Aims: This study aimed to assess whether body mass index (BMI), fasting plasma glucose (FPG) levels, blood pressure (BP), and kidney function were associated with the risk of severe disease or death in patients with COVID-19.

Methods: Data on candidate risk factors were extracted from patients' last checkup records. Propensity score-matched cohorts were constructed, and logistic regression models were used to adjust for age, sex, and comorbidities. The primary outcome was death or severe COVID-19, defined as requiring supplementary oxygen or higher ventilatory support.

Results: Among 7,649 patients with confirmed COVID-19, 2,231 (29.2%) received checkups and severe COVID-19 occurred in 307 patients (13.8%). A BMI of 25.0–29.9 was associated with the outcome among women (aOR, 2.29; 95% CI, 1.41–3.73) and patients aged 50–69 years (aOR, 1.64; 95% CI, 1.06–2.54). An FPG $\geq$ 126 mg/dL was associated with poor outcomes in women (aOR, 2.06; 95% CI, 1.13–3.77) but not in men. Similarly, estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 was a risk factor in women (aOR, 3.46; 95% CI, 1.71–7.01) and patients aged < 70 years.

Conclusions: The effects of BMI, FPG, and eGFR on outcomes associated with COVID-19 were prominent in women but not in men.

1. Introduction

* Corresponding authors at: Artificial Intelligence and Big-Data Convergence Center, Gil Medical Center, Gachon University College of Medicine, Incheon, South Korea (J. Jung).
E-mail addresses: drhormone@naver.com (D.H. Lee), eastside1st@gmail.com (J. Jung).
[1] Contributed equally to this work.
https://doi.org/10.1016/j.diabres.2020.108515
0168-8227/

Coronavirus disease 2019 (COVID-19) caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide and resulted in more than 3.5 million confirmed cases and 1 million deaths as of early October 2020. Most patients with COVID-19 develop mild and self-limiting disease; however, a considerable proportion of patients suffer from severe disease characterized by respiratory or multiorgan failure, or hyperinflammatory syndromes [1]. Multiple factors have been associated with the risk of severe or fatal COVID-19, including hypertension, diabetes mellitus, and chronic cardiopulmonary or renal diseases [2,3]. Furthermore, obesity has been reported to increase the risk of poor outcome [3,4]. Although these conditions are frequently associated with disease severity and fatality in other infectious diseases, their degree of association with severe COVID-19 remains unclear.

The impact of baseline health condition on the disease course is difficult to evaluate using medical records, as the information on premorbid status recorded in admission records and epidemiological reports are often inaccurate or incomplete unless they are collected prospectively on purpose. In addition, plasma glucose levels, body weight, and blood pressure (BP) at admission might already deviate from true baseline due to the effects of acute infection with SARS-CoV-2. As a result, it is plausible that baseline health assessment performed prior to the onset of COVID-19 would provide a more accurate representation of risk factors associated with disease severity.

To examine the association between baseline health status and the risk of severe disease in patients with COVID-19, we performed a case-control study, using data from the nationwide registry of COVID-19 cases and from the biennial health checkup database in South Korea.

2. Materials and methods

This retrospective study compared BP, and metabolic and kidney function parameters between COVID-19 patients with severe disease (including fatalities) and those with mild-to-moderate disease. The study protocol was approved by the institutional review board of the Gil Medical Center, Gachon University College of Medicine and Science (GFIRB2020-118) with a waiver of consent.

2.1. Data sources

Health checkup data were extracted from the National Health Insurance Service (NHIS) database, which was linked to the Korea Centers for Disease Control and Prevention (KCDC) COVID-19 patient registry, dedicated to collecting information on all confirmed cases in Korea. All Korean residents are covered by NHIS, which provides universal access to healthcare. In addition, the NHIS provides a biennial health checkup to all beneficiaries aged $\geq$ 20 years; this database was interrogated for data on baseline health status. The participation rate of NHIS-provided checkups among the eligible population was 78.5% in 2017 [5]. The Korean health checkup data have been previously validated and used in studies that assessed the risk of mortality, cardiovascular events, and diabetes [6–8]. Information on comorbidities (identified using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision) was extracted from the NHIS reimbursement database. The last date of data entry was May 30, 2020.

2.2. Study patients and outcomes

Patients aged $\geq$ 20 years who were diagnosed with COVID-19 and who received the NHIS health checkup in 2018 or later were included in this study. All included patients were diagnosed with COVID-19 based on nasopharyngeal swab or sputum samples examined with a reverse transcriptase polymerase chain reaction (RT-PCR) for the presence of SARS-CoV-2, as per national guidelines [9].

The primary outcome was death or severe COVID-19, defined as requiring any of the following during hospitalization: supplementary oxygen, high-flow nasal cannula, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation.

2.3. Premorbid metabolic profiles, blood pressure, and kidney function

Data on body mass index (BMI), fasting plasma glucose (FPG), BP, serum lipid levels, and the estimated glomerular filtration rate (eGFR) were extracted from last checkup records. BP and FPG were categorized using guidelines from the American College of Cardiologists/American Heart Association and the American Diabetes Association, respectively (Supplementary Table 1) [10,11]. BMI was categorized according to the Korean Society for the Study of Obesity guidelines [12]. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels were classified with commonly used cutoffs. Finally, eGFR was categorized using the Kidney Disease Improving Global Outcomes guidelines [13].

2.4. Statistical analysis

Study variables were compared between patients with severe and non-severe COVID-19. Baseline demographic and clinical characteristics were compared between patient groups using the χ^2 test for categorical variables and Student's *t*-test for continuous variables. The Charlson Comorbidity Index (CCI) was calculated using standard methods and compared using the Wilcoxon rank-sum test, as its distribution was non-normal [14]. Adjusted logistic regression models were constructed, based on the following covariates: age, sex, NHIS expanded coverage for low household income, and comorbidities. Comorbidities were categorized into disease groups (Supplementary Table 2), identified from diagnostic codes included at least twice in reimbursement records covering the past 3 years and dated before COVID-19 onset.

To mitigate the impact of confounders, we constructed propensity score-matched cohorts. Propensity scores (PS) of severe COVID-19 risk were calculated using logistic regression with the following covariates: age, sex, coverage for low income, and CCI. Each patient with severe COVID-19 was matched with up to five patients with non-severe disease by

Table 1 – Baseline characteristics of patients with COVID-19, stratified by disease severity.

Characteristic	Total cohort (N = 2231)			Propensity score-matched cohort (N = 1331)		
	Severity, No. (%)		P	Severity, No. (%)		P
	Severe (n = 307)	Non-severe (n = 1924)		Severe (n = 293)	Non-severe (n = 1038)	
Sex						
Male	146 (47.6)	725 (37.7)	0.001	138 (47.1)	445 (42.9)	0.198
Female	161 (52.4)	1199 (62.3)		155 (52.9)	593 (57.1)	
Age, years						
20–29	3 (1.0)	160 (8.3)	<0.001	3 (1.0)	15 (1.4)	<0.001
30–39	8 (2.6)	225 (11.7)		8 (2.7)	40 (3.9)	
40–49	17 (5.5)	365 (19.0)		17 (5.8)	85 (8.2)	
50–59	67 (21.8)	610 (31.7)		67 (22.9)	335 (32.3)	
60–69	97 (31.6)	400 (20.8)		97 (33.1)	400 (38.5)	
70–79	75 (24.4)	137 (7.1)		75 (25.6)	137 (13.2)	
≥80	40 (13.0)	27 (1.4)		26 (8.9)	26 (2.5)	
Coverage for low income	30 (9.8)	112 (5.8)	0.009	30 (10.2)	82 (7.9)	0.203
Comorbidities						
Charlson comorbidity index, mean (range)	4.5 (0–14)	2.5 (0–12)	<0.001	4.6 (0–14)	3.3 (0–12)	<0.001
Diabetes	180 (58.6)	576 (29.9)	<0.001	175 (59.7)	436 (42)	<0.001
Hypertension	184 (59.9)	545 (28.3)	<0.001	171 (58.4)	437 (42.1)	<0.001
Chronic heart disease	137 (44.6)	365 (19.0)	<0.001	131 (44.7)	283 (27.3)	<0.001
Chronic lung disease	211 (68.7)	882 (45.8)	<0.001	203 (69.3)	557 (53.7)	<0.001
Asthma	115 (37.5)	459 (23.9)	<0.001	110 (37.5)	281 (27.1)	<0.001
Chronic liver disease	228 (74.3)	978 (50.8)	<0.001	224 (76.5)	691 (66.6)	0.001
Chronic kidney disease	60 (19.5)	125 (6.5)	<0.001	59 (20.1)	94 (9.1)	<0.001
Cancer	47 (15.3)	135 (7.0)	<0.001	47 (16.0)	110 (10.6)	0.011
Rheumatologic disease	3 (1.0)	9 (0.5)	0.222	3 (1.0)	7 (0.7)	0.466
Chronic neurologic disease	120 (39.1)	320 (16.6)	<0.001	114 (38.9)	259 (25.0)	<0.001
Mortality	42 (13.7)	0 (0.0)	<0.001	37 (12.6)	0 (0.0)	<0.001

greedy neighbor nearest matching. The model was further adjusted in logistic regression analysis, using age, sex, and low-income coverage as covariates.

Subgroup analyses planned *a priori* were performed for sex and age group. All statistical tests were two-tailed and the threshold for significance was set at P-values < 0.05. All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

3. Results

Among 7,649 patients with a confirmed diagnosis of COVID-19, a total of 2,231 (29.2%) patients had received an NHIS health checkup in 2018 or later and were included in the analysis. Patients who had received checkups tended to be older and have more comorbidities than those who did not receive checkups (Supplementary Table 3). Patients with severe COVID-19 or death comprised 13.8% (n = 307) of the total cohort, including 42 deaths (1.9%). Patients who were male, older in age, with low household income, higher CCI, or underlying conditions (except rheumatologic disease) were more likely to develop severe or fatal COVID-19 than patients without these characteristics (Table 1). The PS-matched cohort showed smaller differences in matching variables (age, sex, income, and CCI), but these differences remained significant.

High BMI, classified as class 1 obesity (25.0–29.9), was associated across subgroups with severe and fatal COVID-19 (Fig. 1). Overall, patients with a BMI 25.0–29.9 were at a significantly increased risk of severe disease (adjusted odds ratio [aOR], 1.73; 95% confidence interval [CI], 1.22–2.45; P = 0.002) compared to those with a BMI < 23.0, while the effect was not significant in other BMI strata. The association between a BMI 25.0–29.9 and the risk of severe or fatal disease was prominent among women (aOR, 2.29; 95% CI, 1.41–3.73; P = 0.001) but not among men (aOR, 1.28; 95% CI, 0.75–2.19; P = 0.363). However, men with morbid obesity (BMI ≥ 30) showed a marginally higher risk of severe disease (aOR, 2.69; 95% CI, 0.92–7.89; P = 0.071), which was not statistically significant; no such trend was observed among women. Among age groups, there was an association between BMI 25.0–29.9 and risk of severe or fatal COVID-19 for patients aged 50–69 years (aOR, 1.64; 95% CI, 1.06–2.54; P = 0.028).

The association between FPG and severity of COVID-19 demonstrated a differential effect by sex (Fig. 2). Women with FPG ≥ 126 mg/dL had a higher risk of severe COVID-19 compared to women with FPG < 126 mg/dL in both total (aOR, 2.28; 95% CI, 1.26–4.13; P = 0.006) and PS-matched (aOR, 2.06; 95% CI, 1.13–3.77; P = 0.019) cohorts; this effect was not observed among men. The effect of FPG levels differed between age groups. FPG ≥ 126 mg/dL was most strongly associated with disease severity among patients aged < 50 years (aOR, 11.46; 95% CI, 1.30–100.76; P = 0.028 in the PS-matched cohort); concurrently, this association was weaker among patients aged 50–69 years (aOR, 1.77; 95% CI, 1.05–3.00; P = 0.032). In contrast, patients aged ≥ 70 years with higher-than-normal FPG levels showed a lower risk of severe disease.

BP was not associated with the risk of severe or fatal COVID-19 in the total and PS-matched cohorts (Fig. 3). However, there was a trend toward an association among men (aOR, 1.01 per mmHg of systolic BP; 95% CI, 1.00–1.03; P = 0.056); in contrast, hypertension classes did not show any significant association. Neither hypertension classes nor systolic BP was associated with disease course among women; a similar lack of association was observed across age groups.

A total of 2,205 patients had eGFR calculated in their health checkup results; of these patients 298 (13.5%) had severe disease (Supplementary Table 4). An eGFR < 60 ml/min/1.73 m^2 was associated with a higher risk of severe COVID 19 (including fatal disease) (aOR, 2.58; 95% CI, 1.52–4.37; P < 0.001; Fig. 4). This association was observed among women (aOR, 3.46; 95% CI, 1.71–7.01; P = 0.001), but not among men (aOR, 1.99; 95% CI, 0.88–4.51; P = 0.100). Moreover, eGFR < 60 ml/min/1.73 m^2 and COVID-19 severity were significantly associated among patients aged < 70 years but not among those aged ≥ 70 years (aOR, 1.53; 95% CI, 0.48–4.91; P = 0.242). Our findings were consistent in the overall and PS-matched cohorts and in linear regression analyses.

Serum lipid profile was not consistently associated with COVID-19 severity (Supplementary Table 5 and Supplementary Fig. 2). In fact, levels of LDL ≥ 70 mg/dL, HDL < 60 mg/dL, and TG ≥ 175 mg/dL did not affect the risk of severe or fatal disease in the present study. However, there was a trend toward increased risk of severe disease associated with low HDL and high TG levels.

4. Discussion

In the present study based on a nationwide COVID-19 registry combined with an independent regular health checkup data, the effect of FPG levels and eGFR on the risk of severe or fatal COVID-19 varied between sex and age groups. High FPG levels and low eGFR were associated with severe COVID-19 among women and patients aged < 70 years; however, this association was not observed among men or older patients. Previous studies have reported that case fatality and severity rates were higher among men than among women with COVID-19 [15–17]. Moreover, official sex disaggregated data from greater than 160 countries and territories have shown that the case fatality rate was lower among women than among men in most countries [18].

The gene coding angiotensin converting enzyme 2 (ACE2) is located on the X chromosome, and estrogen is known to increase the level of ACE2 expression [19,20]. Although ACE2 is a receptor used for cell entry of SARS-CoV-2, downregulation of ACE2 expression is associated with lung injury caused by respiratory viruses, including SARS-CoV [21,22]. This apparent paradox could be explained by the anti-inflammatory function of ACE2 through its role in the renin-angiotensin system (RAS). Male sex, older age, and SARS-CoV-2 binding all lead to lower levels of ACE2 expression, which may cause acute lung injury and organ damage through exaggerated angiotensin II signalling [23]. As estrogen is involved in the regulation of ACE2 and its expression level is higher in women, it has been suggested that estrogen

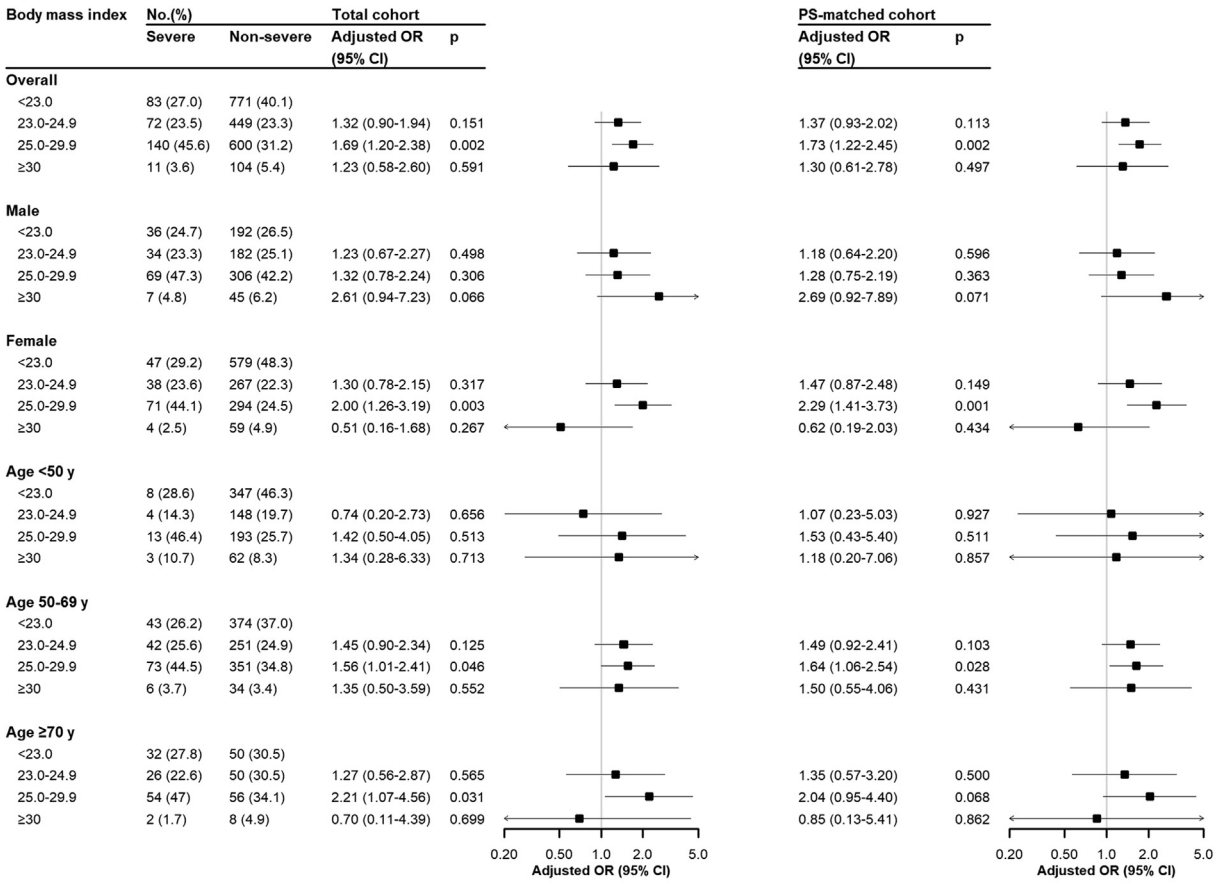

Fig. 1 – Adjusted odds ratios for body mass index and composite of severe COVID-19 or death. PS, propensity score. OR, odds ratio. CI, confidence interval.

levels may have a protective role against respiratory failure and mortality in women with COVID-19 [19,24,25]. Nevertheless, metabolic abnormalities associated with altered ACE2 expression might counteract these benefits in women with COVID-19 in a manner analogous to that observed in cardiovascular and renal disease, where the risk in women with and without diabetes is lower and higher than in male counterparts, respectively [26–29]. It remains unknown whether these documented interactions between sex and metabolic disease-related complications is augmented in patients with COVID-19. Further studies are required on the interaction between sex and COVID-19-related organ damage in patients with specific metabolic characteristics.

In the present study, BMI 25–29.9 was associated with severe or fatal COVID-19 across subgroups, except among males and patients aged < 50 years. Obesity has been reported as a significant risk factor for respiratory failure and mortality in patients with COVID-19 [30–32]. High levels of ACE2 expression by adipocytes, overactive RAS (characterized by higher level of angiotensin II), impaired baseline pulmonary function, endothelial dysfunction, and higher risk of thromboembolism have been proposed as plausible mechanisms linking obesity with the risk of severe or fatal COVID-19 [33]. Our findings are consistent with those from previous reports and *meta*-analyses. Furthermore, the present findings suggest that a BMI 25–30, categorized as "class 1 obesity" in Korean guidelines but "overweight" in Western guidelines, is a significant risk factor for severe disease among women and patients aged 50–69 years. The impact of ethnic differences in metabolic parameters on disease severity should be considered in future research.

Interestingly, high BP was not associated with the risk of severe disease in any of the present study subgroups. Hypertension has been associated with mortality risk since early reports on COVID-19 cases confirmed this in China; this association was replicated in subsequent studies [34,35]. Hypertension alters ACE2 expression, increases the risk of cardiovascular and renal failure, and may cause organ damage; thus, the detrimental effect of hypertension on COVID-19 outcomes seems biologically plausible [36]. However, it remains unclear whether hypertension is an independent rather than a confounding factor for severe COVID-19 [37]. Hypertension is common among older adults and it might reflect their general health status. Our findings suggest that further studies are required to elucidate this uncertainty.

Similarly, serum lipid profiles showed no clear association with the risk of severe or fatal COVID-19. While levels of TG $\geq$ 175 mg/dL were marginally associated with increased risk of severe disease in men, this effect was not statistically significant. Dyslipidemia considered separately from other components of metabolic syndrome did not affect the risk of severe COVID-19 in the present study. A small number of

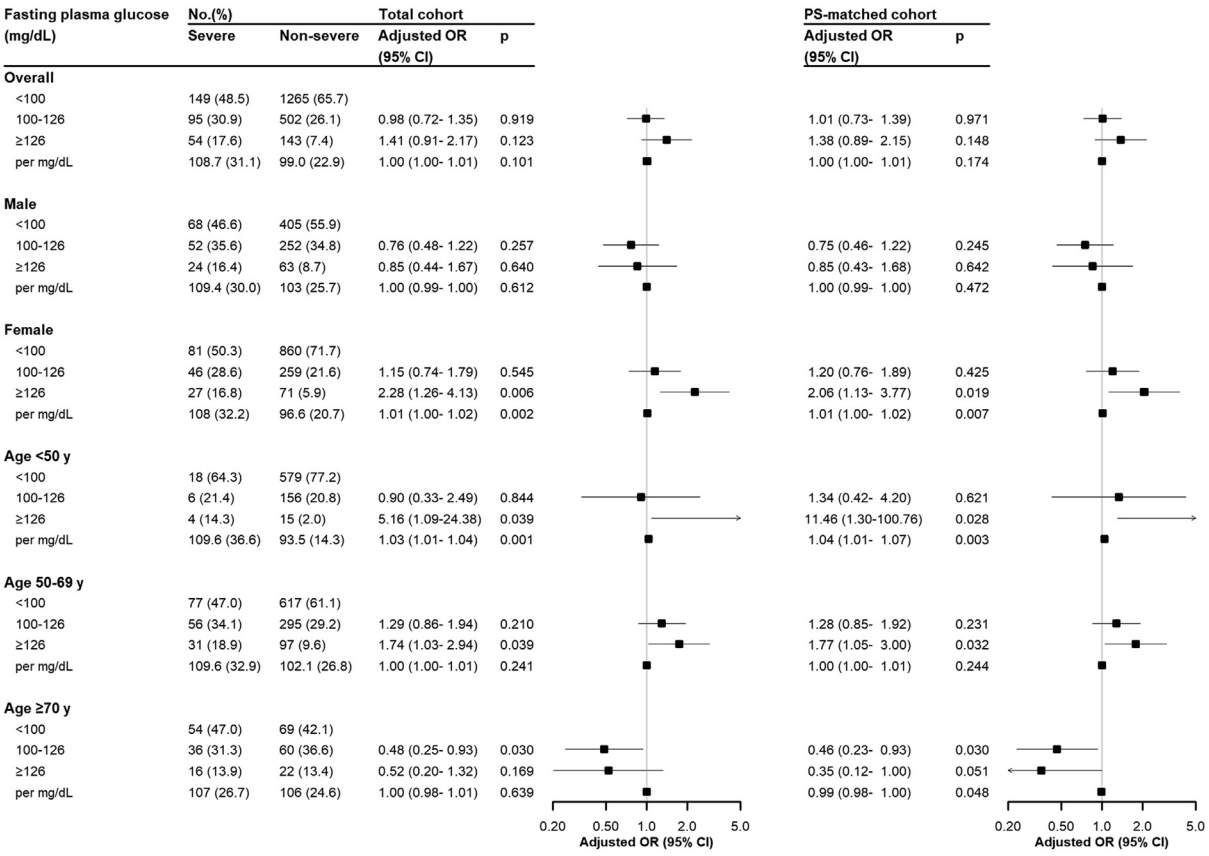

Fig. 2 – Adjusted odds ratios for fasting plasma glucose and composite of severe COVID-19 or death. PS, propensity score. OR, odds ratio. CI, confidence interval.

previous studies investigated cholesterol levels in patients with COVID-19, reporting lower cholesterol levels in patients with severe disease than in those with mild disease [36]. However, the study authors measured serum cholesterol levels after the diagnosis of COVID-19; thus, it remains unclear whether low cholesterol levels were risk factors for COVID-19 or a consequence of the disease. In the present study, serum lipid levels measured before the diagnosis of COVID-19 suggest a lack of association.

Our study has several strengths. First, we used a large, nationwide registry of confirmed COVID-19 cases. South Korea has successfully controlled the COVID-19 epidemic because of an aggressive trace-and-isolate strategy, made possible owing to a large testing capacity, experience from the previous MERS-CoV outbreak, and public cooperation. The dataset used in the present study is unlikely to miss a substantial number of the country's cases, including those of mild disease, allowing the present study to account for patients who did not require hospitalization, a task often difficult if not impossible in other countries. Second, baseline health status data were extracted from a health checkup database, created before the COVID-19 pandemic. As a result, our data were likely an accurate and objective representation of patients' health status before they acquired the SARS-CoV-2 infection.

However, this study has some limitations. First, less than a half of patients diagnosed with COVID-19 had data available from a health checkup performed in 2018 or later. Patients who were older or had more comorbidities were more likely to have received checkups; thus the baseline characteristics of study participants differed from those of patients excluded from the study due to the lack of checkup data. Nevertheless, we compared variables of interest in a robust design, adjusting for underlying conditions and using a PS-matched analysis to mitigate confounding. Second, there was a time gap between the last checkup and SARS-CoV-2 infection. Some of our study variables are prone to temporal change and the measurements recorded during checkups might not fully reflect patient status immediately before infection. Finally, we could not account for the effect of treatment in our analysis.

In our retrospective study using a nationwide health checkup database, high FPG levels and low eGFR were significantly associated with the risk of severe COVID-19 (including fatal disease) among women and patients aged < 70 years. High BMI was associated with severe illness among women. No consistent increase in risk was observed in association with high BP or dyslipidemia. These findings suggest that the baseline metabolic characteristics exert differential sex- and age-related effects on disease severity among patients diagnosed with COVID-19.

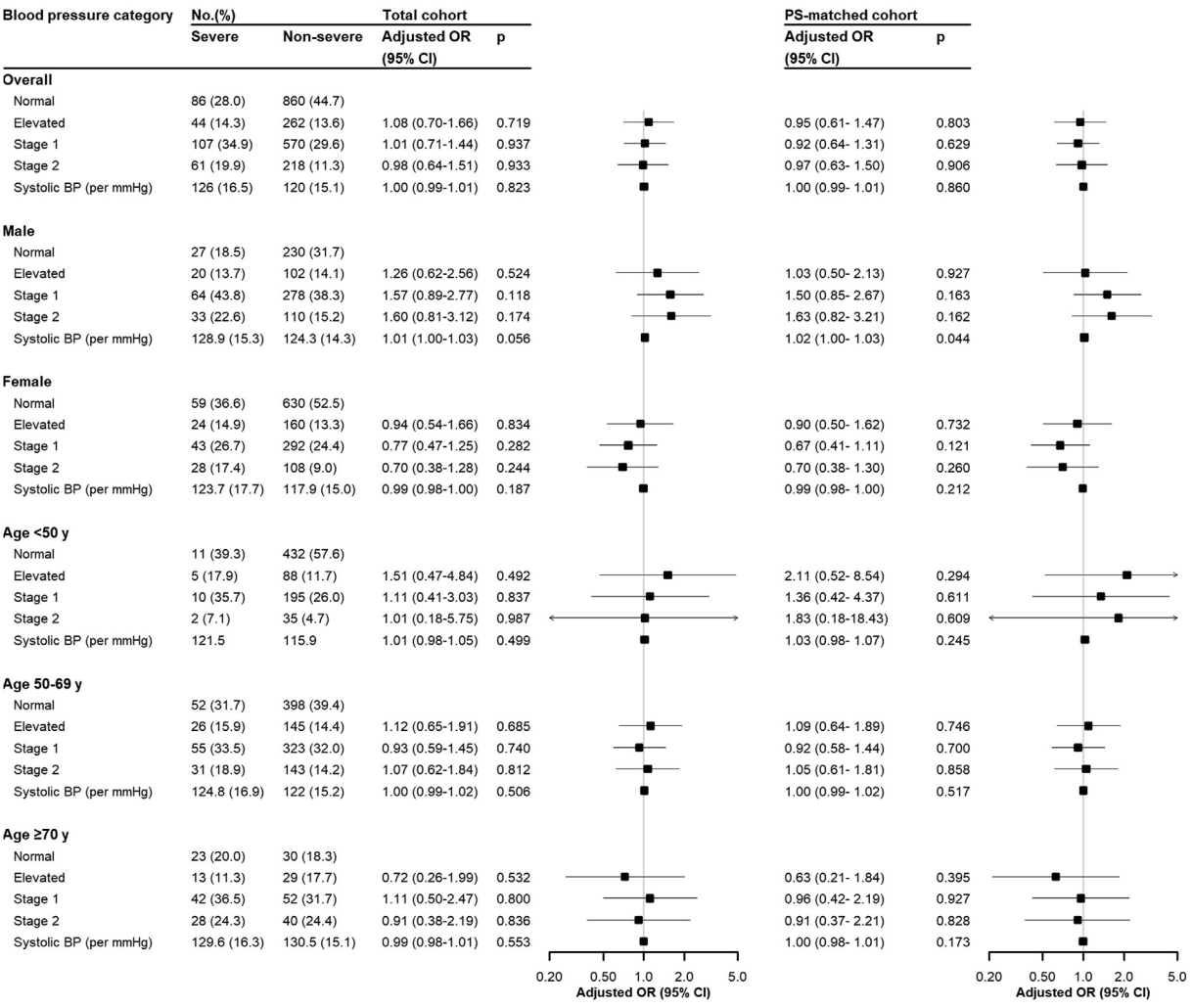

Fig. 3 – Adjusted odds ratios for blood pressure and composite of severe COVID-19 or death. PS, propensity score. OR, odds ratio. CI, confidence interval.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank all healthcare professionals dedicated to treating patients with COVID-19 in Korea and the Ministry of Health and Welfare and the National Health Insurance Service of Korea for sharing invaluable national health insurance claims data in a prompt manner.

Author contributions

Dr. Huh and Jung had full access to all the study data and take responsibility for its integrity and accuracy of analysis.

Concept and design: Huh, Ji, Hwang, DH Lee, Jung.

Acquisition, analysis, or interpretation of data: Huh, R Lee, Ji, Hwang, DH Lee, Jung.

Drafting of the manuscript: Huh, DH Lee.

Statistical analysis: Huh, R Lee, Jung.

Funding/Support

This study was supported by grants from the Gachon University Gil Medical Center (grant numbers 2019-11) and a grant from the Korea Health Technology Research & Development Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Korea (grant numbers HI14C1135). The sponsor of the study was not involved in the study design, analysis, and interpretation of data; writing of the report; or the decision to submit the study results for publication.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and was approved by the appropriate institutional review board of the *Gachon University College of Medicine, Incheon,* Republic of Korea (GFIRB2020-118), and the requirement to obtain written

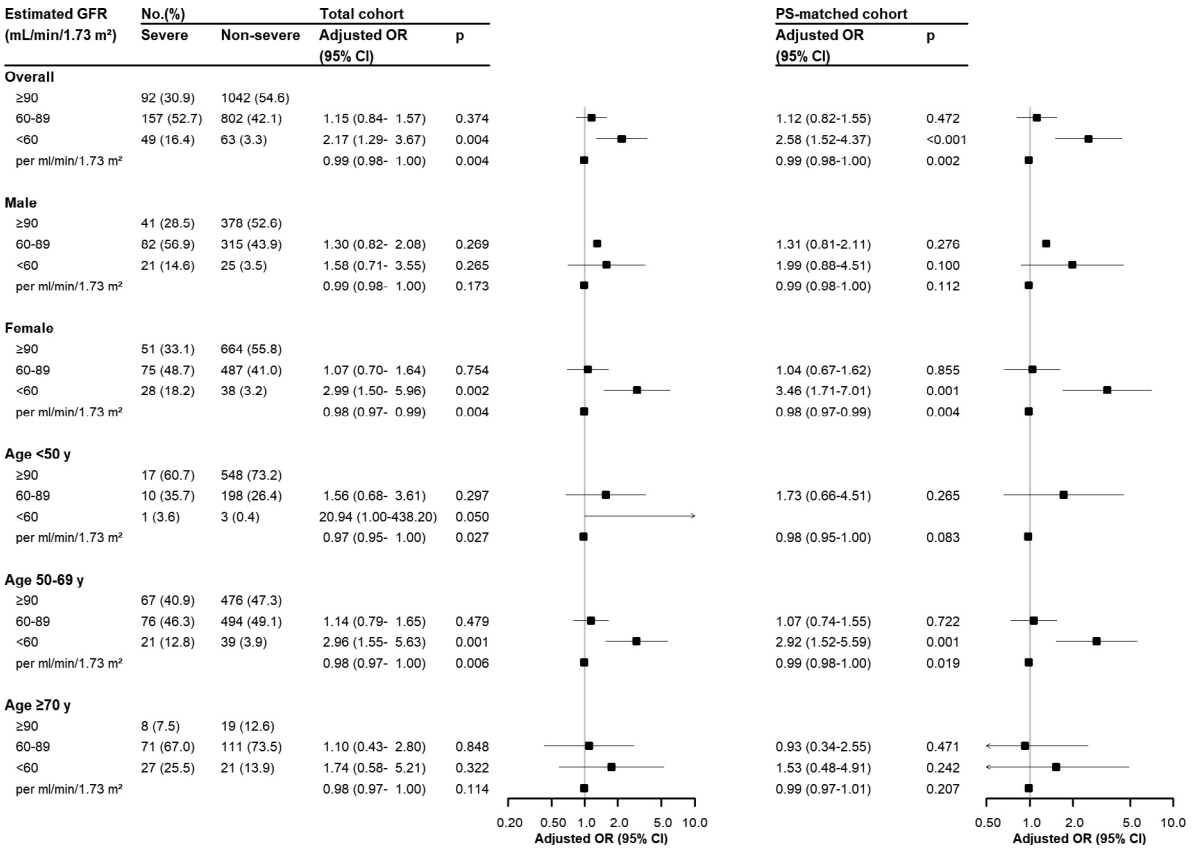

Fig. 4 – Adjusted odds ratios for estimated glomerular filtration rate (GFR) and composite of severe COVID-19 or death. PS, propensity score. OR, odds ratio. CI, confidence interval.

consent was waived due to the human subjects were not involved in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108515.

REFERENCES

[1] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239–42.
[2] Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA 2020;323(18):1775–6.
[3] Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA 2020;323(20):2052–9.
[4] Le Brocq S, Clare K, Bryant M, Roberts K, Tahrani AA. Obesity and COVID-19: a call for action from people living with obesity. Lancet Diabetes Endocrinol. 2020;8(8):652–4.
[5] National Health Insurance Service. 2017 National Health Screening Statistical Yearbook. In:2017: https://www.nhis.or.kr/bbs7/boards/B0159/27944. Accessed Jul 23, 2020.
[6] Ahn C, Hwang Y, Park SK. Predictors of all-cause mortality among 514,866 participants from the Korean National Health Screening Cohort. PLoS ONE 2017;12(9) e0185458.
[7] Cho IJ, Sung JM, Chang HJ, Chung N, Kim HC. Incremental Value of Repeated Risk Factor Measurements for Cardiovascular Disease Prediction in Middle-Aged Korean Adults: Results From the NHIS-HEALS (National Health Insurance System-National Health Screening Cohort). Circ Cardiovasc Qual Outcomes. 2017;10(11) e004197.
[8] Ha KH, Lee YH, Song SO, et al. Development and Validation of the Korean Diabetes Risk Score: A 10-Year National Cohort Study. Diabetes Metab J. 2018;42(5):402–14.
[9] Korea Centers for Disease Control and Prevention. COVID-19 Response Guidelines (Edition 8-1). http://ncov.mohw.go.kr/shBoardView.do?brdId=2&brdGubun=28&ncvContSeq=2447. Published 2020. Accessed Jun 7, 2020.
[10] Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):2199–269.
[11] American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020; 43(Suppl 1):S14-S31.
[12] Seo MH, Lee WY, Kim SS, et al. 2018 Korean Society for the Study of Obesity Guideline for the Management of Obesity in Korea. J Obes Metab Syndr. 2019;28(1):40–5.
[13] Summary of Recommendation Statements. Kidney Int Suppl (2011). 2013; 3(1):5-14.

[14] 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.
[15] Lee JY, Kim HA, Huh K, et al. Risk Factors for Mortality and Respiratory Support in Elderly Patients Hospitalized with COVID-19 in Korea. J Korean Med Sci. 2020;35(23) e223.
[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] Lu L, Zhong W, Bian Z, et al. A comparison of mortality-related risk factors of COVID-19, SARS, and MERS: A systematic review and meta-analysis. J Infect. 2020. (In press). https://doi.org/10.1016/j.jinf.2020.07.002
[18] Global Health 5050. COVID-19 sex-disaggregated data tracker. https://globalhealth5050.org/covid19/sex-disaggregated-data-tracker/. Updated Jul 24, 2020. Accessed Jul 24, 2020.
[19] Hilliard LM, Sampson AK, Brown RD, Denton KM. The "his and hers" of the renin-angiotensin system. Curr Hypertens Rep. 2013;15(1):71–9.
[20] Tukiainen T, Villani A-C, Yen A, et al. Landscape of X chromosome inactivation across human tissues. Nature 2017;550(7675):244–8.
[21] Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11(8):875–9.
[22] Gu H, Xie Z, Li T, et al. Angiotensin-converting enzyme 2 inhibits lung injury induced by respiratory syncytial virus. Sci Rep. 2016;6(1):19840.
[23] AlGhatrif M, Cingolani O, Lakatta EG. The Dilemma of Coronavirus Disease 2019, Aging, and Cardiovascular Disease: Insights From Cardiovascular Aging Science. JAMA Cardiol. 2020;5(7):747–8.
[24] Stelzig KE, Canepa-Escaro F, Schiliro M, Berdnikovs S, Prakash YS, Chiarella SE. Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2020;318(6):L1280–1.
[25] Penna C, Mercurio V, Tocchetti CG, Pagliaro P. Sex-Related Differences in COVID-19 Lethality. Br J Pharmacol. 2020. (In press). https://doi.org/10.1111/bph.15207
[26] Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev. 2016;37(3):278–316.
[27] Villar E, Chang SH, McDonald SP. Incidences, treatments, outcomes, and sex effect on survival in patients with end-stage renal disease by diabetes status in Australia and New Zealand (1991 2005). Diabetes Care 2007;30(12):3070–6.
[28] Tancredi M, Rosengren A, Svensson AM, et al. Excess Mortality among Persons with Type 2 Diabetes. N Engl J Med. 2015;373(18):1720–32.
[29] Gomez-Marcos MA, Recio-Rodriguez JI, Gomez-Sanchez L, et al. Gender differences in the progression of target organ damage in patients with increased insulin resistance: the LOD-DIABETES study. Cardiovasc Diabetol. 2015;14:132.
[30] Földi M, Farkas N, Kiss S, et al. Obesity is a risk factor for developing critical condition in COVID-19 patients: A systematic review and meta-analysis. Obes Rev. 2020. (In press). https://doi.org/10.1111/obr.13095
[31] Hussain A, Mahawar K, Xia Z, Yang W, El-Hasani S. Obesity and mortality of COVID-19. Meta-analysis. Obes Res Clin Pract. 2020. (In press). https://doi.org/10.1016/j.orcp.2020.07.002
[32] Yang J, Hu J, Zhu C. Obesity aggravates COVID-19: a systematic review and meta-analysis. J Med Virol. 2020. (In press). https://doi.org/10.1002/jmv.26237
[33] Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM, Lippi G. Obesity and Outcomes in COVID-19: When an Epidemic and Pandemic Collide. Mayo Clin Proc. 2020;95(7):1445–53.
[34] Zuin M, Rigatelli G, Zuliani G, Rigatelli A, Mazza A, Roncon L. Arterial hypertension and risk of death in patients with COVID-19 infection: Systematic review and meta-analysis. J Infect. 2020;81(1):e84–6.
[35] Roncon L, Zuin M, Zuliani G, Rigatelli G. Patients with arterial hypertension and COVID-19 are at higher risk of ICU admission. Br J Anaesth. 2020;125(2):e254–5.
[36] Zaki N, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: A systematic review. Diabetes Metab Syndr. 2020;14(5):1133–42.
[37] Tadic M, Cuspidi C, Grassi G, Mancia G. COVID-19 and arterial hypertension: Hypothesis or evidence? J Clin Hypertens (Greenwich). 2020. (In press). https://doi.org/10.1111/jch.13925