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Influenza viral infection is a risk factor for severe illness in COVID-19 patients: a nationwide population-based cohort study

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ABSTRACT
In order to prepare for the twindemic of influenza and SARS-CoV-2 infection, we investigated the association between influenza infection and subsequent severity of SARS-CoV-2 infection. A population-based nationwide cohort study was performed using data from the National Health Insurance Service (NHIS) in the Republic of Korea. This study included 274,126 individuals who underwent SARS-CoV-2 PCR testing between 20 January 2020 and 1 October 2020. Among these patients, 28,338 tested positive for SARS-CoV-2, and 4,003 of these individuals had a history of influenza. The control group was selected through 1:1 propensity score matching. In the group of 4,003 COVID-19-positive individuals with no history of influenza, 192 (4.8%) experienced severe illness from COVID-19 infection. In the group of 4,003 COVID-19-positive individuals with a history of influenza, 260 (6.5%) had severe illness from COVID-19, and the overall adjusted odds ratio (aOR) was 1.29 (95% confidence interval 1.04–1.59). Among the 4,003 COVID-19-positive individuals with a history of influenza, severe COVID-19 infection was experienced by 143 of 1,760 (8.1%) with an influenza history within 1 year before the onset of COVID-19, 48 of 1,129 (4.3%) between 1 and 2 years, and 69 of 1,114 (6.2%) between 2 and 3 years before COVID-19 onset, and the aORs were 1.54 (1.20-1.98), 1.19 (0.84-1.70), and 1.00 (0.73-1.37), respectively. In conclusion, individuals who had an influenza infection less than 1 year before COVID-19 infection were at an increased risk of experiencing severe illness from the SARS-CoV-2 infection. To control the public health burden, it is essential that effective public health control measures, which include influenza vaccination, hand washing, cough etiquette, and mask use are in place.

Abbreviations: aOR: adjusted odds ratio; PCR: polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; NHIS: National Health Insurance Service; ICD-10: International Classification of Disease, Tenth Revision; RT–PCR: real-time polymerase chain reaction; ICU: intensive care unit; ECMO: extracorporeal membrane oxygenation; PS: propensity score; SMDs: standardized mean differences; CI: confidence interval; KDCA: Korea Disease Control and Prevention Agency; EUC: European Union Council

Introduction

Influenza virus infection has been a global public health priority for many years [1]. It is still a major cause of morbidity and mortality in many countries, and is frequently associated with respiratory symptoms [1,2]. In December 2019, a novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged as the causative pathogen of COVID-19. The clinical spectrum of SARS-CoV-2 infection ranges from asymptomatic infection to critical illness [3]. A global pandemic was declared in March 2020 [4]. On 1 January 2022,

approximately 300 million confirmed cases and 5.4 million deaths had been reported worldwide [5]. In particular, individuals who died because of COVID-19 experienced severe illness from this infection, and various risk factors for severe outcomes from COVID-19 have been reported [3,6,7].

The COVID-19 pandemic has placed onerous demands on public health systems [8]. Patients with severe COVID-19 infection should be admitted to hospital for careful monitoring because progressive respiratory failure develops in many patients with severe COVID-19 [8,9]. Severe COVID-19 may also lead to acute cardiac, renal, and hepatic injuries,

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cardiac arrhythmias, rhabdomyolysis, shock, thromboembolic complications as well as disorders of the central or peripheral nervous system [9]. This can overwhelm local healthcare resources resulting in shortages of trained staff, ventilators, renal-replacement treatment, and intensive care unit beds [8,9]. Therefore, it is necessary to evaluate and control the risk factors for the progression of COVID-19 to severe illness and prevent that progression.

Recent studies have suggested the possibility of influenza as a risk factor for severe illness from COVID-19 [10–15]. Sequential infection or co-infection with influenza virus and SARS-CoV-2 virus was reported to be associated with a severe course of SARS-CoV-2 [10–13]. Influenza vaccination was reported to lower susceptibility to SARS-CoV-2 infection and prevent progression to severe COVID-19 [14,15], making it possible to infer that influenza infection may be associated with severe COVID-19.

Very few studies have investigated the association between influenza infection and the severity of COVID-19 in the general population [16]. We hypothesized that influenza virus infection within 1 year of COVID-19 onset would be a risk factor for the development of severe COVID-19. The purpose of this population-based nationwide cohort study was to investigate whether influenza infection less than 1 year before COVID-19 onset was a risk factor that may contribute to the severity of COVID-19.

Methods

Patient and public involvement, data sources

This large-scale retrospective cohort study was conducted using the Korean National Health Insurance claim-based database. The National Health Insurance Service (NHIS) is a single insurer managed by the government and contains data from approximately 97% of the Korean population [17]. The Korean government covers the costs of diagnosis and treatment for individuals who meet the relevant criteria associated with COVID-19, encouraging the public to be tested for COVID-19 without delay. During the COVID-19 pandemic, the Korean government offered health insurance services to all Koreans with COVID-19. The NHIS provides a set of health information that includes the following: an eligibility database including data such as age, sex, socioeconomic status, level of income, and type of eligibility; a medical care institution database including data such as medical installation and institution; a medical treatment database with accounts submitted by medical practitioners for medical service expenditure; a health examination database with the results of general health examinations and questionnaires on lifestyle. The medical data for all patients who underwent SARS-CoV-2 testing were provided by the NHIS. In this dataset, we selected hospital records for COVID-19 patients, including death records, hospital visits, prescriptions, diagnostic records, and treatment records for the 3 years from 2017 to 2019. All patient records were anonymized before use.

Study population

We enrolled all patients who underwent SARS-CoV-2 testing between 20 January 2020 and 1 October 2020. An additional 3-month follow-up period was applied after October 1, 2020 to confirm whether severe illness from COVID-19 would develop in patients with confirmed COVID-19 within this period. Laboratory diagnosis of SARS-CoV-2 infection was defined as a positive result from real-time RT–PCR assay of nasal or pharyngeal swabs from patients with a history SARS-CoV-2 (U071) as defined using the International Classification of Disease, Tenth Revision (ICD-10). For each patient who underwent the SARS-CoV-2 test, the cohort entry date was the date of the first SARS-CoV-2 test. We combined claims data from the NHIS (NHIS -2022-1-382) and extracted age, sex, region of residence, and economic status from the insurance eligibility data. Using codes from the International Classification of Disease, Tenth Revision (ICD-10), patient data also included information on history of angina (I20), cancer (any C code), congestive heart failure (CHF, I43 and I50), chronic kidney disease (CKD, N18 and N19), myocardial infarction disease (MI, I21 and I22), diabetes mellitus (DM, E10–14), hypertension (HTN, I10–13, and I15), chronic lung disease (asthma or chronic obstructive pulmonary disease (COPD), J43–46), and chronic liver disease (K74, K703, and B18) where patients received at least two diagnoses within 1 year during the previous 3 years.

Definition

Based on the NHIS data, a history of influenza was defined as a person whose medical history included the diagnostic codes for influenza (J09–J11) during the 3-year period before the diagnosis of SARS-CoV-2. When individuals had a history of two or more influenza infections, the latest infection was included in the analysis. From the NHIS data, severe illness from COVID-19 infection was defined as an end result with one of the following conditions: 1) admission to an intensive care unit (ICU); 2) extracorporeal membrane oxygenation (ECMO) treatment; 3) use of a mechanical ventilator; or 4) death. Data on mortality (death) from COVID-19 were obtained from the NHIS data which included mortality data from the Korea Disease Control and Prevention Agency and Statistics Korea. Complicated influenza was defined as the diagnosis of influenza with any of the following: hospitalization, oxygen supply, dyspnoea, pneumonia, or acute exacerbation of the respiratory system.
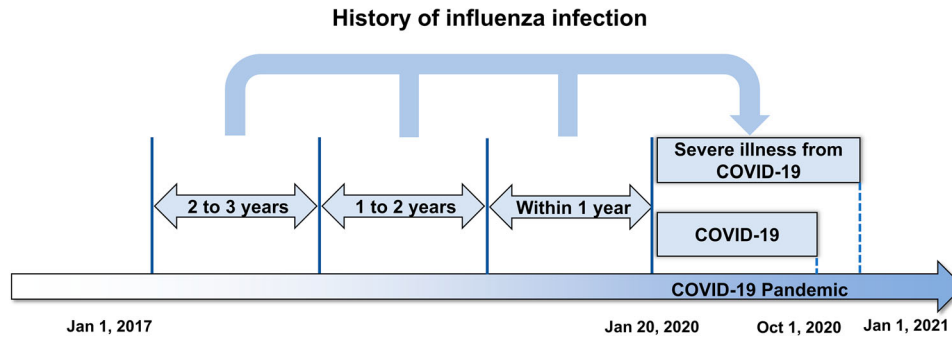
History of influenza infection

Figure 1. The influenza-positive group was classified into five subgroups according to history of influenza infection within 1 year, 1–2 years, 2–3 years before the onset of the COVID-19 pandemic.

Statistical analysis

Descriptive statistics included frequency analysis (percentages) for categorical variables and mean ± standard deviation or median and range for continuous variables. Categorical variables were compared using the Chi-squared test unless >20% of cells had a count <5, in which case Phi and Cramer's V test was used. Categorical and continuous variables were compared using standard mean difference (SMD).

To examine the association between severe illness from COVID-19 infection and history of influenza, we analyzed the data for the COVID-19 patients categorized into two groups. The first group had a history of influenza infection and the second had no history of influenza infection, with both groups having a positive SARS-CoV-2 PCR result during the COVID-19 pandemic. After performing PS matching with a 1:1 ratio between the influenza-positive group and the influenza-negative group, the influenza-positive group was classified into three subgroups based on history of influenza infection within 1 year, 1–2 years, and 2–3 years before the onset of the COVID pandemic (Figure 1). In addition, the influenza-positive group was divided into complicated and uncomplicated influenza groups, which were also classified into three subgroups based on a history of influenza infection within 1 year, 1–2 years, and 2–3 years before COVID-19 infection. Odds ratios (OR) for severe illness due to COVID-19 associated with influenza infection were estimated by year and complication. Among the SARS-CoV-2-tested patients, validated propensity score (PS) matching was performed to eliminate baseline characteristics and potential confounders. Age, sex, economic status, cancer type, hypertension, chronic kidney disease, diabetes mellitus, myocardial infarction, angina, congestive heart failure, chronic lung disease, and chronic liver disease were considered for PS matching using a "greedy nearest neighbour" algorithm with a 1:1 ratio. Confirmation of whether PS matching was successful was judged by the presence or absence of major imbalances at the baseline and standardized mean differences (SMDs) in each group. SMD values that were

<0.1 indicated low levels of covariate imbalances, which implies that the imbalance between covariates had been nullified [18].

The ORs were calculated using a multivariate logistic regression model. Unadjusted OR is a method of analysis that considers only two variables (independent and dependent variables) without considering any others, whereas adjusted OR (aOR) is an analytical procedure that considers all other variables. The OR and 95% confidence interval (CI) were calculated. A two-sided $P < 0.05$ was considered statistically significant. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) were used to analyze the results.

Sensitivity analysis

Sensitivity analysis was performed according to 1) matching ratio, and 2) matching variables. The matching ratio (influenza group vs non-influenza group) was set to 1:3, 1:2, or 1:1. We evaluated the robustness of the odds ratio according to the matching variables (minimally: age + sex + demography, 3 underlying diseases: minimally + HTN + DM + CKD matching, 4 underlying diseases: minimally + HTN + DM + CKD + lung diseases matching, 5 underlying diseases: minimally + HTN + DM + CKD + lung diseases + liver diseases matching, fully matching: minimally + HTN + DM + CKD + lung diseases + liver diseases + cardiac diseases (CHF + angina + MI) + any type of cancer matching). An additional sensitivity analysis was performed to assess the robustness of the results to unmeasured confounding using the E-value methodology [19]. This estimates what the relative risk would have to be for any unmeasured confounder to overcome the observed association of exposure to influenza with severe COVID-19 infection in our study.

Results

The final dataset included 274,126 patients tested for SARS-CoV-2, of whom 28,338 patients tested positive (Table 1, Figure 2). The baseline characteristics of the

Table 1. Demographic characteristics of patients in the Korean nationwide cohort who underwent SARS-CoV-2 testing.

	COVID-19-negative (n = 245,788)	COVID-19-positive (n = 28,338)
Age, years	47.16 ± 23.40	46.02 ± 21.92
<65	198,105 (80.6)	22,755 (80.3)
≥65	47,683 (19.4)	5,583 (19.7)
Sex		
Male	121,629 (49.5)	13,936 (49.2)
Female	124,159 (50.5)	14,402 (50.8)
Socioeconomic status		
High	81,802 (33.3)	8,851 (31.2)
Low	163,986 (66.7)	19,487 (68.8)
Underlying diseases		
History of angina	32,808 (13.3)	2,873 (10.1)
History of cancer	36,979 (15.0)	3,275 (11.6)
History of congestive heart failure	26,398 (10.7)	2,108 (7.4)
History of chronic kidney disease	32,710 (13.3)	3,155 (11.1)
History of myocardial infarction	8,911 (3.6)	945 (3.3)
History of diabetes mellitus	49,911 (20.3)	4,849 (17.1)
History of hypertension	71,725 (29.2)	7,144 (25.2)
History of chronic lung disease	59,998 (24.4)	5,818 (20.5)
History of chronic liver disease	21,722 (8.8)	2,158 (7.6)
Influenza infection	50,346 (20.5)	4,003 (14.1)

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

study cohort are presented in Table 1. Of the 28,338 patients with a positive SARS-CoV-2 test result, 4,003 had a history of influenza. For the remaining 24,335 patients with no history of influenza but with a positive SARS-CoV-2 test result, 4,003 were selected through 1:1 propensity score matching, and the two groups were compared (Table 2, Figure 2). After propensity score matching, there were no significant imbalances in demographics or clinical characteristics between the influenza-positive and influenza-negative groups (all SMDs < 0.1, Table 2).

There was a severe clinical outcome for COVID-19 infection in 260 patients (6.5%) with a history of influenza and 192 patients (4.8%) with no history of influenza (aOR 1.29, 95% confidence interval (CI) 1.04–1.59) (Table 2, Figure 3). In subgroup analysis, severe COVID-19 occurred in 143 cases (8.1%) with a history of influenza infection less than 1 year before COVID-19 infection Table 3; no influenza vs influenza within 1 year: aOR 1.54 (95% CI 1.20–1.98). A history of influenza infection in other periods was not significant for severe illness due to COVID-19 (Table 3). The aOR of complicated influenza infection was 3.00 (95% CI, 2.27–3.97): aOR of complicated influenza within 1 year before COVID-19 onset was 3.45 (95% CI, 2.49–4.79); aOR within 1–2 years was 2.73 (95% CI, 1.45–
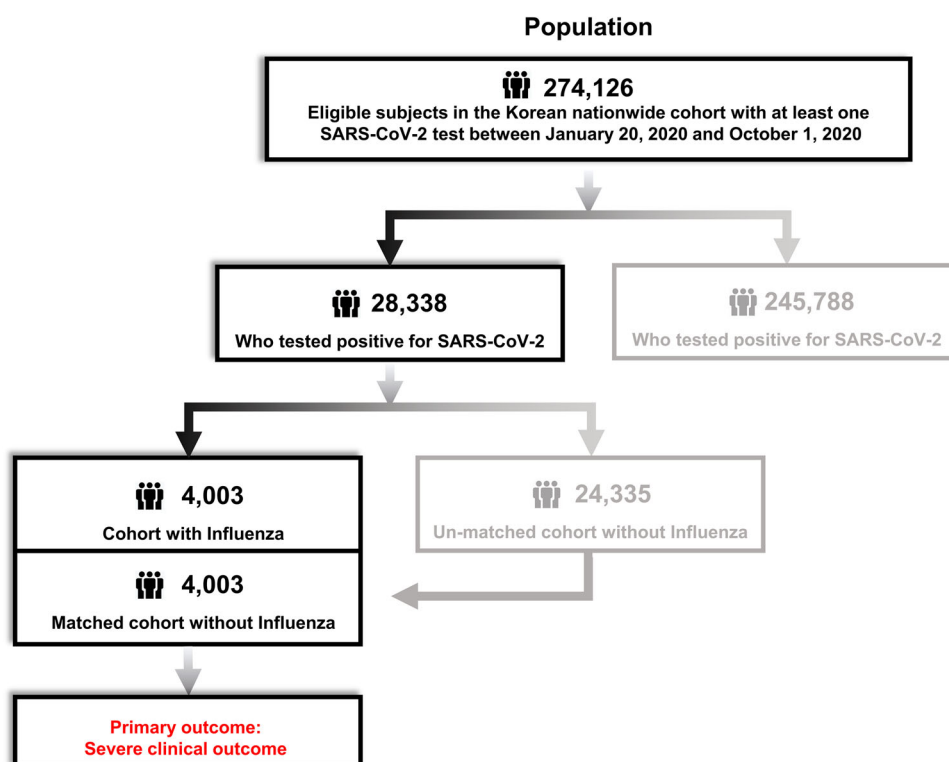

Figure 2. Distribution and flow chart of influenza and SARS-CoV-2 patients in a nationwide Korean cohort.

Table 2. Propensity score-matched baseline characteristics associated with severe illness from COVID-19 infection

	Influenza-negative (n = 4,003)	Influenza-positive (n = 4,003)	SMD
Age, years			0.038
≥ 65	524 (13.1)	544 (13.6)	
<65	3,479 (86.9)	3,459 (86.4)	
Sex			0.005
Male	1,860 (46.5)	1,869 (46.7)	
Female	2,143 (53.5)	2,134 (53.3)	
Socioeconomic status			0.007
Low	2,680 (66.9)	2,694 (67.3)	
High	1,323 (33.1)	1309 (32.7)	
Underlying diseases			
History of angina	268 (6.7)	317 (7.9)	0.047
History of cancer	318 (7.9)	398 (9.9)	0.07
History of congestive heart failure	226 (5.6)	267 (6.7)	0.043
History of chronic kidney disease	326 (8.1)	385 (9.6)	0.052
History of myocardial infarction	107 (2.7)	131 (3.3)	0.035
History of diabetes mellitus	408 (10.2)	493 (12.3)	0.067
History of hypertension	623 (15.6)	700 (17.5)	0.052
History of chronic lung disease	1,153 (28.8)	1,192 (29.8)	0.021
History of chronic liver disease	259 (6.5)	307 (7.7)	0.047
Severe illness from COVID-19	192 (4.8)	260 (6.5)	0.074
Adjusted OR*	1 (reference)	1.29 (1.04 - 1.59)	

Data are presented as mean ± SD or number (%). SMD, standardized mean difference.
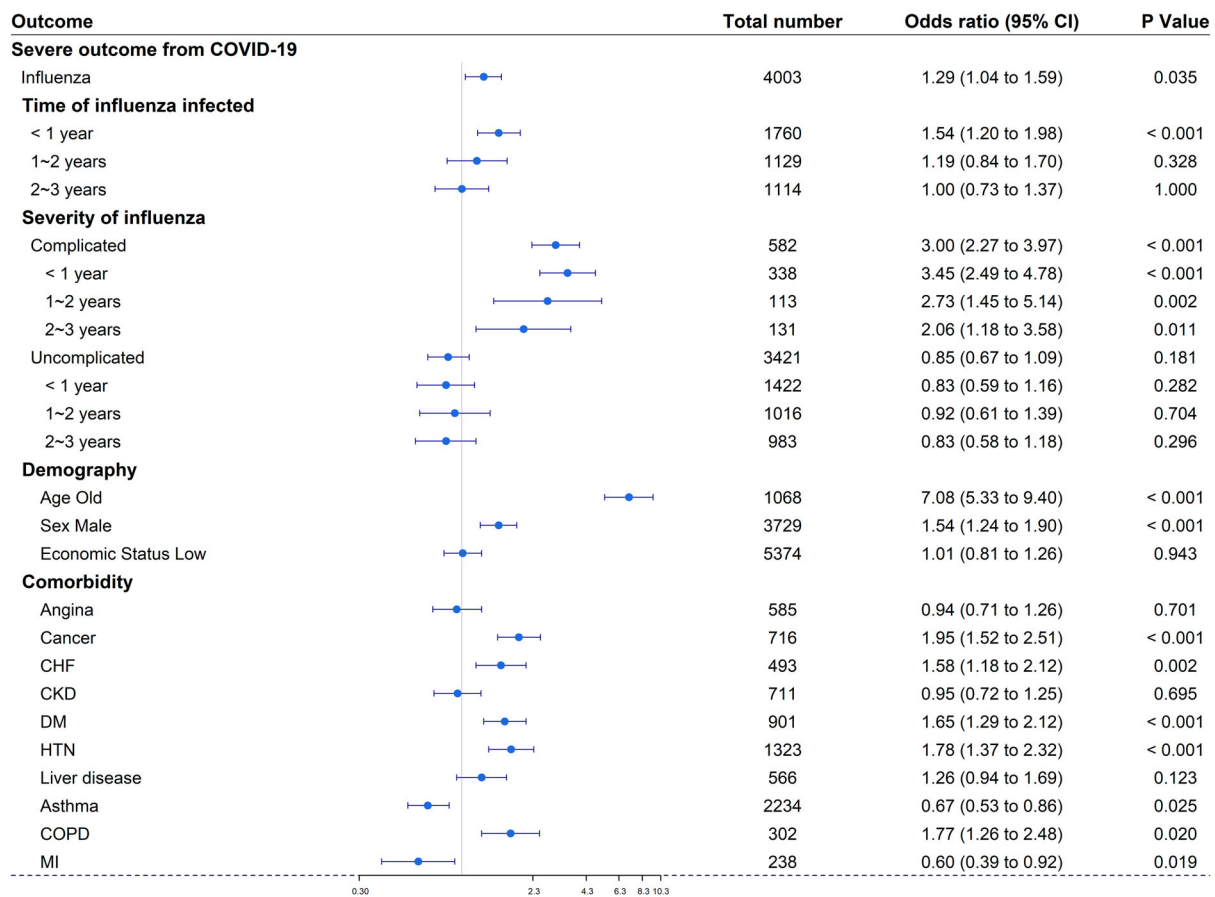* Adjusted by age, sex, socioeconomic status, and underlying diseases.

Outcome	Total number	Odds ratio (95% CI)	P Value
Severe outcome from COVID-19			
Influenza	4003	1.29 (1.04 to 1.59)	0.035
Time of influenza infected			
< 1 year	1760	1.54 (1.20 to 1.98)	< 0.001
1~2 years	1129	1.19 (0.84 to 1.70)	0.328
2~3 years	1114	1.00 (0.73 to 1.37)	1.000
Severity of influenza			
Complicated	582	3.00 (2.27 to 3.97)	< 0.001
< 1 year	338	3.45 (2.49 to 4.78)	< 0.001
1~2 years	113	2.73 (1.45 to 5.14)	0.002
2~3 years	131	2.06 (1.18 to 3.58)	0.011
Uncomplicated	3421	0.85 (0.67 to 1.09)	0.181
< 1 year	1422	0.83 (0.59 to 1.16)	0.282
1~2 years	1016	0.92 (0.61 to 1.39)	0.704
2~3 years	983	0.83 (0.58 to 1.18)	0.296
Demography			
Age Old	1068	7.08 (5.33 to 9.40)	< 0.001
Sex Male	3729	1.54 (1.24 to 1.90)	< 0.001
Economic Status Low	5374	1.01 (0.81 to 1.26)	0.943
Comorbidity			
Angina	585	0.94 (0.71 to 1.26)	0.701
Cancer	716	1.95 (1.52 to 2.51)	< 0.001
CHF	493	1.58 (1.18 to 2.12)	0.002
CKD	711	0.95 (0.72 to 1.25)	0.695
DM	901	1.65 (1.29 to 2.12)	< 0.001
HTN	1323	1.78 (1.37 to 2.32)	< 0.001
Liver disease	566	1.26 (0.94 to 1.69)	0.123
Asthma	2234	0.67 (0.53 to 0.86)	0.025
COPD	302	1.77 (1.26 to 2.48)	0.020
MI	238	0.60 (0.39 to 0.92)	0.019

Figure 3. Propensity score-matched association between influenza and severe clinical outcomes of COVID-19 in patients who tested positive for SARS-CoV-2. Sensitivity analysis was performed according to 1) matching ratio, 2) matching variables (minimally: age + sex + demography, 3 underlying diseases: minimally + HTN + DM + CKD matching, 4 underlying diseases: minimally + HTN + DM + CKD + lung diseases matching, 5 underlying diseases: minimally + HTN + DM + CKD + lung diseases + liver diseases matching, fully matching: minimally + HTN + DM + CKD + lung diseases + liver diseases + cardiac diseases (CHF + angina + MI) matching). (Abbreviations: HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CHF, congestive heart failure; MI, myocardial infarction).

5.14); aOR within 2–3 years before COVID19 onset was 2.06 (95% CI, 1.18–3.58) (Figure 3). In addition to a history of influenza infection within 1 year, age

(aOR 7.08, 95% CI 5.33–9.40), male sex (aOR 1.54, 95% CI 1.24–1.90), cancer (aOR 1.95, 95% CI 1.52-2.51), HTN (aOR 1.78, 95% CI 1.37–2.32), COPD

Table 3. Propensity score-matched adjusted ORs for the risk of severe illness from COVID-19 in patients with previous influenza infection

	No influenza (n = 4,003)	Previous influenza infection before COVID-19 (n = 4,003)		
		Within 1 year (n = 1,760)	1–2 years (n = 1,129)	2–3 years (n = 1,114)
Event of severe illness from COVID-19	260 (6.5%)	143 (8.1%)	48 (4.3%)	69 (6.2%)
Adjusted OR*	1 (reference)	1.54 (1.20-1.98)	1.19 (0.84-1.70)	1.00 (0.73-1.37)
P-value		< 0.001	0.328	1.000
E-value		2.45	1.00	1.00

Data are presented as number (%) or odds ratios (95% confidence interval).
* Adjusted by age, sex, socioeconomic status, and underlying diseases.

(aOR 1.77, 95% CI 1.26-2.48), diabetes mellitus (aOR 1.65, 95% CI 1.29–2.12), congestive heart failure (aOR 1.58, 95% CI 1.18–2.12), and myocardial infarction (aOR 0.60, 95% CI 0.39–0.92) were independently associated with severe illness from COVID-19 infection (Figure 3).

Sensitivity analysis showed the robustness of our results regarding influenza within 1 year before the onset of COVID-19, which did not change according to matching ratio or matching variables (Figure 4). The E-values and lower CI limit for unmeasured confounders between influenza within 1 year and severe illness from COVID-19 were 2.45 and 1.69, respectively.

Discussion

Principal findings

The objective of this population-based nationwide cohort study was to investigate whether a history of influenza infection within 1 year before COVID-19 infection was a risk factor for severe illness from COVID-19. This is the first attempt to evaluate the impact of recent influenza viral infections on the severity of COVID-19 infection in the general population. Our study showed that influenza infection within the year before COVID-19 infection was a risk factor for severe COVID-19 illness. Our study suggests that recent influenza viral infection may contribute to the disease burden of COVID-19.

Findings in relation to other studies

Several studies have reported co-infection or sequential infection from SARS-CoV-2 and influenza during the COVID-19 pandemic. In animal studies using mice, ferrets, and hamsters, sequential SARS-CoV-2 infection after influenza A/H1N1 resulted in the aggravation of pneumonia and increased mortality compared with mono-infection, which demonstrated that host immunity-dependent COVID-19 symptoms could be aggravated by prior influenza A/H1N1 infection [11,12]. Simultaneous co-infection or sequential short-term interval co-infection with influenza before SARS-CoV-2 infection resulted in a lower SARS-CoV-2 viral load, and it was thought that there may be viral interference [11,12]; however, in sequential long-term
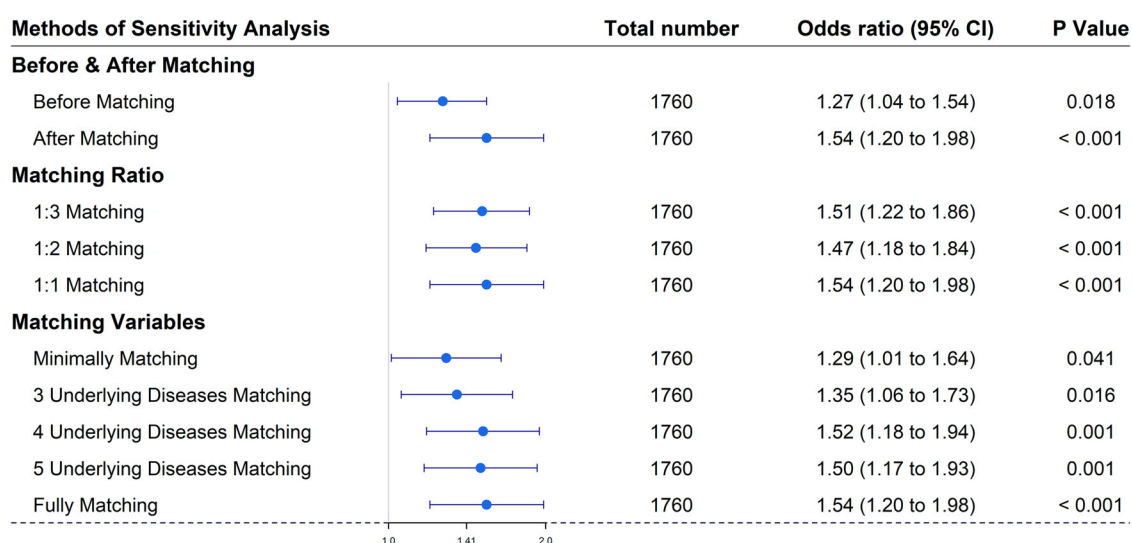
Methods of Sensitivity Analysis	Total number	Odds ratio (95% CI)	P Value
Before & After Matching			
Before Matching	1760	1.27 (1.04 to 1.54)	0.018
After Matching	1760	1.54 (1.20 to 1.98)	< 0.001
Matching Ratio			
1:3 Matching	1760	1.51 (1.22 to 1.86)	< 0.001
1:2 Matching	1760	1.47 (1.18 to 1.84)	< 0.001
1:1 Matching	1760	1.54 (1.20 to 1.98)	< 0.001
Matching Variables			
Minimally Matching	1760	1.29 (1.01 to 1.64)	0.041
3 Underlying Diseases Matching	1760	1.35 (1.06 to 1.73)	0.016
4 Underlying Diseases Matching	1760	1.52 (1.18 to 1.94)	0.001
5 Underlying Diseases Matching	1760	1.50 (1.17 to 1.93)	0.001
Fully Matching	1760	1.54 (1.20 to 1.98)	< 0.001

Figure 4. Sensitivity analysis was performed according to 1) matching ratio, 2) matching variables (minimally: age + sex + demography, 3 underlying diseases: minimally + HTN + DM + CKD matching, 4 underlying diseases: minimally + HTN + DM + CKD + lung diseases matching, 5 underlying diseases: minimally + HTN + DM + CKD + lung diseases + liver diseases matching, fully matching: minimally + HTN + DM + CKD + lung diseases + liver diseases + cardiac diseases (CHF + angina + MI) matching). (Abbreviations: HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CHF, congestive heart failure; MI, myocardial infarction)

interval co-infection with influenza before corona-virus infection, some coronavirus replication was detectable. Ultimately, simultaneous or sequential co-infection with influenza and SARS-CoV-2 leads to more severe disease [11,12,20]. This could be explained by the fact that influenza virus increases the expression of ACE2 in small airway epithelial cells and alveolar type II cells, and SARS-CoV-2 infection in small airways and alveolar epithelium results in compromised respiratory states such as pneumonia or ARDS [21].

ACE2 acts as a receptor for SARS-CoV-2 to enter host cells [22]. Therefore, higher ACE2 expression plays a significant causal role in the susceptibility and severity of COVID-19 [23]. Influenza virus increases the expression of ACE2 in nasal epithelium and lung tissue, such as small airway epithelial cells and alveolar type 2 cells, through the interferon (IFN) signalling response associated with type 1 IFN (IFN α and β) and type 2 IFN (IFN γ) [21,24–26]. In addition, influenza viral infection can progress beyond the acute phase inflammation of a self-limited course reco-vering in 3–7 days to the post-influenza chronic pul-monary inflammation state. The following research results provide evidence for this: cells that have survived for a long period after acute influenza viral infection showed a robust transcriptional response to viral infec-tion, increased interferon stimulation and response, and increased levels of pro-inflammatory cytokines despite viral clearance [27]; the acute phase of viral infection switched to a form of chronic lung disease (airway inflammation, mucus production, hyper-reac-tivity, fibrosis, and emphysema) associated with long-term persistence (105 days) of remnant active viral RNA in lung tissue [28]; long-term IFN-γ/IL-10 produ-cing T cells were observed for more than 95 days after influenza infection [29]. Post-influenza chronic viral inflammation presents not only type 2 inflammation related to IL-13, which reduces the expression of ACE2 [24,28], but also type 1 inflammation associated with IL-10 and IFN-γ, which increases the expression of ACE2 [29–32]. Other studies have reported that epi-thelial cells expressing interferon stimulating genes (ISG) survive infection in both influenza A and B infec-tions [27,33,34]. Therefore, post-influenza viral chronic inflammation is estimated to be similar to the type 1 inflammatory signature [35]. The switch from acute influenza viral infection to post-viral chronic inflam-mation is dependent on the initial viral dose, so the more severe the acute infection, the more likely it was to progress to chronic lung disease [28,35]. In our data, the significant aOR value of 1.54 (95% CI: 1.20–1.98) for influenza infection within the 1 year before COVID-19 onset supports the above mechanism.

In comorbidities associated with severe SARS-CoV-2 infection, ACE2 levels increase in the lungs of patients with COPD and smokers [36,37]. Immune cell alterations, such as the increase in type 1 and type 2 IFN receptors, and the epithelial immune response, such as the increase in type 1 and type 2 IFN and ISG, were observed in patients with COPD [38]. The IFN response associated with the ACE2 increase in COPD is similar to that observed in influenza viral infections [26]. Therefore, ACE2 expressed in the res-piratory tract by the influenza virus might be main-tained for a relatively long period together with post-viral chronic pulmonary inflammation, similar to what occurs in patients with COPD. In the presence of increased ACE2 levels caused by influenza infec-tion, patients are more susceptible to SARS-CoV-2 infection and more likely to progress to severe COVID-19 [23]. Considering that the above processes are viral dose-dependent, even with influenza viral clearance, severe COVID-19 is more likely to occur in patients with severe influenza infection than in those with asymptomatic or mild influenza infection, accompanied by a chronic inflammatory process with increased ACE2. This is supported by our finding that the complicated influenza group, particu-larly those infected less than 1 year before COVID-19 infection, had a higher incidence of severe COVID-19 than the uncomplicated influenza group. However, in the context of viral infection, the role of IFN signalling has been the subject of much debate, with both protec-tive and deleterious effects documented in different experimental systems and clinical settings [39]. At pre-sent, the interaction between type 1 and type 2 inflam-mation with respect to influenza infection is not understood, and how type 1 and type 2 inflammation change and progress over time in lung tissue. It is also not known whether the increase in ACE2 caused by influenza in the respiratory tract can be sustained for a long period or continue chronically beyond the acute phase. Further studies are required to identify the relationship between recent influenza infection and severe COVID-19.

Implications for policy and practice

SARS-CoV-2 and influenza viruses will co-exist or co-circulate in the general population in the future [40]. If this is the case, the control of influenza infection could be an important method for preventing severe illness from SARS-CoV-2 infection [40]. It is already known that influenza vaccination is one of the best interventions to prevent influenza. Recently, it was reported that influenza vaccination can help prevent severe COVID-19, although the mechanism is unclear [14,15]. Considering the results of our study, direct prevention of influenza virus infection by vaccination may be another mechanism for preventing the pro-gression of COVID-19 to severe illness. The results of our study serve as important evidence confirming the results from other studies that showed that

influenza vaccination may reduce the mortality from COVID-19 and may prevent the progression to severe COVID-19 illness [14,15]. Therefore, it is necessary to maintain and encourage policies to increase influenza vaccination rates in the elderly, especially chronically ill or immunocompromised patients.

In addition to influenza vaccination, public health measures are required to effectively control concurrent influenza and SARS-CoV-2 viral infections [40]. Multiple public health interventions such as hand hygiene, cough etiquette, staying at home with respiratory symptoms, and universal mask use in public places, already implemented in Korea to prevent the spread of COVID-19 during the 2019–2020 influenza season, resulted in early termination of influenza and a substantial decrease in seasonal influenza activity along with containment of the spread of COVID-19 [41]. Non-pharmaceutical interventions (NPIs) and behavioural changes in China and the United States play a role in reducing influenza activity [42]. Co-circulating influenza and SARS-CoV-2 may result in a greater health burden on hospital and community capacities and resources than has been experienced during the current COVID-19 pandemic [40]. Therefore, beyond the current epidemic wave of COVID-19, public health measures to control influenza activity, such as hand washing, cough etiquette, mask wearing, and vaccination, are important tools to reduce the risk of progression to severe illness from COVID-19 infection, which increases the burden on the public healthcare system.

Strengths and weaknesses of this study

The strength of this study is that it includes a large cohort formed from the general population in Korea within 10 months before the onset of the COVID-19 pandemic so that the relationship between influenza and SARS-CoV-2 can be evaluated. The 3 T strategy (testing, tracing, and treatment) has been established as an important measure for COVID-19 prevention and control in the Republic of Korea. In this strategy, the COVID-19 diagnostic test plays a major role because early and rapid detection is important to prevent the SARS-CoV-2 infection from spreading [43,44]. The Korean government has made efforts to increase access to diagnostic tests by opening up screening stations where suspected cases could be promptly diagnosed. The maximum daily testing capacity increased from 3000 individuals in February 2020 to approximately 20,000 individuals in April 2020, and real-time RT-PCR tests for SARS-CoV-2 were performed by national central laboratories and 95 non-governmental clinical laboratories [43,45]. Therefore, rapid and widespread PCR testing has been conducted to detect confirmed cases at a relatively early stage of the pandemic. The results of this study were derived from a cohort of approximately 300,000 individuals from the NHIS during the first 10 months of the COVID-19 pandemic.

This study had several limitations. First, we did not evaluate whether influenza vaccination reduced the severity of COVID-19 illness. As we could not access individual histories of influenza vaccination in the Korean NHIS claim-based database, we could not confirm the influenza vaccination history. However, the influenza vaccination rate in the entire population of Korea was low at less than 40%, and the prevalence in elderly patients aged ≥65 who had a > 80% rate of influenza vaccination was less than 20% in this study [46]. Therefore, it is estimated that the influence of influenza vaccination did not significantly affect the results of our study.

Second, we did not fully address selection bias because we did not include patients with asymptomatic or mild influenza infection who did not receive health care. We retrospectively analysed data from individuals diagnosed with influenza held by the National Health Insurance Service. There was a limitation in confirming whether influenza was present in individuals who did not receive medical care. As yet, there have been no research results on the incidence of asymptomatic influenza patients in Korea; however, the seasonal incidence of symptomatic influenza in the United States was reported to be approximately 8% and varied from 3% to 11% among seasons [47]. Therefore, almost 90% of patients with influenza may be asymptomatic. In a prospective cohort study conducted in South Africa, approximately half of the influenza infections were asymptomatic [48]. In addition, in a meta-analysis, estimates of the asymptomatic fraction in outbreak investigations fell within the range of 4% to 28%, with a mean of 16% (95% CI: 13%, 19%) [49]. Estimates of the asymptomatic fraction based on cohort studies without adjustment for other illnesses were spread over a wide range from 0% to 100%, and estimates from studies adjusted for background illnesses ranged from 65% to 85% [49]. Therefore, at present, there is no established range for the proportion of asymptomatic patients with influenza viral infection.

The actual asymptomatic fraction of influenza virus infections can be affected by the study design, the definitions of infection and symptomatic illness, the influenza type, the vaccination status, and the age stratification of patients [49]. There may have been a selection bias in which asymptomatic patients were not included in this study, but there will be limitations in assessing the extent to which this has influenced the results of our study. Almost all Koreans (97%) are enrolled in the National Health Insurance Service, and most receive medical treatment at least once a year [17]. The greatest advantage of these data is that they include virtually the entire population [17].

According to a domestic study on the patient's perspective of common cold and health care utilization, when Koreans detected the symptoms of upper respiratory infection (URI), 90% of them took medication, and approximately 60% of all patients visited the primary care clinic and 40% visited the pharmacy [50]. In particular, people were more likely to visit a physician if they experienced typical URI-related symptoms such as fever, cough, sore throat, rhinorrhea, or if any URI-related symptoms were prolonged [50]. Therefore, although our study did not include asymptomatic individuals or some patients with mild symptoms who did not receive medical care, it was judged that most patients with influenza symptoms were included in this study, even if they had mild symptoms.

Third, we did not adjust for additional unmeasured confounding factors, such as smoking, immunosuppression, and pregnancy, although we included histories of malignancy, diabetes mellitus, angina, myocardial infarction, and chronic kidney disease, which are associated with these factors. Therefore, we calculated the E-value for unmeasured confounders. We found that the observed OR of 1.54 with a 95% CI of 1.20-1.98 could be explained by an unmeasured confounder that was associated with both influenza infection less than 1 year before COVID-19 onset and risk of incident severe illness from COVID-19 by a risk ratio of 2.45 (CI of 1.69), above and beyond the measured confounders, but weaker confounding would not do so. The CI could be moved to include the null by an unmeasured confounder that was associated with both influenza infection less than 1 year before COVID-19 onset and risk of incident severe illness from COVID-19 by a risk ratio of 1.69-fold, above and beyond the measured confounders, but weaker confounding would not do so. In this study, it seems plausible to have an unmeasured confounder with a strong association with both influenza infection less than 1 year before COVID-19 onset and risk of incident severe illness from COVID-19, especially given that the E-value of 2.45 (CI of 1.69) is very similar to or less than that observed for well-known risk factors for severe illness from COVID-19, such as old age, cancer, and HTN. Because the OR of old age is 7.08, which is greater than 2.45, and the OR values of cancer, HTN, and COPD are greater than 1.69, the E-value of 2.45 is relatively modest.

Conclusions

Influenza infection less than a year before SARS-CoV-2 infection is a risk factor for severe illness from SARS-CoV-2 infection. Therefore, effective public health control strategies to minimize the influenza burden, such as hand washing, cough etiquette, and mask wearing, as well as influenza vaccination, should be in place to minimize the enormous impact on the healthcare system at a time of co-existence of influenza and SARS-CoV-2 infections.

Data availability statement

The datasets analyzed in this study are stored in the Korean National Health Insurance claim-based database. The data will be made available for research on reasonable request and with permission from the National Health Insurance Service (NHIS) (NHIS-2022-1-382).

Disclosure statement

No potential conflict of interest was reported by the author (s).

Ethics statements

This study was approved by the Institutional Review Board (IRB) of Jeonbuk National University Hospital (No. 2020-04-067).

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