

The Severity of COVID-19 in Patients with Nonalcoholic Fatty Liver Disease in Korea

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Background: Early identification of patients who are highly likely to develop severe illness among confirmed cases of coronavirus disease 19 (COVID-19) can be expected to lead to effective treatment. This study therefore aimed to determine whether the presence of nonalcoholic fatty liver disease (NAFLD) has an impact on the exacerbation of COVID-19 symptoms.

Methods: The study used the Korean National Health Insurance claim data for treatment of COVID-19 patients in 2020. NAFLD includes nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). The outcome variables used were hospitalization and the use of medical devices. Hospitalization was defined by a length of stay exceeding one day and the use of medical devices was defined as one or more uses of a ventilator or extracorporeal membrane oxygenation. Multivariable logistic regression analysis was performed to determine if there was a difference in the hospitalization and use of medical devices of COVID-19 patients depending on the presence of NAFLD.

Results: The odds ratio of hospitalization was 1.059, indicating slightly higher odds of hospitalization for patients with NAFL or NASH compared to those without the conditions, but it was not statistically significant (0.969-1.156). On the other hand, the odds ratio of use of medical devices was high at 1.667 and was statistically significant (1.111-2.501).

Conclusion: The study results found NAFLD to be a risk factor that can exacerbate symptoms in COVID-19 patients. Accordingly, it is necessary to identify NAFLD patients through preemptive screening and provide them with appropriate treatments.

Keywords: COVID-19; Non-alcoholic fatty liver disease; Severity; Hospitalization; Equipment and supplies; Korea

INTRODUCTION

Ever since the first case of coronavirus disease 19 (COVID-19) in 2019, health authorities around the world have put prevention of the spread of COVID-19 and treatment of confirmed COVID-19 cases as their first priority. Korea saw its first confirmed case of COVID-19 on January 20, 2020, followed by a rapid spread in the local communities, and has been working since then to find effective response measures against COVID-19 outbreaks with limited resources [1,2]. Up to March 2020, in the early stages of the COVID-19 pandemic, all COVID-19 patients in Korea were quarantined and treated in medical institutions. However, when a rapid spread in the local communities

led to a shortage of negative pressure rooms, the guidelines were changed to quarantine asymptomatic patients or patients with mild symptoms who did not need special care in residential treatment centers while quarantining and treating severely ill patients and those who were highly likely to become severely ill in medical institutions [3].

A few pharmaceutical companies successfully developed COVID-19 vaccines in early 2020, but due a highly competitive race among countries to procure the vaccines, the Korean government faced a temporary difficulty in securing a supply of vaccines [4]. COVID-19 is characteristic in that young people or a population without any underlying conditions experience very mild symptoms

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[5]. Therefore, the Korean government decided to first vaccinate populations with high mortality rates when infected with COVID-19. Such a situation highlighted the need to accurately classify patients with a high likelihood of developing severe illness when infected with COVID-19 [6].

In general, socioeconomic status, such as sex, age and income level, are well known risk factors for exacerbating disease severity and so does for COVID-19 cases [7,8]. Various chronic conditions such as hypertension, chronic lung disease, and heart disease have been identified as factors that adversely affect the prognosis of COVID-19 [9,10]. Obesity and metabolic disease are also known as manageable risk factors related to poor prognosis of COVID-19 [11,12]. Nonalcoholic fatty liver disease (NAFLD) is considered a hepatic manifestation of metabolic syndrome, which includes obesity, insulin resistance, diabetes, hypertension, and hyperlipidemia [13]. NAFLD covers a wide range of categories, from simple fat accumulation in the liver of patients without excessive alcohol consumption to liver fibrosis and inflammation, and even more advanced steatosis which is associated with liver cirrhosis and liver cancer. Nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) are also types of NAFLD [14,15]. NAFLD is a common chronic liver disease prevalent in 25% of the global adult population and its prevalence is expected to rise gradually [16]. According to a previous study, the prevalence of NAFLD in Korea is also high at 30.3% [17].

According to a recently published study, NAFLD in COVID-19 patients increased the risk of poor prognosis [18]. NAFLD patients are known to have more comorbidities than the general population, and these effects may be associated with the exacerbation of COVID-19 symptoms [19]. A previous study found that the severity of illness increased in young COVID-19 patients under the age of 60 if they had NAFLD [20]. Another study found that the presence of NAFLD in non-diabetic patients was associated with the exacerbation of COVID-19 symptoms [21]. These findings suggest that NAFLD is a factor that can independently predict the exacerbation of COVID-19 even after adjusting for other risk factors [22].

However, there still is a limited number of studies which evaluate the impact of NAFLD on the prognosis of COVID-19 [19]. Moreover, most studies did not correct for the presence of other underlying conditions such as hypertension which have a negative on the prognosis of COVID-19 [23]. To the best of the authors' knowledge,

this is the first related study on the Korean population with national level long-term data [17]. This study therefore aimed to determine, in the Korean population, whether the presence of NAFLD is associated with the development of severe illness in COVID-19 patients.

METHODS

1. Study data

This study used the claim specifications of national health insurance (NHI) and medical aid beneficiaries submitted to the Health Insurance Review and Assessment Service (HIRA) in Korea to analyze the healthcare usage of COVID-19 patients in Korea. NHI and medical aid are public insurances whose membership is compulsory for all Korean citizens, and the Korean government is utilizing the insurance funds to support screening and treatment of COVID-19 patients. This study used the treatment data from January 20, 2020, when the first case of COVID-19 occurred in Korea, to December 31, 2020, and only the data of cases whose claims review was finalized by March of the following year was included. As this study used de-identified claims data and there is no risk of data breach of study subjects' personal information or bodily harm to the study subjects, exemption of review was granted by the HIRA Institutional Review Board.

2. Study subjects

Patients who were hospitalized or received outpatient treatments with "coronavirus disease 2019, virus identified (U07.1)" as the principal diagnosis or first sub-diagnosis were defined as confirmed cases of COVID-19. In 2020, all COVID-19 patients over the age of 65, who are highly likely to develop severe illness, were hospitalized regardless of the severity of their conditions. Since this study used hospitalization as one of the main dependent variables to evaluate whether COVID-19 patients with NAFL or NASH have a high likelihood of developing severe illness, patients over the age of 65 were excluded from the study subjects to preclude any confusion due to age.

3. Dependent variables

1) Hospitalization

Hospitalization is a variable that can estimate the severity of a patient's condition as it is recommended for severely ill patients who would have difficulty recovering with outpatient treatment. In general, a case with a length of stay exceeding one day is considered an inpatient case. Korea, however, classified patients depending on the severity of illness; patients with mild symptoms were quarantined and treated in residential treatment centers while severely ill patients were quarantined and treated in medical institutions. Therefore, out of the cases with a length of stay exceeding one day, those which incurred residential treatment center management fees (AH351, AH352, AH353) were excluded from the hospitalization cases.

2) Use of medical devices

The use of medical devices was used as another method to estimate the severity of a COVID-19 patient's condition. Considering the characteristics of COVID-19, whose severe cases are accompanied by respiratory symptoms such as pneumonia and decreased oxygen saturation, extracorporeal membrane oxygenation (ECMO), and ventilators were selected as the medical devices for analysis. The use of medical devices was defined as one or more uses of ECMO or a ventilator during the hospitalization period.

4. Variable of interest

NAFL/NASH: This study intended to determine whether patients with NAFL or NASH before COVID-19 infection developed severe illness when infected with COVID-19. Therefore, patients diagnosed with NAFL (K76.0) or NASH (K75.8) as a principal diagnosis or sub-diagnosis from January to December 2019, before the outbreak of COVID-19, were defined as having NAFL or NASH.

5. Control variables

The analysis was corrected for the patient's sex, age, Charlson comorbidity index (CCI), presence of hypertension, and type of insurance, which are known to influence the severity of illness and healthcare usage of COVID-19 patients.

CCI is a leading tool for assessing the severity of a patient's illness from administrative data such as health insurance claim data, which is lacking in clinical information. If a patient's inpatient or outpatient claim specifications from the 2 years preceding the study period

included the 19 diseases used to determine CCI, each disease included was given a weighted value of 1 to 6 in the analysis. A larger value indicates a greater number or greater severity of underlying conditions.

A patient was defined as having hypertension if there were claims for codes I10 to I13 as a principal diagnosis or sub-diagnosis included in the inpatient or outpatient claim specifications from the 2 years preceding the study period. Insurance types were classified into NHI and medical aid.

6. Analysis method

In this study, chi-square tests and *t*-tests were performed to evaluate general differences in the characteristics of COVID-19 patients depending on the presence of NAFL/NASH. In addition, multivariable logistic regression analysis was performed to check for any difference in the hospitalization and medical devices use of COVID-19 patients due on the presence of NAFL/NASH, when corrected for the control variables. All statistical analyses were performed using SAS Enterprise Guide ver. 7.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Table 1 shows the general characteristics of the study subjects. A total of 54,306 confirmed cases of COVID-19 were included and 2,214 (4.08%) of them had NAFL or NASH. Compared to patients who did not have NAFL or NASH (NO), patients with either of the conditions (NAD) were older (NAD: 49.36, NO: 38.55) and had higher CCI (NAD: 0.90, NO: 0.48). Prevalence of NAD was higher among patients with hypertension (yes: 11.24%, no: 3.10%) and medical aid patients (medical aid: 7.00%, NHI: 3.95%).

The odds ratio of hospitalization was 1.059, indicating slightly higher odds of hospitalization for patients with NAFL or NASH compared to those without the conditions, but it was not statistically significant (0.969–1.156) (Table 2). The odds ratio of use of medical devices was high at 1.667 and was statistically significant (1.111–2.501). Males had higher odds of being hospitalized (1.089) or using medical devices (2.492) than females, and were statistically significant.

Table 1. General characteristics of study populations

Characteristic	Total	NAFL or NASH		p-value
		Yes	No	
Sex				
Man	25,851 (47.60)	1,091 (4.22)	24,760 (95.78)	0.107
Woman	28,455 (52.40)	1,123 (3.95)	27,332 (96.05)	
Age (yr)	38.99±16.54	49.36±12.23	38.55±16.56	<0.001
CCI	0.50±0.85	0.90±1.12	0.48±0.83	<0.001
Hypertension				
Yes	6,519 (12.00)	733 (11.24)	5,786 (88.76)	<0.001
No	47,787 (88.00)	1,481 (3.10)	46,306 (96.90)	
Insurance type				
Medical aid	2,258 (4.16)	158 (7.00)	2,100 (93.00)	<0.001
NHI	52,048 (95.84)	2,056 (3.95)	49,992 (96.05)	
Inpatient				
Yes	21,918 (40.36)	1,086 (4.95)	20,832 (95.05)	<0.001
No	32,388 (59.64)	1,128 (3.48)	31,260 (96.52)	
Medical devices				
Yes	223 (0.41)	28 (12.56)	195 (87.44)	<0.001
No	54,083 (99.59)	2,186 (4.04)	51,897 (95.96)	
Total	54,306 (100.00)	2,214 (4.08)	52,092 (95.92)	

Values are presented as number of cases (%) or mean±standard deviation. This table is the result of the chi-square tests and t-tests. The use of medical devices was defined as one or more uses of a ventilator or extracorporeal membrane oxygenation.

NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; CCI, Charlson comorbidity index; NHI, national health insurance.

Table 2. Adjusted odds ratio for hospitalization and using medical devices among coronavirus disease 2019 patients

Variable	Adjusted odds ratio (95% CI)	
	Hospitalization	Using medical devices
NAFL or NASH		
Yes	1.059 (0.969–1.156)	1.667 (1.111–2.501)
No	1.00	1.00
Sex		
Man	1.089 (1.051–1.128)	2.492 (1.877–3.309)
Woman	1.00	1.00
Age	1.026 (1.024–1.027)	1.128 (1.106–1.150)
CCI	0.991 (0.971–1.013)	1.094 (0.981–1.220)
Hypertension		
Yes	1.196 (1.130–1.265)	1.650 (1.249–2.180)
No	1.00	1.00
Insurance type		
Medical aid	1.789 (1.638–1.954)	1.554 (1.023–2.360)
NHI	1.00	1.00
C-statistic	0.632	0.870

This table is the result of the multivariable logistic regression analysis. Adjusted odds ratios were adjusted for NAFL or NASH, sex, age, CCI, hypertension, and insurance type. The use of medical devices was defined as one or more uses of a ventilator or extracorporeal membrane oxygenation.

CI, confidence interval; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; CCI, Charlson comorbidity index; NHI, national health insurance.

As the age increased, the odds of hospitalization (1.026) or use of medical devices (1.128) were significantly higher. The individuals with hypertension had higher odds of hospitalization (1.196) or use of medical devices (1.650) than the individuals without hypertension, and it was statistically significant. The medical aid beneficiaries had 1.789 higher odds of hospitalization and 1.554 higher odds of using medical devices compared to patients who were insured by NHI, all of which were statistically significant.

DISCUSSION

This study closely analyzed the claims data of Korea's HIRA to determine whether NAFLD is a risk factor that leads to the development of severe illness in COVID-19 patients. As a result, we found that NAFLD is a factor influencing the high hospitalization and medical devices use of COVID-19 patients. In addition, our study suggested that COVID-19 severity was higher in male, older age, or low-income COVID-19 patients, and these results were similar to

those of previous studies.

Recent studies found that obesity in patients with COVID-19 increased the risk of major complications and death. In addition, obese patients are at high risk of intubations or mechanical ventilation [24]. Since NAFLD is strongly associated with obesity, it is also likely to be a factor that aggravates the symptoms of COVID-19. A few previous studies actually focused on NAFLD as a risk factor for severe COVID-19, independent of metabolic syndrome [19,25].

Korea classified patients depending on the severity of illness; patients with mild symptoms were quarantined in residential treatment centers while severely ill patients and those who were highly likely to become severely ill were hospitalized and treated in medical institutions [3]. Accordingly, hospitalization after diagnosis with COVID-19 can serve as an indirect indicator of a patient's severity of illness. A review of international literature found that NAFLD increases the risk of hospitalization [23]. Our study results found that patients with NAFLD had slightly higher odds of hospitalization than those without the condition, but it was not statistically significant. This is thought to be attributable to the high hospitalization rate of COVID-19 patients in Korea amounting to nearly 40% of all confirmed cases. In general, less than 20% of all COVID-19 patients are known to be severe cases that require hospitalization, but the ratio of hospitalized patients in our study results were much higher [23]. This suggests that among those hospitalized in Korea, there actually were mild cases that did not need hospitalization.

To derive more accurate results, severe cases were re-defined more conservatively by limiting them to patients who used medical devices for treatment of severe cases during hospitalization. Severe cases of COVID-19 require high-level intensive treatment such as mechanical ventilation and ECMO due to conditions including severe pneumonia, acute respiratory distress syndrome, sepsis, septic shock, and hypoxemic respiratory failure. The World Health Organization and major countries recommended classifying patients in need of a ventilator or ECMO as severe cases in their guidance on COVID-19 response [5]. Therefore, the analysis for this study was performed by classifying ventilators and ECMO as the main medical devices for treatment of severe cases. The analysis results showed that COVID-19 patients with NAFLD had higher odds of using the medical devices for treatment of severe cases than those without the condition. Although our study did not find a statistically significant association between

NAFLD and hospitalization rate, considering Korea's bed allocation policy, the high rate of medical devices use among NAFLD patients suggests that NAFLD affects the exacerbation of COVID-19.

The reasons for the high severity of COVID-19 in patients with NAFLD are presumed to be the following clinical reasons. Fat in the liver is known to raise the odds of testing positive for COVID-19 [26]. Additionally, fat-related inflammation and fibrosis in the liver is thought to cause a cytokine storm that triggers severe COVID-19 illness [27]. In a previous study, patients with NAFLD showed higher fibrosis-4 index and alanine aminotransferase and aspartate aminotransferase than general patients [22]. Furthermore, excess visceral fat in COVID-19 patients may play a role in amplifying the chronic state of inflammation and hypercoagulability created by NAFLD [23]. These previous study results serve as supporting evidence of our results which showed poor prognosis of COVID-19 infection in patients with NAFLD.

The results of our study suggest that more attention should be paid to the management and treatment of NAFLD in order to reduce the likelihood of developing severe illness when infected with COVID-19 in the current situation of an on-going COVID-19 pandemic. The prevalence of NAFLD has increased compared to the past, but recognition and treatment of the condition lag behind and adults with NAFLD have not been very successful with lifestyle modifications and management [22]. NAFLD can be prevented with weight loss through dietary modifications and physical activity. Consumption of vegetables rich in fiber, fish intake, a diet low in fat and carbohydrates, and aerobic and resistance exercise can improve NAFLD [28]. Therefore, the need for early detection and management of NAFLD cannot be stressed enough. Overweight or obese patients need to be screened for NAFLD and they should be informed of the risks related to visceral fat and COVID-19 to enable active lifestyle management and timely treatments.

There are certain limitations of this study as it uses health insurance claims data, which is a type of administrative data. First, the main variables were estimated indirectly. The criterion for NAFLD was not the standard definition based on a liver biopsy, and patients' severity of illness was also indirectly estimated based on the medical services used. Second, the possibility of other hepatitis such as hepatitis B, hepatitis C, autoimmune hepatitis, and toxic hepatitis, could not be excluded. Nevertheless, this study has strengths that set it apart from

previous studies. First, it has representativeness because it used the claims data of NHI to which all Korean citizens are required to subscribe. Second, it used the data from the two years leading up to the COVID-19 pandemic to identify and correct for patients' underlying conditions in more various ways than previous studies.

This study demonstrated the relationship between the presence of NAFLD and exacerbation of COVID-19 symptoms in a situation where there still is an absence of clinical information on COVID-19, a new infectious disease. The study results are expected to serve as scientific evidence in making policy decisions related to infectious disease response, including classification and management of COVID-19 patients and prioritization of vaccination. Continued research will be needed in the future to evaluate whether NAFLD is a risk factor for COVID-19 infection and severe COVID-19 illness.

In conclusion, NAFLD is characterized by chronic inflammation due to fat accumulation in the liver. The study results demonstrate that NAFLD is a significant risk factor in the development of severe illness in COVID-19 patients. These study results suggest the need for preemptive screening and management of NAFLD patients at the government level and the importance of prevention and treatment of the condition through active lifestyle management at the personal level.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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