on univariate analyses. Univariate analyses with a P value <.10 were selected for inclusion in the multivariate model. Disease duration was not significant on univariate analysis ($P = .6$), so was not included in the model. This would be the case regardless of how disease duration is presented in Table 1 (but for the authors' interest, the median disease duration for infliximab-treated patients was 2.5 years (IQR, 1.00–6.90 years) and for ustekinumab-treated patients was 2.7 years (IQR, 1.00–6.73 years; Mann-Whitney $P = .712$).

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COVID-19 Morbidity and Severity in Patients With Nonalcoholic Fatty Liver Disease in South Korea: A Nationwide Cohort Study

Dear Editor:

We read with great interest the article by Fan et al[1] published in *Clinical Gastroenterology and Hepatology* on clinical features of COVID-19-related liver functional abnormality. This study focused on hepatic manifestations of COVID-19. Few other small studies of patients with nonalcoholic fatty liver disease (NAFLD) describe the disease course of COVID-19 in the setting of fatty liver disease, although the clinical course of these patients still remains unclear.[2] Thus, we hypothesized that the presence of NAFLD can influence the epidemiologic aspects related to COVID-19, including infectivity and disease-related outcomes.

We conducted a population-based nationwide cohort study using data from the Korean National Health Insurance Service, which is linked to general health examination records.[3] This study was approved by the Institutional Review Board of Sejong University (SJU-HR-E-2020-003). A total of 74,244 Korean individuals ≥20 years of age who underwent SARS-CoV-2 testing between January 1 and May 30, 2020 were included.

Patients were classified into 3 groups. Preexisting NAFLD was defined when patients met 1 of the following criteria: (1) hepatic steatosis index (HSI) ≥36; (2) fatty liver index (FLI) ≥60; or (3) claim-based definition indicated by the International Classification of Diseases, 10th revision (K75.8 and K76.0), with at least 1 claim within the observation period.[4] We generated 3 cohorts using these definitions: (1) HSI-NAFLD cohort, (2) FLI-NAFLD cohort, and (3) claim-based NAFLD cohort. The main outcomes were the positive laboratory SARS-CoV-2 tests, severe clinical COVID-19 illnesses (requirement of oxygen therapy, administration of mechanical ventilation, intensive care unit admission, COVID-19-related death),[5,6] and COVID-19-related deaths. The observational period was from January 1 to July 30, 2020.

We used Firth logistic regressions (an approach that can be used with small sample size) to adjust for potential confounders: age; sex; region of residence; past medical history/comorbidities (tuberculosis, stroke, cardiovascular disease, hypertension, and dyslipidemia); systolic and diastolic blood pressure; fasting blood glucose; glomerular filtration rate; household income; smoking; alcoholic drinks; sufficient aerobic activity; and current medication for hypertension, dyslipidemia, diabetes mellitus, and cardiovascular disease.[7] A 2-sided $P < .05$ was considered statistically significant. Statistical analyses were performed in SAS version 9.4 (SAS Institute Inc, Cary, NC).

Among 74,244 adults (age groups: 34.4% [20–39 years], 36.6% [40–59 years], and 29.0% [≥60 years]),

36,060 were male (48.5%); and 26,041 (35.1%), 19,945 (73.1%), and 8927 (12.0%) subjects had HSI-NAFLD, FLI-NAFLD, and claims-based NAFLD, respectively. During the observation period, 2251 (3.0%) tested positive for SARS-CoV-2, 438 (0.6%) had severe COVID-19 illness, and 45 (0.06%) suffered COVID-19-related deaths.

Subjects with HSI-NAFLD had a high risk of COVID-19 infection (1413/48,203 [2.9%] for subjects without HSI-NAFLD vs 838/26,041 [3.2%] for those with HSI-NAFLD; adjusted odds ratio [aOR], 1.12; 95% confidence interval [CI], 1.03–1.22), severe COVID-19 disease (259/48,203 [0.5%] vs 179/26,041 [0.7%]; aOR, 1.25; 95% CI, 1.03–1.52), and significant COVID-19-related deaths (21/48,203 [0.04%] vs 24/26,041 [0.09%]; aOR, 2.22; 95% CI, 1.18–4.00). We found similar trends when we used FLI to define NAFLD. Subjects with FLI-NAFLD had higher risk for SARS-CoV-2 infection (561/17,421 [3.2%] for subjects without FLI-NAFLD vs 629/17,421 [3.5%] for those with FLI-NAFLD; aOR, 1.26; 95% CI, 1.14–1.37), severe COVID-19 infection (290/54,299 [0.5%] for subjects without FLI-NAFLD vs 148/19,945 [0.7%] for those with FLI-NAFLD; aOR, 1.41; 95% CI, 1.16–1.73), and COVID-19-related death (25/54,299 [0.05%] for subjects without FLI-NAFLD vs 20/19,945 [0.10%] for those with FLI-NAFLD; aOR, 2.25; 95% CI, 1.25–3.98). Subjects classified as NAFLD based on claims seemed to have higher risk for COVID-19 (1925/65,317 [3.0%] for subjects without claim-based NAFLD vs 323/8830 [3.7%] for those with claim-based NAFLD; aOR, 1.16; 95% CI, 1.02–1.31) and severe COVID-19 progression (349/65,317 [0.5%] for subjects without claim-based NAFLD vs 89/8927 [1.0%] for those with claim-based NAFLD; aOR, 1.70; 95% CI, 1.33–2.15) than non-NAFLD subjects (Figure 1).

Through a large-scale, population-based, nationwide cohort study, we investigated the potential association between the presence of NAFLD and risk of SARS-CoV-2 test positive and COVID-19 severity and mortality. We identified that the NAFLD was associated with a higher risk of SARS-CoV-2 infectivity and COVID-19 severity among 74,244 subjects who underwent SARS-CoV-2

testing in South Korea. Our results suggest that physicians should exercise extra care and give more attention to COVID-19 patients with preexisting NAFLD.[8]

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Reply. The pandemic and inextricable relationship of COVID-19 and nonalcoholic fatty liver disease (NAFLD) have raised worldwide concerns. Although there was no population-based cohort study, some studies indicated NAFLD plays a role in the outcome of COVID-19 and is an independent predictor of severe COVID-19.[1-3] So we read with great interest the cohort study conducted by Yoo et al[4] regarding the effect of NAFLD on COVID-19-related outcomes.
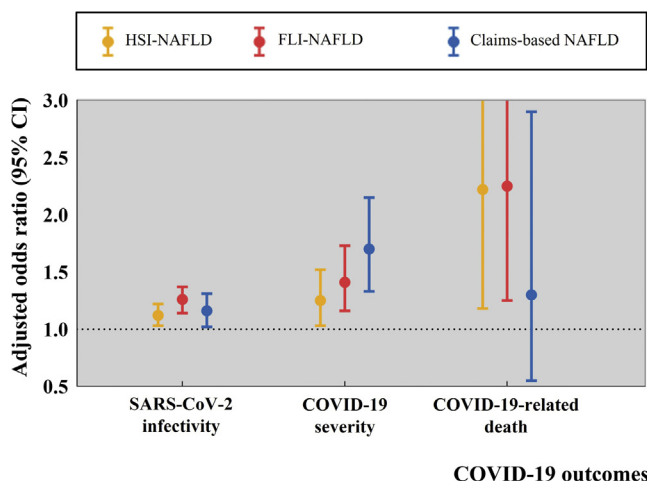

Figure 1. Summary of the main study findings.