Moon *et al. Virology Journal* (2024) 21:202
https://doi.org/10.1186/s12985-024-02464-1

Virology Journal

RESEARCH Open Access

Association between ursodeoxycholic acid use and COVID-19 in individuals with chronic liver disease: a nationwide case-control study in South Korea

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Abstract

Background Conflicting evidence exists regarding the effects of ursodeoxycholic acid (UDCA) on coronavirus disease 2019 (COVID-19). This study investigates the association between UDCA administration and COVID-19 infection and its related outcomes in individuals with chronic liver disease (CLD).

Methods A customized COVID-19 research database ($n = 3,485,376$) was created by integrating data from the National Health Insurance Service (NHIS) and the Korea Disease Control and Prevention Agency's COVID-19 databases. The study focused on patients diagnosed with COVID-19 in 2021, using the NHIS data from 365 days before diagnosis. To create comparable groups with and without UDCA administration before COVID-19, we used propensity score matching. The primary endpoint was the first confirmed positive result for severe acute respiratory syndrome coronavirus-2. In addition, we identified severe COVID-19-related outcomes. Subgroup analysis were conducted based on the dose of UDCA exposure.

Results Data from 74,074 individuals with CLD was analyzed. The participants' average age was 57.5 years, and 52.1% (19,277) of those in each group were male. Those with prior UDCA exposure had a significantly lower risk of COVID-19 infection (adjusted OR: 0.80, 95% CI [0.76–0.85]) compared to the non-UDCA group. Additionally, the UDCA group had a lower risk of severe COVID-19 outcomes (adjusted OR: 0.67, 95% CI [0.46–0.98]). Subgroup analyses indicated that there was a decrease in COVID-19 infection and its related outcomes with increasing UDCA exposure dose.

Conclusions Our large observational study highlights the potential use of readily available UDCA as an adjunctive therapy for COVID-19 in individuals with CLD.

Keywords COVID-19, SARS-CoV-2, UDCA

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Introduction

Since its declaration as a pandemic by the World Health Organization (WHO) in March 2020, COVID-19 has posed a significant challenge to public health, social stability, and the economy [1, 2]. Notably, various factors, such as chronic comorbidities, complications, and demographics, can affect the outcomes of COVID-19 [3, 4]. Specifically, individuals with chronic liver disease (CLD), particularly cirrhosis, have higher rates of morbidity and mortality from COVID-19 [5–9]. Vaccines and medications have been developed to reduce infection rates and prevent progression to severe disease; however, there is still a need for safer, more effective, and more accessible treatment options for individuals with CLD due to the limited duration of vaccine protection and potential side effects of medications [10–13].

Efforts were made to identify therapeutic targets through drug repurposing shortly after COVID-19 was declared a pandemic, leading to research into a prophylactic treatment approach by modulating angiotensin-converting enzyme 2 (ACE2), a critical host receptor of the virus [14]. Brevini et al. showed that ursodeoxycholic acid (UDCA), which has the farnesoid X receptor (FXR) antagonistic effects, downregulates ACE2 expression in experiments using animals and donor organs unsuitable for transplantation [15]. However, subsequent real-world retrospective studies on the relationship between UDCA intake and COVID-19 outcomes have yielded mixed results, with some studies showing positive effects [16–18] and others showing no significant impact [19–22].

This study explored the association between UDCA consumption and COVID-19 within a tailored South Korean COVID-19 cohort of 3,485,376 participants (including 580,896 COVID-19 cases and 2,904,480 controls). The investigation prioritized assessing the effects of UDCA consumption on COVID-19 susceptibility and its consequent outcomes among individuals with CLD within the cohort, while accounting for both the presence or absence of UDCA intake and its dosage, if applicable.

Methods

Data source and study population

A specialized COVID-19 research database was established for this investigation. This extensive repository amalgamates data from two primary origins: the National Health Insurance Service (NHIS) database, encompassing medical claims data for 97% of the Korean populace, and the database on COVID-19 confirmations and vaccinations administered by the Korea Disease Control and Prevention Agency [23]. The NHIS database furnishes a plethora of information, encompassing details regarding diagnoses, prescriptions, procedures, surgeries, insurance disbursements, and healthcare utilization for both inpatients and outpatients. It also incorporates invaluable health screening data, such as laboratory tests, physical measurements, and self-reported questionnaires concerning lifestyle habits. A tailored database was curated, incorporating data from patients diagnosed with COVID-19 between 2020 and 2021, alongside fivefold the number of controls matched for both sex and age with the diagnosed patients.

To ensure clear and efficient data analysis, our analysis only included patients diagnosed with COVID-19 between January 1, 2021, and December 31, 2021, due to the lack of definitive information on COVID-19 diagnosis dates in 2020. The date of diagnosis was defined as the index date, and only participants with NHIS data available from 365 days before the index date were included, particularly for health screening data. COVID-19-related outcomes were monitored until March 31, 2022, which customized the COVID-19 research database provided. Additionally, we utilized the International Classification of Diseases, 10th Revision (ICD-10) codes to differentiate between CLD subtypes. Finally, we matched the COVID-19 and control groups based on propensity scores. Moreover, to investigate the association between UDCA and COVID-19-related outcomes, we extracted individuals with CLD and COVID-19 and matched the event and control groups based on propensity scores.

UDCA exposure

UDCA exposure data encompassing UDCA prescription details (daily dose and duration of prescription) for the 365 days preceding the index date were retrieved. Cumulative exposure metrics, specifically cumulative defined daily dose (cDDD) and cumulative exposure duration (cED), were computed for each participant utilizing the World Health Organization's established daily defined dose (DDD) of 750 mg/day for UDCA [24]. For analytical purposes, participants were stratified into two cohorts: those with prior UDCA exposure and those without. Moreover, participants were further segmented based on UDCA exposure duration using cDDD and cED. The study cohort was delineated into subgroups characterized by exposure durations of in less than one month ($0.75 \times 30 = 22.5$ for cDDD, 30 days for cED), ≥ 1 month to < 3 months ($0.75 \times 90 = 67.5$ for cDDD, 90 days for cED), and ≥ 3 months.

Outcome

The primary endpoint encompassed the initial occurrence of a positive outcome for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) utilizing reverse transcriptase–polymerase chain reaction (RT-PCR) assays conducted on nasopharyngeal or oropharyngeal swabs. Apart from the principal outcome, we explored various other complications associated with COVID-19 as secondary endpoints. These included mortality

attributable to COVID-19, instances of cardiopulmonary resuscitation (M15, M587), the requirement for mechanical ventilation (M585, M5860), renal replacement therapy (O70), extracorporeal membrane oxygenation (O190), and admission to an intensive care unit for critical care (AJ).

Covariate

Demographic information, including age, sex, and income level, was extracted, with income level divided into four quartiles. Underlying diseases (hypertension, diabetes, and dyslipidemia) were assessed based on diagnoses recorded in the NHIS database up to 1 year prior to the COVID-19 diagnosis. Moreover, the Charlson comorbidity index (CCI) was utilized to gauge the burden of comorbidities [25]. CLD diagnoses were categorized as chronic viral infection, chronic liver disease, or liver cirrhosis utilizing ICD-10 codes [26]. Evaluated medications included those for hypertension and diabetes, statins, aspirin, antivirals for chronic hepatitis B, and hepatoprotective agents. Health screening results encompassed body mass index (BMI), systolic and diastolic blood pressure, fasting blood glucose, hemoglobin, glomerular filtration rate (GFR), and liver enzyme levels (aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase). Additionally, participants' current smoking status, alcohol consumption, and regular exercise habits were assessed via a self-reported questionnaire. Study participants were deemed vaccinated against COVID-19 if they had received at least one dose of any vaccine type. Supplementary Table 1 offers further details about the extracted covariates.

Statistical analysis

Baseline characteristics were expressed as mean ± standard deviation for continuous variables and as numbers with percentages (%) for categorical variables. Propensity score matching (PSM) was conducted at a 1:1 ratio, encompassing multiple covariates, such as sex, age, income level, underlying diseases, CCI, COVID-19 vaccination status, medications, BMI, systolic and diastolic blood pressure, fasting blood glucose, hemoglobin levels, GFR, liver enzyme levels, smoking status, alcohol consumption, and regular exercise habits. Exact matching was employed for sex, chronic viral infection, chronic liver disease, liver cirrhosis, COVID-19 vaccination status, antivirals for chronic hepatitis B, and hepatoprotective agents. However, greedy nearest neighbor matching was utilized for other variables, with a caliper set at 0.01 of the propensity scores. The standardized mean difference before and after PSM was utilized to assess the balance of covariate distribution between groups. Subsequently, odds ratios (ORs) and 95% confidence intervals (CIs) were computed through conditional logistic regression analysis post-matching. Additionally, multivariate-adjusted conditional logistic regression analysis was performed, incorporating the covariates. Statistical analyses were executed using SAS Enterprise Guide version 8.3 (SAS Institute Inc., Cary, NC, USA) and R 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). A significance level of $P<0.05$ was considered statistically significant.

Results

Study population

This study utilized a customized COVID-19 research database comprising 3,485,376 participants, including 580,896 confirmed COVID-19 cases and 2,904,480 control participants. After excluding individuals with missing demographic information ($n=73,857$), prior COVID-19 infection before 2021 ($n=34,819$), incomplete health screening data within 1 year of the index date ($n=2,321,109$), or missing health screening data ($n=6,368$), 1,049,223 participants remained. From among these remaining participants, individuals diagnosed with CLD using ICD-10 codes were then identified ($n=287,863$).

PSM was employed to explore the association between UDCA exposure and COVID-19 infection. This technique matched participants with CLD in a 1:1 ratio to those with COVID-19 ($n=37,037$) and control groups ($n=37,037$) (Table 1). Subsequently, to investigate the relationship between UDCA exposure and COVID-19-related outcomes, another 1:1 PSM was performed within the previously matched group to separate participants with and without COVID-19-related outcomes (Baseline characteristics in Supplementary Table 2). The schematic diagram for this case-control study is presented in Fig. 1. Table 1 presents the comparison results of the characteristics of the COVID-19 and control groups before and after PSM.

COVID-19 infection according to UDCA exposure

Table 2 displays the OR and 95% CIs for COVID-19 infection in relation to UDCA exposure. Participants exposed to UDCA exhibited an adjusted OR of 0.80 for COVID-19 infection (95% CI [0.76–0.85], P-value < 0.001) compared with those in the non-exposure group. Upon stratification based on UDCA dose (with the cDDD < 22.5 group as the reference), the adjusted OR was 0.86 (95% CI [0.80–0.93], P-value < 0.001) for the 22.5 ≤ cDDD < 67.5 group and 0.83 (95% CI [0.77–0.90], P-value < 0.001) for the cDDD ≥ 67.5 group. Analogous outcomes were observed when analysing according to cED.

COVID-19-related outcomes according to UDCA exposure

Table 3 presents the association between UDCA exposure and COVID-19-related outcomes. Participants with

Table 1 Baseline characteristics of subjects with chronic liver disease according to COVID-19 infection

Variables	Before PSM ($n=287863$)			After PSM ($n=74074$)		
	Control ($n=239683$)	COVID-19 ($n=48180$)	Standardized mean differences	Control ($n=37037$)	COVID-19 ($n=37037$)	Standardized mean differences
Demographics						
Age (years)	56.6 (13.6)	56.6 (13.5)	0.004	57.5 (13.9)	57.5 (13.4)	0.005
Sex (male, %)	126,312 (52.7)	25,544 (53.0)	0.006	19,277 (52.1)	19,277 (52.1)	0.00
Income level						
1st quintile	4089 (1.7)	800 (1.7)		611 (1.6)	603 (1.6)	
2nd quintile	47,912 (20.0)	9726 (20.2)		7568 (20.4)	7591 (20.4)	
3rd quintile	50,749 (21.2)	10,476 (21.7)		8077 (21.8)	8063 (21.8)	
4th quintile	60,524 (25.3)	12,178 (25.3)		9332 (25.2)	9279 (25.1)	
5th quintile	76,409 (31.8)	15,000 (31.1)		11,449 (30.9)	11,501 (31.1)	
COVID-19 vaccination	232,074 (96.8)	29,985 (62.2)	0.95	29,846 (80.6)	29,846 (80.6)	0.00
Underlying diseases						
Hypertension	123,125 (51.4)	24,871 (51.6)	0.005	19,647 (53.1)	19,670 (53.1)	0.001
Diabetes	104,844 (43.7)	21,992 (45.7)	0.04	17,160 (46.3)	17,143 (46.3)	< 0.001
Dyslipidemia	188,578 (78.7)	37,432 (77.7)	0.02	29,406 (79.4)	29,323 (79.2)	0.005
Chronic viral infection	35,690 (14.9)	7935 (16.5)	0.04	5588 (15.1)	5588 (15.1)	0.00
Chronic liver disease	226,346 (94.4)	45,424 (94.3)	0.007	35,058 (94.7)	35,058 (94.7)	0.00
Liver cirrhosis	5808 (2.4)	1136 (2.4)	0.004	789 (2.1)	789 (2.1)	0.00
Charlson comorbidity index, %	2.1 (1.9)	2.3 (2.0)	0.08	2.3 (2.0)	2.3 (2.0)	0.004
0	43,172 (18.0)	8196 (17.0)		6019 (16.3)	6045 (16.3)	
1	64,467 (26.9)	11,993 (24.9)		9266 (25.0)	9126 (24.7)	
2	54,582 (22.8)	10,866 (22.6)		8417 (22.7)	8417 (22.7)	
3	77,462 (32.3)	17,125 (35.5)		13,335 (36.0)	13,449 (36.3)	
Medication						
Angiotensin-converting-enzyme inhibitor	1898 (0.8)	368 (0.8)	0.003	276 (0.8)	293 (0.8)	0.005
Angiotensin receptor blocker	88,244 (36.8)	30,432 (36.8)	< 0.001	14,159 (38.2)	14,130 (38.2)	0.002
Beta blocker	33,208 (13.9)	6602 (13.7)	0.004	5347 (14.4)	5241 (14.2)	0.008
Calcium channel blocker	69,015 (28.8)	14,181 (29.4)	0.01	11,256 (30.4)	11,283 (30.5)	0.002
Diuretics	41,884 (17.5)	8174 (17.0)	0.01	6688 (18.1)	6639 (17.9)	0.004
Metformin	49,675 (20.7)	9934 (20.6)	0.003	7958 (21.5)	7883 (21.3)	0.005
Sulfonylurea	22,655 (9.5)	4608 (9.6)	0.004	3693 (10.0)	3614 (9.8)	0.007
Thiazolidinedione	8131 (3.4)	1643 (3.4)	< 0.001	1335 (3.6)	1316 (3.6)	0.003
DPP-4 inhibitor	36,496 (15.2)	7184 (14.9)	0.009	5746 (15.5)	5686 (15.4)	0.005
SGLT2 inhibitor	11,040 (4.6)	2244 (4.7)	0.002	1779 (4.8)	1734 (4.7)	0.006
GLP-1 agonist	968 (0.4)	197 (0.4)	< 0.001	144 (0.4)	157 (0.4)	0.006
Insulin	3842 (1.6)	775 (1.6)	< 0.001	611 (1.7)	612 (1.7)	< 0.001
Statin	122,936 (51.3)	23,850 (49.5)	0.04	19,150 (51.7)	19,073 (51.5)	0.004
Aspirin	29,238 (12.2)	5893 (12.2)	0.001	4911 (13.3)	4808 (13.0)	0.008
Viral medication	6927 (2.9)	1181 (2.5)	0.03	843 (2.3)	843 (2.3)	0.00
Biphenyl dimethyl dicarboxylate	29,525 (12.3)	6986 (14.5)	0.06	4739 (12.8)	4739 (12.8)	0.00
Silymarin	10,937 (4.6)	2681 (5.6)	0.05	1704 (4.6)	1704 (4.6)	0.00
Health screening						
Body mass index (kg/m2)	25.0 (3.8)	25.2 (3.8)	0.06	25.1 (3.9)	25.1 (3.7)	0.008
Systolic blood pressure (mmHg)	125.5 (14.6)	125.5 (14.8)	0.002	125.7 (14.8)	125.7 (14.7)	0.005
Diastolic blood pressure (mmHg)	76.7 (10.0)	76.8 (10.2)	0.02	76.7 (10.0)	76.7 (10.1)	0.003
Fasting blood glucose (mg/dL)	107.3 (29.0)	107.4 (29.3)	0.003	107.5 (29.4)	107.5 (28.9)	0.001
Hemoglobin (g/dL)	14.3 (1.6)	14.3 (1.5)	0.004	14.2 (1.6)	14.2 (1.5)	< 0.001
Glomerular filtration rate (mL/min/1.73 m^2)	88.4 (27.0)	87.9 (25.8)	0.02	87.7 (28.1)	87.6 (25.3)	0.005
Aspartate aminotransferase (U/L)	32.0 (34.9)	31.6 (26.5)	0.01	31.3 (22.5)	31.2 (23.5)	0.004
Alanine aminotransferase (U/L)	32.9 (41.5)	32.7 (35.0)	0.007	32.0 (29.9)	31.8 (30.9)	0.005
r-glutamyl transpeptidase (U/L)	41.2 (118.5)	45.2 (68.2)	0.02	43.8 (65.9)	44.1 (64.1)	0.004
Current smoker	43,537 (18.2)	6401 (13.3)	0.13	4991 (13.5)	5023 (13.6)	0.002

Table 1 (continued)

Variables	Before PSM ($n=287863$)			After PSM ($n=74074$)		
	Control ($n=239683$)	COVID-19 ($n=48180$)	Standardized mean differences	Control ($n=37037$)	COVID-19 ($n=37037$)	Standardized mean differences
Alcohol drinking	81,761 (34.1)	17,699 (36.7)	0.05	12,866 (34.7)	12,907 (34.9)	0.002
Regular exercise	113,609 (47.4)	23,230 (48.2)	0.02	17,794 (48.0)	17,666 (47.7)	0.007

Values are presented as number (%) or mean ± standard deviation

Abbreviations COVID-19, coronavirus disease 2019; PSM, propensity score matching

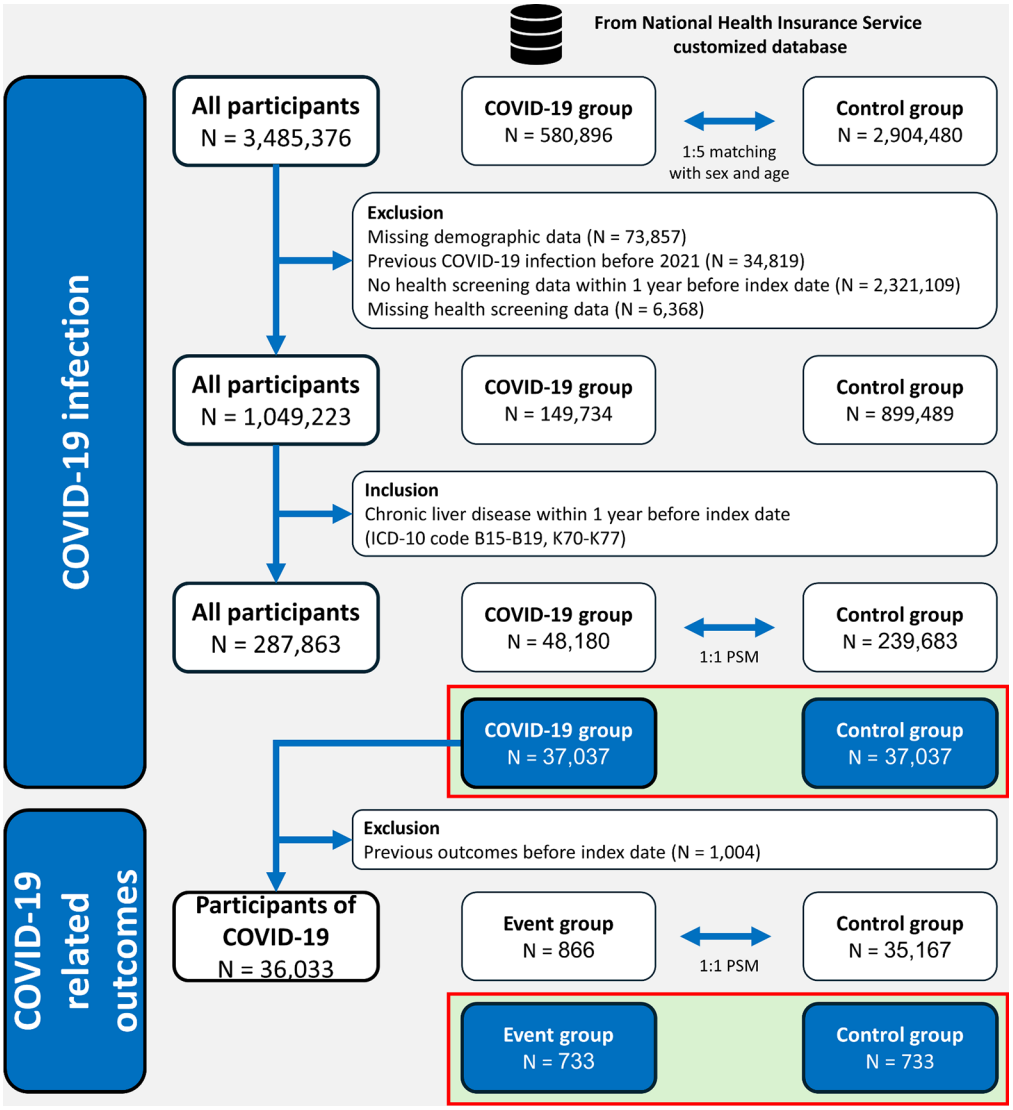

Fig. 1 The flow of study population

UDCA exposure had an adjusted OR of 0.67 for COVID-19-related outcomes (95% CI [0.46–0.98], P-value: 0.04) compared with the non-exposure group. Following an analysis based on UDCA dose (using the cDDD < 22.5 group as reference), the adjusted OR was 0.89 (95% CI [0.50–1.58], P-value: 0.68) for the 22.5 ≤ cDDD < 67.5 group and 0.48 (95% CI [0.27–0.88], P-value: 0.02) for the cDDD ≥ 67.5 group. Similar results were found when an analysis based on cED was done. A forest plot analysis was employed to illustrate the findings presented in Tables 2 and 3 (Supplementary Fig. 1).

Table 2 Odds ratio and 95% confidence interval for COVID-19 infection according to exposure to UDCA

Exposure	Control (%)	COVID-19 (%)	Crude OR (95% CI)	*P*-value	Adjusted OR* (95% CI)	*P*-value
Non-exposure to UDCA	32,285 (87.2)	32,955 (89.0)	1.00		1.00	
Exposure to UDCA	4752 (12.8)	4082 (11.0)	0.84 (0.81–0.88)	< 0.001	0.80 (0.76–0.85)	< 0.001
Cumulative defined daily dose (mg)						
cDDD < 22.5	33,878 (91.5)	34,274 (92.5)	1.00		1.00	
22.5 ≤ cDDD < 67.5	1719 (4.6)	1528 (4.2)	0.88 (0.82–0.94)	< 0.001	0.86 (0.80–0.93)	< 0.001
cDDD ≥ 67.5	1440 (3.9)	1235 (3.3)	0.85 (0.79–0.92)	< 0.001	0.83 (0.77–0.90)	< 0.001
Cumulative exposure duration (days)						
cED < 30	32,285 (87.2)	32,955 (89.0)	1.00		1.00	
30 ≤ cED < 90	1761 (4.7)	1528 (4.1)	0.85 (0.79–0.91)	< 0.001	0.81 (0.75–0.87)	< 0.001
cED ≥ 90	2991 (8.1)	2554 (6.9)	0.84 (0.79–0.88)	< 0.001	0.80 (0.75–0.85)	< 0.001

*adjusted for sex, age, income level, COVD-19 vaccination, underlying diseases (hypertension, diabetes, dyslipidemia, chronic viral infection, liver cirrhosis), Charlson comorbidity index, medications (hypertension, diabetes, dyslipidemia, chronic viral infection), body mass index, blood pressure, fasting glucose, hemoglobin, glomerular filtration rate, aspartate aminotransferase, alanine aminotransferase, r-glutamyl transpeptidase, smoking, alcohol drinking, and regular exercise status

Abbreviations cDDD, cumulative defined daily dose; cED, cumulative exposure duration; COVID-19, coronavirus disease 2019; OR, odds ratio; UDCA, ursodeoxycholic acid

Table 3 Odds ratio and 95% confidence interval for COVID-19 related outcomes according to exposure to UDCA

Exposure	Control (%)	Event (%)	Crude OR (95% CI)	*P*-value	Adjusted OR* (95% CI)	*P*-value
Non-exposure to UDCA	645 (88.0)	670 (91.4)	1.00		1.00	
Exposure to UDCA	88 (12.0)	63 (8.6)	0.69 (0.49–0.97)	0.03	0.67 (0.46–0.98)	0.04
Cumulative defined daily dose (mg)						
cDDD < 22.5	669 (91.3)	689 (94.0)	1.00		1.00	
22.5 ≤ cDDD < 67.5	28 (3.8)	25 (3.4)	0.87 (0.50–1.50)	0.61	0.89 (0.50–1.58)	0.68
cDDD ≥ 67.5	36 (4.9)	19 (2.6)	0.51 (0.29–0.90)	0.02	0.48 (0.27–0.88)	0.02
Cumulative exposure duration (days)						
cED < 30	645 (88.0)	670 (91.4)	1.00		1.00	
30 ≤ cED < 90	24 (3.3)	26 (3.6)	1.04 (0.59–1.84)	0.88	1.07 (0.59–1.97)	0.82
cED ≥ 90	64 (8.7)	37 (5.0)	0.56 (0.37–0.85)	0.006	0.53 (0.34–0.84)	0.006

*adjusted for sex, age, income level, COVD-19 vaccination, underlying diseases (hypertension, diabetes, dyslipidemia, chronic viral infection, liver cirrhosis), Charlson comorbidity index, medications (hypertension, diabetes, dyslipidemia, chronic viral infection), body mass index, blood pressure, fasting glucose, hemoglobin, glomerular filtration rate, aspartate aminotransferase, alanine aminotransferase, r-glutamyl transpeptidase, smoking, alcohol drinking, and regular exercise status

Abbreviations cDDD, cumulative defined daily dose; cED, cumulative exposure duration; COVID-19, coronavirus disease 2019; OR, odds ratio; UDCA, ursodeoxycholic acid

Sensitivity analysis

This study examined data from 365 days before the COVID-19 diagnosis, and the sensitivity analysis used data from 180 days before the COVID-19 diagnosis (Supplementary Tables 3,4). The sensitivity analysis was consistent with the main results.

Discussion

A nationwide population-based cohort study utilizing a tailored COVID-19 research database encompassing 3.4 million individuals was employed to ascertain COVID-19 infection and its associated outcomes concerning UDCA exposure and dosage after PSM following the identification of individuals with CLD. Findings revealed a favorable correlation between COVID-19 infection and its related outcomes in the exposed group compared with the unexposed group (reference) (COVID-19 infection, adjusted OR: 0.80, 95% CI [0.76–0.85]; COVID-19-related outcomes, adjusted OR: 0.67, 95% CI [0.46–0.98]). To our knowledge, this study represents the most comprehensive investigation to date into the association between UDCA and COVID-19.

Prevention of COVID-19 is crucial for individuals with CLD. These individuals face an increased risk of severe complications from COVID-19, with those having cirrhosis experiencing particularly poor outcomes [5–9]. This is supported by findings from the National COVID Cohort Collaborative Study and the Veterans Affairs healthcare system, both of which independently reported that COVID-19 infection raises the risk of death within 30 days by 2.38 and 1.7 times, respectively, in individuals with cirrhosis compared to those without [6, 9]. To further explore this association, we conducted a comparative analysis of COVID-19 infection and its outcomes between individuals with CLD and those with cirrhosis across our entire cohort, utilizing our customized COVID-19 research database. Our results align with previous studies [COVID-19 infection: without liver disease (reference); CLD, 1.11 ($p<0.001$); cirrhosis, 1.01 ($p=0.88$). COVID-19 related outcomes: without liver disease (reference); CLD, 1.79 ($p<0.001$); cirrhosis, 2.75 ($p<0.001$)] (Supplementary Table 5) [6, 9, 27]. Impairments in the complement system, macrophage activation, lymphocyte and neutrophil function, upregulated Toll-like receptors, and intestinal dysbiosis contribute to the increased susceptibility of individuals with CLD to viral infections. These factors trigger cytotoxic T-cell activation and dysregulation of the innate immune response, ultimately leading to liver damage and increased mortality [5, 7, 8].

UDCA is a well-established first-line treatment for primary biliary cholangitis [28–30]. It stimulates bile acid secretion and has shown immunomodulatory and anti-inflammatory effects in experimental studies. It also reduces oxidative stress and protects liver cells from apoptosis [31–36]. Recent research has identified a potential role for bile acids like UDCA in regulating COVID-19 infection, with a focus on the ACE2 receptor, which is a critical entry point for SARS-CoV-2 [37, 38]. Experimental studies suggest that bile acids can act on this pathway in multiple ways: (1) hindering viral entry by disrupting the interaction between ACE2 and the spike protein, (2) influencing ACE2 activity, and potentially (3) regulating ACE2 expression [15, 39, 40]. Additionally, bile acids have shown promise in modulating the cytokine storm, an essential factor in the development of acute respiratory distress syndrome (ARDS), a severe complication of COVID-19 [41, 42]. UDCA has a favorable safety profile and few side effects, making it a potential treatment to prevent infection and mitigate disease progression in patients with COVID-19 [43].

In a landmark decision on May 5, 2023, the WHO declared COVID-19 was no longer a global public health emergency, marking a turning point after a grueling 3-year battle [44–46]. This shift signifies that COVID-19 will transition from a pandemic to an endemic, managed alongside other prevalent illnesses. Factors contributing to this decision include rising herd immunity due to vaccination and natural infection, a reduced burden on healthcare systems, and decreased overall disease severity [44–46]. However, the WHO's declaration does not signal the complete eradication of COVID-19. The emergence of new variants and the potential decline in vaccination rates pose significant challenges to ongoing management efforts [47, 48]. Therefore, continued vigilance is essential. This is especially crucial for patients with pre-existing medical conditions that may make them more vulnerable to COVID-19 or for those living in low-income countries with low vaccination rates [49]. In such instances, UDCA can be used as an additional treatment to vaccines and conventional medications, and it has been proven to be affordable and accessible [50, 51].

Limitations and strengths

This study has some limitations. First, the population's demographic composition is predominantly from a single ethnic group. Second, the study cohort consisted mainly of individuals with CLD because UDCA was prescribed primarily to this group in South Korea. Therefore, it is difficult to explain the relationship between UDCA and COVID-19 in non-CLD groups, and the baseline characteristics of the study population differ from those of the general population. Third, identifying individuals with CLD relied solely on ICD-10 codes, which may not be perfectly accurate. Additionally, the available medical records only covered approximately 2 years. Fourth, there may be discrepancies between UCDA's prescribed and actual usage. Patients with higher prescription rates and

frequent hospital visits might focus more on preventing COVID-19, potentially influencing result interpretations [52, 53]. Fifth, although various factors were adjusted for, misclassification and residual confounding factors may still be present. Sixth, the study did not obtain results regarding SARS-CoV-2 variants or reinfections. However, despite these limitations, we found a positive association between UDCA intake and COVID-19 infection and its related outcomes among 74,074 individuals with CLD who underwent PSM. Specifically, the analysis, stratified by the level of UDCA intake using data from the year before COVID-19 infection, revealed that higher UDCA intake, rather than simply its presence or absence, was associated with more beneficial effects. Unlike COVID-19 vaccines and medications, UDCA does not need to be re-studied for adverse effects, and its relatively low cost and accessibility make it feasible even in developing countries.

In reporting this study, we do not prioritize supplementing research findings with randomized controlled trials (RCTs), as is often suggested to complement observational studies. Conducting RCTs to investigate the association between UDCA and COVID-19 in the current situation, unlike during past severe pandemics, is unrealistic and of little significance. However, we aim to provide helpful information for patients with limited access to COVID-19 vaccines and medications by reporting positive outcomes of UDCA intake in patients with CLD using a large observational study. In addition, we hope that this study will contribute to the discussion of UDCA administration in situations with viruses similar to SARS-CoV-2 in the future [54].

Conclusions

This large-scale observational study has shown that UDCA can reduce COVID-19 infection and its related outcomes in individuals with CLD. These findings suggest that the readily available UDCA could be a valuable addition to the treatment regimens of individuals with CLD susceptible to COVID-19.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-024-02464-1.

Supplementary Material 1

Supplementary Material 2

Acknowledgements
Not applicable.

Author contributions
Sang Yi Moon and Minkook Son contributed equally to this work as first authors. Dr. S. Moon, M. Son, and Y. Baek had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: S. Moon, M. SonAcquisition, analysis, or interpretation of data: S. Moon, M. Son. Drafting of the manuscript: S. Moon, M. Son. Critical review of the manuscript for important intellectual content: Y, Kang, Y. Baek. Statistical analysis: M. Son. Administrative, technical, or material support: Y. Baek. Supervision: Y. Baek. All authors reviewed the manuscript.

Funding
This research was supported by Dong-A University Research Fund.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Dong-A University College of Medicine Institutional Review Board exempted this retrospective study from review due to its design (utilizing de-identified, publicly available clinical data for analysis) (DAUHIRB-EXP-23-026).

Consent for publication
Not applicable.

Additional information
This study used the database of the KDCA and the NHIS for policy and academic research. The research number of this study is KDCA-NHIS-2023-1-567. The KDCA is the Korea Disease Control and Prevention Agency, Republic of Korea. The NHIS is the National Health Insurance Service, Republic of Korea.

Competing interests
The authors declare no competing interests.

Received: 22 May 2024 / Accepted: 7 August 2024
Published online: 27 August 2024

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