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ORIGINAL ARTICLE

Ursodeoxycholic acid does not affect the clinical outcome of SARS-CoV-2 infection: A retrospective study of propensity score-matched cohorts

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Abstract

Background: Ursodeoxycholic acid (UDCA) has been recently proposed as a modulator of angiotensin-converting enzyme 2 (ACE2) receptor expression, with potential effects on COVID-19.

Aim and Study Design: We retrospectively evaluated the clinical course and outcome of subjects taking UDCA admitted to the hospital for COVID-19 compared with matched infected subjects. Differences regarding the severity and outcome of the disease between treated and non-treated subjects were assessed. The Kaplan–Meier survival analysis and log-rank test were used to evaluate the effect of UDCA on all-cause intra-hospital mortality.

Results: Among 6444 subjects with confirmed COVID-19 admitted to the emergency department (ED) from 1 March 2020 to 31 December 2022, 109 subjects were taking UDCA. After matching 629 subjects were included in the study: 521 in the no UDCA group and 108 in the UDCA group. In our matched cohort, 144 subjects (22.9%) died, 118 (22.6%) in the no-UDCA group and 26 (24.1%) in the UDCA group. The Kaplan–Meier analysis showed no significant difference in survival between groups. In univariate regression analysis, the presence of pneumonia, National Early Warning Score (NEWS) score, and Charlson Comorbidity Index (CCI) were significant independent predictors of death. At multivariate Cox regression analysis, age, NEWS, pneumonia and CCI index were confirmed significant independent predictors of death. UDCA treatment was not a predictor of survival both in univariate and multivariate regressions.

Abbreviations: ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; AVPU, Alert, Voice, Pain, Unresponsive scale; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus disease 2019; CTP, Child-Turcotte-Pugh; ED, emergency department; FDA, Food and Drug Administration; FXR, farnesoid X receptor; HF, congestive heart failure; ICU, intensive care unit; LC, liver cirrhosis; LOS, hospital length of stay; MELD, Model for End-stage Liver Disease; NEWS, National Early Warning Score; PAD, peripheral artery disease; PSM, propensity score-matching; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SpO_2, peripheral oxygen saturation; UDCA, ursodeoxycholic acid; VOCAL, Veterans Outcomes and Costs Associated with Liver disease; ZGG, z-guggulsterone.

Giuseppe Marrone and Marcello Covino share co-authorship.

Conclusions: UDCA treatment does not appear to have significant effects on the outcome of COVID-19. Specially designed prospective studies are needed to evaluate efficacy in preventing infection and severe disease.

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

1 | INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a single-stranded RNA beta coronavirus that causes coronavirus disease observed for the first time in China in December 2019 (COVID-19). According to the WHO COVID-19 Dashboard, as of February 2023, there have been 755 385 709 confirmed cases of COVID-19 worldwide, including 6 833 388 fatal cases, making it a global public health crisis. SARS-CoV-2 infection was defined as a Public Health Emergency of International Concern on 30 January 2020 and as a pandemic on 11 March 2020 by the WHO.

COVID-19 has heterogeneous clinical manifestations, with symptoms ranging from mild fever and flu to severe pneumonia and acute respiratory distress syndrome (ARDS), systemic complications including acute kidney injury, liver damage, coagulopathy and multi-organ failure.[1-5] Clinical presentation and severity of the disease have also varied considerably over time due to both the effect of vaccines ad treatments and the development of new virus variants, with different diffusivity and virulence.[6] Since the very beginning of the pandemic, it became evident that frail individuals and those with comorbidities were more susceptible to severe forms of COVID-19 with a higher risk of fatal outcomes.[1,7–10]

Global efforts to develop prevention and treatment strategies have been unprecedented in their speed and scale and have contributed greatly to reducing the severity of the disease in infected individuals.

One of the main issues in the fight against COVID-19 is the need for prophylaxis in high risk and fragile populations, such as immunocompromised individuals, who are not able to mount an appropriate response to vaccines. Vaccines have also shown variable efficacy and reduced protection against new emerging variants over time.[6]

Since the beginning of the pandemic, there has been great interest in identifying drug targets by mapping protein interactions with SARS-CoV-2. Angiotensin-converting enzyme 2 (ACE2) has been identified early in the pandemic as the entryway for SARS-CoV-2. Since then, many efforts have been made to identify strategies to counteract cell infection by targeting virus binding to ACE2.[11] On these principles vaccines and monoclonal antibodies have been introduced in clinical practice. Based on the previously mentioned principles, therapies that modulate ACE2 expression might be also successful against different variants of SARS-CoV2 with a higher genetic barrier to resistance than vaccines and monoclonal antibodies.[12]

In a recently published study, Brevini et al.[13] identified the farnesoid X receptor (FXR) as a regulator of ACE2 expression in multiple COVID-19-affected tissues, including the gastrointestinal and respiratory systems. These authors found that FXR antagonists, including the over-the-counter compound z-guggulsterone (ZGG) and the off-patent drug ursodeoxycholic acid (UDCA), downregulate ACE2 levels and reduce susceptibility to SARS-CoV-2 infection in respiratory epithelia, cholangiocyte and gut organoids.

Moreover, they used discarded liver and lung grafts to confirm the efficacy of UDCA supplementation in reducing SARS-CoV-2 organ infection. Finally, they interrogated two COVID-19 databases, one comprising patients with chronic liver disease (CLD) and the other one including vaccinated liver transplant recipients, showing in both, that patients receiving UDCA had better COVID-19 outcomes compared to matched controls.

UDCA is a hydrophilic bile acid that has been approved by the US Food and Drug Administration (FDA) for dissolving gallstones and for the treatment of several cholestatic liver diseases, such as primary biliary cholangitis.[14,15] UDCA has been found to have non-hepatic effects in various pathophysiological models, such as cystic fibrosis lung disease and airway inflammation, showing significant improvement in all histopathological changes that occurred in the context of airway remodelling.[16,17] These beneficial effects might be ascribed to the efficient modulation of Th-2-derived cytokines and the inhibition of apoptosis of airway epithelial cells.[18]

The repurposing of UDCA, an approved, cost-effective and readily available off-patent drug, alongside vaccination, to prevent SARS-CoV-2 infection, could offer a novel approach against viral infection that is directed towards the host rather than the virus and may be less affected by the emergence of new virus variants.

To evaluate the effects of UDCA in the context of SARS-CoV-2 infection, we evaluated the clinical course and outcome of subjects who were taking UDCA for an approved indication and were admitted to the hospital for COVID-19 compared with a population of matched infected subjects.

Key points

Treatment with ursodeoxycholic acid has no effect on the outcome of SARS-CoV-2 infection in hospitalized subjects.
Age, presence of pneumonia, comorbidities and severity at onset are confirmed as predictors of unfavourable outcomes.

2 | MATERIALS AND METHODS

2.1 | Study population

This is a single-centre, retrospective study, conducted in a tertiary university hospital [Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome]. Informed consent was obtained from patients to enter the study. Patients admitted to the emergency department (ED) because of COVID-19 from 1 March 2020 to 31 December 2022 were enrolled in the study. We compared the clinical outcome of subjects who were taking UDCA for a clinical indication before SARS-CoV-2 infection with a matched cohort of infected controls not taking the drug, using a propensity score-matching (PSM) method. Data regarding the presence of the liver cirrhosis was extracted from the text section of the hospital computer medical record if registered by the staff who oversaw the patient. Medical history data could be reported directly by the patient or derived from available previous clinical records.

2.2 | Study variables

Data were collected from hospital electronic medical records. The patient's health record was used to collect the subject's demographic and clinical characteristics, symptoms at admission, clinical events occurring during the hospital stay and the clinical outcome. Medical charts were also reviewed to assess comorbidities based on the patient's history, UDCA assumption and hospital discharge diagnosis.

The following information was extracted:

1. Demographic data: age and sex.
2. Major symptoms at ED admission and complications: cough, fever, dyspnoea, presence of pneumonia, sepsis, or septic shock, need for intensive care unit (ICU) admission and mechanical ventilation.
3. Vital signs at ED admission: body temperature, heart rate, respiratory rate, systolic blood pressure, and level of consciousness assessed by the response on the AVPU (Alert, Voice, Pain, Unresponsive) scale, peripheral oxygen saturation (SpO_2) in ambient air. Using these parameters, we calculated the National Early Warning Score (NEWS).[19] The patient's illness severity at admission was categorized as NEWS <5 or NEWS ≥5.
4. Relevant comorbidities: hypertension, coronary artery disease (CAD), congestive heart failure (HF), peripheral artery disease (PAD), cerebral vascular disease (previous stroke), diabetes, CLD, liver cirrhosis (LC), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), history of solid and haematological cancer. Comorbidities were overall considered and graded through the Charlson Comorbidity Index (CCI). CCI is a validated score that considers the number and the severity of the comorbid disease and assigns weights, from 1 to 6, to each comorbidity. A CCI score of zero represents no comorbidities, and a score from 1 to ≥6 represents a gradually higher load of comorbidities, with a corresponding increase in mortality.[20]
5. SARS-CoV-2 vaccine status.

2.3 | Outcome measures

The main outcome was all-cause intra-hospital mortality.

2.4 | Statistical analysis

Categorical variables are presented as numbers and percentages. The continuous normally distributed variables are presented as the mean ± standard deviation; the non-normally distributed data are presented as the median [inter-quartile range], and the binary or ordinal variables as absolute frequency (%).

Enrolled patients were matched in a 1:5 ratio by age, sex, disease severity based on NEWS score calculated at the ED admission, CCI, presence of liver cirrhosis and season/year of admission (to match patients with similar SARS-CoV-2 variants). PSM was calculated by a logistic regression model using the nearest neighbour technique with no replacement, and with a calliper size of .2 to avoid poor matching.

A description of the PSM analysis and distribution before and after the match is provided in the Supplementary Materials (Table S1, Figures S1 and S2).

Hospital length of stay (LOS) was calculated from the time of ED admission to the discharge or death.

Survival analysis was performed according to the Kaplan–Meier methods, and the differences in survival were assessed using the log-rank test. Study variables were assessed for the association with all-cause in-hospital death by a univariate Cox regression analysis. The significant variables in the univariate analysis were entered into a multivariate Cox regression model to identify the independent risk factors for survival. The association of factors with in-hospital death in the multivariate analysis is expressed as the hazard ratio (HR) [95% confidence interval]. A two-sided *p*-value of .05 or less was considered significant. Statistical analysis was performed by SPSS v26® (IBM, Armonk, NY, USA).

3 | RESULTS

Overall, 6444 patients with confirmed COVID-19 were identified in the electronic ED database in the analysed period. In total, 6335 patients with COVID-19 were not taking UDCA. In total, 109 subjects were taking UDCA. Among these 19 (17.4%) were taking the drug in the context of non-cirrhotic CLD, and 21 (19.3%) because of LC, the remaining subjects were taking the drug because of other miscellaneous indications including biliary gallstones of previous biliary surgery. A statistically significant difference was found in the number of subjects with CLD and LC between the non-UDCA and the UDCA group (2.1% vs. 17.4% for CLD and 6.3% vs. 19.3% for LC). In total, 69 patients (63.3%) were taking UDCA for other indications. Subjects in the UDCA group were significantly older and showed a significantly lower percentage of ICU admission and need for mechanical ventilation. With regards to comorbidity, patients in the UDCA group

also presented a significantly higher percentage of HF and a history of solid and haematological cancer (details in Table 1). Considering the entire cohort, 1308 subjects with COVID-19 died (20.3%), 1282 (20.2%) in the no-UDCA group and 26 (23.9%) in the UDCA group, with no significant difference.

After PSM a total of 629 subjects were included: 521 in the control group (no UDCA) and 108 in the UDCA group. The median age of the entire cohort was 75 years, with a little prevalence of males (54.5%). No significant differences in disease severity at presentation assessed through NEWS were found between the two groups. A significant difference between UDCA and no-UDCA groups was found regarding SatO2 at presentation (96% vs. 94%) and in the percentage of patients presenting with sepsis (16.7% vs. 8%). As expected, no difference was found in the percentage of subjects suffering from liver cirrhosis but a significantly higher percentage of patients with non-cirrhotic CLD was found in the UDCA group (16.7% vs. 4.6%) (Table 2). Among 629 subjects included after PSM, 144 (22.9%) died, 118 (22.6%) in the no-UDCA group, and 26 (24.1%) in the UDCA group.

Considering that the population was enrolled during a wide period, we divided the study population by year of enrolment (details in Table 3). No significant difference in mortality during the years was found but a significant difference in the need for mechanical ventilation and ICU admission was found.

Regarding SARS-CoV-2 vaccination, no significant differences in vaccine status were found between the two groups (UDCA vs. no UDCA). A significant difference in survival was found between vaccinated and unvaccinated subjects considering the whole matched population ($p = .008$).

TABLE 1 Clinical characteristics of the study population.

	Total (6444)	No UDCA (6335)	UDCA (109)	*p*
Age (years)	69 (56–80)	69 (56–80)	76 (61.5–84)	<.01
LOS (Days)	12.3 (7.0–22.0)	12.3 (7.0–22.0)	13.0 (8–25)	.27
SatO2 (%)	94 (90–97)	94 (90–97)	96 (92–98)	<.01
TC (°C)	36 (36–37.5)	36.7 (36–37.5)	36.5 (36–37)	.06
Male sex	3799 (59.0%)	3744 (59.1%)	55 (50.5%)	.07
Death	1308 (20.3%)	1282 (20.2%)	26 (23.9%)	.35
Mechanical ventilation	1299 (20.2%)	1288 (20.3%)	11 (10.1%)	<.01
ICU admission	1698 (26.4%)	1685 (26.6%)	13 (11.9%)	<.01
NEWS ≥5	618 (9.6%)	607 (9.6%)	11 (10.1%)	.86
Pneumonia	4988 (77.4%)	4924 (77.7%)	64 (58.7%)	<.01
Sepsis	430 (6.7%)	412 (6.5%)	18 (16.5%)	<.01
Septic shock	212 (3.3%)	208 (3.3%)	4 (3.7%)	.82
Fever	4610 (71.5%)	4536 (71.6%)	74 (67.9%)	.39
Dyspnoea	3047 (47.3%)	2999 (47.3%)	48 (44%)	.49
Cough	936 (14.5%)	927 (14.6%)	9 (8.3%)	.06
CCI	2 (0–3)	1 (0–3)	3 (2–5)	<.01
Hypertension	1759 (27.3%)	1724 (27.2%)	35 (32.1%)	.25
CAD	936 (14.5%)	915 (14.4%)	21 (19.3%)	.16
HF	1049 (16.3%)	1019 (16.1%)	30 (27.5%)	<.01
PAD	162 (2.5%)	156 (2.5%)	6 (5.5%)	.04
Previous stroke	180 (2.8%)	177 (2.8%)	3 (2.8%)	.98
COPD	551 (8.6%)	538 (8.5%)	13 (11.9%)	.20
CLD	154 (2.4%)	135 (2.1%)	19 (17.4%)	<.01
LC	422 (6.5%)	401 (6.3%)	21 (19.3%)	<.01
Diabetes	646 (10.0%)	636 (10.0%)	10 (9.2%)	.77
CKD	532 (8.3%)	521 (8.2%)	11 (10.1%)	.48
History of cancer	488 (7.6%)	466 (7.4%)	22 (20. 2%)	<.01
Hematologic cancer	161 (2.5%)	151 (2.4%)	10 (9.2%)	<.01

Abbreviations: CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CLD, chronic liver disease (not cirrhotic); HF, heart failure; HR, heart rate; ICU, intensive care unit; LC, liver cirrhosis; LOS, lenght of stay; NEWS, National Early Warning Score; PAD, peripheral arterial disease.

TABLE 2 Characteristics of the study population after propensity score matching.

	Total (629)	Group A (521)	Group B (108)	*p*
Age (years)	75 (63–83)	75 (63–83)	76 (61–84)	.87
LOS (days)	12 (7–21)	12 (7–21)	13 (8–25)	.11
SatO2 (%)	95 (91–97)	94 (90–97)	96 (92–98)	.02
TC (°C)	36.6 (36.0–37.2)	36.6 (36.0–37.3)	36.5 (36.0–37.0)	.24
Male sex	343 (54.5%)	289 (55.5%)	54 (50%)	.29
Death	144 (22.9%)	118 (22.6%)	26 (24.1%)	.75
Mechanical ventilation	100 (15.9%)	89 (17.1%)	11 (10.2%)	.07
ICU admission	112 (17.8%)	99 (19.0%)	13 (12.0%)	.08
NEWS ≥5	59 (9.4%)	48 (9.2%)	11 (10.2%)	.75
Pneumonia	415 (66%)	351 (67.4%)	64 (59.3%)	.12
Sepsis	62 (9.9%)	44 (8.4%)	18 (16.7%)	<.01
Septic shock	16 (2.5%)	12 (2.3%)	4 (3.7%)	.40
Fever	407 (64.7%)	333 (63.9%)	74 (68.5%)	.36
Dyspnoea	326 (51.8%)	278 (53.4%)	48 (44.4%)	.09
Cough	91 (14.5%)	82 (15.7%)	9 (8.3%)	.05
CCI	3 (2–5)	3 (2–5)	3 (2–5)	1.0
Hypertension	261 (41.5%)	226 (43.4%)	35 (32.4%)	.04
CAD	146 (23.2%)	125 (24.0%)	21 (19.4%)	.31
HF	179 (28.5%)	149 (28.6%)	30 (27.8%)	.86
PAD	33 (5.2%)	28 (5.4%)	5 (4.6%)	.75
Previous stroke	36 (5.7%)	33 (6.3%)	3 (2.8%)	.15
COPD	78 (12.4%)	65 (12.5%)	13 (12.0%)	.90
CLD	42 (6.7%)	24 (4.6%)	18 (16.7%)	<.01
LC	107 (17%)	87 (16.7%)	20 (18.5%)	.65
CTP A	32 (29.9%)	22 (25.3%)	10 (50.0%)	.06
CTP B	33 (30.8%)	30 (34.5%)	3 (15.0%)	
CTP C	42 (39.3%)	35 (40.2%)	7 (35.0%)	
MELD[a]	13 (6–29)	13 (6–25)	12 (6–29)	.83
Diabetes	85 (13.5%)	76 (14.6%)	9 (8.3%)	.08
CKD	78 (12.4%)	67 (12.9%)	11 (10.2%)	.44
History of cancer	85 (13.5%)	63 (12.1%)	22 (20.4%)	.02
Hematologic cancer	37 (5.9%)	27 (5.2%)	10 (9.3%)	.10
SARS-CoV-2 vaccination				
Yes	121 (19.2%)	103 (19.8%)	18 (16.7%)	.79
No	213 (33.9%)	179 (34.3%)	34 (31.5%)	
Unknown	295 (46.9%)	239 (45.9%)	56 (51.8%)	

Abbreviations: CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CLD, chronic liver disease (not cirrhotic); CTP, Child-Turcotte-Pugh; Group A, no UDCA; Group B, UDCA; HF, heart failure; HR, heart rate; ICU, intensive care unit; LC, liver cirrhosis; LOS, length of stay; MELD, Model for End stage Liver Disease; NEWS, National Early Warning Score; PAD, peripheral arterial disease.

[a]Only cirrhotic subjects.

The Kaplan–Meier analysis showed no significant difference in survival between UDCA and no UDCA group (Figure 1).

At univariate Cox regression analysis, deceased subjects resulted significantly older than survivors (median age 80 vs. 73 years, $p < .001$). The presence of pneumonia, a higher value of NEWS at presentation and a higher CCI index were significant independent predictors of death in our cohort. LC and SARS-CoV-2 vaccine status were not not significant predictors of death. The year of enrolment

	2020	2021	2022	p
Total (629)	167 (26.5%)	183 (29.1%)	279 (44.4%)	
Group A (521)	140 (83.8%)	146 (79.8%)	235 (84.2%)	.43
Group B (108)	27 (16.2%)	37 (20.2%)	44 (15.8%)	
Death	49 (29.3%)	37 (20.2%)	58 (20.8%)	.07
Mechanical ventilation	81 (48.5%)	11 (6.0%)	8 (2.9%)	<.01
ICU admission	85 (50.9%)	14 (7.7%)	13 (4.7%)	<.01

Abbreviations: Group A, no UDCA; Group B, UDCA; ICU, intensive care unit.

TABLE 3 Study population characteristics by year of enrolment.

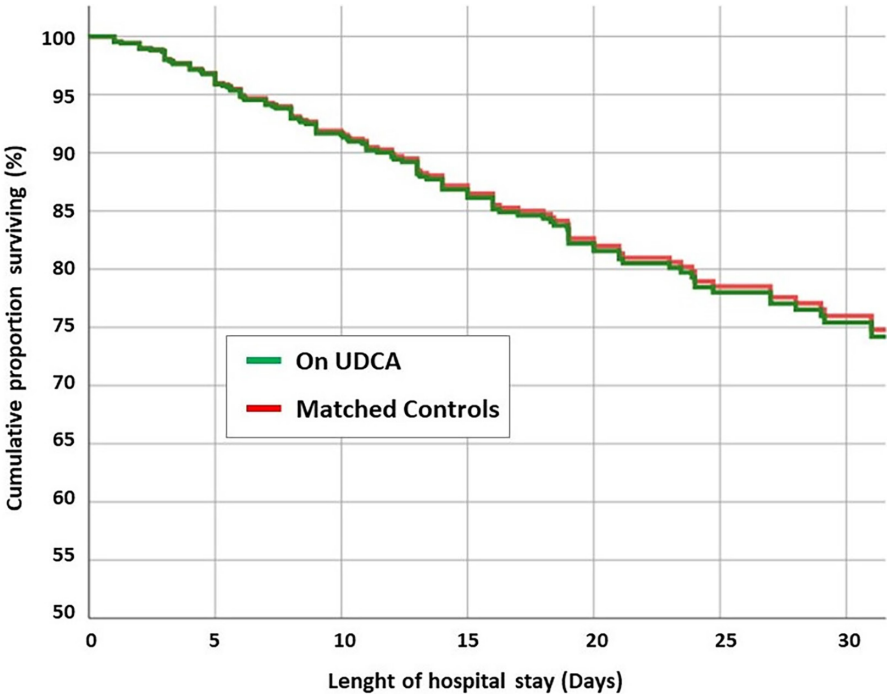

FIGURE 1 Adjusted survival curves (drawn by the Kaplan–Meier method) of the COVID-19 patients exposed to UDCA compared with matched controls.

was not a significant predictor of death in the univariate analysis. In order to weigh our observations and also take into account the different SARS-CoV-2 waves, we decided to force the year of enrolment into the multivariate analysis model.

At multivariate Cox regression analysis, age, NEWS at presentation, pneumonia and CCI index were confirmed to be significant independent predictors of death while the year of enrolment barely achieved statistical significance. UDCA treatment was not a predictor of survival both in univariate and multivariate regressions (Table 4).

4 | DISCUSSION

During the SARS-CoV-2 pandemic, the management of the disease has been continuously improved by the introduction of antiviral therapies, vaccines and specific monoclonal antibodies.

ACE2 is the main receptor for SarsCov2 and allows the virus to enter tissues in which it is expressed, including lungs, digestive tract, biliary cells and cardiovascular system. The receptors directly bind coronavirus spike protein, with a high affinity for SARS-CoV2.[21,22] While antivirals act by interfering with viral replication,[23-25] vaccines and monoclonal antibodies target the binding of endogenous or exogenous immunoglobulins with the spike protein to prevent the virus from entering the cell and thus blocking the propagation of the viral infection in the affected tissue.[26-28] The effectiveness of these treatments is reduced by mutations in the spike protein that alter antibodies' binding affinity so that updates of the vaccines and monoclonal antibodies have become necessary over time due to the emergence of new virus variants. Modulation of ACE2 receptor expression has been recently proposed as an interesting strategy to prevent SARS-CoV2 infection changing the perspective of the therapeutic approach.

In their recently published article, Brevini et al. performed several fine experiments to demonstrate that FXR can regulate ACE2 expression in several tissues. UDCA was found to reduce FXR activity thus downregulating ACE2 expression and reducing SARS-CoV-2 infection in vitro, in vivo and ex vivo.[13] Moreover, the authors found a protective effect of UDCA administration on the development of

TABLE 4 Univariate and Multivariate comparison (Cox regression analysis) of patients deceased vs survivors in the propensity score matched cohort including 108 patients with UDCA and 521 controls.

Variable	Survived n° 485	Deceased n° 144	*p*-value	Univariate hazard ratio (95% CI)	Univ. *p* Value	Multivariate hazard ratio (95% CI)	Multiv. *p* value
On UDCA therapy	82 (16.9%)	26 (18.1%)	.748	.89 [.58–1.36]	.583	1.07 [.69–1.64]	.768
Age	73 [61–81]	80 [71–88]	<.001	1.04 [1.03–1.06]	<.001	1.04 [1.02–1.06]	<.001
Sex (male)	262 (54.0%)	82 (56.3%)	.637	1.14 [.82–1.59]	.434		
NEWS ≥5	32 (6.6%)	27 (18.8%)	<.001	2.23 [1.45–3.41]	<.001	2.49 [1.61–3.86]	<.001
Pneumonia	295 (60.8%)	120 (83.3%)	<.001	2.96 [1.89–4.65]	<.001	2.98 [1.83–4.85]	<.001
CCI index	3 [2–4]	4 [2–6]	<.001	1.16 [1.08–1.24]	<.001	1.15 [1.06–1.25]	.001
CAD	103 (21.2%)	43 (29.9%)	.031	1.49 [1.04–2.14]	.034		
HF	119 (24.5%)	60 (41.7%)	<.001	1.82 [1.31–2.54]	<.001		
COPD	53 (10.9%)	25 (17.4%)	.040	1.42 [.92–2.19]	.128		
Diabetes	69 (14.2%)	16 (11.1%)	.337	.62 [.36–1.07]	.066		
Dementia	31 (6.4%)	29 (20.1%)	<.001	3.02 [2.00–4.56]	<.001		
LC	84 (17.3%)	23 (16.0%)	.706	.85 [.54–1.32]	.455		
CKD	47 (9.7%)	31 (21.5%)	<.001	1.59 [1.06–2.38]	.03		
SARS-CoV-2 vaccination	101 (28.8%)	20 (13.9%)	.008	.63 [.38–1.04]	.06		
2020	118 (24.3)	49 (34.0%)	.07	.83 [.68–1.01	.06	1.25 [1.00–1.55]	.047
2021	146 (30.1)	37 (25.7%)					
2022	221 (45.6)	58 (40.3%)					

Abbreviations: CAD, coronary artery disease; HF, heart failure; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LC, liver cirrhosis; NEWS, National Early Warning Score; UDCA, ursodeoxycholic acid.

severe COVID-19 in two registries including subjects with chronic liver disease.[29,30]

Previous studies had analysed the potential role of UDCA in SARS-CoV-2 infection focusing on various aspects of the potential interaction between this drug and the virus.

In silico analysis has shown that UDCA can interact with spike protein sequences in two distinct regions and reduce the binding between the spike protein binding site and ACE2 receptor. Moreover, UDCA has shown a high affinity towards a virion-like membrane with a potential reduction of SARS-CoV-2 internalization in the host cell.[31,32] In vitro analyses have confirmed that UDCA may inhibit spike protein binding on the ACE2 receptor and exert a positive effect on cell migration, required for airway reparative processes, that is impaired by the spike protein itself.[33]

Considering our entire population, subjects taking UDCA, despite being older, showed a lower percentage of ICU admission and need for mechanical ventilation without any difference in survival but after PSM, we did not confirm the positive effects of UDCA on the outcome of SARS-CoV-2 infection observed by Brevini et al.[13] in COVID-Hep[29] and SECURE-Liver registries.[30] Our results are consistent with what Colapietro et al. recently reported in an indipendent italian cohort.[34]

In our cohort, we observed a significant effect on survival of severe clinical presentation assessed by NEWS, presence of viral pneumonia, advanced age and associated comorbidities.

Considering the high variability of the clinical presentation of COVID-19 over time and the effect of comorbidities, we decided to perform a matching considering several variables known to affect the outcome, to deeper assess the net effect of UDCA on the course of the disease.

The main difference between our study and the analysis of the COVID-Hep and SECURE registry performed by Brevini et al. is matching for comorbidities. We decided to perform such matching using the CCI index because, since the earliest observations during the pandemic, the worst outcomes were noted in subjects with comorbidities, including cardiovascular, cerebrovascular disease, CKD and cancer.[7,35] We believe that comorbidities matching makes our results more generalizable.

We must also consider that our data come exclusively from patients with a need for hospitalization, and it is well known that in such categories of subjects, advanced age and the presence of comorbidities increase the complexity of management and make outcomes worse, even in the absence of COVID-19.[36] Already in the early stages of the pandemic, it became apparent that the various proposed treatments may have different effects between inpatients and outpatients.[37-40] Therefore, the absence of benefit of UDCA treatment in the inpatient setting does not rule out potential benefits in subjects with milder forms of COVID-19 without the need for hospitalization.

A further analysis performed by Brevini et al. looked at the Veterans Outcomes and Costs Associated with Liver disease (VOCAL)

cohort. The authors looked at liver transplant recipients who received at least two doses of a COVID-19 mRNA vaccine. Again, the analysis conducted based on UDCA intake showed a lower risk of moderate, severe or critical COVID-19 in treated patients. As before, although the authors included an adjustment for the type of immunosuppressive therapy, which is known to influence the disease outcome,[41] there was no matching for comorbidities. In solid organ transplant recipients, the presence of cardiovascular and metabolic comorbidities is common, given the effects on glucose and lipid metabolism and blood pressure of common immunosuppressants[42] so we believe that the presence and severity of these conditions may have a major effect on observed disease outcome.

We were able to retrieve data regarding the vaccination status of about half of our population and SARS-CoV-2 vaccination was found to be significantly associated with survival in our sample. In the survival analysis, vaccination status was not found to be a predictor of survival in either univariate or multivariate analysis. We must consider that these results may have been influenced by a considerable percentage of missing data about this item in our population, so it is not possible to draw firm conclusions on this aspect.

Subjects with chronic liver disease are known to have a good seroconversion rate after vaccination for SARS-CoV2 while the liver transplant recipients have a reduced response and need multiple close booster doses.[43] The number of administered doses and the time elapsed between the last administered dose and the time of infection may have influenced our results, but vaccination response to the first dose may also have significantly influenced the data observed in the SECURE-liver registry, as the response to vaccination in transplant recipients can be highly variable.[44,45]

The population we analysed was enrolled over a long period. We did not observe a significant difference in mortality between enrollment periods, but a higher proportion of deaths was noted during the first wave. This is not surprising considering that, especially at the beginning of the pandemic, knowledge about the diagnosis, management and treatment of SARS-CoV-2 infection was very limited and this certainly had a non-negligible impact on mortality. Interestingly, there is a significant difference in the need for intubation and transfer to ICU between the early and later periods. This finding can be interpreted by considering various aspects. Mostly at the beginning of the pandemic, it was not known what the best respiratory support strategy was and what was the role of noninvasive techniques. Over time, knowledge about the best strategies for invasive and noninvasive ventilatory support and oxygen therapy in individuals with SARS-CoV2 pneumonia was gradually gained.[46-48] Similarly, over time, therapeutic protocols that can prevent disease progression and the need for intubation and transfer to the ICU have been introduced. Lastly, vaccine introduction on the one hand, and the spread of less aggressive variants on the other, have changed the severity of the disease and the rate of invasive treatment and ICU admission. To weigh our observation taking into account these aspects we included the year of enrolment in the propensity score matching. We also must note that our population is made up exclusively of affected subjects, so we cannot draw any conclusions about the possible role of the drug in preventing viral infection, which is probably the most intriguing aspect of ACE2 modulation. A recently published retrospective cohort study conducted on data from the VOCAL registry, analysing patients with LC, showed that UDCA exposure has been associated with a decrease in SARS-CoV-2 infection.[49] The potential effects of ACE2 receptor modulation in the general population as a preventive measure for SARS-CoV-2 infection are unknown. In our study, we did not find a protective effect on the course of the disease, but it is possible that in subjects taking the drug, a non-negligible number of infections were prevented.

Lastly, this is a retrospective cohort analysis and therefore we cannot exclude biases and confounding factors typical of this kind of study. A prospective evaluation in double-blinded large clinical trials with the evaluation of ACE2 circulating levels and mucosal expression must be performed to confirm the role of UDCA in preventing viral infection from SARS-CoV-2 and to evaluate the effects on disease course in the affected subjects.

AUTHOR CONTRIBUTIONS

Marcello Covino and Giuseppe Marrone were responsible for the conception and writing of the paper; Marcello Covino, Annamaria Amodeo and Giuseppe Marrone performed data collection, Marcello Covino and Giuseppe Marrone performed data analysis, Maurizio Pompili, Rita Murri, Angela Novelli, Andrea Piccioni and Giuseppe Merra reviewed the manuscript; Francesco Franceschi, Antonio Gasbarrini, Marcello Covino, Giuseppe Marrone performed final editing of the manuscript. All the authors approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors do not have any disclosures to report.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author on request.

ETHICS STATEMENT

This study has been approved by the local Ethics Committee (authorization #001705520) and has been performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments. All the patients gave their informed consent for clinical data analysis.

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