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Liver involvement and mortality in COVID-19: A retrospective analysis from the CORACLE study group

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SUMMARY

Introduction: liver abnormalities are common in COVID-19 patients and associated with higher morbidity and mortality. We aimed to investigate clinical significance and effect on the mortality of abnormal liver function tests (ALFTs) in COVID-19 patients.
Methods: we retrospectively evaluated in a multicentre study all patients admitted with confirmed diagnosis of COVID-19.
Results: 434 patients were included in this analysis. Among overall patients, 311 (71.6%) had normal baseline ALT levels. 123 patients showed overall abnormal liver function tests (ALFTs) at baseline [101 ALFTs <2x UNL and 22 ≥2 UNL]. Overall in-hospital mortality was 14% and mean duration of hospitalization was 10.5 days. Hypertension (50.5%), cardiovascular diseases (39.6%), diabetes (23%) were frequent comorbidities and 53.7% of patients had ARDS. At multivariate analysis, the presence of ARDS at baseline (OR=6.11; 95% CI: 3.03-12.32; $p<0.000$); cardiovascular diseases (OR=4; 95% CI: 2.05-7.81; $p<0.000$); dementia (OR=3.93; 95%CI:1.87-8.26; $p<0.000$) and no smoking (OR=4.6; 95% CI: 1.45-14.61; $p=0.010$) resulted significantly predictive of in-hospital mortality. The presence of ALFTs at baseline was not significantly associated with mortality (OR=3.44; 95% CI=0.81-14.58; $p=0.094$).
Conclusion: ALFTs was frequently observed in COVID-19 patients, but the overall in-hospital mortality was mainly determined by the severity of illness, comorbidities and presence of ARDS.

Keywords: COVID-19, SARS-CoV-2, liver injury, mortality, ARDS.

INTRODUCTION

The coronavirus-19 disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a pandemic illness associated with higher mortality and morbidity related to interstitial pneumonia, acute respiratory distress syndrome (ARDS) and multiorgan involvement [1]. Liver injury has been reported in patients with COVID-19, with no well-defined relationship with mortality or intensive care unit (ICU) admission [2]. The origin of liver involvement in COVID-19 may be related to different mechanisms and conditions [3]:

1) possible direct liver toxicity through the angiotensin-converting enzyme 2 (ACE-2) receptors mainly expressed in the cholangiocytes [4];
2) the systemic inflammatory condition caused by the SARS-CoV-2 infection such as ARDS, multi-

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organ failure (MOF) or thrombotic phenomena in the portal and sinusoidal vessels [5];
3) drug-induced liver injury (DILI) due to antiviral therapies used against COVID-19 pneumonia (e.g., lopinavir/ritonavir, darunavir/ritonavir, darunavir/cobicistat, remdesivir) [6-8] or other pre-existing chronic liver diseases [6-8].

In some studies, liver involvement was strongly associated with the ICU admission and mortality, but this condition appears to be related mainly to grade of COVID-19 severity at the hospital admission, with higher prevalence of abnormal liver function tests (ALFTs) in subjects directly admitted in ICU, with ARDS or need of mechanical ventilation [9-11].Others studies have reported that ALFTs during COVID-19 are common also in non-ICU patients, with mild or moderate illness as expression of systemic manifestation of SARS-CoV-2 infection [12-14].

In this study, we analysed the prevalence and the role of abnormal liver function in patients with COVID-19 pneumonia in relation to ARDS and liver diseases.

PATIENTS AND METHODS

We retrospectively studied a cohort of COVID-19 patients hospitalized in two different hospitals in Italy (Piedmont): «City of Health and Sciences, Molinette Hospital» in Turin, «S. Andrea» in Vercelli, within the CORACLE study register in Piedmont, Italy. All consecutive patients admitted in these hospitals from March to October 2020 with confirmed SARS-CoV-2 infection by nasopharyngeal RT-PCR test were included in this analysis. Clinical, biological, radiological and therapeutic data were collected. The severity of illness was defined by the presence of ARDS criteria according to current guidelines or by the need of direct ICU admission [15]. The patients' history was reported with focusing on medical comorbidities, concomitant therapies and timing of hospital admission from the symptoms' onset.

ALFTs was defined as the detection of alanine aminotransferase (ALT) >40 U/L on admission; ALFTs was stratified according to the level of ALT abnormalities: less than 2x upper normal level (UNL) or more than 2x UNL.

Statistical analysis

Patients' characteristics were summarized using frequencies and percentages for categorical variables, and median and interquartile range (IQR) for continuous variables. These characteristics were assessed for association with baseline ALT levels using the Chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. For the analysis of in-hospital mortality, crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were estimated using univariate and multivariate logistic regression models. All the variables of patients' characteristics were used for adjustment in the multivariate model. Statistical significance was set at $p<0.05$. All analyses were performed by Stata 15.1 software (StataCorp LP, College Station, TX, USA).

RESULTS

During the study period 520 subjects were initially enrolled; patients with missing ALT values (n=86) were afterwards excluded; finally, 434 patients were included in this analysis.

Baseline characteristics of the study population were reported in the Table 1. Among overall patients, 311 (71.6%) had normal baseline ALT levels, 101 (23.3%) had ALFTs <2x UNL, 22 (5%) with ≥2 UNL. Overall in- hospital mortality was 14% (61 deceased) and mean duration of hospitalization was 10.5 days. Most frequent comorbidities were hypertension (n=219, 50.5%), cardiovascular diseases (n=172, 39.6%), diabetes (n=102, 23%). Of note 53.7% (233) of patients had ARDS. At univariate analysis patients with ALTFs>2x were younger and they have more frequently dementia, or cardiovascular diseases (p=0.001; Table 1).

At multivariate analysis, the presence of ARDS at baseline (OR=6.11; 95%CI: 3.03-12.32; $p<0.000$); cardiovascular diseases (OR=4; 95%CI: 2.05-7.81; $p<0.000$); dementia (OR=3.93; 95%CI:1.87-8.26; $p<0.000$) and no smoking (OR=4.6; 95%CI: 1.45-14.61; $p=0.010$) resulted significantly predictive of in-hospital mortality. The presence of ALFTs at baseline was not significantly associated with mortality (OR=3.44; 95%CI=0.81-14.58; $p=0.094$) (Table 2).

DISCUSSION

The debate about the role of liver involvement in the SARS-CoV-2 infection is currently ongoing, with some interesting but contrasting results.

The first point is the timing of liver function assessment: at the time of hospital admission the measurement of ALFTs may reflect the severity of clinical conditions, with higher levels observed in ARDS or in patients requiring ICU admission [3, 16]. The overall ALT elevation was commonly observed in patients with severe disease, while in patients with mild or moderate illness was related to direct cytotoxicity of viral replication or an immune-mediate damage [17].

The rate of ALFT results observed in patients in this study (28.3%) was slightly higher than those reported in the cohorts of Guan et al. and Ponziani et al. (21.3% and 19%, respectively) [18,

Table 1 - Baseline characteristics of the study population according to baseline ALT levels.

	Baseline ALT levels (U/L)				*p-value*
	Normal (N = 311)	*<2X (N = 101)*	*≥2X (N = 22)*	*Total (N = 434)*	
Age, median (IQR):	73.0 (61.0, 82.0)	68.0 (56.0, 78.0)	57.5 (46.0, 67.0)	72.0 (58.0, 81.0)	<0.001
Sex, n(%):					0.034
F	130 (78.8%)	28 (17.0%)	7 (4.2%)	165 (38.0%)	
M	181 (67.3%)	73 (27.1%)	15 (5.6%)	269 (62.0%)	
Smoking[1], n(%):					0.140
Never	199 (76.0%)	46 (17.5%)	17 (6.5%)	262 (60.4%)	
Active	30 (66.7%)	14 (31.1%)	1 (2.2%)	45 (10.4%)	
Previous	72 (73.5%)	23 (23.5%)	3 (3.0%)	98 (22.6%)	
Diabetes[2], n(%):					0.182
No	230 (69.7%)	84 (25.5%)	16 (4.8%)	330 (76.0%)	
Yes	80 (78.4%)	17 (16.7%)	5 (4.9%)	102 (23.5%)	
Overweight[3], n (%):					0.915
No	211 (72.3%)	67 (22.9%)	14 (4.8%)	292 (67.3%)	
Yes	100 (70.9%)	33 (23.4%)	8 (5.7%)	141 (32.5%)	
Hypertension[2], n (%):					0.049
No	141 (66.2%)	60 (28.2%)	12 (5.6%)	213 (49.1%)	
Yes	168 (76.7%)	41 (18.7%)	10 (4.6%)	219 (50.5%)	
Dementia[3], n (%):					0.001
No	235 (67.7%)	93 (26.8%)	19 (5.5%)	347 (80.0%)	
Yes	75 (87.2%)	8 (9.3%)	3 (3.5%)	86 (19.8%)	
Cardiovascular disease[3], n (%):					0.001
No	170 (65.1%)	77 (29.5%)	14 (5.4%)	261 (60.1%)	
Yes	140 (81.4%)	24 (14.0%)	8 (4.6%)	172 (39.6%)	
Lung disease[2], n (%):					0.924
No	262 (71.6%)	86 (23.5%)	18 (4.9%)	366 (84.3%)	
Yes	47 (71.2%)	15 (22.7%)	4 (6.1%)	66 (15.2%)	
ARDS, n (%):					<0.001
No	163 (81.1%)	27 (13.4%)	11 (5.5%)	201 (46.3%)	
Yes	148 (63.5%)	74 (31.8%)	11 (4.7%)	233 (53.7%)	

[1]Data not available for 29 subjects.
[2]Data not available for 2 subjects.
[3]Data not available for 1 subject.

Table 2 - Analysis of factors associated with in-hospital mortality.

	Crude OR (95%CI) N=434	*p-value*	*Adjusted OR (95%CI) N=429*	*p-value*
Baseline ALT				
(36-71) vs Normal	0.93 (0.54-1.58)	0.783	1.17 (0.57-2.40)	0.678
≥72 vs Normal	0.93 (0.33-2.59)	0.883	3.44 (0.81-14.58)	0.094
Sex (M vs F)	1.26 (0.79-2.00)	0.334	1.24 (0.66-2.34)	0.502
Age (continuous)	1.09 (1.06-1.11)	0.000	1.07 (1.04-1.11)	0.000
Smoking				
Active vs Never	1.37 (0.66-2.82)	0.396	2.30 (0.91-5.84)	0.080
Previous vs Never	1.36 (0.79-2.33)	0.264	1.34 (0.64-2.78)	0.437
Not available vs Never	1.98 (0.87-4.50)	0.103	4.60 (1.45-14.61)	0.010
Diabetes	2.05 (1.26-3.34)	0.004	0.92 (0.49-1.75)	0.806
Overweight	0.73 (0.45-1.19)	0.209	1.47 (0.73-2.95)	0.275
Hypertension	2.37 (1.49-3.78)	0.000	1.19 (0.63-2.26)	0.590
Dementia	4.57 (2.75-7.57)	0.000	3.93 (1.87-8.26)	0.000
Cardiovascular disease	5.90 (3.61-9.63)	0.000	4.00 (2.05-7.81)	0.000
Lung disease	2.11 (1.20-3.70)	0.009	1.84 (0.87-3.91)	0.111
ARDS	3.12 (1.91-5.09)	0.000	6.11 (3.03-12.32)	0.000

19]. This reflects that the enrolled patients had similar characteristics, especially the severity of presentation and the rate of ICU admission. In other studies with different patient baseline characteristics, the liver involvement rate was reported to be higher. In a study by Hundt et al., the rate of abnormal liver function was 41%, with 35.7% of cases in patients with severe diseases/ARDS [20]. In addition, in a study by Meszaros et al., the rate of abnormal liver function was 66%, with severe disease occurring in 49% of enrolled patients and the direct need for ICU admission in 35% of enrolled patients [9]. Other studies have confirmed that abnormal liver function in patients with non-severe COVID-19 is a common finding and that it does not negatively affect patient survival [12].

Considering that the observed rate of included patients with chronic liver disease (2.9%) was comparable with the other published studies (2.1% in the cohort by Guan et al) the main impact on the in-hospital mortality was related to the severity of clinical condition [18]. Presence of ARDS, age, cardiovascular diseases were largely demonstrated as predictive factors of mortality in hospitalized patients, and the ALFTs should be considered as a consequence of severe illness and not the cause. In fact, patients with severe disease, ARDS or undergoing mechanical ventilation had major risk of sepsis, multiorgan failure and liver injury with higher rate of observed ALFTs [14]; furthermore, the patients with longer time of hospitalization and severe conditions were frequently treated with more than one drug (i.e antivirals, corticosteroids, supportive agents) with increased risk of DILI [7, 13]. Moreover, the induction of interferon (IFN, especially type I IFN) responses by different viruses can be inhibited by many viral products [21]. IFNs play a variety of roles in the defense against viruses [21]. Cells activated by IFN-I are also less likely to become infected. SARS-CoV-2 suppresses type I IFN induction and action in various ways in vitro, and these data imply that this is a critical virulence factor of SARS-CoV-2 [21]. Theoretically, that increased levels of endogenous IFN may reduce liver damage in SARS-CoV-2 infected patients.

This study has strengths and limitations: our cohort presents similar characteristics to other studies (especially for ARDS condition and chronic liver disease as possible confounding factors) and the mortality evaluation could be applicable in

the large part of patients with COVID-19 related pneumonia; the main limitations are the relatively small simple size and the retrospective design. Liver function was described reporting ALT values. Evaluating prothrombin time and bilirubin values might have provided more significant perspective on liver function.

In conclusion, our study confirmed that ALFTs was a common finding in patients with COVID-19, but the major risk factor for the in-hospital mortality was the presence of ARDS (OR=6.11), dementia and cardiovascular disease (OR=3.93 and 4, respectively) while liver injury was not determinant for patients' survival, however a larger sample could change the final results (OR=3.44; 95%CI=0.81-14.58; p=0.094). Liver injury may reflects a logical consequence of cytokine and general inflammation effect commonly observed in ARDS that have a demonstrated effect on the liver function and tissue damage [13, 22, 23].

Conflicts of interest

All Authors declare no conflicts.

Availability of data and material

The data presented in this study are available on request from the corresponding author.

Ethics approval

Approved by local Ethic Committee (N. Prot. CE 0031285 24 March 2020, n.0000381 31/03/2020).

Consent for publication

All authors have read and agreed to the published version of the manuscript.

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