

World Journal of *Clinical Cases*

World J Clin Cases 2021 October 16; 9(29): 8627-8952



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The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Jia-Hui Li; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

October 16, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Observational Study

Chronic hepatitis-C infection in COVID-19 patients is associated with in-hospital mortality

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Author contributions: Ronderos D and Omar AMS, have conceptualization the study, performed data analysis and wrote the manuscript; Abbas H, Makker J, Baiomi A, Mantri N, Choi, Y, Fortuzi D and Shin D contributed to data buildup and manuscript write-up and Pate; Chilimuri SC did study supervision and assisted in Manuscript write-up and revision.

Institutional review board statement: The study was reviewed and approved by the BronxCare Hospital Center Institutional Review Board.

Informed consent statement: This was a retrospective study and consent forms is waived.

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Abstract

BACKGROUND

There is little evidence about the association of pre-existing hepatitis C infection (HCV) with outcomes in patients with coronavirus disease 2019 (COVID-19).

AIM

To assess the prevalence of history of HCV among patients with COVID-19 and to study the relationship of in-hospital mortality in relation with other predictors of poor outcomes in the presence or absence of COVID-19 induced acute liver injury.

METHODS

In a retrospective single-center study design, 1193 patients with COVID-19 infection were studied. Patients were then classified into those with and without a history of HCV, 50 (4.1%) and 1157 (95.9%) respectively.

RESULTS

Multivariate cox-regression models showed that age, HCV, D-Dimer, and ferritin were the only predictors of in-hospital mortality. Acute liver injury and fibrosis score (Fib-4 score) were not different between both groups. Multivariate cox-regression model for liver profile revealed that aspartate aminotransferase/alanine aminotransferase ratio, Fib-4 score, and HCV were predictors of in-hospital mortality. After propensity score matching HCV was the only predictor of mortality in the multivariate cox-regression model. A model including HCV

Conflict-of-interest statement:

Authors have nothing to disclose.

Data sharing statement: No additional data are available.

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Manuscript source: Unsolicited manuscript

Specialty type: Gastroenterology and hepatology

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

Received: January 29, 2021

Peer-review started: January 29, 2021

First decision: May 2, 2021

Revised: May 20, 2021

Accepted: September 8, 2021

Article in press: September 8, 2021

Published online: October 16, 2021

P-Reviewer: Kumar R, Shahini E

S-Editor: Liu M

L-Editor: A

P-Editor: Li JH



was found to add predictive value to clinical and laboratory parameters.

CONCLUSION

In patients with COVID-19, history of HCV infection leads to an accentuated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virulence, irrespective of baseline comorbidities, admission laboratory variables, or COVID-19-induced liver injury, which may be related to extrahepatic effects of HCV leading to enhanced ACE-2/TMPRSS mechanisms of SARS-CoV-2 viral entry, baseline cytokine-mediated pro-inflammation, and endothelial dysfunction.

Key Words: Hepatitis C; Acute liver injury; Seropositive; COVID-19; Mortality

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Core Tip: In patients with coronavirus disease 2019 (COVID-19), history of hepatitis C infection accentuated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral virulence and is a strong predictor of in-hospital mortality irrespective of baseline comorbidities, laboratory parameters, or COVID-19-induced liver injury. History of hepatitis C infection (HCV) in these patients seems to add a cumulative mortality risk to any clinical or laboratory profile. The mechanisms involved may be related to extra hepatic effects of HCV leading to enhanced ACE-2/TMPRSS mechanisms of SARS-CoV-2 virus and subsequent endothelial dysfunction. The realization is important for better characterization of the disease and triage this sub-group as high risk for therapeutic or prophylactic measures like vaccines.

Citation: Ronderos D, Omar AMS, Abbas H, Makker J, Baiomi A, Sun H, Mantri N, Choi Y, Fortuzi K, Shin D, Patel H, Chilimuri S. Chronic hepatitis-C infection in COVID-19 patients is associated with in-hospital mortality. *World J Clin Cases* 2021; 9(29): 8749-8762

URL: <https://www.wjgnet.com/2307-8960/full/v9/i29/8749.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i29.8749>

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the recently identified novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Since December 2019, COVID-19 has caused a global outbreak and continuously spreading in more than 200 countries. World Health Organization estimates 3.4% mortality for the disease. Epidemiological reports show that mortality is higher in the elderly and in patients with underlying comorbidities like diabetes, hypertension, and heart disease. Identifying the predictors of mortality in patients with COVID-19 gains significant importance given the efforts to develop a new vaccine, as this could be an initial step towards the selection of the population at risk which can benefit the most from the developing vaccines at an earlier stage of the disease.

Besides the initial pulmonary manifestations of COVID-19, multi-organ involvement such as cardiovascular, neurologic, renal, and gastrointestinal manifestations have been reported. Hepatic manifestations, in particular, occur in about 50% of patients with COVID-19 which can range from asymptomatic transaminitis to, less frequent acute liver failure[1]. The etiology behind the hepatic manifestations of COVID-19 remains unclear and postulated mechanisms include ischemic liver injury, immune-mediated liver injury, drug-induced liver injury, and a direct viral cytopathy [1,2]. The correlation of the worse outcomes of COVID-19 and pre-existing viral hepatitis is unclear, as there is little evidence to support this association.

The effect of preexisting chronic hepatitis C virus (HCV) infection, which is known to cause several extrahepatic manifestations independent of liver injury[3], in COVID-19 patients has not been studied. In one meta-analysis of the COVID-19 patients have reported an estimate of 3% prevalence of pre-existing chronic liver disease[4]. To the best of our knowledge, this data does not provide specific information regarding the prevalence and impact of viral hepatitis, specifically HCV in COVID-19 patients. Initial reports have suggested that COVID-19 patients with HCV are at increased risk for

poor outcomes especially if accompanied by other risk factors such as advanced age and hypertension. The aim of our work was to assess the prevalence of the history of HCV among patients with COVID-19 and to study the relationship between in-hospital mortality with other predictors of poor outcomes in the presence or absence of baseline liver dysfunction or COVID-19 induced acute liver injury (ALI).

MATERIALS AND METHODS

Our study is a retrospective review and included all hospitalized patients at our institution with COVID-19 between March 15, 2020 and May 30, 2020. All patients had nasal swabs positive for SARS-CoV-2. Patients below the age of 18 years were excluded from study.

We reviewed medical charts and the laboratory parameter (HCV antibody) to obtain the HCV infection status. The patient who did not have HCV antibody testing was not included in the analysis. HCV viral load levels were abstracted from the electronic medical records. Patients were then divided into two groups based on the presence or absence of a history of HCV and their demographic, clinical, laboratory variables, and outcomes were compared. The primary endpoint of our study was in-hospital mortality.

Statistical analysis

Continuous variables were expressed as mean \pm SD, and nominal and categorical variables were expressed as numbers (%). The independent sample *t*-test and one-way ANOVA were used to compare the mean values of different groups, and chi-square test was used for comparison of nominal and categorical variables. Predictors of mortality were checked using univariate and multivariate Cox regression models. Propensity score matching was used between patients with and without HCV to create subgroups matched for age, sex, body mass index (BMI), and all co-morbidities and all models were repeated for subgroups. Kaplan-Myer survival curves were used to test the difference in cumulative in-hospital outcomes. A 2-log likelihood ratio was initiated to compare 4 different models for the prediction of in-hospital mortality. The first model (clinical model) consisted of clinical parameters reported in the literature to be associated with mortality in COVID-19 patients, namely, age, sex, hypertension (HTN), diabetes mellitus (DM), history of respiratory disease, and history of cardiac disease. The second model (laboratory model) consisted of laboratory values reported in the literature to be associated with worse in-hospital mortality, namely D-dimer, lactate dehydrogenase (LDH), high sensitivity C-reactive protein (hsCRP), and serum creatinine. The third model was a combined clinical and laboratory model, and the fourth model was the combined model with the addition of the history of HCV. For all statistical tests, a *P* value < 0.05 was considered statistically significant. All analyses were performed with commercially available software (SPSS version 23.0; SPSS, Inc).

RESULTS

During the study period, 1207 patients with confirmed COVID-19 were identified. Seven patients were excluded as their age was ≤ 18 years and another 7 patients were excluded as their HCV status was not clear and accordingly 1193 patients were included in the analysis. The baseline demographic, clinical, laboratory and imaging criteria for all patients are summarized in Supplementary Table 1. Of the study group, 50 (5%) had HCV infection, and 1157 (95%) did not have HCV infection. Baseline demographic clinical and laboratory data compared for patients with and without HCV are summarized in Table 1. Briefly, HCV patients had lower BMI, higher incidence of HIV, asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and chronic kidney disease (CKD) at baseline. In addition, patients with HCV presented to the hospital earlier than patients without HCV, and, on hospital admission, had higher lymphocytic count and lower CRP, however, had worse serum creatinine, aspartate aminotransferase (AST), conjugated bilirubin, higher pro-calcitonin, lower hemoglobin, and lower platelet count. All other demographic, clinical, and laboratory values were not different between both groups.

The use of hydroxychloroquine, azithromycin, and tocilizumab was not different between both groups, however, it's to be noted that none of the HCV patients received tocilizumab. Importantly, both mortality and in-hospital mechanical ventilation were

Table 1 Comparison between patients with and without hepatitis C virus, *n* (%)

	All patients (<i>n</i> = 1193)			Propensity score matched ¹ (<i>n</i> = 98)		
	No HCV (<i>n</i> = 1143)	HCV (<i>n</i> = 50)	<i>P</i> value	No HCV (<i>n</i> = 48)	HCV (<i>n</i> = 50)	<i>P</i> value
Age (yr)	62 ± 16	64 ± 9	0.402	64 ± 15	64 ± 9	0.803
Gender (female)	456 (39.90)	14 (28.00)	0.092	20 (41.67)	14 (28.00)	0.155
Body mass index (kg/m ²)	30 ± 7	27.7 ± 8.5	0.026	27.9 ± 6.8	28 ± 9	0.917
Hypertension	703 (61.50)	31 (62.00)	0.944	33 (68.75)	31 (62.00)	0.483
Diabetes mellitus	530 (46.37)	17 (34.00)	0.086	17 (35.42)	17 (34.00)	0.883
Human immune-deficiency virus	58 (05.07)	21 (42.00)	< 0.001	17 (35.42)	21 (42.00)	0.504
Asthma	144 (12.60)	10 (20.00)	< 0.001	9 (18.75)	10 (20.00)	0.612
Chronic obstructive pulmonary disease	105 (09.19)	14 (28.00)	< 0.001	9 (18.75)	14 (28.00)	0.280
Hepatitis B infection	1 (00.09)	3 (06.00)	< 0.001	0 (00.00)	3 (06.00)	0.085
Congestive heart failure	105 (09.19)	12 (24.00)	0.001	10 (20.83)	12 (24.00)	0.707
Coronary artery disease	119 (10.41)	6 (12.00)	0.720	6 (12.50)	6 (12.00)	0.940
Chronic kidney disease	89 (07.79)	9 (18.00)	0.01	5 (10.42)	9 (18.00)	0.284
End stage renal disease	77 (06.74)	5 (10.00)	0.372	2 (04.17)	5 (10.00)	0.262
Fever	753 (65.88)	31 (62.00)	0.525	26 (54.17)	31 (62.00)	0.585
Cough	771 (67.45)	24 (48.00)	0.003	27 (56.25)	24 (48.00)	0.294
Shortness of breath	787 (68.85)	40 (80.00)	0.110	34 (70.83)	40 (80.00)	0.478
Myalgia	352 (30.80)	11 (22.00)	0.175	19 (39.58)	11 (22.00)	0.04
Chest discomfort	144 (12.60)	5 (10.00)	0.572	3 (06.25)	5 (10.00)	0.538
Atypical symptoms	392 (34.30)	19 (38.00)	0.611	20 (41.67)	19 (38.00)	0.585
Symptom onset to hospitalization (d)	5.85 ± 5.56	3.79 ± 4.04	0.034	6.2 ± 5.7	3.8 ± 4.04	0.053
Length of hospital stay (d)	8.05 ± 7.05	6.2 ± 4.3	0.072	7 ± 5.79802	6.2 ± 4.3	0.454
Hemoglobin	13.0 ± 2.2	12.2 ± 2.7	0.021	12.5 ± 2.1	12.2 ± 2.7	0.598
Total white count	8.6 ± 6.6	9.8 ± 13.1	0.244	7.78 ± 3.5	9.8 ± 13.1	0.300
Platelets	221.7 ± 103.3	183 ± 73.5	0.015	234.4 ± 100	183 ± 73	0.007
Neutrophilic count	6.8 ± 4.05	6.1 ± 3.8	0.224	6.3 ± 3.4	6.1 ± 3.8	0.780
Lymphocyte count	1.18 ± 4.86	2.86 ± 12.3	0.037	0.99 ± 0.52	2.86 ± 12.3	0.302
D-dimer	3115 ± 9997	2270 ± 5383	0.582	6883 ± 28017	2270 ± 5383	0.293
Lactate dehydrogenase	581 ± 393	623 ± 391	0.477	523 ± 419	623 ± 391	0.248
High sensitivity C-reactive protein	143 ± 113	98 ± 76	0.013	129 ± 89	98 ± 75	0.095
Ferritin	1148 ± 1574	1265 ± 2098	0.647	1053 ± 1267	1265 ± 2098	0.576
Lactate	2.3 ± 1.9	2.7 ± 2.6	0.265	2.07 ± 1.3	2.7 ± 2.6	0.189
Prothrombin time (s)	14 ± 10.7	13.4 ± 2.5	0.716	13.6 ± 2.3	13.4 ± 2.4	0.700
Activated partial thromboplastin time (s)	32.2 ± 7.9	32.7 ± 6.3	0.67	31.4 ± 5.4	32.7 ± 6.3	0.317
Creatinine	1.9 ± 2.6	3.3 ± 3.5	< 0.001	2.01 ± 2.4	3.3 ± 3.5	0.039
Alanine transaminase	43.7 ± 66.4	53.2 ± 121.7	0.386	40.8 ± 37.5	53.2 ± 121.7	0.538
Aspartate transaminase	68.6 ± 90.8	128.1 ± 367.2	0.001	59.8 ± 43.5	128.2 ± 367	0.246
Alkaline phosphatase	94.2 ± 86.4	111.5 ± 143	0.224	82.3 ± 40.7	111.5 ± 143	0.217
Total bilirubin	0.6 ± 0.7	0.8 ± 0.86	0.111	0.54 ± 0.41	0.8 ± 0.9	0.087
Combined bilirubin	0.27 ± 0.45	0.45 ± 0.68	0.02	0.26 ± 0.28	0.45 ± 0.68	0.115

Total protein	6.98 ± 0.83	7.2 ± 0.98	0.163	6.91 ± 0.72	7.2 ± 0.98	0.175
Albumin	3.59 ± 0.55	3.44 ± 0.56	0.089	3.6 ± 0.5	3.4 ± 0.6	0.209
Procalcitonin	2.34 ± 9.4	7.27 ± 21.4	0.02	3.08 ± 8.8	7.3 ± 21.4	0.453
Hydroxychloroquine	878 (76.82)	36 (72.00)	0.711	33 (68.75)	36 (72.00)	0.725
Azithromycin	839 (73.40)	32 (64.00)	0.303	35 (72.92)	32 (64.00)	0.343
Tocilizumab	78 (06.82)	0 (00.00)	0.149	4 (08.33)	0 (00.00)	0.054
Mechanical ventilation	449 (39.28)	29 (58.00)	0.003	4 (08.33)	29 (58.00)	< 0.001
Death	386 (33.77)	28 (56.00)	0.004	7 (14.58)	28 (56.00)	< 0.001

¹Patients without hepatitis C virus (HCV) were matched to patients with HCV using propensity score matching for age, sex, body mass index, and all risk factors. HCV: Hepatitis C virus.

significantly higher in patients with HCV.

Predictors of in-hospital mortality

The overall predictors of in-hospital mortality are summarized in Table 2. Univariate Cox-regression model showed that the independent predictors of in-hospital mortality were age, sex, HTN, DM, HIV, COPD, HCV, CHF, CKD, neutrophilic count, D-dimer, LDH, hsCRP, ferritin, total and conjugated bilirubin, albumin, pro-calcitonin levels, and platelet count. Multivariate cox-regression models however showed that age, HCV, D-Dimer, and ferritin were the only predictor of in-hospital mortality, while all other variables lost statistical significance. Kaplan-Meier curves were initiated for patients with and without HCV and revealed that patients with HCV have worse cumulative in-hospital mortality compared to patients without HCV ($P < 0.001$, Figure 1).

Chronic liver disease and ALI in association to HCV

Liver function tests were available in only 1065 patients. Liver enzymes [AST and alanine aminotransferase (ALT)] were normal in 416 patients. Only ALT was elevated in 6 patients (all of whom did not have HCV), only AST was elevated in 423 patients, and both AST and ALT were elevated in 201 patients. Overall, AST was higher than ALT in 633 patients with a mean absolute AST/ALT of 1.88 ± 1.5 in all patients. It was noted that, with the exception of the absolute AST/ALT ratio which was higher in patients with HCV ($P = 0.023$), none of the previous parameters was different between the two groups. Moreover, history of fatty liver disease, history of cirrhosis, and the fibrosis score (Fib-4 score) was not different between both groups.

ALI, was defined in our study as an increase in both admission AST and ALT 2 times above the upper normal limit or elevation of either admission AST or ALT 2 times above the upper normal limit in addition to at least one of the following: Elevated admission combined bilirubin, elevated admission total bilirubin or elevated admission PT more than 2 times the normal limit. Based on our definition, ALI occurred in 107 (10%) of all patients and was not different between patients without or with HCV (100 vs 7, respectively, $P = 0.127$).

Univariate Cox-regression models revealed that ALI, AST/ALT ratio, the presence of any elevation of liver enzyme even if it was less than 2 times the normal value, and overall AST more than ALT levels, and Fib-4 score were all predictive of in-hospital mortality in addition to HCV. The multivariate Cox-regression model, however, revealed that only AST/ALT ratio, Fib-4 score, and HCV were predictors of in-hospital mortality.

Propensity score matching

Next, propensity score matching was initiated between patients with and without HCV for age, sex, BMI, HTN, DM, HIV, COPD, CHF, and CKD. As seen in Table 1, almost all differences between the groups were eliminated after matching with the exception of lower platelet count in patients with HCV. It is important to note that the worse in-hospital mortality and need for mechanical ventilation in patients with HCV persisted despite matching. Moreover, univariate and multivariate models for in-hospital mortality prediction were re-initiated and it was found that sex, HTN, and HCV were the only univariate predictors of mortality, while HCV was the only predictor of mortality in the multivariate model as sex and HTN lost statistical

Table 2 Cox regression model for all patients and hepatitis C virus patients for prediction of mortality

	All patients (n = 1193)				Propensity score matched (n = 98)			
	Univariate		Multivariate		Univariate		Multivariate	
	Exp (B)	Sig.	Exp (B)	Sig.	Exp (B)	Sig.	Exp (B)	Sig.
Age (yr)	1.028	< 0.001	1.029	< 0.001	1.022	0.183	-	-
Gender (female)	0.675	< 0.001	0.865	0.42	0.488	0.05	0.714	0.110
Body mass index (kg/m ²)	0.991	0.184	-	-	1.014	0.514	-	-
Hypertension	1.611	< 0.001	0.843	0.386	2.87	0.004	2	0.051
Diabetes mellitus	1.394	0.001	1.208	0.277	1.06	0.864	-	-
Human immune-deficiency virus	1.797	< 0.001	1.251	0.492	1.92	0.064	-	-
Asthma	0.864	0.341	-	-	1.39	0.357	-	-
Chronic obstructive pulmonary disease	1.435	0.013	1.043	0.879	1.222	0.591	-	-
Hepatitis B infection	1.984	0.237	-	-	1.04	0.962	-	-
HCV	2.224	< 0.001	2.435	0.041	3.88	0.001	3.46	0.004
Congestive heart failure	1.4	0.02	1.249	0.356	1.253	0.545	-	-
Coronary artery disease	1.387	0.023	1.092	0.734	1.05	0.923	-	-
End stage renal disease	1.208	0.305	-	-	1.013	0.983	-	-
Chronic kidney disease	1.437	0.016	1.188	0.535	1.024	0.957	-	-
Hemoglobin	0.966	0.123	-	-	0.925	0.337	-	-
Total white count	1.006	0.376	-	-	1.004	0.736	-	-
Platelets	0.998	< 0.001	0.999	0.438	0.999	0.525	-	-
Neutrophilic count	1.023	0.028	0.991	0.658	1.072	0.145	-	-
Lymphocyte count	0.993	0.641	1	0.163	1.000	0.976	-	-
D-dimer	1	< 0.001	1.001	< 0.001	1.000	0.09	-	-
Lactate dehydrogenase	1.001	< 0.001	1.001	0.374	1.000	0.714	-	-
High sensitivity C-reactive protein	1.002	< 0.001	1	0.553	0.999	0.788	-	-
Ferritin	1	0.002	1.053	0.028	1.000	0.902	-	-
Prothrombin time (s)	1.001	0.89	-	-	1.1	0.281	-	-
Activated partial thromboplastin time (s)	0.998	0.804	-	-	0.966	0.281	-	-
Creatinine	1.072	< 0.001	-	-	1.08	0.91	-	-
Alanine transaminase	0.999	0.325	-	-	0.998	0.371	-	-
Aspartate transaminase	1	0.391	-	-	0.999	0.402	-	-
Alkaline phosphatase	0.999	0.222	-	-	0.275	0.995	-	-
Total bilirubin	1.131	0.002	1.026	0.925	1.16	0.475	-	-
Combined bilirubin	1.327	< 0.001	1.091	0.733	1.17	0.510	-	-
Total protein	0.932	0.235	-	-	0.892	0.560	-	-
Albumin	0.681	< 0.001	0.933	0.678	0.613	0.114	-	-
Procalcitonin	1.014	< 0.001	1.001	0.793	1.008	0.544	-	-

HCV: Hepatitis C virus.

significance (Table 2). Kaplan Meier curves were also reinitiated for matched patients with and without HCV and revealed that patients with HCV continued to have worse cumulative in-hospital mortality compared to patients without HCV ($P < 0.001$, Figure 2)

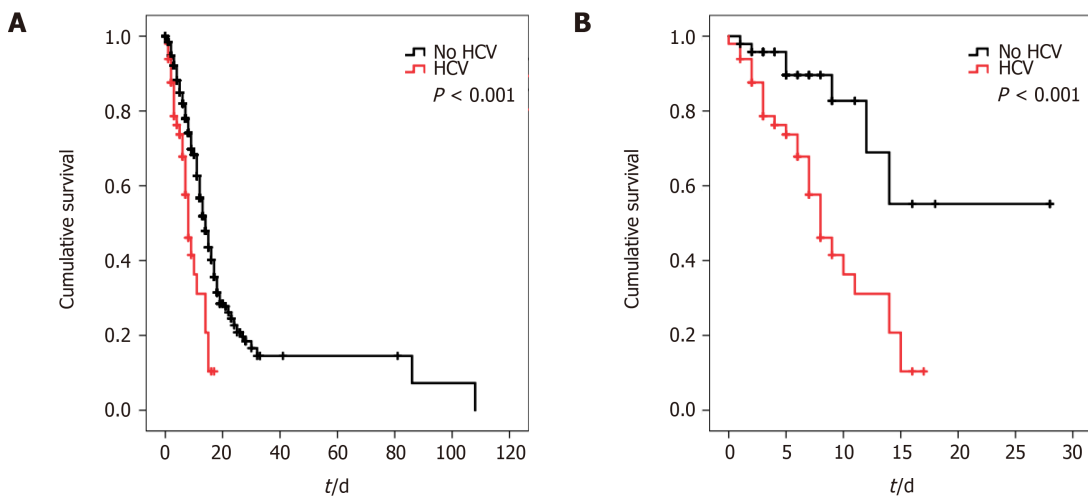


Figure 1 Kaplan-Myer curves for in-hospital survival in patients with and without hepatitis C virus. A: In the overall study group; B: After propensity score matching. HCV: Hepatitis C virus.

Comparison for parameters of liver functions, chronic liver disease, and ALI was similar in the matched and unmatched groups as AST/ALT ratio and history of chronic liver disease remained significantly higher in the HCV group (Table 3). Importantly, univariate Cox-regression models revealed that only HCV and Fib-4 score were predictive of mortality, while the multivariate cox-regression model showed that HCV was the only predictor of mortality among all liver function parameters (Table 4). HCV: 65%, no HCV: 34%, $P < 0.001$ ALI: 53% *vs* 34% and 34% in patients without HCV and without ALI, respectively.

Comparison between chronic HCV and matched controls

It is to be noted that, all HCV patients in our study received anti-viral treatment. Twenty-six of these patients had sustained viral response. Viral load was still detectable in the remaining 24 patients (chronic HCV, viral loads: 1688184 ± 1439771 , median: 1380000, SE: 434107, minimum: 269, maximum: 3610259 IU/mL). Comparisons between this the subgroup of chronic HCV patients and matched controls continued to show no differences in baseline demographic, clinical, and laboratory variables, however, death and need for mechanical ventilation continued to be observed more frequently in chronic HCV patients (Table 5). A subgroup Cox-regression analysis for predictors of in-hospital mortality (matched controls and chronic HCV, $n = 72$) showed that hypertension and HCV were the only predictors of mortality in the univariate analysis. While both HCV and hypertension retained their predictive ability in the multivariate model, HCV was significantly stronger as an independent predictor of mortality (Table 5).

Comparison between predictive models

Model comparisons were done using the -2-log likelihood test which was initiated to assess the cumulative predictive abilities of 4 different models for in-hospital mortality. The first model was composed of the most reported clinical predictors of mortality (clinical model), the second model was composed of the most important reported laboratory variables associated with in-hospital mortality (laboratory model), the third model was a combination of clinical and laboratory model, and the fourth model represented the third model with the addition of history of HCV. It was found that, while the clinical and laboratory models seem to be additive for the prediction of mortality, the addition of HCV to any of these models including the combined model increased the predictive accuracy for in-hospital mortality (Figure 3).

DISCUSSION

The findings of our study can be summarized as follows: First, in a cohort of COVID-19 patients in a single-center, the frequency of history of chronic HCV infection is 4.1%, the frequency of COVID-19 induced ALI is 10%, both of which were associated with significant in-hospital mortality compared to patients without HCV or ALI.

Table 3 Comparison between liver enzymes, acute liver injury, chronic liver disease, and fibrosis score between patients with and without hepatitis C virus, *n* (%)

	All (<i>n</i> = 1065)	ALI patients (<i>n</i> = 1065)			Propensity score matched (<i>n</i> = 81)		
		No HCV (<i>n</i> = 1014)	HCV (<i>n</i> = 41)	<i>P</i> value	No HCV (<i>n</i> = 40)	HCV (<i>n</i> = 41)	<i>P</i> value
AST/ALT	1.88 ± 1.5	1.86 ± 1.5	2.4 ± 1.3	0.023	1.8 ± 0.88	2.4 ± 1.27	0.015
Any liver enzyme elevated	639 (60)	610 (60)	29 (71)	0.174	25 (63)	29 (71)	0.423
Normal liver enzymes	416 (39)	311 (31)	10 (24)	0.242	15 (38)	10 (24)	0.223
Only ALT elevated	6 (1)	6 (1)	0 (0)		0 (0)	0 (0)	
Only AST elevated	432 (41)	409 (40)	23 (56)		15 (38)	2356	
Both elevated	201 (19)	195 (19)	6 (15)		10 (25)	6 (15)	
AST > ALT	423 (40)	399 (39)	20 (49)	0.394			0.394
All AST > ALT	633 (59)	604 (60)	29 (71)	0.153	25 (63)	29 (71)	0.423
Fatty liver	50 (5)	48 (5)	2 (5)	0.931	1 (3)	2 (5)	0.582
History of cirrhosis	6 (1)	5 (1)	1 (2)	0.228	2 (5)	1 (0)	0.534
Fib-4 score	3.43 ± 5.5	3.47 ± 5.6	3.1 ± 3.6	0.642	3.4 ± 2.25	3.1 ± 3.6	0.249
ALI ¹	107 (10)	100 (10)	7 (17)	0.128	3 (8)	7 (17)	0.166

¹Acute liver injury; defined as any of the following criteria: Both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated 2 times above the upper normal; and Limit or any of AST or ALT elevated 2 times above the upper normal level, and at least one of the following: Elevated combined bilirubin, total bilirubin or elevated PT more than 2 times the normal limit. HCV: Hepatitis C virus; ALI: Acute liver injury AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Table 4 Comparison between Liver enzymes, acute liver injury, and fibrosis score between patients with and without hepatitis C virus for prediction of mortality, *n* (%)

	ALI patients (<i>n</i> = 1065)				Propensity score matched (<i>n</i> = 81)			
	Univariate		Multivariate		Univariate		Multivariate	
	Exp (B)	Sig.	Exp (B)	Exp (B)	Sig.	Exp (B)	Sig.	Sig.
AST/ALT	1.1	< 0.001	1.06	< 0.001	1.204	0.221	-	-
Any liver enzyme elevated	1.427	0.002	0.001	0.823	1.204	0.624	-	-
All AST > ALT	1.455	0.001	0.001	0.852	1.204	0.624	-	-
History of cirrhosis	1.368	0.659	-	-	1.95	0.513	-	-
ALI ¹	1.418	0.015	1.045	0.792	1.132	0.817	-	-
Fib-4 score	1.02	< 0.001	1.022	< 0.001	1.1	0.042	1.1	0.08
HCV	2.224	< 0.001	2.15	< 0.001	3.88	0.001	3.75	0.002

¹Acute liver injury; defined as any of the following criteria: Both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) elevated 2 times above the upper normal; and Limit or any of AST or ALT elevated 2 times above the upper normal level, and at least one of the following: Elevated combined bilirubin, total bilirubin or elevated PT more than 2 times the normal limit. HCV: Hepatitis C virus; ALI: Acute liver injury AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Second, in those patients, HCV seems to be an independent predictor of in-hospital mortality and seems to be stronger than the traditionally reported predictors of mortality in COVID-19 patients. The predictive ability of history of HCV infection for mortality in COVID-19 persists independent of baseline liver functions, fibrosis, and the acute COVID-19 induced ALI. Finally, the history of HCV infection seems to add cumulative predictive ability to other traditional clinical and laboratory risk factors for in-hospital mortality.

Table 5 Subgroup comparisons and cox-regression predictors of outcomes for a subset composed of patients with chronic hepatitis C virus and propensity score matched patients without hepatitis C virus, *n* (%)

	Propensity score matched (<i>n</i> = 72)						
	Comparison between groups			Cox-regression analysis			
	NO HCV (<i>n</i> = 48)	HCV with viral load (<i>n</i> = 24)	<i>P</i> value	Univariate Exp (B)	Sig.	Multivariate Exp (B)	Sig.
Age (yr)	64.4 ± 15.1	64.4 ± 9.8	0.995	1.021	0.293	-	-
Gender (female)	28 (58)	17 (71)	0.302	0.481	0.088	-	-
Body mass index (kg/m ²)	27.9 ± 6.8	26.0 ± 6.2	0.252	1.014	0.625	-	-
Hypertension	33 (69)	16 (67)	0.858	3.03	0.014	2.55	0.035
Diabetes mellitus	17 (35)	7 (29)	0.596	1.05	0.902	-	-
Human immune-deficiency virus	17 (35)	9 (38)	0.862	1.79	0.185	-	-
Asthma	9 (19)	4 (17)	0.828	1.81	0.251	-	-
Chronic obstructive pulmonary disease	9 (19)	5 (21)	0.833	1.386	0.483	-	-
Hepatitis B infection	1 (0.2)	0 (0)	0.476	1.04	0.976	-	-
HCV	0 (0)	24 (100)	-	3.47	0.007	3.2	0.014
Congestive heart failure	10 (21)	5 (21)	1.000	1.41	0.448	-	-
Coronary artery disease	6 (13)	2 (8)	0.596	1.12	0.845	-	-
End stage renal disease	2 (0.4)	1 (4)	1.000	1.65	0.628	-	-
Chronic kidney disease	5 (10)	6 (25)	0.105	1.1	0.875	-	-
Hemoglobin	12.5 ± 2.1	11.7 ± 2.6	0.166	0.921	0.424	-	-
Total white count	7.8 ± 3.5	12 ± 17.9	0.122	1.006	0.618	-	-
Platelets	234.4 ± 100.3	185 ± 86.2	0.051	1.000	0.978	-	-
Neutrophilic count	6.27 ± 3.4	6.24 ± 4.3	0.981	1.11	0.056	-	-
Lymphocyte count	0.99 ± 0.5	4.62 ± 17.0	0.145	1.002	0.897	-	-
D-dimer	6883 ± 28017	1154 ± 1807	0.333	1.000	0.054	-	-
Lactate dehydrogenase	523 ± 419	649 ± 484	0.273	1.000	0.898	-	-
High sensitivity C-reactive protein	129 ± 90	113 ± 89	0.518	0.999	0.751	-	-
Ferritin	1053 ± 1267	1373 ± 2775	0.533	1.000	0.661	-	-
Prothrombin time (s)	13.6 ± 2.3	13.5 ± 2.5	0.820	1.05	0.636	-	-
Activated partial thromboplastin time (s)	31.4 ± 5.4	32.9 ± 7.28	0.365	0.935	0.138	-	-
Creatinine	2.01 ± 2.4	3.2 ± 4.	0.132	1.06	0.315	-	-
Alanine transaminase	40.8 ± 37.5	62.1 ± 169.8	0.448	0.998	0.427	-	-
Aspartate transaminase	59.8 ± 43.5	169.8 ± 518.6	0.185	0.999	0.433	-	-
Alkaline phosphatase	82.3 ± 40.7	114.5 ± 165.7	0.246	0.996	0.376	-	-
Total bilirubin	0.54 ± 0.4	0.93 ± 1.1	0.05	1.236	0.336	-	-
Combined bilirubin	0.26 ± 0.28	0.58 ± 0.9	0.05	1.223	0.428	-	-
Total protein	6.91 ± 0.72	7.0 ± 0.95	0.618	0.813	0.380	-	-
Albumin	3.6 ± 0.51	3.3 ± 0.52	0.073	0.509	0.079	-	-
Procalcitonin	3.1 ± 8.8	4.6 ± 11.7	0.695	0.984	0.538	-	-
Hydroxychloroquine	33 (69)	18 (75)	0.582	-	-	-	-

Azithromycin	35 (73)	13 (54)	0.112	-	-	-	-
Tocilizumab	4 (8)	0 (0)	0.146	-	-	-	-
Mechanical ventilation	4 (8)	15 (63)	< 0.001	-	-	-	-
Death	7 (15)	15 (63)	< 0.001	-	-	-	-

HCV: Hepatitis C virus.

Chronic HCV, ALI, and in-hospital mortality in COVID-19 patients

In this single-center study, traditional predictors of mortality in patients with COVID-19 were strongly associated with in-hospital mortality as reported in several studies which was in agreement with previous reports. Interestingly, however, HCV was overall strongly associated with in-hospital mortality. The incidence of history of HCV infection in our study was on the higher side of that reported in the literature (50 patients, 4.1%). In a large series of 5700 hospitalized patients with COVID-19, HCV infection was encountered in < 0.1% of patients[5]. There is a local higher prevalence of injection drug abuse in the community wherefrom the study cohort was included (Bronx, New York), which is reportedly significantly associated with increased incidence and prevalence of HCV and may explain the higher HCV prevalence in our cohort[6]. Initial reports have suggested that COVID-19 patients with HCV are at increased risk for poor outcomes especially if accompanied by other risk factors of poor outcomes such as advanced age and hypertension[5]. In our study, despite that HCV adds a cumulative increased risk of mortality to both clinical and laboratory predictors of mortality risk, HCV stood out as the only strong predictor of mortality after matching patients with and without HCV for all other baseline confounding clinical and laboratory predictors of mortality which may suggest that the pathological effect of the COVID-19 virus is accentuated in HCV patients compared to patients without HCV irrespective of their age, baseline clinical status, or admission laboratory parameters.

Moreover, in our study, the incidence of COVID-associated ALI was comparable to previous studies[7] (107 patients, 10%) and was associated with 53% mortality, which was significantly higher than patients without ALI (34%, $P < 0.001$). However, almost all parameters of ALI, chronic liver disease, as well as liver fibrosis, despite associated with mortality, were not different between patients with and without HCV, and, moreover, HCV outperformed ALI as a predictor of mortality, both overall and after matching, which brings the question whether ALI in patients with COVID-19 is a result of direct SARS-CoV-2 viral effect on the liver or just a result of cytokine storm, multi-organ failure or even medication-induced. The lack of differences of ALI between patients with and without HCV may also indicate that liver injury in HCV patients was not the primary cause of the accentuated mortality effect of the SARS-CoV-2 virus.

Postulated mechanisms

A review of the pathophysiology of the infection of HCV and SARS-CoV-2 elucidates several overlapping mechanisms (Figure 3). SARS-CoV-2 uses the ACE-2 receptor as a main point of entry to the target cell[8]. ACE2 receptors exist on the surface of the cholangiocytes indicating that the liver could be a potential target for SARS-CoV-2, however[8], data so far shows that SARS-CoV-2 seldom affects the liver severely. One molecule that has been identified to potentiate SARS-CoV-2 viral entry is the transmembrane protease serine 2 (TMPRSS2), which is suggested to affect the S protein at the cell surface and induces SARS-CoV-2-cellular membrane fusion[9]. Importantly, TMPRSS2 is over-expressed in patients with HCV which may lead the exaggerated SARS-CoV-2 infection in these patients[10]. Second, HCV is a systemic disease, associated with significant extrahepatic morbidity despite that can occur independently of liver injury[11]. Reportedly, HCV antibodies seropositivity was associated with 1.5-folds increased non-liver-related mortality[12]. The mechanisms may involve the induction of circulating immune complexes and immune-mediated cellular toxicity, which is reported to occur in SARS-CoV-2 and may be related to the potentiated effects on the virus in HCV patients. Third, there seems to be an immune response overlap between chronic HCV and SARS-CoV-2 infection[13]. Studies have shown that in chronic HCV infection there is a correlation between the production of pro-inflammatory cytokines, such as INF- γ and TNF- α , and progressive liver injury, while the regulatory cytokines such as IL-4 and IL-10 may modulate the pro-inflam-

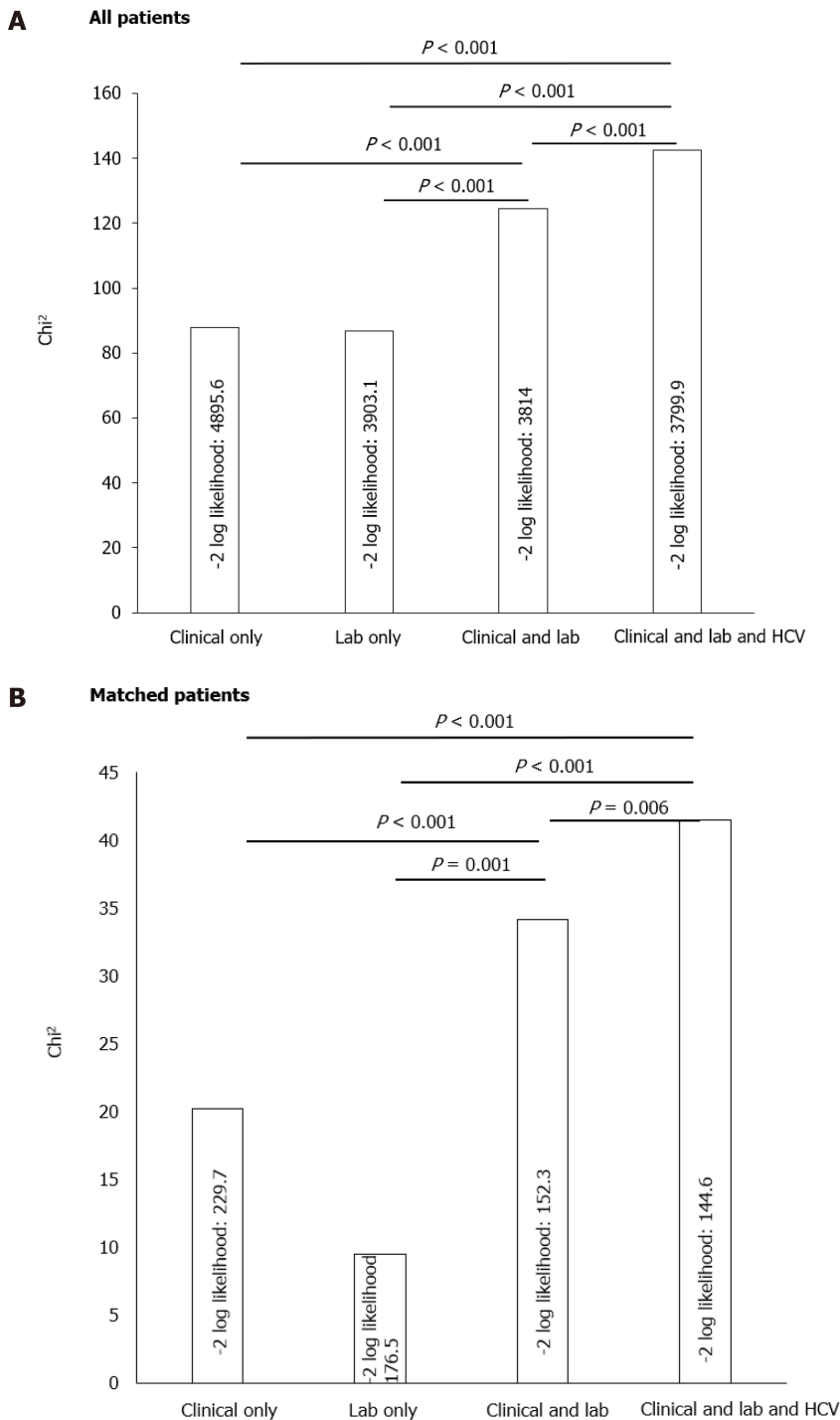


Figure 2 Comparison between different models for prediction of coronavirus disease 2019 associated in-hospital mortality. Comparisons were done using the -2-log likelihood ratio. The first model (clinical model) consisted of clinical parameters (age, sex, hypertension, diabetes mellitus, history of respiratory disease, and history of cardiac disease). The second model (laboratory model) consisted of laboratory values (D-dimer, lactate dehydrogenase, high sensitivity C-reactive protein, and serum creatinine). The third model was a combined clinical and laboratory model, and the fourth model was the combined model with the addition of history of hepatitis C virus. A: In the overall study group; B: After propensity score matching. HCV: Hepatitis C virus.

matory immune response induced by the virus[14,15]. Importantly, several cytokines are elevated in SARS-CoV-2 and are significantly associated with mortality[16-18]. A recent study showed that higher levels of INF- γ , elevated in both conditions, are associated with elevated mortality in patients with COVID-19[16]. Moreover, HCV triggers a systemic cytokine response controlled by TNF and IL-10. This may indicate that a baseline inflammatory status in patients with HCV could be related to the higher mortality in those patients when contracting COVID-19. Reportedly, the cytokine response to HCV infection mirrors the liver fibrosis score[17], which sheds the light on the fact that despite the FIB-4 score in our study was not different between HCV and non-HCV patients, it was the only other predictor of mortality in the

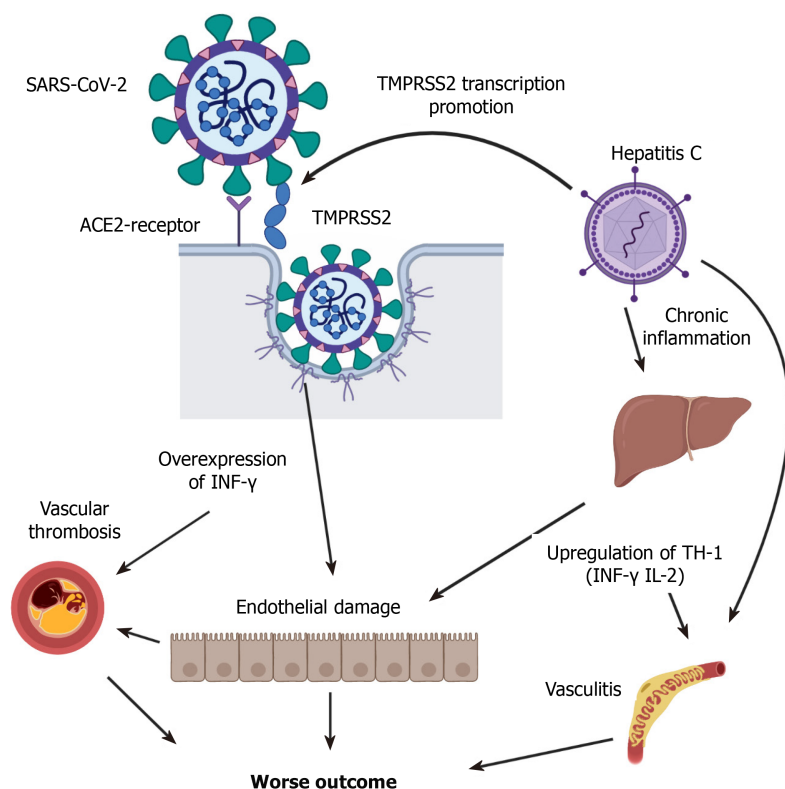


Figure 3 Relationship between Chronic hepatitis C and severe acute respiratory syndrome coronavirus 2 physiopathology. Postulation of 4 possible mechanisms involved. SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; TMPRSS2: Transmembrane protease serine 2.

matched group.

Finally, Vascular endothelial dysfunction is another overlapping mechanism between HCV and SARS-CoV-2 viruses. Reportedly, chronic HCV accelerates atherosclerotic process by inducing endothelial dysfunction and is significantly influenced by the progression of liver fibrosis[18,19]. Recent pathological reports have shown that viral elements exist within endothelial cells of patients with COVID-19 associated with the accumulation of inflammatory cells, causing endotheliitis[15]. Reportedly, the integrity of the endothelial function and immune system is crucial for a regulated immune response good enough to control the virus spread[20,21]. As such, direct endothelial infection in COVID-19 patients can be aggravated by the baseline endothelial dysfunction reported to occur in patients with chronic HCV infection.

Limitations

The following limitations existed in our study and should be investigated in future studies: First, the sample size particularly that of HCV patients is small, however, this is a limitation that arises from the prevalence of HCV in COVID-19 patients. Future studies and meta-analyses should be done to check if the findings of the current study can be reproduced. Second, viral loads were not obtained for all the patients with a history of HCV, and as such, the status of their HCV infection, viral clearance and its effects on mortality could not be assessed precisely. Third, despite the fact that the postulated mechanisms are all dependent on pathological, functional, or microbiological evidence, none of these have been measured in our study. Information regarding differences in cytokines, endothelial function, and ACE-2 activity should be evaluated in future studies between COVID-19 patients with and without HCV.

CONCLUSION

In patients with COVID-19, a history of HCV and seropositive HCV infection leads to accentuated SARS-CoV-2 viral virulence and is a strong predictor of in-hospital mortality irrespective of baseline comorbidities, admission laboratory variables, or COVID-19-induced liver injury. The history of HCV in these patients seems to add a cumulative mortality risk to any clinical or laboratory profile. The mechanisms

involved may be related to extrahepatic effects of HCV leading to enhanced ACE-2/TMPRSS mechanisms of SARS-CoV-2 viral entry and may also be related to baseline cytokine-mediated pro-inflammation and endothelial dysfunction. The realization and understanding of these mechanisms may help in better characterization of the disease and investigating possible therapeutic options in this subgroup of patients, which is of significant importance as an initial step towards the selection of at-risk groups that can benefit the most of the developing vaccines at an earlier stage of the disease.

ARTICLE HIGHLIGHTS

Research background

The effect of preexisting chronic hepatitis C infection in coronavirus disease 2019 (COVID-19) patients has not been studied. Initial reports have suggested that COVID-19 patients with hepatitis C virus (HCV) are at increased risk for poor outcomes especially if accompanied by other risk factors such as advanced age and hypertension.

Research motivation

We have found that hepatitis C is associated with increased in-hospital mortality in patients hospitalized with COVID-19.

Research objectives

We aimed at assessing the relationship between in-hospital mortality with other predictors of poor outcomes in the presence or absence of baseline liver dysfunction or COVID-19 induced acute liver injury.

Research methods

We reviewed retrospectively the medical charts of patients with COVID-19 admission and the laboratory parameter in patients with and without history of HCV infection. Patients were then divided into two groups based on the presence or absence of a history of HCV and their demographic, clinical, laboratory variables, and outcomes were compared. The primary endpoint of our study was in-hospital mortality.

Research results

Multivariate cox-regression model for liver profile revealed that aspartate aminotransferase/ alanine aminotransferase ratio, Fib-4 score, and HCV were predictors of in-hospital mortality. After propensity score matching HCV was the only predictor of mortality in the multivariate cox-regression model. 2-log likelihood ratio was done to compare different diagnostic models and it was found that a model including HCV add a predictive value to clinical and laboratory parameters.

Research conclusions

HCV infection accentuated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) viral virulence in our study and had a strong association with in-hospital mortality irrespective of baseline co-morbidities, admission laboratory variables, or COVID-19-induced liver injury. The mechanisms involved may be related to extra-hepatic effects of HCV, baseline cytokine-mediated pro-inflammation, and endothelial dysfunction. Understanding of these mechanisms may help in better characterization of the disease and investigating possible therapeutic options in this subgroup of patients.

Research perspectives

COVID-19 is significantly heterogeneous. Predictors of Mortality are numerous and association of baseline risk and co-morbidities are still developing. Based on an observation of HCV association with increased risk in our institution we sought to investigate the relationship between HCV and COVID-19 mortality

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