Chronic Viral Hepatitis Do Not Affect 2019 Novel Coronavirus Disease-Related Outcomes: An Observational Retrospective Study.

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Research article

Keywords: viral hepatitis, SARS-CoV-2, COVID-19, HCV, HBV

DOI: https://doi.org/10.21203/rs.3.rs-99544/v1

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Abstract

BACKGROUND: To date, data about prevalence and clinical impact of viral hepatitis in COVID-19 are scarce and conflicting.

METHODS: We conducted an observational, retrospective study including all subjects tested positive for SARS-CoV-2 from March to May 2020. We evaluated prevalence of chronic viral hepatitis and we performed a matched cohort analysis of patients with and without chronic viral hepatitis comparing COVID-related outcomes.

RESULTS: 980 subjects resulted positive to SARS-CoV-2 on oropharyngeal swabs. Among them 12 (1.2%) were HBsAg positive and 6 (0.6%) had detectable HCV RNA. No one was receiving antiviral therapy. None of these had a documented liver cirrhosis.

We identified 80 SARS-CoV-2 positive individuals with negative viral markers for HBV and HCV for the matched analysis. No statistical differences in hospitalization, need for MV and mortality rates (p 0.79, p 0.28 and p 0.8, respectively) were found. Although not statistically significant (p 0.12), a higher rate of those positive for viral hepatitis were admitted to ICU (29% Vs 15%). Median time of virus clearance was 27.5 (IQR 20,38) days, with no difference between the two groups (p 0.39, 95% CI (-12;4.8)). We found older age and male sex as factors associated with worse outcomes.

CONCLUSION: Our analysis documented similar rates of chronic viral hepatitis among subjects with SARS-CoV-2 infection and general population. Furthermore, in our population, pre-existing viral liver infection did not have any impact on the clinical and virological course of COVID-19.

Background

The novel coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first described in December 2019 in Wuhan, China, and was declared pandemic by the World Health Organization (WHO) on March 11th, 2020.

Recently, it has been documented that, similarly to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), liver impairment affects 14–53% of SARS-CoV-2 positive cases over the course of the disease and seems to be more prevalent in severe COVID-19 cases than in mild ones. Furthermore, prevalence of pre-existing liver comorbidities is described in about 2–11% of SARS-CoV-2 patients, with variations between different studies (1).

Whether patients with pre-existing viral hepatitis have a greater risk for COVID-19 and for a more severe evolution of this disease is still unclear.

Concerning the prevalence of viral hepatitis in SARS-CoV-2 infected population, conflicting data are reported in China and United States, probably reflecting different prevalences in the general population. A large hospitalized patients series from Wuhan, China, observed that 2.1% of patients with COVID-19 was
HBV infected, in contrast to 0.1% found in a similar analysis conducted in Northeastern United States; regarding HCV these analysis reported a prevalence lower than 0.1% (2). Only two reports from China described a higher morbidity, mortality and a prolonged SARS-CoV-2 clearance in patients with HBV infection (3, 4).

We aimed to determine the prevalence of pre-existing viral hepatitis in a population of SARS-CoV-2 infected subjects and to evaluate whether this subgroup of patients experienced a more severe progression of COVID-19.

**Methods**

We retrospectively included in our study all the subjects who have been tested positive for SARS-CoV-2 on oropharyngeal swabs performed from March to May 2020, either in Emergency Room or after admission (due to suspected COVID-19) to hospital wards, at S.Orsola Hospital in Bologna.

We evaluated the prevalence of HBsAg, isolated HBcAb and HCV antibody positive subjects and we described COVID-19-related outcomes for the patients with HBsAg positive and/or HCV RNA detectable.

Afterwards, we created a matched cohort from the overall population to compare subjects with HbsAg and/or HCV RNA positivity with subjects with documented negative HBsAg and HCV RNA, to evaluate COVID-related outcomes (hospitalization, ICU admission, Mechanical Ventilation and death) in the two groups. Subjects with documented viral hepatitis were matched to individuals with negative markers for HBV and HCV with respect to age, sex and ward of swab execution. All patients positive for hepatitis were matched 1:5, except for two patients that were matched 1:2 and 1:3. Subjects with HIV-infection or isolated HBcAb positivity were excluded from this analysis. We run logistic regressions to predict the risk for the established clinical outcomes in the two groups of patients.

**Results**

During the study period, 980 SARS-CoV-2 positive subjects were considered overall.

Among them 12 (1.2%) were HBsAg positive, 43 (4.4%) were HBsAg negative/HBcAb positive and 23 (2.3%) were HCV antibody positive. We also observed 6 HBsAg negative/HBcAb positive subjects who had concomitant positive HCV serology. Six out of the 23 HCV-positive individuals resulted also with detectable HCV RNA. Totally, we found 18/980 (1.8%) subjects with a chronic HBV or HCV -related infection (i.e. positive HBsAg or HCV RNA), (Fig. 1). No one was receiving antiviral therapy. None of these had a documented liver cirrhosis. We observed a patient affected by both chronic HCV infection and HIV who was then excluded from the matched analysis, as specified in methods.

Therefore, we included 97 SARS-CoV 2 positive individuals in the matched analysis: 17 subjects with viral hepatitis and 80 subjects with negative viral markers for HBV and HCV.
Among this selected population, 49 (50.5%) were men and the mean age was 69 (range 33–100) years. 71 (73.2%) required hospitalization, 17 (17.5%) needed intensive care and 10 (10.3%) needed Mechanical Ventilation (MV). Mortality rate was 32% (31 individuals out of 97), with death occurring after a median of 7 (IQR 2–17) days from COVID-19 diagnosis.

With respect to the 17 patients with documented viral hepatitis, 29% died, 70.6% required hospitalization and 29% was admitted to ICU. When we compared the two groups, no statistical differences were found in hospitalization and mortality rates (p 0.79 and p 0.8, respectively). Moreover, patients with hepatitis did not require MV more frequently when compared to the other group (p 0.28). Although not statistically significant (p 0.12), a higher rate of those positive for viral hepatitis (rather than of HBV/HCV negative) were admitted to an ICU (29% Vs 15%). In details, 4 of these had HBV and 1 had HCV (Table 1).

Furthermore, we found a median time of virus clearance of 27.5 (IQR 20,38) days, with no difference between the two groups (p 0.39, 95% CI (-12;4.8)).

As expected, factors associated with hospitalization, ICU and MV resulted older age and male sex. Interestingly, albeit not significantly, women died more frequently than men in our cohort (61% Vs 39%): this finding may be explained by an older mean age in the female group (p 0.003).

Conclusion

Recent reports about HBV and HCV infections among the overall population in Italy showed a prevalence of HBsAg positivity between 0.5% and 1% and about 2.3% of HCV Ab positivity (5, 6). Our analysis documented similar rates (i.e. 1.2% was positive for HBsAg and 2.3% for HCV Ab) among the overall subjects with SARS-CoV-2 infection in our cohort. Therefore, one could hypothesize that viral hepatitis are not associated with a greater risk for SARS-CoV-2 acquisition.

Furthermore, in our population, pre-existing viral liver infection did not have any impact on the clinical and virological course of COVID-19.

The retrospective nature and the small sample size represent the major limits of our study, along with the lack of liver function parameters and their trend before and during SARS-CoV-2 infection. In conclusion, our findings suggest that chronic viral hepatitis (in absence of liver cirrhosis) might not affect the risk and the prognosis of SARS-CoV-2 disease, although further confirmations from larger and prospective studies will be needed in order to provide clinicians with more specific information to manage COVID-19 in patients with viral hepatitis.

Declarations

FUNDING

No funding to declare.
**CONFLICT OF INTEREST**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

**ETHICS APPROVAL**

This study has been approved by local ethics committee.

**CONSENT FOR PUBLICATION**

Not applicable.

**AVAILABILITY OF DATA AND MATERIAL** (data transparency)

No additional data are available.

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**Table**
### Table 1.
COVID-19 clinical outcomes in the matched cohort and sorted by HBV/HCV status.

|                | Matched cohort (n. 97) | HBV/HCV+ group (n. 17) | HBV/HCV- group (n. 80) | p value (95% CI) |
|----------------|------------------------|------------------------|------------------------|------------------|
| Death          | 31 (32%)               | 5 (29%)                | 26 (32.5%)             | 0.8 (0.28;0.272) |
| Hospitalization| 71 (73%)               | 12 (70.6%)             | 59 (73.8%)             | 0.79 (0.27;2.71) |
| ICU            | 16 (18%)               | 5 (29%)                | 11 (13.8%)             | 0.12 (0.76;10.74) |
| MV             | 10 (10%)               | 3 (17.6%)              | 7 (8.8%)               | 0.27 (0.52;10.97) |

Abbreviations: ICU, intensive care unit; MV, Mechanical Ventilation