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The Reciprocal Relation between Coronavirus 2019 Disease and Inactive Hepatitis B Carrier State

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Abstract

Background: Coronavirus Disease 2019 (COVID-19) associated liver injury is defined as any liver damage occurring during disease progression and treatment of COVID-19 in patients with or without pre-existing liver disease. Chronic Hepatitis B Virus (HBV) infection results in high morbidity and mortality worldwide.

Aims: To determine the reciprocal relation between COVID-19 infection and inactive chronic HBV state.

Methods: A retrospective study conducted at Department of Gastroenterology and liver diseases, Shaare Zedek Medical Center, Jerusalem. We reviewed files of hospitalized patients with positive COVID-19 from February the first until 20th of May 2020. Hospitalized patients with COVID-19 and inactive chronic HBV infection were included in our study. The inactive Hepatitis B surface Antigen (HBsAg) carrier state was diagnosed by repeatedly normal Alanine Aminotransferase (ALT) levels, absence of Hepatitis B envelop Antigen (HBeAg), presence of anti-Hepatitis B envelop Antibody (anti-HBe AB) and undetectable or low levels of HBV Deoxyribonucleic Acid (DNA) in Polymerase Chain Reaction (PCR) -based assays. Reactivation of chronic HBV was considered upon ALT elevation and HBV DNA exceeding 2000 IU/mL, at least 10 folds increase of HBV DNA or seroconversion from anti-Hbe Ab to positive HbeAg.

Results: Six subjects of 445 (1.35%) with inactive chronic HBV and COVID-19 were included in our study. The mean age was 63 ± 12 years; five of them were males (83.3%). Mean ALT was133.4 ± 22.3 U/L and mean HBV DNA was 130.66 ± 14. No case of death or fulminant hepatitis was reported, however, among patients with HBV-negative the crude mortality was 6.1%. No case of reactivation of inactive chronic HBV was detected. One of the six (16.6%) patients suffered from severe COVID-19 infection.

Conclusion: It seems that the bidirectional effect of COVID-19 and inactive hepatitis carried state is negligible.

Keywords: Hepatitis B; Coronavirus; Liver function; HBV DNA; COVID-19

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Abbreviations

COVID-19: Coronavirus Disease 2019; HBV: Hepatitis B Virus; HBsAg: Hepatitis B surface Antigen; ALT: Alanine Aminotransferase; HBeAg: Hepatitis B envelop Antigen; anti-HBe Ab: Anti-Hepatitis B envelop Antibody; DNA: Deoxyribonucleic Acid; PCR: Polymerase Chain Reaction; AST: Aspartate Transaminase; HCC: Hepatocellular Carcinoma; anti-HBs Ab: Hepatitis B surface Antibody; anti-HBc: Hepatitis B core Antibody; ALP: Alkaline Phosphatase; GGT: Gamma-Glutamyl Transferase; CRP: C-Reactive Protein; SD: Standard Deviation; BMI: Body Mass Index

Introduction

Coronavirus Disease 2019 (COVID-19) is a recently encountered disease that has been declared a pandemic in 2020 [1]; the disease became a global public health concern with rapid spreading worldwide [1]. The COVID-19 pandemic represents the major global public health crisis since the 1918 influenza pandemic that was the most severe pandemic in recent history [1]. COVID-19 associated liver injury is defined as any liver damage occurring during disease progression and treatment of COVID-19 in patients with or without pre-existing liver diseases [2,3]. Overall, the incidence of elevated serum liver biochemistries in hospitalized patients with COVID-19, primarily

elevated Aspartate Transaminase (AST) and Alanine Transaminase (ALT), and slightly elevated bilirubin, ranges from 14% to 53%. Increased liver enzymes are observed more commonly in males and in more severe than in milder cases. Up to now, there is no report of acute or acute or chronic liver failure in COVID-19 patients, however, emerging evidence and past experience from other coronaviruses suggests that people with underlying liver disease including viral hepatitis could be at risk of disease severity and mortality [3,4]. Chronic Hepatitis B Virus (HBV) infection is an extensive global public health problem. Despite the accessibility of a protective vaccine for more than 3 decades, the prevalence of infection remains high. Worldwide it is estimated there are 257 million persons with chronic HBV infection, which results in 887,000 deaths annually primarily from complications of cirrhosis and Hepatocellular Carcinoma (HCC) [5,6]. The aim of this retrospective study was to determine the impact of COVID-19 infection on subjects with inactive carrier state of HBV.

Methods

We searched our database for HBV patients diagnosed with COVID-19 infection between the 1st of February until 20th of May 2020. COVID-19 positivity was defined as positive result by real-time reverse transcriptase- Polymerase Chain Reaction (PCR) assay of oropharyngeal and nasal swab specimens. COVID-19 severity was assessed according to diagnosis and treatment protocol for novel Coronavirus pneumonia released by National Health Commission and State Administration of Traditional Chinese Medicine on March 03rd, 2020) (trial version 7) [7]. Patients that met any of the following criteria were considered to have severe COVID-19 disease: Respiratory distress (equal or more than 30 breaths per minute), oxygen saturation equal or below 93% at rest, arterial Partial Pressure of Oxygen (PaO_2)/ Fraction of Inspired Oxygen (FiO_2) equal or less than 300 mmHg. HBV diagnosis was based on several serological markers, including Hepatitis B surface Antigen (HBsAg), Hepatitis B surface Antibody (anti-HBs Ab), Hepatitis B envelop Antigen (HBeAg) and Hepatitis B envelop Antibody (anti-HBe Ab), in addition to Hepatitis B core Antibody (anti-HBc) IgM and IgG immunoglobulins. Inactive HbsAg carrier state is diagnosed by absence of HbeAg and presence of anti-Hbe Ab, undetectable or low levels of HBV DNA in PCR-based assays, repeatedly normal ALT levels, and minimal or no necroinflammation, slight fibrosis, or even normal histology on biopsy [8]. Reactivation of chronic HBV was considered when patients showed elevated ALT and HBV DNA >2000 IU/mL, at least 10 folds increase of HBV DNA or seroconversion from anti-Hbe to positive HbeAg [9]. All medical records of eligible patients were reviewed and the following parameters were collected: Demographic data (age, gender, body mass index), background diseases (diabetes mellitus, ischemic heart disease, congestive heart failure, chronic renal failure, and smoking), laboratory tests (ALT, AST, Alkaline Phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), total bilirubin, amylase, C-Reactive Protein (CRP), HBV-specific serological markers and HBV DNA levels. Patients with other known hepatic pathology or autoimmune phenotypes (such as alcoholic liver disease, drug-induced liver injury, autoimmune hepatitis, nonalcoholic steatohepatitis, cholestatic liver disease and metabolic/genetic liver disease) were excluded. The study protocol complied with the Declaration of Helsinki and was approved by the local Ethics Committee Review Board of Sharee Zedek Medical Center, Jerusalem, Israel. The data were coded to keep anonymity of the patients. Informed consent was waived because of the non-interventional retrospective study design.

Statistical analysis

Data was reported as mean ± Standard Deviation (SD) for quantitative continuous variables, and frequencies (percentages) for categorical variables. Univariate analysis was used to estimate the correlation of baseline factors with reactivation of HBV. All analyses were carried out using the statistical analysis software (SAS *vs.* 9.4 Copyright (c) 2016 by SAS Institute Inc., Cary, NC, USA.).

Results

During the study period, among 445 patients with COVID-19, we identified 6 patients with viral markers of HBV and proven COVID-19 infection (prevalence of 1.34%). They were mainly males, 5 in number (83.3%) with a mean age of 63 ± 12 years. All included subjects were HBsAg positive, and HBeAg negative. Most of the patients showed low HBV viremia, four (all males) had detectable HBV viral loads of 122, 136, 131 and 134 copies/mL, with mean of 130.66 ± 14 copies/mL and two patients were with undetectable viral load. No one was on antiviral therapy for HBV infection as all were considered as inactive carriers. Five HBsAg positive patients (83.3%) had at least one comorbidity, mainly dyslipidemia (33.3%), diabetes mellitus (16.6%), arterial hypertension (33.3%). Other baseline characteristics of the study group are presented in Table 1. Almost all patients had elevated liver function test during the hospitalization. Liver tests abnormal tests became more evident within 2 weeks of hospitalization, with 4 (66.6%), 3 (50%), 2 (33.3%) and 2 (33.3%) patients having ALT, AST, total bilirubin and GGT levels elevated to more than 2x the upper limit of normal, respectively. Only one patient has severe lung disease (respiratory rate ≥ 30 breaths/min; resting pulse oxygen saturation ≤ 93% in room air), and he required mechanical ventilation, with full recovery and discharge from hospital. Notably, the single patients with severe COVID-19 disease suffered from multiple co-morbidities including obesity with Body Mass Index (BMI) >30, diabetes and dyslipidemia. No death cases were reported among the HBV infection cohort. For comparative purposes, the crude mortality rate of the HBV-negative COVID-19 patients in our hospital was 6.1%. Five of

Table 1: Baseline characteristics of COVID-19 subjects with HBV.

Variable	Patients with HBV (n=6)
Male gender	5 (83.3%)
Age, years	63 ± 12
BMI, kg/m^2	28.3 ± 5.3
Hypertension, N (%)	2 (33.3%)
Diabetes, N (%)	1 (16.1 %)
Smoking, N (%)	1 (16.1 %)
Dyslipidemia, N (%)	2 (33.3%)
Glycated hemoglobin, %	5.8 ± 0.9
Triglyceride, mg/dL	187.2 ± 45.2
CRP, mg/L	5.7 ± 2.3
HDL-C, mg/dL	42.7 ± 10.4
LDL-C, mg/dL	138.6 ± 32.4
AST, U/L	127 ± 33.4
ALT, U/L	133.4 ± 22.3
Severe COVID-19, N (%)	1 (16.6 %)

Abbreviations: HBV: Hepatitis B Virus; BMI: Body Mass Index; CRP: C-Reactive Protein; HDL: High-Density Lipoprotein Cholesterol; LDL: Low-Density Lipoprotein Cholesterol; ALT: Alanine Transaminase; AST: Aspartate Transaminase

Table 2: Baseline characteristics of severe and non-severe COVID-19 subjects.

Variable	Severe COVID-19	Non-Severe COVID-19	P value
Number of patients	1	5	
Male gender, N (%)	1 (100)	4 (80)	0.06
BMI>30 kg/m^2, N (%)	1 (100)	3 (60)	0.0009
Active smoking, N (%)	1(100)	1 (20)	0.0001
CRP, mg/L	5.9 ± 2.5	1.7 ± 2.9	0.025
AST, U/L	121.43 ± 22.31	83.12 ± 21.73	0.004
ALT, U/L	99.1 ± 32.4	83.4 ± 30.62	0.11
GGT, U/L	142.5 ± 33.8	117.9 ± 35.5	0.05
Lymphocyte × 10^3/μL	1.09 ± 0.8	1.41 ± 1.1	<0.001

Abbreviations: BMI: Body Mass Index; CRP: C-Reactive Protein; HDL: Alanine Transaminase; AST: Aspartate Transaminase

the patients (83.3%) recovered 13 ± 7 days after symptom onset, with no significant difference between the females and males (10 ± 6 *vs.* 13 ± 8 days; p=0.337). Only one patient (16.6%) was treated with the potential anti-COVID-19 treatment hydroxychloroquine, however, other treatments like azithromycin, tocilizumab and remdesivir, were not used in study cohort. Overall, in our study cohort, there were 5 patients (83.3%) with non-severe COVID-19 and only one (16.6%) with severe disease (Table 2). The Subject with severe COVID-19 was more obese (BMI >30 Kg/m^2) compared with 60% from the non-severe patients (p=0.0009); and he was current active smokers *vs.* 20% among the non-severe COVID-19, (p=0.0001). This patient with severe COVID-19 disease, had higher CRP levels 5.9 ± 2.5 *vs.* 1.7 ± 2.9 (p=0.025), higher AST levels 121.43 ± 22.31 *vs.* 83.12 ± 21.73 (p=0.004), higher ALT levels 99.1 ± 32.4 *vs.* 83.4 ± 30.62 (p=0.111), higher GGT levels 142.5 ± 33.87 *vs.* 117.9 ± 35.5 (p=0.057), and lower lymphocyte count 1.09 ± 0.8 *vs.* 1.41 ± 1.1 (p<0.001).

Discussion

In this retrospective study examining the impact of COVID-19 infection on subjects with inactive chronic HBV, we did not find any significant influence of COVID-19 on morbidity or mortality, however, increased liver enzymes were shown. Hepatic manifestations of COVID-19 patients are present in up to 50% of infected individuals [8]. The spectrum of hepatic involvement ranges from asymptomatic abnormalities in liver function tests to the rare case of acute liver failure [10]. The cause for hepatic manifestations is uncertain at this stage and may be caused by multifactorial mechanisms, such as secondary to a systemic illness, ischemic liver injury, immune mediated liver injury, drug induced liver injury, or a direct toxic effect of the virus [11]. COVID-19 subjects may suffer from concomitant viral infections, such as HBV. To the best of our knowledge, the impact of COVID-19 disease on inactive HBV carrier state was not reported, and our study is the first one to address this issue. We aimed to assess the possible deleterious effect of COVID-19 disease on inactive chronic HBV infection. In our cohort, the prevalence of HBV viral markers was 1.34%, and all were inactive carrier of HBV. Our findings showed that despite abnormal liver function tests that were noted in all HBV patients, non-developed HBV reactivation. Additionally, only one patient with multiple comorbidities, known as risk factors for disease severity, suffered from severe COVID-19 disease. Overall, in our study cohort, only 1 patient (16.6%) suffered from severe COVID-19 disease. This subject suffered from obesity, diabetes and dyslipidemia and he was current active smokers. He also had higher CRP levels, higher ALT, AST and GGT levels and lower lymphocyte count. Our study has several limitations; the main limitation is the retrospective design with the drawback of selection bias, which afflicts all case-control studies of this kind. Hence, we were unable to reassess diagnosis and prevalence of HBV on a later time, thus follow-up and natural history learning were unfeasible. Second, self-reported viral hepatitis, and/or other liver diseases may have introduced recall bias. Finally, the small number of COVID-19 patients with HBV may cause bias.

In conclusion, inactive HBV carrier state didn't have deleterious effect on patients with COVID-19 in terms of increased risk of morbidity or mortality. The potential effect of COVID-19 on inactive chronic HBV remains to be elucidated by large prospective future studies.

Author Contributions

Mahmud Mahamud and Eran Gold in contributed to the design of the manuscript. All authors contributed to data collection and analysis. Wiliam Nseir and Wisam Sbeit contributed wrote the initial draft. Tawfik Khoury, Wiliam Nseir and Wisam Sbeit revised the manuscript for intellectual contents. All authors approved the final version to be published.

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