Original Article

Covid-19 In HCV Treated Versus Non-Treated Patients: A Case Control Study

Mohamed A. Abdelrady*, Zein El-Abdeen A. Said, Ahmed G. Qenawy, Yasser A. Diab

Department of Internal Medicine, Faculty of Medicine, Aswan University, Aswan, Egypt

Corresponding author: *Mohamed A. Abdelrady*
Email: *mohammedabdo3493@gmail.com*
DOI: 10.47750/pnr.2023.14.S01.35

Abstract

Background: COVID-19 poses a major health threat to healthy individuals and those with comorbidities. SARS-CoV-2 virus causes liver damage and worsens pre-existing chronic liver disease that yields higher mortality rates. However, it remains unknown whether those with chronic liver disease are at increased risk for SARS-CoV-2 virus infection and how these risks were further affected by the patient's demographics. **Aim:** this study aimed to determine the incidence of mortality and degree of severity of covid-19 infection among the studied cohort. **Subject and methods:** This case-control study was conducted on 124 patients: (Group A): COVID-19 patients with previous history of treated HCV and (Group B): COVID-19 patients with previous history of untreated HCV. **Result:** There was high significant difference between both groups as regard mortality rate. Also, active HCV infection was associated with more severe disease and higher mortality in patients co-infected with SARS-CoV-2, HCV viral load being an independent risk factor for all-cause mortality and liver impairment. The severity of liver impairment was associated with poor clinical outcomes in COVID-19 patients. **Conclusion:** These results suggested that close monitoring and careful treatment for active-HCV patients with COVID-19 are needed to avoid health deterioration and fatal outcome.

Keywords: *SARS-CoV-2; COVID-19; chronic liver disease; chronic hepatitis C.*

INTRODUCTION

Since the end of 2019, a novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) has caused an outbreak of corona virus disease 2019 (COVID-19), resulting in an emerging global threat rapidly spreading throughout the world1. On March 11th, 2020, the WHO declared the COVID-19 as a pandemic2.

In general, patients with pre-existing morbidities are at higher risk of a severe course of COVID-19. However, liver disease was not specifically listed in the published studies so far3. It is possible that patients with advanced liver disease are at increased risk of SARS-CoV-2 infection due to cirrhosis-induced immunodeficiency4.

One of the major causes of liver-related mortality and morbidity worldwide is hepatitis C virus (HCV) infection. Globally it was estimated that 1% of the population (71 million) are infected with HCV. However, most HCV-infected people are unaware of their infection5, 6. Chronic HCV infection leads to a progressive disease, with about 15% of infected patients developing cirrhosis and approximately 7% of adult patients with cirrhosis progressing to hepatocellular carcinoma7.

Patients with chronic liver disease including cirrhosis may be at higher risk of death resulting from COVID-19, but risk factors in specific liver diseases have not been defined8. Both liver and bile duct cells express angiotensin-converting enzyme 2. Thus, the liver is a potential target for SARS- COV-2 infection. The incidence of liver disease in death cases of COVID-19 was as high as 58% to 78%9.

In 2016, the WHO released a global health sector strategy for eliminating viral hepatitis by 2030 that includes global and country-wide targets for the testing, treatment, and prevention of CHC10. Since 2015, the development and approval of novel, oral, interferon-free, antiviral treatment with direct-acting antivirals (DAAs) has substantially improved the treatment of HCV infection11. With an efficacy approaching 100% and a short duration of therapy, DAAs are highly effective, safe, and well-tolerated alternative for previously used therapies based on interferon11, 12.

Despite the fact that CHC does not seem to increase the risk of a severe course of COVID-19, in case of co-infection, an early admission and inclusion to the experimental antiviral therapy of COVID-19 should be considered, following local recommendations. One of the DAAs, sofosbuvir alone or in combination with ribavirin, has been suggested for the experimental treatment of COVID-193.

The current study aimed to determine the incidence of mortality and degree of severity of COVID-19 infection in treated versus untreated HCV patients at Aswan university hospital.

PATIENTS AND METHODS

This case-control study was conducted at **the isolation sector,** Aswan University Hospital, in the period from November 2021 to March 2022. Sample size calculation was conducted using STATA-16 software, with an alpha error 0.05, and power 80%, and mortality reduction from 30% in untreated HCV to 10% in treated HCV cases. The minimum required sample size was 124 in 1:1 ratio (62 in each group).

Patients aged ≥ 18 years, with confirmed positive COVID-19 infection, of any race, gender, or occupation, with positive history of HCV **and with CHILD-A score** were included while those with confirmed negative COVID-19, **without liver cirrhosis** and pregnant women were excluded. **Sovaldi was administered to the treated group.**
All patients were subject to:

Clinical assessment:

Clinical History:

including socio-demographics (age, sex, residency, occupation) clinical data (smoking, presenting complaint, jaundice, itching, abdominal pain, weight loss), history of previous hepatic encephalopathy, previous antiviral treatment, previous bilharziasis/anti-bilharzial treatment and presence of comorbidities (diabetes mellitus/hypertension.

Clinical examination:

- General examination
- Abdominal examination
- Laboratory Investigation: including CBC and Liver function
- Abdominal ultrasonography
- Ultrasonography Examination: Abdominal US using single operator pelvi-abdominal ultrasound (Toshiba: grey scale ultrasound with color Doppler, curvilinear probe 3.5 MHZ).
- Transient elastography (TE): It was measured with the standard M-probe using the right lobe of the liver. Eleven valid readings were taken for each case aiming for an interquartile range of <30% with at least 66% success rate.
- Liver Stiffness and Controlled Attenuation Parameter (CAP) measurement: CAP range is commonly between 100 and 400 dB/m, and the presence of liver steatosis is defined by a median CAP ≥236 dB/m. As for liver biopsies, it was possible to determine 3 grades of steatosis according to the level of CAP. The values commonly chosen to indicate steatosis as absent (S0), mild (S1), moderate (S2) and severe (S3) are: S0 <236 dB/, S1 ≥236 dB/m, S2 ≥270 dB/, and S3 ≥302 dB/m.

The main outcome measured were mortality rate, severity of the disease using PRIEST COVID-19 clinical severity score, PRIEST COVID-19 Clinical Severity Score (ScHARR) and Treatment administrated during admission. The PRIEST COVID-19 clinical severity score is essentially: The NEWS2 score + 2 points for age 50-65, 3 points for age 66-80, 4 points for age ≥80 + 1 point for male sex + 1 point for each level of performance status below unrestricted normal activity.

Statistical analysis:

Analysis of data was carried out using Statistical Package for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described as mean and standard deviation (SD). Qualitative variables were described as frequency and percent. Shapiro-Wilk test was used to test for normality. In order to compare parametric quantitative variables between two groups, Student t-test was performed. Qualitative variables were compared using chi-square (X2) test or Fisher's exact test as appropriate. Pearson's correlation coefficient/Spearman Ranked correlation coefficient was used to assess for the association between two variables as appropriate. A p-value ≤ 0.05 was considered significant.

Ethical Consideration:

IRB approval was obtained from the Medical Ethic Committee, Faculty of Medicine, Aswan University **(IRB no 550/7/21).**

The study was carried out in accordance with the Helsinki Declaration guidelines.

An official written administrative permission letter was obtained from dean of faculty of medicine, Aswan university hospital, and head of internal medicine department. The title and objectives of the study were explained to them to ensure their cooperation

A written informed consent was obtained from the patient before the participation in the study. All collected data was confidential and was used for the purpose of scientific research only. Every research participant had the complete right and freedom to withdraw at any time from the study without any consequences on the medical service provided.

RESULTS:

A total of 124 HCV patients were recruited from **the isolation sector**, Aswan University Hospital, in the period from November 2021 to March 2022. **Fig. 1** showed the flow diagram of the current study. The two groups were comparable with respect to the age, sex, smoking, HCV duration, weight and MBI ($p > 0.05$) **(Table 1).**

Table 2 showed the difference in laboratory findings between groups. The mean AST level in treated HCV cases group (26 ± 8.5 U/L) was significantly ($p<0.001$) lower than the level in those untreated (75 ± 20.6 U/L). Also, total bilirubin level was significantly ($p=0.001$) lower (2.55 ± 8.8 mg/dl) than the level in those untreated (48 ± 7.1 mg/dl). Likewise, the mean direct bilirubin level was significantly ($p<0.001$) lower (0.19 ± 0.02 mg/dl) than the level in those untreated (0.9 ± 0.01 mg/dl). Similarly, serum albumin level was 3.53 ± 0.01 g/dl in treated HCV cases which was significantly ($p<0.001$) higher than 3.11 ± 0.01 g/dl in the untreated group. As well, the mean INR was significantly ($p=0.009$) lower (1.2 ± 0.1) than in those untreated (1.4 ± 0.2). On the other hand, the mean ALT level was insignificantly ($p=0.108$) higher in treated HCV cases (25.5 ± 8.8 U/L) than in untreated group (48 ± 7.1 mg/dl). Likely, there was statistically insignificant ($p=0.712$) difference in the mean PT between the two studied groups. The mean PT in treated HCV group was lower (12.6 ± 2.1 seconds) than in the untreated group (14.9 ± 2.2).

The difference in the CBC parameters between groups was illustrated in **table 3**. The mean RBCs count in treated HCV cases group (4.1 ± $0.7*10^3/ml^3$) was significantly ($p=0.005$) lower than the level in those untreated (4.5 ± $0.5*10^3/ml^3$). Also, mean platelet count was significantly ($p=0.002$) higher in treated HCV patients (189.9 ± 12.2 $*10^3/ml^3$) than the count in those untreated (181.5 ± 19.8 $*10^3/ml^3$). Conversely, the mean WBCs count was insignificantly ($p=0.194$) higher in treated HCV patients (6.52 ± 1.2 $*10^3/ml^3$) than the count in those untreated (6.22 ± 1.1 $*10^3/ml^3$). Alike, the mean hemoglobin level in treated HCV cases group (10.4 ± 1.4 g/dl) was statistically insignificantly ($p=0.610$) lower than the level in those untreated (13.5 ± 1.4 g/dl). Moreover, the mean BUN level in treated HCV cases group (35 ± 10.9) was significantly ($p<0.001$) lower than that in those untreated (42.5 ± 3.9). Unlikely, the mean serum creatinine level in treated HCV case group (0.92 ± 0.2 mg/dl) was insignificantly ($p = 0.122$) lower than that in those untreated (0.96 ± 0.2 mg/dl) (**Table 3)**.

Table 4 showed the difference in abdominal ultrasound parameters between groups. The mean right liver lobe diameter in treated HCV cases group (13.3 ± 1.3 cm) was significantly ($p=0.01$) lower than that in those untreated (14.5 ± 0.9 cm). Unlikely, the mean splenic diameter in treated HCV cases group (12.9 ± 1.7 cm) was insignificantly ($p=0.923$) lower than that in those untreated (15.1 ± 1.7 cm).

Moreover, the mean PRIECT score was higher (5.52 ± 0.9) in untreated HCV cases than in treated cases (5.01 ± 0.9) and this was statistically insignificant (p=0.673). Regarding the mortality rates among cases, it was significantly higher among untreated cases (n=5, 8.1%) compared with those previously treated (n = 1, 1.6%) with statistically significant results **(Table 5).**

Table (1): Comparison between the studied groups as regard demographic data

	Group A (n=62)	Group B (n=62)	Test	P
• **Age**			T=1.01	0.94*
✓**Mean ± SD**	40.12 ± 3.5	39.3 ± 3.5		
• **Sex**			χ^2= 0.03	0.85**
✓**Male**	33	32		
✓**Female**	29	30		
• **Smoking history**	12	10	χ^2= 0.22	0.63**
• **HCV duration (years)**	10.2±1.54	9.98±1.52	1.026	0.91*
• **Weight**	76.2 ± 3.1	76.4 ± 3.2	**T=1.03**	0.90*
• **BMI**	26.2 ± 2.1	26.4 ± 2.4	**T=1.30**	0.29*

***Independent t-test was used to compare the mean difference between groups.**
****Chi-square test was used to compare the proportion difference between groups.**

Table (2): Comparison between the studied groups as regard Laboratory investigations

	Group A (n=62)	Group B (n=62)	Test	P
AST (U/L)	26.0 ± 8.5	75.0 ± 20.6	22.24	<0.001*
ALT(U/L)	25.5 ± 8.8	48.0 ± 7.1	1.513	0.108**
Total-Bilirubin (mg/dl)	0.9 ± 0.02	2.1 ± 0.4	4.84	0.001*
Direct Bilirubin (mg/dl)	0.19 ± 0.01	0.9 ± 0.01	86.77	<0.001*
Serum albumin(g/dl)	3.53 ± 0.4	3.11 ± 0.1	12.25	<0.001*
INR	1.2 ± 0.1	1.4 ± 0.2	2.77	0.009*
PT(s)	12.6 ± 2.1	14.9 ± 2.2	1.097	0.71

***Independent t-test was used to compare the mean difference between groups.**

Table (3): Comparison between the studied groups as regard CBC and Kidney Function Parameters

	Group A (n=62)	Group B (n=62)	Test	P
• **WBCs (x10³ /ml³)**	6.52 ± 1.2	6.22 ± 1.1	1.39	0.19
• **RBCs (x10³ /ml³)**	4.1 ± 0.7	4.5 ± 0.5	2.07	0.005*
• **Hemoglobin (g/dl)**	10.4 ± 1.4	13.5 ± 1.4	1.13	0.61
• **Platelet (x10³ /ml³)**	189.9 ± 12.2	181.5 ± 19.8	2.63	0.002*
• **BUN**	35.0 ± 10.9	42.52 ± 3.9	7.61	<0.001*
• **Creatinine**	0.92 ± 0.2	0.96 ± 0.2	1.49	0.12

***Independent t-test was used to compare the mean difference between groups.**

Table (4): Comparison between the studied groups as regard Abdominal Ultrasonography

	Group A (n=62)	Group B (n=62)	Test	P
Right liver lobe (cm)	13.25 ± 1.3	14.52 ± 0.9	1.93	0.01
Spleen diameter (cm)	12.91 ± 1.7	15.02 ± 1.7	1.023	0.92

***Independent t-test was used to compare the mean difference between groups.**

Table (5): The PRIEST COVID-19 Clinical Severity Score and Mortality of studied cases

	Group A (n=62)	Group B (n=62)	Test	P
PRIEST score	5.01 ± 0.9	5.52 ± 0.9	1.114	0.67*
Mortality	1 (1.6%)	5 (8.1%)	62.67	<0.001**

***Independent t-test was used to compare the mean difference between groups.**
****Chi-square test was used to compare the proportion difference between groups.**

DISCUSSION

In recent years, the treatment landscape for chronic hepatitis C (CHC) virus infection has been dramatically improved with the advent of all-oral, interferon-free, DAA therapies. Since 2016, three pan-genotypic DAA regimens have been approved for the treatment of CHC by the European Medicines Agency These regimens achieve high rates of sustained virology response (>95%) with good safety profiles, and as such are recommended by international guidelines [13]. Furthermore, DAAs can be prescribed by a wide range of health care professionals (HCPs) experienced in treating patients with HCV (general practitioners and specialists across different relevant disciplines). Despite these advances, 71 million people globally are chronically infected with HCV and up to 80% of them remain undiagnosed[14].

In 2016, the World Health Organization (WHO) adopted their "Global Health Sector Strategy on Viral Hepatitis, 2016–2021," setting a target of eliminating viral hepatitis as a major public health threat by 2030 by reducing new chronic infections by 90% and mortality from CHC by 65%. However, few countries are on target to meet WHO elimination targets by 2030. Germany has one of the largest numbers of CHC cases in Europe commensurate with its large population size[15]. After the COVID-19 pandemic and its disruption to the access to health care, globally, despite the availability of effective therapies, many patients diagnosed with CHC remain untreated[16].

This work aimed to study the incidence of mortality and degree of severity of covid19 infection in HCV treated patients versus HCV not treated patients in Aswan university hospital. This study showed that there was insignificant difference between both groups as regard age, sex, Smoking history or HCV duration. A study by Buggisch et al (2021)[15], as well as a US study by Niederau, et al.[17] conducted in the interferon era, showed a lower uptake of treatment in women compared with men, in agreement with the Buggisch et al (2021) conducted in the DAA era. The sex factor was unexpected because men have been shown to have a lower use of medical services than women both in the USA and Germany.

This study reported that there was insignificant difference between both groups as regard weight or BMI. Ji et al (2020)[18] showed that consecutive patients with confirmed COVID-19 and information relating NAFLD status were studied. Progressive diseases patients were older, with higher BMI.

Also, this study results illustrated that there were significant difference between both groups as regard AST, Total-Bilirubin, Direct Bilirubin, Serum albumin and INR. Iavarone et al (2020)[19] showed that the mean AST was 48, the mean ALT was 48, the mean total bilirubin was 1.8, the mean Serum albumin was 2.8, the mean INR was 1.4. Several papers reported on the impact of SARS-CoV-2 infection on transaminase levels in the general population, although

they did not specifically focus on the clinical significance of these alterations in terms of both morbidity and mortality, especially in patients with cirrhosis[20].

Recently, Dong et al (2020)[20] reported a 50% ALT increase in 202 consecutive patients with confirmed COVID-19, which included 38% with NAFLD. Interestingly, the authors reported that patients with NAFLD had a higher likelihood of abnormal liver function tests from admission to discharge (70% vs. 11.1%). Also, Iavarone et al (2020)[19] was the first reporting on the impact of SARS-CoV-2 infection on ALT levels in patients with cirrhosis, showing that acute liver injury was observed in nearly 50% of patients with previously normal transaminases values. Moreover, a hepatitis flare was not uncommon at SARS-CoV-2 diagnosis. However, more data are needed to clarify the impact of an ALT increase on the natural history of patients with cirrhosis and SARS-CoV-2 infection, and to better explain the pathogenic mechanism of coronavirus in causing liver damage at the level of liver cells. A potential direct cytopathic effect has been suggested, since the abundant angiotensin-converting enzyme 2 receptors in the liver might favor SARS-CoV-2 entry into the hepatocytes. Otherwise, the liver might be indirectly involved in the severe inflammatory response following SARSCoV-2 infection, as it contains a large number of macrophages and is a potent cytokine producer[19].

Additionally, the current findings reported that there were highly significant differences between both groups as regard RBCs and Platelet. This was in agreement with Iavarone et al (2020)[19] who found that the mean WBCs count/mm was $4.5*10^3$, the mean PLT was $115*10^3$. As well, Qi et al (2021)[21] showed that the mean White cell, ×109 /L was 4.34, the mean Neutrophils, ×109 /L was 2.64, the mean Platelets, ×109 /L was 120. Likely, Buggisch et al (2021)[15] showed that there was insignificant difference between both groups as regard Platelet. This study showed that there was significant difference between both groups as regard BUN. Iavarone et al (2020)[19] showed that the mean Creatinine was 1.00 mg/dl. Also, Qi et al (2021)[21] showed that the mean BUN was 5.5 mmol/L and the mean Creatinine kinase was 87 U/L.

Furthermore, this work revealed that there was high significant difference between both groups as regard Mortality rate. Although baseline Child-Pugh scores, baseline MELD, and CLIFC organ failure score were all significantly associated with mortality, their ability to effectively discriminate those who survived or died following SARS-CoV-2 infection was limited. However, patients with advanced liver disease did have a particularly poor prognosis following SARS-CoV-2 infection with diminishing chances of recovery as they moved through the disease course. Only 46% of hospitalized patients with Child-Pugh C cirrhosis survived, and this proportion dropped to 21% in those admitted to ICU and further still to 10% in those receiving invasive ventilation. These findings have important prognostic implications and highlight the need for careful monitoring of patients with cirrhosis throughout their hospital admission. Our data will also help inform clinical decisions regarding both the escalation of care to ICU and the use of COVID-19 palliative care guidelines in patients with advanced liver disease who undergo rapid inpatient clinical deterioration[19].

Boettler et al. showed that the high mortality in patients with cirrhosis should also prompt consideration of novel targeted therapies such as dexamethasone with proven efficacy in hospitalized patients with COVID-19. However, our data show that patients with cirrhosis are significantly less likely to received targeted antiviral therapy than CLD patients without cirrhosis, which may reflect clinician concerns regarding the safety profile of various agents currently in development. This highlights the importance of carefully evaluating drug hepatotoxicity during COVID-19 clinical trials to ensure that patients with cirrhosis are not unnecessarily denied potentially disease-modifying treatments[3].

In Iavarone et al (2020) study[19], the 30-day mortality rate was higher in patients with moderate/severe respiratory failure and in those who had worse liver function, as indicated by the increased MELD and CLIF-OF scores at COVID-19 diagnosis. While the association between severity of lung failure and early mortality was expected, their study is the first to define the predictive role of CLIF and MELD scores in the setting of acute failure of chronic liver disease due to COVID-19.

The current study encountered some limitations; the retrospective design of the study may have recall bias and affect the temporal sequence of relations. The short follow-up after diagnosis of SARS-CoV-2 infection and the low number of patients admitted to ICUs are other limitations. However, it is believed that this last point might not only be a consequence of the retrospective collection of data but also of the effective limited access to ICUs of patients with severe comorbidities, such as cirrhosis. In fact, during the study period, dramatic scarcities of ICU beds were present.

CONCLUSION

In conclusion, active HCV infection was associated with more severe disease and higher mortality in patients co-infected with SARS-CoV-2, HCV viral load being an independent risk factor for all-cause mortality and liver impairment. The severity of liver impairment was associated with poor clinical outcomes in COVID-19 patients. Further research is required to confirm our findings in prospective studies and larger samples. Our results suggest that close monitoring and careful treatment for HCV patients with COVID-19 are needed to avoid health deterioration and fatal outcome.

Disclosure Statement: The authors have no conflicts of interest to declare.

Acknowledgement: The authors expressed their thanks for the help and support of the medical and administrative staff of the surgical departments, Aswan University Hospital. Also, we acknowledge the eminent role of the participants; it was not possible to finish this work without their help, support, and approval.

Data Availability: Data is available upon request from the corresponding author

Funding Sources: None

Author Contributions: Mohamed A. Abdelrady (MAA); concept, design, literature search, clinical studies, statistical analysis, manuscript preparation, editing and review, **Zein El-Abdeen A. Said (ZAS);** design, literature search, manuscript preparation and review**, Ahmed G. Qenawy (AGQ);** literature search, clinical studies, manuscript editing and final draft, **Yasser A. Diab (YAD):** clinical studies and laboratory work.

References

1. Rasmussen S. and Thompson L. Coronavirus Disease 2019 and Children: What Pediatric Health Care Clinicians Need to Know? JAMA Pediatr. 2020; 174(8): 743–744. doi:10.1001/jamapediatrics.2020.1224.
2. WHO (2022). World Health Organization coronavirus disease 2019 (COVID-19) situation report. https:// www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
3. Boettler T., Newsome, P., Mondelli, M., Maticic, M., et al. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. JHEP Reports, (2020) 2(3), 100113. https://doi.org/10.1016/ j.jhepr.2020.100113
4. Albillos, A., Lario, M., Álvarez-Mon, M. Cirrhosis-associated immune dysfunction: Distinctive features and clinical relevance. Journal of Hepatology, (2014):61(6), 1385–1396. https://doi.org/10.1016/j.jhep.2014.08.010
5. Indolfi, G., Easterbrook, P., Dusheiko, G., El-Sayed, et al. Hepatitis C virus infection in children and adolescents. The Lancet Gastroenterology & Hepatology, (2019): 4(6), 477–487. https://doi.org/10.1016/S2468-1253(19) 30046-9
6. Stanaway, J., Flaxman, A., Naghavi, M., Fitzmaurice, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. The Lancet, (2016):388(10049), 1081–1088. https://doi.org/10.1016/ S0140- 6736(16)30579-7
7. Blachier, M., Leleu, H., Peck-Radosavljevic, M., Valla, D.-C., Roudot-Thoraval, F. The burden of liver disease in Europe: A review of available epidemiological data. Journal of Hepatology, (2013):58(3), 593–608. https://doi.org/10.1016/j.jhep.2012.12.005
8. Fix, O., Hameed, B., Fontana, R., Kwok, R., McGuire, et al. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers during the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. Hepatology, (2020https://doi.org/10.1002/hep.31281
9. Xu, L., Liu, J., Lu, M., Yang, D., Zheng, X. Liver injury during highly pathogenic h):72(1), 287–304. uman coronavirus infections. Liver International, (2020):40(5), 998–1004. https://doi.org/10.1111/liv.14435
10. WHO (2016). Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. World Health Organization. https://apps.who.int/iris/handle/10665/246177
11. Indolfi, G., Bailey, H., Serranti, D., Giaquinto, et al. Treatment and monitoring of children with chronic hepatitis C in the Pre-DAA era: A European survey of 38 paediatric specialists. Journal of Viral Hepatitis, (2019):26(8), 961–968. https://doi.org/10.1111/jvh.13111
12. Pawlowska, M., Sobolewska-Pilarczyk, M., & Domagalski, K. Hepatitis C virus infection in children in the era of direct-acting antiviral. World Journal of Gastroenterology, (2018):24(24), 2555–2566. https://doi.org/ 10.3748/ wjg.v24.i24.2555
13. Welzel, T., Yang, M., Sajeev, G., Chen, Y., Pinsky, B., Bao, Y. and Dieterich, D. Assessing patient preferences for treatment decisions for new direct acting antiviral (DAA) therapies for chronic hepatitis C virus infections. Advances in therapy, (2019): 36(9), 2475-2486.
14. Lazarus, J., Roel, E. and Elsharkawy, A. Hepatitis C virus epidemiology and the impact of interferon-free hepatitis C virus therapy. Cold Spring Harbor perspectives in medicine, (2020):10(3), a036913.
15. Buggisch, P., Heiken, H., Mauss, S., Weber, B., Jung, M. C., Görne, H., and Berg, T. Barriers to initiation of hepatitis C virus therapy in Germany: A retrospective, case-controlled study. PLOS one, (2021):16(5), e0250833.
16. Salmon, J., and Thompson, S. Pharmaceuticals, Hospitals, Nursing Homes, Drug Store Chains, and Pharmacy Benefit Manager/Insurer Integration. In The Corporatization of American Health Care (2021) (pp. 61-113).
17. Niederau C, Huppe D, Zehnter E, Moller B, Heyne R, Christensen S. Chronic hepatitis C: treat or wait? Medical decision making in clinical practice. World J Gastroenterol. 2012; 18(12):1339–47.
18. Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y. Implication of non-alcoholic fatty liver diseases (NAFLD) in patients with COVID19: a preliminary analysis. J Hepatol, (2020). PII: S0168-8278(20) 30206-3
19. Iavarone, M., D'Ambrosio, R., Soria, A., Triolo, M., Pugliese, N., Del Poggio, P. Lampertico, P. High rates of 30-day mortality in patients with cirrhosis and COVID-19. Journal of hepatology, (2020):73(5), 1063-1071.
20. Dong, Y., Mo, X., Hu, Y. et al. Epidemiology of COVID-19 among children in China. Pediatrics (2020) 145 (6): e20200702.

21. Qi, X., Liu, Y., Wang, J., Fallowfield, J., Wang, J., Li, X., Rockey, D. Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. Gut, (2021):70(2), 433-436.