Negm *et al.*
Ain-Shams Journal of Anesthesiology (2023) 15:96
https://doi.org/10.1186/s42077-023-00396-6

Ain-Shams Journal of Anesthesiology

ORIGINAL ARTICLE

Open Access

Prevalence and outcome of chronic hepatitis C patients admitted with COVID-19 to intensive care units: a blessing in disguise

Essamedin M. Negm[1*], Rehab H. El-Sokkary[2], Mai M. Malek[2], Heba M. Ezzat[3], Ahmed E. Tawfik[3], Heba Ali Abed[4], Seham Mahmoud ELdeeb[5], Mohamed Sorour Mohamed[6], Hamdy M. Kassem[7], Ahmed Mosallem[1] and Sherif M. S. Mowafy[1]

Abstract

Background Managing COVID-19 pneumonia is, in reality, one of the biggest challenges in the history of intensive care medicine. The link between comorbidity and COVID-19 remains unclear. Worldwide, Egypt has the highest prevalence of hepatitis C virus (HCV). The study's objectives were to assess the prevalence of chronic hepatitis C as a risk factor among COVID-19 patients and to investigate the impact of it and the prior exposure to different HCV management protocols on the clinical characteristics and outcome of COVID-19 patients.

Results Of 2106 confirmed cases of COVID-19, CLD, malignancy, and chronic kidney disease were significant risk factors for death [OR (95% CI) = 2.78 (1.29–5.98), 2.72 (1.14–6.46) and 3.79 (1.39–10.36) respectively]. The mortality rate was 24.3%. A total of 99 cases (4.7%) with CLD were investigated during the study period; 69 patients (3.3%) were categorized as HCV-positive. Among the positive HCV cases, 49 patients (2.3%) received anti-hepatitis C medications. The mortality rate was 46.4% and 73.3% between HCV and non-HCV hepatic patients, respectively. Triple therapy showed a statistically significant association with a better outcome (p value = 0.009).

Conclusions In the present report, chronic liver diseases, chronic kidney disease, and malignancy were significant risk factors for mortality among COVID-19 patients. The Egyptian mass management of chronic hepatitis C may explain the favorable outcome of COVID-19 among these patients. Intervention trials are required to prove that direct-acting antivirals are effective in preventing COVID-19.

Keywords COVID-19, Comorbidities, CLD, Hepatitis C, DAAs

Background

The Egyptian coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is part of a worldwide pandemic. On February 14, 2020, it was confirmed that the virus had invaded Egypt (Saied et al. 2021). At the time this article was written, SARS-CoV-2 had infected nearly 515,667 in Egypt and killed around 24,624 (Africa CDC 2022). Egypt's low COVID-19 prevalence does not represent reality and might be attributed to various variables (Perlman and Netland 2009).

*Correspondence:
Essamedin M. Negm
alpherdawss@gmail.com
[1] Anesthesia, Intensive Care, and Pain Management, Zagazig University, Zagazig, Egypt
[2] Medical Microbiology and Immunology, Zagazig University, Zagazig, Egypt
[3] Clinical Pharmacy, Zagazig University Hospital, Zagazig, Egypt
[4] Clinical Pharmacy, Banha Teaching Hospital, Banha, Egypt
[5] Public Health and Community Medicine, Zagazig University, Zagazig, Egypt
[6] Internal Medicine, Zagazig University, Zagazig, Egypt
[7] Critical Care Medicine, Imam Abdulrahman Alfaisal, Ministry of Health, Riyadh, Saudi Arabia

Although the number of people currently diagnosed with COVID-19 has dramatically multiplied, the link between comorbidity and COVID-19 remains unclear (Albadawy et al. 2021). Worldwide, COVID-19-related mortality has been linked in the literature to various factors; however, most data comes from high-income countries (Jassat et al. 2021). Race, ethnicity, and poverty were linked to an elevated risk of mortality in COVID-19 cases (Sze et al. 2020; Ranzani et al. 2021; Williamson et al. 2020).

Egypt is at the top of the list of nations where the hepatitis C virus (HCV) is prevalent, estimated to be 8–10 million people, with genotype 4 dominating (Waked et al. 2014; Centers for Disease Control Prevention 2012). Since 2007, HCV treatment has been one of Egypt's top national goals. The Egyptian National Committee for the Control of Viral Hepatitis has taken all appropriate action to provide direct-acting antivirals (DAAs) to HCV patients (Omran et al. 2018).

The cellular receptor for SARS-CoV-2 is angiotensin-converting enzyme 2(ACE2) (Ni et al. 2020). Hyperinflammation ("Cytokine storm"), hypercoagulability (microthrombosis in the pulmonary circulation), and the resulting severe hypoxemia (impaired oxygen absorption) are the three pathologic processes that contribute to multi-organ failure and poor outcomes in COVID-19 (Abdelzaher et al. 2021). The role of ACE-2 in liver disease is especially important because numerous lines of evidence suggest that, like other organs, the renin-angiotensin system (RAS) is involved in the control of hepatic inflammation, tissue remodeling, and fibrosis after liver injury (Abbas et al. 2011; Mak et al. 2015). ACE-2 plays a protective function in lung disease similar to that observed in liver disease (Oarhe et al. 2015; Skurk et al. 2001). Anti-hepatic C virus medications could prevent COVID-19 by modulating RAS, according to the theory (Negm 2022).

A modern iteration of Occam's razor deduces that "the simplest explanation is usually correct and entities should not be multiplied without necessity." The simplest explanation is that COVID-19 has a single mechanism that is shared by both predicted and unexpected features (Czick et al. 2020). Although early reports of COVID-19 cases highlighted hepatic manifestation, the mechanism of liver impairment remains unclear (Ronderos et al. 2021).

To the best of our knowledge, data do not provide specific information regarding the prevalence and impact of viral hepatitis, specifically, HCV in COVID-19 patients, and its relation to the severity and outcome is still a dilemma (Ronderos et al. 2021; Zhang et al. 2020; Wang et al. 2020; Kulkarni et al. 2020). Thus, this study aimed to assess the prevalence of chronic hepatitis C as a risk factor among COVID-19 patients and to investigate the impact of it and the prior exposure to different HCV management protocols on the clinical characteristics and outcome of COVID-19 hospitalized patients.

Methods

Study design and setting

This retrospective cohort study included ICU-admitted confirmed severe and critical COVID-19 cases from May 30, 2020, to May 30, 2022, at Zagazig University Hospitals Isolation ICUs. Zagazig University Hospitals are Egyptian tertiary care teaching hospitals that receive patients from the East Delta, Suez Canal, and Sinai governorates. Thirty beds in 2 isolation ICUs (15 in each one) were available at the time of data collection.

Participants and case definition

The study enrolled all adult patients (≥ 18 years) with laboratory-confirmed SARS-CoV-2 infection and radiological evidence of pneumonia. The microbiological diagnosis of SARS-CoV-2 infection was defined by real-time polymerase chain reaction of a nasal-pharyngeal swab specimen. Patients with incomplete or missing clinical and laboratory data at baseline were excluded from the study. Ward cases (mild to moderate cases) were excluded because they were asked to continue their care at home shortly after admission to the investigated university and discharged against medical advice with missed data. Patients who received vaccinations were also not included.

According to Chinese guidelines for COVID-19 management; severe COVID-19 was categorized as the presence of radiographic evidence of $^{>}$ 50% lung infiltrate plus one of the following: respiratory rate of 30 breaths or more per minute; oxygen saturation (SaO2) < 94% with breathing ambient air at rest; or ARDS, which is defined as the ratio of arterial oxygen partial pressure (PaO2) to a fraction of inspired oxygen (FiO2) (PaO2: FiO2) of ≤ 300 mmHg. Critical COVID-19 was categorized as respiratory failure requiring ventilator support, either invasive or non-invasive, septic shock, and/or any organ dysfunction that requires ICU-supportive treatment (Lin and Li 2020).

Data collection

Historical, clinical, laboratory, and radiological data were obtained retrospectively by team members from patients' records. Requirements for antiviral, anticoagulants, steroids, antibiotics, as well as other anti-COVID-19 measures, were administered in the ICU on the basis of indication and patient situation guided by the Ministry of Health (MOH). Patients were discharged from critical care according to the MOH recommendations. Patient mortality was the primary outcome. Morbidity

parameters such as ICU length of stay (LOS) and ventilator days (non-invasive or invasive) were recorded.

Patients were then classified into those with chronic liver disease (CLD) and those without CLD. We reviewed medical charts and laboratory parameters (HCV antibody) to obtain the HCV infection status and its management protocols. Any history of receiving HCV treatment (Ribavirin and Interferon), (Daclatasvir and Sofosbuvir), or (Daclatasvir and Sofosbuvir plus Ribavirin) was recorded after confirmation by related documentation. The prevalence of chronic hepatitis C COVID-19 patients was estimated.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) software version 27 (IBM SPSS Statistics for Windows, Version 27 2020). Kolmogorov–Smirnov and Levene tests were used to determine the distribution characteristics of variables and variance homogeneity. Descriptive statistics were generated for all variables. Comparison between survived and dead patients was performed using the appropriate tests of significance. Student's t test was used to analyze continuous normally distributed variables. The Mann–Whitney U test was used to analyze continuous not normally distributed variables. The chi-squared test and Fisher's exact test were used to analyze qualitative variables as appropriate. All factors that were significantly associated with the outcome were run in a binary logistic regression model to determine the independent predictors of death. Survival analysis was done using the Kaplan–Meier diagram and log-rank test. The level of statistical significance was set at $p < 0.05$.

Results

The study cohort distribution is summarized in a flowchart (Fig. 1). Of 2106 enrolled confirmed cases with COVID-19, 99 (4.7%) cases with CLD were included during the study period, and 96 of the 99 cases were cirrhotic. A total of 69 patients (3.3%) were categorized as HCV-positive. Among the positive HCV cases, 49 patients (71%) received anti-hepatitis C viral medications, whereas the remaining 20 (29%) did not. Of those who received treatment, 31 patients (63.3%) survived. Fourteen cases (70%) of those who didn't receive treatment died.

The mortality rate for the study cohort was 24.3% (Fig. 2). Some comorbidities were associated with death;

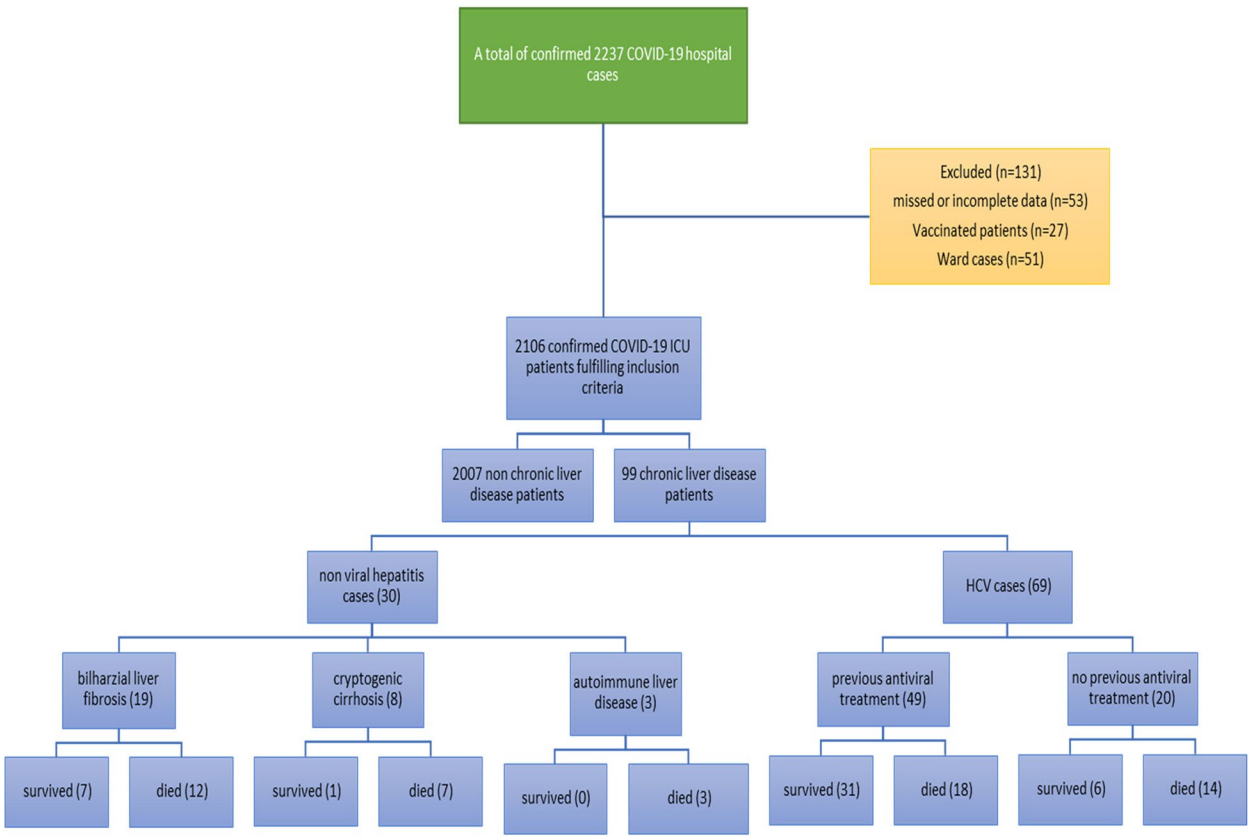

Fig. 1 Flow chart of investigated cohort

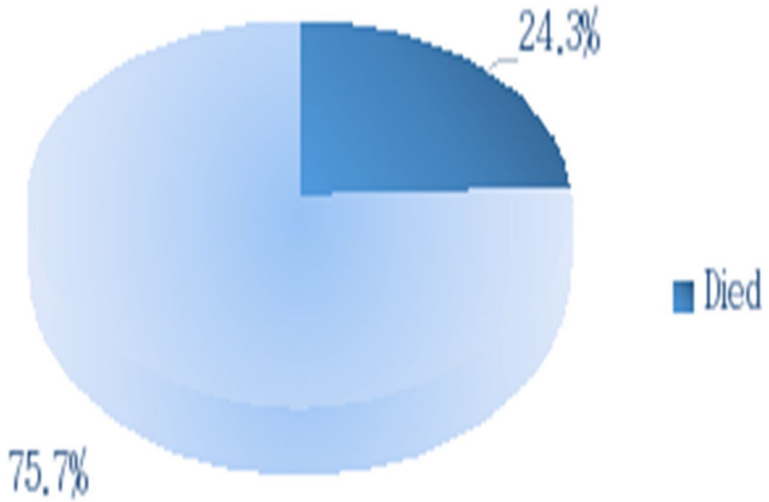

Fig. 2 Outcome of the COVID-19 patients

diabetes mellitus, hypertension, ischemic heart disease, hepatic diseases, malignancy, chronic kidney disease, and organ transplantation (Table 1). The length of ICU stay was significantly longer in survivors with median (11) days versus (8) days in the mortality group (Table 1, Fig. 3).

59.8% of cases (1260 cases) were supported by noninvasive mechanical ventilation, where 39.7% of them (500 cases) died. The median noninvasive ventilator duration was 14 days. 24.12% of cases (508 cases) were supported by invasive mechanical ventilation, and 99.21% of them (504 cases) died. The median invasive ventilator duration was 5 days. Mechanical ventilation was significantly associated with death (Table 1).

A regression analysis model was used to determine the predictors of death in the investigated COVID-19 patients. Patient age was a significant predictor of death with an OR (95% CI) = 8.07 (2.05–21.09). The severity of COVID-19 at admission also was a significant predictor with OR (95% CI) = 6.17 (2.26–10.21). Regarding comorbidities, hepatic diseases, malignancy, and chronic kidney disease were significant risk factors for death in the study of COVID-19 patients [OR (95% CI) = 2.78 (1.29–5.98), 2.72 (1.14–6.46), and 3.79 (1.39–10.36) respectively]. Also, invasive mechanical ventilator was a predictor for mortality in the study cohort (Table 2).

Regarding the COVID-19 patients being studied with hepatic diseases, the mortality rate was 54.5% (Table 3). The mortality rate was 46.4%**,** and 73.3% between HCV and Non-HCV patients, respectively (Fig. 4). A statistically significant association was between outcome and some variables. The length of stay was significantly longer in survivors (median = 15 days) than in dead patients (median = 9 days) (Table 3, Fig. 5).

71.7% of hepatic cases (71 cases) were supported by noninvasive mechanical ventilation, and 76.1% of them (54 cases) died. The median noninvasive ventilator duration was (14) days and longer in surviving cases (22 days). Of the cases, 54.5% (54 cases) were supported by invasive mechanical ventilation, and 100% of them (54 cases) died. The median invasive ventilator duration was 2 days. Mechanical ventilation was significantly associated with death. All invasively ventilated hepatic patients had poor outcomes (Table 3).

Among the study COVID-19 patients with hepatic diseases, HCV patients had better outcomes than non-HCV patients as 82.2% of the survivors had HCV (Table 3). Patients who presented for admission with signs of hepatic encephalopathy were significantly associated with mortality. Table 3 shows a significant correlation between the degree of cirrhosis and the outcome. Decreased serum albumin level and platelet count and elevated both conjugated bilirubin and liver enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], as baseline laboratory data at admission, were associated with mortality (Table 3).

Among the COVID-19 patients being studied with chronic liver diseases, there was a statistically significant association between outcome and treatment of hepatitis C. Non-treatable hepatitis C patients had a poor outcome as 43.8% of the deceased patients had not received hepatitis C management. Alternatively, triple antiviral therapy was associated with a better outcome as 40.5% of surviving patients had received triple therapy alone and 5.4% had received ribavirin and interferon (patients who received triple therapy were more 4.77 times more likely to survive than other therapies) (Table 4).

Table 1 Characteristics and outcomes of COVID-19 patients in the study cohort

Variables	Total COVID-19 patients ($n = 2106$)	Outcome		*p* value
		Survived ($n = 1594$)	Died ($n = 512$)	
Age (years): Mean ± SD	54.9 ± 14.1	52.0 ± 13.6	63.9 ± 11.8	< 0.001**
Sex: *n* (%)				
Male	1211 (57.5%)	916 (57.5%)	295 (57.6%)	0.9
Female	895 (42.5%)	678 (42.5%)	217 (42.4%)	
Sever COVID-19 cases at admission, *n* (%)	1687 (80.1%)	1573(98.7%)	114 (22.3%)	< 0.001**
Critical COVID-19 cases at admission, *n* (%)	419 (19.9%)	21 (1.3%)	398 (77.7%)	
Comorbidities: *n* (%)				
Diabetes mellitus	622 (29.5%)	388 (24.3%)	234 (45.7%)	< 0.001**
Hypertension	701 (33.3%)	442 (27.7%)	259 (50.6%)	< 0.001**
Ischemic heart disease	227 (11.3%)	116 (7.3%)	111 (21.7%)	< 0.001**
Chronic liver disease	99 (4.7%)	45 (2.8%)	54 (10.5%)	< 0.001**
Malignancy	67(3.3%)	34 (2.1%)	33 (6.4%)	< 0.001**
Chronic kidney disease	53 (2.5%)	24 (1.5%)	29 (5.7%)	< 0.001**
Thyroid dysfunction	26 (1.2%)	24 (1.5%)	2 (0.4%)	0.08
Heavy smoking	24 (1.1%)	18 (1.1%)	8 (1.6%)	0.6
Organ transplantation	10 (0.5%)	2 (0.1%)	8 (1.6%)	0.002*
Respiratory symptoms at presentation (cause of ICU admission), *n* (%)	2079 (98.7%)	1588(99.6%)	491 (95.9%)	< 0.001**
Neuropsychiatric symptoms at presentation (cause of ICU admission), *n* (%)	27 (1.3%)	2 (0.1%)	25 (4.9%)	< 0.001**
Length of stay (days): median (range)	8 (1–70)	11 (1–70)	8 (1–30)	< 0.001*
Noninvasive mechanical ventilation: *n* (%)	1260 (59.8%)	760 (47.7%)	500 (97.7%)	0.03*
Noninvasive mechanical ventilator days: median (range)	14 (1–61)	14(1–61)	12(1–22)	< 0.001**
Invasive mechanical ventilation: *n* (%)	508 (24.1)%	4 (0.25%)	504 (98.4%)	< 0.001**
Invasive mechanical ventilator days: median (range)	5 (1–20)	12 (11–13)	5 (1–20)	< 0.001**
Drug therapy: *n* (%)				
Corticosteroids	1848 (87.7%)	1382(86.7%)	466 (91.0%)	0.06
Iverzine	571 (27.1%)	486 (30.5%)	85 (16.6%)	< 0.001**
Tocilizumab	344 (16.3%)	108 (6.8%)	236 (46.1%)	< 0.001**
Remdesivir	254 (12.1%)	80 (5.0%)	174 (34.0%)	< 0.001**
Favipiravir	189 (9.0%)	104 (6.5%)	85 (16.6%)	< 0.001**
Plaquenil	158 (7.5%)	148 (9.3%)	10 (2.0%)	< 0.001**
Colchicine	134 (6.4%)	54 (3.4%)	80 (15.6%)	< 0.001**
Pirfenex	80 (3.8%)	22 (1.4%)	58 (11.3%)	< 0.001**
Anti-fungal	157 (7.5%)	49 (3.1%)	108 (21.1%)	< 0.001**

P chi-square test, independent *t* test and Mann-Whitney test, *ICU* intensive care unit

*Statistically significant

**Statistically highly significant

A regression analysis model was used to determine the predictors of death in the investigated COVID-19 patients with hepatic disease. The severity of COVID-19 at admission was a significant predictor for death with OR (95% CI) = 4.77 (1.79–7.92). Hepatic encephalopathy was also a significant predictor for death with OR (95% CI) = 7.35 (3.28–16.5). Regarding laboratory findings, high ALT, high AST, high total bilirubin, and high direct bilirubin were significant risk factors for death [OR (95% CI) = 1.69 (1.01–2.99), 1.99 (1.05–3.76), 2.32 (1.13–4.75) and 3.19 (1.14–8.98) respectively]. Also, invasive mechanical ventilator 6.92 (1.38–14.63) and Grade C liver cirrhosis 2.28 (1.01–5.12) were predictors for mortality, while HCV and treated HCV had better outcomes when compared with other hepatic cases (OR = 0.56 and 0.37 respectively) (Table 5).

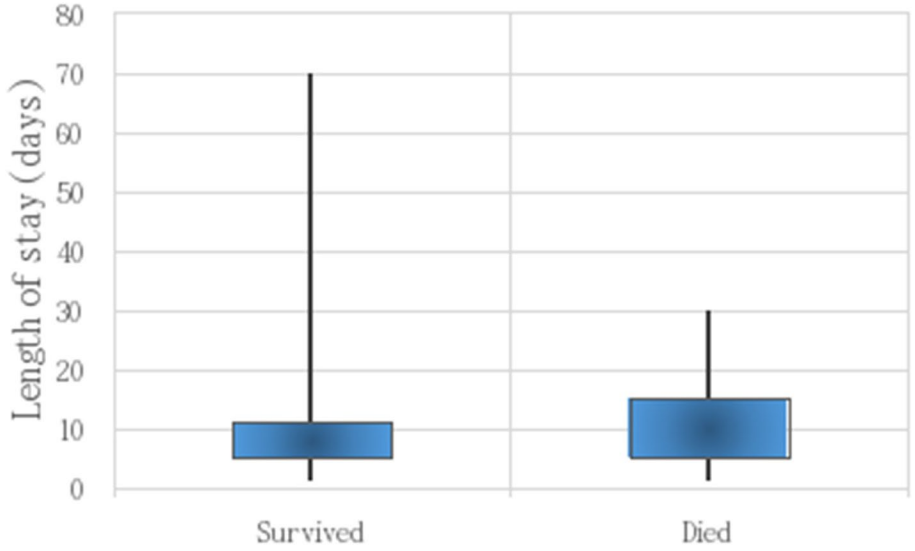

Fig. 3 Length of stay of the COVID-19 patients according to outcome

Table 2 Binary logistic regression analysis of the outcome of the COVID-19 patients with significantly related independent variables

Variables	*B*	S.E.	Wald	*P*	Odds Ratio	95% CI
Old age	0.07	0.01	69.3	< 0.001**	8.07	2.05–21.09
Severity of COVID-19 at admission	2.9	1.4	8.2	< 0.001**	6.17	2.26–10.21
Comorbidities:						
Diabetes mellitus	− 0.11	0.23	0.21	0.6	0.90	0.57–1.41
Hypertension	− 0.11	0.24	0.20	0.7	0.90	0.56–1.44
Ischemic heart disease	0.18	0.33	0.30	0.6	1.20	0.63–2.28
Chronic liver disease	1.0	0.39	6.8	0.009*	2.78	1.29–5.98
Malignancy	1.0	0.44	5.1	0.02*	2.72	1.14–6.46
Chronic kidney disease	1.3	0.51	6.8	0.009*	3.79	1.39–10.36
Organ transplantation	0.85	1.2	0.47	0.5	2.33	0.21–26.32
Respiratory symptoms at presentation	− 3.7	1.3	7.8	0.005*	0.03	0.002–0.34
Neuropsychiatric symptoms at presentation	2.4	1.2	3.8	0.05*	9.7	1.1–13.3
Long length of stay	− 0.29	0.13	4.9	0.03*	0.75	0.58–0.97
Mechanical ventilation days	− 0.12	0.27	0.25	0.5	0.89	0.58–1.39
Mechanical ventilation	1.1	0.41	7.2	< 0.001**	2.89	1.31–6.71
Drug therapy:						
Iverzine	− 0.96	0.25	14.5	< 0.001**	0.38	0.23–0.63
Tocilizumab	2.0	0.27	57.9	< 0.001**	7.68	4.54–12.98
Remdesivir	1.6	0.30	28.1	< 0.001**	4.85	2.70–8.69
Favipiravir	− 0.03	0.32	0.01	0.9	0.97	0.52–1.81
Plaquenil	− 0.98	0.56	3.1	0.08	0.38	0.13–1.13
Colchicine	0.86	0.45	3.7	0.06	2.35	0.98–5.64
Pirfenex	0.60	0.56	1.1	0.3	1.83	0.61–5.51
Anti-fungal	0.78	0.51	2.4	0.1	2.18	0.81–5.89

S.E. standard error, *CI* confidence interval, *P* all the factors that were significantly associated with outcome were run in a binary logistic regression model

*Statistically significant

**Statistically highly significant

Table 3 Characteristics and outcomes of COVID-19 patients with chronic liver disease

Variables	Total chronic liver disease patients ($n = 99$)	Outcome		Mortality rate %	*p* value
		Survived ($n = 45$)	Died ($n = 54$)		
Age (years): Mean ± SD	61.4 ± 11.9	61.3 ± 10.8	61.5 ± 12.9		0.9
Sex: *n* (%)					
Male	69 (69.0%)	29 (63.0%)	40 (74.1%)	58%	
Female	30 (30.3%)	16 (35.6%)	14 (25.9%)	46.7%	0.4
Sever COVID-19 at admission, *n* (%)	82 (82.8%)	45 (100.0%)	37 (68.5%)	45.1%	< 0.001*
Critical COVID-19 at admission, *n* (%)	17 (17.2%)	0 (0.0%)	17 (31.5%)	100%	
Comorbidities: *n* (%)					
Diabetes mellitus	51 (51.5%)	26 (57.8%)	25 (46.3%)	49%	0.3
Hypertension	53 (53.5%)	25 (55.6%)	28 (51.9%)	52.8%	0.9
Ischemic heart disease	16 (16.2%)	6 (13.3%)	10 (18.5%)	62.5%	0.7
Malignancy	8 (8.1%)	2 (4.4%)	6 (11.1%)	75%	0.4
Heavy smoking	3 (3.0%)	1 (2.2%)	2 (3.7%)	66.7%	0.9
Chronic kidney disease	2 (2.0%)	0 (0.0%)	2 (3.7%)	100%	0.4
Respiratory symptoms at presentation, *n* (%)	95 (96.0%)	44 (97.8%)	51 (94.4%)	53.7%	0.7
Hepatic encephalopathy on admission, *n* (%)	9 (9.1%)	0 (0.0%)	9 (16.7%)	100%	< 0.001*
Baseline liver function results					
Alanine transaminase (U/L), median (range)	38 (28–52)	34 (27–44)	59 (40–95)		0.004*
Aspartate transaminase (U/L), median (range)	47 (27–77)	42 (23–54)	67 (47–98)		0.003*
Serum albumin (g/dL), mean ± SD	3.25 ± 0.9	2.84 ± 0.7	2.56 ± 0.5		0.02*
Total bilirubin (mg/dL), mean ± SD	3.2 ± 4	4.8 ± 0.6	5.2 ± 0.7		0.003*
Direct bilirubin (mg/dL), mean ± SD	2.3 ± 3.4	2.5 ± 0.7	3.1 ± 0.9		0.004*
Alkaline phosphatase (U/L), median (range)	273 (295–90)	268 (289–65)	278 (201–82)		0.3
Platelet count (× 1000/cmm), Mean ± SD	207.69 ± 98.06	210.69 ± 81.06	180.59 ± 65.14		0.04*
INR, mean ± SD	1.3 ± 0.32	1.02 ± 0.2	1.1 ± 0.3		0.1
PTT, mean ± SD	35 ± 11.1	33 ± 10	36 ± 12		0.2
Length of stay (days): Median (range)	12 (1–63)	15 (1 – 63)	9 (1–20)		0.04*
Drug therapy: *n* (%)					
Corticosteroids	74 (74.7%)	30 (66.7%)	44 (81.5%)	59.5%	0.1
Iverzine	10 (10.1%)	6 (13.3%)	4 (7.4%)	40%	0.5
Tocilizumab	29 (29.3%)	4 (8.9%)	25 (46.3%)	86.2%	0.001*
Remdesivir	17 (17.2%)	2 (4.4%)	15 (27.8%)	88.2%	0.005*
Favipiravir	22 (22.2%)	7 (15.6%)	15 (27.8%)	68.2%	0.1
Colchicine	18 (18.2%)	8 (17.8%)	10 (18.5%)	55.6%	0.9
Pirfenex	8 (8.1%)	6 (13.3%)	2 (3.7%)	25%	0.08
Anti-fungal	11 (11.1%)	5 (11.1%)	6 (11.1%)	54.5%	0.9
Noninvasive mechanical ventilation: *n* (%)	71(71.7%)	17(37.8%)	54(100%)	76.1%	< 0.001*
Noninvasive mechanical ventilator days: median (range)	14 (1–50)	22 (5–50)	17 (1–20)		0.02*
Invasive mechanical ventilation: *n* (%)	54(54.5%)	0 (0.0%)	54(100%)	100%	< 0.001*
Invasive mechanical ventilator days: median (range)	2 (1–5)	–	2 (1–5)		–
HCV patients, *n* (%)	69 (69.7%)	37 (82.2%)	32 (59.3%)	46.4%	
Non-HCV patients, *n* (%)	30 (30.3%)	8 (17.8%)	22 (40.7%)	73.3%	0.01*
Treated HCV patients, *n* (%)	49 (71.0%)	31 (83.8%)	18 (56.3%)	36.7%	
Non-treated HCV patients, *n* (%)	20 (28.9%)	6 (16.2%)	14 (43.7%)	70%	0.01*
Child-Pugh score, *n* (%)					
Grade A	32 (32.3%)	20 (44.4%)	12 (22.2%)	37.5%	< 0.001*
Grade B	38 (38.4%)	22 (48.9%)	16 (29.7%)	42.1%	
Grade C	29 (29.3%)	3 (6.7%)	26 (48.1%)	89.7%	

P chi-square test, independent *t* test and Mann-Whitney test, *INR* international normalized ratio, *PTT* partial thromboplastin time
*Statistically significant
**Statistically highly significant

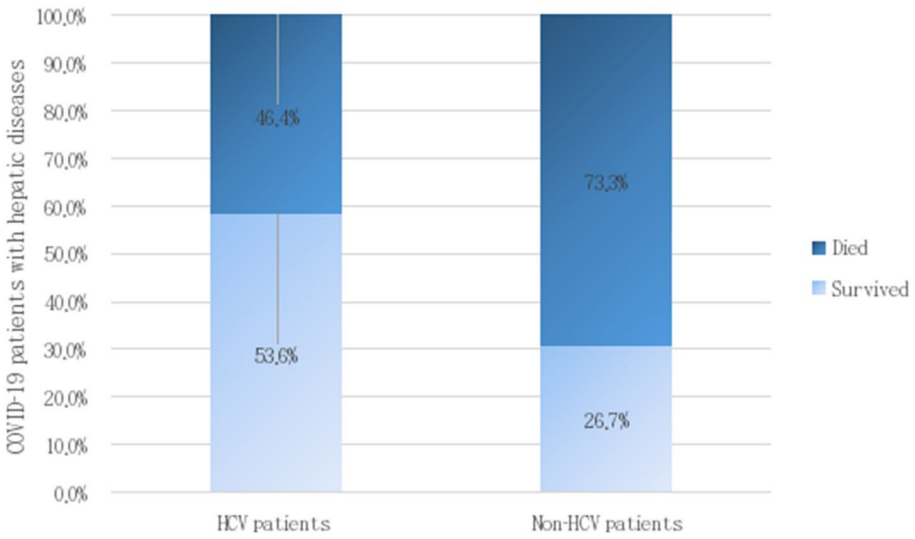

Fig. 4 Outcome of the COVID-19 patients with chronic liver diseases

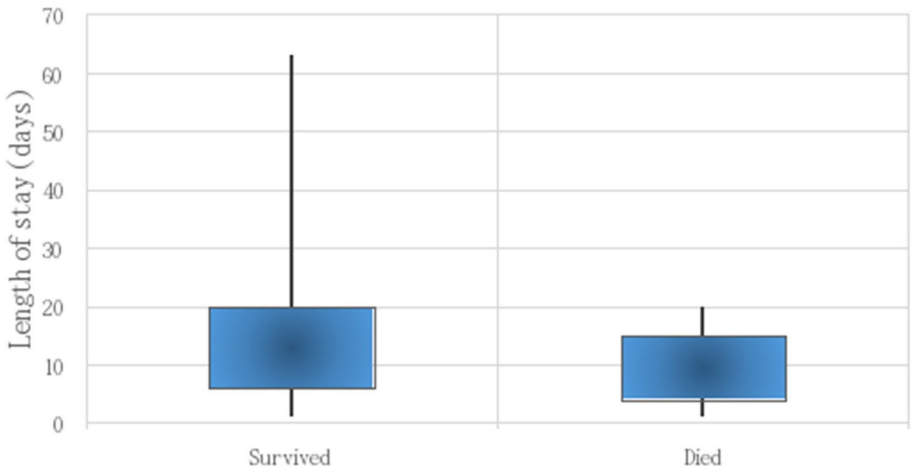

Fig. 5 Length of stay of the COVID-19 patients with chronic liver disease according to outcome

Survival analysis using the Kaplan–Meier method was used to determine the relation between treatment and survival in the investigated COVID-19 patients with hepatic disease. There was a statistically significant increase in median survival among cases who received HCV treatment compared to non-treated cases. In addition, there was a statistically significant increase in median survival among cases that received triple therapy either alone or associated with other drugs compared to other treatment types (Table 6, Fig. 6). Table 7 shows a significant increase in the survival rate among Child A and C-treated cases compared to non-treated cases.

Discussion

Egypt has the highest HCV prevalence in the world (Kouyoumjian et al. 2018). In September 2018, the Egyptian government released the "100 Million Healthy Lives" campaign with a fruitful nationwide HCV screening and treatment program (Blagosklonny 2020). To the best of our knowledge, this is the first study in Egypt focusing on the analysis of the prevalence, characteristics, and outcomes of chronic liver disease patients among a large cohort of severe and critical COVID-19 patients throughout a considerable time (24 months) in a large Egyptian tertiary care hospital, as

Table 4 Outcomes of the COVID-19 patients with HCV

Treatment	Outcome		*p* value	OR (95%CI)
	Survived ($n = 37$)	Died ($n = 32$)		
No treatment, *n* (%)	6 (16.2%)	14 (43.8%)	0.01*	0.25 (0.08–0.76)
Triple therapy, *n* (%)	15 (40.5%)	4 (12.5%)	0.009*	4.77 (1.39–16.43)
Ribavirin and interferon, *n* (%)	8 (21.6 %)	12 (37.5%)	0.15 NS	0.26 (0.16–1.33)
Double therapy, *n* (%)	6 (16.2%)	2 (6.3%)	0.20 NS	2.90 (0.54–15.53)
Triple+ribavirin and interferon, *n* (%)	2 (5.4%)	0 (0%)	0.57 NS	–

P chi-square test

*Statistically significant

Table 5 Binary logistic regression analysis of the outcome of the COVID-19 patients who had chronic liver disease with significantly related independent variables

Variables	*B*	S.E.	Wald	Sig.	Odds ratio	95% CI
Severity of COVID-19 at admission	1.33	0.36	12.18	< 0.001**	4.77	1.79–7.92
Hepatic encephalopathy at presentation	1.99	0.41	23.39	< 0.001**	7.35	3.28–16.5
High alanine transaminase (U/L)	0.53	0.29	3.21	0.05*	1.69	1.01–2.99
High aspartate transaminase (U/L)	0.69	0.33	4.43	0.04*	1.99	1.05–3.76
Low serum albumin (g/dL)	0.54	0.20	0.83	0.26	1.85	0.74–3.12
High total bilirubin (mg/dL)	0.84	0.36	5.30	0.02*	2.32	1.13–4.75
High direct bilirubin (mg/dL)	1.16	0.52	4.82	0.02*	3.19	1.14–8.98
Low platelet count (× 1000/cmm)	0.45	0.12	1.03	0.72	1.36	0.71–2.39
Length of stay	−0.19	0.10	0.53	0.61	0.63	0.34–1.88
Drug therapy:						
Tocilizumab	−0.16	0.14	0.58	0.13	0.48	0.13–1.12
Remdesivir	−0.22	0.17	0.73	0.09	0.77	0.55–2.21
Mechanical ventilation	1.93	0.82	5.54	0.02*	6.92	1.38–14.63
Mechanical ventilation duration	0.43	0.11	0.72	0.34	1.46	0.51–4.24
HCV	−0.98	0.43	4.13	0.03*	0.56	0.32–0.83
Treated HCV	−0.86	0.35	3.81	0.04*	0.37	0.21–0.76
Grade C liver cirrhosis	1.24	0.58	3.62	0.04*	2.28	1.01–5.12

S.E. standard error, *CI* confidence interval, *HCV* hepatitis C virus

*Statistically significant

**Statistically highly significant

Table 6 Median Survival of COVID-19 patients with HCV

Treatment	Median (day)	Log rank	*P*
No treatment	22.05	11.98	0.001*
Treatment	42.22		
No treatment	22.05	18.35	< 0.001**
Triple therapy	50.26		
Ribavirin and interferon	30.80		
Double therapy	48.75		
Triple+ribavirin and interferon	60		

*Statistically significant

**Statistically highly significant

well as, the effect of different types of anti-hepatitis C therapy on the outcome.

The mean age of the current study ICU patients was (54.9 ± 14.1). Evidence suggests that the protective counterbalancing arms of RAS are diminished in the elderly, making them more sensitive to the harmful effects of the ACE axis (Czick et al. 2020). Aging is linked not only with severe illness but also mortality (Waked et al. 2020; Onder et al. 2020).

The median ICU length of stay ranged from 6 to 12 days in China, compared with 4 to 19 days in other countries (Rees et al. 2020). The median length of ICU stay in

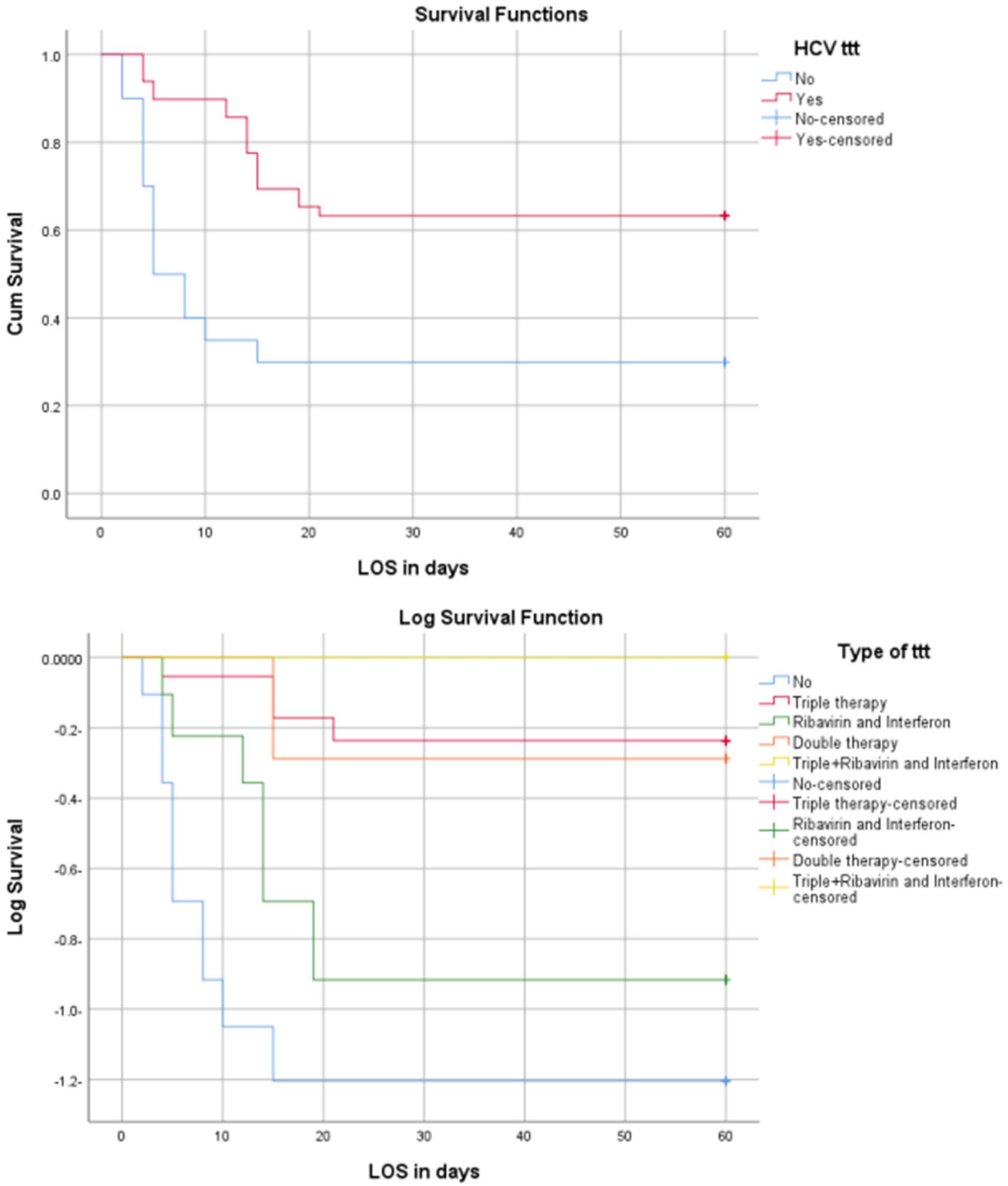

Fig. 6 Kaplan–Meir survival of HCV cases according to HCV treatment

Table 7 Outcomes of the COVID-19 patients with chronic liver disease according to treatment and Child–Pugh classification

Treatment	Outcome		*p* value
	Dead ($n = 54$)	Survived ($n = 45$)	
Child A not treated	7 (63.6%)	4 (36.4%)	**0.03***
Child A treated	5 (23.8%)	16 (76.2%)	
Child B not treated	9 (50 %)	9 (50%)	0.35 NS
Child B treated	7 (35%)	13 (65%)	
Child C not treated	20 (100%)	0(0%)	0.006*
Child C treated	6 (66.7%)	3 (33.3%)	

*Statistically significant

the current study was 8 days. This could be due to differences in the admission and discharge criteria. Furthermore, many Egyptian caregivers gained more expertise and proficiency in managing the condition at home upon patients' request and for their psychological pleasure, which impacted the results between close centers.

Although males had higher levels of RAS than premenopausal females, the male-to-female ratio suggests a higher incidence of males with the same outcome (Czick et al. 2020). In this study, the percentage of males was (57.5%) with an equal survival rate as females. Another Egyptian study showed no significant association between male gender and disease severity (Ramadan et al. 2020). Males were nearly 2.5 times more likely to die from COVID-19 in another study (Jin et al. 2020).

In a meta-analysis of 24 observational studies including 10,150 patients, ICU mortality rates ranged from 0 to 84% (Armstrong et al. 2020). Although nearly one-quarter of our COVID-19 patients died, the mortality rate in our cohort (24.3%) was lower than that reported in previous large cohorts (Grasselli et al. 2020a; Richards-Belle et al. 2020). This could be due to differences in ICU admission criteria, a less-stressed healthcare system in a university hospital setting, and the ability to maintain typical management standards. Another Egyptian study found a 24.4% total ICU/hospital death rate, which is substantially similar to our findings (Nassar et al. 2021).

Comorbidities are extensively proven to be key contributors to serious presentation and death in COVID-19 patients, allowing clinicians to construct risk stratification of COVID-19 patients as early as possible. The most prevalent chronic diseases in our cohort that also constituted risk factors for mortality were ischemic heart disease, hypertension, and diabetes mellitus. These findings are similar to those of a meta-analysis study by Emami et al. (Emami et al. 2020) and Ghweil et al. (Ghweil et al. 2020). Diabetes was shown to be a preexisting comorbidity in 33.8% of COVID-19 patients in a case study of 5700 hospitalized patients (Richardson et al. 2020). In an Italian case study, 49% of 1591 COVID-19 patients admitted to the ICU were hypertensive, and 21% had cardiovascular diseases (Grasselli et al. 2020b). CLD, malignancy, chronic kidney disease, organ transplantation, and neuropsychiatric symptoms at presentation were also associated with mortality in the current study. All exhibited a fingerprint of RAS imbalance, suggesting that RAS is a common offender (Czick et al. 2020).

Patients with CLD had greater rates of mortality than those without liver disease in a study of 2780 patients with COVID-19 (including 250 patients with CLD) (Singh and Khan 2020). The outcomes of adult patients with COVID-19 who were discharged from acute and post-acute care in France were investigated, including mechanical ventilation needs and day 30 mortality. COVID-19 mortality risk was not increased in patients with mild hepatic disease, compensated cirrhosis, acquired immunodepression syndrome, or organ transplantation, including liver transplantation. COVID-19-related mortality was higher in patients with alcohol abuse disorders, decompensated cirrhosis, and hepatocellular carcinoma, but the need for mechanical ventilation was less likely. The findings show that medical effort limitations may be linked to increased mortality in French residents with liver disease or an alcohol abuse disorder (Mallet et al. 2021).

The following are the study's key findings for our cohort: CLD was found to be present in 4.7% (99 patients) of COVID-19 patients. Approximately 3.3% (69 patients) had HCV-positive serology, and 2.3% (49 patients) received antiviral therapy. CLD was found to be a risk factor for mortality, and HCV patients had better outcomes than non-HCV patients. The stage of cirrhosis was associated with the outcome, where grade C liver cirrhosis was a predictor of mortality. In addition, there was a statistically significant correlation between hepatitis C virus treatment and outcome; nevertheless, analyses showed that individuals who received triple DAA medication had a better prognosis. Survival was observed between double DAA therapies as well but was not considered in the statistics. We found no advantage in terms of outcome from the old-fashioned antiviral treatment, including ribavirin and interferon. The explanation could be the specificity of these medications (DAAs) in protecting by a unique mechanism or the close proximity of delivery, which is why we propose the use of DAAs in prophylactic techniques to combat the pandemic together with current vaccination.

Another study attempted to evaluate the possible reciprocal effect of COVID-19 and pre-existing cirrhosis, which reported results comparable to those of the current study. This includes 332 COVID-19 patients hospitalized at three Italian hospitals during the pandemic, as well as

two large cohorts of HCV patients from real-world antiviral treatment studies (pangenotypic sofosbuvir/velpatasvir combination). Cirrhosis was associated with higher mortality, with metabolic cirrhosis accounting for most deaths. They concluded that the very low prevalence of COVID-19 in HCV cohorts suggests that HCV antibodies may have a protective effect (Mangia et al. 2020). The claim that only possessing hepatitis C antibodies is sufficient to explain and understand the observation is in conflict with our findings and with other interesting findings that identified hepatitis C as a significant predictor of in-hospital death (Ronderos et al. 2021; Cerbu et al. 2021). A history of hepatitis C infection accentuates SARS-CoV-2 viral virulence and raises the probability of a cumulative mortality risk to any other clinical or laboratory characteristics. The underlying processes might be connected to HCV extrahepatic effects, which would boost the ACE-2/TMPRSS mechanisms of the SARSCoV-2 virus, resulting in endothelial dysfunction (Ronderos et al. 2021). Another retrospective cohort analysis was performed to assess the risk of liver damage and all-cause mortality. When comparing the proportion of severe COVID-19 cases in the active and non-active HCV infection groups, the study found a statistically significant higher prevalence in the active HCV group. These findings suggest that active HCV patients with COVID-19 should be closely monitored and treated to avoid health deterioration and fatal outcomes (Cerbu et al. 2021).

Nassar et al. investigated the characteristics, risk factors, and outcomes of critically ill COVID-19 pneumonia patients admitted to Cairo University Hospitals in Egypt and found that patients with chronic liver disease patients had the lowest incidence of all comorbidities, with zero mortality (Nassar et al. 2021). Ain-Shams University Isolation Hospital showed a low rate of CLD patient ward admission and zero percent ICU admission in a retrospective analysis that identified risk factors for patients needing ICU admission during their stay (Fouad et al. 2021). Other supporting evidence was discovered in numerous Egyptian institutions (Khamiss et al. 2021; Omran et al. 2021; Hafez et al. 2021). A multicenter retrospective Egyptian study evaluated the impact of cirrhosis on the outcome of COVID-19, stating that even though cirrhotic patients were more likely to experience severe COVID-19 and death, only decompensated patients exhibited cirrhotic mortality (Afify et al. 2021).

Indirect findings from a SARS epidemiological investigation revealed that the hepatitis B virus (HBV) infection was a risk factor for ARDS progression (Peiris et al. 2003). The absence of hepatitis B as a risk factor in the current study cannot exclude the possibility that with the wide spread of vaccination, its incidence in the community declined. HBV infection was found in 2.1% of SARS-CoV-2 patients from China, indicating a higher local prevalence of HBV (Guan et al. 2020). Ronderos D et al. discussed the incidence of hepatitis C between COVID-19 patients in their locality with a similar explanation. The incidence of history of HCV infection in their study was on the higher side (4.1%) (Ronderos et al. 2021) than that reported in the literature, where HCV infection was found in less than 0.1% of COVID-19 patients in a sizable study of 5700 hospitalized patients (Richardson et al. 2020). In the community where the study cohort was drawn from (Bronx, New York), there is a higher prevalence of injection drug abuse, which has been linked to a higher incidence of HCV, which could explain the higher HCV prevalence in their cohort (Des Jarlais et al. 2018).

Postulated mechanisms

Our finding; the value of anti-hepatitis C medications in COVID-19 protection, was explained and supported by 3 mechanisms proposed and widely debated (Negm 2022).

Our study has certain limitations. Although there is a significant prevalence of HCV among elderly individuals living in rural areas in Sharkia governorate and other areas served by the university (Emam et al. 2015; el Gohary et al. 1995), our cohort may not be representative of hepatic patients with COVID-19 admitted to all Egyptian ICUs. According to our university's experience, non-critical patients who were admitted to the hospital or who were stable and discharged from the ICU preferred to stay back home to complete their management, therefore ward cases were excluded. Viral variant identification was not available at our institution. Unfortunately, HCV PCR was not performed, and we defined HCV status based on an antibody test for confirmation of positivity. Finally, the multivariate analysis may be limited by the included variables, and the impact of unmeasured confounders cannot be ruled out.

Conclusions

In this report, we demonstrated that chronic liver disease, chronic kidney disease, and malignancy were significant risk factors for death among COVID-19 patients. The Egyptian mass management of chronic hepatitis C may explain the favorable outcome of COVID-19 among these patients. Invasive mechanical ventilation and advanced liver cirrhosis were predictors of mortality. Further Egyptian and international multicenter studies are required to confirm or deny our results. Understanding the mechanisms may aid in better characterizing the disease and discovering novel therapeutic strategies. Intervention studies are needed to demonstrate the efficacy of DAAs as COVID-19 prophylactics. We will observe and monitor if our results, with existing immunization, will help Egypt's herd immunity build more rapidly.

Abbreviations

COVID-19	Coronavirus disease-2019
HCV	Hepatitis C virus
ICUs	Intensive care units
CLD	Chronic liver disease
DAAs	Direct antiviral agents
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
ACE2	Angiotensin-converting enzyme 2
ARDS	Acute respiratory distress syndrome
SaO2	Oxygen saturation
PaO2	Arterial oxygen partial pressure
FiO2	Fraction of inspired oxygen
MOH	Ministry of Health
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
RAS	Renin-angiotensin system
TMPRSS 2	Transmembrane protease, serine 2
HBV	Hepatitis B virus

Acknowledgements
We thank the isolation ICU, laboratory, and radiological electronic information system staff for providing the necessary data to conduct this study. Special thanks to Dr. Doaa Habib (Family medicine consultant), Dr. Shady Hammad (ICU specialist), and Mr. Mostafa Abdelmoaty (Archive Officer) for their great efforts in providing us with data.

Authors' contributions
E.N., R.E., and S.M. contributed to the conception and design of the study. E.N., H.M., H.A., H.K., A.M., M.S., and A.T. organized the database. M.M. and S.E. performed the statistical analysis. M.M. and S.E. plotted the figures and tables for this work. E.N., R.E., and M.S. wrote the first draft of the manuscript. E.N., R.E., and S.M. wrote sections of the manuscript. All authors contributed to the manuscript revision and read and approved the submitted version.

Funding
The authors received no specific funding for this work.

Availability of data and materials
Data can be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Under the approval by the research ethical committee of the Faculty of Medicine, Zagazig University (reference number ZU-IRB#: 6733-24-2-2021 with the consideration of the retrospective design of the study, patient informed consent was waived. The study was registered at ClinicalTrials.gov (NCT04757272). All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Received: 15 February 2023 Accepted: 7 November 2023
Published online: 16 November 2023

References

Abbas G, Silveira MG, Lindor KD (2011) Hepatic fibrosis and the reninangiotensin system. Am J Ther 18(6):202–208
Abdelzaher MA, Ibrahim AS, Negm EM (2021) Increasing fetal hemoglobin as a possible key for improvement of hypoxia and saving last breath in COVID-19 patient: "postulating a hypothesis". Egypt J Bronchol 15(*1*):*33*
Afify S, Eysa B, Hamid FA et al (2021) Survival and outcomes for co-infection of chronic hepatitis C with and without cirrhosis and COVID-19: A multicenter retrospective study. World J Gastroenterol 27(42):7362–7375
Albadawy RM, Jadoon BA, Mogahed MM et al (2021) The impact of comorbidities on the outcomes of Egyptian COVID-19 patients: a follow-up study. J Environ Public Health:6662476. https://doi.org/10.1155/2021/6662476
Armstrong RA, Kane AD, Cook TM (2020) Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. Anaesthesia 75(10):1340–1349
Blagosklonny MV (2020) From causes of aging to death from COVID-19. Aging 12(11):10004–10021
Centers for Disease Control Prevention (2012) Progress toward prevention and control of hepatitis C virus infection—Egypt, 2001–2012. MMWR Morb Mortal Wkly Rep 61(29):545
Cerbu B, Pantea S, Bratosin F et al (2021) Liver impairment and hematological changes in patients with chronic hepatitis C and COVID-19: a retrospective study after one year of pandemic. Medicina (Kaunas) 57(6):597
Czick M, Shapter C, Shapter R (2020) COVID's razor: RAS imbalance, the common denominator across disparate, unexpected aspects of COVID-19. Diabetes Metab Syndr Obes 13:3169–3192
Des Jarlais DC, Cooper HLF, Arasteh K, Feelemyer J, McKnight C, Ross Z (2018) Potential geographic "hotspots" for drug-injection related transmission of HIV and HCV and for initiation into injecting drug use in New York City, 2011–2015, with implications for the current opioid epidemic in the US. PLoS One. 13:e0194799
el Gohary A, Hassan A, Nooman Z et al (1995) High prevalence of hepatitis C virus among urban and rural population groups in Egypt. Acta Trop 59(2):155–161
Emam M, Radwan MI, Refaey MM, Shaheen NE, Abd-ElMoez S, Gerges MA (2015) Prevalence of hepatitis C virus in an elderly population in rural areas of Sharkia governorate, Egypt. Egypt Liver J 5(2):29–33
Emami A, Javanmardi F, Pirbonyeh N, Akbari A (2020) Prevalence of underlying diseases in hospitalized patients with COVID-19: a systematic review and meta-analysis. Arch Acad Emerg Med 8(1):35
Fouad SH, Allam MF, Ibrahim S et al (2021) ICU admission of COVID-19 patients: identification of risk factors. Egypt J Anaesth 37(1):202–207
Ghweil AA, Hassan MH, Khodeary A et al (2020) Characteristics, outcomes and indicators of severity for COVID-19 among sample of ESNA Quarantine Hospital's patients, Egypt: a retrospective study. Infect Drug Resist 13:2375–2383
Grasselli G, Greco M, Zanella A et al (2020a) Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med 180(10):1345–1355
Grasselli G, Zangrillo A, Zanella A et al (2020b) Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 323(16):1574–1581
Guan WJ, Ni ZY, Hu Y et al (2020) Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382:1708–1720
Hafez MZE, Nassar AY, Nassar GAY (2021) Epidemiology of Coronavirus Disease (COVID-19) in Assiut Province in Egypt. AJRID 6(2):19–25
IBM SPSS Statistics for Windows, Version 27. Armonk, NY: IBM Corp.; 2020 [cited 2021 Oct 24]. Available from: http://www01.ibm.com/support/docview.wss?uid=swg27049428.
Jassat W, Cohen C, Tempia S et al (2021) Risk factors for COVID-19-related in-hospital mortality in a high HIV and tuberculosis prevalence setting in South Africa: a cohort study. Lancet HIV 8(9):554–567
Jin JM, Bai P, He W et al (2020) Gender differences in patients with COVID-19: focus on severity and mortality. Front Public Health 8:152. https://doi.org/10.3389/fpubh.2020.00152
Khamiss AM, El-Dahshan M, El-Ghamery F, Aggag M, Hashim A, Eliwa A (2021) Outcomes of COVID-19 in Egyptian patients. Al-Azhar. Med. J 50(1):765–782
Kouyoumjian SP, Chemaitelly H, Abu-Raddad LJ (2018) Characterizing hepatitis C virus epidemiology in Egypt: systematic reviews, meta-analyses, and meta-regressions. Sci Rep 8(1):1661
Kulkarni AV, Kumar P, Tevethia HV et al (2020) Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. Aliment Pharmacol Ther 52(4):584–599
Lin L, Li TS (2020) Interpretation of guidelines for the diagnosis and treatment of novel coronavirus (2019- nCoV) infection by the National Health Commission (Trial Version 5). Zhonghua Yi Xue Za Zhi 100:E001. https://doi.org/10.3760/cma.j.issn.0376-2491.2020.0001
Mak KY, Chin R, Cunningham SC et al (2015) ACE2 therapy using adeno-associated viral vector inhibits liver fibrosis in mice. Mol Ther 23(9):1434–1443

Mallet V, Beeker N, Bouam S, Sogni P, Pol S, Demosthenes research group (2021) Prognosis of French COVID-19 patients with chronic liver disease: A national retrospective cohort study for 2020. J Hepatol. 75(4):848–855. https://doi.org/10.1016/j.jhep.2021.04.052
Mangia A, Cenderello G, Verucchi G et al (2020) Is positivity for hepatitis C virus antibody predictive of lower risk of death in COVID-19 patients with cirrhosis? World J Clin Cases 8(22):5831–5834
Nassar Y, Mokhtar A, Elhadidy A et al (2021) Outcomes and risk factors for death in patients with coronavirus disease-2019 (COVID-19) pneumonia admitted to the intensive care units of an Egyptian University Hospital. A retrospective cohort study. J Infect Public Health 14:1381–1388
Negm EM (2022) Does mass management of chronic hepatitis C protect the Egyptian population against fulminant coronavirus disease-2019? "Postulating a hypothesis". Egypt J Bronchol 16:19
Ni W, Yang X, Yang D et al (2020) Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care 24(1):422. https://doi.org/10.1186/s13054-020-03120-0
Oarhe CI, Dang V, Dang M et al (2015) Hyperoxia downregulates angiotensin-converting enzyme-2 in human fetal lung fibroblasts. Pediatr Res 77(5):656–662
Omran D, Al Soda M, Bahbah E et al (2021) Predictors of severity and development of critical illness of Egyptian COVID-19 patients: a multicenter study. PLoS One 16(9):e0256203
Omran D, Alboraie M, Zayed RA et al (2018) Towards hepatitis C virus elimination: Egyptian experience, achievements and limitations. World J Gastroenterol 24(38):4330–4340. https://doi.org/10.3748/wjg.v24.i38.4330
Onder G, Rezza G, Brusaferro S (2020) Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. https://doi.org/10.1001/jama.2020.4683
"Outbreak brief 124: Coronavirus disease 2019 (COVID-19) pandemic". Africa CDC. 2022. p. 4. Retrieved 7 June 2022.
Peiris JS, Chu CM, Cheng VC et al (2003) Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 361:1767
Perlman S, Netland J (2009) Coronaviruses post-SARS: update on replication and pathogenesis. Nat Rev Microbiol 7:439–450. https://doi.org/10.1038/nrmicro2147
Ramadan HK-A, Mahmoud MA, Aburahma MZ et al (2020) Predictors of severity and co-infection resistance profile in COVID-19 patients: first report from Upper Egypt. Infect Drug Resist 13:3409–3422
Ranzani OT, Bastos LSL, Gelli JGM et al (2021) Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. Lancet Respir Med 9:407–418
Rees EM, Nightingale ES, Jafari Y et al (2020) COVID-19 length of hospital stay: a systematic review and data synthesis. BMC Med 18(1):270
Richards-Belle A, Orzechowska I, Gould DW et al (2020) COVID-19 in critical care: epidemiology of the first epidemic wave across England, Wales and Northern Ireland. Intensive Care Med 46(11):2035–2047
Richardson S, Hirsch JS, Narasimhan M et al (2020) Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 323(20):2052–2059
Ronderos D, Omar AMS, Abbas H et al (2021) Chronic hepatitis-C infection in COVID-19 patients is associated with in-hospital mortality. World J Clin Cases 9(29):8749–8762
Saied AA, Metwally AA, Madkhali NAB, Haque S, Dhama K (2021) Egypt's COVID-19 recent happenings and perspectives: a mini-review. Front Public Health 9:696082. https://doi.org/10.3389/fpubh.2021.696082
Singh S, Khan A (2020) Clinical characteristics and outcomes of coronavirus disease 2019 among patients with preexisting liver disease in the United States: a multicenter research network study. Gastroenterology 159:768
Skurk T, Lee YM, Hauner H (2001) Angiotensin II and its metabolites stimulate PAI-1 protein release from human adipocytes in primary culture. Hypertension 37(5):1336–1340
Sze S, Pan D, Nevill CR et al (2020) Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis. EClinicalMedicine 29:100630
Waked I, Doss W, El-Sayed M et al (2014) The current and future disease burden of chronic hepatitis C virus infection in Egypt. Arab J Gastroenterol 15:45–52
Waked I, Esmat G, Elsharkawy A et al (2020) Screening and treatment program to eliminate hepatitis C in Egypt. N Engl J Med 382(12):1166–1174
Wang B, Li R, Zhong L, Huang Y (2020) Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging 12(7):6049–6057
Williamson EJ, Walker AJ, Bhaskaran K et al (2020) Factors associated with COVID-19-related death using OpenSAFELY. Nature 584:430–436
Zhang C, Shi L, Wang FS (2020) Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol 5:428

Publisher's Note