The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89, Page 5175- 5180

Morbidity And Mortality Among Patients with Compensated Cirrhosis Infected with COVID-19

Usama Mohamed Basha, Alaa Ahmed Farag, Mohamed Ali Ramadan*, Ashraf Khalifa Elnagar, Ahmed Esmail Ahmed

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

***Corresponding author:** Mohamed Ali Ramadan, **Mobile:** (+20) 01062404267, **E-Mail:** dr.mohamedali244@gmail.com

ABSTRACT

Background: Patients with liver cirrhosis, due to immunological dysfunction, are at a significant risk for getting SARS-Cov-2 infection, which accounts for 1.2 million deaths annually around the world.

Objective: To study impact of COVID-19 on morbidity and mortality among patients with compensated cirrhosis.

Patients and Methods: Our prospective cohort study was done at Ahmed Maher Teaching Hospital, and Internal Medicine Department of Zagazig University Hospitals, this study was performed on 180 patients. The included patients are classified into two groups; ninety COVID-19-infected patients with chronic liver disease (CLD) and ninety non-CLD patients with COVID. PCR, liver functions as well as pelvi-abdominal Ultrasound were done to all patients.

Results: There is statistically significant difference between both groups regarding mortality. About 18% and 7% within CLD with COVID and non-CLD with COVID groups respectively died by the end. There is statistically significant relation between mortality among CLD patients with COVID and CRP and ESR levels (both were significantly lower among survivors). There is statistically significant relation between hepatic encephalopathy among CLD patients with COVID and ESR levels (both were significantly lower among those with hepatic encephalopathy).

Conclusion: Both preexisting medical issues and those that arise during hospitalisation appear to have a significant impact on the mortality of COVID-19 patients. Hospitalized cirrhotic individuals whose survival rates have been studied for the impact of SARS-CoV-2 infection can provide further additional details.

Key words: Morbidity, mortality, compensated cirrhosis, COVID-19.

INTRODUCTION

Patients with cirrhosis are particularly vulnerable to complications from 2019 coronavirus illness (COVID-19). When comparing patients with decompensated cirrhosis to those with compensated cirrhosis, and when comparing patients with cirrhosis to those with noncirrhotic chronic liver disease, the morbidity and mortality associated with COVID-19 are much higher [(1)]. Type 2 alveolar cells, cholangiocytes, enterocytes, and myocardial cells all include angiotensin-converting enzyme (ACE) receptors, which act as the virus's entry point. This could help explain why people with preexisting conditions tend to have more severe forms of the disease and why coronavirus tends to affect multiple systems at once [(2)].

Despite the absence of chronic liver disease, patients with COVID-19 frequently exhibit abnormal liver function tests (LFT). According to a study of the literature conducted by **Ghoshal *et al.*[(3)]** individuals with COVID-19 were more likely to have elevated liver enzymes (10.5%-53%), while only 5.1%-18% of patients developed jaundice due to an increase in total bilirubin. Multiple studies have also noted a drop in serum albumin levels. Abnormalities in liver function tests were more common in patients with severe COVID-19-associated illness[(3)].

Among people infected with COVID-19, 2–11% already had some sort of liver illness. Only 0.4% of participants in the New York research had cirrhosis at the outset. Cirrhosis has been linked to higher mortality in individuals with acute respiratory distress syndrome, while its effect on COVID-19 illness is still unclear (ARDS). Cirrhotic have low immune function and worse outcomes when critically ill, so severe patients with COVID-19 who also have liver disease need more intense surveillance or individualized therapy methods [(4)]. With a compromised immune system, people with liver cirrhosis are at increased risk for contracting SARS-CoV-2, which is responsible for an estimated 1.2 million fatalities annually around the world. The virus causes liver damage, which can progress to cirrhosis's worsening stage or even cause death, in these patients. Because of this, it's possible that the high mortality rate among cirrhotic patients who have COVID-19 can be explained [(5)]. The study aims to study impact of COVID-19 on morbidity and mortality among patients with compensated cirrhosis.

PATIENTS AND METHODS

Our prospective cohort study was done at Internal Medicine Department of Zagazig University Hospitals, this study was done on 180 subjects. The included patients were classified into two groups ninety COVID-19-infected patients with chronic liver disease (CLD) and ninety non-CLD patients with COVID.

Inclusion Criteria: All the members of this group were adults (more than 18 years), and patients hospitalized with compensated chronic liver disease with a positive RT-PCR or characteristic CT scan findings have been found to have COVID-19 infection.

Exclusion Criteria: Patients with COVID-19 negativity, people who are under the age of 18, patients with decompensated liver disease who are not cirrhotic, and patients who are fall outside the inclusion criteria.

All patients were subjected in the following:

1- **Complete history talking:** Personal history (name, age, sex, occupational, special habits), present history, and past history.

Received: 13/6/2022
Accepted: 21/8/2022

2- **Full clinical examination**.
3- **Investigation:**
   A) **Laboratory investigations in the form of:** Complete blood count (CBC), kidney function tests, coagulation profile (PT, INR, PTT), inflammatory markers (ESR- CRP- D. dimer), liver function tests, HCV antibody, HBs antigen, and COVID-19 PCR.
   B) **Radiological:** Following the release of the initial SARS-CoV-2 sequences to the public via the GISAID database.
4- **CT chest**.
5- **Pelvi-abdominal ultrasound:** For detection of liver cirrhosis.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

In order to analyze the data acquired, Statistical Package of Social Sciences version 20 was used to execute it on a computer (SPSS). In order to convey the findings, tables and graphs were employed. The quantitative data was presented in the form of the mean, median, standard deviation, and confidence intervals. The information was presented using qualitative statistics such as frequency and percentage. The student's t test (t) is used to assess the data while dealing with quantitative independent variables. Pearson Chi-Square and Chi-Square for Linear Trend (χ^2) were used to assess qualitatively independent data. The significance of a P value of 0.05 or less was determined.

RESULTS

In addition to the 90 CLD patients, another 90 COVID patients who did not have CLD were also enrolled in the study. There is no statistically significant difference in age or gender between the two groups. CLD patients with COVID-19 have considerably lower body weight and body mass index than the control group (Table **1**).

Table (1) Demographics:

Parameter	Group		Test	
	CLD with COVID-19	Non-CLD COVID-19	χ^2/t	p
	N=90 (%)	N=90 (%)		
Gender:				
Female	33 (36.7%)	37 (41.1%)	0.374	0.571
Male	57 (63.3%)	53 (58.9%)		
Age (year):				
Mean ± SD	50.13 ± 5.29	49.28 ± 4.34	1.178	0.24
Weight(kg)				
Mean ± SD	75.45 ± 2.89	76.92 ± 2.98	-3.361	0.001**
BMI:				
Mean ± SD	25.89 ± 2.03	26.48 ± 1.93	-1.991	0.048*

There is statistically significant difference between both groups regarding AST, ALT, total, direct bilirubin, INR, BUN and PT (all are significantly higher in CLD patients with COVID-19). There was statistically significant difference between both groups regarding serum albumin, platelet count and CRP (both are significantly lower in CLD patients with COVID-19). There was statistically significant difference between both groups regarding ESR, and D-Dimer (both are significantly higher in CLD patients with COVID-19). There was statistically non-significant difference between both groups regarding white blood cells, red blood cells, hemoglobin (Table **2**).

Table (2): Laboratory data:

Parameter	Group		Test	
	CLD with COVID-19	Non-CLD COVID-19	t	p
	Mean ± SD	Mean ± SD		
AST (U/L)	73.31 ± 6.82	34.27 ± 7.3	17.931	<0.001*
ALT (U/L)	48.13 ± 7.11	31.89 ± 6.3	11.049	<0.001*
T. bilirubin (µmol/L)	2.1 ± 0.44	1.16 ± 0.16	15.893	<0.001*
D. bilirubin (µmol/L)	0.89 ± 0.13	0.76 ± 0.12	5.107	<0.001*
Albumin (g/L)	3.08 ± 0.12	3.37 ± 0.32	-7.958	<0.001*
INR	1.38 ± 0.19	1.18 ± 0.13	8.151	<0.001*
Prothrombin time (U/mL)	15.23 ± 1.99	12.63 ± 1.23	10.539	<0.001*
WBCs (mcL)	6.44 ± 1.09	6.49 ± 1.37	-0.241	0.81
RBCs (mcL)	4.09 ± 0.87	4.0 ± 0.85	0.694	0.488
Hemoglobin (g/dL)	10.3 ± 0.97	10.04 ± 1.25	1.589	0.114
Platelet (mcL)	110.45 ± 11.42	190.22 ± 9.88	0.084	0.933
BUN (mg/dL)	42.88 ± 4.39	34.73 ± 9.92	7.13	<0.001*
Creatinine (mg)	0.94 ± 0.28	0.96 ± 0.23	-0.403	0.688
CRP (mg/L)	65.49 ± 14.8	50.32 ± 12.22	-7.38	<0.001*
ESR (mm/hr)	55.52 ± 12.63	39.0 ± 7.41	0.986	0.326
D dimer (µg/mL	827.09 ± 15.62	338.15 ± 46.45	-1.596	0.112

*: Significant

There was statistically significant difference between both groups regarding mortality. About 18% and 7% within CLD with COVID and non-CLD with COVID groups respectively died by the end (Table **3**).

Table (3): Outcomes comparison:

Parameter	Group		Test	
	CLD with COVID-19	Non-CLD COVID-19	χ^2/t	p
	N=90(%)	N=90 (%)		
Mortality	16 (17.8%)	6 (6.7%)	5.178	0.023*

There was statistically non-significant relation between mortality rate amongst CLD patients with COVID and either gender, weight or body mass index. There was statistically significant relation between mortality rates amongst CLD patients with COVID age (Table **4**).

Table (4): Relation for mortality and demographic data among CLD patients with COVID-19:

Parameter	Died	Survivors	Test	
	N=16	N=74	χ^2	p
Male gender:	8 (50%)	49 (66.2%)	1.49	0.222
	Mean ± SD	Mean ± SD	t	p
Age	54.51 ± 8.52	49.46 ± 4.52	2.3	0.034*
Weight	76.67 ± 3.76	75.19 ± 2.63	1.495	0.152
BMI	26.63 ± 1.36	25.73 ± 2.12	1.627	0.107

There was statistically significant relation between mortality among CLD patients with COVID and CRP and ESR levels (both were significantly lower among survivors). There was statistically non-significant relation between mortality among CLD patients with COVID and other laboratory data (Table **5**).

Table (5): Relation for mortality and laboratory data amongst CLD patients with COVID-19:

Parameter	Died	Survivors	Test	
	Mean ± SD	Mean ± SD	t	p
AST (U/L)	72.81 ± 15.75	73.42 ± 17.14	-0.13	0.897
ALT (U/L)	46.94 ± 4.52	48.39 ± 7.55	-1.016	0.316
T. bilirubin (µmol/L)	2.23 ± 0.28	2.07 ± 0.13	1.307	0.195
D. bilirubin (µmol/L)	0.89 ± 0.13	0.9 ± 0.14	-0.192	0.848
Albumin (g/L)	3.08 ± 0.08	3.08 ± 0.13	-0.035	0.972
INR	1.39 ± 0.29	1.38 ± 0.16	0.123	0.904
Prothrombin time (U/mL)	16.02 ± 2.04	15.06 ± 1.96	1.762	0.082
WBCs (mcL)	6.75 ± 0.93	6.38 ± 1.12	1.237	0.219
RBCs (mcL)	4.19 ± 0.95	4.07 ± 0.83	0.498	0.62
Hemoglobin (g/dL)	10.01 ± 0.95	10.37 ± 0.97	-1.326	0.188
Platelet (mcL)	108.38 ± 8.82	110.92 ± 11.92	0.944	0.353
BUN (mg/dL)	42.39 ± 3.51	42.99 ± 4.58	-0.491	0.625
Creatinine (mg)	1.01 ± 0.24	0.93 ± 0.28	1.033	0.305
CRP (mg/L)	57.99 ± 9.63	48.87 ± 11.27	3.048	0.004*
ESR (mm/hr)	45.94 ± 10.33	37.41 ± 7.63	4.394	0.001*
D. dimer (µg/mL)	826.98 ± 36.2	812.24 ± 48.75	0.367	0.715

*: Significant

On doing multivariate analysis of mortality predictors among CLD patients with COVID-19, comorbid diabetes, severe COVID, older age, increasing CRP and ESR levels independently increase risk of morality (AOR were 15.816. 9.963, 1.107, 1.014 and 1.119 respectively) (Table **6**).

Table (6): An examination of risk variables for death in COVID patients with CLD using multivariate regression:

	β	p	AOR	95% C.I.	
				Lower	Upper
Diabetes	2.761	.015*	15.816	1.721	145.329
Severe COVID	2.299	.015*	9.963	1.570	63.213
Age	.101	.337	1.107	.900	1.361
CRP	.014	.703	1.014	.942	1.092
ESR	.112	.007*	1.119	1.031	1.214

There was statistically significant relation between ascites among CLD patients with COVID and ESR levels (significantly higher among those with ascites) and serum albumin (significantly lower in ascites group).

There was statistically non-significant relation between ascites among CLD patients with COVID and other laboratory data (Table **7**).

Table (7): Relation between ascites and laboratory data among CLD patients with COVID-19:

Parameter	Ascites	Absent	Test	
	Mean ± SD	Mean ± SD	t	p
AST (U/L)	73.56 ± 13.51	73.25 ± 17.63	0.069	0.945
ALT (U/L)	49.89 ± 5.65	47.69 ± 7.4	1.174	0.244
T. bilirubin (µmol/L)	2.01 ± 0.41	3.6 ± 0.45	-13.63	<0.001*
D. bilirubin (µmol/L)	2.14 ± 0.34	2.09 ± 0.46	0.456	0.65
Albumin (g/L)	0.9 ± 0.11	0.89 ± 0.12	0.236	0.814
INR	1.41 ± 0.26	1.37 ± 0.17	0.783	0.435
Prothrombin time (U/mL)	15.77 ± 2.43	15.1 ± 1.87	1.278	0.205
WBCs (mcL)	6.56 ± 0.98	6.42 ± 1.12	0.48	0.632
RBCs (mcL)	4.11 ± 1.02	4.08 ± 0.84	0.121	0.904
Hemoglobin (g/dL)	10.18 ± 1.09	10.33 ± 0.94	-0.608	0.545
Platelet (mcL)	105 ± 5.14	110.69 ± 11.76	0.944	0.353
BUN (mg/dL)	42.9 ± 3.73	42.88 ± 4.57	0.012	0.991
Creatinine (mg)	0.99 ± 0.17	0.93 ± 0.3	1.105	0.275
CRP (mg/L)	53.81 ± 10.74	49.66 ± 11.22	1.06	0.29
ESR (mm/hr)	49.0 ± 15.82	38.4 ± 9.83	2.69	0.014*
D dimer (µg/mL)	830.98 ± 36.2	815.24 ± 48.75	0.792	0.432

*: Significant

There was statistically significant relation between hepatic encephalopathy among CLD patients with COVID and ESR levels (both were significantly lower among those with hepatic encephalopathy). There was statistically significant relation between hepatic encephalopathy among CLD patients with COVID and RBCs (significantly higher among those with hepatic encephalopathy). There was statistically non-significant relation between hepatic encephalopathy among CLD patients with COVID and other laboratory data (Table **8**).

Table (8): Relation between hepatic encephalopathy and laboratory data among CLD patients with COVID-19:

Parameter	HE	Absent	Test	
	Mean ± SD	Mean ± SD	t	p
AST (U/L)	69.09 ± 15.53	73.9 ± 17.0	-0.887	0.377
ALT (U/L)	48.73 ± 4.08	48.05 ± 7.45	0.455	0.654
T. bilirubin (µmol/L)	2.23 ± 0.32	2.09 ± 0.45	1.012	0.314
D. bilirubin (µmol/L)	0.93 ± 0.13	0.89 ± 0.13	0.902	0.37
Albumin (g/L)	3.09 ± 0.09	3.08 ± 0.12	0.254	0.8
INR	1.35 ± 0.31	1.39 ± 0.17	-0.412	0.689
Prothrombin time (U/mL)	16.37 ± 2.54	15.07 ± 1.87	1.639	0.128
WBCs (mcL)	6.91 ± 0.94	6.38 ± 1.1	1.517	0.131
RBCs (mcL)	4.64 ± 0.51	4.01 ± 0.88	2.281	0.025*
Hemoglobin (g/dL)	10.24 ± 1.22	10.31 ± 0.94	-0.24	0.811
Platelet (mcL)	194.18 ± 10.17	189.82 ± 11.54	1.189	0.238
BUN (mg/dL)	43.79 ± 3.5	42.76 ± 4.51	0.73	0.468
Creatinine (mg)	0.98 ± 0.16	0.94 ± 0.29	0.602	0.554
CRP (mg/L)	58.17 ± 11.24	49.42 ± 12.12	1.863	0.066
ESR (mm/hr)	52.73 ± 12.31	38.82 ± 9.21	2.613	0.024*
D. dimer (µg/mL)	825.51 ± 3.06	822.74 ± 8.53	0.183	0.855

*: Significant

DISCUSSION

Patients with cirrhosis may be at a higher risk for SARSCoV-2 infection due to their impaired immune systems. Furthermore, the severity of COVID-19 and the rate of complications may be greater in these patients than in the general population, which may result in an increase in liver-related mortality[6].

The aim of work of the current study was to study impact of COVID-19 on morbidity and mortality among patients with compensated cirrhosis.

In this study, there were male predominance as 63.3% in CLD with COVID-19 group and 58.9% in non-CLD COVID 19 group that agree with the study done by **Saris *et al.*[7]** there were 94.1% of the studied cases were males.

Mean age of participants in our study was 50.13 ± 5.29 years, 49.28 ± 4.34 years in both groups that agreed with results of **Ramatillah and Isnaini[8]** who determined that the COVID-19 patient population had a mean age of 56 (range: 18-87).

In our study, in CLD with COVID-19 group the mean AST was 73.31 ± 16.82, the mean ALT was 48.13 ± 7.11, the mean Total-Bilirubin was 2.1 ± 0.44, the mean Serum albumin was 3.08 ± 0.12 and the mean INR was 1.38 ± 0.19, that results was in line with **Iavarone *et al.*[6]** who showed that the mean AST was 48.0, the mean ALT was 48 (± 7.12 SD), the mean Total-Bilirubin was 1.8, the mean Serum albumin was 2.8, the mean INR was 1.4 (± 0.2 SD). Another study by **Guan *et al.*[9]** also found that there was a significant difference between the ALT and AST levels of severe and mild patients (28 vs. 39 percent) (20 percent and 18 percent, respectively)

In the current study, in CLD with COVID-19 group the mean platelet count was 109.36 ± 11.42, and the mean WBCs count/mm was 6.44 ± 1.09 which was in line with **Qi *et al.*[10]** 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. Also, **Iavarone *et al.*[6]** showed that the mean WBCs count/mm was 4.500, the mean PLT was 115000.

According to the mean Creatinine in CLD with COVID-19 group it was 0.94 ± 0.28, which agree with the **Qi *et al.*[10]** who showed that the mean Creatinine kinase, U/L was 87 and **Iavarone *et al.*[6]** showed that the mean Creatinine, mg/dl was 1.00.

In the present study, in CLD with COVID-19 group the mean CRP was 50.49 ± 14.8 which coincide with by **Iavarone *et al.*[6]** who showed that the mean CRP, mg/dl was 5.00.

In the present study, about 18% of CLD patients with COVID died and 7% non-CLD with COVID groups by the end, that actually agree with **Premkumar *et al.*[11]** as although antiviral medication was administered promptly, 82% of patients with cirrhosis and A/H1N1/09 died from pneumonia and acute respiratory distress syndrome. The severity of respiratory distress and kidney impairment were independent predictors of mortality [6].

Ji *et al.*[12] stated that individuals with NAFLD/NASH may have more severe disease/mortality due to the common relationship with diabetes, obesity, and metabolic syndrome than patients with non-cirrhotic chronic liver disease (CLD).

That also agree with **Singh and Khan[13]** they conducted a multicentric study contrasting a group of 250 patients with liver disease (NASH being the most common sitology) with a group of 2530 participants without liver disease. Patients with liver disease tended to be older and more likely to have many medical conditions at once. Patients with liver illness were shown to have a considerably higher risk of mortality, according to the study's authors.

In this study, there was non-significant relation between mortality among CLD patients and sex which in agreement with **Jin *et al.*[14]** who stated that no significant difference regarding gender for COVID severity. But in the study done by **Huang *et al.*[15]** stated that males may experience more severe disease than females.

In our study, there was a statistical significant difference in between mortality among CLD patients with COVID and age which coincide with **Ioannou *et al.*[16]** who stated that Patients with cirrhosis and SARS-CoV-2 had a higher risk of dying if they were older, in a state of decompensation, or had a high model for end-stage liver disease (MELD) score.

Consistent with the findings of **Zhu *et al.*[18]** who compared 7337 patients with COVID-19 and type 2 diabetes, we found a statistically significant association between diabetes and death in the CLD group, hospital stays for those with type 2 diabetes were found to necessitate more medical intervention than stays for people without the disease. Poor blood glucose control was associated with a higher risk of death overall compared to improved glucose control.

Although **Izcovich *et al.*[18]** conducted a systematic review of 207 studies and found several variables that provided prognostic information about severe disease and/or mortality, the current study did not find any statistically significant differences between the groups with regard to liver function tests and mortality. Severe illness is linked to elevated blood levels of aspartate aminotransferase (AST), a reduction in albumin, and elevated bilirubin. A poorer prognosis is expected for patients whose LFTs are aberrant compared to those whose LFTs are normal.

As regard to mortality predictors among CLD patients with COVID-19, comorbid diabetes, severe COVID, older age, increasing CRP and ESR levels independently increase risk of morality, while in the study done by **Elhence *et al.*[19]** who found that Total leukocyte count (TLC), total bilirubin, creatinine, international normalized ratio (INR), critical illness

prognosis (CTP), mild to extreme organ dysfunction syndrome (MELD), and need for invasive ventilation are all risk factors for death.

Also in another study by **Marjot *et al.*[(20)]** age, cardiovascular disease, and serum creatinine at baseline were all significantly linked with mortality in patients with CLD.

As fourteen individuals were already complex, 20% had ascites, 14% experienced bleeding, and 12% had hepatic encephalopathy, we also assessed the effect of chronic liver illness on the severity of COVID-19 in our study. That also agree with **Elhence *et al.*[(19)]** as our findings are similar to those found in 12 (46.2% of) COVID-19 patients who also had cirrhosis and presented with cirrhosis-related sequelae. Patients with cirrhosis who also suffer from severe lung injury and chronic liver failure have a lower chance of a successful outcome according to the COVID-19 study.

CONCLUSION

Both preexisting medical issues and those that arise during hospitalization appear to have a significant impact on the mortality of COVID-19 patients. It can be emphasized even more by calculating how much of an effect SARS-CoV-2 infection has on the survival of cirrhosis patients while they are in the hospital.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Choudhary N, Dhampalwar S, Saraf N *et al.* (2021):** Outcomes of COVID-19 in Patients with Cirrhosis or Liver Transplantation. Journal of Clinical and Experimental Hepatology, 11(6): 713–719.
2. **Yang X (2020):** Clinical Course and Outcomes of Critically Ill Patients with SARS-CoV-2 Pneumonia in Wuhan, China: A Single-Centered, Retrospective, Observational Study. The Lancet Respiratory Medicine, 8: 475-481.
3. **Ghoshal U, Ghoshal U, Dhiman R *et al.* (2020):** Gastrointestinal and hepatic involvement in severe acute respiratory syndrome coronavirus 2 infection: a review. Journal of Clinical Experimental Hepatology, 10: 622-628.
4. **Richardson S, Hirsch J, 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.
5. **Liu X, Xiao X, Wei X *et al.* (2020)** Composition and Divergence of Coronavirus Spike Proteins and Host ACE2 Receptors Predict Potential Intermediate Hosts of SARS-CoV-2. Journal of Medical Virology, 92: 595-601.
6. **Iavarone M, D'Ambrosio R, Soria A *et al.* (2020)** High Rates of 30-Day Mortality in Patients with Cirrhosis and COVID-19. Journal of Hepatology, 73: 1063-1071.
7. **Saris A, Reijnders T, Nossent E *et al.* (2021):** Distinct cellular immune profiles in the airways and blood of critically ill patients with COVID-19. Thorax, 76(10):1010-1019.
8. **Ramatillah D, Isnaini S (2021):** Treatment profiles and clinical outcomes of COVID-19 patients at private hospital in Jakarta. PLOS One, 16: e0250147. https://doi.org/10.1371/journal.pone.0250147
9. **Guan W, Ni Z, Hu Y *et al.* (2020):** Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med., 382: 1708-1720.
10. **Qi X, Liu Y, Wang J *et al.* (2021):** Clinical course and risk factors for mortality of COVID-19 patients with pre-existing cirrhosis: a multicentre cohort study. Gut, 70: 433-436.
11. **Premkumar M, Devurgowda D, Dudha S *et al.* (2019):** A/H1N1/09 influenza is associated with high mortality in liver cirrhosis. Journal of Clinical Experimental Hepatology, 9: 162-170.
12. **Ji D, Qin E, Xu J *et al.* (2020):** Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. Journal of Hepatology, 73: 451-453.
13. **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: 768-771.
14. **Jin J, Bai P, He W *et al.* (2020):** Gender differences in patients with COVID-19: focus on severity and mortality. Frontiers in Public Health, 8: 152-56.
15. **Huang C, Wang Y, Li X *et al.* (2020):** Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet, 395: 497-506.
16. **Ioannou G, Liang P, Locke E *et al.* (2020):** Cirrhosis and SARS-CoV-2 infection in US Veterans: risk of infection, hospitalization, ventilation and mortality. Hepatology, 74(1):322-335.
17. **Izcovich A, Ragusa M, Tortosa F *et al.* (2020):** Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PloS One, 15: e0241955. https://doi.org/10.1371/journal.pone.0269291
18. **Zhu L, She Z, Cheng X *et al.* (2020):** Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab., 31: 1068-1077.
19. **Elhence A, Vaishnav M, Kumar R *et al.* (2020):** Poor outcomes in patients with cirrhosis and Corona Virus Disease-19. Indian Journal of Gastroenterology, 39: 285-291.
20. **Marjot T, Moon A, Cook J *et al.* (2021):** Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: an international registry study. Journal of Hepatology, 74: 567-577.