Systematic Review

Liver Function Tests Profile in COVID-19 Patients at the Admission Time: A Systematic Review of Literature and Conducted Researches

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Abstract

Background: Since the start of coronavirus epidemic in Wuhan, China, in early December 2019, many literatures addressed its epidemiology, virology, and clinical presentation. In this review, we systematically reviewed the published literature in the field of liver function tests profile in COVID-19 patients at the admission time. **Materials and Methods:** systematic literature search were performed in EMBASE, PubMed, Science Direct, and Scopus using "severe acute respiratory syndrome 2 coronavirus (SARS-CoV-2)", "SARS," "SARS-CoV," "coronavirus," "novel coronavirus," "liver," "hepatitis," "Liver function" keywords. The search was limited to range from 2019 to May 19, 2020. **Results:** From a total 7298 articles, 145 were screened and 18 were eligible for further analysis. The highest rate of liver associated comorbidities was reported 11%. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were the most frequent assessed enzymes. Increase in AST level was seen in 10%–53% of patients while The ALT increase was seen in 5%–28% of COVID-19 patients at the admission time. The prothrombin time was increase in 7%–12% of patients and the D-dimer was reports increase in 14%–36% of COVID-19 patients at the admission time. Furthermore, albumin decrease was seen in 6%–98% of COVID-19 patients at the admission time. **Conclusion:** In conclusion, by using the results of study, it could be suggested that the liver function tests assessment is critical assessment in COVID-19 patients at the admission time. This liver function test could be used as potential prognostic factor in COVID-19 severity in future.

Keyword: *COVID-19, liver function tests, liver, SARS-CoV-2, systematic review*

Introduction

Coronaviridae members are enveloped viruses with the RNA genome length 26–32 Kilo base and causative agent for respiratory and enteric infections in animals and humans. The name coronavirus mentions to the envelope spikes which presents virus-specific morphology.[1] In human host, the coronaviruses infect respiratory and enteric cells. This infection manifestation could be range as asymptomatic, self-limiting to sever bronchitis and pneumonia with renal complications.[2] *Coronaviridae* classified as *Nidovirales* order, *Coronavirinae* subfamily and includes *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus,* and *Deltacoronavirus* genera. The *Alphacoronavirus* and *Betacoronavirus* are causative agent for respiratory human infections and animals enteric infection while the *Gammacoronavirus* and *Deltacoronavirus* genera mostly associated with birds.[3] In human hosts with a competent immune system HCoV-NL-63, HCoV-229E, HCoV-OC43, and HKU-1 cause mild upper respiratory infections, while highly pathogenic coronaviruses such as MERC-CoV and severe acute respiratory syndrome coronavirus (SARS-CoV) can induce severe respiratory diseases.[4,5] HCoV-229E and HCoV-OC43 are responsible for 15%–29% of the common colds cases. These two viruses are known as prototypes of the *Alphacoronavirus* and *Betacoronavirus*, respectively.[6] The *Alphacoronavirus* and *Betacoronavirus* genus includes some emerging viruses in animals which can cause the economical lost.[7-9] The origin of the HCoV-229E, HCoV-OC43, MERC-CoV, and SARS-CoV are bats while the HCoV-OC43 and HKU-1 origin seems to be rodents.[4,5] Domestic animals could be important in the transmission of coronaviruses due to their role as intermediate hosts.[10-13] It could be assumed that, the major reservoir for the

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Alphacoronaviruses are bats.[3] Frist reported emerging coronavirus was seen in 2002–2003 in Guangdong, China. This virus named as SARS-CoV and causes an epidemic condition worldwide.[14] After a decade, the MERS-CoV in 2012 introduce as new epidemic virus from the Middle East and UKA (the United Kingdome Arabia).[15] In the SARS-CoV epidemy, the Civet cats transmitted the virus to the human population.[16-19] Further investigations indicated these civet cats were infected from other animal sources.[17,18] These investigations leads to finding a group of *Betacoronavirus* named as SARS-like coronaviruses or SARS-CoV-related coronaviruses in horseshoe or genus Rhinolophus bats.[20] The assessment of these bats shows that the horseshoe bats are the natural reservoir and civet cats are intermediate host for SARS-CoV.[18,21,22]

In December 30, 2019, pneumonia with an unknown etiology was seen in sea food market Wuhan, China.[23] By December 31, 2019, 27 cases of pneumonia with unexplained cause were reported.[24] This condition leads to 41 cases of 2019-novel coronavirus (2019-nCoV) (which later rename as SARS-COV-2) by January 2, 2020.[25] First death by the virus reported in January 11, 2020, in a 61-year-old male with abdominal tumors and chronic liver disease.[26]

Further investigations leads to the, sequencing of the virus genome,[27] reporting first case in other countries,[28] first case in the USA[29] and number of infected people and number of mortality by the WHO. Furthermore, in January 30, 2020, this virus introduce as Public Health Emergency of International Concern by the WHO.[30] Since the January 2020, there are a great number of scientific publications about the SARS-COV-2 virological features, disease and epidemic condition.

COVID-19 patients show different symptoms, these symptoms are includes fever, headache, cough, and other respiratory symptoms. Regardless of respiratory symptoms COVID-19 patients shows gastro intestinal symptoms such as diarrhea, nausea, and liver damage symptoms.[31,32] The angiotensin-converting enzyme 2 (ACE-2) introduced as cell receptor for SARS-CoV-2 attachment and infectivity.[33] The tissue distribution of ACE-2 in bile duct epithelial cells suggested a possible tropism for virus to the liver.[34] There are verities of liver function presentation in COVID-19 patients.[35] In this review, we systematically reviewed the published literature in the field of liver function tests profile in COVID-19 patients at the admission time.

Materials and Methods

Search strategy

The conducted studies were obtained using systematic literature search. Systematic search was performed in EMBASE, PubMed, Science Direct, Scopus, and relevant studies in Google scholar using "SARS-CoV-2," "SARS," "SARS-CoV," "coronavirus," " nCoV," "liver," "hepatitis," "Liver function" keywords. The search was limited to the range from 2019 to May 19, 2020. Furthermore, for preventing the narrowing due to the limited date range and number of studies we used the "OR" between all of keywords in search query. The search strategy flow chart is illustrated in Figure 1.

Inclusion criteria

Inclusion criteria were including all of relevant studies which there are extractable results about liver function tests profile includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), prothrombin time (PT), and D-dimer in COVID-19 patients at the admission time. Furthermore, all relevant original studies in all of the study settings were assessed for the relevance to the current study subject.

Literature review on scientific publications

The relevant studies were listed in endnote Version X7 (Thomson Reuters) and met the inclusion criteria. The screening and data extraction were conducted by two independent authors. The data extraction from records was including first author's name, liver function tests profile, gender, and sample size.

Results

Search result and severe acute respiratory syndrome coronavirus-2 patients

Conducted search using the mentioned keywords leads to the 7298 documents. After the screening of the documents based on the title and abstract 145 documents were selected. Further investigations based on the study strings

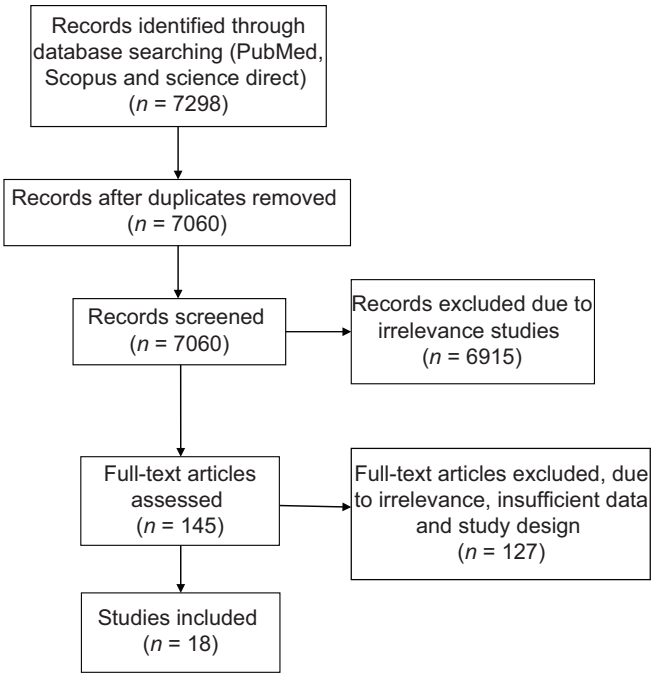

Figure 1: The search strategy flow chart for conducted research in liver function tests in COVID-19 patients

and full text leads to 18 original research articles in the field of liver function tests profile in COVID-19 patients at the admission time. By the assessment of 18 included studies, the mean age of patients was ranged from 47 to 56 years. In different studies, the male gender portion of patients was ranged from 40% to 73%. Different studies reports different conditions about the comorbidities. The highest rate of liver associated comorbidities was reported 11%. The demographic and laboratory extracted data from 18 studies are listed in Table 1.

Liver function tests profile in COVID-19 patients

Liver enzymes

The AST and ALT were the most frequent assessed enzymes. By the assessment of all 18 included studies, the lowest and highest AST reported levels were 6 and 107 U/L, respectively. The mean AST level in COVID-19 patients was ranged from 21 to 40 U/L. In the 16 studies, the up regulation of the AST in COVID-19 patients at the time of the admission was reported and this increase in AST level was seen in 10%–53% of COVID-19 patients. In addition, the maximum and minimum reported values for ALT were 115 and 13, respectively. Mean ALT level at the admission time was ranged from 18 to 46 in COVID-19 patients. The ALT up regulation was reported in 14 different studies. The ALT increase was seen in 5%–28% of COVID-19 patients at the admission time. Furthermore, the GGT and ALP were assessed in limited number of studies. By considering 5 studies in the field of GGT assessment, the GGT levels were increased in 12%–17% of COVID-19 patients at the admission time and mean GGT level was 36 to 45 U/L. In addition, the ALP was reported to be increased in COVID-19 patients in 4 individual studies and the maximum ALP level was 144 U/L in assessed studies [Table 1].

Coagulation test

The PT and D-dimer were the most important coagulation tests in COVID-19 patients. The PT results were reports increase in 7 individual studies in 7%–12% of the COVID-19 patients at the admission time. The mean PT time in COVID-19 patients was 10–13.5 seconds. In addition, the D-dimer value was ranged from 0.2 to 1.97 mg/L in 10 studies. Maximum D-dimer level was reports 3.7 in COVID-19 patients at the admission time. The D-dimer was reports increase in 14%–36% of COVID-19 patients at the admission time [Table 1].

Albumin and total bilirubin

Another important marker for COVID-19 patients seems to be the decrease in ALB level. The ALB decrease was seen in 6%–98% of COVID-19 patients at the admission time in different studies. The total bilirubin level seems to be increase in 5%–21% of the COVID-19 patients at the admission time. By the assessment of all 6 studies for total bilirubin assessment, the lowest and highest bilirubin reported levels were 6 and 46 g/L, respectively [Table 1].

Discussion

Acute respiratory infections are caused by different microbial agents which need to mention that 80% of acute respiratory infections are due to the viruses.[51] Accurate and rapid diagnosis of viral respiratory infections is essential for prescribe appropriate treatment prevent epidemics and even pandemics conditions. Antibiotics use cases are also reduced by the correct detection and distinguish of viral infections from other pathogens such as bacteria. Virus culture and IFA are two of the most common methods for detecting viruses, but time consuming.[52] Furthermore, highly sensitive methods such as nucleic acid amplification tests and point-of-care tests could be useful.[53] Common tests for the detection of coronaviruses include reverse transcription polymerase chain reaction (RT-PCR), real-time RT PCR, RT loop-mediated isothermal amplification (RT-LAMP), and RT-LAMP.[54-58] Another approach used is RT-LAMP, which identifies the N gene and the ORF1a gene region without cross-reactivity with other viruses.[59] One of the most important and priorities in the outbreak of an infectious agent is an early reliable diagnosis. The RT-PCR is common method for detection viral agents in respiratory secretions. Some studies have shown that collaboration between public and academic laboratories and the use of real time-PCR method can be lead to a strong diagnosis of viral isolates based on defined protocols at the time of international emergencies.[60-66] With the outbreak of the nCoV respiratory infection, the virus genome was reported on January 10[67] by community online resource virological.org "Wuhan-Hu-1, GenBank accession number MN908947" for immediate health support. In the following, four sequences genome was sequenced on January 12 in the Sharing All Influenza Data (GISAID). Initial diagnostic methods revealed that the nCoV genome was very similar to the SARS coronavirus the causative of the outbreak on 2002–2003 among human populations.[68]

Regardless of respiratory syndromes, COVID-19 patients could face with a verity of symptoms include liver damage symptoms.[35] Conducted researches, suggested that the expression of the ACE-2 in bile duct epithelial cells could be important in liver pathogenesis of the SARS-CoV-2 in COVID-19 patients.[34] In addition, conducted research in SARS-CoV shows virus particles in liver and hepatic vascular cells in autopsies samples.[69] In conducted study by Wang *et al*.[36] the patients data analysis shows that the abnormality in liver enzymes is associated with disease severity. In addition, Cai *et al*.[37] finding suggested same results about the severity of the disease in COVID-19 patients. These results could indicate the importance of the liver enzyme assessment in the COVID-19 at the admission time as prognostic

Table 1: The extracted data from 18 included articles for liver function tests in coronavirus disease-2019 patients

Authors	Patients					Laboratory parameters					
						AST		ALT		Albumin	
	Total	Age (mean±SD or median [range])	Abnormal liver function at the admission time	Male (%)	Liver background conditions (%)	Mean or range (U/L)	Up/down regulation and Abnormal patients (%)	Mean or range (U/L)	Up/down regulation and Abnormal patients (%)	Mean or range (g/L)	Up/down regulation and Abnormal patients (%)
Wang	156	51.1±17.4	64	59	-	45.5 (38.0-60.0)	Up	50 (40-70)	Up	37 (33-41)	Up
Fan	148	50 (36-64)	55	49	6	37-107	Up 21%	41-115	Up 18%	-	-
Cai	417	47 (34-60)	170	47.5	5	24.3-43	Up 17%	18-39.5	Up 5%		
Sun	63	47 median	-	-	3.17	40.89	Up	39.05±59.03	UP	38.61±5.38	Down
Zhang	115	49.52±17.06	17	49	-	28.30±15.66	Up (in sever cases)	25.71±21.08	Up	38.79±4.39	Down (in severe cases)
Pan	204	52.91±15.98	103 (with digestive symptoms)	52	1	31.36±25.55	Up	35.98	Up	36.16±6.49	-
Guan	1099	47 (35-58)	173	58	2.1	>40	Up 22%	>40	Up 21%	-	-
Chen	99	55.5	-	68	-	>40	Up 35%	>50	Up 28%	<40	Down 98%
Xu	62	41 (32-52)		56	11	26 (20-32)	Up 16%	22 (14-34)	-	-	-
Huang	41	49 (41-58)	-	73	2	>40	Up 37%	32 (21-50)	Up (in ICU admitted patients)	31·4 (28·9-36)	Down (in ICU admitted patients)
Zhou	191	56 (46-67)	-	62	-	-	-	30 (17-46)	Up (in nonsurvivor patients)	32·3 (29·1-35·8)	Down (in nonsurvivor patients)
Shi	81	49.5	-	52	9	>40	Up 53%	46·2	-	32·9	-
Chen	249	51 (36-64)	-	50	0.8	25 (20-33)	-	23 (15-33)	-	40.8 (37.9-43.0)	-
Huang	34	56.24±17.14	-	41	2.9	-	Up 20%	-	Up 23%	-	Down 73%
Qian	91	50 (36.5-57)	-	40.66	-	21 (17-28)	Up 10%	18 (13-28)	Up 8%	40 (37.85-42)	Down 47%
Yang	149	45.11±13.35	-	54	-	23	Up 18%	20	Up 12%	41.65	Down 6%
Wan	135	47 (36-55)		53.3	1.5	33.4 (27.8-43.7)	Up (in severe cases)	26 (12.9-33.15)	-	40.5 (37-43.4)	Down (in severe cases)
Jin	651	46.14±14.19	74 patients with GI symptoms	50	10.8	29.3 (20.8-38.6)	Up (in patients with GI symptoms)	25 (15.75-38.47	Up (in patients with GI symptoms)	40.13 (35.95-42.6)	Down (in patients with GI symptoms)

Contd...

Table 1: Contd..

Authors	Laboratory parameters										References
	GGT		ALP		Total bilirubin		PT		D-dimer		
	Mean or range (U/L)	Up/down regulation and Abnormal patients (%)	Mean or range (U/L)	Up/down regulation and Abnormal patients (%)	Mean or range (µmol/L)	Up/down regulation and abnormal patients (%)	Mean or range seconds	Up/down regulation and Abnormal patients (%)	Mean or range (mg/L)	Up/down regulation and Abnormal patients (%)	
Wang	45 (28-78)	Up	61 (49-76)	Up	10.5 (8.2-15.4)	-	12	Up	0.53	Up	[36]
Fan	48-159	Up17.5%	102-144	Up 4%	21-46.6	Up 6%	-	-	-	-	[31]
Cai	36.45	Up 12%	52-79	Up	10.9 (8.3-16.3)	Up 21%	-	-	-	-	[37]
Sun	38.84±31.37	UP	77.33±40.89	UP	11.92±6.69	-	13.52±9.63	-	1.97±1.83	Up	[38]
Zhang	36.14±45.02	Up (in severe cases)	73.72±24.37	Down (in severe cases)	11.31±5.18	-	INR 1.17±0.11	Up (in severe cases)	-	-	[39]
Pan	-	-	-	-	13.65±10.26	-	13.13±1.88	Up	-	-	[40]
Guan	-	-	-	-	>17.1	Up 10.5%	-	-	>0.5	Up	[32]
Chen	-	-	-	-	>21	Up 18%	<10	Down 30%	0·9 (0.5-2.8)	Up 36%	[41]
Xu	-	-	-	-	-	-	-	-	0.2 (0.2-0.5)	-	[42]
Huang	-	-	-	-	11.7 (9.5-13.9)	Up (in ICU admitted patients)	11.1 (10.1-12.4)	Up (in ICU admitted patients)	0.5 (0.3-1.3)	Up (in ICU admitted patients)	[25]
Zhou	-	-	-	-	-	-	11.6 (10.6-13.0)	Up (in Non-survivor patients)	0.8 (0·4-3.2)	Up (in Non-survivor patients)	[43]
Shi	-	-	-	-	11.9	-	10.7	-	-	-	[44]
Chen	-	-	-	-	-	-	-	-	-	-	[45]
Huang	-	-	-	-	-	Up 8%	-	-	-	Up 15%	[46]
Qian	-	-	-	-	-	-	-	-	0.3 (0.1-0.45)	Up 24%	[47]
Yang	-	-	-	-	9.9	Down 5%	12.20±1.53	Up 12%	0.22	Up 14%	[48]
Wan	-	-	-	-	8.6 (5.9-13.7)	-	10.9 (10.5-11.4)	Up (in severe cases)	0.4 (0.2□0.6)	Up (in severe cases)	[49]
Jin	-	-	-	-	10.0 (7.15-13.8)	-	10.0 (7.15-13.8)	-	-	-	[50]

SD: Standard division, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyltransferase, ALP: Alkaline phosphatase, PT: Prothrombin time, Up: Upper than normal range, Down: Downer than normal range, GI: Gastro intestinal tract, INR: International normalized ratio

factor for further therapeutic actions. Regardless of liver function at the admission time, Fan *et al*.[31] show that in mean range of 7 to 11 days after the admission the liver enzymes were elevated in COVID-19 patients. Which it could represents the disease progression or the treatment related liver injuries. In addition, conducted research by Zhang *et al*.[39] indicated that the liver enzymes in COVID-19 patients are statistically significant higher than community acquired pneumonia patients. These findings highlighted that importance of the liver function assessment in COVID-19 patients. By considering all these research about the liver associated pathogenesis of COVID-19, a conducted study by Hong *et al*.[70] introduced a case of liver transplantation from SARS-CoV-2-infected donor to an un infected patient. In this study, the liver donor-derived transmission of SARS-CoV-2 through the liver recipient was not seen. This finding could be in conflict with SARS-CoV-2 transmission through the organ donation. However, this matter needs further investigation. It should be noted that, the major limitation in our study was the limitation of the included studies which it makes hard to concludes a clear results. Furthermore, the advantage of the current study in compare with all other studies in the field of liver function and pathogenesis in COVID-19 patients are a comprehensive search, focusing in liver enzymes, and coagulation markers range and numerical results and including the patients' data from the admission time.

In 2002, when SARS-CoV was first time reported or the MERS-CoV in 2012,[14,15] there are no licensed vaccines toward the prevention or specific treatment against the MERS-CoV infection, and the current treatments are symptomatic, supportive or nonspecific antiviral treatment.[71,72] In this state, antiviral drug resistance is not out of the question. It can assumed that, the knowledge gained from the two previous outbreaks of SARS-CoV and MERS-CoV will be helpful for therapies approaches to the 2019 nCoV (SARS-CoV-2).[73] For instance, combined treatment approaches for MERS-CoV include the use of convalescent sera, anti-inflammatory drugs such as corticosteroids, interferon, ribavirin, and protease inhibitors.[71,72,74,75] However, other studies have also investigated various *in vitro* antiviral agents that had promising results and are still expanding.[76,77] There are verities of conducted research in the field of the possible therapeutic options for COVID-19 around the world.[78] In should be noted that, some of this treatments are associated with liver damage in COVID-19 patients. In the conducted study by Cai *et al*.,[37] some of the patients show a liver damage during hospitalization and treatment. This finding suggested the importance of the liver function test monitoring during the COVID-19 patients.

Conclusion

By using the results of study, it could be suggested that the liver function testes assessment is critical assessment in COVID-19 patients at the admission time. This liver function test could be used as potential prognostic factor in COVID-19 severity in future. The liver function tests assessment should be considered as important matter during COVID-19 patients' treatment. By the considering the importance of the liver enzyme assessment in COVID-19 patients, this filed clearly needs further investigations.

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Conflicts of interest

There are no conflicts of interest.

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