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Changes in liver function in patients with COVID-19 and the demographics of the disease in a mid-sized city of Turkey: A retrospective analysis

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Abstract

Objective: To define the clinical characteristics of patients hospitalized with COVID-19 in ICU and ward and to evaluate the significance of liver function test results. A new disease caused by SARS-CoV-2 has been devastating the world affecting millions of patients worldwide and leading the significant mortality and morbidity.

Material and Methods: The demographic features of a cohort of 125 hospitalized patients between March 2020 and May 2020 were recorded. The clinical characteristics, laboratory findings, and mortality rates were analyzed.

Results: A total of 125 patients hospitalized for COVID-19 diagnosis where 113 (90.4%) were followed-up in the ward and 12 (9.6%) were in ICU were included in the study. The mean age of the patients was 44.05±16.95 and 88 (70.4%) of the patients were male. The most common symptoms were in the following order: cough in 80 patients (64%), dyspnea in 40 (32%) and fever in 33 (26.4%). The leukocyte and neutrophil counts were significantly higher in ICU patients with COVID-19 compared to patients in the ward ($p=0.002$, $p<0.05$; respectively). The CRP and D-Dimer levels were found elevated in ICU patients with COVID-19 than in the ward ($p<0.05$; $p<0.05$, respectively). The AST level of patients with COVID-19 in ICU was significantly heightened than patients in the ward.

Conclusion: The present study revealed that patients with elevated AST level were at great risk of progressing to severe disease those require close monitoring.

Keywords: coronavirus, epidemiology, pandemics, Severe Acute Respiratory Syndrome, AST, ALT, Liver enzymes

Introduction

Since February 2019 a new disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been devastating the world. As of today, 12 million people have been diagnosed with coronavirus disease-19 (COVID-19) and more than 550,000 patients died. The US with 3 million infected patients and 132,000 deaths is the leading country followed by Brazil (1,2). In relation, approximately 200,000 confirmed cases have been detected in Turkey with 5,000 deaths which is low compared to several European Countries. Several reports have been coming about the clinical manifestations and blood biochemical results those might play an essential role for the estimation of the progress of the patients and the management of therapy. However, there is no specific treatment defined.

Thus, the distribution of the clinical and demographic characteristics of COVID-19 in different regions seems to be important to prevent the spread of the disease. A recent study showed that SARS-CoV-2 have the ability to bind to angiotensin-converting enzyme 2 (ACE2) on cholangiocytes causing disruption in the cell functions and triggering a systemic inflammatory response led to liver injury (1). In addition, various studies revealed elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzymes ranging from 14% to 53% (3,4). Furthermore, pathological findings have also indicated moderate microvesicular steatosis and mild lobular and portal activity (5). The present study aims to report the clinical and biochemical course of the patients hospitalized with COVID-19, and the importance of liver function test results on the course of the disease.

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Materials and Methods

After approval of the Ethics Committee and Ministry of Health, this study was initiated with a retrospective design enrolled patient hospitalized with COVID-19 in the study hospital between March 2020 and May 2020. The study was completed in compliance with the World Medical Association Declaration of Helsinki. All patients had a positive PCR (polymerase chain reaction) test result of SARS-CoV-2. Patients aged below 18, had a history of liver malignancy, liver failure, cirrhosis, hepatitis, receiving medical treatment led to impairment in liver function tests were excluded. The demographic features, clinical and laboratory findings were obtained from hospital database. All data were recorded into a standardized data sheet.

Statistical Analysis

The distribution of the variables was analyzed using Kolmogorov-Smirnov test. Quantitative data were presented as mean and standard deviation where qualitative data as median (interquartile range [IQR] 25%-75%) values, and also with numbers and percentage. The analysis of the demographic characteristics was conducted using Fisher's exact test. The comparison of the laboratory findings was completed by Mann-Whitney U test. All data was analyzed using Statistical Package for Social Sciences (SPSS) version 20 program. The significance level was set at $p<0.05$.

Results

A total of 125 patients were hospitalized for COVID-19 diagnosis where 113 (90.4%) were followed-up in the ward and 12 (9.6%) were in ICU. The mean age of the patients was 44.05±16.95 and 88 (70.4%) were male.

A total of nine patients (7.2%) had asthma where only two (1.6%) had chronic obstructive pulmonary disease (COPD). For cardiovascular comorbidities; 26 patients (20.8%) had hypertension where seven patients (7.2%) had coronary artery disease.

A total of 12 patients (9.6%) had type 1 or type 2 diabetes. A total of 41 patients (32.8%) had one or more comorbidities, of those 32 (28.3%) were received treatment in the ward and 9 (75%) in ICU (p=0.002). The most common symptoms were in the following order: cough in 80 patients (64%), dyspnea in 40 (32%) and fever in 33 (26.4%). Other symptoms including sore throat (6.4%), fatigue (4%) and myalgia (3.2%) are the less common symptoms (Table 1). The leukocyte and neutrophil count, and CRP and D-Dimer levels were significantly higher in ICU patients with COVID-19 compared to patients in ward ($p = 0.002$; $p < 0.05$; $p < 0.05$; $p < 0.05$, respectively). The AST levels of patients with COVID-19 in ICU were significantly heightened than patients in ward. A total of 11 patients have died of COVID-19, and all of 11 have died while receiving treatment in ICU (Table 3). The mortality rate was 8.8% with a mean age of 66 years ranged from 50 to 81 years. Eight (72.7%) of the deaths had one or more comorbidities where three of them had none ($p = 0.006$). One of the eight deaths with comorbidities had COPD and seven of them had mainly cardiovascular diseases. Patients with higher AST levels are prone to be died from COVID-19 compared to patients with normal AST levels ($p = 0.01$; Table 4). It is also found that patients who died from COVID-19 had significantly higher AST levels than patients with COVID-19 discharged from hospital.

Table 1. Demographic characteristics of patients hospitalized with COVID-19

Variable	All patients	Ward	ICU	p
Age, years, (median, range)	44 (17 – 84)	41 (17 – 84)	64 (48 – 81)	< 0.05*[a]
Gender				
Female	37 (30%)	35 (31%)	2 (17%)	0.507[b]
Male	88 (70%)	78 (69%)	10 (83%)	
Comorbidities				
Hypertension	26 (21%)	20 (18%)	6 (50%)	**0.018***[b]
Diabetes	12 (9.6%)	8 (7.1%)	4 (33.3%)	**0.016***[b]
Coronary artery disease	7 (5.6%)	5 (4.4%)	2 (16.7%)	0.135[b]
COPD	2 (1.6%)	1 (0.9%)	1 (8.3%)	0.183[b]
Asthma	9 (7.2%)	8 (7.1%)	1 (8.3%)	>0.05[b]
Symptoms				
Fever	33 (26.4%)	31 (27.4%)	2 (16.7%)	0.515[b]
Cough	78 (62.4%)	71 (62.8%)	7 (58.3%)	0.763[b]
Dyspnea	40 (32%)	30 (26.5%)	10 (83.3%)	**<0.05***[b]
Fatigue	5 (4%)	4 (3.5%)	1 (8.3%)	0.402[b]
Myalgia	4 (3.2%)	3 (2.7%)	1 (8.3%)	0.336[b]
Sore throat	8 (6.4%)	8 (7.1%)	–	>0.05[b]
Headache	8 (6.4%)	8 (7.1%)	–	>0.05[b]
Abdominal pain	1 (0.8%)	–	1 (8.3%)	0.096[b]

*p<0.05. aMann-Whitney U test. bFisher's exact test. ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.

Table 2: Laboratory results of the patients hospitalized with COVID-19

	Normal range†	Total	Ward	ICU	p
Leukocyte ($10^3/\mu L$)	4.8 – 10.8	6.23 (4.36 – 15.37)	6.08±.45	9.3±3.43	**0.002***
Lymphocyte ($10^3/\mu L$)	1 – 4.8	1.46 (0.62 – 3.69)	1.65±0.71	1.72±0.95	0.887
Neutrophil ($10^3/\mu L$)	1.8 – 7.7	4.26 (2.72 – 13.6)	3.79±1.97	6.9±3.19	**<0.05***
NLR	–	2.43 (0.21 – 13.08)	2.7±1.74	5.44±4.2	**0.014***
AST (U/L)	0 – 35	38.38 (18 – 71.2)	27.66±22.72	43.23±27.19	**0.022***
ALT (U/L)	0 – 45	27.2 (19 – 63.3)	26.88±31.25	32.69±25.27	0.139
TBL (mg/dL)	0.3 – 1.2	0.59 (0.31 – 1.34)	0.46±0.25	0.59±0.3	0.118
ALB (g/dL)	3.5 – 5.2	4 (3.46 – 5.01)	4.4±0.38	3.43±0.59	**<0.05***
GGT (U/L)	0 – 55	33 (16 – 373)	26.76±23.57	78.25±100.6	**0.003***
Creatinine (mg/dL)	0.88 – 1.06	0.88 (0.79 – 1.32)	0.9±0.19	0.97±0.41	0.557
CRP (mg/L)	0.3 – 1.2	36.89 (2.07 – 378)	11.35±16.21	142.94±126.52	**<0.05***
D-Dimer (ng/mL)	< 500	180 (10 – 718)	308.4±811.06	865.5±969.8	**<0.05***
ESR	0 – 30 mm/h	31 (10 – 70)	28.72±20.89	48.25±20.75	0.117

*p<0.05.†Obtained from the medical biochemistry laboratory of the hospital. Mann-Whitney U test. ICU, intensive care unit; NLR, neutrophil to lymphocyte ratio.

Table 3: The outcomes of the patients hospitalized with COVID-19

		Total n (%)	Ward n (%)	ICU n (%)	p
Status	**Discharge**	114	113	1 (8.3)	**<0.05*†**
	Died	11	–	11 (91.7)	
		Mean±SD	**Mean±SD**	**Mean±SD**	
Hospital stay (days)		7 (4 – 25)	7.88±2.93	11±5.73	**0.022*‡**

*p<0.05. †Chi-square test. ‡Mann-Whitney U test. ICU, intensive care unit.

Table 4: The distribution of liver function test results

		Status		
		Discharge n (%)	Died n (%)	p
AST	**Normal**	94 (94.9)	5 (5.1)	**0.01*†**
	High	20 (76.9)	6 (23.1)	
ALT	**Normal**	96 (92.3)	8 (7.7)	0.393†
	High	18 (85.7)	3 (14.3)	
		Median (Range)	**Median (Range)**	**p**
AST		21.65 (8.3 – 160)	36.9 (15.7 – 96)	**0.026*‡**
ALT		18 (3.6 – 222)	21.9 (6.4 – 93)	0.187‡

*p<0.05. †Fisher's exact test. ‡Mann-Whitney U test. AST, aspartate aminotransferase; ALT, alanine aminotransferase.
Normal range for AST: Female (0 – 31 U/L); Male (0 – 35 U/L). Normal range for ALT: Female (0 – 34 U/L); Male (0 – 45 U/L). Ranges obtained from the medical biochemistry laboratory of the hospital.

Discussion

To the best of our knowledge, this study was the first one including hospitalized patients infected with SARS-CoV-2 from the study site. An 9.6% of the patients required ICU admission. Hypertension with the rate of 50% and diabetes with 33.3% alone were the evident comorbidities for admission to the ICU. Although the most frequently detected symptom was cough (62.4%), the prevalence of dyspnea (83.3%) was higher in patients admitted to ICU. The overall mortality rate was 8.8%: and 81.8% of the deaths were above 60 years with a mean age of 66 years. Among the 11 deaths, three had no comorbidities where the rest of the deaths had one or two of the following: diabetes, hypertension, and coronary artery disease.

The leukocyte and neutrophil count, and AST, GGT, CRP, and D-Dimer levels were found elevated in patients admitted to ICU, where albumin level was lower in the same patients. Increased AST levels were shown in patients who died from COVID-19. Chronic diseases including hypertension and diabetes may trigger the conditions to prone the patient to be susceptible for being infected with SARS-CoV-2. It is known that chronic diseases share common pathways with infectious diseases including proinflammatory changes and the beginning of the immune response. As of today, the pathophysiology of the disease related to the comorbidities remains unexplained, only various hypotheses have been suggested.

Studies have demonstrated that hypertension is one of the most frequent comorbidities in patients with COVID-19 which had a reported prevalence of 15% and 23.4% in patients with severe COVID-19 (2,6). A meta-analysis showed that hypertension is rare in discharged patients compared to patients died from COVID-19 and a positive correlation was found between hypertension and disease severity as well as ICU admission(7). Li et al. revealed that the prevalence of hypertension in patients with COVID-19 is 17.1%, and it is two-folds higher in ICU patients compared to the ward (8). The present study showed a frequency of 21% among patients with COVID-19, with a 3.6 folds incidence in patients admitted to ICU than in the ward. It is very close to the Asian population reported in the previous studies. This finding could be associated with the usage of Angiotensin-Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) among hypertensive patients which mostly result in an upregulation of ACE-II which is believed to be the location of SARS-CoV-2 surface antigen binding site.

Furthermore, diabetes is the other most prevalent comorbidity among patients with COVID-19. While the frequency of diabetes in patients with COVID-19 varies from one study to another, a recent meta-analysis demonstrated that the prevalence of diabetes is found higher in ICU patients than in the ward (9,10). Chinese data showed a prevalence between 15% and 25% and it is reported as two to four folds higher in ICU patients (6,11,12). Despite Chinese reports, a prevalence over the 50% has been shown in the United States in patients admitted to ICU with severe COVID-19 (13). One study from China revealed significant data that milder symptoms would be seen at the beginning of the infection such as fever was less prevalent leading a delay in the diagnosis of the disease (14). In addition, diabetes causes elevated inflammatory markers, tissue enzymes, and clotting abnormalities which may be associated with severe multi-organ damage and tendency to thromboembolic events as well as cytokine storm which is an aggravating factor for COVID-19 (14,15). A retrospective analysis showed that diabetes or cardiovascular disorders are detected at 85.5% of severe patients with COVID-19 than mild counterparts (16). Several studies indicate variable frequencies in which the present study showed a prevalence of 9.6% in the overall study group and 33.3% in ICU patients with COVID-19 compared to 7.1% in the ward (2,4,17,18). The difference between ICU and ward suggested that diabetes seems to be a prognostic factor for the poor prognosis of COVID-19. However, it is inevitable that this conclusion requires a study with larger sample size.

Moreover, COVID-19 appears to have variable clinical presentations where the most prevalent symptoms in the severe disease group were cough, fever, and fatigue. However, cough, fever, and dyspnea were the most frequent symptoms admitted to the ICU. The prevalence of dyspnea was reported as 67.2% in ICU admitted patients with COVD-19 compared to 10.2% in the ward. Dyspnea could be a sign of pulmonary involvement of the disease, where some reports indicated a phenomenon called “silent hypoxia” characterized by progressive respiratory failure without the presence of dyspnea (19). Chinese data showed that the frequency of dyspnea was 37.2% in severe cases admitted to ICU which was 14.7% in cases of the ward (20,21). In contrast to the information obtained from Chinese studies, the present study revealed a prevalence of 83.3% in ICU admission for dyspnea, where 26.5% in the ward with an overall frequency of 32%. The higher percentage of dyspnea in ICU deserves an importance for predicting ICU admission, therefore future research should focus on the evaluation of early hospital admission and treatment management in patients with dyspnea.

Nevertheless, leukocyte count has been reported as decreased or normal in patients with COVID-19, however critical cases have leukocytosis frequently. A comprehensive study by Guan et al.(6) revealed that leukocytosis was observed in 25% of the severe cases. In general, and asymptomatic patients seem to be normal or decreased in patients with COVID-19 during admission and tend to elevate with disease progression (22,23). In contrast to the leukocyte count that was higher in ICU patients compared to the ward, the number of leukocytes is in the normal range in the present study. It can be declared that leukocytosis in ICU patients with COVID-19 may be associated with several factors including co-infections, medications, and the variable response of the immune system. Similar findings have been found for neutrophil numbers as it was higher in ICU patients than in the ward, however, it stayed in normal ranges. Most of the studies reported that neutrophil count was normal in non-severe cases but was elevated in patients with severe disease (24,25). In relation, neutrophil to lymphocyte ratio (NLR) is accepted as a prognostic factor for COVID-19. Studies indicated that it consistently elevated in severe patients with COVID-19 (25,26). Feng et al. reported that higher NLR detected during admission might be an independent predictor of severe pneumonia in patients with COVID-19 (27). Another study conducted by Zhang et al. noted that %94 of the patients who died from COVID-19 had an NLR over 5 (28). The current study has shown a higher NLR in severe patients admitted to the ICU than in the ward, hence it suggested that increased NLR may be a useful tool for predicting high-risk patients associated with the consistency and proven importance of it.

Another biochemical finding of the present study is slight hypoalbuminemia in ICU patients with COVID-19 which was normal in the ward. A cohort study from Spain revealed that hypoalbuminemia was common in critical patients infected with SARS-CoV-2. The authors also concluded that albumin levels might be associated with poor outcomes as increased mortality and hospital stay (29). It can be speculated that the slight decrease in albumin level can be related to the inflammatory response of the host to the SARS-CoV-2 infection.

Inflammatory markers including CRP and D-Dimer have been reported to be elevated in patients with COVID-19 (3,29,30). Studies revealed an increased CRP and D-Dimer ranged from 60.7% to 86.3% and 36.4% to 46.4% of the patients infected with SARS-CoV-2, respectively (2,4,6,31). Significantly higher levels were detected in the present study for CRP and D-Dimer in patients admitted to

ICU compared to the ward those also observed in various infections for severe cases as well.

The main study parameter of the present study is liver function enzymes especially AST and GGT which were also elevated in ICU patients. Studies indicated an elevated level of GGT that is considered as the cholangiocyte-related enzyme. However, GGT is mainly located in the cell membranes of several tissues such as the heart, brain, kidneys, pancreas, bile duct, spleen, gall bladder and seminal vesicles. Therefore, merely a higher GGT level could be associated with drug-induced liver injury or damage in other organs (32). In contrast, an elevated AST level was more frequent in severe cases where higher level of AST is reported to be more than three-folds according to the normal range in 5.66% of the patients with COVID-19 during hospitalization. Similarly, a three-folds higher level of AST was found in ICU patients compared to the ward and 23.1% of the patients those also have elevated AST died from COVID-19. Limited data is available related to the variability of liver function tests. In this context, Chen et al. showed no changes in AST level were found in patients with COVID-19 (33). However, Cai et al. (34) revealed a three-folds increase in 12% of the patients with SARS-CoV-2 infection. Additionally, the authors also noted that medications including non-steroidal anti-inflammatory drugs, antibiotics, and herbal medications may induce liver injury and were related to disease severity in cases with abnormal liver test findings. Therefore, it is suggested to closely follow-up cases receiving these particular treatments, particularly in those who had impaired liver function test levels at admission to the hospital.

Consequently, the present study revealed an overall mortality rate of 8.8% with a number of 11 cases of those all in admitted to the ICU. The mortality rate of the ICU was 91.7%, unfortunately, one patient was merely discharged from ICU. Several studies reported dispersed mortality rates where a recent Chinese study noted 31.4% and it is 21% in a US study. Another study reported an apparent mortality rate of 4% in China, 13% in Italy, 11% in Spain and 15% in France (35). In relation, distinct outcomes have been obtained from several studies as the mortality rate of ICU in China is reported as 37.7%, Italy as 25.6%, the USA as 23.6%, Spain as 29.2% and Denmark as 41.2%, Germany as 24.3% and UK as 8% (36). The unexpected mortality rate in ICU observed in this study could highly be associated with the smaller sample size compared to the studies in other countries. It should be closer or lower after enrolling more cases in the study.

Previous studies included age, gender, and comorbid diseases as the risk factors of COVID-19, this is one of the reports to exhibit abnormal liver function test results those associated with severe disease. It can be speculated that SARS-CoV-2 may lead to severe multi-organ dysfunction in humans and the findings of the present study could support some part of this hypothesis.

The present study has some limitations. First, the biggest limitation of this study is the very small sample size thus inhibits the meaningful conclusions obtained from the present study. Second, patients enrolled in this study were from a single, large city of Turkey restricting the generalizability of the results to the rural areas or other regions. Lastly, most of the patients in our cohort were Caucasian, hence study findings can not be extended to other ethnicities. Large prospective multiethnic studies are required to provide comprehensive data about the COVID-19 pandemic.

Conclusions

We present a very first reported data on all cases infected with SARS-CoV-2 from a mid-size city of Turkey. Cough, dyspnea and fever are the most observed symptoms of the disease. Hemocytometric changes particularly elevated NLR in patients infected with SARS-CoV-2 might be a useful tool for the prediction of the disease progression. The remarkable outcome of the present study is that patients with elevated AST level were at great risk of progressing to severe disease those require close monitoring.

Author Contributions: HAD: Project design, Review of the literature, Data collection and statistical analyzes **HAD:** Writing and Revisions

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References

1. Zhao B, Ni C, Gao R, Wang Y, Yang L, Wei J, et al. Recapitulation of SARS-CoV-2 infection and cholangiocyte damage with human liver ductal organoids. Vol. 11, Protein & cell. 2020. p. 771–5.

2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020 Feb;395(10223):497–506.

3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England). 2020 Feb;395(10223):507–13.

4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020 Mar;323(11):1061–9.

5. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Vol. 8, The Lancet. Respiratory medicine. 2020. p. 420–2.

6. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med [Internet]. 2020 Feb 28;382(18):1708–20. Available from: https://doi.org/10.1056/NEJMoa2002032

7. Hu Y, Sun J, Dai Z, Deng H, Li X, Huang Q, et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Virol Off Publ Pan Am Soc Clin Virol. 2020 Jun;127:104371.

8. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020 May;109(5):531–8.

9. Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. Vol. 43, Journal of endocrinological investigation. 2020. p. 867–9.

10. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr. 2020;14(4):395–403.

11. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Jul;180(7):934–43.

12. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475–81.

13. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med. 2020 May;382(21):2012–22.

14. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020 Mar;e3319.

15. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020 Jun;80(6):607–13.

16. Wu J, Li W, Shi X, Chen Z, Jiang B, Liu J, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). J Intern Med. 2020 Jul;288(1):128–38.

17. Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy. 2020 Jul;75(7):1730–41.

18. Wang X, Fang J, Zhu Y, Chen L, Ding F, Zhou R, et al. Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2020 Aug;26(8):1063–8.

19. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Vol. 46, Intensive care medicine. 2020. p. 1099–102.

20. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The Clinical and Chest CT Features Associated With Severe and Critical COVID-19 Pneumonia. Invest Radiol [Internet]. 2020;55(6):327—331. Available from: https://europepmc.org/articles/PMC7147273

21. Xu Y-H, Dong J-H, An W-M, Lv X-Y, Yin X-P, Zhang J-Z, et al. Clinical and computed tomographic imaging features of novel coronavirus pneumonia caused by SARS-CoV-2. J Infect. 2020 Apr;80(4):394–400.

22. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020 May;63(5):706–11.

23. Tan M, Liu Y, Zhou R, Deng X, Li F, Liang K, et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. Immunology. 2020 Jul;160(3):261–8.

24. Lo IL, Lio CF, Cheong HH, Lei CI, Cheong TH, Zhong X, et al. Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. Int J Biol Sci. 2020;16(10):1698–707.

25. Khartabil TA, Russcher H, van der Ven A, de Rijke YB. A summary of the diagnostic and prognostic value of hemocytometry markers in COVID-19 patients. Crit Rev Clin Lab Sci [Internet]. 2020 Aug 17;57(6):415–31. Available from: https://doi.org/10.1080/10408363.2020.1774736

26. Song R, Han B, Song M, Wang L, Conlon CP, Dong T, et al. Clinical and epidemiological features of COVID-19 family clusters in Beijing, China. J Infect. 2020 Aug;81(2):e26–30.

27. Feng Z, Yu Q, Yao S, Luo L, Duan J, Yan Z, et al. Early Prediction of Disease Progression in 2019 Novel Coronavirus Pneumonia Patients Outside Wuhan with CT and Clinical Characteristics. medRxiv [Internet]. 2020; Available from: https://www.medrxiv.org/content/early/2020/02/23/2020.02.19.20025296

28. Zhang B, Zhou X, Qiu Y, Song Y, Feng F, Feng J, et al. Clinical characteristics of 82 cases of death from COVID-19. PLoS One. 2020;15(7):e0235458.

29. de la Rica R, Borges M, Aranda M, del Castillo A, Socias A, Payeras A, et al. Low albumin levels are associated with poorer outcomes in a case series of COVID-19 patients in Spain: a retrospective cohort study. medRxiv [Internet]. 2020 Jan 1;2020.05.07.20094987. Available from: http://medrxiv.org/content/early/2020/07/15/2020.05.07.20094987.abstract

30. Ge H, Wang X, Yuan X, Xiao G, Wang C, Deng T, et al. The epidemiology and clinical information about COVID-19. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol. 2020 Jun;39(6):1011–9.

31. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ. 2020 Feb;368:m792.

32. Dillon JF, Miller MH. Gamma glutamyl transferase "To be or not to be" a liver function test? Ann Clin Biochem. 2016 Nov;53(6):629–31.

33. Chen L, Liu HG, Liu W, Liu J, Liu K, Shang J, et al. [Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese J Tuberc Respir Dis. 2020 Feb;43(0):E005.

34. Cai Q, Huang D, Yu H, Zhu Z, Xia Z, Su Y, et al. COVID-19: Abnormal liver function tests. J Hepatol. 2020 Sep;73(3):566–74.

35. Ceylan Z. Estimation of COVID-19 prevalence in Italy, Spain, and France. Sci Total Environ. 2020 Aug;729:138817.

36. Quah P, Li A, Phua J. Mortality rates of patients with COVID-19 in the intensive care unit: a systematic review of the emerging literature. Vol. 24, Critical care (London, England). 2020. p. 285.