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Liver biomarkers for prognosis in COVID-19

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Abstract

The novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Mortality attributable to COVID-19 remains considerably high, with case fatality rates as high as 8-11%. Early medical intervention in patients who are seriously and critically ill with COVID-19 reduces fatal outcomes. Thus, there is an urgent need to identify biomarkers that could help clinicians determine which patients with SARS-CoV-2 infection are at a higher risk of developing the most adverse outcomes, which include intensive care unit (ICU) admission, invasive ventilation, and death. In COVID-19 patients experiencing the most severe form of the disease, tests of liver function are frequently abnormal and liver enzymes are found to be elevated. For this reason, we examine the most promising liver biomarkers for COVID-19 prognosis in an effort to help clinicians predict the risk of ARDS, ICU admission, and death at hospital admission. In patients meeting hospitalization criteria for COVID-19, serum albumin < 36 g/L is an independent risk factor for ICU admission, with an AUC of 0.989, whereas lactate dehydrogenase (LDH) values > 365 U/L accurately predict death with an AUC of 0.943. The clinical scores COVID-GRAM and SOFA that include measures of liver function such as albumin, LDH, and total bilirubin are also good predictors of pneumonia development, ICU admission, and death, with AUC values ranging from 0.88 to 0.978. Thus, serum albumin and LDH, together with clinical risk scores such as COVID-GRAM and SOFA, are the most accurate biomarkers in the prognosis of COVID-19.

Keywords: *Albumin. Lactate dehydrogenase. Bilirubin. Prognosis. COVID-19. SARS-CoV-2.*

Introduction

Since the coronavirus disease 2019 (COVID-19) outbreak began in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has quickly spread worldwide[1]. COVID-19 presentation is heterogeneous and ranges from asymptomatic disease to severe illness characterized by pneumonia, acute respiratory distress syndrome (ARDS), and sepsis that may eventually lead to death[2]. Despite the concerted efforts of health systems around the globe, mortality attributable to COVID-19 remains considerably high with case fatality rates as high as 9-11%[3]. Early medical intervention in seriously and critically ill COVID-19 patients may reduce fatal outcomes[4]. Therefore, there is an urgent need for novel biomarkers that can help clinicians identify patients with poorer prognosis. Early implementation of more aggressive drug regimens in these patients could not only increase survival rates but also optimize intensive care unit (ICU) resources.

Due to the extensive extrapulmonary manifestations of COVID-19, evaluation of patients typically includes comprehensive blood panels that allow the clinician to simultaneously estimate the effects of the disease on multiple organ systems[5]. Liver function tests (LFT) are commonly included in laboratory analyses and

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measure a variety of molecules such as transaminases, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin[6] that indicate the global function and integrity of the liver.

Large-scale descriptive studies have been conducted to examine the relationship between altered liver function and SARS-CoV-2 infection, but only a few of them describe factors that might be used to predict the most adverse outcomes of COVID-19, including ARDS development, ICU admission, and/or death[7-9]. Herein, we summarize the most promising liver biomarkers for COVID-19 prognosis in an effort to help clinicians rapidly, easily, and inexpensively predict the risk of ARDS, ICU admission, and death at hospital admission.

Serum albumin

Serum albumin (SA) is the most abundant protein in human blood (35 to 50 g/L)[10]. SA is synthesized in hepatocytes as preproalbumin and then released to the rough endoplasmic reticulum, where an N-terminal peptide is removed to facilitate the conversion of the protein to proalbumin. Proalbumin is in turn processed in the trans-Golgi apparatus to form mature albumin that is subsequently released into circulation[11]. SA plays multiple physiological roles, including regulation of plasma colloid oncotic pressure, transportation of endogenous and exogenous molecules, anticoagulation, and antioxidation responses[10]. In clinical practice, SA level is commonly used as an indicator of mortality risk in severely ill patients such as those experiencing sepsis, trauma, or cancer[12].

Numerous studies support the use of SA as a biomarker of poor prognosis in COVID-19 patients, especially those at much higher risk of ICU admission or death. Three meta-analyses that evaluated several laboratory parameters reported decreased SA at admission in patients with severe COVID-19 (3.50 g/dL, 95% CI 3.26–3.74 g/dL) as compared to non-severe patients (4.05 g/dL 95% CI 3.82–4.27 g/dL)[13-16]. Hypoalbuminemia (SA < 30 g/L) also correlates with the severity of COVID-19 (p < 0.0001) in patients from Italy[17]. Two additional meta-analyses showed that SA levels correlate with disease severity but fail to find associations among other liver parameters[9,16].

When considering these liver markers in the context of critical care, it is noteworthy that ICU patients with COVID-19 generally have lower SA values at admission than patients admitted to regular hospital floors (31.3 ± 5.2 g/L *versus* 36.5 ± 5.7 g/L; p = 0.001). In fact, SA predicts ICU admission with a HR score of 1.87, 95% CI 1.05–3.32, p = 0.034[18]. A study conducted in 63 COVID-19 patients from Turkey revealed that SA at admission predicts ICU admission with a cutoff point of ≤ 36 g/L, AUC of 0.989 (95% CI 0.924–1.00; p < 0.001), sensitivity of 96.7%, and specificity of 93.9%[19]. On the other hand, a study of 128 COVID-19 patients from Dubai showed that SA failed to predict ICU admission (AUC 0.256, 95% CI 0.146-0.366)[20]. Thus, the use of SA as a predictor of ICU admission in seriously ill patients with COVID-19 should be performed with caution, and clinicians must take into account the genetic background and variability among the patient populations with which they work.

Regarding mortality, a meta-analysis evaluating eleven studies predominantly conducted in China indicated that SA values tend to be lower in non-survivors than survivors (-3.7 g/L, 95% CI -5.3 – -2.1; p < 0.00001)[21]. A separate study conducted on 207 patients from Italy showed that hypoalbuminemia correlates with death in COVID-19 patients (p = 0.003)[17]. Another study in 319 patients from Italy concluded that SA < 32 g/L is a risk factor for mortality, with HR of 2.48 (95% CI 1.44–4.26; p = 0.001)[18]. Concurrently, two additional studies conducted in COVID-19 patients from China revealed that decreased SA at admission was an independent risk factor for mortality (OR = 1.929, 95% CI 1.199–3.104, p = 0.007, and OR, 6.394; 95% CI 1.315-31.092, p = 0.021, respectively)[22]. This evidence supports the idea that SA is an independent risk factor for ICU admission and death in patients that meet hospitalization criteria for COVID-19. As we have shown, critical consideration of SA levels may help clinicians identify patients with SARS-CoV-2 infection who are at much higher risk of developing adverse outcomes than other patients. Having a reliable and easy-to-detect biomarker at their disposal would enable clinicians to provide these high-risk patients with more aggressive medical treatments that will increase their probability of survival.

Bilirubin

Bilirubin derives from the breakdown of the heme group in hemoglobin, which occurs in the spleen, bone marrow, and liver[23]. In these tissues, heme oxygenase, an enzyme found in macrophages, can catalyze iron release to form carbon monoxide and biliverdin. Biliverdin is in turn reduced to form unconjugated bilirubin, also referred to as indirect bilirubin, which is poorly water soluble[24]. The 200-300 mg of bilirubin produced by the human body per day is typically excreted.

Excretion of bilirubin occurs when indirect bilirubin (IBIL) is released into the plasma, where it binds albumin that is in turn transported to the liver[25]. Then, bilirubin is conjugated to uridine diphosphate sugars (UDP) via UDP-glucuronyltransferase. This increases IBIL solubility and allows its excretion through the bile. Conjugated bilirubin, also referred to as direct bilirubin (DBIL), is broken down into urobilinogens by intestinal bacteria. At this point, a small quantity of DIBIL can be deconjugated and re-absorbed by intestinal epithelial cells[23]. Any increase in the rate of release of the heme group or failure to completely excrete bilirubin leads to a concomitant elevation of total bilirubin, direct bilirubin, or indirect bilirubin depending on the step of bilirubin metabolism that is impaired[25].

Common clinical laboratory tests include measures of total bilirubin (TBIL), IBIL, and/or DBIL, which can help establish the cause of hyperbilirubinemia[24]. Elevation of bilirubin in patients with SARS-CoV-2 infection is not common. However, among COVID-19 patients who do show abnormal liver function test results during hospitalization, TBIL levels have been found to be elevated as high as 18%[8,26,27]. A large study conducted in 5771 patients from China suggested that TBIL values are independent of the severity of COVID-19[28]. Indeed, the average values of TBIL, DBIL, and IBIL fell within normal ranges of values in all patients enrolled in this study (10.4 μmol/L, IQR 7.9-14.1, 3.0 μmol/L, IQR 2.1-4.4, and 7.4 μmol/L, IQR 5.2-10.3, respectively)[28].

Conversely, emerging evidence now supports the use of bilirubin values at hospital admission to estimate a patient's risk of developing severe COVID-19. Seriously ill patients have higher TBIL and DBIL levels at admission than non-severe patients (for TBIL, 10.6 μmol/L, IQR 7.9-15.0 *versus* 10.3 μmol/L, IQR 7.9-14.0, $p = 0.053$, respectively; for DBIL, 3.3 μmol/L, IQR 2.2-5.2 0 *versus* 2.9 μmol/L, IQR 2.0-4.20, $p < 0.001$, respectively)[28]. In addition, the peak of TBIL correlates with mortality risk, where TBIL maximum values of 21-63 μmol/L confer a 3-fold increased mortality risk (HR 3.28 95% CI 2.47-4.35; $p < 0.001$), while patients with TBIL greater than 63 μmol/L show 8-fold increased mortality risk (HR 7.98 95% CI 3.88-16.41; $p < 0.001$)[28]. Higher TBIL levels also confer ~3-fold increased risk of developing severe COVID-19 (OR 2.94, 95% CI 2.18-3.97)[29]. Likewise, TBIL values are elevated in ICU patients relative to non-ICU patients (15.8 ± 6.8 μmol/L *versus* 9.1 ± 3.6 μmol/L, $p = 0.0082$, respectively)[30]. In a population of pediatric COVID-19 patients, Wang and collaborators also reported higher TBIL values in seriously ill patients than in non-severe individuals (10.13 μmol/L *versus* 6.40 μmol/L, $p = 0.05$, respectively) with OR of 1.316, 95% CI 0.575-3.014, $p = 0.516$)[4]. These studies suggest that bilirubin can be used to estimate the risk of mortality or ICU admission in adult and pediatric patients with COVID-19, especially TBIL and DBIL[31].

Lactate dehydrogenase

Lactate dehydrogenase (LDH) is a ubiquitous enzyme in human cells. LDH consists of four polypeptide chains that constitute five different isoforms located in the cytosol and mitochondria[32]. In the cytosol, LDH catalyzes the conversion of lactate to pyruvate by transferring a hydride group from NAD+ to NADH[33]. In the mitochondria, LDH catalyzes the conversion of lactate to pyruvate by transferring a hydride group from ferricytochrome c to ferrocytochrome c. Release of LDH into cells occurs primarily as a result of necrosis[32,33]. Serum LDH is elevated in a variety of clinical scenarios including hemolysis, infection, sepsis, infarction, liver and kidney diseases, pancreatitis, bone fracture, rhabdomyolysis or myositis, hypoxia, shock, and cancer[34].

LDH elevation is one of the most commonly reported laboratory anomalies in COVID-19 patients around the world. In fact, 50-80 percent of patients with SARS-CoV-2 infection show abnormally high LDH levels[13]. Numerous studies report a strong positive correlation between LDH levels and COVID-19 severity, with higher levels present in severe or critical patients. A study conducted in 548 patients reported 250 U/L and > 445 U/L as two cutoff values for LDH that can help distinguish non-severe patients from critically ill patients who are at a much higher risk of death. Patients with LDH > 445 U/L at admission were at a 4.4-fold increased risk of developing severe COVID-19 (OR, 4.4, 95% CI 2.6-7.6) and a 2-fold increased risk of death (HR 2.0, 95% CI, 1.2-3.3; p = 0.007)[35]. In a meta-analysis of 19 papers that gathered clinical information from more than 3000 patients, LDH elevation at admission carried an 8-fold increased risk of developing severe COVID-19 (OR 8.28, 95% CI 4.75 - 14.46). LDH values were higher in patients who required ICU admission, with an OR of 5.78 (95% CI 1.65 – 20.28; $p < 0.001$)[36]. Numerous studies and meta-analyses report significantly increased LDH levels in non-survivors with respect to survivors ($p < 0.001$)[36]. This increase in LDH also associates with mortality risk, with OR values ranging from 4.09 to 10.88 depending on the study ($p < 0.001$)[37]. In line with this, a study conducted in 375 COVID-19 patients from China reported that LDH

Table 1. Liver biomarkers as predictors of pneumonia development, intensive care unit admission, and death in patients with COVID-19

Liver biomarker	Cutoff point	Clinical outcome	AUC (95% IC)	Sensitivity (%), Especificity (%)	Country (Reference)
HSA	< 36 g/L	ICU admission	0.989 (0.924-1.00)	96.7, 93.9	Turkey (Uyar et al.)
	NA	ICU admission	0.256 (0.146-0.366)	NA	United Arab Emirates (Hachim et al.)
LDH	> 365 U/L	Death	0.943 (NA)	NA	China (Yan et al.)
	> 303 U/L	Death	0.829 (0.745-0.895)	NA	China (Feng et al.)
	> 353.5 U/L	Death	0.949 (NA)	94.4, 89.2	China (Dong et al.)
AST/ALT ratio	> 1.38	Death	0.71 (0.67-0.74)	NA	China (Qin et al.)
	> 1.49	Death	0701 (0.603-0.787)	74, 70	Italy (Zinellu et al.)
	> 1.65	Death	0.713 (0.618-0.807)	57.5, 82.3	Turkey (Medetalibeyoglu et al.)
	> 1.26	ICU	0.636 (0.564-0.709)	64.9, 60.4	
	> 1.55	Pneumonia	0.577 (0.529-0.625)	61.0, 55.6	
Fibrinogen/ Albumin Ratio	≤ 0.0883	Pneumonia	0.730 (NA)	NA	China (Bi et al.)
COVID-GRAM		Pneumonia	0.88 (0.85-0.91)	NA	China (Liang et al.)
LDH CRP Lymphocyte	> 365 U/L < 41.2 mg/L > 14.7%	Death	0.978 (NA)	NA	China (Yan et al.)
SOFA score	≥ 3	Death	0.890 (0.826-0.955)	90.00, 83.18	China (Liu et al.)

Summary of the most accurate liver biomarkers for prognosis in COVID-19. Liver biomarkers are accompanied by specific cutoff value, main clinical outcome, AUC, sensitivity, specificity, and country of origin.
NA: non available; AUC: area under the curve; CI: confidence interval; ICU: intensive care unit admission; AST: aspartate aminotransferase; ALT: alanine aminotransferase; SA: serum albumin; LDH: lactate dehydrogenase; CRP: C reactive protein; SOFA: sequential organ failure assessment.

> 365 U/L predicts mortality with an AUC of 0.943. Similarly, Feng and coworkers found that LDH > 303 U/L predicts death with an AUC of 0.829. Finally, another study conducted in 119 severe-to-critical COVID-19 patients estimated that LDH > 353.5 U/L predicts mortality with an AUC of 0.949, sensitivity of 94.4%, and specificity of 89.2%[38]. As we have outlined here, LDH appears to be a reliable independent risk factor for mortality in patients who meet hospitalization criteria concurrent with severe-to-critical COVID-19.

Ratios and clinical scores based on measures of liver function

Liang and coworkers proposed the use of the COVID-GRAM score to predict the development of critical COVID-19. The assessment takes into account such factors as lactate dehydrogenase, direct bilirubin, chest radiography, age, hemoptysis, dyspnea, unconsciousness, cancer history, neutrophil-to-lymphocyte ratio, and number of comorbidities [39]. This score has an AUC of 0.88 (95% CI 0.85-0.91) for predicting the proportion of patients at higher risk of needing critical care for COVID-19[39].

Notably, Yan and collaborators proposed a score based on LDH > 365 U/L, C reactive protein < 41.2 mg/L, and lymphocyte count > 14.7% that was shown to reliably predict mortality in COVID-19 patients, with an AUC of 0.978. In fact, use of this score permitted 100% accurate prediction of a patient's outcome ten days prior its occurrence[38].

Another score based on LDH, procalcitonin, smoking history, oxygen saturation, and lymphocyte count predicts ICU admission of COVID-19 patients with an AUC of 0.761 (95% CI 0.71–0.81; $p < 0.001$), sensitivity of 10.5%, and specificity of 99.2%. Likewise, the combined use of LDH, procalcitonin, history of chronic obstructive pulmonary disease (COPD), oxygen saturation, heart rate,

and age predicts mortality in COVID-19 patients with an AUC of 0.87 (95% CI 0.83–0.92; $p < 0.001$), sensitivity of 7.1%, and specificity of 100%[36].

Finally, the Sequential Organ Failure Assessment (SOFA) is commonly used to predict mortality in seriously ill patients with sepsis[40]. The SOFA score includes oxygenation index, mean arterial pressure, the Glasgow coma scale, creatinine or urine volume, platelets, and TBIL[40]. Liu and collaborators found that SOFA score at admission predicts mortality of COVID-19 patients with a cutoff point ≥ 3 points, AUC of 0.890 (95% CI 0.826–0.955), sensitivity of 90.00%, and specificity of 83.81%[40]. This information supports the idea that scores that take parameters of liver function into account are better predictors of pneumonia, ICU admission, and death in patients with COVID-19.

Conclusion

As we have outlined here, liver impairment is commonly reported in COVID-19 patients, especially those with severe or critical disease who frequently experience the worst outcomes[26]. The cause of abnormal liver function in these cases remains unclear, although several hypotheses have been proposed. Firstly, hepatocytes, cholangiocytes, and endothelial cells express the angiotensin-converting enzyme 2 (ACE2) receptor that acts as the main SARS-CoV-2 entry point[41] into cells. Upon SARS-CoV-2 infection, liver cells may undergo necrosis and/or apoptosis. This can, in turn, contribute to inflammation and lead to hepatic damage. It is also believed that ARDS, hypoxia, and coagulation disorders might contribute to liver damage by increasing hepatic isquemia[42]. Further, exacerbation of the inflammatory response directly contributes to the cytokine storm often observed in severe COVID-19 cases, which in turn promotes multiple organ failure, including failure of the liver[43]. Finally, the use of hepatotoxic drugs such as acetaminophen might also alter liver function tests in patients with COVID-19[42,44].

In terms of liver function tests, serum albumin and LDH are better predictors of ICU admission and death than levels of transaminases, ALP, bilirubin, and GGT[45]. Clinical scores that include indicators of liver function such as albumin, LDH, and total bilirubin are also accurate predictors of the most adverse outcomes, including pneumonia, ICU admission, and death, in patients with SARS-CoV-2 infections. Therefore, prognosis in COVID-19 should be assessed using scores that take liver function tests such as albumin and LDH into account, together with other demographic or clinical parameters. Liver function tests greatly enhance the ability of clinicians to identify patients at higher risk of developing the most severe cases of COVID-19, which could help increase survival rates and optimize hospital resources throughout the current pandemic.

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Conflicts of interest

The authors declare that do not exist conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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References

1. Liu W, Yue XG, Tchounwou PB. Response to the COVID-19 Epidemic: The Chinese Experience and Implications for Other Countries. Int J Environ Res Public Health. 2020;17(7). [PMID: 32235413 DOI: 10.3390/ijerph17072304]
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. [PMID: 32109013 DOI: 10.1056/NEJMoa2002032]
3. Lau H, Khosrawipour T, Kocbach P, Ichii H, Bania J, Khosrawipour V. Evaluating the massive underreporting and undertesting of COVID-19 cases in multiple global epicenters. Pulmonology. 2021;27(2):110-5. [PMID: 32540223 DOI: 10.1016/j.pulmoe.2020.05.015]
4. Rong XM, Yang L, Chu HD, Fan M. Effect of delay in diagnosis on transmission of COVID-19. Math Biosci Eng. 2020;17(3):2725-40. [PMID: 32233563 DOI: 10.3934/mbe.2020149]
5. 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. 2020;395(10223):497-506. [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5].

6. Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large U.S. Cohort. Hepatology. 2020;72(3):807-17. [PMID: 32473607 DOI: 10.1002/hep.31404]
7. Da BL, Mitchell RA, Lee BT, Perumalswami P, Im GY, Agarwal R, et al. Kinetic patterns of liver enzyme elevation with COVID-19 in the USA. Eur J Gastroenterol Hepatol. 2020;32(11):1466-9. [PMID: 32501877 DOI: 10.1097/MEG.0000000000001792]
8. Bertolini A, van de Peppel IP, Bodewes FAJA, Moshage H, Fantin A, Farinati F, et al. Abnormal Liver Function Tests in Patients With COVID-19: Relevance and Potential Pathogenesis. John Wiley and Sons Inc; 2020. p. 1864-72. [PMID: 32702162 DOI: 10.1002/hep.31480]
9. Abdulla S, Hussain A, Azim D, Abduallah EH, Elawamy H, Nasim S, et al. COVID-19-Induced Hepatic Injury: A Systematic Review and Meta-Analysis. Cureus. 2020;12(10):e10923. [PMID: 33194489 DOI: 10.7759/cureus.10923]
10. Chen Z, He Y, Shi B, Yang D. Human serum albumin from recombinant DNA technology: challenges and strategies. Biochim Biophys Acta. 2013;1830(12):5515-25. [PMID: 23644036 DOI: 10.1016/j.bbagen.2013.04.037]
11. Rabbani G, Ahn SN. Structure, enzymatic activities, glycation and therapeutic potential of human serum albumin: A natural cargo. Int J Biol Macromol. 2019;123:979-90. [PMID: 30439428 DOI: 10.1016/j.ijbiomac.2018.11.053]
12. Gatta A, Verardo A, Bolognesi M. Hypoalbuminemia. Intern Emerg Med. 2012;7 Suppl 3:S193-9. [PMID: 23073857 DOI: 10.1007/s11739-012-0802-0]
13. Ghahramani S, Tabrizi R, Lankarani KB, Kashani SMA, Rezaei S, Zeidi N, et al. Laboratory features of severe vs. non-severe COVID-19 patients in Asian populations: a systematic review and meta-analysis. Eur J Med Res. 2020;25(1):30. [PMID: 32746929 DOI: 10.1186/s40001-020-00432-3
14. Rod JE, Oviedo-Trespalacios O, Cortes-Ramirez J. A brief-review of the risk factors for covid-19 severity. Rev Saude Publica. 2020;54:60. [PMID: 32491116 DOI: 10.11606/s1518-8787.2020054002481]
15. Aziz M, Fatima R, Lee-Smith W, Assaly R. The association of low serum albumin level with severe COVID-19: a systematic review and meta-analysis. Crit Care. 2020;24(1):255. [PMID: 32456658 DOI: 10.1186/s13054-020-02995-3].
16. Ahmed J, Rizwan T, Malik F, Akhter R, Malik M, Ahmad J, et al. COVID-19 and Liver Injury: A Systematic Review and Meta-Analysis. Cureus. 2020;12(7):e9424. [PMID: 32864250 DOI: 10.7759/cureus.9424]
17. Bassoli C, Oreni L, Ballone E, Foschi A, Perotti A, Mainini A, et al. Role of serum albumin and proteinuria in patients with SARS-CoV-2 pneumonia. Int J Clin Pract. 2020:e13946. [PMID: 33332691 DOI: 10.1111/ijcp.13946]
18. Violi F, Cangemi R, Romiti GF, Ceccarelli G, Oliva A, Alessandri F, et al. Is Albumin Predictor of Mortality in COVID-19? Antioxid Redox Signal. 2020. [PMID: 32524832 DOI: 10.1089/ars.2020.8142]
19. Uyar E, MerdİN A, Yamanyar S, EzgÜ MC, Artuk C, TaŞkin G, et al. Could serum albumin value and thrombocyte/lymphocyte ratio be an important prognostic factor in determining the severity of COVID 19? Turk J Med Sci. 2020. [PMID: 33350294 DOI: 10.3906/sag-2008-285]
20. Hachim MY, Hachim IY, Naeem KB, Hannawi H, Salmi IA, Hannawi S. D-dimer, Troponin, and Urea Level at Presentation With COVID-19 can Predict ICU Admission: A Single Centered Study. Front Med (Lausanne). 2020;7:585003. [PMID: 33363185 DOI: 10.3389/fmed.2020.585003]
21. Tian W, Jiang W, Yao J, Nicholson CJ, Li RH, Sigurslid HH, et al. Predictors of mortality in hospitalized COVID-19 patients: A systematic review and meta-analysis. J Med Virol. 2020;92(10):1875-83. [PMID: 32441789 DOI: 10.1002/jmv.26050]
22. Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. Risk Factors for Severe Disease and Efficacy of Treatment in Patients Infected with COVID-19: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis. Clinical Infectious Diseases. 2020;71(16):2199-206. [PMID: 32407459 DOI: 10.1093/cid/ciaa576]
23. Billing BH, Black M. Bilirubin metabolism. Gut. 1969;10(4):250-4. [PMID: 4889525 DOI: 10.1136/gut.10.4.250]
24. Fevery J. Bilirubin in clinical practice: a review. Liver Int. 2008;28(5):592-605. [PMID: 18433389 DOI: 10.1111/j.1478-3231.2008.01716.x]
25. Kamisako T, Kobayashi Y, Takeuchi K, Ishihara T, Higuchi K, Tanaka Y, et al. Recent advances in bilirubin metabolism research: the molecular mechanism of hepatocyte bilirubin transport and its clinical relevance. J Gastroenterol. 2000;35(9):659-64. [PMID: 11023036 DOI: 10.1007/s005350070044]
26. Fan Z, Chen L, Li J, Cheng X, Yang J, Tian C, et al. Clinical Features of COVID-19-Related Liver Functional Abnormality. Clin Gastroenterol Hepatol. 2020;18(7):1561-6. [PMID: 32283325 DOI: 10.1016/j.cgh.2020.04.002]
27. Bao J, Li C, Zhang K, Kang H, Chen W, Gu B. Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. Clin Chim Acta. 2020;509:180-94. [PMID: 32511971 DOI: 10.1016/j.cca.2020.06.009]
28. Lei F, Liu YM, Zhou F, Qin JJ, Zhang P, Zhu L, et al. Longitudinal Association Between Markers of Liver Injury and Mortality in COVID-19 in China. Hepatology. 2020;72(2):389-98. [PMID: 32359177 DOI: 10.1002/hep.31301]
29. Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS One. 2020;15(11):e0241955. [PMID: 33201896 DOI: 10.1371/journal. pone.0241955]
30. Wang F, Yang Y, Dong K, Yan Y, Zhang S, Ren H, et al. Clinical characteristics of 28 patients with diabetes and COVID-19 in Wuhan, China. Endocr Pract. 2020;26(6):668-74. [PMID: 32357072 DOI: 10.4158/EP-2020-0108]
31. Wang Y, Zhu F, Wang C, Wu J, Liu J, Chen X, et al. Children Hospitalized With Severe COVID-19 in Wuhan. Pediatr Infect Dis J. 2020;39(7):e91-e4. [PMID: 32384397 DOI: 10.1097/INF.0000000000002739]
32. Ketchum CH, Robinson CA, Hall LM, Grizzle WE. Lactate dehydrogenase isolated from human liver mitochondria: its purification and partial biochemical characterization. Clin Biochem. 1988;21(4):231-7. [PMID: 3409525 DOI: 10.1016/s0009-9120(88)80006-7].
33. Usher DJ, Shepherd RJ, Deegan T. Serum lactate dehydrogenase isoenzyme activities in patients with asthma. Thorax. 1974;29(6):685-9. [PMID: 4450178 DOI: 10.1136/thx.29.6.685]
34. Erez A, Shental O, Tchebiner JZ, Laufer-Perl M, Wasserman A, Sella T, et al. Diagnostic and prognostic value of very high serum lactate dehydrogenase in admitted medical patients. Isr Med Assoc J. 2014;16(7):439-43. [PMID: 25167691]
35. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-8. [PMID: 32294485 DOI: 10.1016/j.jaci.2020.04.006]
36. Zhao Z, Chen A, Hou W, Graham JM, Li H, Richman PS, et al. Prediction model and risk scores of ICU admission and mortality in COVID-19. PLoS One. 2020;15(7):e0236618. [PMID: 32730358 DOI: 10.1371/journal.pone.0236618]
37. Kiss S, Gede N, Hegyi P, Németh D, Földi M, Dembrovszky F, et al. Early changes in laboratory parameters are predictors of mortality and ICU admission in patients with COVID-19: a systematic review and meta-analysis. Med Microbiol Immunol. 2021;210(1):33-47. [PMID: 33219397 DOI: 10.1007/s00430-020-00696-w]
38. Yan L, Zhang H-T, Goncalves J, Xiao Y, Wang M, Guo Y, et al. An interpretable mortality prediction moderl for COVID-19 patients. Nature Machine Intelligence. 2020(2):283-8. [DOI: 10.1038/s42256-020-0180-7].
39. Liang W, Liang H, Ou L, Chen B, Chen A, Li C, et al. Development and Validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med. 2020;180(8):1081-9. [PMID: 32396163 DOI: 10.1001/jamainternmed.2020.2033]
40. Liu S, Yao N, Qiu Y, He C. Predictive performance of SOFA and qSOFA for in-hospital mortality in severe novel coronavirus disease. Am J Emerg Med. 2020;38(10):2074-80. [PMID: 33142178 DOI: 10.1016/j.ajem.2020.07.019]
41. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40(5):998-1004. [PMID: 32369209 DOI: 10.1002/jmv.25972]
42. Feng G, Zheng KI, Yan QQ, Rios RS, Targher G, Byrne CD, et al. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. J Clin Transl Hepatol. 2020;8(1):18-24. [PMID: 32274342 DOI: 10.14218/JCTH.2020.00018]
43. Beltrán-García J, Osca-Verdegal R, Pallardó FV, Ferreres J, Rodríguez M, Mulet S, et al. Sepsis and Coronavirus Disease 2019: Common Features and Anti-Inflammatory Therapeutic Approaches. Crit Care Med. 2020;48(12):1841-4. [PMID: 32826431 DOI: 10.1097/CCM.0000000000004625]
44. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. Lancet Gastroenterol Hepatol. 2020;5(6):529-30. [PMID: 32203680 DOI: 10.1016/S2468-1253(20)30084-4].
45. Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth. 2000;85(4):599-610. [PMID: 11064620 DOI: 10.1093/bja/85.4.599]