Review Article

Coronavirus Disease (COVID-19): A Biochemical Perspective

Abstract

The Coronavirus disease 2019 (COVID-19) is a primarily a respiratory disease but can cause a multi-organ injury like acute cardiac injury, kidney injury, , and liver dysfunction. COVID-19 patients had different degrees of blood biochemical abnormalities, which might indicate multiple organ dysfunction.

Hence the aim of the present study is to provide an overview on organ injury and alteration in biochemical parameters in Covid-19 patients.

The common laboratory abnormalities in COVID-19 patients includ elevated inflammatory markers like CRP, ferritin, procalcitonin, cytokines and IL-6, IL-2, IL-7 and coagulation dysfunction like elevation of prothrombin time and D-dimer. The cardiac injury is reflected by elevation of LDH, CK-MB and cTn levels and brain natriuretic peptide (BNP).

In impaired liver and kidney function mild or moderate elevation of ALT, AST, total bilirubin, ALP, GGT, hypoalbuminemia, BUN, creatinine and electrolyte disturbances were seen.

Hence reviewing currently available data, the present study can suggest that monitoring of the biochemical parameters may help in prediction of organ damage and thus in prevention disease progression by the institution of early interventions.

Key words: 2019 novel coronavirus, Covid-19, Biochemical parameters, interleukins etc

Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In December 2019 the first case was identified in Wuhan, China and since its spread worldwide, leading to an ongoing pandemic.

In January 2020, the WHO recommended 2019-nCoV as severe acute respiratory disease (1) and the official names COVID-19 and SARS-CoV-2 were issued on 11 February 2020 (2).

The SARS-CoV-2 is a β-coronavirus, which is enveloped non-segmented positive-sense RNA virus (subgenus *sarbecovirus*, *Orthocoronavirinae* subfamily) (1). Coronaviruses (CoV) are divided into four genera, including α−/β−/γ−/δ-CoV. α- and β-CoV are able to infect mammals, while γ- and δ-CoV tend to infect birds (3)

Coronaviruses can infect animals and/or humans, with some strains being zoonotic. The SARS-CoV outbreak in 2002 originated from bats in China (4) and the MERS-CoV outbreak in 2012 from dromedary camels, though also likely transmitted from bats, in the Middle East (5). It has

been hypothesized that SARS-CoV-2 might be transmitted by bats (6), snakes (7), or pangolins (8). It is a virus highly transmissible from human to human through respiratory droplets and aerosols.

A number of published articles have reported the epidemiological and clinical characteristics of patients with COVID-19 disease, but biochemical investigations data of infected individuals is limited.

Hence the perspective of present study is to provide an overview on organ biochemical parameters in Covid-19 patients.

Material and Methods

The authors had searched data from published article in PubMed, Embase, Scopus, WHO, Google scholar and Cochrane, Elsevier, Wikipedia, Web of science etc,

General Aspects of pathogenesis of Coronavirus Disease.

The initial step of virion entry to the host cell is facilitated by interactions between the S protein and its receptor. The spike (S) protein of SARS-CoV2 is cleaved by a cellular enzyme named furin at the S1/S2 site. This cleavage is essential for viral entry to the lung cells. The activated S protein is primed by the *TMPRSS2* and finally attaches ACE 2 receptors to enter the host cells (Fig 1)(9.10).

ACE2, found in the lower respiratory tract of humans, is known as cell receptor for SARS-CoV (11) and regulates both the cross-species and human-to-human transmission (12). After membrane fusion, the viral genome RNA is released into the cytoplasm, and the uncoated RNA translates two polyproteins, pp1a and pp1ab (13), which encode non-structural proteins, and form replication-transcription complex (RTC) in double-membrane vesicle (14). Continuously RTC replicate and synthesize a nested set of subgenomic RNAs (15), which encode accessory proteins and structural proteins. Mediating endoplasmic reticulum (ER) and Golgi apparatus (16), newly formed genomic RNA, nucleocapsid proteins and envelope glycoproteins assemble and form viral particle buds. Lastly, the virion-containing vesicles fuse with the plasma membrane to release the virus.

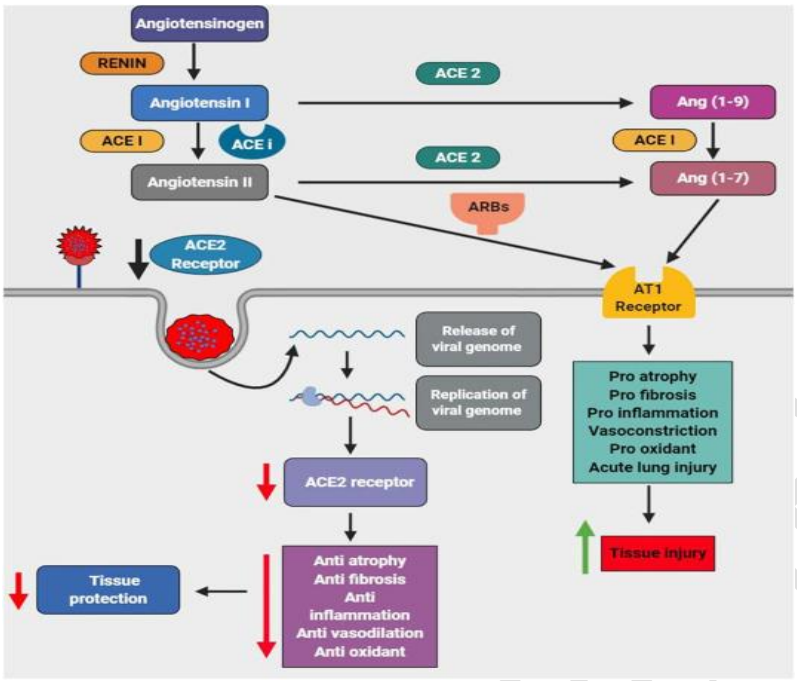

Fig.1 : pathogenesis of Coronavirus Disease

When infecting humans, CoVs can cause diseases of varying severity, from upper respiratory tract infections similar to a common cold, to liver, enteric, neurological diseases and lower respiratory tract infections such as pneumonia, bronchitis and severe acute respiratory syndrome (SARS) (17,18,19).

Laboratory diagnosis for coronavirus disease (COVID-19)

For diagnosis of COVID-19 tests used are real-time reverse transcription-polymerase chain reaction (RT-PCR); serologic tests for SARS-CoV-2 (Anti-SARS-CoV-2 IgA, IgM and/or IgG), in addition to SARS-CoV-2 antigen test in upper respiratory tract specimens (20,21,22).

The RT-PCR is the gold standard for SARS-CoV-2 detection and it is the laboratory test of choice for the diagnosis of symptomatic patients in the acute phase (23).

Inflammation in Covid 19 patients

Patients develop acute respiratory distress syndrome (ARDS) characterized by a rapid onset of bilateral inflammation in the lungs. The inflammation involves an acute increase in several proinflammatory cytokines, a process termed “cytokine storm.” This severe inflammatory response causes increased leakiness of the blood vessels and an induction of a procoagulant state, eventually increasing the risk of multiorgan damage.

Persistent elevation of cytokines, predominantly IL-1b and interleukin-6 (IL-6), predicts a higher likelihood of an unfavorable outcome, including death (24,25) Increased levels of several inflammatory biomarkers, including cytokines such as IL-6, IL-2, IL-7, TNF-α, interferon (IFN)-γ, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α,

granulocyte colony stimulating factor (G-CSF), and procalcitonin (PCT), erythrocyte sedimentation rate (ESR) and ferritin, have been reported in COVID-19 patients.

C-reactive protein (CRP) is a plasma protein produced by the liver and induced by various inflammatory mediators such as IL-6. Despite being non-specific, this acute phase reactant is used clinically as a biomarker for various inflammatory conditions. CRP levels has increased significantly at the early stage of the disease, and showed a positive correlation (26,27,28,29). Tan et al. (30) showed that CRP has a strong indicator to reflect the presence and severity of COVID-19 infection.

Immune dysregulation mediator is Ferritin, especially under extreme hyperferritinemia. The direct immune-suppression and pro-inflammatory effects, contributing to the cytokine storm.

Chen et al. analyzed the clinical characteristics of 99 patients, in which 63 of them had abnormal serum ferritin level (31). Elevated ferritin levels were found in autopsies of 12 patients whose cause of death was SARS-CoV-2 infection (32). Therefore, this study was concluded that serum ferritin levels were closely related to the severity of COVID-19 (33).

Abnormal Coagulation function in Covid 19

Fibrinogen is an acute phase protein and essential part of the blood coagulation cascade which is induced by interleukin 6 and associated with inflammatory responses (32). In infection hepatic synthesis of fibrinogen increases 2 to 10 times (33). Severe COVID-19 patients present hypercoagulability than consumptive coagulopathy (34, 35).

Prolonged prothrombin time (PT) are linked to anticoagulant, coagulation factor deficiency, and fibrinolysis, which have been used as laboratory tools to predict bleeding (36, 37)

Coagulopathy and D-dimer elevations were seen in COVID-19 patients (38, 39) D-dimers are one of the fragments produced when plasmin cleaves fibrin to break down clots.. D-dimer > 1 μg/ml is one of the risk factors for mortality in adult inpatients with COVID-19 (40).

Organ Injury and alteration biochemical investigations in Covid 19 patients

The present data shows in addition to respiratory failure of COVID-19 patients have acute kidney injury, acute cardiac injury, and liver function damage (41,42)

Some patients with COVID-19 had different degrees of blood biochemical abnormalities, which might indicate multiple organ dysfunction.(Fig 2)

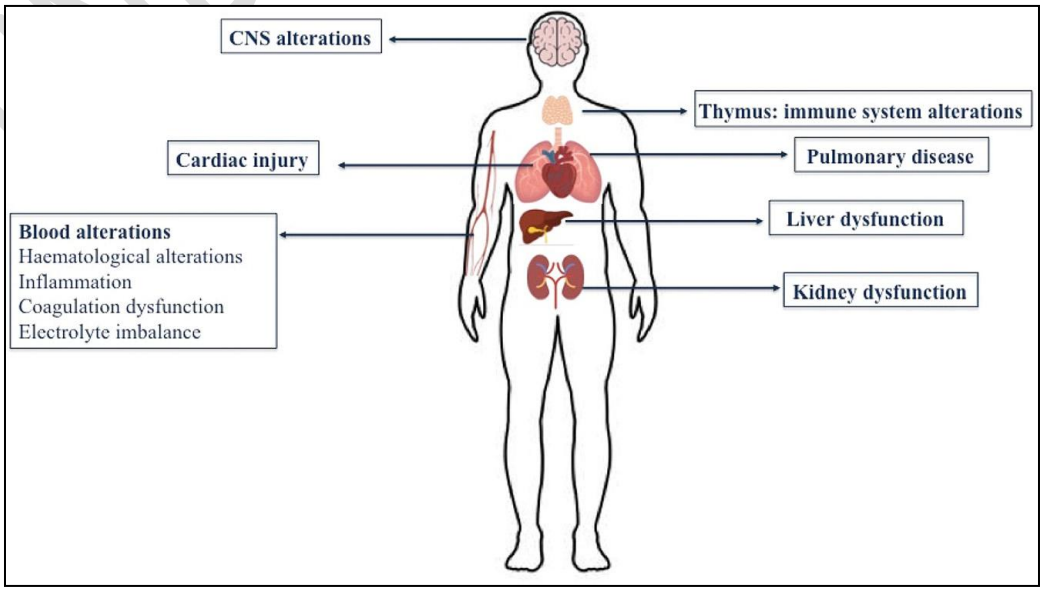

Figure 2: Main biochemical alterations associated with COVID-19.

Cardiac Injury and biochemical parameters

Patients with COVID-19 infection may experience a variety of cardiac manifestations, such as arrhythmia, myocardial injury, and even cardiac arrest may lead to sudden deterioration in cardiac function.

SARS-CoV-2 damages myocardial cells and induces changes of laboratory cardiac markers . The increase of cardiac troponin (cTn) and brain natriuretic peptide (BNP) has been associated with worse prognosis (27).

Han *et al*. reported that higher concentrations of some biomarkers, such as myohemoglobin (MYO), creatine kinase-MB (CK-MB), N-terminal pro-brain natriuretic peptide (NT-proBNP)), and cTnI were linked to the severity and rate of fatal cases in patients with COVID-19 infection (45).

The meta-analysis showed abnormalities in CK. The overall proportion of CK abnormalities in patients with COVID-19 was 0.13 (95% CI) (44).

The lactate dehydrogenase enzyme is required for conversion of pyruvate to lactate. LDH secretion is triggered by necrosis of the cell membrane, hinting to viral infection or lung damage, such as the pneumonia induced by SARS-CoV-2. The value of LDH was significantly higher in severe patients than in non-severe patients (44). Huang et al. reported that LDH levels were increased ICU patients.

Liver dysfunction and biochemical parameters

Individuals with severe COVID-19 seem to have a higher incidence of mild, severe and transient liver impairment (47). With the current evidence, it is clear that elevated liver enzymes are observed predominantly in severe and critical cases of COVID-19.

Xiaoling Deng et al (48) meta analysis reported ALT abnormalities. The overall proportion of ALT abnormalities in patients with COVID-19 was 0.16 (95% CI) also showed AST abnormalities . The overall proportion of AST abnormalities among patients was 0.20 (95% CI).

The study of Xiaoling Deng et al (48) meta analysis evaluated albumin abnormalities in COVID-19 patients albumin is decreased in151 patients.

Xiaoling Deng et al (48) also reported abnormal quantitative synthesis of total bilirubin. It showed an increase in total bilirubin and overall proportion of total bilirubin abnormalities was 0.06 (95%).

The ACE2 expression in bile duct cells is much higher compared with liver cells. Bile cells are involved in liver regeneration and the immune response, so liver injury in individuals with COVID-19 may be caused by damage to bile duct cells, but not liver cells (47). Although the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) indicating abnormal liver function are not generally high on admission, a multi-centre study on 1099 individuals documented increased levels of AST and ALT in 22.2% and 21.3% of COVID-19 patients, respectively.

Wang et al. (49), patients who had increased transaminase levels presented higher concentrations of γ-glutamyl transferase. It is worth noting that drug-induced liver injury and preexisting chronic infections are possible contributing factors for the observed abnormalities in liver blood tests (43,27).

Zhang et al. conducted a case-control type study of 240 patients (50) and showed mild ALP elevation as compared to 15.79% in the community acquired pneumonia (CAP) patients.

Renal dysfunction and biochemical parameters

Renal failure on admission in patients with SARS-CoV-2 infection is frequent and is associated with a greater number of complications and in-hospital mortality.

Some studies reported, the association of acute kidney injury (AKI) and COVID-19 has a high mortality (51). However, the incidence of reported AKI associated with COVID-19 varies widely (51,52). It would be expected that kidney involvement is frequent since the virus enters the cell through the angiotensin-converting enzyme 2 (ACE2), which is expressed, in addition to pulmonary type 2 alveolar cells, on renal proximal tubular cells, glomerular visceral and parietal epithelium, and the cytoplasm of the distal tubules and collecting ducts (53,54).

Xiang J et al (55) studies have demonstrated significantly higher levels of renal biomarkers such as serum urea, creatinine and markers of glomerular filtration rate in severe cases (55)

Cheng Y et al (56) study revealed 701 patients had elevated serum creatinine levels on admission which is correlated with severity due to significant abnormalities in the coagulation pathway.

In a prospective cohort study of 701 individuals with COVID-19, it was reported that increased baseline blood urea nitrogen, increased baseline serum creatinine, proteinuria and haematuria could be independent risk factors for in-hospital death after adjusting for age, sex, disease severity, co-morbidity and leucocyte count (56).

Some authors described alterations of electrolyte levels, including sodium, potassium, chloride, and calcium, in COVID-19 patients (57, 43). Specifically, hyponatremia, hypokalemia, and hypocalcemia have been associated with severe disease (58).

Conclusion

The different degrees of blood biochemical abnormalities in COVID-19 patients, which might indicate multiple organ dysfunction.

The common laboratory abnormalities in COVID-19 patients included elevated inflammatory markers like CRP, ferritin, procalcitonin, cytokines and IL-6, IL-2, IL-7 and coagulation dysfunction includes elevation of prothrombin time and D-dimer. The cardiac injury is reflected by elevation of LDH, CK-MB and cTn levels and brain natriuretic peptide (BNP).

In impaired liver and kidney function mild or moderate elevation of ALT, AST, total bilirubin, ALP, GGT, hypoalbuminemia, BUN, creatinine and electrolyte disturbance were seen.

Hence reviewing currently available data, the present study can suggest that monitoring of the biochemical parameters may help in prediction of organ damage and thus in prevention disease progression by the institution of early interventions.

References

1. "Novel Coronavirus (2019-nCoV) Situation Report – 10" (PDF). World Health Organization (WHO). 30 January 2020.
2. "Naming the coronavirus disease (COVID-19) and the virus that causes it". World Health Organization (WHO). Archived from the original on 28 February 2020. Retrieved 13 Mar
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;382(8):727–733.
4. Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science 2005;310: 676–9.
5. Corman VM, Ithete NL, Richards LR, Schoeman MC, Preiser W, Drosten C, et al. Rooting the phylogenetic tree of middle East respiratory syndrome coronavirus by characterization of a conspecific virus from an African bat. J Virol 2014;88:11297–303.
6. Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. Front Med 2020;14:126–35.
7. Ji W, Wang W, Zhao X, Zai J, Li X. Cross-species transmission of the newly identified coronavirus 2019-nCoV. J Med Virol 2020;92:433–40.
8. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020;63:364–74.
9. Kaviyarasi Renu Pureti Lakshmi Prasanna Abilash Valsala Gopalakrishnan. Coronaviruses pathogenesis, comorbidities and multi-organ damage – A review .Life Sciences; Volume 255, 15 August 2020
10. Hoffmann M, Kleine-Weber H, Pohlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol. Cell. 78(4), 779–784.
11. Jia HP, Look DC, Shi L, Hickey M, Pewe L, Netland J, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *J Virol.* 2005;79(23):14614–14621.
12. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS. J Virol. 2020. 10.1128/JVI.00127-20
13. de Wilde AH, Snijder EJ, Kikkert M, van Hemert MJ. Host factors in coronavirus replication. *Curr Top Microbiol Immunol.* 2018;419:1–42.
14. Sawicki SG, Sawicki DL. Coronavirus transcription: a perspective. *Curr Top Microbiol Immunol.* 2005;287:31–55.
15. Hussain S, Pan J, Chen Y, Yang Y, Xu J, Peng Y, et al. Identification of novel subgenomic RNAs and noncanonical transcription initiation signals of severe acute respiratory syndrome coronavirus. *J Virol.* 2005;79(9):5288–5295.
16. Perrier A, Bonnin A, Desmarets L, Danneels A, Goffard A, Rouille Y, et al. The C-terminal domain of the MERS coronavirus M protein contains a trans-Golgi network localization signal. *J Biol Chem.* 2019;294(39):14406–14421.

17. P.C. Woo, S.K. Lau, Y. Huang, K.Y. Yuen, Coronavirus diversity, phylogeny and interspecies jumping, Exp. Biol. Med. (Maywood) 234(10) (2009) 1117–1127.
18. Schoeman D., Fielding B.C. Coronavirus envelope protein: current knowledge. Virol. J. 2019;16(1):69.
19. Hui D.S. An overview on severe acute respiratory syndrome (SARS) Monaldi Arch. Chest Dis. 2005;63(3):149–157.
20. WHO Use of laboratory methods for SARS diagnosis. World Health Organization, Geneva. 2020.
21. Vashist S.K. In, Vitro Diagnostic Assays for COVID- 19: Recent Advances and Emerging Trends. Diagnostics (Basel) 2020;10(4)
22. CDC, Interim Guidelines for Collecting, Handling, and Testing Clinical Specimens from Persons for Coronavirus Disease 2019 (COVID-19), Centers of Disease and Control and Prevention, Georgia, 2020.
23. Brasil, Acurácia dos testes diagnósticos registrados para a COVID-19 Ministério da Saúde, Brasília, 2020
24. Voiriot G, Razazi K, Amsellem V, Tran Van Nhieu J, Abid S, Adnot S, et al. Interleukin-6 displays lung anti-inflammatory properties and exerts protective hemodynamic effects in a double-hit murine acute lung injury. Respir Res. 2017;18(1):64.
25. Gong J, Dong H, Xia SQ, Huang YZ, Wang D, Zhao Y et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. Med Rxiv. 2020.02.25
26. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19): a multi-center study in Wenzhou city, Zhejiang, China. J Infect 2020;80:388–93.
27. 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. J Am Med Assoc 2020;323:1061–69.
28. Matsumoto H, Kasai T, Sato A, Ishiwata S, Yatsu S, Shitara J, et al. Association between C-reactive protein levels at hospital admission and long-term mortality in patients with acute decompensated heart failure. Heart Ves 2019;34:1961–8.
29. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect 2020; 50:332–4.
30. Tan C, Huang Y, Shi F, Tan K, MaQ, Chen Y, et al. C-reactive protein correlates with CT findings and predicts severe COVID-19 early. 370 Ciaccio and Agnello: Biomarkers in COVID-19 J Med Virol 2020. [Epubahead of print].
31. 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. 2020; 395(10223):507–13
32. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and Cardiac Pathology in Covid-19: The First Autopsy Series from New Orleans. medRxiv 2020.04.06-20050575;
33. Tao Liu, Jieying Zhang, Yuhui Yang, Hong Ma, Zhengyu Li, Jiaoyu Zhang, et al. The potential role of IL-6 in monitoring severe case of coronavirus disease 2019. medRxiv 2020.03.01.20029769
34. Kerr R, Stirling D, Ludlam CA. Interleukin 6 and haemostasis. Br J Haematol. 2001;115(1):3-12.

35. Dowton SB, Colten HR. Acute phase reactants in inflammation and infection. Semin Hematol. 1988;25(2):84-90.
36. Spiezia L, Boscolo A, Poletto F. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020;120(6):998-1000.
37. Pavoni V, Gianesello L, Pazzi M, Stera C, Meconi T, Frigieri FC. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. J Thromb Thrombolysis. 2020;50:281-286.
38. Tripodi A. Thrombin generation assay and its application in the clinical laboratory. Clin Chem. 2016;62(5):699-707.
39. Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. Mayo Clin Proc. 2007;82(7):864-873.
40. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507–13.
41. Wu J, Liu J, Zhao X, Liu C, Wang W, Wang D, Xu W, Zhang C, Yu J, Jiang B,et al. Clinical Characteristics of Imported Cases of COVID-19 in Jiangsu Province: A Multicenter Descriptive Study. Clin Infect Dis. 2020;29:
42. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020; 395(10229): 1054-62.
43. 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;395:497–506.
44. Liu C, Jiang ZC, Shao CX, Zhang HG, Yue HM, Chen ZH, et al. Preliminary study of the relationship between novel coronavirus pneumonia and liver function damage: a multicenter study Zhonghua Gan Zang Bing Za Zhi 2020;28:148–52.
45. HanH, XieL, LiuR, et al. Analysis of heart injury laboratory parameters in 273 COVID-19 patients in one hospital in Wuhan, China. J Med Virol. 2020 Jul;92(7):819–823.
46. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet gastroentrol hepatol 2020;(5):428-430.
47. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40:998–1004.
48. Xiaoling Deng, Beibei Liu, Jiahuan Li, Junli Zhang, Yajuan Zhao and Keshu Xu* Blood biochemical characteristics of patients with coronavirus disease 2019 (COVID-19): a systemic review and meta-analysis. Clin Chem Lab Med 2020; 58(8): 1172–1181.
49. Wang Y, Liu S, Liu H, Li W, Lin F, Jiang L, et al. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. J Hepatol 2020.
50. Zhang Y, Zheng L, Liu L, Zhao M, Xiao J, Zhao Q. Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single centre in Wuhan city, China. *Liver Int.* 2020;[Epub ahead of print]
51. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. kidney Int. 2020 Jul;98(1):209–18.

52. Fanelli V, Fiorentino M, Cantaluppi V, Gesualdo L, Stallone G, Ronco C, et al. Acute kidney injury in SARS-CoV-2 infected patients. Crit Care. 2020;24(1):155.
53. Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. bioRxiv. 2020. Posted 2020 Jan 31
54. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020 Jul;98(1):219–27.
55. Xiang J., Wen J., Yuan X., Xiong S., Zhou X., Liu C. Potential biochemical markers to identify severe cases among COVID-19 patients. medRxiv. 2020 Mar 23; 2020.03.19.20034447.
56. Cheng Y., Luo R., Wang K., Zhang M., Wang Z., Dong L. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int.* 2020 May 1;97(5):829–838.
57. 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.
58. Lippi G, South AM, Henry BM. Annals express: electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem 2020