DOI: https://doi.org/10.53350/pjmhs221611013

**ORIGINAL ARTICLE**

# Biochemical and Haematological Manifestations as Predictor for Covid-19: A Case-Control Study

SHER AZIZ[1], ABDULLAH[1], SAQIB MARWAT[1], MUHAMMAD ASIF ZEB[1], AMAN ULLAH[1]
*[1]Department of Medical Lab. Technology, Institute of Paramedical Sciences, Khyber Medical University, Peshawar*
*Corresponding author: Muhammad Asif Zeb, Email: Muhammadasif.ipms@kmu.edu.pk, Cell: 03455928281*

## ABSTRACT

**Background:** Corona virus causes severe pneumonia of idiopathic nature. The clinical manifestation ranges from mild to severe respiratory problems. Due presences of target receptors and the release of chemical mediators, it also affect other organs including the liver and kidney.

**Objective:** The purpose of this study was to determine the effect of COVID-19 infection on hematological parameters, liver function and renal function.

**Methods:** This multicenter case-control observational study was conducted at Lady reading hospital, Hayatabad medical complex and Khyber teaching hospital Peshawar. A total of 340 samples were processed including 170 COVID-19 patients and 170 control groups. Complete blood count, liver function tests and renal function tests were performed to determine the effect of COVID infection on these parameters. The data were statistically analyzed using SPSS version 22.0.

**Results:** In complete blood count, the mean WBC count was 16632.34±7339.94 which was statistically significant with p value less than 0.05. In differential leukocyte count, the mean neutrophil values were 87.79±7.36 which was statistically significant (p=0.00). The mean value of ALT and ALP were 49.47±100.08, 114.43±64.71 respectively which were higher than the control group. Mean value of urea and creatinine were 70.58±41.89, 1.31±1.12 respectively and was statistically significant (p=0.00).

**Conclusion:** it is concluded that COVID-19 infection affects hematological and biochemical parameters including ALT, ALP, urea and creatinine. Hence these manifestations can be used collectively as a diagnostic and prognostic biomarker.

**Keywords:** Covid-19, liver function tests, Kidney Function Tests, blood cell count

## INTRODUCTION

A patient with severe pneumonia of idiopathic nature was admitted to hospital in December 2019 in Wuhan city of Hubei province China. In early January 2020, the unknown cases of pneumonia were discovered to be caused by a new virus. This new virus was from corona varidea family called severe acute respiratory syndrome corona virus -2 (SARS-COV-2). At the end of January 2020 world health organization (WHO) declared SARS COV-2 infection as a public health emergency of international origin.[1] Many efforts were done to control its spread, but this epidemic spread to many other countries in Asia and Europe.[2] In Pakistan, 287,300 cases and 6153 deaths were reported as of August 2020.[3]

Corona virus is of zoonotic origin.[2] It is an enveloped, single-stranded RNA virus. It has a spherical or pleomorphic shape and is covered with glycoprotein spikes of crown-like appearance so-called "corona" virus.[4] It transmits from one person to another, through airborne droplets during sneezing, talking, and coughing.[5] It enters the cell through a specific receptor called Angiotensin-converting enzyme -2 (ACE-2), present on vascular endothelial and epithelial cells in the lungs.[6] The clinical manifestation ranges from subclinical infection to severe respiratory failure. Most common symptoms include dry cough, fatigue, myalgia, fever, dyspnea, headache, diarrhea and sputum.[7] Patients with comorbidities like hypertension, Old age, diabetes mellitus, cerebrovascular disease, obesity and coronary heart diseases are at high risk.[8]

Reverse transcriptase Polymerase chain reaction (PCR) testing is the gold standard method for the diagnosis of this infection. As this technique is costly, unavailability of PCR kits, require skilled personals and is time consuming which delay diagnosis. Hence these limitations make RT-PCR unsuitable for routine diagnosis.[9] Early and alternative diagnosis is necessary for corona Patients. There is an urgent need to find ways to diagnose corona patients. A single parameter might not reflect the complexity of covid-19. Hence many biochemical and hematological parameters might be used collectively for diagnosis.[9] A study in Iraq reported leukopenia, lymphocytopenia and increased level of D-dimer, Lactate dehydrogenase (LDH), ferritin and C-reactive protein (CRP).[10] While, lymphopenia, leukocytosis, and thrombocytopenia were reported by another study.[2] A controversy exists among studies conducted on hematological and biochemical parameters in COVID-19 patients. In addition, most of the studies were retrospective cohort studies and systematic reviews. Therefore, this case-control study was conducted to determine hematological parameters, liver function and renal function in patients with COVID-19 infection.

## MATERIAL AND METHODS

This multicenter case-control, observational study was conducted in Lady reading hospital, Hayatabad medical complex and Khyber teaching hospital Peshawar. A total of 340 samples were collected including 170 COVID-19 patients and 170 normal control samples. In out 170 samples 73 were females and 97 were males with a 1:1.3 ratio. Nonprobability convenient sample technique was used for sample collection using standard operating procedures (SOPs) for COVID-19. Control samples were collected from the same hospitals from where cases were

collected. Patients above 30 years of age having positive RT-PCR were included. ICU admitted patients were excluded from the study. Informed consent was taken from patients before sample collection. All these patients were positive for coronavirus as detected by RT-PCR (MIC q PCR bimolecular system) by using a nasopharyngeal swab. Venous blood of 2 ml was collected in sodium citrate tube for coagulation studies, 1.5 ml in ethylene diamine tetra acetic acid (EDTA) tube for hematology parameters and 2ml in heparin tube for biochemical parameters in aseptic technique. Complete blood count was performed through a hematology analyzer (Sysmex). Liver function tests (LFTs) including bilirubin, ALP and ALT and renal function test (RFTs) including creatinine and urea were performed by a chemistry analyzer (Cobas e622 Roch Company).

The data were analyzed using SPSS version 22. For description statistic frequencies were calculated and presented in tabulated form while an independent sample t-test was applied on the patient and control group.

## RESULTS

In this study, a total of 340 patients have included out of which 170 individuals were positive for COVID-19 infections. Out of 170 patients, 97(57%) were males and 73(43%) were females, their mean age and standard deviation were 53.7 ± 15.8. Common symptoms observed included fever, pharyngitis, malaise, and shortness of breath. These cases were compared with 170 control group having negative RT-PCR. Out of 170 control group 65 (57%) were males and 105 (42%) were females(table-1)

In complete blood count, the mean WBCs value of cases and control were 16632.34±7339.94 and 9928.243596.45 respectively with a p-value of 0.00 at a 95% confidence interval. The mean RBCs value of cases and control were 4570952±805343.20 and 4611941±754226.98 with a p-value of 0.628. For hemoglobin, cases and control values were 13.14±2.24 and 12.26±2.07 with a p-value of 0.00, for HCT, MCV, MCH and MCHC no marked difference was observed between the two study groups. The mean platelet value of cases and controls were 270823±108763.85 and 344594.48±517810.54 respectively with a p-value of 0.70. The mean differential leukocyte value of neutrophils and lymphocytes were 87.79±7.36, 8.46±6.09 for cases and 65.85±11.99, 26.40±10.36 for control with a p-value of 0.00 and 0.00 respectively.

Mean values of biochemical parameters including ALT, ALP, bilirubin, urea, and creatinine were 49.47±100.08, 114.43±64.71, 0.53±0.36, 70.58±41.89, 1.31±1.12 for cases and 36.43±20.39, 106±36.80, 0.65±0.35, 39.56±33.15, 0.83±0.67 for control respectively with p-values 0.09, 0.66, 0.01, 0.00, 0.00 respectively at 95% of confidence interval (table-2)

Table 1: Gender-based distribution of COVID-19 patients and control group

| Gender | COVID-19 Positive group | Control group | Total |
|---|---|---|---|
| Male | 97 (57.6%) | 65 (38%) | 162 (48%) |
| Female | 73(43) | 105(62%) | 178 (52%) |
| Total | 170 (100%) | 170 (100%) | 340(100%) |

Table 2: Comparison for biochemical and hematological parameters between COVID-19 group and control group

| Parameters | COVID-19 Positive group (n=170) | | Control group (n=170) | | P- value | T-test |
|---|---|---|---|---|---|---|
| | Mean | Standard deviation | Mean | Standard deviation | | |
| White blood cells (/ul) | 16632.34 | 7339.94 | 9928.24 | 3596.45 | 0.00 | 10.69 |
| Red blood cells (/ul) | 4570952 | 805343.20 | 4611941 | 754226.98 | 0.628 | -0.48 |
| Hemoglobin (g/dl) | 13.14 | 2.24 | 12.26 | 2.07 | 0.00 | 3.77 |
| Platelets (/ul) | 270823 | 108763.85 | 344594.48 | 517810.54 | 0.70 | -1.81 |
| Percent neutrophil | 87.79 | 7.36 | 65.85 | 11.99 | 0.00 | 20.34 |
| Percent lymphocytes | 8.46 | 6.09 | 26.40 | 10.36 | 0.00 | -19.61 |
| Alkaline transaminases (u/l) | 49.47 | 100.08 | 36.43 | 20.39 | 0.09 | 1.66 |
| Alkaline phosphatases (u/l) | 114.43 | 64.71 | 106 | 36.80 | 1.32 | 1.509 |
| Urea (mg/dl) | 70.58 | 41.89 | 39.56 | 33.15 | 0.00 | 7.57 |
| Creatinine (mg/dl) | 1.31 | 1.12 | 0.83 | 0.67 | 0.00 | 1.31 |
| Bilirubin (mg/dl) | 0.53 | 0.36 | 0.65 | 0.35 | 0.01 | 3.03 |

## DISCUSSION

In this study, complete blood count was performed both on patients and the control group. In complete blood count, the important parameters are Hemoglobin, platelets, leukocytes, and types of leukocytes. The mean value of hemoglobin was increased in COVID patients than the control group with p-value less than 0.05 (0.00). This may be due to compensatory erythropoiesis during hypoxia. The mean value of hemoglobin in COVID patients was within the normal range. In the current study, most patients have mild to moderate signs and symptoms, therefore, have a normal level of hemoglobin. A previous study reported a reduced level of hemoglobin as most of the patients were aged and severely infected.[11] In addition, moderately infected patients have no anemia.[12]

The current study reported marked leukocytosis which is statistically significant with p- values less than 0.05. The findings of this study is similar to the study conducted by Amir et al. in Iran[13] COVID-19 infection is associated with lung injury and the release of cytokines including tumor necrosis factor.[14] Tumor necrosis factor is a strong chemotactic factor that attracts leukocytes towards the site

of injury and acts on bone marrow, leading to leucopoiesis.[15]

Neutrophilia is another important prognostic and diagnostic predictor of the current study which was statistically significant. The findings of the current study were parallel with a study conducted by Anupam et.al that shows neutrophilia with left shift myeloid cells.[16] The immunopathology of COVID-19 is not fully understood. However recent studies reveal that COVID-19 attack on the epithelial lining of respiratory mucosa causes the increased secretion of cytokines and chemokines like IL-1B, IL-6, IL-8 and Interferon-Gamma (cytokine burst). These chemical mediators act upon neutrophilic progenitor/precursor cells causing their increased proliferation and differentiation that leads to neutrophilia.[17] Our results showed marked lymphopenia which was statistically significant. These findings are similar to a retrospective analysis performed by Hongmei et al. showed marked lymphopenia in COVID-19 patients.[18] COVID-19 virus may attack lymphocytes and destroy its component which results in a reduced number of lymphocytes in the peripheral blood.[19]

In this study renal function (RFTs) tests including urea and creatinine were performed which were statistically significant as the p-values were less than 0.05. These findings were supported by a study conducted by Luwen et al.[20] COVID-19 virus directly invades renal parenchymal cells through ACE2 receptors that lead to protein leakage, tubular necrosis, glomerulopathy and impairment of mitochondria leads to impaired renal function.[21] Recent literature also suggests that SARS-CoV-2 can also invade target cells by CD147 that plays a role in several kidney diseases through immune-mediated responses and deregulated cell cycle. In the kidney, CD147 is highly expressed on the cell surface of proximal tubular epithelium upon which COVID-19 enter into the cells and cause renal damage.[21] Other studies show that abnormal RFTs in COVID-19 patients are due to maladaptive systemic inflammatory immune response, cytokines release syndrome and micro thrombosis in a renal circulation that leads to acute kidney impairment.[22]

In this study liver function was also evaluated through liver enzymes including ALT and ALP. The mean values for ALT and ALP were high in COVID patients but were not statistically significant. A study conducted by Safiya et al. shows a marked increase in ALT and ALP in COVID-19 positive patients.[23] According to Guan et al. elevated LFTs are due to damage hepatic cells of the liver in COVID patients.[24] Other studies suggested that liver injury during COVID-19 infection is because of hypoxic hepatitis that leads to abnormal liver function tests.[25] Furthermore, overexpression of ACE2 receptors on hepatocytes and cholangiocytes also induce cytopathic effect leading to elevated ALT and ALP levels in the blood.[26] Moreover, inflammatory reactions during COVID-19 infection may add to liver injury. Cytokines that are IL-1, IL-6 and tumor necrosis factor develop cytokines storm that leads to hepatocellular immune-mediated damage due to viral-induced cytotoxic T-cell.[27]

## CONCLUSION

It is concluded COVID-19 infection affects hematological parameters including total leukocytes count, hemoglobin and percent neutrophils. In addition, it also affects biochemical parameters including ALT, AST, urea and creatinine. Therefore, these parameters can be used collectively as a predictor of COVID-19 infection. As these parameters vary with the severity of infection, therefore, can also be used for the prognostic purpose.

## REFERENCES


1. Martins-Chaves RR, Gomes CC, Gomez RS. Immunocompromised patients and coronavirus disease 2019: a review and recommendations for dental health care. Brazilian oral research. 2020;34.
2. Frater JL, Zini G, d'Onofrio G, Rogers HJ. COVID-19 and the clinical hematology laboratory. International journal of laboratory hematology. 2020;42:11-8.
3. Saeed U, Sherdil K, Ashraf U, Younas I, Butt H, Ahmad S. Identification of potential lockdown areas during COVID-19 transmission in Punjab, Pakistan. Public health. 2021;190:42-51.
4. Singhal T. A review of coronavirus disease-2019 (COVID-19). The indian journal of pediatrics. 2020;87(4):281-6.
5. Vella F, Senia P, Ceccarelli M, Vitale E, Maltezou H, Taibi R, et al. Transmission mode associated with coronavirus disease 2019: a review. Health. 2020;1:2.
6. Ivanov V, Ivanova S, Niedzwiecki A, Rath M, Niedzwiecki A. Effective and safe global public health strategy to fight the COVID19 pandemic: Specific micronutrient composition inhibits Coronavirus cell-entry receptor (ACE2) expression. J Cellular Medicine and Natural Health. 2020.
7. He F, Deng Y, Li W. Coronavirus disease 2019: What we know? Journal of medical virology. 2020;92(7):719-25.
8. Mitra P, Suri S, Goyal T, Misra R, Singh K, Garg M, et al. Association of comorbidities with coronavirus disease 2019: a review. Annals of the National Academy of Medical Sciences (India). 2020.
9. Huang D, Yang H, Yu H, Wang T, Chen Z, Yao R, et al. Diagnostic Value of Hematological and Biochemical Parameters Combinations for Predicting Coronavirus Disease 2019 (COVID-19) in Suspected Patients. The American Journal of the Medical Sciences. 2021.
10. Najim RH. Biochemical and hematological parameters as a predictor for COVID-19 infection in 65 patients diagnosed by real time? PCR in Kirkuk city. Systematic Reviews in Pharmacy. 2020;11(5):797-9.
11. Benoit JL, Benoit SW, de Oliveira MH, Lippi G, Henry BM. Anemia and COVID-19: A prospective perspective. Journal of medical virology. 2020.
12. Henry BM, De Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM). 2020;58(7):1021-8.
13. Norooznezhad AH, Eskandarion S, Akbari R, Alimohammadi S, Nabavian SM, Giti S, et al. Changes of leukocytes, neutrophils, and lymphocytes count and dependent variables in pregnant women with coronavirus disease 2019 before and after cesarean delivery. Journal of Medical Virology. 2021;93(2):664-6.
14. Zabaneh ID, Fonseca PK, Prime JT, Alla SB. Severe leukocytosis and cytokine storm in a patient with covid-19 pneumonia. World Journal of Advanced Research and Reviews. 2021;9(3):215-7.
15. Lee S-J, Maza PAMA, Sun G-M, Slama P, Lee I-J, Kwak J-Y. Bacterial Infection-Mimicking Three-Dimensional Phagocytosis and Chemotaxis in Electrospun Poly (ε-caprolactone) Nanofibrous Membrane. Membranes. 2021;11(8):569.

16. Attiyah S, Elsayed H, Al-Mughales J, Moharram A, Abdel-Fattah M. Critical cases of COVID-19 patients can be predicted by the biomarkers of complete blood count. Indian Journal of Science and Technology. 2021;13(48):4739-45.
17. Xiong Y, Liu Y, Cao L, Wang D, Guo M, Jiang A, et al. Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. Emerging microbes & infections. 2020;9(1):761-70.
18. Zhang H, Cao X, Kong M, Mao X, Huang L, He P, et al. Clinical and hematological characteristics of 88 patients with COVID-19. International journal of laboratory hematology. 2020;42(6):780-7.
19. Xu PP, Tian RH, Luo S, Zu ZY, Fan B, Wang XM, et al. Risk factors for adverse clinical outcomes with COVID-19 in China: a multicenter, retrospective, observational study. Theranostics. 2020;10(14):6372.
20. Wang L, Li X, Chen H, Yan S, Li D, Li Y, et al. Coronavirus disease 19 infection does not result in acute kidney injury: an analysis of 116 hospitalized patients from Wuhan, China. American journal of nephrology. 2020;51(5):343-8.
21. Su H, Yang M, Wan C, Yi L-X, Tang F, Zhu H-Y, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney international. 2020;98(1):219-27.
22. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. The Lancet Respiratory Medicine. 2020;8(7):738-42.
23. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. Jama. 2020;323(20):2052-9.
24. Yazar H, Kayacan Y, Ozdin M. De Ritis ratio and biochemical parameters in COVID-19 patients. Archives of Physiology and Biochemistry. 2020:1-5.
25. Li Y, Xiao SY. Hepatic involvement in COVID-19 patients: Pathology, pathogenesis, and clinical implications. Journal of medical virology. 2020;92(9):1491-4.
26. Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19. Hypertension Research. 2020;43(7):648-54.
27. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The lancet. 2020;395(10229):1033-4.