DOI: https://doi.org/10.53350/pjmhs221611054

ORIGINAL ARTICLE

Levels of Electrolytes, Troponin and association of O_2 saturation with D–Dimer and Ferritin in hospitalized COVID-19 patients

MUHAMMAD ABBAS[1], AZIZ UR REHMAN[2], ZAHOOR AHMAD[3], SULEMAN KHAN[4], SALIH NOOR[5], RABIA MAZHAR[6], MUHAMMAD UBAID[7], Hussain Ahmad[4]
[1, 2, 3, 7]Khyber Medical University Institute of Paramedical Sciences Peshawar Pakistan
[4]Department of Health and biological sciences Abasyn University Peshawar Pakistan
[5]Lecturer surgical department at Pakistan instituted of medical and management sciences warsak Road Peshawar
[6]MS-Microbiology and Molecular Genetics, University of Punjab
Corresponding author: Mr. Aziz Ur Rehman. E-mail: azizrehmanktk45@gmail. Contact: +92331-9067739

ABSTRACT
A cluster of atypical pneumonia cases were reported in Wuhan china at the end of 2019. The disease was subsequently named covid-19. Later on it spread across the globe and WHO declared it as greatest pandemic of 21st century. Previous studies show that majority of the patients have hyponatremia, hypokalemia and hypochloremia. Recent study also suggests that the value of D-Dimer, ferritin and troponin I increasewhile O_2 saturation drops in covid-19 patients.A cross sectional observational study was carried out in Peshawar Pakistan. A total of 195 patients above 18 years of age, confirmed through real time PCR were studied. Most of the patients have normal levels of electrolytes (Reference range of sodium 135-150mmol/L, potassium 3.5-5.1mmol/L, chloride 96-112mmol/L)while the patients with abnormal levels includedhyponatremic patients (having sodium level less than 135mmol/L), hyperkalemic patients (having potassium level higher than 5.1mmol/L) and hypochloremic patients (having chloride level less than 96mmol/L). The abnormal level of electrolytes is due to renal abnormalities. An association of O_2 saturation exists with ferritin and D-Dimer. The level ofTroponin I raisestwofold in COVID-19 patients, which is an important circulatory biomarker associated with myocardial injury.
Key words: COVID-19, Electrolyte imbalance, O_2 saturation, Troponin I, D-Dimer

INTRODUCTION
In the month of December 2019 a series of atypical acute respiratory pneumonia cases were reported in “Wuhan” China. Latter on it spread globally and due to excessive increase in the number of new cases WorldHealth Organization (WHO) in the mid of march 2020, declared this as a greatest global pandemic of the 21st century(1, 2).The novel corona virus was named as Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) due to high similarity with Severe Acute Respiratory Syndrome Corona Virus family(3). According to World Health Organization a total of 146 million cases and 3.09 million deaths reported till April 2021.Corona viruses are enveloped, icosahedral, large viruses with 80-220nm in diameter having spike like projection on their membranes giving them the shape of crown and hence they named corona. Corona virus belongs to family coronaviridae, sub family orthocoronavirinae, and genus betacoronavirus. Corona virus consists of single stranded, positive sense, non segmented RNA genome ranging from 26-33kb in size(4). The route of transmission of this novel corona virus is directly from human to human through droplets, aerosols and indirectly through contaminated objects. Studies suggest that bats are the primary sources while pangolins are the intermediate host of the corona virus(5).

The patients with COVID-19 commonly present cough, fever, dyspnea, myalgias, diarrhea, nausea and vomiting(6).Death rate varies from region to region for unknown reason. The most challenging task in minimizing the death rate is the uncertain nature of the disease. In early stages of the diseases the patient may show mild or no sign and symptoms but the severity of the disease rapidly increases during the latter stages or the process of recovery(7).Studies suggest that the severity of COVID-19 is associated with the low levels of electrolytes particularly Hypokalemia, Hyponatremia and Hypocalcaemia. This low electrolytes levels is due to variation Rennin Angiotensin Aldosterone pathway which is responsible for electrolytes balance and blood pressure regulation(8, 9). Angiotensin converting enzyme 2 (ACE 2) is a known cellular entry receptor for SAR COV-2 spike complex. Upon binding to ACE 2 receptor many metabolic disorders occurs due to electrolytes imbalance(10).The investigation of the arterial blood gases is crucial for the monitoring of acid base balance, effective gaseous exchange and normal voluntary control ofthe respiration (7).Oxygen saturation have a negative association with D-Dimer levels, patients having low oxygen saturation will have higher d-dimer levels and vice versa (12).The levels of D-Dimer are profoundly high in all severe patients and the patients who died due to COVID-19 as compared those who survived (13).Ferritin is an important biomarker in the diagnosis and prognosis of COVID-19 infection. Studies show that the level of ferritin in non survivors is predominantly higher than the patients who survived,Co-morbidity like diabetes, acute liver injury and cancer also play an important role in amplification of ferritin level(14, 15). The elevated troponin I was found in 51% of the patients in which poor outcomes were approximately 8 times higher than the patients with better outcomes due to disturbed oxygen supply and demand(16). ElevatedTroponin I, a biochemical marker of myocardial injury, is the most common finding in COVID-19 patient and is independently associated with cardiovascular abnormalities,severity and mortality of the patients(17).

In one study only potassium level was studied and correlated with 30 days mortality rate(7).Pooled analysis was done in which there was no heterogeneity observed in calcium level (11).Most of the research papers studied only one parameter and their correlation with severity and mortality.Some studies had very limited sample size and

were conducted for a very short period of time in emergency department. Therefore the main objectives of this cross sectional study is to determine level of electrolytes, Troponin I, ABGs, D-dimer, ferritinand the correlation of Oxygen saturation with ferritin and D-Dimer in SARS-COV-2 patients.

MATERIALS AND METHODS

A cross sectional observational study was carried out at Lady Reading Teaching Hospital Peshawar from December 2020 to April 2021. A total of 195 samples were collected from COVID-19 patients. The study contains 58.5% men and 41.5% women above the age of 18. Ethical approval was taken from Khyber Medical University ethical and research committee.All of the patients included in our study were confirmed through Real Time Qualitative Polymerase Chain Reaction (RT-PCR). The samples for Electrolytes, troponin I and ferritin analysis were collected in heparin tube, while the samples for D-Dimer were collected in sodium citrate tube and their analysis was performed on Cobas c501 chemistry analyzer. For oxygen saturation Arterial blood Gases from artery were taken in 5ml syringe and immediately sent to laboratory for rapid investigation within 10 minutes.

The patients with typical signs, symptoms and positive PCR test were selected for the study. Both suspected and infected hospitalized patients were included.

Patients with chronic renal, heart diseases, pneumonia of other diseases and Diabetes mellitus were excluded from the study. The patients who refused to take part in the research and those patients who lost to follow up or discharged from the hospital were also excluded from the study.

For data analysis SPSS version 22 was used. For descriptive statistics frequencies were determined and presented in tabulated form while independent sample T test was applied for troponin I. An association of O_2 saturation with ferritin and D-Dimer was determined by Pearson correlation.

RESULTS

A total of 195 patients were included in this study in which 114 (58.5%) were male and 81 (41.5%) female with a ratio was 1.407:1.The samples were classified into three age groups, 27 patients were of 18-40(13.84%) years, 135 patients were of 41-70 (69.23%) years and 34 (17.43%) patients were above 70 years of age. Mean and standard deviation of age was found to be 57.52 ±14.58 (Table 1). The common clinical manifestation included fever, cough, dyspnea, myalgias, diarrhea, nausea and vomiting.

Table 1Gender based distribution of COVID-19 patients

Gender	COVID-19 positive	Percentage (%)
Male	114	58.5
Female	81	41.5
Total	195	100

Table 2 Descriptive statistics of biochemical parameters

Parameters	Mean Statistic	Std. Deviation Statistic
Sodium	135.60mmol/L	12.38
Potassium	4.64mmol/L	1.04
Chloride	98.99mmol/L	10.59
Ferritin	1077.73ng/mL	657.19
PH	6.66	2.17
PCO_2	39.61mmHg	21.33
PO_2	73.16mmHg	47.88
HCO_3	20.92mmol/L	8.99
Base excess	-1.97mmol/L	5.54
O_2 saturation	79.63%	29.10
Troponin	0.88ng/L	3.48
D-Dimer	2012.51µg/L	2394.18
Valid N (list wise)		

Table 3 Descriptive statistics of electrolytes

Electrolytes	Lower range	Normal	Upperrange	Total cases
Sodium	73 (39.8%)	102 (55.73%)	8 (4.37%)	183
Potassium	17 (9.28%)	114 (62.29%)	52 (28.4%)	183
Chloride	58 (31.69%)	112 (61.20%)	13 (7.1%)	183

Table 4 Pearson correlation of ferritin and O_2 saturation

		Ferritin	O_2 saturation
Ferritin	Pearson Correlation	1	-0.011
	Sig. (2-tailed)		0.9
	N	150	111
O_2 saturation	Pearson Correlation	-0.011	1
	Sig. (2-tailed)	0.9	
	N	111	136

Table 5 Pearson correlation of D-Dimer and O_2 saturation

		O_2 saturation	D Dimer
O_2 saturation	Pearson Correlation	1	-0.138
	Sig. (2-tailed)		0.3
	N	136	54
D Dimer	Pearson Correlation	-0.138	1
	Sig. (2-tailed)	0.3	
	N	54	63

Table 6 One sample T Test of Troponin I

	N	Mean	Std. Deviation	Std. Error Mean
Troponin I	35	1.43	4.37	0.74

The mean value and standard deviation of sodium, potassium, chloride and ferritin was 135.60±12.38mmol/L, 4.64±1.04mmol/L, 98.99±10.59mmol/L, 1077.73±657.19ng/mL respectively, and that of ph, pCO_2, pO_2, HCO_3, Base excess, O_2 saturation, troponin-1 and D-Dimer was 6.65±2.16, 39.61±21.33mmHg, 73.16±47.87mmHg, 20.92±8.99mmol/L, -1.97±5.54mmol/L, 79.63±29.10%, 0.88±3.48ng/mL, 2012.51±2394.18µg/L respectively (table 2). A total of 183 patients were studied in which hyponatremia, hyperkalemia and hypochloremia were independently associated with COVID-19 patients (table 3).

The 2 tailed Pearson correlation between ferritin and oxygen saturation of p-value (-0.011) shows a weak negative correlation in COVID-19 patients (table 4). The 2 tailed Pearson correlation between D-Dimer and O_2 saturation of p-value (-0.138) also shows a weak negative correlation in COVID-19 patients (table 5). The independent sample T test was applied on troponin I with mean and standard deviation of 1.43±4.37ng/mL

respectively and significant 2 tailed p value of 0.269 and 95% confidence interval (table 6 and 7).

Table 7 One sample T test of troponin I

	Test Value = 0.6					
					95% Confidence Interval of the Difference	
	T	Df	Sig. (2-tailed)	Mean Difference	Lower	Upper
Troponin I	1.12	34	0.27	.83	-.67	2.33

DISCUSSION

In this cross sectional study an association was determined among the biochemical parameters in COVID-19 patients. Out of 183 COVID-19 patients, hyponatremia was found in 73(39.8%) patients, hypokalemia in 17 (9.28%) patients and hypochloremia in 58 (31.69%) patients. Normal levels of sodium, potassium and chloride was found in 102 (55.73%), 114 (62.29%) and 112 (61.2%) patients respectively. Hypernatremia was found in 8 (4.37%) patients, hyperkalemia in 52 (28.4%) patients and hyperchloremia in 13 (7.1%) patients. The current study show o

oa decrease in sodium and chloride level in COVID-19 patients while in contrast to other studies potassium is increased in 28.2% of the total patients.Other studies reported hypokalemia and hyponatremia in 50% ofCOVID-19 patients that can be correlated with renal abnormalities(18). Alfano G et.al in his study reported a mild decrease in potassium level in 41% of the patients which is in contrast to this study(19).

The Pearson correlation between O_2 saturation and ferritin was -0.011 with a P value 0.9 at 95% confidence interval. There is weak negative correlation between O_2 saturation and ferritin which is not statistically significant. The study shows that O_2 saturation is inversely related to the level of ferritin in COVID-19 patients. As the O_2 saturation drops, the hypoxic condition develops which enhance the level of ferritin in order to cope with the low O_2 saturation. Hippchen T and Lin Z et.al through hisretrospective cohort study predicted that the severity of COVID-19 is directly associated withhyperferritinemia. High level and disturbed metabolism of serum ferritin not only predict the severity of COVID-19 patients but it also leads to lung injury(20, 21).In another study, it was reported that ferritin level increased based on the severity of the patient that is from mild to severe cases. (22).The periodic regulation of ferritin plays a vital role in host regulatory system. In addition to its homeostatic role, it is also a key biomarker ofdeveloping inflammatory disease, its prognosisand plays a role in native immune response through its signaling pathway (23).

The Pearson correlation between O_2 saturation and D-Dimer was -0.138 with a P value 0.3. A weak negative correlation exists between O_2 saturation and D-Dimer which is not statistically significant. Elevation of D-Dimer with decreased value of O_2 saturation was also a significant finding of this study. D-Dimer is a degradation product of fibrin which is normally undetectable or present in a very low amount in the blood. A high D-Dimer value indicates a significant blood clot formation and break down in the body(24).Study conducted by Yao Y et.al also show that along its association with disease severity D-Dimer is also a good predictive marker for deaths in hospitalized COVID-19 patients (25).A high D-Dimer level and low O_2 saturation may have serious adverse effect on the lungs(12).In the previous studies it has been found that 50% of COVID-19patients with high D-Dimer values have low survival rate because of heavy blood clot formation in pulmonary arteries(26).

Two tailed one sample T test was applied on troponin I as its sample size was less than 50. The mean and standard deviation of Troponin I was 1.43±4.37 with P value was 0.27 which is not statistically significant.It has been found from this research, that the value of troponin I increases 2 times from its normal range in covid-19 patients which mean SARS COV-2 have severe effect on the cardiac muscles of the heart.Troponin is an important circulatory biomarker that is normally undetectablein healthy person. Troponin complex consist of three protein involving troponin I, troponin C, troponin T. Troponin I is an inhibitory protein that is particularly released due to myocardial injury. Elevatedtroponinlevelsplay a vital role in the detection very minor myocardial injuries includingacute and chronic heart failure, necrosis of the heart muscles, damage due to inflammatory mediators and many more(27, 28).Manocha KK et. al in his observation cohort study concluded thathospitalized COVID-19 patients commonly have elevated troponin I levels which is an important indicator for in-hospital mortality in a month (29).Özyılmaz S et.al retrospectively reviewed medical records of COVID-19 patients and reported that the patient with troponin I levels higher than 7.8pg/ml was an important risk factor for in-hospital mortality.Hospitalized patients having troponin I level higher than 7.8pg/ml had mortality rate of 33% while the patient having troponin I levels less than 7.8pg/ml had mortality rate of 2.4%(30). Similarly Shi et.al reported 51.2% mortality rate in patients having high troponin levels (31).

CONCLUSION

Majority of the COVID-19 patients have normal electrolytes level while 39.8% of the patients have low sodium level, 28.4% have higher potassium level and 31.69% have low chloride levels. In COVID-19 patient sodium and chloride decreases from its normal level, while potassium increases. Abnormal electrolyte levels are mainly associated withrenal abnormalities. Patients with normal electrolyte level have no indication of renal injury while patients having abnormal levels of electrolytes indicate renal injury. As the oxygen saturation drops the level of ferritin and D-Dimer raises. With amplification of ferritin level the severity of disease increases, while due to high value of D-Dimer the mortality rate raises up to 50% in hospitalized COVID-19 patients. Hence the level of ferritin and D-Dimer can be used for predicting the severity and prognosis of COVID-19 patients. It has also been found from this study that troponin I is 2 times increased inCOVID-19 patients which shows myocardial injury.

Limitations: In this cross sectional study only hospitalized COVID-19 patients were studied.

All the parameters studied were not clinically correlated with other diseases that elevates.

Severe and non severe patients were not differentiated.

Acknowledgement: First of all we would like to thank to our respected supervisor MR. AsifZeb for his continuous support, motivation, enthusiasm and encouragement throughout research project. We are very grateful to LRH staff for their kind behavior especially senior phlebotomist Mr. Murtaza Malik and Mr. Iraq Shah for helping us in collection of the sample and data retrieval. We are also very thankful to Mr. Farooq Nawaz for cooperating in the sample processing and analyzing.

Conflict of interest: The author declares no conflict of interest.

Funding: This research is not funded by any government or non-government organizations.

Abbreviations

SARS-COV-2Severe Acute Respiratory Syndrome Corona Virus-2

RNARibonucleic acid

COVID-19Corona Virus Disease 2019

ACE-2Angiotensin converting enzyme 2

ABGsArterial Blood Gases

PCRPolymerase Chain Reaction

REFERENCES

1. De Carvalho H, Richard MC, Chouihed T, Goffinet N, Le Bastard Q, Freund Y, et al. Electrolyte imbalance in COVID-19 patients admitted to the Emergency Department: a case–control study. Internal and Emergency Medicine. 2021:1-6.
2. Roy S, Dutta P, Panesar S, Goyal P, Lal S, Jana P. Role of Arterial Blood Gas Analysis in Rapid Assessment of Hypokalaemia in Covid–19.
3. Lakhani J, Kapadia S, Pandya H, Gill R, Chordiya R, Muley A. Arterial Blood Gas Analysis of Critically Ill Corona Virus Disease 2019 Patients. Asian Journal of Research in Infectious Diseases. 2021:51-63.
4. Sawicki S, Sawicki D. Coronavirus transcription: a perspective. Coronavirus replication and reverse genetics. 2005:31-55.
5. Bal A, Agrawal R, Vaideeswar P, Arava S, Jain A. COVID-19: an up-to-date review–from morphology to pathogenesis. Indian Journal of Pathology and Microbiology. 2020;63(3):358.
6. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of COVID-19 in New York city. New England Journal of Medicine. 2020;382(24):2372-4.
7. Liu S, Zhang L, Weng H, Yang F, Jin H, Fan F, et al. Association Between Average Plasma Potassium Levels and 30-day Mortality During Hospitalization in Patients with COVID-19 in Wuhan, China. International Journal of Medical Sciences. 2021;18(3):736.
8. Tezcan ME, Dogan Gokce G, Sen N, Zorlutuna Kaymak N, Ozer RS. Baseline electrolyte abnormalities would be related to poor prognosis in hospitalized coronavirus disease 2019 patients. New Microbes New Infect. 2020;37:100753.
9. Lim JH, Jung HY, Choi JY, Park SH, Kim CD, Kim YL, et al. Hypertension and Electrolyte Disorders in Patients with COVID-19. Electrolyte & blood pressure : E & BP. 2020;18(2):23-30.
10. Sarvazad H, Cahngaripour S, Roozbahani NE, Izadi B. Evaluation of electrolyte status of sodium, potassium and magnesium, and fasting blood sugar at the initial admission of individuals with COVID-19 without underlying disease in Golestan Hospital, Kermanshah. New Microbes and New Infections. 2020;38:100807.
11. Lippi G, South AM, Henry BM. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Annals of clinical biochemistry. 2020;57(3):262-5.
12. Yalçin KS, Kasapoglu B, Alanli R, Küçükay MB, Kosar A. The association of oxygen saturation, tomography findings and d-dimer levels in coronavirus disease 2019 patients. Blood Coagulation & Fibrinolysis. 2020;31(8):558-61.
13. Shah S, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, et al. Elevated D-dimer levels are associated with increased risk of mortality in coronavirus disease 2019: a systematic review and meta-analysis. Cardiol Rev. 2020.
14. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. Journal of clinical laboratory analysis. 2020;34(10):e23618.
15. Vargas-Vargas M, Cortés-Rojo C. Ferritin levels and COVID-19. Revista Panamericana de Salud Pública. 2020;44:e72.
16. Malik P, Patel U, Patel NH, Somi S, Singh J. Elevated cardiac troponin I as a predictor of outcomes in COVID-19 hospitalizations: a meta-analysis. Infez Med. 2020;28:500-6.
17. Lombardi CM, Carubelli V, Iorio A, Inciardi RM, Bellasi A, Canale C, et al. Association of troponin levels with mortality in Italian patients hospitalized with coronavirus disease 2019: results of a multicenter study. JAMA Cardiol. 2020;5(11):1274-80.
18. Hong X-w, Chi Z-p, Liu G-y, Huang H, Guo S-q, Fan J-r, et al. Analysis of early renal injury in COVID-19 and diagnostic value of multi-index combined detection. MedRxiv. 2020.
19. Alfano G, Ferrari A, Fontana F, Perrone R, Mori G, Ascione E, et al. Hypokalemia in Patients with COVID-19. Clinical and experimental nephrology. 2021;25(4):401-9.
20. Hippchen T, Altamura S, Muckenthaler MU, Merle U. Hypoferremia is Associated With Increased Hospitalization and Oxygen Demand in COVID-19 Patients. Hemasphere. 2020;4(6):e492-e.
21. Lin Z, Long F, Yang Y, Chen X, Xu L, Yang M. Serum ferritin as an independent risk factor for severity in COVID-19 patients. Journal of Infection. 2020;81(4):647-79.
22. Gandini O, Criniti A, Ballesio L, Giglio S, Galardo G, Gianni W, et al. Serum Ferritin is an independent risk factor for Acute Respiratory Distress Syndrome in COVID-19. J Infect. 2020;81(6):979-97.
23. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol. 2017;29(9):401-9.
24. Weitz JI, Fredenburgh JC, Eikelboom JW. A Test in Context: D-Dimer. Journal of the American College of Cardiology. 2017;70(19):2411-20.
25. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. Journal of intensive care. 2020;8(1):1-11.
26. Alonso-Fernández A, Toledo-Pons N, Cosío BG, Millán A, Calvo N, Ramón L, et al. Prevalence of pulmonary embolism in patients with COVID-19 pneumonia and high D-dimer values: A prospective study. PLoS One. 2020;15(8):e0238216.
27. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure: prevalence, mechanisms, and clinical implications. Journal of the American College of Cardiology. 2010;56(14):1071-8.
28. Agewall S, Giannitsis E, Jernberg T, Katus H. Troponin elevation in coronary vs. non-coronary disease. European heart journal. 2011;32(4):404-11.
29. Manocha KK, Kirzner J, Ying X, Yeo I, Peltzer B, Ang B, et al. Troponin and Other Biomarker Levels and Outcomes Among Patients Hospitalized With COVID-19: Derivation and Validation of the HA2T2 COVID-19 Mortality Risk Score. J Am Heart Assoc. 2021;10(6):e018477.
30. Özyılmaz S, Ergün Alış E, Ermiş E, Allahverdiyev S, Uçar H. Assessment of the relationship between mortality and troponin I levels in hospitalized patients with the novel coronavirus (COVID-19). Medicina. 2020;56(12):693.
31. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-10.