Clinical and Biochemical Characteristics of COVID-19 Patients During the Delta-Omicron Wave with Risk Assessment of Adverse Outcomes

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ABSTRACT

Objective: To compare clinical and biochemical characteristics of hospitalised COVID-19 patients and risk assessment of disease outcomes

Study Design: Descriptive study.

Place and Duration of the Study: Department of Pathology, Dow International Medical College and Sindh Infectious Diseases Hospital and Research Centre, from January to March 2022

Methodology: *SARS CoV-2* PCR-positive hospitalised patients were enrolled. Delta or omicron variants infected patients were followed till the last recorded event of hospitalisation. After a detailed history, clinical and biochemical profiles were recorded during the hospitalisation. Length of hospitalisation, ICU admission and in-hospital mortality were taken as outcomes and odd ratios were calculated.

Results: During the study period, omicron was the predominant *SARS CoV-2* variant. Omicron-infected patient were older (67 *vs.* 62 years) and had a significantly shorter duration between appearance of symptoms and hospitalisation (5 *vs.* 8 days), when compared with the delta patients. Median values of LDH, ferritin and TLC were significantly higher in delta patients ($p<0.05$). Delta infected patients have a 3.9 times more risk of prolonged hospital stay. In patients with increased TLC, the risk of prolonged hospitalisation and ICU admission was found 16% and 23%, respectively. However, the aOR for ICU admission and in- Hospital mortality were not found significant for the delta and omicron–infected patients.

Conclusion: The clinical course and biochemical profiles are diverse in delta and omicron patients. Hospitalised patients with omicron infection exhibit shorter stays. High values of TLC are found associated with an increased risk of longer hospital stay and ICU admissions.

Key Words: *COVID-19, Delta variant, Omicron variant, Hospitalised patients, Outcomes, In-hospital mortality, Biochemical markers, Clinical severity.*

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INTRODUCTION

SARS CoV-2 has shown marked genetic variations over a short period.[1] To date, five variants of concern are responsible for the major burden of the COVID-19 pandemic. The emerging and fading pattern of these variants has been observed one after the other, with the specific period of a dominant circulating virus type.[2]

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Along with the change in the circulating virus type, the clinical presentation, disease course, and outcomes of COVID-19 have also transformed.[3] Within the evolved variant, the different frequencies of mutations in different populations are also affecting the presentation and severity of disease among them. Moreover, a diverse pattern of inflammatory and biochemical markers has been observed across infected individuals and causative variants.[4]

In the latter half of 2021, the delta variant was found as the dominant circulating variant of *SARS CoV-2*. However, after a short overlapping period of delta and omicron, finally, the omicron variant emerged with numerous mutations and superseded the delta variant very rapidly.[5] Similar findings were observed among COVID-19 affected population in Pakistan. The frequency of emergency unit visits and hospitalisation increased during the third wave of the pandemic.[6,7]

Since the commencement of COVID-19 pandemic, factors affecting the disease pathogenesis, management and progression are widely studied.[8] However; the information about the disease manifestation, its course and outcomes of emerging variants of *SARS CoV-2* are needed to identify the evolved dynamics of COVID-19 in populations. For this reason, the local data about the variants of *SARS CoV-2* and disease should be updated for upcoming waves. Such data is very scanty in Pakistan. This study was aimed to compare the clinical and biochemical characteristics during hospitalisation in patients infected with delta and omicron variants of *SARS CoV-2* and to assess the risk of adverse outcomes in association with the study variables.

METHODOLOGY

It was a prospective descriptive study, carried out at the Pathology Department of Dow International Medical College and Sindh Infectious Diseases Hospital and Research Center of Dow University of Health Sciences. *SARS CoV-2* PCR-positive patients were recruited from January to March 2022 through a purposive technique. The sample size was calculated using PASS software with Cox Regression Power Analysis. For a power of 95% to detect a hazard ratio of 1.67[9] for variants of concerns at the 5% significant level, 100 samples were collected. Pregnant females and children were excluded. From 100 *SARS CoV-2* positive patients, a subgroup of ninety-one patients was enrolled for this study, infected with delta or omicron variants.

After taking informed written consent, a detailed demographic and clinical history was recorded at the time of admission. Length of hospitalisation was calculated from the day of hospitalisation till the last recorded event of hospitalisation (either discharge or leave against the medical advice or death). Clinical and biochemical findings of all patients were recorded on every alternate day starting from the day of hospitalisation till the last event. Total length of hospital stay, ICU admission and in-hospital mortality were taken as outcomes for patients infected with delta or omicron variants of *SARS CoV-2*.

The patient's clinical information including temperature, pulse, respiratory rate, blood pressure, oxygen saturation (SO_2) and need of intensive care was monitored. Study subjects were divided into non-severe, severe and critical clinical groups, according to the national guidelines of COVID-19 severity.[10,11] To obtain biochemical information, a predefined battery of blood tests including blood urea nitrogen (BUN), creatinine (Cr), electrolytes, lactate dehydrogenase (LDH), C- reactive protein (CRP), ferritin, CBC and D-dimer was performed on patients' blood samples. Samples for biochemical analyses were stored at -80°C if not processed immediately. Biochemical parameters were analysed on ADVIA (Siemens Diagnostics). D-dimer and CBC were analysed on Sysmex CS 2500 and XN 9000 by immunoturbidimetric and flow cytometry methods, respectively. Samples were analysed according to manufacturer-provided guidelines. The available results of Pro-calcitonin, Troponin- I and NT- Pro BNP were also recorded from the laboratory information system if requested by primary team.

On all RT-PCR confirmed samples of *SARS CoV-2*, genetic analysis was done through SNPsig® *SARSCoV-2* (EscapePLEX) kit (Primer Design, UK) that targets K417N/T, E484K, and P681R mutations. Samples with E484K, E484K+K417N, E417N, E484K+K417T and P681R mutations were interpreted as alpha, beta, omicron, gamma and delta variants, respectively.

The data were analysed through SPSS version 26. Frequency and percentages were calculated for demographic characteristics, presenting complaints and clinical severity of patients. The normality of data was checked by Shapiro -Wilk test. Mean (±SD) or median (IQR) was calculated for the clinical and biochemical characteristics of patients during hospitalisation. P-Value was calculated through chi-square, independent- t-test and Mann - Whitney tests for categorical, continuous parametric and non-parametric data. Binary logistic regression was used to evaluate the relationship between patients' characteristics and outcomes; length of hospital stay, intensive care admission and in-hospital mortality. The multivariate model was adjusted only for variables with p-values <0.05 in univariate analysis. Results were reported as adjusted odd ratios, 95% confidence interval and p-values. The result was considered significant if the p-value was found <0.05.

RESULTS

On genetic analysis, 96 from 100 samples were identified with *SARS CoV-2* variants. Of these 96 results; 05 (5.2%) variants were non-delta or omicron; 31 (32.3%) and 60 (62.5%) revealed the presence of delta or omicron variant; respectively. Frequencies and percentages of demographic characteristics, presenting complaints and clinical severity of delta and omicron-infected patients (n=91) are shown in Table I. The mean age of patients infected with the omicron variant was found 67 years; higher than the mean age of delta-infected patients (p<0.05). No gender predominance was found in both groups. A history of pre-existing medical conditions was found in 46 (50.5%) study subjects, among them combined hypertension and diabetes mellitus were predominant and found in 22 (47.8%) subjects.

The mean duration of 6±4 days was observed between commencing of symptoms and hospitalisation among all study subjects. However, patients infected with the omicron variant had a shorter mean duration of five days (p<0.05). Among all presenting complaints, fever was the most frequent (91.2%) complaint. History of SO_2 <94%; recorded on pulse oximeters at home was reported by 27 (29.6) patients, among them 5 and 22 patients were infected by delta and omicron variants, respectively (p<0.05). Besides respiratory complaints, the extrapulmonary symptom of diarrhea was found in 04 (12.9%) *versus* 01 (1.7%) patients in delta and omicron-infected patients, respectively (p<0.05). Among study subjects, 39 (42.9%) were critically ill. Patients infected with delta variants experienced more critical disease (51.6%) when compared to omicron infected patients (38.3%).

Table I: Demographics and clinical characteristics of study subjects.

	Total (n=91)	Delta (n=31)	Omicron (n=60)	p-value
Demographics				
Age, years mean (±SD)	66 (13.0)	62 (13.0)	67 (13.0)	0.048*
Male, n (%)	48 (52.7%)	16 (51.6%)	32 (53.3%)	0.876**
Female, n (%)	43 (47.3%)	15 (48.4%)	28 (46.7%)	
COVID Vaccinated, n (%)	26 (28.6%)	7 (22.6%)	19 (31.7%)	0.363**
Comorbidities				
Diabetes, n (%)	4 (8.7%)	1 (5.6%)	3 (10.7%)	0.401**
Hypertension, n (%)	16 (34.8%)	5 (27.8%)	11 (39.3%)	
Diabetes and hypertension, n (%)	22 (47.8%)	9 (50.0%)	13 (46.4%)	
Others, n (%)	4 (8.7%)	3 (16.7%)	1 (3.6%)	
Presenting complaints				
Duration between the appearance of symptoms and hospitalisation, days mean (±SD)	6 (4.2)	8 (4.2)	5 (3.8)	<0.001*
Fever, n (%)	83 (91.2)	29 (93.5)	54 (90.0)	0.571**
Cough, n (%)	80 (87.9)	27 (87.1)	53 (88.3)	0.864**
Flue like symptoms, n (%)	31 (34.1)	7 (22.6)	24 (40.0)	0.097**
Body aches, n (%)	12 (13.2)	5 (16.1)	7 (11.7)	0.551**
Sore throat, n (%)	6 (6.6)	0 (0)	6 (10.0)	0.068**
Difficulty in breathing, n (%)	67 (73.6)	21 (67.7)	46 (76.7)	0.360**
History of SO_2 <94%, n (%)	27 (29.6)	5 (16.1)	22 (36.7)	0.042**
Diarrhea, n (%)	5 (5.5)	4 (12.9)	1 (1.7)	0.026**
Clinical severity				
Non severe, n (%)	36 (39.6%)	10 (32.3%)	26 (43.3%)	0.465**
Severe, n (%)	16 (17.6%)	5 (16.1%)	11 (18.3%)	
Critical, n (%)	39 (42.9%)	16 (51.6%)	23 (38.3%)	

** p-value is calculated from independent-t test, ** p-value is calculated from chi-square test.*

Table II: Clinical and biochemical characteristics and outcomes of study subjects.

	Total (n=91)	Delta (n=31)	Omicron (n=60)	p-value
General Physical Signs				
Temperature ˚F, mean (±SD)	98.5 (2.0)	98.1 (3.3)	98.8 (0.9)	0.090*
Respiratory rate/min , mean (±SD)	26 (4.6)	26 (4.7)	26 (4.6)	0.898*
Pulse/min, mean (±SD)	87 (12.2)	90(10.3)	85(12.8)	0.063*
Systolic BP mmHg, mean (±SD)	128 (12.9)	130(9.4)	127 (14.4)	0.432*
Diastolic BP mmHg, mean (±SD)	77 (8.6)	78(8.3)	76(8.7)	0.326*
Saturation of oxygen %,mean (±SD)	94 (3.8)	95(1.9)	94(4.5)	0.227*
Biochemical Characteristics				
Creatinine mg/dl, median (IQR)	1.06 (0.80 - 1.60)	1. 9(0.8-1.5)	0.9 (0.7-1.9)	0.592***
Blood urea nitrogen mg/dl, median (IQR)	33.6 (22-57.8)	39.1(22.8-27.8)	32.5 (22-61.7)	0.913***
Sodium mEq/L, median (IQR)	141 (138-144)	141(139-144)	141(138-145)	0.808***
Potassium mEq/L, median (IQR)	4.7 (4.3-5.1)	4.7(4.2-5.1)	4.6(4.3-5.0)	0.963***
Chloride mEq/L, median (IQR)	101 (98-105)	100 (97-104)	101(98-105)	0.552***
Bicarbonate mEq/L, median (IQR)	25.4 (22.3-27.8)	25.4 (22.3-27.2)	25.4 (21.6-28.6)	0.558***
C-reactive protein mg/L, median (IQR)	48.4 (24.3-118.7)	46.6 (23.5-120)	48.5(25.5-118)	0.657***
LDH U/L, median (IQR)	429.5 (318.6-654.5)	606 (403-765.2)	390.5(286-543.5)	0.001***
Ferritin ng/ml, median (IQR)	508.8 (267.3-1076)	782.3 (435-1257)	412.0 (215-751)	0.002***
D-Dimer mg/L, median (IQR)	1.9 (0.9-3.4)	2.0(0.9-3.7)	1.8 (0.8-3.4)	0.434***
HB g/dl, median (IQR)	11.8 (10-13.7)	12.5 (10.8-13.8)	11.5 (9.7-13.5)	0.150***
TLC 10^9/L, median (IQR)	11.8 (8.4-15.3)	12.6 (11.0-16.7)	10.7 (8.0-14.1)	0.045***
Neutrophil %, median (IQR)	88 (82-91)	88.4 (84.0-91.1)	87 (81.2-91.8)	0.451***
Lymphocyte %, median (IQR)	7 (4-11)	6.5 (5.3-10.1)	7.1 (4-12.2)	0.654***
Platelets 10^9/L, median (IQR)	257 (187-340)	279(199-424)	256(169-330)	0.317***
Outcomes				
Length of hospital stay, median (IQR)	5.0(3.0-9.0)	11.0(5.0-12.0)	4.0(2.0-7.0)	<0.001*
ICU admission, n (%)				
No	34(37.4)	6(19.4)	28(46.7)	0.011**
Yes	57(62.6)	25(80.6)	32(53.3)	
In-hospital mortality n (%)				
No	62(68.1)	21(67.7)	41(68.3)	0.954**
Yes	29(31.9)	10(32.3)	19(31.7)	

**p-value is calculated from independent-t test, **p-value is calculated from chi-square test, ***p-value is calculated from Mann-Whitney test.*

Table III: Association of variant and patient's characteristics with outcomes.

Characteristics	Prolonged length of stay >5 days aOR (95% CI)	p-value	ICU admission aOR (95% CI)	p-value	In-hospital mortality aOR (95% CI)	p-value
Variant						
Omicron	Ref.		Ref.		Ref.	
Delta	3.95 (1.09-14.26)	0.036	3.15 (0.81-12.15)	0.095	0.84 (0.23-3.06)	0.801
Age	0.96 (0.91-0.99)	0.033	1.00 (0.96-1.04)	0.827	1.06 (0.97-1.05)	0.465
Gender						
Male	Ref.		Ref.		Ref.	
Female	2.26 (0.81-6.33)	0.118	1.15 (0.40-3.36)	0.786	1.70 (0.58-4.98)	0.333
Complaint of diarrhea						
No	Ref.		Ref.		Ref.	
Yes	0.19 (0.01-2.20)	0.186	1.54 (0.12-19.65)	0.739	0.54 (0.04-6.36)	0.627
History of SO_2 <94%						
No	Ref.		Ref.		Ref.	
Yes	1.05 (0.34-3.17)	0.931	4.23 (1.22-14.62)	0.023	2.79 (0.89-8.79)	0.078
Duration between the appearance of symptoms and hospitalisation	0.99 (0.80-1.05)	0.229	1.01 (0.88-1.16)	0.809	0.99 (0.88-1.13)	0.988
Mean Ferritin	1.00 (1.00-1.01)	0.143	1.00 (0.99-1.00)	0.927	1.00 (0.99-1.00)	0.451
Mean LDH	1.00 (0.99-1.00)	0.972	1.00 (0.99-1.00)	0.361	1.00 (0.99-1.00)	0.195
Mean TLC	1.16 (1.03-1.30)	0.011	1.23 (1.06-1.42)	0.007	1.10 (0.97-1.25)	0.138

aOR: Adjusted odds ratio for variables had p-value≤0.050 in univariate analysis; CI: Confidence interval.

During hospitalisation, the clinical and biochemical characteristics of the study subjects are shown in Table II. Besides all predefined battery of laboratory tests, results of troponin I, NT- Pro BNP and procalcitonin of all study subjects were retrieved from the laboratory information system if available. Among the total study subjects (n=91), 55, 64 and 75 patients were tested for troponin I, NT- Pro BNP and procalcitonin, respectively at a certain time during hospitalisation. However, abnormal results were found only in 4 (43.6%), 52 (81.2%), and 16 (21.3%) patients tested for troponin I, NT-Pro BNP and procalcitonin, respectively.

All outcomes of the study including length of hospitalisation, ICU admissions and in-hospital mortality are shown in Table II. The median duration of hospitalisation was observed 11 *vs*. 4 days in delta and omicron subjects, respectively. Among delta-infected patients, 80.6% required intensive care during hospitalisation (p<0.05), when compared with the omicron group.

On comparing the study outcomes multivariate-adjusted model (Table III) showed that the risk of prolonged hospital stay was four times higher (aOR: 3.95, 95% CI 1.09-14.26) in delta patients, when compared with omicron-infected patients. However, no significant risk was observed of ICU admission and in-hospital deaths for both of the groups. Another finding was that the ICU admissions were 4.23 times higher (aOR: 4.23, 95% CI 1.22-14.62) in those study subjects who provided history of SO2 <94% before hospitalisation. Among laboratory markers, a high mean TLC in patients was found associated with the risk of long hospital stay (aOR: 1.16, 95% CI 1.03-1.30) and ICU admissions (aOR: 1.23, 95% CI 1.06-1.42). The risk of in-hospital mortality was not found significant when compared to the selected variables from univariate analysis.

DISCUSSION

Omicron was the most frequently identified variant of *SARS CoV-2* during the study period. The finding of omicron prevalence is in line with the other studies' results carried out during the same period.[12,13] Among various predisposing factors, age is an important variable for the disease outcome.[14] The mean age of the study subjects was 66±13 years; however, the authors did not find any association between the adverse outcomes and the age of the study subjects. In contrast with the delta-infected patients, patients with omicron infection were comparatively older and admitted to the hospital early after the appearance of symptoms. The finding of a shorter duration between the appearance of symptoms and hospitalisation in patients infected with the omicron variant is also reported in a study by Menni *et al*. They noted that the mean duration of acute symptoms and a hospital visit was two days shorter in the omicron-infected patients when compared with the delta patients.[13] The rapid onset of symptoms and exacerbation might be associated with the rapid multiplication of the omicron variant inside the respiratory tract.

The prevalence of different presenting complaints was found diverse in the delta and omicron-infected patients (Table I). Upon comparing the presenting complaints, diarrhoea was reported more by the delta-infected patient. The involvement of extrapulmonary systems in COVID-19 is found associated with increased disease severity and adverse outcomes.[14] In this study, the complaint of diarrhoea was more frequently present in delta-infected patients (12.9% *vs*. 1.7%). In another study by Sukharani *et al.*, diarrhoea was a risk factor for adverse outcomes among COVID-19 patients.[15] However, the authors did not find such risk in the study subjects. The complaint of SO_2 <94 %, prior to the admission, was significantly more reported by omicron patients. This finding is in contrast with the previously published data where omicron

infection is not commonly associated with lower respiratory system complaints including decreased SO_2.[16] However since the complaint was reported by self-monitoring of SO_2 by pulse oximeter at home, hence, the information bias could not be excluded.

Among all general physical signs, mean respiratory rate and SO_2 during hospitalisation were found borderline for labelling the respiratory function compromised. However, no significant difference was observed between delta and omicron-infected patients. The role of biochemical markers for the assessment of disease severity and prediction of outcomes is important in COVID-19. Inflammatory markers are implicated as an indicator of disease progression.[17] After evaluating the biochemical data, the authors found that among all study subjects (n=91), the median values of BUN, CRP, LDH, ferritin, D-dimer, TLC, and neutrophils were found higher than the upper reference limit of respective analytes. However, the median values of LDH, ferritin and TLC results were significantly higher in patients infected with the delta variant (Table II). The finding of this study is supported by other studies that reported the high values of inflammatory markers in critical patients who need intensive care during hospitalisation.[18,19] On comparing the results of cardiac markers (Trop-I, NT-proBNP) and procalcitonin, no significant difference was observed between omicron and delta-infected patients.

On comparing the study outcomes (Table II), the median length of hospital stay (4 *vs*. 11 days) was found significantly less in patients infected with the omicron variant ($p<0.05$). We found that the majority (80.6%) of delta-infected patients needed ICU admission. Bozid *et al.* also reported a significant need for ICU admission (11.4 percentage point difference) in delta patients on comparing with the other variant.[20] The overall in-hospital mortality was found 31.9% in this study. The finding is slightly higher than the results reported by Alam *et al.* who reported all-cause mortality of 28.7%.[21] However, no significant difference was found between delta and omicron-infected patients for in-hospital mortality.

The adjusted risk of prolonged hospital stay was found a 3.9 times more in patients with delta variant when compared to the omicron-infected patient (aOR: 3.95, CI=1.09-14.26). This is in line with the finding by Maslo *et al.,* where they reported a shorter hospital stay in omicron patients.[13] Similarly, patients with an increased TLC also observed 16% more risk of prolonged hospital stay 1.16 (1.03-1.30). Increased level of TLC is also reported by Iftikhar *et al*. when haematological markers were analysed in critical patients of COVID-19.[22] After adjustment analysis for the risk of ICU admission, it was found 4 times more in patients where information of decreased SO2 was present before the hospital admission (Table III). However the accuracy of results monitored at home through pulse oximeters is based on various factors and might be associated with discrepant results.[23] Further, the adjusted risk of ICU admission was found 23% more in patients with increased TLC. These findings are consistent with the findings of other studies in which leukocytosis was significantly associated with ICU admission.[24,25]

There are certain limitations to this study, amongst which the most prominent is the absence of a treatment regime. The important data on Interleukin-6 (IL-6) is also not available due to financial constraints. However, there is no missing data for any of the study variables and outcomes. The study can associate the increased disease severity and laboratory markers levels in the delta-infected patients.

CONCLUSION

The presenting complaints, clinical course and biochemical profiles are diverse in patients with delta and omicron-infected patients. Hospitalised patients with omicron infection exhibit shorter stays. Moreover, higher values of TLC are found associated with an increased risk of longer hospital stay and ICU admissions.

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ETHICAL APPROVAL:
An Ethical Approval was obtained from the Institutional Ethical Committee (IRB2427/DUHS/Approval/2022/763, dated: 12.02.2022).

PATIENTS' CONSENT:
A well informed written consent was taken from study subjects.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
SI: Principal investigator, manuscript writing, laboratory work, and interpretation of data.
SK: Research concept, question development, and final approval.
MAQ: Review manuscript and results analysis.
MA: Clinical assessment, follow-up of patients, and review of manuscript.
BA: Result analysis and literature search.
SZ: Statistical analysis and data interpretation.
HF: Assistance of laboratory work.
WR: Assist in patients' recruitment and clinical work.
All the authors have approved the final version of the manuscript to be published.

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