ORIGINAL ARTICLE

Severe COVID-19 Pneumonia Treated with Tocilizumab in a Pakistani Population: Variables Impacting Outcomes

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Abstract

Background: The association of severity of COVID-19 with raised Interleukin-6 (IL-6) levels led to Tocilizumab (TCZ) approval for treatment based on its IL-6 inhibiting mechanism of action. Treatment outcomes reported have been variable, with little data from Pakistan.

Objective: To identify demographic, clinical, and laboratory variables impacting outcomes (recovery or death) of patients with severe COVID-19 pneumonia treated with intravenous tocilizumab in a Pakistani hospital setting.

Methods: A single-center, retrospective, descriptive case series was conducted at the National Hospital Postgraduate Training and Medical Centre, Lahore from April to December 2020. Severe COVID-19 pneumonia (oxygen saturation below 90%, chest HRCT severity score more than 15) administered intravenous tocilizumab was included. Not fulfilling the above inclusion criteria. Data was analysed to identify significant differences between expired patients and those discharged after recovery.

Results: Forty-nine patients were admitted to intensive care/ high dependency units (ICU/HDU) with severe COVID pneumonia and treated with intravenous tocilizumab during the study period. The mean age was 60.8 years, with male predominance. Of the 49 patients, 23 (47%) expired. In the expired group lactate dehydrogenase (LDH), and neutrophil to lymphocyte ratio (NLR) were significantly higher throughout the admission course, while D-Dimers plus the last available white blood cell (WBC) count, were significantly higher post-TCZ, as was odds of co-infection evidenced by positive blood cultures.

Conclusion: Mortality correlated with increased inflammatory markers LDH and NLR ratio. Post TCZ raised D-Dimers may be indicators of fibrin microthrombi and prophylactic anticoagulation with TCZ may benefit such patients. High odds of secondary bacterial infection post-TCZ had a significant negative impact on recovery.

Keywords: *CoronaVirus-19, COVID-19, COVID-19 Pneumonia, Tocilizumab, Microthrombi, IL-6, Anticoagulation.*

INTRODUCTION

COVID-19 is a term used by WHO for illnesses caused by SARS-CoV-2 [1]. At the end of 2019, this novel coronavirus was identified as the cause of a cluster of cases of atypical pneumonia in Wuhan, China. It rapidly spread and was declared a global pandemic, by the WHO, on March 11, 2020 [2].

At the start of the pandemic, management of COVID-19 in hospitalised adults was based on limited evidence and evolved as clinical data emerged. Interim guidance was issued by the World Health Organisation (WHO) [3]. In severe COVID-19 patients, pathogenic white blood cells with high IL-6 secretion may enter the pulmonary circulation causing an inflammatory storm, which refers to an excessive inflammatory response, resulting in an out-of-control and dysfunctional immune system [4]. Tocilizumab (TCZ), the first Food and Drug Administration (FDA) approved IL-6 blocking agent, with proven safety and effectiveness for use in rheumatic diseases and cytokine release syndrome (CRS), was hypothesised to deter disease progression in severe COVID-19 pneumonia with acute respiratory distress syndrome (ARDS) [4]. Its use in COVID-19 patients was described in observational studies [4], and later evaluated in clinical trials for the treatment of COVID-19, which showed its effectiveness [5, 6]. The United States of America (USA) FDA issued an emergency use authorization (EUA) in June 2021 [7] and WHO added it to its list of prequalified treatments for severe or critical COVID-19 in Feb 2022 [8]. FDA fully approved TCZ for intravenous treatment of severe COVID-19 hospitalised patients in the same year [9]. It remains an approved in-patient treatment for severe COVID-19 infections to date [10]. In Pakistan, TCZ was approved by the Punjab government for treating critically ill patients in May 2020 [11]. Most physicians were unfamiliar with this drug other than rheumatologists, who have been using it for rheumatoid arthritis since 2010 [12]. Hence, the rheumatology department in our hospital was consulted for most of our study patients.

Notably, the pandemic continued into 2021, 2022, and 2023, only being taken off as a health emergency by the WHO on 5th May 2023 [13]. However, cases are still being recorded in Pakistan to date [14, 15].

This study was designed to look at outcomes of patients with severe COVID pneumonia treated with tocilizumab

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Received: July 26, 2023; Revised: January 15, 2024; Accepted: January 20, 2024
DOI: https://doi.org/10.37184/jlnh.2959-1805.2.1

  ISSN: 2960-2963 (Online) *Journal of Liaquat National Hospital 2024; 2(1): 14-22*

in a tertiary care hospital in Lahore and to identify the demographic, clinical, and laboratory variables impacting the outcome *viz* recovery/discharge or death.

METHODOLOGY

This was a single-center, retrospective, descriptive case series. After approval from the hospital's ethical review board, patient data was gathered from April to December, 2020 and included all severe COVID-19 pneumonia patients (diagnosed clinically plus chest HRCT with or without positive COVID PCR) [16] admitted in the ICU and/or HDU of National Hospital and Medical Centre, Lahore, and treated with intravenous tocilizumab. Severe COVID-19 pneumonia was defined as oxygen saturation below 90% and, a chest HRCT severity score of more than 15 [17, 18]. The dose of intravenous tocilizumab used in our study patients was 8mg/kg) [19]. Patient data regarding demographics, comorbidities, presenting complaints, diagnostic data, treatment modalities used, and the development of co-infection was obtained from hospital files. Data for laboratory tests included blood cell counts, inflammatory markers, namely, C - reactive protein (CRP), Ferritin, Procalcitonin, LDH, IL-6, and NLR, and the coagulation marker D-Dimer. Data for each patient was entered into a spreadsheet, with the laboratory values tracked over several days to assess any changes over time. Statistical analyses were conducted using SPSS Version 23.0.0.2 and Jamovi Version 1.2.22.

Patients were then characterised, based on outcomes, into two groups *viz*., death or recovery/ discharge.

A comparison of demographic variables and laboratory parameters was done between the two groups. Continuous variables were presented as Mean ± Standard Deviation where normally distributed (as determined by the Shapiro-Wilk test for normality) and as median (interquartile range) in the absence of normal distribution.

The differences between expired and discharged patients were compared as follows: 1- independent samples t-test in the case of normal distribution and homogeneity of variances (as determined by Levene's test) 2- Welch's T-test in the case of normal distribution but heterogeneity of variances 3- Mann-Whitney U test in the absence of normal distribution. Categorical data was compared using the Chi-square test or Fisher's exact test (where at least one of the values was < 5).

In the case of a significant p-value for Chi-square or Fisher's exact test, the odds ratio (OR) was calculated to assess the odds of an event in the expired group compared to the discharged group. A p-value<0.05 was considered statistically significant (2-tailed) for all the tests mentioned above.

RESULTS

A total of 49 patients were included in the study. The mean age of patients was 60.8 years with 31 (63.3%) of them being male. A significant proportion of them had comorbidities; 31 (63.3%) had hypertension, 25 (51%) had diabetes and 16 (32.7%) had chronic heart disease, with no significant differences between the two groups. Demographic variables, as well as the type and number of comorbidities, were compared between the expired and discharged groups, as shown in Table **1**.

There was a clear pattern when it came to presenting complaints; 42(85.7%) had a fever, 41(83.7%) had shortness of breath and 27(55.1%) had a dry cough, but with no significant differences between the two groups. These were recorded at the time of presentation in the emergency department. The median number of presenting complaints (limited to those mentioned in **Table 1** below) was also recorded and found to be three in both groups (p=0.301).

The median number of days from the onset of the first symptom till hospital admission was 7 (IQR: 3 - 7) with no significant difference between expired and discharged patients (p=0.713). The median day of admission on which tocilizumab was started was 3 (2 - 5) with no significant difference between expired and discharged patients (p=0.271).

The median number of days patients spent in the hospital was 10 (8 - 14), with a significant difference (p=0.008) between expired [9 (7 - 11)] and discharged patients [12 (10 - 16.75)]. Statistically, a significant number of patients required non-invasive ventilation (p=0.003, OR=6.25) and invasive ventilation (p<0.001, OR=57.1) in the expired group as compared to the discharged group. Finally, vasopressors were administered to eight expired patients (34.8%), which was significantly higher (p=0.009, OR=12.8) than discharged patients (1 patient; 4.0%). There was no significant difference between expired and discharged patients concerning the other treatment options, as shown in Table **1**.

A positive COVID PCR was found in 35 patients (71.4%, p=0.125). Bilateral pulmonary infiltrates were found in all patients on chest X-ray and chest HRCT.

Procalcitonin is commonly used as a marker of infection in a hospital/ICU environment. In COVID, however, it has limited utility as an indicator of co-infection since it is found to be raised in most if not all severe COVID pneumonia cases [20]. As expected, in our study procalcitonin was found to be raised in all the patients with no statistical difference between the two groups. Blood cultures were sent for all patients and a positive result was used to confirm

Table 1: Demographics and categorical data.

Demographics and Comorbidities				
Parameter	**All Patients N=49 n (%)**	**Expired N=23 n (%)**	**Discharged N=26 n (%)**	**p-value**
Mean Age in Years ± SD	60.8 ± 14.9	61.7 ± 13.1	59.9 ± 16.6	0.683
Age Groups:				
20-29 years	2 (4.1)	1 (4.3)	1 (3.8)	
30-39 years	2 (4.1)	0 (0.0)	2 (7.7)	
40-49 years	6 (12.2)	2 (8.7)	4 (15.4)	0.772
50-59 years	13 (26.5)	7 (30.4)	6 (23.1)	
60-69 years	10 (20.4)	6 (26.1)	4 (15.4)	
70-79 years	11 (22.4)	5 (21.7)	6 (23.1)	
80-89 years	4 (8.2)	2 (8.7)	2 (7.7)	
90-99 years	1 (2.0)	0 (0.0)	1 (3.8)	
Sex:				
Male	31 (63.3)	14 (60.9)	17 (65.4)	0.744
Female	18 (36.7)	9 (39.1)	9 (34.6)	
Diabetes Mellitus	25 (51.0)	13 (56.5)	12 (46.2)	0.469
Hypertension	31 (63.3)	14 (60.9)	17 (65.4)	0.744
Chronic Heart Disease	16 (32.7)	6 (26.1)	10 (43.5)	0.357
Chronic Pulmonary Disease	1 (2.0)	1 (4.35)	0 (0)	0.469
Chronic Kidney Disease	2 (4.1)	1 (4.35)	1 (3.85)	1.000
Dementia	0 (0.0)	0 (0)	0 (0)	-
Asthma	2 (4.1)	1 (4.35)	1 (3.85)	1.000
Malignancy	1 (2.0)	1 (4.35)	0 (0)	0.469
Rheumatic Disease	3 (6.1)	0 (0)	3 (11.5)	0.237
Chronic Neurological Disease	1 (2)	1 (4.35)	0 (0)	0.469
Smoker	5 (10.2)	2 (8.70)	3 (11.5)	1.000
Liver Disease	0 (0.0)	0 (0)	0 (0)	-
Presenting Complaints on Hospital Admission				
Parameter	**All Patients N=49 n (%)**	**Expired N=23 n (%)**	**Discharged N=26 n (%)**	**p-value**
Fever	42 (85.7)	20 (87.0)	22 (84.6)	1.000
Shortness of Breath	41 (83.7)	20 (87.0)	21 (80.8)	0.706
Dry Cough	27 (55.1)	11 (47.8)	16 (61.5)	0.336
Productive Cough	5 (10.2)	2 (8.70)	3 (11.5)	1.000
Fatigue/Malaise	1 (2.0)	0 (0)	1 (3.85)	1.000
Altered Consciousness	3 (6.1)	2 (8.70)	1 (3.85)	0.594
Diarrhoea	8 (16.3)	2 (8.70)	6 (23.1)	0.254
Nausea/Vomiting	2 (4.1)	1 (4.35)	1 (3.85)	1.000
Sore Throat	9 (18.4)	3 (13.0)	6 (23.1)	0.472
Anosmia	0 (0.0)	0 (0)	0 (0)	NaN
Nasal Congestion	1 (2.0)	0 (0)	1 (3.85)	1.000
Chest Pain	4 (8.2)	3 (13.0)	1 (3.85)	0.330
Headache	3 (6.1)	1 (4.35)	2 (7.69)	1.000
Muscle Aches	9 (18.4)	2 (8.70)	7 (26.9)	0.145
Joint Pain	0 (0.0)	0 (0)	0 (0)	-
Treatment Modalities				
Parameter	**All Patients N=49 n (%)**	**Expired N=23 n (%)**	**Discharged N=26 n (%)**	**p-value**
O2 at Home	14 (28.6)	8 (34.8)	6 (23.1)	0.365
Low Flow O2	13 (26.5)	3 (13.0)	10 (38.5)	0.057
High Flow O2	36 (73.5)	18 (78.3)	18 (69.2)	0.475
Non-invasive Ventilation	21 (42.9)	15 (65.2)	6 (23.1)	0.003
Invasive Ventilation	17 (34.7)	16 (70.0)	1 (3.85)	<0.001
Remdesivir	9 (19.1)[a]	2 (9.1)[b]	7 (28.0)[c]	0.144
Hydroxychloroquine	9 (18.8)[d]	7 (30.4)	2 (8.0)[c]	0.068

Azithromycin	40 (83.3)[d]	19 (82.6)	21 (84.0)[c]	1.000
Systemic Steroids	46 (95.8)[d]	21 (91.3)	25 (100.0)[c]	0.224
Antibiotic (Other than Azithromycin)	46 (95.8)[d]	21 (91.3)	25 (100.0)[c]	0.224
Vasopressors	9 (18.8)[d]	8 (34.8)	1 (4.0)[c]	0.009
Anticoagulation	46 (95.8)[d]	21 (91.3)	25 (100)[c]	0.240
Convalescent Plasma	6 (12.5)[d]	3 (13.0)	3 (12.0)[c]	1.000
Renal Transplant	1 (2.1)[d]	0 (0)	1 (4.0)[c]	1.000
Tracheostomy	0 (0)[d]	0 (0)	0 (0)	-

Abbreviations: *SD = Standard Deviation, [a]Percentage was out of 47 because treatment data for 2 patients was missing, [b]Percentage was out of 22 because treatment data for 1 patient was missing, [c]Percentage was out of 25 because treatment data for 1 patient was missing, [d]Percentage was out of 48 because treatment data for 1 patient was missing.*

the presence of a co-infection. Co-infection was observed in a total of 12 patients, 10 of whom expired and 2 were discharged, with a significant difference between the two groups (p=0.008, OR=8.21).

Lab values for all patients were assessed on multiple days. Baselines were collected from Day 1 of TCZ administration, Day 3 of TCZ administration, and the last available labs before discharge on expiry. The p values (expired *vs.* discharged group) of all the assessed labs can be found in Table **2**. Of those labs, the medians of the ones with significant p values have been graphed in **Fig.** (**1**).

DISCUSSION

The mean age of the patients in our study was 60.8 years with a male predominance, similar to a study by Docherty *et al.* which showed a higher disease incidence in the middle-aged and older population with a male-skewed pattern [21]. However, their mortality rate was associated with invasive/mechanical ventilation only, whereas we saw high mortality in both invasive and non-invasive ventilation. Notably, the increased mortality seen associated with various comorbidities in their research, such as chronic cardiac disease, was in line with other studies including a local study from Lahore [22] but was not reflected in our study. Additionally, we found that the duration of symptoms pre-hospital did not correlate with mortality.

LDH and D-Dimers were consistently higher in the expired group, similar to Han *et al.* who found both to be higher in severe illness compared to mild illness and concluded that LDH in particular could allow for early recognition of lung injury and disease severity [23]. Ferner *et al.* analysed multiple case series and found that both micro and macro thrombotic events occurred in COVID-19 patients [24]. The cytokine storm may damage the endothelium at an early stage, leading to microthrombosis, especially in the lungs, resulting in high D-Dimers, high LDH, and mortality. A study by Wadowski *et al.*, published in January 2023, discusses this and describes how COVID-19 disturbs the equilibrium between platelets and the vessel wall, leading to microthrombi formation and being a possible major factor driving the deterioration of patient disease course in severe COVID-19 [25]. This is supported by postmortem reports of COVID patients [26, 27].

A recent study by Bhoopat *et al.* found that the use of therapeutic doses of heparin had a survival benefit in COVID-19 patients, with no incidence of major bleeding events [28]. This was expanded upon by preliminary results from three international, multicenter clinical trials which posited that full-dose anticoagulation reduced mortality if administered early, when patients were moderately ill, but could potentially be harmful if started in ICU patients [29].

In our study expired patients had high LDH both pre and post-TCZ, however a significant difference of elevated D Dimers between the two groups, even without major overt thrombotic events, occurred post-TCZ suggesting that microthrombosis may have been their cause of death possibly due to ongoing disease activity non-responsive to TCZ. A transient elevation of D-dimer in COVID-19 patients who received TCZ and a trend towards increased death secondary to thromboembolism has been reported by Chan *et al.* [30]. This, in conjunction with our findings on significantly elevated D-Dimers, post TCZ in the expired group, strongly suggests that further research on early D-Dimer guided thromboprophylaxis may be the key to reducing mortality in patients with COVID-19 receiving TCZ.

Expired patients in our study had a higher WBC count, which is in line with other studies such as Peng *et al*. (2020) and Sun *et al*. (2020) which found patients with severe disease have higher WBC counts than those with mild-moderate disease. Based on these findings leukocyte differential count may provide more details and may serve as a predictor for the degree of disease severity and prognosis of the patient [31]. High NLR was associated with mortality, and shown as a poor prognostic marker, as has been shown in existing data [32, 33].

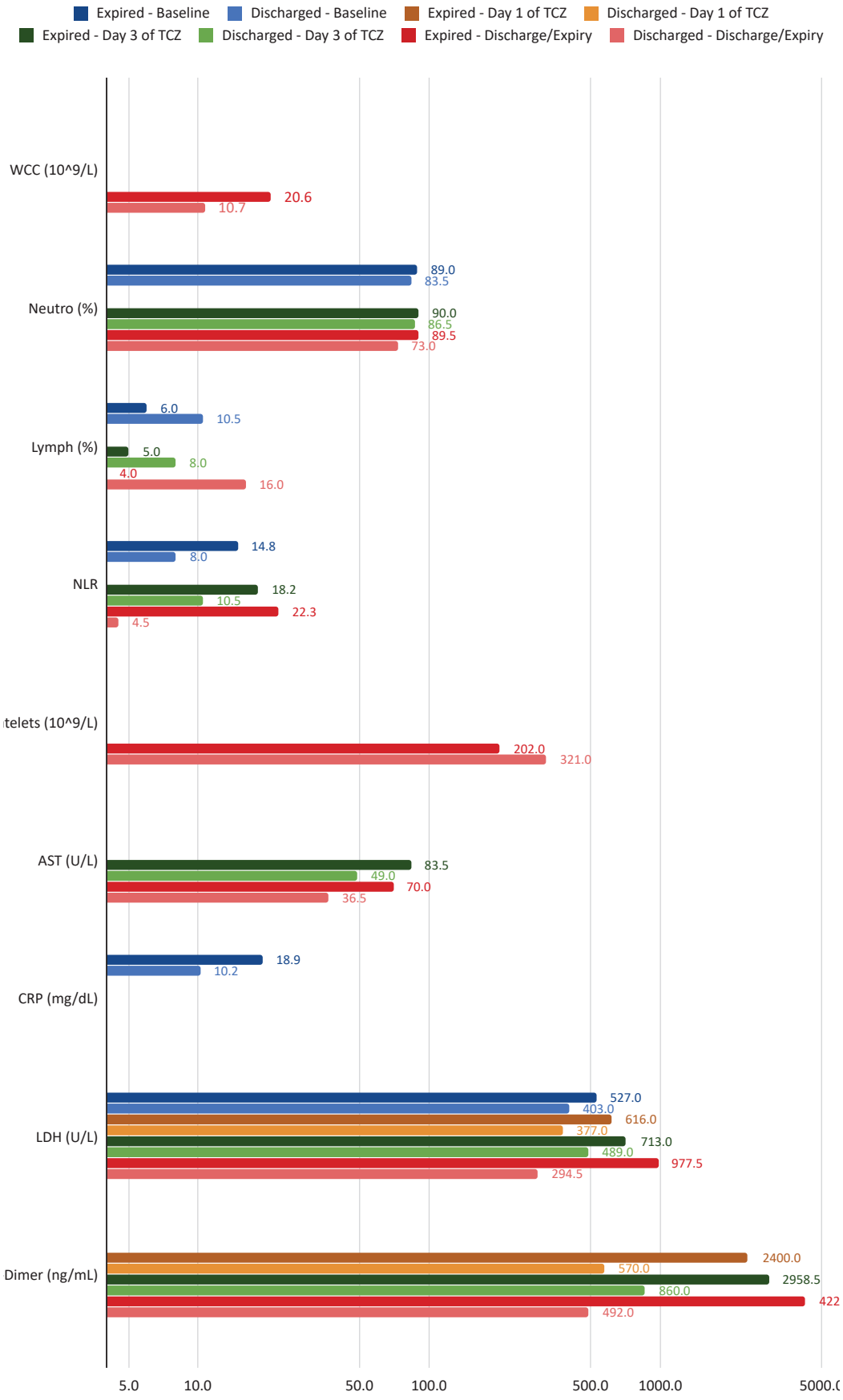

Fig. (1): Median lab values for expired and discharged patients with $p<0.05$.

Table 2: Labs - statistical comparison of laboratory parameters between expired and discharged patients.

Parameters (Normal Range)	Baseline (Mean ± S.D)			Day 1 of TCZ (Mean ± S.D)			Day 3 of TCZ (Mean ± S.D)			At Discharge or Expiry (Mean ± S.D)		
	Discharged	Expired	p-value	Discharged	Expired	p-value	Discharged	Expired	p-value	Discharged	Expired	p-value
Haemoglobin (12.1-17.2 g/dL)	12.99 ± 1.55	12.76 ± 1.68	0.625	12.90 ± 1.53	12.72 ± 1.69	0.714	13.20 ± 1.71	12.52 ± 1.99	0.228	13.18 ± 2.12	12.86 ± 1.92	0.597
WBC (4.5-11 x 10^9/L)	10.14 ± 5.60	9.94 ± 5.50	0.992	12.95 ± 5.18	14.65 ± 6.81	0.336	11.75 ± 4.46	15.18 ± 7.01	0.056	11.35 ± 4.13	21.35 ± 8.70	< 0.001
Neutro % (40-60%)	80.35 ± 10.65	86.50 ± 6.13	0.023	86.44 ± 7.30	89.23 ± 3.91	0.274	84.04 ± 8.72	88.85 ± 5.35	0.007	71.68 ± 17.84	89.23 ± 4.65	< 0.001
Lympho % (18-45%)	14.38 ± 9.50	9.00 ± 5.27	0.027	8.44 ± 4.95	6.23 ± 3.87	0.101	10.38 ± 7.34	5.95 ± 4.26	0.002	15.12 ± 8.26	5.55 ± 3.99	< 0.001
NLR (1-2)	8.93 ± 6.70	13.35 ± 7.26	0.022	14.32 ± 8.46	20.61 ± 12.9	0.135	11.94 ± 9.49	20.87 ± 11.20	0.003	7.61 ± 9.30	26.1 ± 20.43	< 0.001
Platelets (150-450 x 10^3/ml)	254.5 ± 110.4	238.7 ± 85.69	1.000	322.4 ± 105	285 ± 126.8	0.127	343.3 ± 101.7	289.4 ± 128.3	0.128	329.1 ± 120.9	228.9 ± 113.9	0.006
INR (≤1.1)	2.76 ± 3.88	1.20 ± 0.25	0.617	3.80 ± 3.81	1.18 ± 0.19	0.469	2.35 ± 1.76	1.13 ± 0.11	0.508	0.65 ± 0.91	1.40 ± 0.20	0.451
Creatinine (0.6-1.3 mg/dL)	1.29 ± 1.63	1.26 ± 0.67	0.273	1.23 ± 1.53	1.39 ± 1.05	0.444	1.38 ± 2.00	1.22 ± 0.66	0.448	1.45 ±1.69	1.62±1.14	0.388
ALT (19-33 IU/L)	59.38 ± 59.0	39.42 ± 19.77	0.633	56.50 ± 48.61	45.80 ± 61.91	0.080	69.30 ± 55.95	69.63 ± 51.37	0.824	72.71 ± 62.99	80.67 ± 49.43	0.345
AST (8-33 U/L)	69.58 ± 56.40	78.26	0.441	48.95 ± 23.40	79.15 ± 98.98	0.252	54.70 ± 34.29	107.3 ± 89.87	0.024	40.25 ± 15.15	106.5 ± 72.12	< 0.001
Total Bilirubin (0.1-1.2 mg/dL)	0.58 ± 0.200	0.65 ± 0.58	0.398	0.68 ± 0.33	0.76 ± 0.57	0.885	0.80 ± 0.57	0.75 ± 0.37	1.000	0.64 ± 0.27	0.61 ± 0.48	0.078
Troponin I (0-0.04 ng/mL)	0.09 ± 0.227	0.68 ± 1.43	0.404	1.51 ± 2.46	0.99 ± 1.68	0.548	NaN	17.20 ± 29.28	NaN	NaN ± NaN	17.14 ± 26.23	NaN
CK-MB (5-25 IU/L)	44.57 ± 43.55	26.60 ± 15.8	0.626	48 ± 2.82	56.7 ± 42.91	0.804	48 ± NaN	36 ± Nan	NaN	22.50 ± 6.36	124 ± NaN	NaN
Pro-BNP (≤125 pg/mL)	4626 ± 9429	1006 ± 997.7	0.186	104.3 ± 97.53	2453 ± 4160	0.071	37.85 ± 8.27	17896 ± 24191	0.486	99.29 ± 80.20	12977 ± 16663	0.376
CRP (≤0.3 mg/dL)	11.32 ± 8.81	17.73 ± 9.09	0.019	9.14 ± 8.40	12.58 ± 8.17	0.114	2.88 ± 3.48	4.48 ± 4.63	0.084	1.25 ± 1.94	3.02 ± 5.05	0.080
IL-6 (≤18 ng/mL)	127.8 ± 139.2	24.15 ± 18.81	0.266	622.4 ± 776.8	264.4 ± 226.8	0.486	559.1 ± 348.2	55.57 ± NaN	0.337	1449 ± NaN	2519 ± 3509	NaN
Ferritin (24-336 mg/L)	1654 ± 2141	830.6 ± 650.2	0.219	1440 ± 1345	1050 ± 809.5	0.403	1263 ± 984	1110 ± 876.6	0.626	1051 ± 808.1	1623 ± 1767	0.742
Procalcitonin (≤0.1 ng/mL)	0.55 ± 1.34	3.16 ± 11.61	0.207	0.78 ± 1.44	0.37 ± 0.55	0.728	1.29 ± 2.66	0.46 ± 0.51	0.798	1.87 ± 3.17	0.26 ± 0.30	0.517
LDH (140-280 U/L)	423.4 ± 149.5	572.2 ± 248.9	0.033	446.1 ± 161.1	674.7 ± 194	< 0.001	487.3 ± 171.6	826 ± 318.1	0.003	280.3 ± 167.8	969.9 ± 269.2	< 0.001
D-Dimer (≤0.5 mg/L)	621 ± 663.2	2464 ± 3295	0.098	1280 ± 1528	5928 ± 13039	0.027	1688 ± 1983	4453 ± 4662	0.029	1077 ± 1431	5603 ± 5192	< 0.001

Red Highlighted: *Significant difference between lab values of discharged and expired patients (P < 0.05).* ***Abbreviations:*** *WCC = White Blood Cell, Neutro = percentage of Neutrophils, Lymph = percentage of Lymphocytes, NLR = Neutrophil to Lymphocyte ratio, INR = International Normalised Ratio, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, CK-MB = Creatine Kinase-MB, Pro-BNP = Pro Brain Natriuretic Peptide, CRP = C-Reactive Protein, IL-6 = Interleukin 6, LDH = Lactate Dehydrogenase.*

The expired group had a significantly lower platelet count which is a trend seen across various studies; a meta-analysis by Lippi *et al*. (2020) shows that patients with lower platelet counts are seen in severe COVID-19 compared to those with a milder form of the disease. Several other types of research such as Guclu *et al*. found that surviving patients expressed a significantly higher platelet count compared to the expired patients. Data from Wuhan shows that patients with thrombocytopenia have a higher mortality rate than those with normal thrombocyte count and for every 50 x 109 /L increase in platelet there is a 40% reduction in mortality risk [34].

We also found bacterial co-infections and raised AST to be associated with higher mortality. The use of TCZ is known to be associated with, and may have contributed to, both [35, 36]. In our study co-infection was observed

in a total of 12 patients, 10 of whom expired and 2 were discharged. This meant in our study patients who expired were 8.21 times more likely to have suffered a co-infection, specifically bacterial. According to a study by Peng *et al.*, there is a significantly increased risk of fungal co-infection in COVID-19 pneumonia patients receiving tocilizumab [37]. Unfortunately, our study patients were not tested for any fungal co-infection, however, precautionary steps should be taken to prevent all co-infections and in case they do occur, early diagnosis and treatment should be the goal when treating with tocilizumab. Aseptic measures should also be followed within hospitals, applicable to all patient areas, with zero tolerance for ICUs and HDUs. This is even more important for developing countries, such as ours, that suffer from extremely high infection rates in the ICUs [38] as compared to developed countries, such as the USA [39].

Few studies have been conducted locally in Pakistan on tocilizumab use in COVID-19 patients. In a small study from Peshawar a fall of ≥50% in CRP was reported as one of the predictors of a positive response to tocilizumab [40], however in our study, despite a fall in CRP post tocilizumab infusion, there was no significant difference in patient's outcome. Another study from Pakistan showed the benefit of tocilizumab in patients with moderate to severe disease not requiring mechanical ventilation [41]. The same was the case in our setting in which invasive ventilation was associated with poor outcomes.

We realise the limitations of the present study. First, the clinical characteristics of the included cases may have had gaps in documentation due to the resource limitations of the COVID-19 pandemic. The small sample size, lack of random sampling, non-parametric nature of part of the data, as well as the retrospective and single-center nature of the study make it less than ideal. However, valuable information has been collected which we deem useful in looking at all variables impacting COVID outcomes in a Pakistani hospital setting, including but not exclusive to, the administration of tocilizumab.

CONCLUSION

This study found a marked difference in D-Dimers and LDH between the two groups, being consistently elevated in the expired group, supporting a hypothesis that micro thrombosis may be the cause of death in these patients. Interestingly, D-Dimer's significant difference coincided with TCZ infusion and raises the question of whether these may be used as indicators for early anticoagulation in those given TCZ, but larger studies are needed before a definitive conclusion.

In line with other studies of COVID pneumonia treated with intravenous tocilizumab, our study also showed a significantly higher rate of co-infection in the expired group, therefore we need strict application of aseptic measures and guidelines for minimising the risk of infection in those currently considered for treatment with intravenous tocilizumab in an ICU/HDU setting.

ETHICAL APPROVAL

Ethical approval was obtained from the Institutional Review Committee of National Hospital and Medical Center, Lahore Cantt (REF letter No. NHMC/ l0H07, dated: 20-07-2011). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/ or national research committee and with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from the participants.

AVAILABILITY OF DATA

The data set may be acquired from the corresponding author upon a reasonable request.

FUNDING

Declared none.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Prof. Hasan Tahir - Concept of study and critical input.

Dr. Nauman Ismat Butt - Data acquisition.

Dr. Tashia Malik - Data acquisition.

Dr. Sarah Tahir - Data acquisition.

AUTHOR'S CONTRIBUTION

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Muhammad Ahmed Saeed: Writing - review & editing.

Nadia Majeed: Data Curation.

Nighat Mir Ahmad: Concept of Study, Critical Input, Review.

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