CLINICAL AND LABORATORY CHARACTERISTICS AND OUTCOME OF COVID-19 PATIENTS ADMITTED TO THE ISOLATION WARD OF A PUBLIC SECTOR HOSPITAL

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■ABSTRACT

Objective: To evaluate the clinical and laboratory presentation and outcome of COVID-19 patients admitted to a public sector hospital in Pakistan.

Methodology: This is a retrospective, cross sectional chart review of COVID-19 patients admitted to Dr. Ruth K.M Pfau Civil Hospital Karachi Isolation Ward from 28th February till May 28th 2020.

Results: Out of 306 admitted patients, 216 (70%) tested SARS CoV-2 positive of whom median age was 45. COVID-19 was asymptomatic in 35 (16.2%), non-severe in 112 (51.9%), severe in 55 (25.5%) and critical in 14 (6.5%) patients. Severe/critical as compared to asymptomatic/non-severe disease was associated with co-morbidities (37 [53.6%] vs 35 [23.8%], p value <0.001), shortness of breath (50 [72.5%] vs 34 [23.1%], p value <0.001). Median [IQR] values demonstrated lower oxygen saturation (90 [87-92] vs 97 [97-98], p value <0.001) and lower absolute lymphocyte counts (1.3×109/L [0.9-1.82] vs 1.7×109/L [1.1-2.2], p value <0.001) with higher neutrophil to lymphocytic ratio (5.2 [3.3-8.4] vs 2.5 [1.6-3.7], p value <0.001), lactate dehydrogenase level (360U/L [271-566] vs 296U/L [207-377], p value <0.001), C-reactive protein (89mg/L [36-179] vs 19mg/L [0.9-91], p value <0.001) and ferritin level (580mg/L [331-1021] vs 341mg/L [163-679], p value <0.001). Of 216 patients, 2 (0.9%) died in the ward, whereas 13 (6%) were shifted to ICU of whom 12 died. Overall mortality was 14 (6.5%).

Conclusion: In COVID-19 patients admitted to a public sector hospital, severe disease was associated with co-morbidities and elevated inflammatory markers. Mortality was very high in those that required ICU care.

Key Words: COVID-19; Hospital; Management; Pakistan.

■ INTRODUCTION

COVID-19 cases were first diagnosed in December 2019 in China and SARS CoV-2 coronavirus pandemic was declared in March 2020.[1] Worldwide, over 142 million cases and 3 million deaths had been recorded one year later by April 2021.[2] The first case in Pakistan was in the province of Sindh and was diagnosed on February 26th 2020 during the first wave of coronavirus which peaked in June. A second wave of COVID-19 became evident in November 2020. In the following year, by February 2021, a third wave was already underway in the provinces of Khyber Pakhtunkhwa and Punjab and by April 2021, over 750,000 cases and more than 16,000 deaths had been recorded in Pakistan.[2]

Pakistan is a country with a population of approximately 224 million with only 4% of the population above 60 years of age. The young population in Pakistan could be a contributing factor to the less devastating impact of coronavirus so far. There is limited data of the clinical characteristics of COVID-19 in Pakistan. A recent study from Karachi describes 299 patients with severe and critical COVID-19 that were admitted to a public sector hospital during the peak months of the first wave.[3] Our study, however, covers the initial months of the first wave of coronavirus in patients presenting across the COVID-19 clinical spectrum. A similar study of 100 patients during the first wave of coronavirus has also been reported from Pakistan.[4] Our study provides an opportunity to describe our experience at a public sector hospital when faced with this new and formidable challenge at a time of heightened fear and anxiety. It describes the clinical and laboratory characteristics, management and outcome of these patients.

■ METHODOLOGY

This is a retrospective, cross sectional descriptive study of patients who presented to Dr. Ruth KM Pfau Civil Hospital Karachi (CHK) in relation to COVID-19,

and were admitted to the Isolation Ward. CHK is a tertiary care public sector hospital providing care free of cost and is also a teaching hospital affiliated with the Dow University of Health Sciences.

The study spans a 3 month period commencing with the first admission (who was also the second reported case in the province of Sindh) to the 18 bedded Isolation Ward on February 28th 2020 till May 28th 2020. Subsequently, within the premises of CHK, the COVID-19 outpatient clinic, triage center and a testing facility for PCR for SARS CoV-2 were established and were fully functional within four weeks by March 2020. In April 2020, a building within CHK with a capacity of 50 beds was designated as an additional COVID-19 Isolation facility and a 12 bedded COVID-19 medical ICU with negative pressure was readied for patients.

In order to assess the number of patients that presented to the CHK COVID-19 triage center during the initial stages of the epidemic, data was obtained from the registration counter electronic data and also tallied with the hand written COVID-19 Register. The number of PCR tests performed by the Central Laboratory of CHK during the study period was obtained from the computerized data of the IT department. Initially, when it was still early days of COVID-19 and containment protocols were not mature and well defined, we admitted all patients with suspected or confirmed COVID-19.

Those that were confirmed COVID-19 remained admitted until they tested negative for SARS CoV-2 coronavirus by PCR. When home isolation was allowed by the Sindh Government in April, we allowed clinically stable patients to go home after testing, and only those requiring hospitalization were admitted.

Our study inclusion criteria were all patients admitted to the COVID-19 Isolation ward. We however excluded admitted patients that had been initially treated at outside healthcare facilities or were stepped down to the Isolation Ward after initial admission to COVID-19 Medical ICU at the hospital.

Medical records of all admissions to the two Isolation Wards were reviewed. Data sheets for all admissions that met the inclusion criteria were filled. For those that had a confirmed diagnosis of COVID-19, we documented the demographics, clinical presentation, laboratory and radiological data, management and outcome. Those that tested negative, and were found to have an alternate diagnosis, were analyzed as non-COVID-19 admissions and data sheet was filled for demographics and diagnoses.

Disease classification of COVID-19 for study purposes was according to the NIH National Guidelines of December 2020.[5] Asymptomatic COVID-19 was described as patients having no symptoms. Non-severe was described for patients with oxygen saturation of $\geq$ 94% and respiratory rate of $\leq$ 25 breaths/minute. Severe was described as oxygen saturation of $<$ 94% or respiratory rate $\geq$ 25 breaths/minute. Critical disease was when presence of respiratory compromise severe enough to require non-invasive ventilation (NIV) or mechanical ventilation (MV). During the study period, COVID-19 patients had been managed in accordance with the earlier national guidelines of April 2020.[6] Primary outcome studied was discharge or death.

Data was entered on the IBM SPSS version 24. Continuous variables were expressed as medians, interquartile ranges. Student t test was used for continuous data and categorical data was presented as frequency and percentages. To see the association, we used the Chi-squared test or Fischer's exact as appropriate for categorical variables. Significance was set at α less than or equal to 0.05.

Approval for the study was obtained from the Institutional Review Board of Dow University of Health Sciences (IRB-1790/DUHS/approval/2021/).

RESULTS

During the study period, 5405 patients presented to the COVID-19 triage center of the government hospital. Its Central Laboratory performed 8083 PCR tests of which 1879 (23%) were positive for SARS CoV- 2 coronavirus. During the three month study period, 306 patients who met the study inclusion criteria were admitted to the two Isolation Wards. Of 306, 216 (70%) were SARS CoV-2 positive and 90 (30%) tested negative.

Of 216 confirmed COVID-19 patients, the median age was 45 (IQR 31-55) with a range of 13-90 years, 166 (76.9%) were males. 14 (6.4%) patients were health care workers. 72 (33.3%) patients had one or more co-morbidities with diabetes mellitus and hypertension most commonly reported in 43 (19.9%) and 40 (18.5%) respectively. (Table No 1)

At presentation, the median duration of symptoms since onset was 5 (IQR 1.2-7) days. Most frequently reported symptoms were fever in 130 (60.2%), cough in 106 (49.1%) and shortness of breath in 84 (38.9%). COVID was categorized at presentation as asymptomatic in 35 (16.2%), non-severe in 112 (51.9%), severe in 55 (25.5%) and critical in 14(6.5%)

At presentation, in 216, median absolute lymphocyte count (ALC) was 1.7×10^9/L (IQR 1.1-2.2) with a median neutrophil lymphocyte ratio (NLR) of 3.0 (IQR 1.8-5.3), median C-reactive protein was 9.8 mg/L (IQR 0.9-91), median lactate dehydrogenase was 296 U/L (IQR 203-307). Chest X-rays were available in 208 of whom 76 (36.5%) had bilateral infiltrates. Oxygen therapy was required in

69 (31.9%) patients. (Table No 1)

Comparison between COVID-19 patients with severe/critical and asymptomatic/non-severe is shown in Table No 2. Severe/critical disease was associated with the presence of co-morbidities (37 [53.6%] vs 35 [23.8%], p value: <0.001), shortness of

breath (50 [72.5%] vs 34 [23.1], p value: <0.001), lower median [IQR] oxygen saturation (90 [87-92] vs 97 [97-98], p value: <0.001), lower median [IQR] absolute lymphocyte counts (1.3×10⁹/L [0.9-1.82] vs 1.7×10⁹/L [1.1-2.2], p value: <0.001), higher median [IQR] neutrophil to lymphocytic ratio (5.2 [3.3-8.4] vs 2.5 [1.6-3.7], p

value: <0.001), higher median [IQR] lactate dehydrogenase level (360U/L [271-566] vs 296U/L [207-377], p value: <0.001), higher median [IQR] C-reactive protein (89mg/L [36-179] vs 19mg/L [0.9-91], p value: <0.001) and higher median [IQR] ferritin level (580mg/L [331-1021] vs 341mg/L [163-679], p value: <0.001). Significantly more patients with severe/critical COVID-19 had bilateral infiltrates on chest X-ray at presentation (54 [78%] vs 22 [15.7%], p value: <0.001).

Out of 216 patients, 81 (37.5%) had a documented negative PCR, considered recovered, and discharged after a median stay of 14 (IQR 10-18) days whereas 82 (37.9%) were discharged to complete isolation at home without repeat PCR testing. Two died in the ward, and 13 were transferred to ICU of whom 12 (92%) died. Of 216, overall mortality was 14 (6.5%) patients with all deaths occurring in patients with severe and critical disease (p value: <0.001). The overall median duration of hospitalization was 6 (IQR 2-13) days.

There were 90 admissions to the Isolation Ward that subsequently were reported to be SARS 2 PCR negative. Most (75 %) of these patients who turned out to be PCR negative were admitted during the first four weeks of the opening of the Isolation ward. Of 90, on further evaluation, 88 patients were found to not fit the case definition for suspected or probable COVID-19 and were counseled and discharged. However, two were highly suspicious for COVID-19 and retained and managed as such. Median age was 32 years, and two-thirds (67.8%) were male. Diagnoses included upper respiratory tract infection in 65 (72.2%). Median duration of stay in the Isolation Ward of SARS 2 PCR negative patients was 1 (IQR 1-2) days. (Table No 3)

■ DISCUSSION

Our study has shown that a public sector

Table 1: Characteristics and Outcome of Patients with Covid-19 Admitted to A Public Sector Hospital Isolation Ward (N=216)

Demographics	n (%)
Age (Median-IQR)	45(31-55)
Male	166(76.9)
Female	50(23.5)
Admitted from	
COVID-19 Outpatient Clinic/Triage	164(75.90)
Outside healthcare facility	26(12.1)
Intra-hospital transfer	18(8.3)
Field Epidemiology and Laboratory Training Program(FELTP)	4(1.9)
Emergency Room	4(1.9)
Occupation	
Healthcare worker	14(6.4)
Travel and Contact History	
International and domestic travel within 21 Days	29(13.4)
Contact history with known or suspected COVID-19	47(21.8)
Co-morbidities	
None	
Diabetes Mellitus	43(19.9)
Hypertension	40(18.5)
Ischemic Heart diseases	8(3.7)
COPD	3(1.4)
Chronic Kidney Diseases	2(0.9)
Days Since Onset of Symptoms at Presentation (Median-IQR) n=181	5(1.2-7)
Symptoms	
Asymptomatic	35(16)
Fever	130(60.2)
Cough	106(49.1)
Shortness of breath	84(38.9)
Sore throat	16(7.4)
Rhinorrhea	16(7.4)
Diarrhea	6(2.8)
Headache	9(4.2)
Nausea and vomiting	6(2.8)
Altered level of consciousness	3(1.40)
Myalgia	19(8.8)
Disease Category at Presentation	
Asymptomatic	35(16.2)

Non-severe	112(51.9)
Severe	55(25.5)
Critical	14(6.5)
Laboratory Findings at Admission (Median- IQR)	
Absolute Lymphocyte Count (ALC) (109/L)	1.7(1.1-2.2)
Neutrophil Lymphocyte Count Ratio (NLR)	3.0(1.8-5.3)
Total Leukocyte Count (TLC) (109/L)	7.4(5.6-10.2)
Hemoglobin(g/L)	13.2(11.9-14.3)
Platelets(109/L)	223(166-301)
C-Reactive Protein (CRP) (mg/L) n=141	19.8(0.9-91)
Lactate Dehydrogenase(LDH) (U/L) n=136	296(203-307)
Ferritin (mg/L) n=140	341(163-679)
Chest X-ray findings (n=208)	
Clear	106(51)
Bilateral Infiltrates	76(36.5)
Unilateral Infiltrates	24(11.5)
Pleural effusion	2(0.96)
Management	
Oxygen (nasal cannula/face mask/non-rebreather)	69(31.9)
Antibiotics	89(41.2)
Hydroxychloroquine	100(46.3)
Steroids	60(27.8)
Enoxaparin	39(18.1)
Outcome	
Recovered with negative PCR (test based strategy for de-isolation)	81(37.5)
Discharged to home isolation (without negative PCR documentation)	82(37.9)
Transferred to another healthcare facility for isolation	21(9.7)
Left against medical advice	17(7.9)
Died in ward	2(0.9)
Transferred to ICU	13(6.0)
Died in ICU	12 (92%)
Overall mortality	14 (6.5%)

hospital with limited resources had established the full spectrum of COVID-19 facilities within 4 weeks of the first patient admission. Indeed the global pandemic of COVID-19 has been an enormous test of governments worldwide due to high pressure on health systems and increased demand for essential medical supplies.[7] A study from a public sector hospital in Lahore, province of Punjab, describes how it prepared for COVID-19, and despite limited resources, established systems and policies, with the conclusion that all is possible in the public sector if there is political will.[8]

Our study highlights that almost one-third of admitted patients tested negative for COVID-19 and who, on further evaluation, were considered to have an alternative diagnosis. This is a reflection of panic and fear in both the public and healthcare workers at the time. Heightened anxiety in the general public is well exemplified by a young girl admitted to the Isolation Ward when brought by her parents for "cough that developed after shaking hands with a foreign tourist'. Similarly, there was a tendency for doctors to over-diagnose COVID-19, sometimes delaying the diagnosis and management of patients with alternative, often serious, con-

ditions. Indeed, the pandemic has taken a toll on patients without COVID-19.[9] Anxiety amongst healthcare workers remained at high levels throughout the span of this study with not enough support afforded by the institution.[10] Mental health and psychosocial considerations must be addressed.[10,11]

The median age of COVID-19 inpatients was 45 years which is much lower than those reported from other studies including the study of 299 patients with severe disease from Pakistan in which the median age was 60 years.[3] This is because over two-thirds of our patients were asymptomatic or with non-severe disease which is found in younger patients. A study from Pakistan of 100 patients in the first wave of COVID-19 reported an average age of 52 years.[4]

Three-fourths were male as has been shown in numerous studies reporting male predominance in COVID-19.[12] Risk factors for severe disease included the presence of co-morbidities.[4] Shortness of breath is a clinical indicator of severe disease. Elevated inflammatory markers were also significantly elevated in severe disease in our study as has been demonstrated in many studies including a meta-analysis comprising 3962 patients.[13]

In early 2020, hydroxychloroquine was considered effective in COVID-19, and supplies were expeditiously secured by the hospital. Initially our patients received hydroxychloroquine but it was stopped once studies did not support its efficacy. In a randomized controlled trial among patients hospitalized with COVID-19, those who received hydroxychloroquine did not have a lower incidence of death at 28 days than those who received usual care.[14] We gave steroids to most patients requiring oxygen, and the Recovery Trial has demonstrated a significant mortality benefit in such patients.[15] Over half of our patients received antibiotics but studies now do not support antibiotics as part of standard

Table 2: Comparison of Severe/Critical Covid-19 with Asymptomatic/Non-Severe Covid-19 In 216 Patients Admitted to the Isolation Ward

Variables	Severe /Critical 69(31.9%) n (%)	Asymptomatic /Non-Severe 147(68%) n (%)	p-value
<60 Years of age	52(75.4)	121(82.3)	0.156
≥60 years of age	17(26.4)	26(17.7)	
Male	50(72.5)	116(78.90)	0.190
Female	19(27.5)	31(21.50)	
Co-morbidities	37(53.6)	35(23.8)	<0.001
Diabetes Mellitus	24(34.8)	19(12.9)	<0.001
Hypertension	17(34.8)	23(15.6)	0.083
Fever	50(72.5)	80(54.4)	0.008
Cough	42(60.9)	64(43.5)	0.013
Shortness of breath	50(72.5)	34(23.1)	<0.001
Altered Level Of Consciousness	3(4.3)	0(0.0)	0.032
Laboratory Values On Day Of Admission (Median-IQR)			
Oxygen saturation	90(87-92)	97(97-98)	<0.001
Absolute Lymphocyte Count (ALC)(109/L)	1.3(0.9-1.82)	1.7(1.1-2.2)	<0.001
Neutrophil Lymphocyte Ratio(NLR)	5.2(3.3-8.4)	2.5(1.6-3.7)	<0.001
C-Reactive Protein(CRP) (mg/L) n=141	89(36-179)	19(0.9-91)	<0.001
Lactate Dehydrogenase(LDH) (U/L)n=136	360(271-566)	296(207-377)	<0.001
Ferritin(mg/L)n=140	580(331-1021)	341(163-679)	<0.001
Total Leukocyte Count (TLC) (109/L)	9.3(5.7-12.4)	7.4(5.6-10.2)	0.007
Hemoglobin(g/L)	12(11.1-14.1)	13(11.9-14.3)	0.15
Platelets(109/L)	215(167-273)	223(166-301)	0.614
Chest X-ray Findings n=208			
Clear	1(1.5)	105(75.0)	<0.001
Bilateral Infiltrates	54(78)	22(15.7)	
Unilateral Infiltrates	12(17.6)	12(8.5)	
Outcome			
Recovered (with negative PCR)	27(39.1)	54(36.7)	<0.001
Home isolation	17(24.6)	65 (44.2)	
Transferred To Another Healthcare Facility For Isolation	1(1.4)	20(13.6)	
Transferred To ICU	13(18.8)	0(0.0)	
Left Against Medical Advice	9(13.0)	8(5.4)	
Died (in ward and ICU)	14(20)	0(0.0)	

care and should be reserved for secondary bacterial infection.[16]

There was no mortality in patients that presented with non-severe disease in our study. Overall mortality in our study was 6.5% which is higher than 3.77% reported from Wuhan, [17] but lower than reported from Pakistan where 22% was reported in a similar population, as well as 37.7% in severe cases. [3,4] We found a very high mortality in those patients that required ICU care, as is reported from Pakistan and worldwide.[3,18]

Limitations of our study include that it is retrospective with missing information.

Moreover, management guidelines were changing even during the short study duration so that comparison between modalities of treatment cannot be done. We do not have follow-up of patients who were discharged on isolation recommendations and therefore cannot comment on their final outcome.

CONCLUSION

During the first wave of COVID-19 in Pakistan, patients across the clinical spectrum of the disease were admitted to the Isolation Ward of a public sector hospital. A male predominance was demonstrated. Severe disease was associated with the presence of co-morbidities, elevated neutrophil-to-lymphocyte ratios and high inflammatory markers. Mortality was very high in those that required ICU care.

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REFERENCES

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. Jama. 2020; 323(11):1061-9.

2. World health Organization (WHO). Covid-19 coronavirus-19 pandemic. Geneva: WHO; 2021.

3. Baqi S, Naz A, Sayeed MA, Khan S, Ismail H, Kumar V, et al. Clinical Characteristics and Outcome of Patients With Severe COVID-19 Pneumonia at a Public Sector Hospital in Karachi, Pakistan. Cureus. 2021; 13(2).

4. Asghar MS, Kazmi SJH, Khan NA, Akram M, Khan SA, Rasheed U, et al. Clinical

Table 3: Characteristics Of 90 Patients Admitted To The Covid-19 Isolation Ward That Tested Negative For Pcr Sars-Cov 2

Demographics	n(%)
Age (Median-IQR)	32(24-45)
Male	61(67.8)
Female	29(32.2)
Occupation	
Health Care Workers	4(4.4)
Discharge Diagnosis	
Upper Respiratory Tract Infection	65(72.2)
Community Acquired Pneumonia	10(11.1)
COVID Related Anxiety/Hyperventilation	7(7.8)
Highly Suspected COVID/False Negative PCR	2(2.2)
Other Diagnoses	6(6.7)
Hospital Stay (Median IQR) days	1(1-2)

profiles, characteristics, and outcomes of the first 100 admitted COVID-19 patients in Pakistan: A single-center retrospective study in a tertiary care hospital of Karachi. Cureus. 2020; 12(6).

5. Issued by Ministry of Health Services: Clinical Management Guidelines for COVID-19 Infections. GoPMoNHS; 2020 Dec. Report No.: 12-04.

6. Issued by Ministry of Health Services: Clinical Management Guidelines for COVID-19 Infections. GoPMoNHS; 2020 April. Report No.: 12-01.

7. Mazzucato M, Kattel R. COVID-19 and public-sector capacity. Oxford Review of Economic Policy. 2020; 36(S1):S256-S69.

8. Ayyaz M, Chima KK, Butt UI, Khan WH, Umar M, Farooka MW, et al. Combating COVID 19 in a public sector hospital in Pakistan. Ann Med Surg. 2020.

9. Rosenbaum L. The untold toll—the pandemic's effects on patients without Covid-19. Mass Medical Soc. 2020.

10. Adibe B, Perticone K, Hebert C. Creating wellness in a pandemic: a practical framework for health systems responding to COVID-19. NEJM Catal Innov Care Deliv. 2020.

11. World health Organization (WHO). Mental health and psychosocial considerations during the COVID-19 outbreak. Geneva: WHO; 2020.

12. Yang X, Yu Y, Xu J, Shu H, Liu H, Wu Y, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Resp Med. 2020; 8(5):475-81.

13. Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L, et al. Association of inflammatory markers with the severity of COVID-19: a meta-analysis. Int J Infect Dis. 2020; 96:467-74.

14. Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. MedRxiv. 2020.

15. Group TRC. Dexamethasone in hospitalized patients with Covid-19—preliminary report. The N Eng J Med. 2020.

16. Furtado RH, Berwanger O, Fonseca HA, Corrêa TD, Ferraz LR, Lapa MG, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet. 2020; 396(10256):959-67.

17. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clinical Mic Inf. 2020; 26(6):767-72.

18. Quah P, Li A, Phua J. Mortality rates of patients with COVID-19 in the intensive care unit: a systematic review of the emerging literature. Crit Care. 2020; 24:1-4.

Author's Contribution

Conflict of Interest

Grant Support and Financial Disclosure

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.