ORIGINAL ARTICLE

CORONA VIRUS DISEASE-19 CLINICAL AND LABORATORY CHARACTERISTICS ASSOCIATED WITH DISEASE SEVERITY IN PATIENTS PRESENTING AT A TERTIARY CARE HOSPITAL OF PESHAWAR

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Background: Coronavirus disease-19 has a wide range of clinical presentations and varied outcomes. It is a new disease and researchers are trying to explore its clinical presentation and outcome to know more about the course of the disease. The objective of the present study was to determine the clinical and laboratory characteristics of Coronavirus disease-19 associated with severity of the disease. **Methods:** This cross-sectional study was conducted at Rehman Medical Institute, Peshawar from April to August 2020. All patients presented to the hospital and were diagnosed as COVID-19 were enrolled in this study. Disease characteristics and clinical outcomes were noted in both mild and severe cases. Patients were divided into 2 groups based on the disease severity and a comparison was made between these groups in terms of demographics, lab parameters and outcomes. Data were analysed by using SPSS version 24. **Results:** Out of 227 patients, 80.2% (n=182) were males while 19.8% (n=45) were females. The mean age of the patients was 54.44±14.35 yrs. 61.2% (n=139) had co-morbidities with diabetes being the most common. 26.9% (n=61) had severe disease and 18.1% (n=41) died.20.7% (n=47) had lymphopenia, 48.45% (n=110) had leucocytosis and thrombocytopenia was seen in 11.89% (n=27). CRP, D-dimers, ferritin and LDH were raised in 83.25% (n=189), 80.17% (n=182), 81.05% (n=184), 77.09% (n=175) of the patients respectively. Comparing our designated patient groups revealed that old age, comorbidities, leucocytosis, lymphopenia, raised inflammatory markers were associated with severe disease and that mortality was high in the severe disease group. **Conclusion:** Middle-aged males with comorbidities were the most affected subset of patients. Disease severity was associated with old age, comorbidities and certain lab abnormalities. The outcome was poor in case of severe disease. However, no gender correlation was found with disease severity.

Keywords: Clinical characteristics; Coronavirus; COVID-19; Mortality; Outcome

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INTRODUCTION

The Coronavirus-19 (COVID-19) pandemic emerged as a challenge, the likes of which the world had not encountered before and this is especially true for the healthcare systems and scientific communities of the world.[1] It emerged from Wuhan and quickly clutch the world in its menacing grip and soon led to 23 million individuals being infected and 815 thousand deaths around the globe.[2,3]

Pakistan, like most of the countries worldwide had its fair share of COVID-19 cases, reaching its peak in the last couple of months. Records show 294 thousand confirmed cases to-date, with a death toll of 6267. Khyber Pakhtunkhwa province reported a total of 35 thousand confirmed cases and 1248 deaths at the time this study was conducted.[3]

The disease exhibits a spectrum that ranges from mild to critical, however, most infections are said to be mild to moderate.[4–7] This was highlighted in the study including 44000 patients with confirmed COVID-19, where 81% had a mild disease while 14% and 5% patients suffered from severe and critical disease respectively. The overall mortality was 2.3% and no death was reported in case of non-severe disease.[8] Various studies from China, the United States of America, the United Kingdom, Italy, Canada and Singapore found a multifariousness in age and gender of patients affected by COVID-19. Studies also outlined variation in how patients present & progress through the disease depending upon the region & country.[2]

It has been established through various studies conducted during the pandemic that there are particular risk factors associated with severe disease

& adverse outcomes. These risk factors include gender, age, presence of comorbidities, certain clinical features & laboratory findings, as well as the treatment rendered.[8–10] There is also evidence that risk factors may affect outcomes & severity of disease differently among different ethnic groups, thus making even certain ethnicities a risk factor.[11,12]

There is a deficiency of literature regarding characteristics of severe disease at the national level, however, India has reported a few studies describing the course and outcome of COVID-19 in their population.[13] We have only a couple of studies at the national level so far, elucidating this aspect of the disease. One study including 100 patients from Karachi, during the early days of the pandemic. described that old-aged males suffered more from disease. The most frequently encountered symptom was fever, followed by respiratory symptoms. Laboratory parameters also exhibited characteristic dynamic changes. The mortality rate was 22%[14], however, the study was deficient in highlighting factors associated with poor patient outcomes.

Diversity in disease presentation, course and outcome exhibit a strong reliance on the region, surroundings, social conditions, healthcare systems and facilities of the affected territory and its population. Literature in this regard is glaringly deficient locally at Khyber Pakhtunkhwa province. It is important to pinpoint these details to discern at the time of diagnosis, patients that are likely to develop severe disease to intervene in a timely fashion and reduce mortality. Our study aims to describe the characteristics of COVID-19 disease and also outlines the factors associated with a severe disease in patients presented to Rehman Medical Institute, Peshawar.

MATERIAL AND METHODS

This cross-sectional study was conducted in Rehman Medical Institute, Peshawar from April to July 2020. Ethical approval was obtained from Rehman Medical Institute Research Ethics Committee. All patients who presented to the hospital and were diagnosed as COVID-19 were enrolled in the study. Informed written consent was taken from all patients or their surrogates whichever appropriate and convenient at the time.

Diagnosis of COVID-19 infection was based on positive reverse transcriptase polymerase chain reaction (RT-PCR) performed on nasopharyngeal swab as is the criteria for diagnosis,[15] but due to its limited sensitivity and probability of technical errors, the results can be false negative.[15] In that instance we took into consideration the typical CT-Scan chest findings of COVID-19, as defined by the American Radiology Association as a means of diagnosis when clinical suspicion was high.[16,17]

Patient's demographic profile, duration of illness, comorbidities and laboratory parameters were noted in a pre-designed proforma. Patients were categorized based upon disease severity as per guidelines issued by the National Institute of Health Pakistan.[18] Patient's clinical outcomes in terms of death/alive were noted. Further the patients were categorized into two groups.

Group-I comprised of patients with mild and moderate disease and was named the non-severe disease group. Group II included patients with severe and critical disease and was labelled the severe disease group. Comparison between these 2 groups was made with respect to age, gender, duration of illness, resolution of symptoms and lab parameters.

Data was entered and analysed on SPSS version 24. For quantitative variables e.g., Age, duration of disease, blood counts, recovery time etc. mean±SD was calculated. For qualitative variables e.g., gender, outcome, blood group, disease severity etc. frequency and percentages were calculated. Groups were compared against different variables to look for statistically significant difference. Chi^2-test and ANNOVA test were applied wherever appropriate. p-value ≤ 0.05 was taken statistically significant.

RESULTS

A total 227 COVID-19 patients were enrolled in this study. Demographics, pre-morbid status, outcome, severity of the disease with management place, duration of disease and resolution of symptoms are all shown in table-1.

When compared the two groups based on severity of COVID-19 disease, there was statistically significant association of age, comorbidities, outcome and resolution of symptoms with severe disease. (p-value<0.05). However, there was no association of gender and duration of disease with the severity of disease as shown in table-2. When overall lab parameters were analysed, TLC was raised in 48.45% (n=110) patients, while only 3.08% (n=7) had leukopenia. Lymphopenia was observed in 20.70% (n=47) patients, thrombocytopenia in 11.89% (n=27) and C-reactive protein was elevated in 83.25% (n=189) patients. The rest of the inflammatory markers were done in limited number of patients, whenever needed. D-dimers were raised in 80.17% (n=182). Ferritin was raised in 81.05% (n=184) while LDH was elevated in 77.09% (n=175).

On comparison of the two groups on the basis of lab parameters, there was statistically significant association of leucocytosis, lymphopenia, raised D-dimmers, LDH and serum ferritin levels (p-value<0.05) with the severity of COVID-19 disease as shown in table-3.

Table-1: Demographic and other characteristics of study population

Features		% (n=227)
Gender	Male	80.2 (182)
	Female	19.8 (45)
Age in years (mean±SD)		54.44 (±14.35)
Premorbid status	DM	18.1 (41)
	HTN	6.6 (15)
	IHD	2.2 (5)
	Asthma	1.8 (4)
	Multiple comorbidities	31.7 (72)
	Nil	38.8 (88)
Outcome	Alive	73.1 (166)
	Death	18.1 (41)
	Discharged on will	6.6 (15)
Disease Severity	Mild	33 (75)
	Moderate	40.1 (91)
	Severe	12.8 (29)
	Critical	14.1 (32)
Place of Management	Ward	36.6 (83)
	ICU/HDU	18.1 (41/9)
	Home	41.4 (= 94)
Duration of illness (days) (Mean±SD)	8.68 (±4.04)	
Resolution of symptoms (days) (Mean±SD)	9.16 (±5.86)	

Table-2: Comparison of demographic and clinical characteristics of two groups

Features		Group I	Group II	*p*-value
Gender	Male	81.1% (n=116)	81.3% (n=52)	0.982
	Female	18.9% (n=27)	18.8% (n=12)	
Age (mean±SD)		53.00±14.807	57.27±13.397	0.049
Premorbid status	DM	20.3% (n= 29)	15.6% (n=10)	0.002
	HTN	7.0% (n= 10)	7.8% (n=5)	
	IHD	1.4% (n= 2)	4.7% (n=3)	
	Asthma	2.1% (n=3)	1.6%(n=1)	
	Multiple comorbidities	22.4% (n=32)	46.9%(n=30)	
	Nil	46.9% (n=67)	21.9%(n=14)	
Outcome	Alive	89.8% (n=149)	27.9% (n=17)	< 0.05
	Death	1.2% (n=2)	63.9% (n=39)	
	Discharged on will/Left against medical advice	9.0% (n=15)	8.2% (n=5)	
Duration of illness (days)		8.95±4.24	8.60±5.25	0.761
Resolution of symptoms (days)		8.60±5.89	12.28±7.54	0.004

Table-3: Comparison of laboratory parameters between two groups

Lab parameters	Group I	Group II	*p*-value
Hemoglobin	15.21±12.02	14.79±10.07	0.367
Total Leukocyte count	10.82±4.955	14.52±37.92	0.036
Platelets	275.00±191.39	278.52±177.90	0.671
Lymphocyte count	1.67±1.11	1.50±1.046	< 0.05
C-reactive protein	14.96±43.80	13.39±10.03	0.778
D dimmers	537.40±959.46	2634.26±5357.25	0.001
LDH	372.46±182.84	566.72±244.28	< 0.05
Ferritin	851.00±699.94	1178.04±773.15	0.005

DISCUSSION

The average age of our study population was 54.4 years. This finding of our study was supported by studies conducted at China and Pakistan, which described the mean age as 55 years and 52.58 years respectively.[14,19] However many studies from China and some from India have described relatively younger patients effected by COVID-19.[20–22] On the other hand studies published in the UK and the USA have described older patients e.g., >65 years.[23–25] The reason might be that the mean age of the European population is higher than our region.

Male gender was significantly dominant in our study. There have been other studies that described a relatively higher disease occurrence in males.[14,22–24] but no study before this has documented such a high ratio of males being affected. As a matter of fact, many studies describe an almost equal gender distribution in this disease.[19–21,25] The explanation for this difference can be the relatively mild disease found in females as compared to males, hence no

need to seek medical attention.[9,26] Moreover, Pathan females are less likely to seek and get medical attention as compared to Pathan males.[27]

Duration of illness in our study was 8.6 days, which was similar to a study by Frederick S *et al*. where patients presenting to the hospital had symptoms for 5 days or longer.[25]A Chinese study found this to be 4.5 days[20] while a study from India described a shorter duration of illness e.g., 2.1 days.[22]

Several studies have emerged during the pandemic that have documented the variation in the severity of the disease. A study from China reported 17.6% patients with severe disease[20] while in Washington state, 49% patients suffered from severe disease.[25] A report by the Chinese Center for Disease Control and Prevention that included approximately 44,500 confirmed cases described 19% patients with severe infection.[8]

In our study 26.9% patients had severe disease. This variation can be explained by different factors like population demographics, duration of illness prior to presentation, presence of co-morbidities etc. 61.2% of our patients had comorbidities, out of which 31.7% suffered from multiple comorbidities, with diabetes being the most common one. Other studies have documented variable percentages of comorbidities in COVID-19 infected patients. In a study from United Kingdom, 77.5% patients had comorbidities with IHD being top of the list, followed by diabetes,[23] while the American population showed an even higher rate of comorbidities e.g. 93%.[25] On the other hand, there are also studies that have reported 46.4%[28] and 32% co-morbidities.[29]Wan S *et al* described that 31.9% patients had underlying diseases with hypertension (13 [9.6%]) and diabetes (12 [8.9%]) being the most frequent.[21] Three studies that described a lower percentage of comorbidities came from China, and what was noteworthy was that the age of the study population was lower than our study and other studies describing patients with higher comorbidities, therefore this difference may be explained by the discrepancy in the age of the patient populations.

22.1% of our patients were managed in high dependency or intensive care units. The proportion of patients admitted to critical care in our study was slightly higher than that reported in Italy (17%),[30,31] the UK and New York (14.2%),[32,33] but significantly higher than China (5.0%)[34].

We found leucocytosis in 48.45% patients while only 3.08%had leucopoenia. Thrombocytopenia was observed in 11.89% patients. Among inflammatory markers, C-reactive Protein was elevated in 83.25%, while Ferritin, D-dimers and LDH was raised in 80.95%, 80.4% and 77.09% patients respectively.

Several studies have described a wide variation of results regarding lab findings in COVID-19. Leucopoenia, lymphopenia and thrombocytopenia was observed in 9.1–33.7%, 35.3–82.1% and 5.0–36.2% of patients respectively in several different studies.[19,25,35,36]

In a study of the inflammatory markers of 63 patients, 41% showed an increase in lactate dehydrogenase and 67% showed a rise in C-reactive protein.[37]In a study from US ,100% patients had raised CRP and 80% had elevated LDH levels. The numerical differences in lab values can be explained by the duration and severity of the disease.

Mortality in our patients was 18.1%. However, in China it was 5.4%[22] while studies from US and UK stated 33% and 26% of deaths.[23,25] The difference in mortality can be explained on demographic features, disease severity and health care facilities of the study population.

A comparison between our severe and non-severe disease group found that old age was significantly associated with severe disease. Our finding is consistent with literature from China, Italy, US and UK.[8–10,23]

We did not find any association between gender and severe disease. This result is different from known literature where male gender has been described as associated with disease severity and poor outcomes.[9,10,23,26] This disparity in findings can be due to racial and ethnic differences and warrants further research.

Comorbidities have been associated with severe illness and mortality for example a study of several long-term care facilities affected by COVID-19 in Washington State, showed that 94 percent of the study population had a chronic underlying condition; the hospitalization and preliminary case fatality rates were 55 and 34 percent, respectively.[26] In an analysis of nearly 300,000 confirmed COVID-19 cases in the United States, the mortality rate was 12 times as high amongst patients with co-morbidities.[38] In a report of 355 patients who died of COVID-19 in Italy, the mean number of pre-existing comorbidities was 2.7, and only 3 patients had no underlying condition.[10] Our study also found a significant association between severe disease and the presence of co-morbidities.

Our study found a positive association between lymphopenia, leucocytosis, elevated inflammatory markers and disease severity, a finding that is supported by many studies, such as a study that highlighted the findings of lymphopenia and raised d-dimers in non-survivors vs survivors.[36] Another study from China compared non-critical patients to critical patients and found lower levels of lymphocytes and higher levels of CRP.[38]Asghar MS

et al, stated that leucocytosis, CRP, LDH and Lymphopenia were associated with disease severity.[14] Mortality was higher in severe disease group. This finding is well supported by other studies in literature.[19,23]

Some limitations of our study are that firstly it is a single center study. Secondly, it doesn't focus on disease symptoms. Our main focus was lab parameters and that too at the time of admission. There was no timely follow up at regular intervals through the course of the disease.

CONCLUSION

The present study concludes that the most commonly affected population was middle-aged males. Severe disease was found in 26.9% of our study population. Disease severity was associated with old age but no specific link between gender and severity could be established. The most commonly observed lab abnormalities were inflammatory markers elevation and the lab parameters most commonly associated with severe disease were leucocytosis, lymphopenia, and ferritin, LDH and D-dimmer elevation. Comorbidities were common in all our patients and were strongly linked with the severe disease. Mortality rate was 18.1%, with majority of the patients belonging to the severe disease group.

AUTHORS' CONTRIBUTION

WQ: conception and design of the study, manuscript writing, data analysis and interpretation. SAK: data collection and manuscript writing LS: data collection and manuscript writing MJ: data analysis and critical review of manuscript MFK: manuscript writing and its critical review. IU: data interpretation and critical review.

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