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Original Research Article

CROSS-SECTIONAL STUDY OF COVID-19 PATIENTS AND THEIR INFLAMMATORY MARKERS IN TERTIARY CARE HOSPITALS OF PESHAWAR, PAKISTAN

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***Abstract*:** *Coronavirus is one of the pandemic diseases that infect millions of people worldwide. The aim of the study was a cross-sectional study of COVID-19 and its inflammatory markers in tertiary care hospitals in Peshawar, Pakistan. Samples of nasopharyngeal swabs were collected from 150 COVID-19 patients. Blood samples were collected aseptically in three different tubes to measure serum ferritin, D-dimer and CBC. The samples were further analysed at the PCR laboratory, Hayatabad Medical Complex, Peshawar. In the study, 100 samples were found positive based on PCR among 150 patients in which the D-dimer was reported to have a high relationship (95%) with inflammatory markers. Abnormal ferritin (87%), Hb (26%), neutrophil (73%) and abnormal lymphocytes were reported (63%) in patients. The relationship between the age factors with risk of inflammatory markers revealed that in the age group 61-80, ferritin, D-dimer, Hb, Neutrophil and lymphocytes were observed with abnormal levels 18, 20, 05, 14 and 13, respectively. The prevalence of COVID-19 infection was recorded as higher in males than females. The study showed that COVID-19 infection significantly affects the parameters, including abnormal ferritin levels in males 55% and females 32%. The male was reported with a high-level abnormal D-dimer (58%) than the female (37%). The other inflammatory markers, such as abnormal neutrophils and lymphocytes, counted 44 and 37% in males and females at 30 and 29%, respectively. The study concludes that an increase in inflammatory markers correlates with disease severity; this could be used as a significant prognostic factor of the disease. More advanced immunological studies need to explore the mechanism of COVID-19 with inflammatory markers.*

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Keywords: Coronavirus, Inflammatory markers, Serum Ferritin, D-dimer

Introduction

Worldwide, Coronavirus disease is one of the infectious diseases that cause SARS-CoV-2. The viruses infected millions of populaces worldwide. The viruses belong to the family Coronavirdae and single-stranded positive RNA viruses. The genome size of this virus is approximately 32 kb. The first alert was observed in late December 2019, a cluster of new cases of human pneumonia has been spreading in Wuhan, China. The earliest date for signs to appear is December 1, 2019. The cause of these patients' symptoms was determined to be viral pneumonia, which developed as a dry cough, fever, malaise and dyspnea (Huang et al., 2020; Khalid et al., 2021; Tabassum et al., 2020). According to whole-genome sequencing, the causative agent is a novel COVID-19; initially, this disease was named Wuhan pneumonia (Wu et al., 2020). SARS-CoV-2 was transferred to other species; it originated in animals, most likely bats, where it eventually infected humans, according to phylogenetic studies (Li et al., 2020). The World Health Organization (WHO) declared a pneumonia outbreak in Wuhan City on December 31, 2019. In the cultural and economic center of central China, with a population of 11 million people, 59 cases were reported as of 5 January, with none being fatal. The WHO gave the new 2019 coronavirus novel (2019-nCoV) and officially named COVID-19. Based on phylogeny and taxonomy, the virus was formally called severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is a severe acute viral syndrome by the International Committee on Virus Taxonomy (ICTV) on February 12, 2020 (Li et al., 2020).

On February 26, 2020, the Pakistani Ministry of Health confirmed the first case of COVID-19 in Karachi, Sindh and the second case on the same date in Islamabad by the Federal Ministry (Sahin et al.,

2020). The Ministry of Health in Mardan, KP Pakistan, confirmed the first death due to COVID-19 infection on March 18, 2020. Shortness of breath, fever, dry cough, salivary formation, tiredness, muscle aches; joint pain, sore throat, headache and gastrointestinal discomfort are common symptoms of COVID-19 infection. Nausea, vomiting and diarrhea are some of the symptoms. The more serious predictors include cytokine storm, respiratory failure, sepsis and septic shock. Coughing and sneezing, as well as direct contact with infected surfaces or items, are ways for this pandemic to spread from person to person. Latest studies have also shown that urine, feces, saliva and semen contain the virus (Kasinathan and Sathar, 2020; Mady et al., 2020; Siddique et al., 2020). SARS-CoV is spread by respiratory aerosol droplets or contact with contaminated objects (Cao et al., 2021). The human angiotensin-converting enzyme 2 (ACE2) host receptor has a strong affinity for this spike protein (as well as many other animals such as pigs, primates and cats (Yao et al., 2020). The respiratory syndrome was the second largest infection attributed to the coronavirus MERS-CoV (Middle East respiratory syndrome coronavirus) in China. The identification of the virus in 2012 in Saudi Arabia as the source of a fatal infection (Azhar et al., 2019; Ishaque et al., 2021).

The virus belongs to a family known as coronaviridae and the nidovirus class. It's possible to identify COVID-19 into four generations: alpha, beta, delta and gamma. Human COVID-19 belongs to alpha or beta, while gamma and delta corona viruses affect birds. Seven different coronaviruses can infect humans. Three of the most lethal coronaviruses include MERS-CoV, SARS-CoV and SARS-CoV-2. In humans, they induce severe pneumonia by infecting the lower respiratory tract, resulting in diffuse alveolar destruction and an increase in morbidity and death. Two Indian geneticists studied 3600 COVID-19 strains from 55 countries and identified that a new virus strain known as Type 2a had taken the place of the parenteral variant seen in Wuhan. According to their findings, the strain originated in China and then spread within and outside the country (Upadhyay et al., 2020). The COVID-19 projection comprises three parts: an active domain, a single-pass transmittance anchor, and a brief intracellular tail. The ectodomain comprises two subunits: S1, which binds to receptors and S2, which fuses membranes. According to electron microscopy, the spike is a living-shaped trimmer with three S1 heads and a traumatic static S2. S1 binds to the host cell receptor during virus entry (Li, 2016). Angiotensin II (ACE2), a human transmembrane converting enzyme 2, has been shown to act as a SARS-CoV-2 receptor. The (ACE2) is the receptor-binding to the glycoprotein and virus binding to the host cell surface. Therefore, the viral RNA replicates as it reaches the host cell (Martins-Filho et al., 2020). The aim of the current study is the cross-sectional study of COVID-19 and its inflammatory markers in the tertiary care hospital of Peshawar, Khyber Pakhtunkhwa.

Materials and Methods

Sample collection for PCR

Nasopharyngeal swabs samples from 150 suspected COVID-19 patients were collected from symptomatic patients registered at different HMC and KTH quarantine centres in Peshawar. The samples were subjected to the PCR laboratory, Department of Microbiology at HMC Peshawar.

RNA extraction

The current research work "High pure viral nucleic acid kit" manufactured by Roche Company, was used to extract viral RNA. About 200 µl specimen was taken in a nuclease-free Eppendorf tube. Then, 300µl binding buffer, 50µl Proteinase K, 5µl internal control was added and incubated for 10 minutes at 72ºC. Then specimen was transferred to a filter tube and was centrifuged at 8000rpm for 1 minute in the collector tube, and then the liquid was discarded from the collection tube. After that, the filter tube was half filled with wash buffer for washing and was centrifuged at 8000rpm for 1 minute and again flow liquid was discarded. The washing step was repeated. Finally, 50 µl elution buffer was applied and centrifuged for 1 minute at 8000 rpm to elute the viral nucleic acid. The eluted viral nucleic acid was stored at – 15 to 20ºC for further analysis and subjected to PCR.

Samples collection for inflammatory markers

The blood samples were collected aseptically in three different tubes; Lithium Heparin for Serum Ferritin, Sodium Citrate for D-dimer and EDTA for CBC. All the samples were transferred in an ice box to the laboratory for further assessment.

Serum Ferritin analysis

The use of Roche kits immuno-turbidimetry principle measured ferritin. The Hitachi 912 clinical analyzer was used for measurement. The basic principle of immuno-turbidimetry is; Latex bound ferritin antibodies react with the antigen in the sample to form an antigen/antibody complex. The agglutination was measured turbidometrically. The turbidity formed is proportional to the ferritin concentration and is measured at 700nm (primary wavelength). The normal value of ferritin is 20 – 250 ng/ml.

Blood D-dimer Analysis

Latex particles coated with antibodies specific to human D-dimer fragments were used. The immune complexes of antigen/antibody cause an increase in light scattering, which is proportional to the concentration of D-dimer in the plasma sample. The light scattering is measured by reading turbidity at 570 nm. The normal value of D-dimer was less than 0.50.

Hematological analysis

The Sysmex KX-21 is a quantitative automated hematology analyzer for the diagnostic of CBC. Examination of the numerical and morphological findings of the CBC, including Hb with normal value

12.5 to 16.0gm/dl, WBC, platelets count and other parameters. Differential leukocytes count useful in the diagnosis of diseases such as anemia, leukemia, allergic reactions and viral, bacterial, and parasitic infections were noted. The normal differential leukocyte count was, i.e. neutrophil (Normal Value: 40 – 70%) and lymphocytes (Normal Value: 20 – 40%). To check the accurate results, one normal and abnormal sample was run.

Gender	**No. of Variables**					
	Age	**Ferritin**	**D-dimer**	**Neutrophil**	**Lymphocyte**	**Hemoglobin**
Mean (X)	55.939	932.686	32.174	80.525	16.808	13.210
Standard deviation (SD)	13.477	801.886	75.9741	11.318	10.417	2.064
			Female			
	Age	Ferritin	D-dimer	Neutrophil	Lymphocyte	Hemoglobin
Average (X)	59.648	1145.810	41.867	82.378	14.378	13.416
Standard deviation (SD)	11.102	900.224	118.827	12.052	10.662	2.086
			Male			
	Age	Ferritin	D-dimer	Neutrophil	Lymphocyte	Hemoglobin
Average (X)	57.096	994.741	37.693	80.080	17.064	17.064
Standard deviation (SD)	13.245	778.004	93.556	11.586	10.561	10.561

Statistical analysis

The results were interpreted statistically by using MS Excel and GraphPad prism software. One-way ANOVA analysis and t-test were performed for the significance (p) of different inflammatory markers correlation.

Results

Relationship of inflammatory markers with COVID-19 patients

Among the 150 suspected COVID-19 patients, 100 samples were found positive based on PCR. The current study showed that among the 100 COVID-19-positive patients, D-dimer has a high relationship (95%) with an inflammatory marker. The ferritin was normal in 13% of patients and abnormal in 87% of patients. The normal D-dimer and Hb were 5% and 74%, respectively, while abnormal was 95% and 26%, respectively. Similarly, other inflammatory markers such as the neutrophil were 27% normal, abnormal (73%), and normal lymphocyte (37%) and abnormal lymphocyte were reported in 63% of patients. These results are summarized in Figure 4.1, and all inflammatory markers significantly affect (p-value<0.005) COVID-19 patients. The average mean and standard deviation of the gender and inflammatory markers are shown in Table 1. The inflammatory markers show significance (p-value) as shown in table 2.

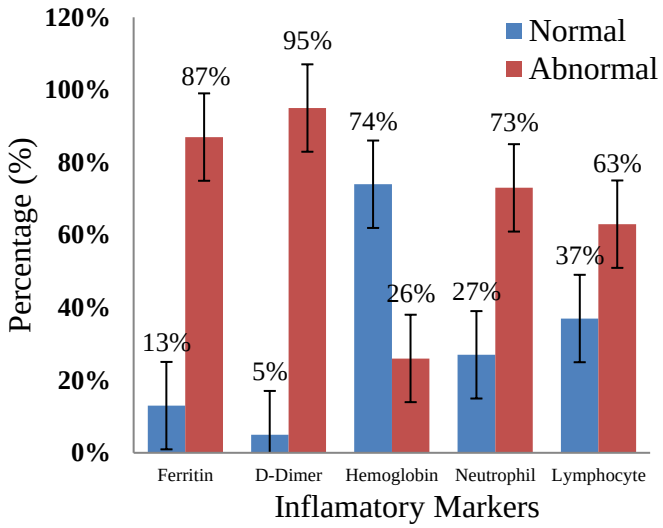

Fig. 1. Relationship of normal and abnormal inflammatory markers with COVID-19 patients.

Table 1. Demographic characteristics of different variables of COVID-19.

Table 2. One-way analysis of variance in COVID-19 inflammatory markers.

One-way analysis of variance	
P value	< 0.0001
P value summary	***
Are means signif. different? (P < 0.05)	Yes
No. of inflammatory groups	5
F	122.5
R squared	0.5000
Bartlett's test for equal variances	
Bartlett's statistic (corrected)	2521
P value	< 0.0001
P value summary	***
Do the variances differ signif. (P < 0.05)	Yes

Age-wise distribution of inflammatory markers with COVID-19 patients

The current study showed the relationship between the age factor and the prevalence of COVID-19 infection with risk of inflammatory markers in all age

groups. In the age groups between (20-40) normal ferritin levels were 01, and abnormal was 04. Similarly, other inflammatory markers, normal D-dimer, Hb, Neutrophils and lymphocytes were reported to be 0, 04, 0 and 01, respectively. In comparison, the result showed abnormal inflammatory markers, D-dimer (04), Hb level (0), Neutrophil (04) and lymphocyte (03). Similarly, these parameters were observed in the age group (41-60), normal ferritin level (04) and abnormal was 33. The D-dimer normal level was (02) and abnormal (34), the Hb normal level (27) and abnormal (09) and normal neutrophil was 07, and the abnormal level was 29. The lymphocyte's normal and abnormal level was reported 15 and 20, respectively. The risk of these parameters ferritin, D-dimer, Hb, Neutrophil and lymphocyte were observed with abnormal levels 18, 20, 05, 14 and 13, respectively, in age group (61-80). The normal level of ferritin was 02, D-dimer (02), the Hb (17), neutrophil (08) and the lymphocytes (10), as shown in Fig. 2.

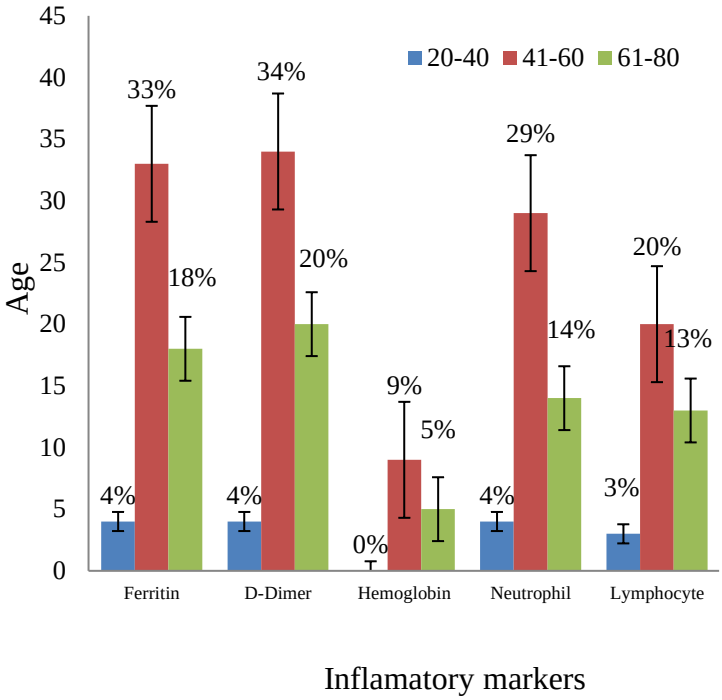

Fig. 2. Age-wise distribution of inflammatory markers with COVID-19 patients.

Gender	Ferritin		D-dimer		Hemoglobin (Hb)		Neutrophil		Lymphocyte	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Male	07	55	04	58	48	14	18	44	25	37
Female	06	32	01	37	15	23	08	30	09	29

Table 3. Gender-wise distribution of inflammatory markers with COVID-19 patients.

Gender-wise distribution of inflammatory markers with COVID-19 patients

The study showed that the prevalence of COVID-19 infection is influenced by gender, and a high percent infection was recorded in males compared to females. The study also showed that infection with COVID-19 has a significant effect on these parameters, including abnormal ferritin levels in males was 55% (55/100), and in females 32% (32/100). The male was reported with high-level abnormal D-dimer 58% (58/100) than female 37% (37/100). The other inflammatory markers, such as Hb and neutrophils level, were 14 % and 23% in males and females, respectively. The abnormal neutrophil and lymphocyte counts were 44% and 37% in males and in females 30% and 29% respectively, summarized in Table 3.

Discussion

Covid-19 is one of the pandemic issues that loom out the world. Millions of people have died, and still, the populations face different problems. Pakistan is a developed country that faces many challenges in protecting and treating the infected population. In this study, we present different inflammatory markers and their cross-section study. The male-female differences in the reported SARS-CoV-2 infections are age-related in all countries, with females of 10 to 50 years of age having a higher incidence than males of 10 to 50. Males in Spain, Germany, Switzerland, Belgium and Norway have a greater death rate than females in all age groups older than 20 years (Marina and Piemonti, 2020). There are age-related male-female differences in confirmed SARS-CoV-2 infections in seasonal and pandemic influenza epidemics (Wong et al., 2019). Similarly, our study showed the highest prevalence of COVID-19 in males than females. The study showed the relationship between the age factor and the prevalence of infection with COVID-19, as the virus can infect all age groups. Still, high abnormal inflammatory markers were obtained in the age group 41-60. A study documented that patients with potentially adverse outcomes could reliably be identified on the age basis, lymphopenia and leukocytosis (Xu et al., 2020). We have found from the previous study that an age of more than 50

years is significantly associated with adverse outcomes (Zhang et al., 2020). In addition, clinical parameters numerous scores have been developed by various factors that affect infection of COVID-19, most important, sex and the age of the patient. However, the male sex relates to the danger of increasingly extreme COVID-19 results (Scully et al., 2020). Similarly, the current study showed that infection with COVID-19 has a significant effect related to sex, such as abnormal ferritin and D-dimer level in males was higher than in females. The result reported abnormal ferritin and D-dimer level at 55% and 58% respectively in males while ferritin was at 32% and D-dimer at 37% in females. The relationship between the age factor and high abnormal inflammatory markers were ferritin 87%, D-dimer 95%, Hb 26%, neutrophil 73% and lymphocytes 63%. Another outcome of the study was levels of ferritin in the patient's serum COVID-19, which were significantly found to be high (87%). We observed high neutrophils, lymphocytes, ferritin and D-dimer in COVID-19 Patients. All these inflammatory have significant *p*-value and correlation with one another. Different studies revealed that people infected by the bacterial disease had higher ferritin levels than infection with the virus. The increase of ferritin levels in serum predicts a weak outcome in the hospital with infection by influenza (Zhang et al., 2020). Infection with COVID-19 affects a biomarker of the body, such as ferritin levels. COVID-19 patients had higher ferritin levels in their blood, according to the research (Qu et al., 2020).

Conclusion

The study concludes that the patients infected with COVID-19 lead risk parameters such as D-dimer ferritin, Hb, Neutrophil and Lymphocyte. The relationship between the age factor and the prevalence of infection with COVID-19, as the virus can infect all age groups but mostly affect those>40 yrs. As the increase in inflammatory markers correlates with disease severity, regular monitoring by using these parameters can improve the disease outcome and thus could be used as significant prognostic markers of the disease.

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Conflict of interest

No potential conflict of interest.

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