Differential Haematological and Inflammatory Markers in Symptomatic and Asymptomatic COVID-19 Patients: A Retrospective Cohort Study

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ABSTRACT

BACKGROUND

COVID-19, which is caused by severe acute respiratory syndrome coronavirus 2, has proved difficult to contain in terms of transmission due to the high number of individuals who are asymptomatic. Knowledge about these changes in haematological and inflammatory markers in symptomatic and asymptomatic patients is important for better diagnosis and further public health management.

METHODS

The present study is a retrospective cohort study that aimed to assess the immunological profile of 100 COVID-19 patients attending Faisalabad Teaching Hospital, Pakistan. The differences between marked haematological and inflammatory markers that consist of haemoglobin, red blood cells, neutrophils, lymphocytes, c-reactive protein (CRP), lactate dehydrogenase (LDH), and between those with symptoms and those who are asymptomatic were analysed. The results were analysed using the Mann–Whitney U Test since the data distribution proved to be non–parametric and the accepted level of significance was fixed at 0. 05.

RESULTS

CRP, LDH, neutrophil percentage, lymphocyte percentage, and total leukocyte count were significantly higher among symptomatic patients than asymptomatic patients, proving that the immune response is stronger in symptomatic patients. There were no significant differences in haemoglobin, platelets, eosinophil percentage, and monocyte percentage in the two groups.

CONCLUSION

The highlighted demographic, inflammatory, and haematological differences between symptomatic COVID-19 cases can be applied towards optimizing clinical treatment strategies and formulating relevant public health guidelines. This work has highlighted the need to employ specific diagnostic strategies in relation to various presentations of the patients.

Keywords: SARS–CoV-2, COVID-19, Asymptomatic, Symptomatic, Haematological markers, Inflammatory markers, Non–parametric statistics

Background and Introduction

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS–CoV-2) virus, has resulted in a global pandemic, significantly affecting public health. A notable challenge in managing the disease is the presence of asymptomatic individuals who can still spread the virus.

Coronavirus Disease 2019 (COVID-19) is caused by the novel SARS–CoV-2 was a novel virus, first identified in Wuhan, China, in December 2019. The disease quickly spread into a global pandemic, significantly affecting public health, economies, and daily life worldwide. The World Health Organisation (WHO) called it a Public Health Emergency of International Concern on 30th January 2020 and a pandemic on 11th March 2020.[1] While the majority of the affected individuals present symptoms that range from mild to severe respiratory illness, a considerable number are asymptomatic, making them the silent agents undermining containment strategies.[2] The separation of symptomatic and asymptomatic patients has also been the subject of various studies, with recent works pointing out that individuals with a lack of symptoms can also suffer from lung lesions.[3] It is important to comprehend the differences in immune response between the symptomatic and asymptomatic populations. The investigation plan comprises the evaluation of haematological and inflammatory indices between these groups, expecting that symptomatic patients will demonstrate increased concentrations of c-reactive protein (CRP) and lactate dehydrogenase (LDH), which reflects a heightened inflammatory process. The purpose of this study is to increase the diagnostic accuracy and treatment plans as they intend to be implemented in such areas as Faisalabad in Pakistan considering the scarce healthcare facilities.

The clinical symptoms of COVID-19 are believed as not only the direct outcome of the viral infection but also the inflammatory response of the host.[4,5] Lymphocyte and haematologic factors including Red blood cells (RBCs), Platelets (PLTs), neutrophils, lymphocytes, CRP, and LDH have become significant measures of the immune response and have been used to predict COVID-19 severity.[6] For example, lymphopenia was reported to be associated with poor prognosis, whereas, high CRP and LDH defined higher inflammation and tissue destruction, respectively.[7]

The dynamics of these markers, however, have not been as clearly defined in asymptomatic individuals, who may be infected with the virus but have no symptoms. Understanding the levels of these markers in asymptomatic patients is essential, as they may reveal subclinical pathophysiology and help identify individuals at risk for developing post–infection sequelae.[8] Moreover, delineating the haematological and inflammatory profiles of symptomatic versus asymptomatic patients could aid in improving the clinical management of the disease, assessing the risk of transmission, and tailoring public health strategies.[9,10]

Within the geographical framework of Faisalabad, Pakistan, the COVID-19 issue exhibited parallels with the worldwide crisis, posing significant challenges to both the healthcare system and the scientific community. The true number of asymptomatic patients remained unknown despite major efforts to stop the spread, partly because of gaps in broad testing and molecular tracking.[11] Considering the socioeconomic and healthcare–related difficulties prevalent in Faisalabad and comparable areas, it is crucial to develop a comprehensive comprehension understanding of disease progression, enhanced by laboratory findings, particularly for a pathogen recognized for its clinical heterogeneity.

The present study aims to enhance this knowledge gap by comparing the inflammatory and haematological markers in symptomatic and asymptomatic patients who have demonstrated positive results for COVID-19 in Faisalabad. By examining the levels of RBCs, PLTs, Neutrophils, Lymphocytes, CRP, and LDH, this study seeks to elucidate the immunological and haematological characteristics that distinguish symptomatic from asymptomatic cases. In addition, the study intends to contribute to the limited data on asymptomatic infections in a Pakistani cohort, thereby enhancing the demographic diversity of COVID-19 research.

Materials and Methods

This study was done using a retrospective cohort approach to determine how different haematological and inflammatory markers affected the clinical presentations of COVID-19 in both symptomatic and asymptomatic patients. The study maintained a high standard of reporting through the application of STROBE guidelines for reporting observational studies.

Study Design

This study used a retrospective cohort design, therefore relying on archived clinical data and biological samples from COVID-19 patients. This approach enabled the evaluation of relationships between haematological indices, including RBCs, PLTs, neutrophils, lymphocytes, CRP, and LDH with symptoms and clinical severity in symptomatic and asymptomatic groups.

Setting and Study Population

This research was carried out at Government General Hospital Ghulam Muhammad Abad, Faisalabad, Pakistan, which is a tertiary healthcare hospital, among COVID-19 patients from the period July 2022 to December 2022. All 100 patients who participated in the study tested positive for COVID-19 using the Polymerase chain reaction (PCR) test. According to the patients' records in the medical files, they were classified as symptomatic or asymptomatic.

Ethical Considerations

Ethical approval was obtained from the Research Ethics Committee of Riphah International University, and the study was conducted according to the ethical guidelines established by the Centers for Disease Control and Prevention. Patient confidentiality was maintained by anonymizing all data, and informed consent was obtained from all participants or their legal guardians. This study was registered with the Research Registry, and the unique identifying number is researchregistry10636.

Participant Recruitment

Participants were retrospectively selected from hospital records based on a confirmed COVID-19 diagnosis via PCR testing. Eligibility criteria included all COVID-19-positive patients, regardless of symptom presentation. Exclusion criteria encompassed patients with severe respiratory diseases or significant comorbidities, such as tuberculosis, which could confound the association between haematological markers and COVID-19 symptoms.

Data Collection

Demographic information (age, gender, medical history) and blood samples were obtained from participant records. Blood samples were collected in vacutainers and subsequently analysed for biochemical and haematological markers. Data collection adhered to the ethical approval process, ensuring that all collected data were anonymized and securely stored.

Clinical Assessment

Clinical assessments were performed using a comprehensive chart that included both questionnaires and medical examinations. Patients were categorized into symptomatic and asymptomatic groups based on recorded symptoms such as fever, cough, and shortness of breath. The presence or absence of these symptoms was documented based on information recorded in the patient's medical history.

Laboratory Analysis

Laboratory analyses focused on some key haematological and inflammatory markers, including Complete blood count, CRP, and LDH. Blood samples were collected using standard venipuncture techniques and prepared for analysis using the HumaCount 5D analyser. This analyser quantified RBCs, PLTs, white blood cells (WBCs), and differential WBC counts, including neutrophils, lymphocytes, monocytes, and eosinophils. The results were interpreted using the analyser's software. Serum samples, free from haemolysis, were prepared and analysed using specific assays on the Huma Star 200 analyser. Quality control checks were regularly performed to ensure the accuracy and precision of the results.

Data Sources and Measurement

Major sources of instrument data were hospital records from the Government General Hospital Gulamaabad. Data were manually abstracted and normalized, to make certain entities aligned between the asymptomatic and symptomatic groups in accordance with rigorous procedures to preserve the quality of the data.

Bias

To minimize bias, patients with significant comorbidities were excluded, and standardized methods were used for data collection. Although the retrospective design reduces selection bias, potential biases in data availability and quality were acknowledged. Multiple imputation techniques were employed to address any missing data and ensure robust statistical analysis.

Study Size

The study size was determined based on the availability of patient records during the study period. A total of 100 patients were included, with the sample size chosen to balance the need for statistical power with practical constraints in data availability. The chosen sample size was deemed sufficient to detect significant differences between the groups under study.

Quantitative Variables

Quantitative variables, including haematological markers and clinical parameters, were analysed in their continuous forms. Variables were categorized where necessary based on clinically relevant cut–off values to facilitate comparison between groups.

Statistical Methods

Data analysis was conducted using SPSS version 23.0. The normality of data distribution was assessed using the Shapiro–Wilk test, which informed the choice of statistical tests. For comparisons between symptomatic and asymptomatic groups, the Mann–Whitney U Test was employed due to the non–normal distribution of the data. The Mann–Whitney U Test was used to compare median values between groups. Potential confounders were controlled for using multivariate analysis, ensuring the validity of the comparisons. Multiple imputation techniques were used to handle missing data, reducing the potential for bias. Statistical significance was set at a conventional alpha level of 0.05. Sensitivity analyses were performed to test the robustness of the findings under different assumptions about missing data and variable categorization.

Results

Patient Demographics and Distribution

The study cohort consisted of 100 individuals who tested positive for SARS–CoV-2, comprising a near–equal gender distribution, with 51% male (n = 51) and 49% female (n = 49). Among these, a significant disparity was observed in the distribution of symptomatic and asymptomatic cases, with 71% (n = 71) classified as symptomatic and 29% (n = 29) as asymptomatic. The median age of symptomatic patients was 55 years (IQR: 48–63) compared to 52 years (IQR: 45–60) in the asymptomatic group. In total, 60% of symptomatic patients had at least one comorbidity compared to 50% of asymptomatic patients, though these differences were not statistically significant (P > 0.05).

Normality of Distribution

To determine whether the haematological and inflammatory markers in both symptomatic and asymptomatic groups followed a normal distribution, the Shapiro–Wilk test was employed. The results, detailed in Table 1, reveal a significant deviation from normality for most markers under investigation. Specifically, inflammatory markers such as CRP, LDH, and NLR exhibited p–values less than 0.05, indicating that these markers are not normally distributed in either symptomatic or asymptomatic patients. This finding necessitates the use of non–parametric statistical methods, which are more appropriate for data that do not meet the assumptions of normality.

The stability of haemoglobin levels across both symptomatic and asymptomatic groups, as indicated

Table 1 | Shapiro-Wilk Normality Test Results

Markers		Symptomatic / Asymptomatic	Sample Size	Statistic	Sig.
Inflammatory Markers	C-Reactive Protein	Symptomatic	79	0.932	0.001*
		Asymptomatic	21	0.289	0.0001*
	LDH enzyme	Symptomatic	79	0.767	0.0001*
		Asymptomatic	21	0.594	0.0001*
	Neutrophils	Symptomatic	79	0.905	0.0001*
	Lymphocyte	Asymptomatic	21	0.843	0.001*
	Ratio Total Leukocyte count	Symptomatic	79	0.299	0.0001*
		Asymptomatic	21	0.919	0.029*
Heam Atological Markers	Neutrophil Percentage	Symptomatic	79	0.897	0.0001*
		Asymptomatic	21	0.924	0.039*
	Lymphocytes Percentage	Symptomatic	79	0.885	0.0001*
		Asymptomatic	21	0.912	0.019*
	Monocytes Percentage	Symptomatic	79	0.906	0.0001*
		Asymptomatic	21	0.892	0.006*
	Eosinophils Percentage	Symptomatic	79	0.802	0.0001*
		Asymptomatic	21	0.808	0.0001*
	Platelets	Symptomatic	79	0.96	0.023*
		Asymptomatic	21	0.91	0.017*

Table 2 | Mann-Whitney U Test Results for Comparison of Haematological and Inflammatory Markers

Markers	Variable Name	Symptomatic	Asymptomatic	U Statistic	P-Value
		Median			
Inflammatory Markers	C-Reactive protein	49.00	0.80	4.00	0.0001*
	LDH enzyme	884.00	623.00	685.50	0.009*
	Neutrophils Lymphocyte ratio	8.10	3.80	546.50	0.0001*
Heamatological Marker	Neutrophil Percentage	83.00	75.00	544.50	0.0001*
	Lymphocytes Percentage	10.00	20.00	545.00	0.0001*
	Total Leukocyte count	13700.00	8900.00	615.00	0.002*
	Hemoglobin	12.30	11.90	905.00	0.344
	Platelets	227000.00	201000.00	968.00	0.640
	Eosinophils Percentage	2.00	2.00	982.00	0.698
	Monocytes Percentage	3.00	3.00	1010.00	0.879

Note: An asterisk (*) denotes significance at $P < 0.05$.

by non–significant p-values ($p > 0.05$), suggests that haemoglobin may not be as sensitive to the presence of COVID-19 symptoms as the other markers. The normal distribution of haemoglobin means that it will be easier to interpret about COVID-19 and its role, but a lack of variability between the groups may not be very useful in diagnosing COVID-19.

Some of the results are highlighted in Table 1 below and are important in determining the appropriate statistical tests to apply in subsequent analyses, climaxing in to the generation of reliable conclusions.

Comparison of Haematological and Inflammatory Markers

Following the assessment of normality, the Mann–Whitney U test was used to compare the median values of haematological and inflammatory markers between symptomatic and asymptomatic patients. This non–parametric test was chosen because most of the markers were not normally distributed as evaluated in the previous analysis. The relationships generated from this comparison are depicted in Table 2.

When it comes to comparing the mean level of CRP, LDH, and NLR between the symptomatic and asymptomatic patients, it was observed that all three parameters have been significantly raised in symptomatic patients and independent samples t-test p-value < 0. 01. These data indicate that these markers are highly correlated with the existence of symptoms in COVID-19 and may indicate an inflammatory process, which might be a reason for coronavirus disease severity. Higher rates of CRP are associated with acute inflammation, and raised LDH denotes higher turnover of cells and tissue injury, which are features typical in severe COVID-19. The NLR, a well–known marker of systemic inflammation, was also markedly higher in symptomatic patients, reinforcing its potential as a prognostic indicator in COVID-19, as supported by previous studies.

Significant differences were also observed in several haematological parameters. Symptomatic patients exhibited a higher median neutrophil percentage, and a lower lymphocyte percentage compared to asymptomatic patients ($P < 0.05$ for both), indicative of an acute inflammatory response and lymphopenia, respectively. These shifts in WBC populations are consistent with the body's immune response to viral infections and have been linked to worse clinical outcomes in COVID-19. The Total Leukocyte Count was also significantly higher in symptomatic patients ($P < 0.05$), further supporting the notion of an active immune response in these individuals.

In contrast, some markers, including Haemoglobin, PLTs, Eosinophil Percentage, and Monocyte Percentage, did not show significant differences between symptomatic and asymptomatic groups ($p > 0.05$). The stability of these markers suggests that they may not be as directly influenced by the presence of symptoms, or they may reflect other aspects of the patient's overall health that are not specifically related to the severity of COVID-19.

The detailed results presented in Table 2 provide a clear comparison of these markers between symptomatic and asymptomatic patients, offering valuable insights into the biological processes that differentiate these two groups. To further illustrate these differences, Figures 1–3 present box plots that visually compare the distributions of key markers across the patient groups:

These figures illustrate the distribution of CRP levels, LDH, NLR ratio, Neutrophil, Lymphocytes, TLC, HB, Platelets, Monocytes and Eosinophils Percentages among the study participants. The box plot compares the symptomatic group to the asymptomatic group, with the central line of the box representing the median value, the edges of the box depicting the interquartile range (IQR), and the whiskers extending to the highest and lowest values excluding outliers, which are represented by individual points.

Discussion

Specifically, the goal of this study was to investigate haematological and inflammatory biomarker profiles in symptomatic and asymptomatic COVID-19 patients to identify the differences in pathophysiology that may have implications for prognosis. Regarding the primary

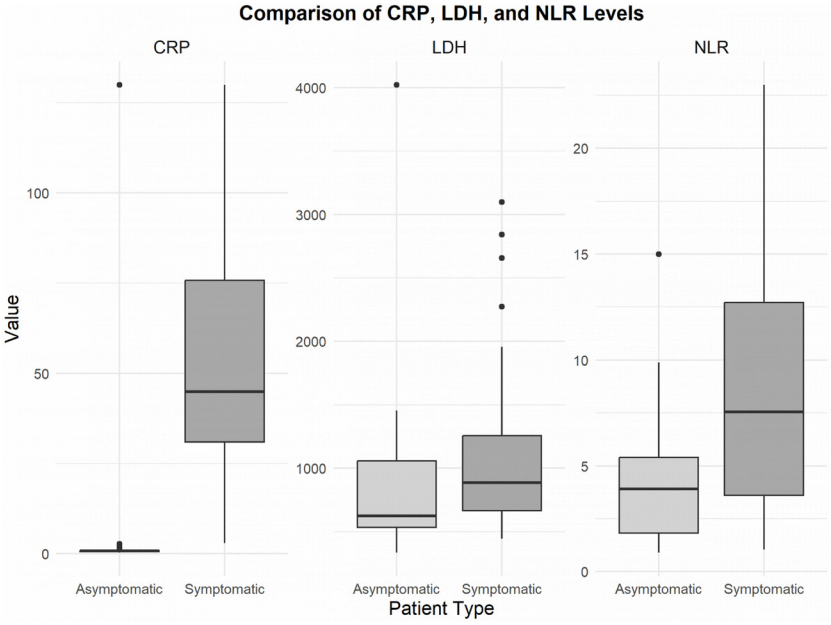

Fig 1 | Box plots depicting the distribution of CRP, LDH, and NLR levels in asymptomatic vs. symptomatic patients

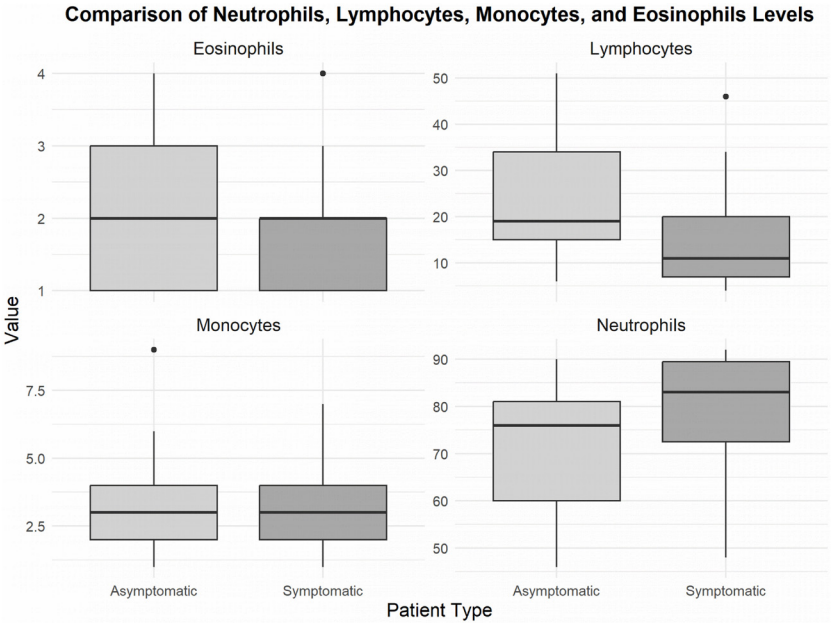

Fig 2 | Box plots illustrating the distribution of white blood cell types in asymptomatic vs. symptomatic patients

objective, the study set out to identify immunological responses that are known biomarkers including CRP, LDH, and NLR while relating these to severity of symptoms. Analysis of the data showed that CRP, LDH, and NLR increased in symptomatic patients as compared to the asymptomatic group. These findings are consistent with the possibility that these markers may be useful for measuring the severity of the disease.

CRP and LDH Elevations

These findings concerning the elevated CRP levels in patients with COVID-19 symptoms also correspond to its role in acute–phase response that indicates a higher level of inflammation that is associated with the progression of the disease.[12] Similarly, LDH is an enzyme in the blood which is elevated when there is tissue damage or cellular turnover; hence, the higher levels seen in the symptomatic group indicate chronic cellular injury and a more active inflammation.[13]

These findings are consistent with prior studies that have identified CRP and LDH as biomarkers of COVID-19 disease progression. For example, it has been observed that elevated CRP levels signify poor outcomes and can predict the need for mechanical ventilation or shifting to ICU).[14] On the contrary, LDH is related to pulmonary involvement and other organ dysfunction in severe COVID-19, making it a good prognosis marker.[15]

Neutrophil–to–Lymphocyte Ratio

Another acute–phase predictor that has recently received attention is the NLR, which has been shown to have prognostic significance in COVID-19 and other infections. An indexing of NLR as recorded in symptomatic patients in this study means that there is an immune system dysregulation characterized by high levels of neutrophils and low levels of lymphocytes or lymphopenia. This situation represents a state that is shifting to more inflammation and, as a rule, reflects severe viral pathologies.[16]

As previously established, NLR has been previously identified as being a prognostic factor in COVID-19. Elevated NLR values have been reported to be linked to higher mortality and a higher risk of severe disease manifestations.[17] The increased NLR in symptomatic patients in this study indicates that these people are experiencing a steeper and probably toxic level of immune response that would raise the risk of acquiring severe manifestations and complications.[18]

Stable Markers (Haemoglobin, Platelets, etc.)

However, not all the haematological markers reached a significant difference between the symptomatic and asymptomatic groups. The other parameters included in the study such as haemoglobin, PLT count, eosinophil percentage, and monocyte percentage were not found to be significantly different between the two groups. This stability may be attributed to the fact that these markers have specific functions in the body's instance during an infection.

Haemoglobin levels are generally well maintained and do not decrease unless there is bleeding, homolysis, or chronic disease, none of which are major features of COVID-19. Since PLTs are implicated in inflammation, they may not exhibit significant alterations in COVID-19 unless accompanied by coagulopathy or thrombocytopenia, as reported by Maggi et al. in the studied patient population[19] In the same way, eosinophils and monocytes belong to the immune system but can be less engaged in the immediate response to SARS–CoV-2, especially if there are no allergic or parasitic comorbidities.[20]

These observations indicate that although there may be alterations in the CRP, LDH, and NLR indexes

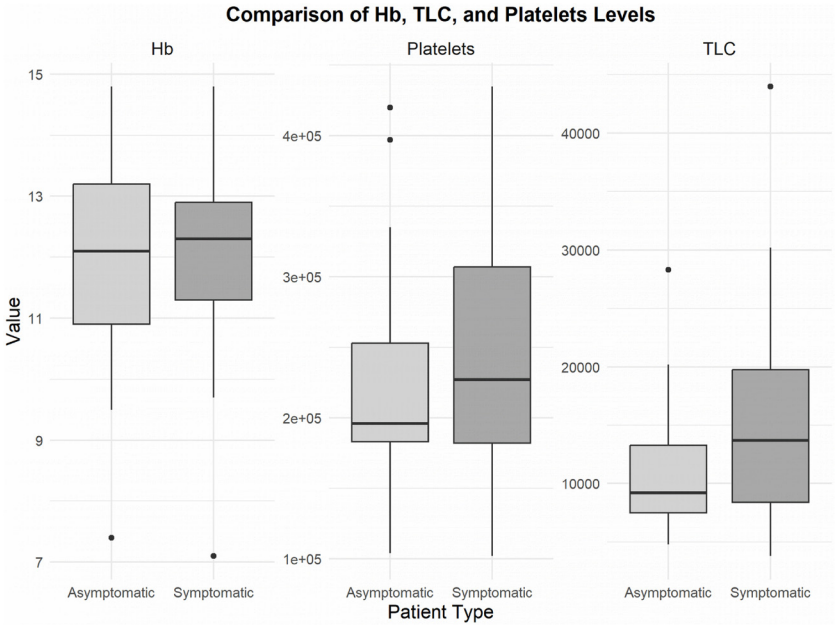

Fig 3 | Box Plots Comparing Hemoglobin (Hb), Total Leukocyte Count (TLC), and Platelet Levels Among Asymptomatic and Symptomatic Patients

in a severe inflammatory reaction in COVID-19, other markers can be elevated even in asymptomatic individuals. Such a differential response demonstrates the intricate interplay of the immune system to SARS–CoV-2 and justifies the necessity of using a panel of biomarkers for diagnosing the severity of the disease.

The current study findings are parallel with earlier studies that provided evidence of higher CRP, LDH, and NLR levels in COVID-19 symptomatic patients. In particular, Huang et al. (2020) and Tiwari et al. (2020) identified that these biomarkers correlate with a higher degree of inflammation and a more severe outcome of COVID-19.[13,17] Certain coherencies from such studies suggest that the severity of symptoms in COVID-19 is attributable to a similar pathophysiological mechanism.

However, there are differences that are mainly related to the stability of certain indexes like haemoglobin and PLTs. When similar studies were performed in different geographical locations for example, Italy and India, differences in these markers were noticed, and this could be explained by various factors including population, health status, and healthcare facilities that exist in such areas. For instance, normal haemoglobin levels observed in our Pakistani sample might not indicate existing untreatable anaemia and bleeding disorders, which could be present in other populations.

Clinical Implications

The analysis of the increased concentrations of CRP, LDH, and NLR in symptomatic patients indicates that these biomarkers may provide a convenient operating characteristic for differentiated asymptomatic and symptomatic COVID-19 cases. Implementing these markers into daily practice may help identify such patients at an early stage, thus increasing the likelihood of early management. For example, those with high CRP and NLR may require more frequent check–ups or earlier intervention, which may lead to a better prognosis and a lower burden on the healthcare systems.[21]

It has been seen that such biomarkers could be very useful in places like Faisalabad where available healthcare is already strained for resources. Therefore, if healthcare providers can determine which patients are at a higher risk of developing severe diseases, they can accordingly divert the limited resources including the ICU beds and the ventilators to the right patients most in need. Such an approach was easier to implement and could also decrease the general societal cost of COVID-19 by eradicating the need for hospitalization, and consequently, costly interventions in severe cases. Further, these biomarkers could help public health planning to identify the population that may require extra careful prevention, such as reports for vaccination or regular compulsory therapy to prevent the spread of diseases, thus contributing positively to the health of the community.

Strengths and Limitations of the Study

Strengths

A major advantage of this study is that it was conducted on a diverse group of patients in a region where scarce resources are available, and therefore it can help elucidate the effects of COVID-19 among such a group. The study of CRP, LDH, and NLR in combination gives a holistic view of the biomarkers' involvement in the severity and symptomology of a disease. This is helpful to know about COVID-19, especially concerning areas such as Faisalabad, where access to healthcare facilities and high–quality clinical diagnostic equipment might be scarce. The findings of the study suggest a demographic profile supported by insights that may be valuable for designing better clinical and community health approaches among contextually similar populations.

Limitations

Nevertheless, the research is not without its weaknesses. The retrospective design inherently restricts the ability to prove causality, and there is concern about selection bias because data are collected from hospital records. Further, the limited sample size might put a limit on the extent to which the results can be applied to the rest of the population due to possibly significant variability among the population. Other sources of bias might also stem from the differences in recording methods and the general quality of the hospital records employed. These limitations indicate that although the current study provides an important result, these should be generalized with caution, especially to other populations or contexts.

Future Research Directions

Further studies should also attempt to examine more longitudinal studies that follow the changes in biomarkers in COVID-19 patients from diagnosis to the next stage of the disease or recovery. Any of such

studies would offer more insight into how these markers relate to disease progression and/or recovery and may be timely intervention points. Further, intervention in studies with larger and more diverse populations is necessary for the replication of the study and to examine the generalization of the results for other demographical and geographical settings.

Exploring further biomarkers not examined in this study like IL-6, D-dimer, or others could offer further valuable insights into the inflammatory and coagulopathic disorders of COVID-19. In addition, research on how the treatment regimens affect the identified biomarkers like anti–viral or immune modulatory therapies can help in providing insights on how better treatment regimens can be developed to treat COVID-19 patients.

Conclusion

This paper helps in understanding the potential of CRP, LDH, and NLR as biomarkers for differentiating between symptomatic and asymptomatic COVID-19 patients. These results, in consideration of the current knowledge regarding these markers' possibilities, suggest that they could be particularly useful in diagnostics and treatment approaches, especially in settings such as Faisalabad, which may present more constraints in terms of resources. These biomarkers might be very useful for the identification of patients with poor prognosis as early as possible and, therefore, help to design effective preventive strategies and allocate healthcare resources most efficiently. The study reinforces the call for more research on different populations to acquire more information on COVID-19 and devise means of combating the disease around the world.

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