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RESEARCH ARTICLE

INFLAMMATORY MARKER PROFILING IN COVID-19: UNRAVELING COMORBIDITY AND GENDER INFLUENCES

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COVID-19, Inflammatory Markers, Comorbidities, Gender-Based Differences, Disease Severity, Cytokine Storm

Abstract

Background: The 2020 WHO-declared COVID-19 pandemic has left a profound global imprint. Notably, inflammatory markers have gained prominence in predicting disease severity, especially concerning the characteristic cytokine storm in severe cases. Alongside, comorbidities and gender have emerged as influential factors in disease outcomes. Thus, unraveling the intricate relationships between inflammatory markers, comorbidities, and gender is pivotal for optimal patient care. This study examines inflammatory marker roles in COVID-19, focusing on comorbidity presence and gender impacts.

Methods: Conducted retrospectively at Bengaluru's Abhaya Hospital from March 2020 to September 2021, this observational study examined C-reactive protein (CRP), lactate dehydrogenase (LDH), D-Dimer, creatine phosphokinase (CPK), Interleukin-6 (IL-6) and serum ferritin as inflammatory markers in COVID-19 patients. Patient cohorts with and without comorbidities, as well as male and female patients, underwent comparisons. Descriptive statistics, Kruskal-Wallis tests, and t-tests were used for data analysis.

Results & Discussion: Among patients with and without comorbidities, no statistically significant differences in inflammatory markers were identified. This finding suggests a complex, indirect relationship between comorbidities and distinct inflammatory responses, as measured by these markers. In contrast, gender-based analysis demonstrated significant variations in CRP, IL-6, CPK, and Ferritin levels among male and female COVID-19 patients. Hormonal, genetic, and immunological variations potentially underlie these disparities, impacting disease severity. This study underscores the intricate interplay between inflammatory markers, comorbidities, and gender within the COVID-19 context.

Conclusion: In conclusion, this study advances the comprehension of inflammatory markers in COVID-19 patients. While comorbidities did not exhibit marker-specific links, significant gender-based differences in CRP, IL-6, CPK, and Ferritin levels emerged. This underscores the need for gender-specific investigations in disease progression. Continued research is pivotal to unveil underlying mechanisms and to tailor treatment strategies based on these gender-specific disparities.

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Introduction:-

The emergence of the novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) in December 2019 marked the beginning of a global health crisis, leading to the coronavirus disease 2019 (COVID-19) pandemic [1]. With its rapid transmission, the World Health Organization (WHO) declared COVID-19 a pandemic in March 2020 [2]. The pandemic's profound impact has been witnessed worldwide, with a staggering number of confirmed cases and fatalities reported [3]. Among the countries affected, India experienced a significant burden of COVID-19 cases, with a substantial number of infections and deaths [3].

Understanding the pathogenesis of COVID-19 and identifying reliable markers for disease severity are critical for effective patient management and public health interventions. Inflammatory markers have garnered attention for their potential role in predicting disease outcomes. In particular, markers such as procalcitonin (PCT), serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6) have been linked to the severity and prognosis of COVID-19 [5]. These markers are known to play pivotal roles in driving the cytokine storm, a characteristic feature of severe COVID-19 cases [6].

Furthermore, the presence of comorbidities has been identified as a significant risk factor for severe COVID-19 outcomes. Patients with pre-existing conditions such as diabetes, cardiovascular diseases, hypertension, and chronic respiratory diseases are more susceptible to developing life-threatening complications upon contracting the virus [7,8]. Exploring the interplay between comorbidities and inflammatory markers can provide insights into the underlying mechanisms driving severe outcomes in these individuals.

This study aims to contribute to our understanding of COVID-19 by comparing inflammatory markers in different subgroups of patients. Specifically, the study focuses on comparing markers between patients with and without comorbidities and between male and female patients. By evaluating these markers, we aim to discern potential differences in the inflammatory responses of these subgroups, which could have implications for disease severity and outcomes.

Objectives of the Study:-

The primary objective of this study is to assess the role of inflammatory markers in determining the severity of COVID-19 in hospitalized patients. The study will focus on comparing these markers between patients with and without comorbid conditions and between male and female patients. The specific markers under investigation include C-reactive protein (CRP), Interleukin-6 (IL-6), lactate dehydrogenase (LDH), D-Dimer, creatine phosphokinase (CPK), and ferritin.

Significance of the Study

The significance of this study lies in its potential to uncover insights into the factors contributing to the variability in COVID-19 outcomes. By comparing inflammatory markers between different patient subgroups, the study aims to shed light on the role of comorbidities and gender in influencing disease severity. The findings could inform clinical decision-making, allowing for more personalized treatment approaches based on patient characteristics.

Furthermore, the study's outcomes could contribute to the broader understanding of COVID-19 pathogenesis and provide avenues for future research. As the pandemic continues to evolve, the insights gained from this study may have implications for public health strategies aimed at mitigating severe outcomes and improving patient care.

In the subsequent sections, we will delve into the methodology employed in the study, including data collection, sample selection, and statistical analysis. By rigorously examining the data, we aim to draw meaningful conclusions that contribute to the existing body of knowledge surrounding COVID-19 and its impact on patients with different characteristics.

Methodology:-

Study Design:

The methodology of this research involved a retrospective observational study conducted at Abhaya Hospital in Bengaluru, Karnataka. The study aimed to compare inflammatory markers among different groups of COVID-19 patients, specifically focusing on the presence or absence of comorbidities and gender-based differences.

Study Duration:
The study was conducted over a period spanning from March 2020 to September 2021. This timeframe allowed for the inclusion of data from the initial and subsequent waves of COVID-19 in India.

Data Collection:
The primary source of data for this study was the hospital records of Abhaya Hospital. Data on inflammatory markers were collected for each patient included in the study. The markers analysed included C-reactive protein (CRP), lactate dehydrogenase (LDH), D-Dimer, Inerleukin-6, creatine phosphokinase (CPK), and serum ferritin. These markers were selected based on their established significance in reflecting the immune response and disease severity in COVID-19 patients.

Study Participants:
The study included both male and female patients of all age groups who had tested positive for SARS-CoV-2 using RT-PCR. Patients meeting the following criteria were included:
1. Confirmed positive RT-PCR result for SARS-CoV-2.
2. Both genders were considered eligible.
3. All age groups were considered.

Patients meeting any of the following criteria were excluded:
1. Patients with incomplete sample referral forms.
2. Patients with a negative RT-PCR result for SARS-CoV-2.
3. Non-admitted patients were not included in the study.

Data Analysis:
The collected data were subjected to descriptive statistical analysis. The demographic characteristics of the study participants were summarized using measures such as mean, standard deviation, and frequency distributions.

To analyse the impact of comorbidities on inflammatory markers, a comparative analysis was conducted between patients with and without comorbid conditions. The Kruskal-Wallis test was employed for non-parametric data, while t-tests were used for normally distributed data.

Similarly, gender-based differences in inflammatory markers were examined by comparing levels between male and female patients. The Kruskal-Wallis test and t-tests were utilized based on the distribution of the data.

Ethical Considerations:
Ethical clearance for this study was obtained from the Institutional Review Board of Padmashree Group of Institutions. All data used for analysis were handled in compliance with ethical guidelines and patient confidentiality was maintained.

Results and Data Analysis:-

Groups:
Males vs Females; Comorbidities present vs absent

Exploratory Analysis

Comorbidity					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	32	43.8	45.7	45.7
	Yes	38	52.1	54.3	100.0
	Total	70	95.9	100.0	
Missing	6666	3	4.1		
Total		73	100.0		

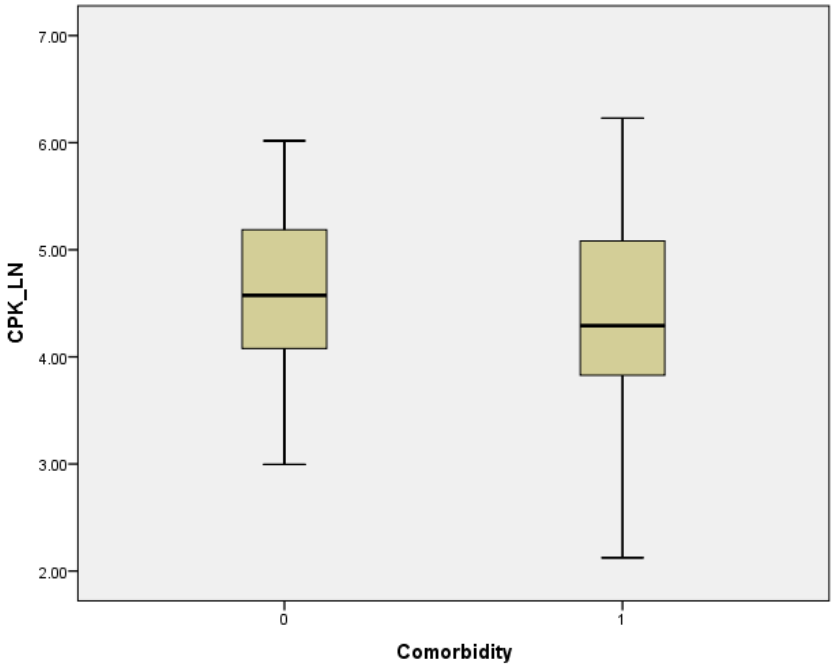
GENDER					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	F	41	56.2	56.2	56.2

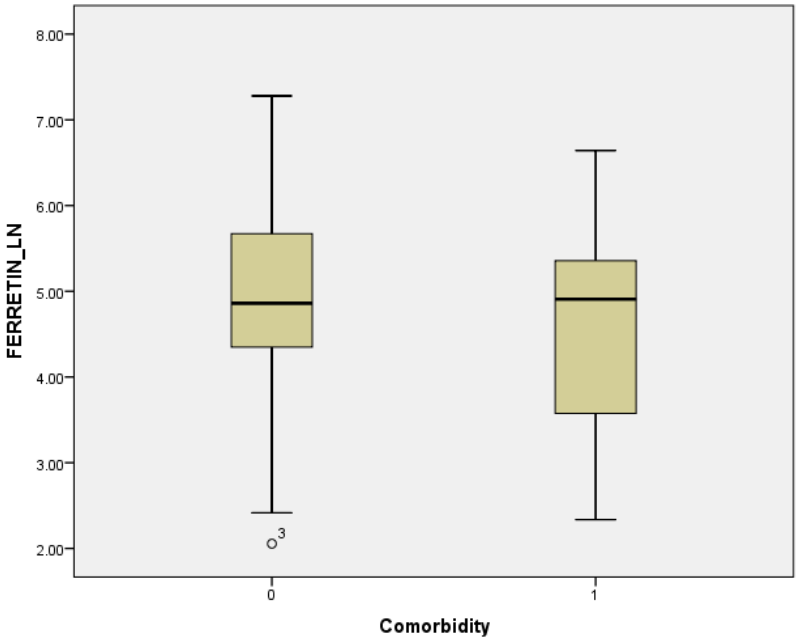
	M	32	43.8	43.8	100.0
	Total	73	100.0	100.0	

Comorbidity-Wise
CPK and Ferritin: log-transformed for achieving normality
None of the variables have varied significantly among patients with and without co-morbidities

Variable	Comorbidity	25th percentile	Median	75th percentile	Kruskall Wallis P
CRP	NO	5.95	9.4	19.3	1
	YES	5.8	9.1	20.8	
LDH	NO	181	206	244	0.628
	YES	186	216	281	
D DIMER	NO	0.11	0.31	1.03	0.478
	YES	0.16	0.41	0.63	

Variable (log-transformed)	Comorbidity	Mean	Standard deviation	Normality P	T-TEST equal variance	T-TEST unequal variance
CPK	NO	4.6615	0.87829	0.83	0.353	0.345
	YES	4.3533	0.95571	0.551		
Ferritin	NO	4.9268	1.31968	0.692	0.402	0.407
	YES	4.6080	1.20063	0.303		

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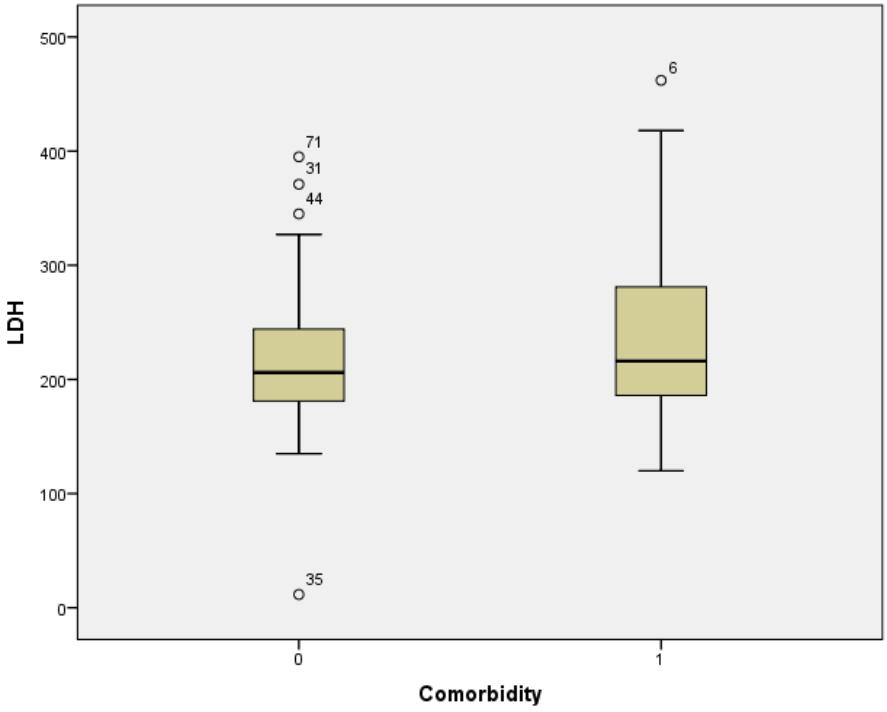
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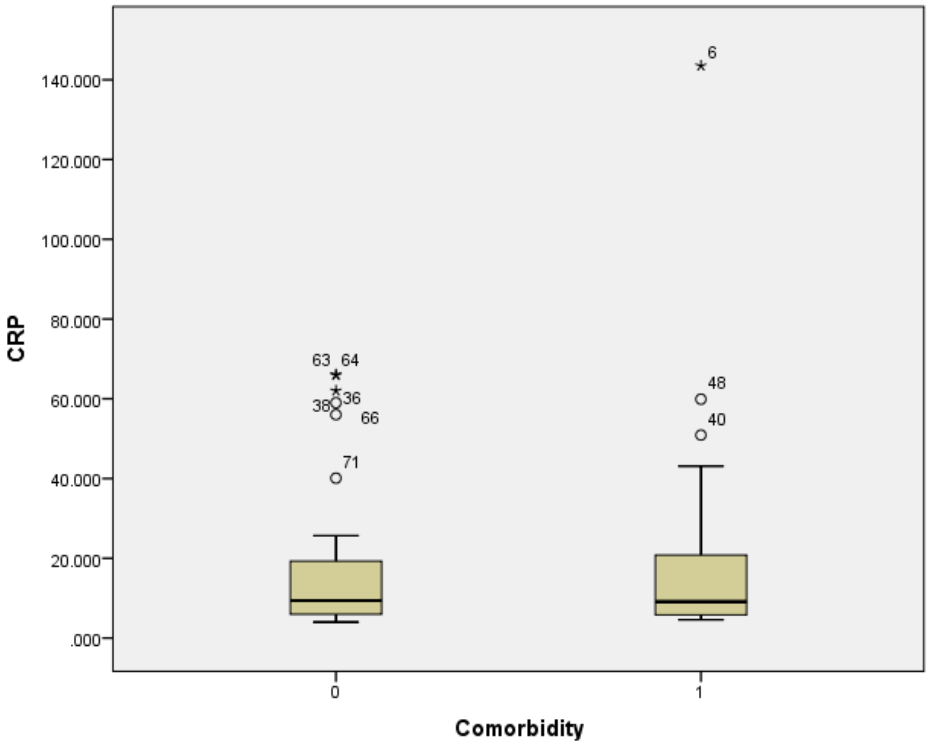
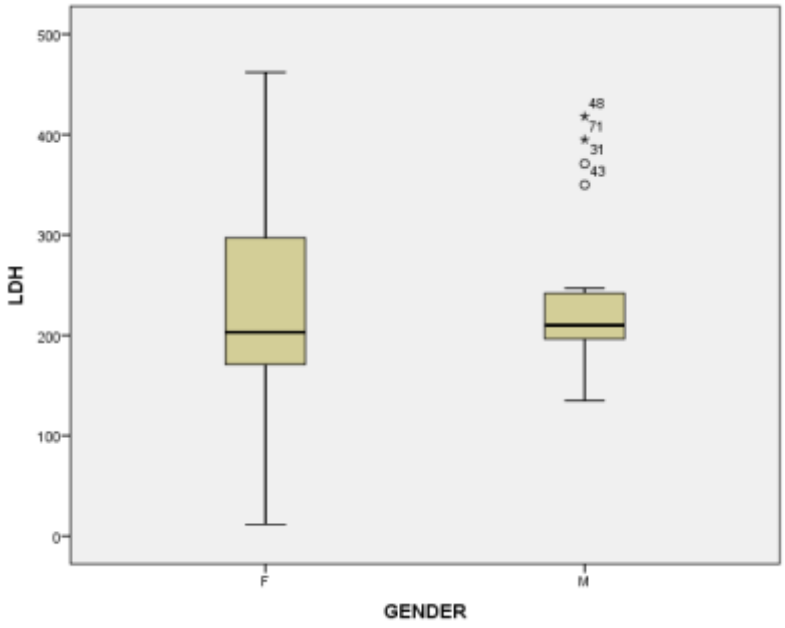


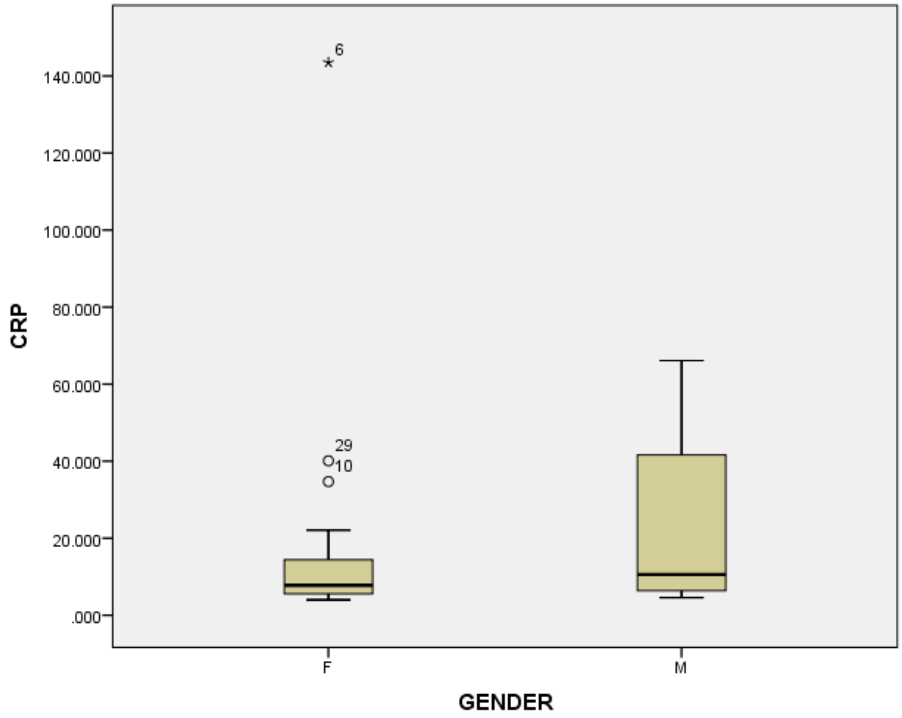
Gender-Wise
Variables not in analysis: IL6 (too many missing values)
CPK and Ferretin: log-transformed for achieving normality

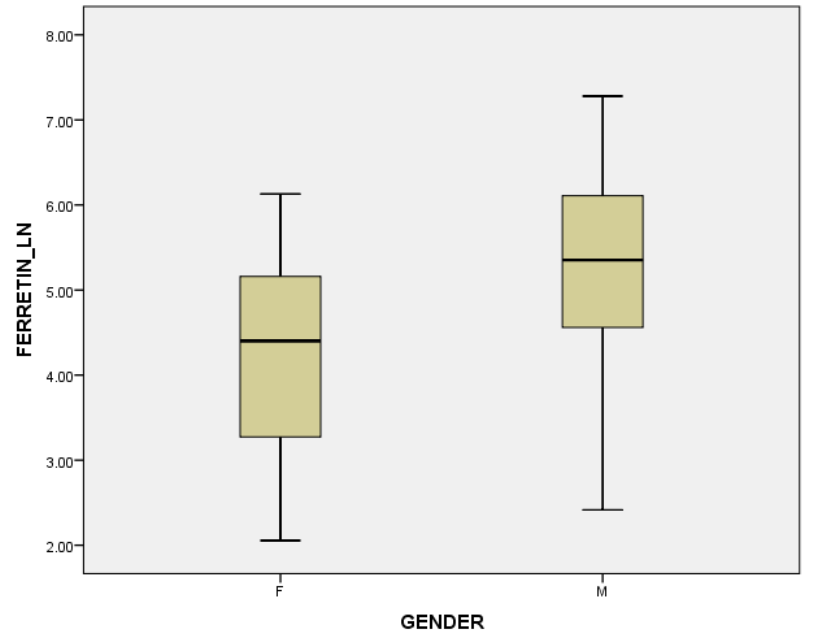
Variable	GENDER	25th percentile	Median	75th percentile	Kruskall Wallis P
CRP	F	5.60000	7.80000	14.40000	**0.035**
	M	6.40000	10.60000	41.60000	
LDH	F	171.00	203.10	297.05	0.673
	M	196.50	210.05	242.00	
D DIMER	F	.15000	.36000	.54000	0.801
	M	.13000	.34000	1.04000	

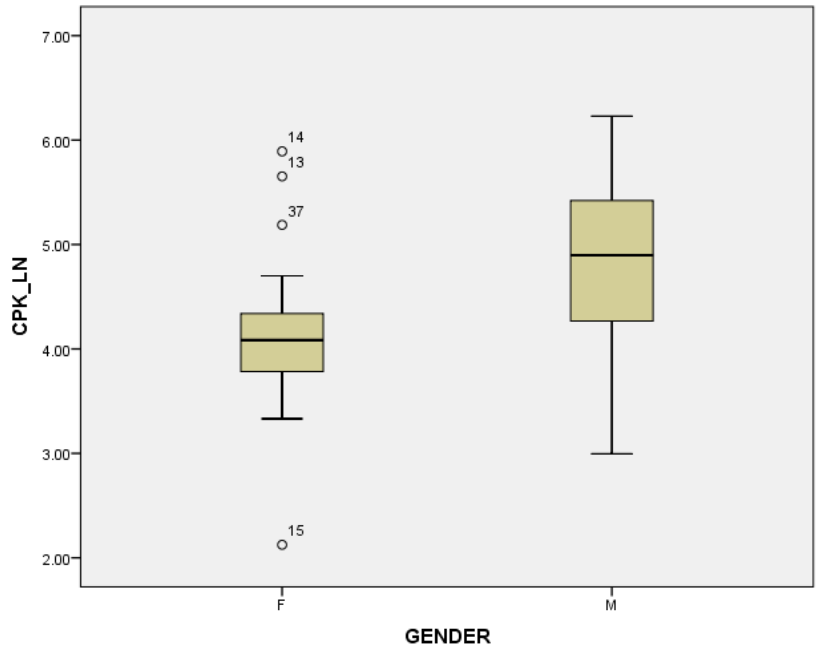
Variable (log-transformed)	GENDER	Mean	Standard deviation	Normality P	T-TEST equal variance	T-TEST unequal variance
CPK	F	4.1487	0.81658	0.137	**0.017**	**0.019**
	M	4.8801	0.89155	0.919		
Ferretin	F	4.2392	1.15027	0.205	**0.003**	**0.003**
	M	5.2735	1.09291	0.558		

Significant increase in CRP, CPK and ferritin levels in males among covid patients (P=0.035, 0.017, 0.003 respectively). LDH increased while D-Dimer levels reduced among males, but was not statistically significant.









Discussion:-

The present study aimed to investigate and compare inflammatory markers among different groups of COVID-19 patients, specifically focusing on the presence or absence of comorbidities and gender-based differences. The analysis of these markers provides valuable insights into the potential implications of these factors on disease severity and outcomes. The discussion below highlights the key findings, their implications, and the broader context of the study.

Comorbidity-wise Analysis:

The investigation into inflammatory markers among COVID-19 patients with and without comorbidities yielded interesting insights. The analysis covered a range of markers including CRP, LDH, D-Dimer, IL-6, CPK, and Ferritin. However, the results indicated that none of these markers demonstrated statistically significant variations between patients with and without comorbidities. This observation suggests that the presence of comorbidities might

not directly correlate with distinct inflammatory responses in COVID-19 patients, at least as measured by these specific markers.

It is important to acknowledge that the absence of statistically significant differences does not necessarily negate the influence of comorbidities on COVID-19 severity. Other factors such as the type and number of comorbidities, treatment protocols, and individual patient responses could contribute to the overall disease progression. Therefore, while this study did not find significant associations, further research with a larger sample size and consideration of additional markers might unveil more nuanced relationships.

Gender-wise Analysis:
The investigation of gender-based differences in inflammatory markers among COVID-19 patients revealed noteworthy findings. Among the markers studied, CRP, IL-6, CPK, and Ferritin levels were found to be significantly higher in male patients compared to female patients. This gender-based disparity could indicate potential differences in immune responses or underlying physiological factors that influence the inflammatory processes in COVID-19. However, LDH and D-Dimer levels did not demonstrate statistically significant gender-based variations.

These findings align with previous research suggesting that gender might play a role in the severity and outcomes of COVID-19. Hormonal, genetic, and immunological differences between males and females could contribute to divergent responses to the virus. The observed elevation of CRP, CPK, IL-6, and Ferritin in males might be indicative of a more robust inflammatory reaction, which has been associated with severe disease outcomes. Further studies exploring the mechanisms underlying these gender-specific differences could contribute to the development of personalized treatment strategies.

Clinical Implications and Future Research
The insights gained from this study have several clinical implications. Understanding the role of inflammatory markers in COVID-19 patients can aid in predicting disease severity and guiding treatment decisions. The gender-based disparities in certain markers emphasize the need to consider gender-specific factors when designing treatment plans and interventions for COVID-19 patients.

However, it's important to acknowledge the limitations of this study. The sample size might influence the statistical power to detect significant differences, and the study's retrospective nature could introduce biases. Additionally, the analysis focused on a specific set of markers, while other factors could also contribute to disease severity.

Future research could build upon these findings by incorporating a larger and more diverse patient cohort, considering a broader array of inflammatory markers, and investigating the mechanisms that underlie the observed differences. Longitudinal studies could provide insights into the dynamics of inflammatory responses throughout the course of the disease. Moreover, exploring the interactions between comorbidities, gender, and inflammatory markers could offer a more comprehensive understanding of COVID-19 pathogenesis.

Conclusion:-
This study aimed to compare inflammatory markers in different groups of COVID-19 patients. While no significant variations were observed between patients with and without comorbidities, there were notable gender-based differences in the levels of CRP, IL-6, CPK, and Ferritin among COVID-19 patients. These findings could provide insights into the potential impact of gender on disease severity and outcomes in COVID-19 patients. Further research is warranted to understand the underlying mechanisms and clinical implications of these observations.

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