

Significance of serum ferritin, interleukin 6 and erythrocyte sedimentation rate as a marker of COVID 19 disease Severity.

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Abstract

Introduction: Inflammatory responses play a critical role in the COVID-19 disease. These Markers have been reported to be significantly associated with the high risks of developing severe COVID- 19. Our study highlights the role of interleukin 6 (IL6), erythrocyte sedimentation rate (ESR) and serum ferritin in predicting the severity COVID-19.

Objectives

To investigate and correlate inflammatory markers Erythrocyte sedimentation rate (ESR), Interleukin 6 and Serum Ferritin with the severity of Covid-19.

Key words

Covid 19, Interlukin6, Serum ferritin,Erythrocyte sedmentation rate,Disease severity.

Results

Out of 307 patients, we found all the three inflammatory markers (IL6, ESR and serum ferritin) correlate with disease severity the mean ESR in mild, moderate and severe COVID 19 disease was 35,42 and 55.5 respectively. The mean IL6 in mild, moderate and severe COVID 19 disease was 14,33 and 61 respectively and the mean serum ferritin in mild, moderate and severe COVID 19 disease was 253,373 and 801 respectively.

Conclusions

These inflammatory parameters could be used in for prompt identification of severe covid-19 disease patients and subsequently triaging them for initiation of treatment protocols

Introduction.

On 31st December 2019, Wuhan health commission in the Hubei province of the Republic of China notified the National Health Commission, China CDC, and WHO of a cluster of 27 cases of pneumonia of unknown etiology[1,2]. The WHO declared this viral pneumonia as an outbreak on 30th January 2020. On 11th March 2020, due to the global logarithmic expansion of the cases of the corona virus disease (COVID-19) was declared as a pandemic by the WHO.

Accumulating evidence suggested that inflammatory responses play a critical role in the progression of COVID-19 disease[3]. Inflammatory responses triggered by rapid viral replication of SARS-CoV-2 and cellular destruction can recruit macrophages and monocytes and induce the release of cytokines and chemokines. These cytokines and chemokines [4]attract immune cells and activate immune responses and many a times leading to cytokine storms [5]. Several inflammatory markers have some tracing and detecting accuracy for disease severity and fatality [6]. Markers such as d-dimer, serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), Neutrophil Lymphocyte ratio (NLR), and interleukin-6 (IL-6) have been reported to be significantly associated with the high risks of developing severe COVID- 19. Moreover, increased levels of serum amyloid A (SAA) are shown to be involved in COVID-19 pathogenesis

and may serve as a potential biomarker for monitoring disease progression. However, these results remain controversial due to no observed difference in the levels of IL-6, SAA, ESR and CRP by other studies. Our study highlights the role of inflammatory markers interleukin 6 (IL6), erythrocyte sedimentation rate (ESR) and serum ferritin predicting the severity of COVID-19 which may assist to monitor and evaluate the severity and prognosis of COVID-19 in the future for prompt triaging and application of management protocols as indicated.

Aims and objectives

To investigate and correlate inflammatory markers Erythrocyte sedimentation rate (ESR), Interleukin 6 and Serum Ferritin with the severity of Covid-19.

Materials and Methods

This observational and cross-sectional type of study was conducted in the Department of Medicine at government medical college (GMC) Srinagar and was approved by ethical committee of government medical college Srinagar with On 20th Jan 2021. The study was conducted for a period of 2 years Jan 2021 to Dec 2022.

COVID-19 patients with positive RT-PCR were included in this study and classified as mild, Moderate, and Severe disease according to the Ministry of Health and Family Welfare definition of clinical severity and assessment parameters version 3[7]

MILD	<ol style="list-style-type: none"> 1. Patients with uncomplicated upper respiratory tract infection, may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache 2. Without evidence of breathlessness or Hypoxia (normal saturation).
Moderate	<ol style="list-style-type: none"> 1. Pneumonia with no signs of severe disease 2. Adults with the presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO₂ <94% (range 90-94%) on room air, Respiratory Rate more or equal to 24 per minute.
Severe	<ol style="list-style-type: none"> 1. Severe Pneumonia 2. Adults with clinical signs of Pneumonia plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO₂ <90% on room air.

Patients were stratified accordingly and the lab results of the inflammatory marker (**ESR, Serum Ferritin, IL6**) obtained on day one of admission and entered.

All the blood sampling was done on day one of admission and subsequently processed on the same day. Westergren method was used to obtain ESR. ADVIA XP analyzer was used to obtain results interleukin 6 and serum Ferritin.

STATISTICAL ANALYSIS

The recorded data was compiled and entered in SPSS Version 26.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar and line diagrams. Student's independent t-test and ANOVA were employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. A P-value of less than 0.05 was considered statistically significant. All P-values were two-tailed.

Results

During the study period of two years 307 patients of RTPCR documented covid 19 patients were enrolled. Males 53.1% {n=163} and females were 46.9%. {n=144}. The age distribution of our study participants shows a Mean of 56.37 years and a Median of 57.0 years with a standard deviation(SD) of 15.63. The range was 70 with a minimum 20 years and a maximum 90 years. The Disease severity of studied patients is depicted in table 1.

Table 1 Disease severity wise distribution of study participants

Disease Severity	Frequency	Percent
MILD	81	26.4
MODERATE	95	30.9
SEVERE	131	42.7
Total	307	100.0

The mean ESR of the total study population is 45.67with a standard deviation of22.58 and ranges from 8 (minimum) to 133(maximum). While in the different categories the mean ESR was 35.71 in mild disease with a standard deviation of 20.8, in moderate disease the mean ESR was 42 with a standard deviation of 16 and in severe disease, the mean ESR was 55.5 with standard deviation of 24.32 image 2.On analysing the data, the Pearson correlation coefficient was found to be**0.369** with a **p-value of 0.00** which is <0.005 and hence a **significant** correlation was found with disease severity and ESR table 2.

Table 2. Correlations between Disease severity and ESR

		SEVERITY	ESR
SEVERITY	Pearson Correlation	1	.369**
	Sig. (2-tailed)		.000
	N	307	215
ESR	Pearson Correlation	.369**	1
	Sig. (2-tailed)	.000	
	N	215	215

** . Correlation is significant at the 0.01 level (2-tailed).

Table 3. Correlations between Disease severity and IL6

		SEVERITY	IL6
SEVERITY	Pearson Correlation	1	.235**
	Sig. (2-tailed)		.000
	N	307	305

IL6	Pearson Correlation	.235**	1
	Sig. (2-tailed)	.000	
	N	305	305
**. Correlation is significant at the 0.01 level (2-tailed).			

The mean IL6 (pg. /mL) of total study population is 36.1 with a standard deviation of 86.7 and range from 0(minimum) to 1205(maximum). While in the different categories the mean IL6 was 14.37 in mild disease with a standard deviation of 33.12, in moderate disease the mean was 19.93 with a standard deviation of 20.79 and in the severe disease the mean was 61.4 with standard deviation of 124.86Image 1.On analysing the data, the Pearson correlation

coefficient was found to be**0.235** with a **p-value of 0.00** which is <0.005 and hence a **significant** correlation was found with disease severity and IL-6 table 3.

The mean ferritin (ng/mL) of the total study population is 520.8 with standard deviation of 680.0 and range from 6(minimum) to 3000(maximum). While the mean ferritin was 252.9 in mild disease with a standard deviation of 222, in moderate disease the mean was 373.3 with a standard deviation of 550.5 and in the severe disease, the mean was 800.84 with a standard deviation of 841.6 Image 3.On analysing the data, the Pearson correlation coefficient was found to be**0.342** with a **p-value of 0.00** which is <0.005 and hence a **significant** correlation was found with disease severity and Serum Ferritin table 4.

Table 4. Correlations between Disease severity and ferritin

		SEVERITY	FERRITIN
SEVERITY	Pearson Correlation	1	.342**
	Sig. (2-tailed)		.000
	N	307	302
FERRITIN	Pearson Correlation	.342**	1
	Sig. (2-tailed)	.000	
	N	302	302
**. Correlation is significant at the 0.01 level (2-tailed).			

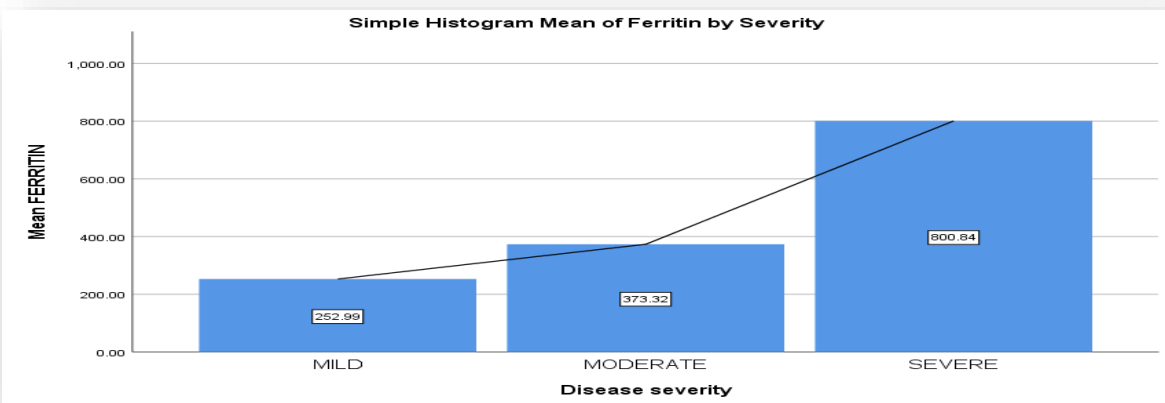
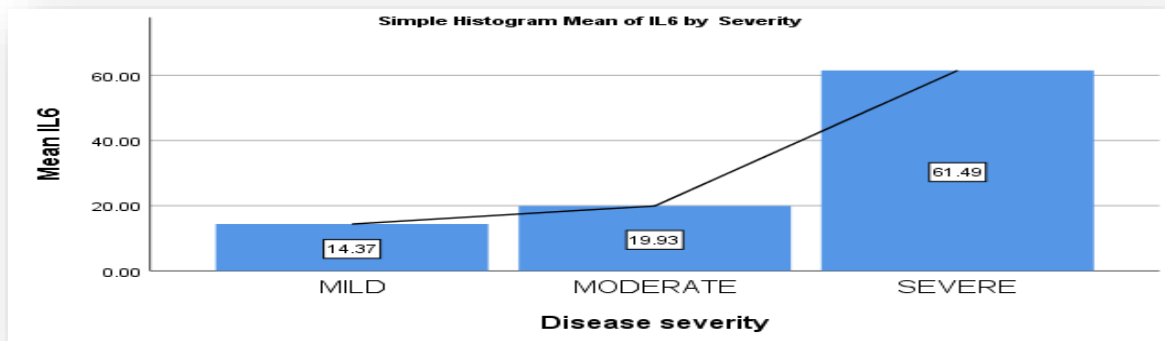
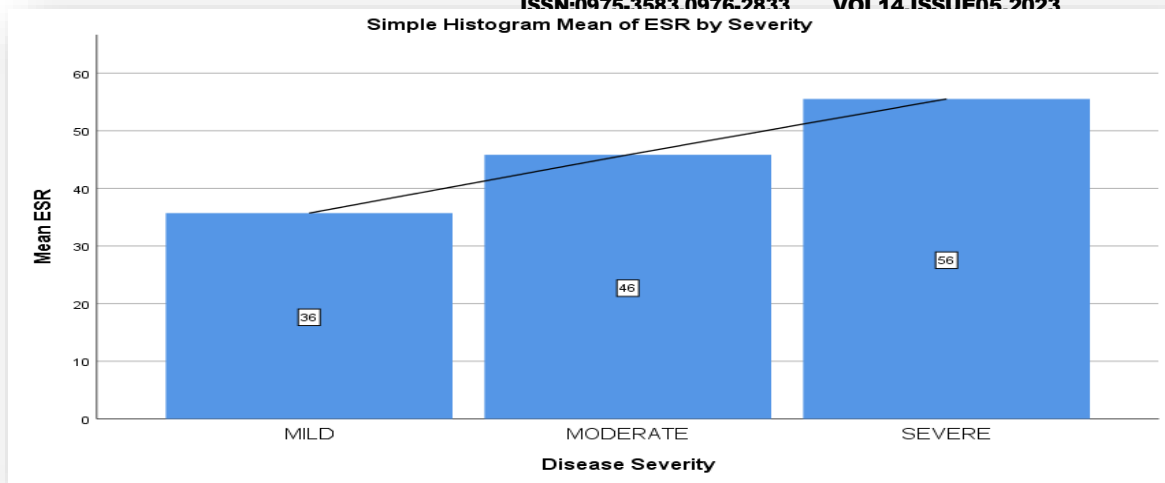


Image 1,2 and 3 showing Mean IL6, ESR and serum Ferritin in mild Moderate and Severe Disease Respectively.

Discussion

This study was conducted between January 2020 to Dec 2021 for one year in the post-graduate Department of Medicine, GMC Srinagar, to assess the correlation between biochemical markers and the severity of covid 19. A total number of 307 patients were taken who were diagnosed as covid positive after taking their nasopharyngeal samples and analyzed using real-time RTPCR method by ICMR accredited laboratories and were categorized as Mild, Moderate, and Severe according to the guideline's issues by the Ministry of health and family welfare through Clinical Management Protocol Version 3[7]. In our study, we found a statistically significant correlation between disease severity and the level of biomarkers. It was seen that biomarkers, ESR, serum Ferritin, and IL-6 had a significant correlation with the severity and thus mortality of the covid-19. Systemic review [8] of literature studying the role of biomarkers in the diagnosis of Covid 19 concluded that biomarkers such as CRP, SAA, IL-6, LDH, NLR, D-dimer, Cardiac troponin, renal biomarkers showed significantly higher levels in severe disease compared to non-severe (mild) disease counterparts, which is also revealed in our study for IL-6, ESR and serum ferritin. Patients with severe MERS-CoV and SARS-CoV infections showed higher levels of interleukin-6 (IL-6), a pro-inflammatory cytokine, and chemokines in their serum compared to those with mild disease [9]. IL-6 has received special attention. IL-6 plays a key role in cytokine storm syndrome. It has both anti-inflammatory and pro-inflammatory effects. IL-6 binds to its transmembrane and soluble receptors, which result in the activation of the inflammatory response potentially leading to cytokine storm [10]. IL-6 levels have been shown to be 2.9 folds higher in patients with complicated disease, mainly those requiring ICU admission, compared to those with mild disease, with higher levels associated with a higher incidence of death [11]. Our study found IL 6 increased with increase in disease severity, in moderate disease the mean IL6 was 19.93 with a standard deviation of 20.79 and in the severe disease the mean IL 6 was 61.4 with standard deviation of 124.86. The ESR is not specific for any one disease but is used in combination with other tests to determine the presence of increased inflammatory activity. The ESR has long been used as a "sickness indicator" due to its reproducibility and low cost. Erythrocyte sedimentation rate (ESR) is used as a marker that indicates inflammation. ESR was reported to be able to predict the disease activity and prognosis in some other disorders [12-14]. There are few studies available evaluating ESR as a single predictor of the prognosis and mortality in COVID-19 patients. In our study patients with mild COVID 19 disease the mean ESR was 35.7, in moderate disease the mean ESR was 42 and in severe disease, the mean ESR was 55.5, which means there is consistent increase in ESR with increase in disease severity.

Conclusion

Our study showed a significant increase in the concentration of biochemical markers ESR, IL-6 and serum ferritin compared with respect to the severity of disease and showed statistically significant results, hence correlating with the severity of the disease. These inflammatory parameters could be used in the future for prompt identification of severe covid-19 disease patients and subsequently triaging them for initiation of treatment protocols. This study is a single-center study and it is thus suggested to conduct more powerful and multicentric studies on this topic.

Main Points

1. In our study we found that mean erythrocyte sedimentation rate (ESR) is elevated in all categories of COVID-19 infections (Mild, Moderate and Severe COVID disease) however as the disease severity increases there is steady increase in ESR.
2. There was little difference in levels of Serum ferritin and interleukin 6 between mild COVID 19 disease and moderate COVID 19 diseases, however there was sudden rise in these two markers in severe COVID 19 diseases.
3. These inflammatory markers especially high levels Serum ferritin and interleukin 6 could serve as an indicator of severe COVID 19 disease and an indication for intensive care management.

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