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Dynamics of inflammatory markers, neutrophil lymphocyte ratio, platelet lymphocyte ratio in COVID-19 deaths

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Abstract

Introduction: Various inflammatory markers and laboratory parameters were identified as the predictors of severity and mortality in COVID -19 infection. However, the progression of inflammatory markers and their gender difference in COVID-19 deaths has not been extensively studied. The aim of the study was to analyze the progression of inflammatory markers, neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) in COVID-19 deaths, and the correlation between NLR, PLR and inflammatory markers.

Materials and methods: A retrospective observational study based on records was done on 104 patients who died due to COVID-19 infection. In addition to baseline investigations, NLR (Neutrophil Lymphocyte ratio), PLR (Platelet Lymphocyte Ratio), ferritin, D-dimer and CRP (C reactive protein) was collected for all patients on day one, day three and day five**.**

Results: Out of 104 patients, 68 were males and 36 were females. Mean NLR was 5.7, 7.3 & 7.5 on day one, three and five respectively. Mean PLR was 145.9, 166.6 and 173.7 on day one, three and five respectively. Mean CRP was 37.6mg/l, 51mg/l & 57.2mg/l, mean ferritin was 780.9ng/ml, 852.5ng/ml &1033ng/ml and mean D-dimer was 2373ng/ml, 3149ng/ml & 3686ng/ml on day one, three and five respectively. There was a strong positive correlation of NLR with ferritin (0.598), CRP (0.663) and D-dimer (0.53) on day one and on day five, but only a weakly positive correlation observed on day three. There was a negative correlation between PLR and inflammatory markers. No significant difference in the inflammatory markers and their progression was noted between males and females.

Conclusion: In this retrospective cohort study of 104 COVID-19 deaths, there was progressive increase of inflammatory markers. Serial measurements of inflammatory markers help in early identifications of patients who may deteriorate. Progression of NLR has strong correlation with inflammatory markers and could be used as a surrogate marker to prioritise treatment in resource limited settings.

Keywords: COVID-19; neutrophil lymphocyte ratio; platelet lymphocyte ratio; ferritin; C reactive protein; D-dimer

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), emerged in China and then spread to other countries rapidly to become a global public health problem. More than 590 million people were affected, and six million people died over the last two years worldwide. More than 40 million people were affected and 0.5 million people died in India due to the disease [1].

The spectrum of clinical symptoms, cause of mortality and post COVID-19 symptoms varied over the period due to mutation of the virus. Among the infected, 14-15% of patients developed severe disease and 5% patients succumbed to death during the initial stages

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of the pandemic [2]. The percentage of in hospital mortality ranged from 6.3 to 26.85% in different countries worldwide [3]. Even though there is no difference in incidence of COVID-19 infection between males and females, the need for intensive care unit (ICU) admission and mortality is higher in males. [4] Various laboratory parameters and inflammatory markers were identified as the predictors of severe disease and mortality. Increase in the neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and the levels of inflammatory markers were studied as the predictors of severe disease [5]. However, the progression of these markers and the gender difference were not extensively studied in the COVID-19 deaths.

The aim of the study was to analyze the dynamics of inflammatory markers, neutrophil lymphocyte ratio, platelet lymphocyte ratio in patients who died due to COVID-19. This included assessment of progression of NLR, PLR and inflammatory markers as well as correlation between NLR, PLR and the inflammatory markers. Since there was a significant difference in mortality between males and females due to COVID-19, we also assessed the gender difference in inflammatory markers.

Methodology

Study design

A retrospective observational study based on records was done on 104 patients who died due to confirmed COVID-19 infection. COVID-19 infection diagnosed by RTPCR or antigen, admitted to Government Medical College, Kollam between April 2020 and March 2021 and died due to the infection were included in the study. Ethical committee approval was obtained for the study.

Exclusion criteria: (a) COVID-19 positive patients who became negative prior to death, (b) Patients who were proven COVID-19 positive, post-mortem without an antemortem diagnosis were excluded from the study, (c) Below 18 years of age, (d) Death within 2 days of admission, (e) Incomplete data on NLR, PLR, ferritin, D-dimer and CRP.

Data collection

Epidemiological, clinical and laboratory parameters were collected retrospectively from records of patients who died due to COVID-19 infection during the period from April 2020 to March 2021. These patients had the diagnosis confirmed by a positive COVID-19 test either RTPCR or antigen. Only patients who were COVID-19 positive during death were included in the study. All data was recorded in the data collection forms, reviewed and double checked. Data collection forms contained details regarding demographic data, medical history, history of exposure to infection, symptoms, signs, laboratory findings and duration of illness before death. NLR, PLR, ferritin, D-dimer and CRP was collected for all patients on day one, day three and day five.

Statistical analysis

Categorical and quantitative variables were expressed as frequency and mean ± SD respectively. Karl Pearson Correlation Coefficient was used to find out relationship of quantitative parameters. Paired t test was used to find significance in progression in markers. Independent 't' test was used to compare quantitative parameters between categories. For all statistical interpretations, $p<0.05$ was considered as statistically significant. Statistical analysis was performed by using a statistical software package SPSS, version 20.

Results

During the study period, 130 patients died due to COVID-19 infection in our institute. 15 patients were diagnosed with COVID-19 post-mortem and 11 patients who were initially COVID-19 positive had become COVID-19 negative before death. So, these patients were excluded from the study and finally 104 patients were included in the study for statistical analysis.

During the study period 104 deaths were documented in the ICU satisfying the inclusion criteria. Among them, the oldest was 100 years of age and the youngest was 25 years of age. 75 patients (72 %) were above 60 years of age. 81 patients were between the age of 50 and 80. 54.8% patient had ICU stay of less than five days and 5.8 % had hospital stay of more than 10 days before death. The mean ICU stay was 5.9 days (Table 1).

Table 1: Baseline characteristics of the study population.

Age ≤60	*29*
Age >60	75
Mean Age	67.7 ±12.9
Males	68
Females	36
Mean days of ICU admission	5.9 ±3.6
Baseline mean NLR (Day 1)	5.7 ± 1.2
Baseline mean PLR (Day 1)	145.9 ± 84.4
Baseline mean CRP (Day 1)	37.6 ± 21.5
Baseline mean ferritin (Day 1)	780.9 ±561.3
Baseline mean D-dimer (Day 1)	3373.3 ± 809.1

The progression of neutrophil lymphocyte ratio, platelet lymphocyte ratio, ferritin, CRP and D-dimer was assessed from day 1 of ICU admission. These values were assessed on day one, day three and day five (Table 2).

Table 2: Progression of NLR, PLR and inflammatory markers from day1 to day 5.

	Days	*Mean ± SD*	*Pair*	*Paired t*	*P value*
NLR	Day 1	5.7 ± 1.2	Day 1 Vs day 3	5.13	p<0.01
	Day 3	7.3 ± 2.9	Day 3 Vs day 5	0.16	0.875
	Day 5	7.5 ± 2.9			
PLR	Day 1	145.9 ± 84.4	Day 1 Vs day 3	1.58	0.118
	Day 3	166.6 ± 126.8	Day 3 Vs day 5	0.07	0.948
	Day 5	173.7 ± 125.6			
CRP(mg/l)	Day 1	37.6 ± 21.5	Day 1 Vs day 3	4.1	p<0.01
	Day 3	51 ± 23.3	Day 3 Vs day 5	2.4	0.019
	Day 5	57.2 ± 21.1			
Ferritin (µg/ml)	Day 1	780.9 ± 561.3	Day 1 Vs day 3	1.05	0.298
	Day 3	852.5 ± 354.3	Day 3 Vs day 5	2.95	0.004
	Day 5	1033 ± 309.9			
D-dimer (ng/ml)	Day 1	2373.3 ± 809.1	Day 1 Vs day 3	6.13	p<0.01
	Day 3	3149.8 ± 767.8	Day 3 Vs day 5	3.81	p<0.01
	Day 5	3686 ± 953.4			

It is observed that there is a significant elevation of NLR values from day one to day three. There is no significant elevation of NLR value from day three to day five even though the mean value of NLR has increased among patients who died due to severe COVID-19.

The mean value of PLR on day one was 145.5. It increased to 166.6 and 173.7 on day three and day five respectively. It was observed that even though there was no statistically significant elevation of PLR value, there was a progressive increase in the PLR value over the period. It was observed that there was progression of both NLR and PLR among those patients who deteriorated and died due to COVID-19 infection.

Assessing the progression of ferritin over five days, there was no statistically significant progression of ferritin in the first three days, but a significant elevation of ferritin was noted from day three to day five among patients who died due to severe COVID-19. The levels of CRP was 37.6mg/L on the first day. There was significant elevation of CRP to 51mg/l on the day three. Even though CRP further increased on day five, there was no statistically significant progression of CRP from day three to day five.

The mean D-dimer value on day one was 2373.3ng/ml and there was a statistically significant elevation on day three and day five. All studied inflammatory markers, mean CRP, ferritin and D-dimer progressively increased in all the patients who died due to COVID-19.

The correlation of the inflammatory markers like ferritin, CRP and D-dimer were assessed in relation to NLR. A strong positive correlation was noticed between NLR and serum ferritin, CRP and D-dimer levels on day one and day five and a weak positive correlation on day three (Table 3).

Table 3: Relationship of NLR with other 3 inflammatory markers.

NLR	*Ferritin*		*CRP*		*D-dimer*	
	*r**	*p*	*r*	*p*	*r*	*P*
Day 1	0.598	<0.001	0.6629	<0.001	0.526	<0.001
Day 3	0.361	0.0003	0;2194	0.033	0.255	0.013
Day 5	0.554	< 0.001	0.3139	0.008	0.566	<0.001

*correlation coefficient.

The correlation of the inflammatory markers like ferritin, CRP and D-dimer were assessed in relation to PLR. No significant relationship was noticed between PLR over the five days with serum ferritin level (Table 4).

Table 4: Relationship of PLR with other 3 inflammatory markers.

PLR	*Ferritin*		*CRP*		*D-dimer*	
	r	*p*	*R*	*p*	*r*	*P*
Day 1	-0.111	0.263	-0.106	0.282	-0.071	0.472
Day 3	0.154	0.139	-0.187	0.071	0.155	0.136
Day 5	0.013	0.913	-0.251	0.036	0.106	0.383

A negative correlation was noticed in the level of CRP on day one, three and day five compared with the PLR value. No significant correlation was noticed in the levels of D-dimer and PLR value over the period of five days.

The difference in levels of NLR, PLR, CRP, ferritin and D-dimer in both genders were analysed. The mean of NLR in males on day one, three and five were 5.7, 7.7 and 7.6 respectively and in females 5.5, 6.5 and 7.4 respectively and there is no statistically significant difference. The mean of PLR in males on day one, three and five are 146.3,182.1 and 169.5 respectively and 150.1,135.3 and 181.2 in females. The mean of CRP in males on day one, three and five are 39.5, 51.0 and 59.4 respectively and 35.6. 51.0 and 53.0 in females. The mean of ferritin in males on day one, three and five are 849.4, 865.4 and 1039.5 respectively and 696.2, 826.3 and 1021.2 in females. The mean of D-dimer in males on day one, three and five are 2425.7, 3208.6 and 3741.0 respectively and 2244.6, 3030.3 and 3587.0 in females. Even though the mean of NLR, PLR, ferritin, CRP and D-dimer were higher in males compared to females, there was no statistically significant difference between males and females over the five days.

Discussion

The clinical presentation of corona virus infection ranges from asymptomatic cases to mild and critically ill disease. A small percentage of patients may progress to severe pneumonia, ARDS and death. Because COVID-19 spreads rapidly and causes significant morbidity and mortality, it is important to anticipate in which patients it can be more fatal. Inflammatory markers, NLR, PLR have been reported to be predictors of mortality in patients with COVID-19 disease [6-10]. Various studies have showed that these markers of inflammation are associated with severe illness and mortality. We conducted a retrospective analysis of 104 patients who died due to COVID-19 infection. We found that inflammatory markers like ferritin, CRP, and D-dimer were significantly elevated in these patients. Mean NLR was 5.7, PLR was 145.9, CRP was 37.6mg/l, D-dimer was 2373ng/ml and ferritin was 780.9µg/ml on the first day of ICU admission.

The immune response to infection is a dynamic process involving activation of humoral and cellular component resulting in fluctuation of inflammatory marker expression over time. Some studies showed fall in inflammatory markers after 10 days in patients with clinical improvement. Here we longitudinally analysed the pattern of the common inflammatory markers like ferritin, CRP, D-dimer, NLR and PLR over time in patients who died due to COVID-19. Our analysis showed a progressive increase in inflammatory markers over time which indicated cytokine storm as the cause of death in patients with COVID-19.

Several studies have been conducted to ascertain the relationship between these markers and the overall outcome of patients with COVID-19 disease.

The cytokine storm due to the release of pro-inflammatory mediators like those reported in other infections has been found to be a major cause of death in patients with severe COVID-19 disease [11].

Earlier studies have shown that D-dimer levels at the time of admission predicted mortality in patients with COVID-19 infection [12, 13]. In the study by Poudel et al., mean baseline D-dimer at the time of admission among survivors was 1067 ng/ml whereas among patients who died it was 3208 ng/ml and the cut off value was 1500 ng/ml for predicting mortality [12]. In our study the mean baseline D-dimer value of patients who died due to COVID -19 was 2373 ng/ml, much higher than the cut off value of 1500 ng/ml.

Serum ferritin, an acute phase reactant protein is also used as a marker of acute infection. High serum ferritin values at later stages of the illness were more significantly associated with death than raised ferritin at baseline or the progressive change in serum ferritin values during the course of the disease [9]. High baseline serum ferritin values have been independently associated with a severe course of the disease [14].

Studies have shown that acute respiratory distress syndrome in COVID-19 is associated with raised serum ferritin [15]. It is also associated with more severe course of the disease [16]. In a study by Qeaden et al., the serum ferritin cut off value for predicting mortality was 714nµg/ml [17]. Another study showed predictive cut off value of ferritin > 723µg/ml and CRP > 45.5mg/l to predict mortality [18]. In our study mean serum ferritin values on all the 3 days in COVID-19 deaths were above this value. Since ours was a retrospective study, we could not rule out all confounding factors for raised ferritin values.

Earlier reports have shown that baseline CRP levels and CRP levels before terminal events indicate poor prognosis in patients with COVID-19 [19]. Higher baseline CRP values were also associated with higher CT severity scores [20]. Higher CRP values have been associated with increased mortality in COVID-19 patients [21]. In this study mean CRP levels were

elevated on day one, day three and day five in patients who died due to COVID-19.

Neutrophil Lymphocyte Ratio (NLR) is a well-established inflammatory marker and can be easily calculated from blood count analysis which is routinely done in all patients. A rise in NLR signifies increased inflammatory process in COVID -19. One of the earliest studies from Wuhan, 8% increase in mortality was reported with each unit rise in NLR [22]. A meta-analysis conducted by Mahat et al observed that elevated NLR is associated with severe COVID-19 and increased mortality [23]. Many studies have shown that an increase in NLR can serve as an early warning sign of COVID-19. The baseline NLR was 5.7 in our study, and it progressively increased to 7.5 by day five, much higher than the cut off value described in most studies.

PLR, a novel inflammatory marker is inexpensive and can be easily obtained from total blood count. In a meta-analysis by Simadibrata et al., it was found that PLR on admission was elevated in patients with severe COVID-19 compared with those with mild disease [24]. PLR was also elevated in our study. Baseline PLR was 145.9 and it progressed to 173.9 on day five.

In a longitudinal study on inflammatory markers from Wuhan, China, it was reported that exuberant inflammatory responses within 24 hours of admission in patients with COVID-19 correlated with disease severity and mortality. The critically ill patients showed higher concentration of inflammatory markers like ferritin and CRP [25]. In our study in addition to the baseline inflammatory markers, we have assessed the serial progression of these markers. A definite progressive increase in the level of inflammatory markers was observed among cases when following them till death. A progressive increase in inflammatory markers in the initial days in patients with severe disease should be an indication for more aggressive management of the patient to reduce mortality. So, serial measurement of inflammatory markers is as important as baseline inflammatory markers to assess severity and to monitor progression in COVID-19.

On bivariate correlation analysis in our study, we have assessed the correlation between NLR and PLR with inflammatory markers. A statistically significant positive correlation was found between NLR and the inflammatory markers. In resource limited settings serial measurement of inflammatory markers will be difficult. In such situations, serial measurements of NLR can be done as a surrogate test to more expensive inflammatory markers.

Even though there was progressive increase in PLR over the five days, our study showed no significant correlation with ferritin and D-dimer on day three and day five. There was a negative correlation between all inflammatory markers and PLR on day one. All three days showed a negative correlation of PLR with CRP. Hence PLR cannot be used as a substitute for the inflammatory markers in COVID-19.

Global epidemiological data has shown a similar prevalence of viral infection between males and females. There is a definite difference between males and females in the severity of disease including mortality, with a more favourable outcome in females [26]. Previous reports have shown that inflammatory markers were higher in males compared to females [25, 27, 28]. But our study did not reveal any significant gender difference in inflammatory marker levels. Only severe cases resulting in death were included in our study resulting in higher inflammatory markers both in males and females without any difference.

Limitations

The limitations of our study included the small sample size and the retrospective nature of the study. Effect of treatment including anti-inflammatory therapy like tocilizumab, systemic steroids and other supportive therapies also could not be studied, as this was a retrospective study. Another major limitation is lack of a control group of patients. Further research with a control group of COVID-19 patients who survived a severe infection requiring ICU care should be done to assess the difference in dynamics of inflammatory markers between survivors and deaths. This study was done in a tertiary care centre and the sample size is small. So, the findings of this study cannot be generalised for the population.

Conclusion

Even though the peak of COVID-19 infection is over worldwide, new mutations can result in further new waves of infection. Since COVID-19 infection spreads rapidly and does serious harm, it is important to anticipate in which patients it can be severe and fatal. Inflammatory markers have been widely studied in COVID-19 infection. In this retrospective cohort study of 104 patient's progressive increase of inflammatory markers has been observed in COVID-19 deaths. Serial measurements of inflammatory markers will be useful in intensive care units for early identifications of patients who may deteriorate. Progression of NLR has strong correlation with inflammatory markers and could be used as a surrogate marker to prioritise treatment in resource limited settings.

Conflicts of interest

The authors declare no conflicts of interest.

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