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DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF EOSINOPHIL COUNT COMPARED TO CRP AND IN ASSESSING SEVERITY OF ILLNESS IN COVID 19 CASES

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ABSTRACT

- Coronaviruses are enveloped viruses. Inside the envelope, nucleocapsid proteins (N protein) are wrapped with a single-stranded, non-segmented, positive-sense RNA.[1] Coronaviruses are a large family of viruses that are known to cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS).[2] A novel coronavirus (COVID-19) was identified in 2019 in Wuhan, China. This is a new coronavirus that has not been previously identified in humans. The SARS-CoV-2 is currently causing the worldwide outbreak of infection (COVID-19).[2,3]
- Due to high contagious power of the disease rapid and accurate diagnostic tools are required to rapidly identify potentially infected patients and that will help to manage moderate to severe symptomatic patients. Hence we conducted a restrospective study to assess role of Eosinophil count and CRP levels in diagnosing covid19 when highly suspicious and its prognostic significance and role in assessing severity of illness.

KEYWORDS - covid 19, high contagious power, accurate diagnostic tool, rapidly identify, Eosinophils, CRP, prognostic significance, severity.

INTRODUCTION

- Globally, by 2 November 2021, there have been 246,951,274 confirmed cases of COVID-19, including 5,004,855 deaths, reported to WHO. During the week 25 to 31 October 2021, a slight upward trend (3% increase) in new weekly cases was observed, with just over 3 million new cases reported. New weekly deaths increased by 8% as compared with the previous week, with over 50 000 new fatalities. The observed rise in new weekly deaths has been mainly driven by the South-East Asia Region.[4]

- COVID-19 patients at disease onset presented with fever, non-productive cough, and myalgia, fatigue. In severe cases they presented with dyspnoea as, pneumonia, acute respiratory distress syndrome, myocarditis, and multiple organ failure.[5,6] RT PCR from nasopharyngeal swab or BAL is the gold standard for diagnosis of COVID19.[7,8]

- A unique finding associated with SARS-CoV-2 infection was a decline of eosinophil levels (eosinopenia)[17,18,19,20,21] and rise in inflammatory markers like CRP.[10,11,12,13,14,15,16,] Eosinophils are circulating and leukocytes in tissues that have potent proinflammatory effect in number of diseases. Eosinophils have been shown to have various other functions, including immunoregulation and antiviral activity.

- Meta-analysis and meta-regression studies revealed significant relationship between IL-6 and COVID-19 severity, independent of age and sex.[18] Coronaviruses were found to activate excessive and dysregulated host immune responses that contribute to the development of acute respiratory distress syndrome (ARDS).[19,20] Autopsy analyses of patients with Covid-19 with ARDS revealed hyperactivation of cytotoxic T-cells, with high concentrations of cytotoxic granules.[21] Reports describing the immunological profile of critically ill

patients with Covid-19 suggest hyperactivation of the humoral immune pathway—including interleukin (IL)-6—as a critical mediator for respiratory failure, shock, and multiorgan dysfunction.

- Meta-analysis of available data indicates that such increased levels are significantly associated with adverse clinical outcomes, including ICU admission, ARDS, and death.[21] The development of cytokine release syndrome (CRS) is the pathologic cause for disease progression of severe Covid-19, characterizing this dysregulation of host immune responses. Patients with complicated forms of Covid-19 had nearly threefold higher serum IL-6 levels than those with noncomplicated disease.[26]

- CRP has a functional role in inflammatory processes in general. It is well established that CRP is an acute marker of inflammation and that its concentration increases in circulation during inflammatory events. CRP is deposited at sites of inflammation and tissue damage in both naturally occurring and experimental conditions. CRP is the principal downstream mediator of the acute-phase response following an inflammatory event and is primarily synthesized by IL-6-dependent hepatic biosynthesis.[25] Thus, there is relation between rise in CRP levels and IL 6 in diagnosing and assessing progress of covid 19 illness. However, IL-6 is not routinely available or is costly, but being linked to CRP makes CRP a better candidate tool for front-line hospital usage.

OBJECTIVES OF THE STUDY
- To assess the significance of eosinophils and CRP levels on day of admission for diagnosing the illness and its severity.
- To find the correlation between eosinophils and CRP levels at day of admission and after one week of admission

MATERIALS AND METHODS
This is a retrospective observational cross-sectional study conducted on patients admitted in covid wards and ICU s under Department of General Medicine, Kempegowda institute of medical sciences, Bangalore Karnataka.110 patients who were admitted with COVID 19 RTPCR positive during a period of 3 months were included in the study. They were examined clinically and categorized as a,b,c based on severity of illness and routine blood investigation and inflammatory markers were sent and data collected and analysed progression of illness based on the markers.

DATA COLLECTION
Data of patients that includes age, sex, comorbidities, RTPCR for COVID 19,. Patients were monitored daily and categorised patients based on severity of illness, in to category A B and C. Routine blood investigations and were sent and chest xray taken. Complete haemogram

(assessing eosinophils on day 1 and 7), CRP levels on day 1 and 7 collected.

OUTCOME MEASURES The correlations between Eosinophils and CRP on day 1 and 7 to each other and their variations on each day with change in severity of illness assessed by daily monitoring the patients saturation levels, xray etc and daily categorisation of patients.

STATISTICAL ANALYSIS
Statistical Package for Social Sciences [SPSS] for Windows Version 22.0 Released 2013. Armonk, NY: IBM Corp., used to perform statistical analyses.

Descriptive Statistics
Descriptive analysis of all the explanatory and outcome parameters were done using frequency and proportions for categorical variables, whereas in Mean & SD for continuous variables.

Inferential Statistics
Kruskal Wallis Test followed by Mann Whitney Post hoc Test was used to compare the mean Eosinophil count and CRP levels based on the severity of disease on Day 1 & Day 7.

Mann Whitney Test was used to compare the mean Eosinophil count and CRP levels based on the Survival status of patients on Day 1 & Day 7.

Spearman's correlation test to assess the relationship between Eosinophil count and CRP levels on Day 1 & 7 among Survivors and Non-Survivors.

ROC Curve analysis was performed for Eosinophil count & CRP levels on day 1 for determining the cut-off between Survivors and Non-Survivors and also to compare the ROC Curves of the same at Day 1 & Day 7. The level of significance was set at $P < 0.05$.

RESULTS
Age group includes 21-90 years .59.5 % males

Age distribution among study patients			
Variable	Category	n	%
Age	21-30 yrs.	4	3.6%
	31-40 yrs.	13	11.7%
	41-50 yrs.	19	17.1%
	51-60 yrs.	18	16.2%
	61-70 yrs.	29	26.1%
	71-80 yrs.	18	16.2%
	>80 yrs.	10	9.0%
		Mean	SD
	Mean & SD	50.63	14.15
	Range	21 - 90	

Gender distribution among study patients			
Variable	Category	n	%
Gender	Males	66	59.5%
	Females	45	40.5%

63.1 % were non-survivors and all belong to category C.

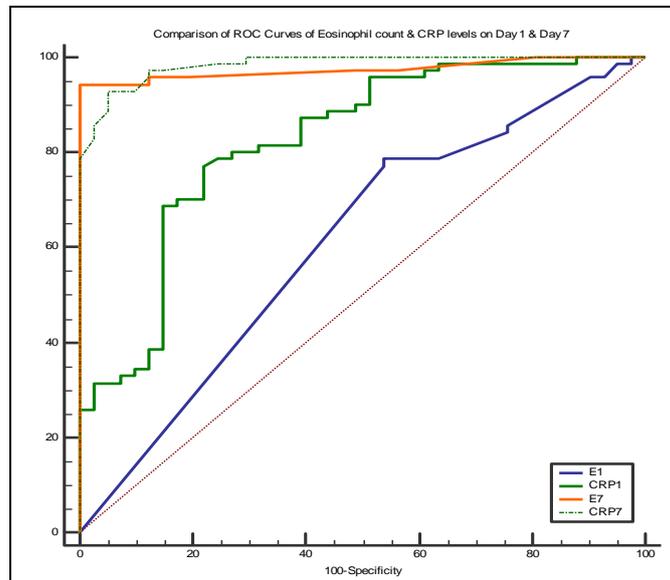| Distribution of study patients based on Severity of Patients			
Variable	Category	n	%
Severity	Category A	17	15.3%
	Category B	16	14.4%
	Category C	78	70.3%

Comparison of Survival status based on severity of disease among study patients using Chi Square Test						
Severity	Survivors		Non-survivors		c^2 Value	P-Value
	n	%	n	%		
Category A	17	41.5%	0	0%	90.462	<0.001*
Category B	16	39.0%	0	0%		
Category C	8	19.5%	70	100%		
Total	41	36.9%	70	63.1%		

Day1 eosinophil count of non survivors were lower than lower limit of normal, compared to survivors and it further decreased on day 7 and vice versa for CRP and is statistically significant with p<0.001. Spearmann **ROC** curve analysis on day 1 for detecting cutoff for survivors and non survivors showed CRP cutoff 5 have good sensitivity and specificity than eosinophil cut off of 0.2 % and both are statistically significant. AUC showed predictive accuracy of crp7 >e7>crp1>e1.

correlation showed negative correlation between CRP on day 1&7 and eosinophil for non survivors which is statistically significant.

Comparison of mean Eosinophil count and CRP levels based on the Survival status of patients on Day 1 & Day 7 using Mann Whitney Test							
Parameter	Time	Status	N	Mean	SD	Mean Diff	P-Value
Eosinophil Count	Day 1	Survivor	41	1.03	2.16	0.59	0.02*
		Non-Survivor	70	0.44	0.96		
	Day 7	Survivor	41	2.03	2.19	1.96	<0.001*
		Non-Survivor	70	0.08	0.36		
CRP Levels	Day 1	Survivor	41	3.81	4.19	-6.68	<0.001*
		Non-Survivor	70	10.49	7.19		
	Day 7	Survivor	41	1.64	1.98	-12.48	<0.001*
		Non-Survivor	70	14.12	6.21		

* - Statistically Significant

Spearman's correlation test to assess the relationship between Eosinophil count and CRP levels on Day 1 & 7 among Survivors and Non-Survivors					
Correlation	Survival	Variable	Values	CRP	
				Day 1	Day 7
Eosinophil vs CRP	Survivor	Eosinophil	rho	0.08	0.11
			P-Value	0.51	0.35
	Non-Survivor	Eosinophil	rho	-0.63	-0.69
			P-Value	<0.001*	<0.001*

Comparison of ROC Curves of Eosinophil count & CRP levels on Day 1 & Day 7

DISCUSSION
Eosinophil count and CRP levels were used in many studies for assessing the severity illness but only a few studies were available regarding which is more reliable in diagnosing and in assessing the prognosis of patients

based on the values on day of admission and on follow up days.

In our study it is observed that Eosinophil count and CRP can be used for diagnosis of COVID 19 suspected cases with high CRP being more statistically significant

than eosinopenia on day1.As the severity of illness increases, CRP increase to more than 5 and eosinophil count decreases to less than 0.2 percent in non survivors and thus helps in assessing prognosis and severity of illness. Predictive accuracy of CRP on day 7 greater than that of day 1 CRP levels and that of eosinophils on day 1 &2 in assessing severity of illness. In conclusion, Eosinophil levels and CRP are reliable markers for predictions in COVID 19 illness.

RESULT

CRP and eosinophil levels can be used as diagnostic and prognostic markers in COVID 19 illness and cut off values for both parameters can be used to assess the severity of illness on day of admission and thus helps in prognosis.

Limitation of study-Retrospective analysis and study conducted with limited number of patients in single institute. Need the study to be conducted in large population as COVID 19 infection is persisting in community and still have the propensity for pandemic.

BUDGET AND PROPOSED FUNDING

NO CONFLICT OF INTEREST
ETHICAL CONSIDERATIONS

The work has been approved by the appropriate ethical committees related to KIMS bangalore on February 2021 in which it was performed and that subjects gave informed consent to the work.

1. There was no financial burden on the patients as the said investigations are part of normal protocol for COVID 19 patients.

AUTHOR CONTRIBUTION

Dr Diana David Conceptualization, Methodology, Software, Data curation, Writing- Original draft preparation, investigation,reviewing. Dr **Rajeev H** Visualization, Supervision, and Editing.

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