<u>Original research article</u>

CRP in COVID-19: Disease severity assessment in vaccinated and unvaccinated patients with CRP levels at KB Bhabha Hospital

[1]Dr. Ujwala Valvi, [2]Dr. Vaibhav Mistry, [3]Dr. Lalsing Padvi

[1]Assistant Professor, Department of General Medicine, K.B. Bhabha Hospital, Bandra, Mumbai, Maharashtra, India

[2]DNB Teacher Grade-1, Department of General Medicine, K.B. Bhabha Hospital Bandra, Mumbai, Maharashtra, India

[3]Junior Resident, Department of General Medicine, K.B. Bhabha Hospital, Bandra, Mumbai, Maharashtra, India

Corresponding Author:
Dr. Vaibhav Mistry (vaibhavmistry@hotmail.com)

Abstract

Background: Covid immunization gives protection against COVID-19 infection and severity of disease. CRP level could early predict COVID-19-associated severe pneumonia or mortality. Vaccination is associated with reduced level of CRP in infected but immunized patients. This study's objective was to compare CRP levels between vaccinated (Single/Double dose vaccinated population) and Non vaccinated group), so as to assess severity of infection on admission and use it as prognostic marker.

Methodology: Present retrospective study was conducted on 203 patients of laboratory confirmed (by RT-PCR) COVID 19 infection, admitted to peripheral hospital facilities in K.B. Bhabha Hospital. We assessed the severity of the Covid-19 sickness with the help of CRP (C-reactive Protein) levels. Based on Vaccination, patients were classified in 2 groups and demographic variable, CRP and outcome were this to whether or not they had received a vaccination. The data was entered and analysed using SPSS version 22.0. The statistical analysis used descriptive statistics like percentage and inferential statistics like the Chi-Square test. Statistics were considered significant for P-values less than 0.05.

Results: In the present study, mean age was 48.38 ± 16.37 years. Slight male preponderance was seen (52.7% males and 47.3% females). 33% patients had Comorbidities. 36(17.7%) were vaccinated, only 1st dose was taken by 15(7.4%) patients and both 1st and 2nd Dose by 21(10.3%) patients. 167(82.3%) were not vaccinated. 176(86.7%) patients were discharged with recovery and 13.3% patients died. 18.8% of discharged patients were vaccinated and only 11.1% of died patients were vaccinated (p value 0.333). Mean CRP levels was significantly higher than lower age group, in patients with Co-morbidities (76.4 ± 73.3 vs 36.0 ± 58.2 mg/dL), in unvaccinated patients (54.2 ± 66.5 vs 28.2 ± 61.8 mg/dL) and in died patients (133.7 ± 81.6 vs 36.7 ± 53.2 mg/dL) (all p value <0.01). In vaccinated patients, CRP can predict mortality with 100% Sensitivity and Specificity of 90.1%, cut off value being 59.65 mg/dL. AUC was 0.970 and p value 0.033. In unvaccinated patients, CRP can predict mortality with Sensitivity of 79.7% and Specificity of 79.2%, cut off value being 70.59 mg/dL. AUC was 0.866 and p value 0.030.

Conclusion: Mean CRP level was significantly lower in vaccinated group. CRP levels had better Sensitivity and Specificity for prediction for mortality in vaccinated group (cut off value 59.65 mg/dL) compared to unvaccinated group (cut off value 70.59 mg/dL). Also, mortality was lesser in vaccinated patients when compared to the unvaccinated ones.

Keywords: COVID-19 infection, c-reactive protein, vaccinated, unvaccinated patients, outcomes

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious illness brought on by the SARS-CoV-2 coronavirus, which causes the severe acute respiratory syndrome. Kerala reported the first COVID-19 cases in India on January 30, 2020. Covid immunization gives protection against COVID-19 infection and severity of disease [1]. The Indian Council of Medical Research (ICMR) and Bharat Biotech India Ltd (BBIL), both of Hyderabad, announced that Covaxin had an overall efficacy of 77.8% against symptomatic COVID. Additionally, the two-dose vaccine was 63% protective against asymptomatic COVID and 93.4% effective against severe illness. 9 The mechanisms through which various

vaccinations provide protection vary [2]. Markers of disease activity like ferritin, C-reactive protein (CRP) and D-dimers are frequently monitored to detect the best opportunity for intensive treatment. Recent studies showed that C-reactive protein (CRP) is positively correlated with the severity of different infections [3]. Also, the early expansion of plasma CRP level is shown to increase the likelihood of developing plasma leakage, complications and mortality. Hence, CRP level could early predict COVID-19-associated severe pneumonia or mortality. Therefore, investigation of the CRP level might have paramount importance for early diagnosis and appropriate management of COVID-19-related complications. Vaccination again associated with reduced level of CRP in infected but immunized patients [4].

This study's objective was to compare CRP levels between vaccinated (Single/Double dose vaccinated population) and Non vaccinated group), so as to assess severity of infection on admission and use it as prognostic marker.

Material and Methods

Present retrospective study was started after getting approval from Institutional Ethical Committee. Total 203 patients of laboratory confirmed (by RT-PCR) COVID 19 infection, were enrolled between January 2022 to May 2022. After getting informed consent, patients' data collection was started regarding demographic characterises, clinical data laboratory data and outcomes of the patients. Using the universal sample technique, the data of all patients admitted to peripheral hospital facilities in K.B. Bhabha Hospital.

We assessed the severity of the Covid-19 sickness with the help of CRP (C-reactive Protein) levels. Based on Vaccination, patients were classified in 2 groups and demographic variable, CRP and outcome were this to whether or not they had received a vaccination.

Group 1: CRP on admission of Covid-19 Vaccinated patients.

Group 2: CRP on admission of unvaccinated patients.

The data was entered and analysed using SPSS version 22.0. The statistical analysis used descriptive statistics like percentage and inferential statistics like the Chi-Square test. Statistics were considered significant for P-values less than 0.05.

Results

Demographic and Clinical characteristics of the patients

Table 1 shows that majority, 42% of the patients were from age group 41 to 60 years and 32.5% were from age group 21 to 40 years. Mean age was 48.38 ± 16.37 years, ranging from 11 to 19 years. Slight male preponderance was seen (52.7% males and 47.3% females).

33% patients had Comorbidities, Diabetes being most common in 47.3% patients followed by Hypertension in 12.3% patients. Diabetes and Hypertension both were seen in 10.8% patients.

Vaccination Status shows that 36 (17.7%) were vaccinated, out of which only 1st dose was taken by 15 (7.4%) patients and 1st and 2nd Dose in 21 (10.3%) patients (Fig. 1). 167 (82.3%) were not vaccinated. In the present study, 176 (86.7%) patients were discharged with recovery and 13.3% patients died.

Table 1: Demographic and Clinical characteristics of the patients

| Variables		Frequency	Percent
Age (Years)	≤ 20	7	3.4
	21 to 40	66	32.5
	41 to 60	85	41.9
	61 to 80	41	20.2
	≥ 80	4	2.0
Gender	Male	107	52.7
	Female	96	47.3
Comorbidities	Diabetes	25	12.3
	Hypertension	17	8.4
	HTN and DM	22	10.8
	COPD	1	0.5
	IHD	3	1.5
	No Comorbidities	135	66.5
Vaccination Status (n=36)	Yes 1st Dose only	15	7.4
	1st and 2nd Dose	21	10.3
	Not vaccinated	167	82.3
Outcomes	Discharge	176	86.7
	Expired	27	13.3
Total		203	100
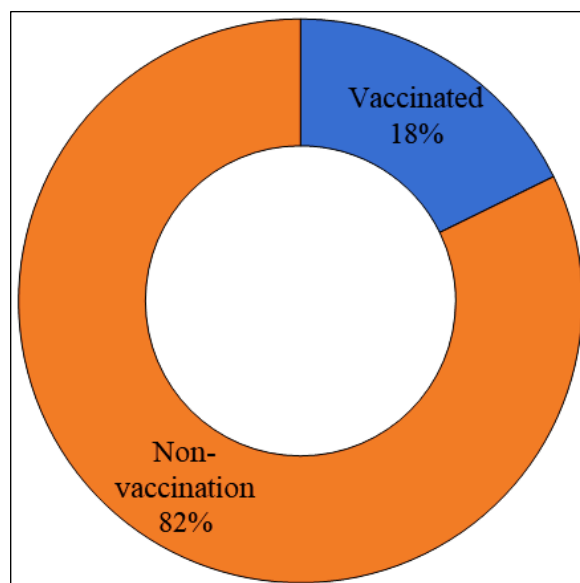
Fig 1: Vaccination Status of the Patients

Table 2: Vaccination status and Outcomes

Vaccination status	Outcomes		Total	P value	Odd's Ratio
	Discharge	Expired			
Yes	33 (18.8%)	3 (11.1%)	36 (17.7%)	0.333	1.85 (0.52 to 6.5)
No	143 (81.2%)	24 (88.9%)	167 (82.3%)		
Total	176 (100%)	27 (100%)	203 (100%)		

Table 2 shows that 18.8% of discharged patients were vaccinated and only 11.1% of died patients were vaccinated but the association between vaccinated status and mortality was not significant (p value 0.333).

Table 3: Demographic and Clinical variables and Mean C-reactive Protein (CRP)

Variables		CRP level (mg/dL)	P value
Age (Years)	≤ 20	15.0±18.0	0.000*
	21 to 40	21.7±39.0	
	41 to 60	65.8±76.6	
	61 to 80	57.1±55.0	
	≥ 80	146.5±132.1	
Gender	Male	50.4±65.5	0.854
	Female	48.7±67.5	
Co-morbidities	Yes	76.4±73.3	0.000*
	No	36.0±58.2	
Vaccination Status	Yes	28.2±61.8	0.032*
	No	54.2±66.5	
Outcome	Discharged	36.7±53.2	0.000*
	Expired	133.7±81.6	

Table 2 shows comparison of mean CRP levels among various patient characteristics. Mean CRP levels of age group 41 to 80 and ≥ 80 years were significantly higher than lower age groups (p value <0.01). CRP level increases as the age advances. Mean CRP levels of males were comparable with females (50.4±65.5 and 48.7±67.5 mg/dL respectively) (p value 0.854). It was significantly higher in patients with Co-morbidities (76.4±73.3 vs 36.0±58.2 mg/dL), in unvaccinated patients (54.2±66.5 vs 28.2±61.8 mg/dL) and in died patients (133.7±81.6 vs 36.7±53.2 mg/dL) (all p value <0.01).
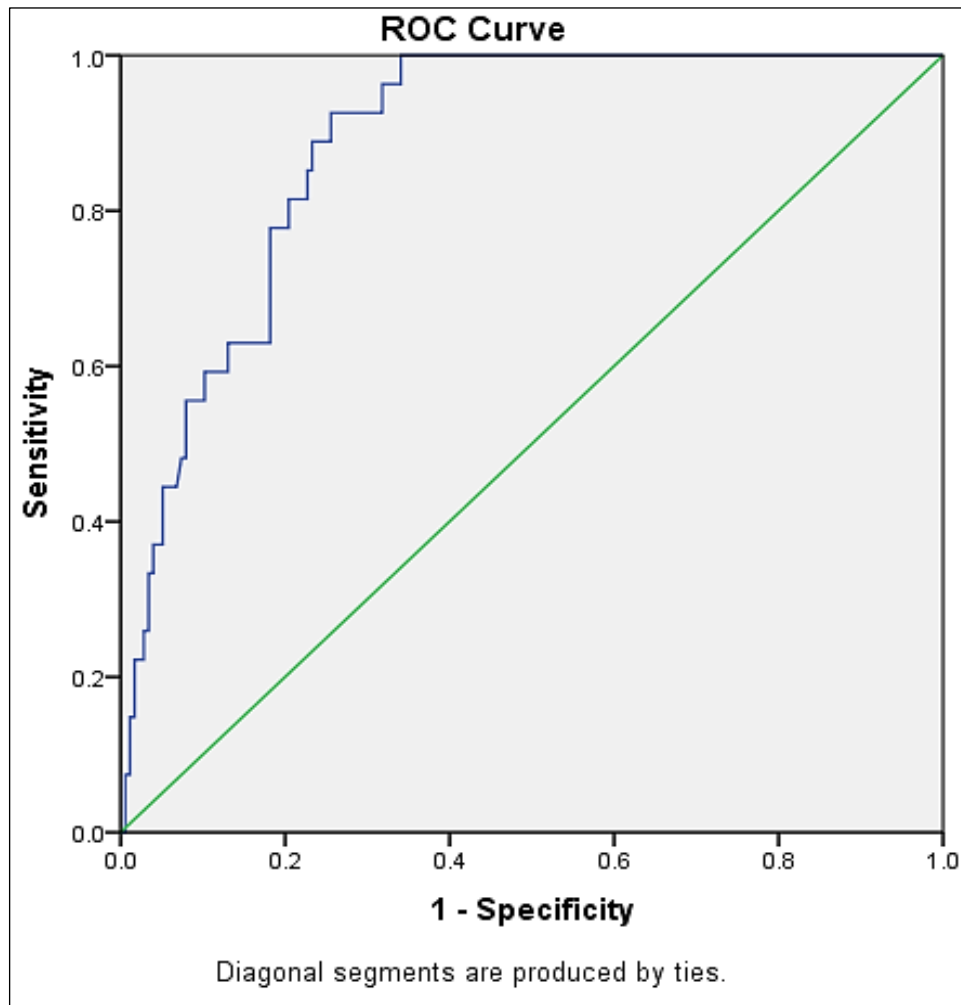
ROC Curve for prediction of mortality by CRP Levels

Fig 2: ROC Curve for prediction of mortality by CRP Levels

Table 4: Area Under the Curve for prediction of mortality by CRP Levels

Area Under the Curve				
Area	Std. Error	P value	Asymptotic 95% CI	
			Lower Bound	Upper Bound
0.886	0.025	0.000	0.836	0.936

Table 5: CRP in predicting Outcomes

Sensitivity	Specificity	Cut off value
79.5	81.5	64.35

Fig. 2 shows ROC curve of CRP for prediction of mortality with a Sensitivity of 79.5% and Specificity of 81.5%, cut off value being 64.35 mg/dL. AUC was 0.886 and p value <0.01.
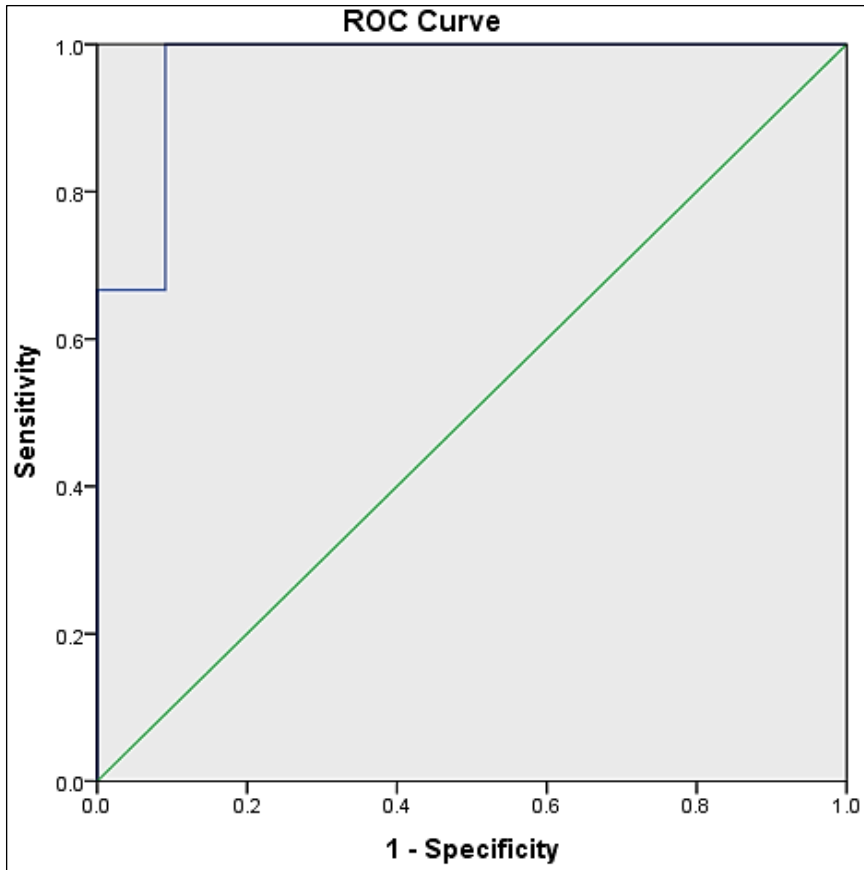
Fig 3: ROC Curve for prediction of mortality by CRP Levels in Vaccinated patients
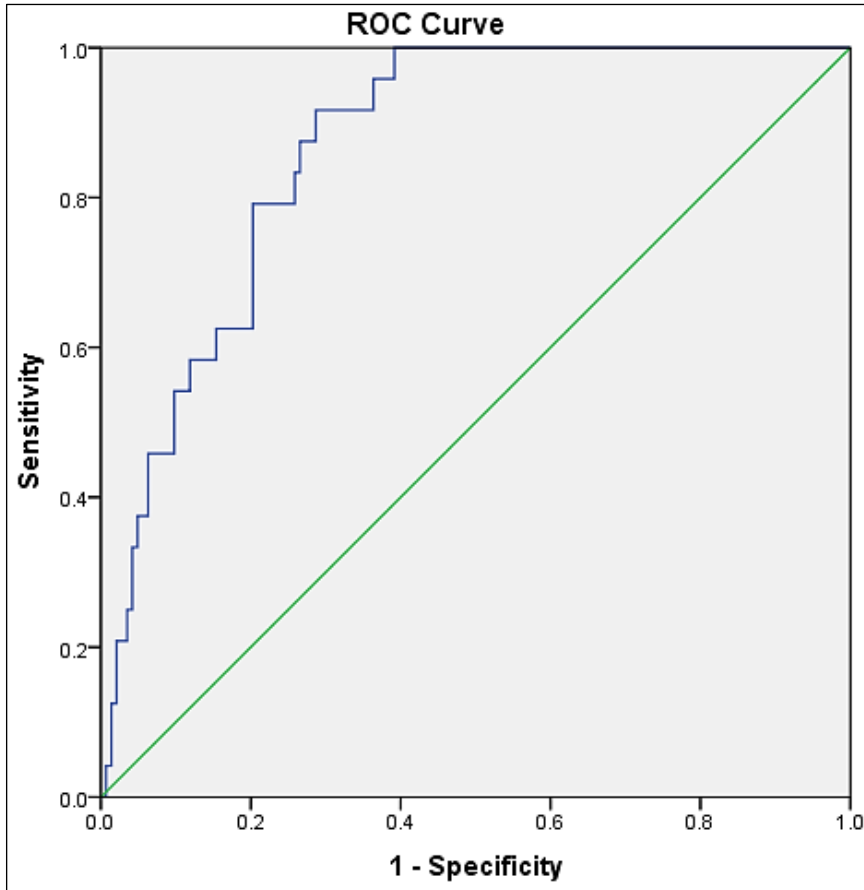

Fig 4: ROC Curve for prediction of mortality by CRP Levels in unvaccinated patients

Table 6: Comparison of Area Under the Curve for prediction of mortality by CRP in Vaccinated patients

Vaccination Status	Area Under the Curve				
	Area	Std. Error	P value	Asymptotic 95% CI	
				Lower Bound	Upper Bound
Vaccinated	0.970	0.033	0.008	0.905	1.000
Unvaccinated	0.866	0.030	0.000	0.806	0.926

Table 7: Comparison Sensitivity and Specificity of CRP in predicting Outcomes in Vaccinated patients

Vaccination Status	Sensitivity	Specificity	Cut off value
Vaccinated	100%	90.1%	59.65 mg/dL
Unvaccinated	79.7%	79.2%	70.59 mg/dL

Fig. 3 shows ROC curve in vaccinated patients, CRP can predict mortality with 100% Sensitivity and Specificity of 90.1%, cut off value being 59.65 mg/dL. AUC was 0.970 and p value 0.033. Fig. 4 shows ROC curve in unvaccinated patients, CRP can predict mortality with Sensitivity of 79.7% and Specificity of 79.2%, cut off value being 70.59 mg/dL. AUC was 0.866 and p value 0.030.

Discussion

During India's coronavirus crisis, it was killing thousands of people a day. Later India celebrated the delivery of its 1 billionth dose, a feat that until recently seemed improbable, public health experts are sounding a new warning: The turnaround is losing steam. Vaccinations are slowing down. Many people have not taken even the first vaccine. Unvaccinated population remains deeply vulnerable [5].

In the present study, a total of 203 patients were evaluated 167 (82%) were not vaccinated and 36 (18%) were vaccinated with either single or both doses. CRP, for prediction of mortality has Sensitivity of 79.5% and Specificity of 81.5%, cut off value being 64.35 mg/dL. AUC was 0.886 and p value <0.01.A study in UK showed that CRP of more than 40mg/L was associated with higher chances of mortality [6].

Therefore, complete vaccination of individuals is necessary to fight the pandemic and vaccine hesitancy is one of the main reason to compliance to vaccine as women from some parts of Jammu and Kashmir believe it can cause problems in menstruation, pregnancy and fertility, there were also reports of about 200 residents of a village in Uttar Pradesh jumped into the river to evade vaccination as they believed that COVID-19 vaccine is harmful as people are getting hospitalized and dying after getting the shot [7]. Some rumours prevailing in Indian villages is that the vaccine causes impotence in men. These are some of the reasons of vaccine hesitancy which needs to be looked upon and public needs to be educated of the importance of vaccination.

Haas EJ *et al*. [8] conducted a national surveillance study in Israel, among them 71.4% (3201) were unvaccinated and 8.1% (364) were fully vaccinated. The reported mortality was 64.2% and 12.4% in unvaccinated patients and vaccinated patients, respectively, similar to present study, which shows that 82% patients were unvaccinated and mortality was 14.4% and 8.33% in unvaccinated patients and vaccinated patients, respectively. 18.8% of discharged patients were vaccinated and only 11.1% of died patients were vaccinated but the association between vaccinated status and mortality was not significant (p value 0.333). Papagoras *et al*. from Greece [9] also reported better outcomes in vaccinated patients.

Comparative findings seen in another surveillance study conducted in Australia demonstrated on COVID-19 patients, observed that the vast majority (63.1%) of them were unvaccinated. Most of the patients who died were unvaccinated, and the mortality among fully vaccinated patients was 5.8%. Vaccination did decrease the risk of serious infection and death, and patients who died had an average age of 82 years with multimorbidity [10].

Sagiraju HKR *et al*. [11] from India conducted a similar study and reported a lower mortality rate in vaccinated patients; however, only 3% of patients in their study cohort were completely vaccinated as contrast to 18% patients in our study. Compared to vaccinated individuals, unvaccinated individuals had high CRP levels. It was significantly higher in in unvaccinated patients in the present study also (54.2±66.5 vs 28.2±61.8 mg/dL) (p value <0.01).

Balachandran *et al*. [12] compared outcomes among vaccinated and unvaccinated in a retrospective study in South Kerala, India, and reported 4.21 timer higher odds of mortality among unvaccinated patients; similar to results reported in our study, Odd's ratio was 1.84. Muthukrishnan *et al*. [13] from India also conducted a hospital-based cross-sectional study and reported a higher mortality rate of 31.45% vs 12.5% among unvaccinated as compared to those fully vaccinated. Moreover 70% lower risks of mortality were reported in the fully vaccinated cohort. Hu *et al*. [14] from China reported no differences in CRP levels between vaccinated and unvaccinated patients, which was contrast to our study. Lee *et al*. [15] reported no significant differences in CRP levels were noted between the vaccinated and unvaccinated patient in their study.

It is possible that we found difference in the CRP level when comparing the vaccinated and unvaccinated patients as we only compared the admission CRP level. However, there is a possibility that the trend of CRP may be of more value in predicating the severity of disease among vaccinated and unvaccinated

individuals.

Conclusion

Mean CRP level is which is significantly lower in vaccinated group compared to unvaccinated group (28.2±61.8 and 54.2±66.5 mg/dL respectively), so the difference in group was significant (p value 0.032). CRP levels had prediction for mortality in vaccinated group with 100% Sensitivity and Specificity of 90.1%, cut off value being 59.65 mg/dL and in unvaccinated group, with Sensitivity of 79.7% and Specificity of 79.2%, cut off value being 70.59 mg. Also, mortality was lesser in vaccinated patients when compared to the unvaccinated ones.

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