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Elevated inflammatory markers as predictors of mortality in people with diabetes and COVID-19

Abstract

Introduction: Diabetes Mellitus is a risk factor for COVID-19 infection, however data on specific biomarkers for monitoring the progress and predicting the mortality of diabetic subset of patients admitted with COVID-19is scanty. Our study aims to see the utility of biomarkers in predicting mortality, hospital /ICU stay, necessity of ventilatory support in diabetic patients admitted with COVID-19 infection.

Methodology: A retrospective multicentered analysis of data of COVID-19 positive patients who were admitted in two tertiary care hospitals of Kolkata, Eastern India between 1st September 2020 – 15th December 2020 was collected and set which fulfilled the inclusion and exclusion criteria were sent for analysis

Results: After accounting for the inclusion and exclusion criteria, a total of 133 subjects' data (84 males.63.16% and 49 females.36.84%) with mean age of 55.96 ± 11.94 years was available for analysis. Primary outcome viz. mortality was seen in 15 patients (10.9%), whereas the median hospital stays and ICU stay was 10 days and 4 days respectively and a large percentage of patients 47.37 % (63 patients) required ventilatory support. D dimer was the inflammatory marker which had the highest predictive value for mortality, the primary outcome, with an asymptotic significance of <0.001 and the area under the ROC (receiver operator curve) being 1.00. Ferritin, Interleukin -6 and CRP all showed fair to excellent predictability for mortality with the asymptotic significance being < 0.05 for all.

Conclusion: Biomarkers namely D-dimer, serum ferritin, C reactive protein (CRP) and interleukin-6 (IL-6) are reliable predictors of mortality in hospitalized COVID-19 patients with diabetes where D dimer showed the highest sensitivity and specificity. Glycated hemoglobin levels did not predict or affect mortality.

Keywords: COVID-19, inflammatory biomarkers, diabetes, mortality

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Introduction

In 2019, as the year preceded towards an end a novel virus causing severe acute respiratory illness (SARI), transgressed the international borders and spread globally from Wuhan, China. The World Health Organization (WHO) declared it as a Public Health Emergency on January 2020.[1] and later on as a pandemic on 11th March, 2020. The clinical features of this viral infection were seen to be similar to that of viral pneumonia and on perusal of the respiratory samples, the expert group of CDC (Centre for Disease Control) labelled this pneumonia as severe acute respiratory syndrome caused by member of the coronavirus family called SARS COV-2 and later named it as nCOVID19.[2] Globally, as of 03 April 2021, there have been 129,902,402 confirmed cases of COVID-19, including 2,831,815 deaths, reported to WHO.[3]

The entire world is now facing a resurgence of the n COVID-19 infection and confirmed cases are of late building up in geometric progression signaling the second wave which historically occurred with all the pandemics that have hit the globe at an approximate gap of hundred years. Over the past 15-16 months, we have come to recognize that COVID-19 infection represents a spectrum of clinical illnesses of varied severity resulting in asymptomatic carrier individuals to critical pneumonia, acute respiratory distress syndrome (ARDS) and even death (Guan et al 2020).[4] The growing body of evidence has also suggested that inflammatory responses play a critical role in the progression of COVID-19.[5]

Diabetes Mellitus is a risk factor for COVID-19 infection.[6] and therefore monitoring of the inflammatory markers may be able to predict not only severe and critical pneumonia but also mortality outcomes due to the disease. However specific biomarkers for monitoring the progress and predicting the mortality of diabetic subset of patients admitted with COVID-19 has not been established. Our study aims to see the utility of biomarkers in predicting mortality, hospital /ICU stay, necessity of ventilatory support in diabetic patients admitted with COVID-19 infection.

Materials and methods

A retrospective multicentered analysis of data of COVID-19 positive patients who were admitted in two tertiary care hospitals of Kolkata, Eastern India between 1st September 2020 – 15th December 2020 were collected and the data set which fulfilled the inclusion and exclusion criteria were sent for analysis.

Inclusion criteria

1) Diabetic patients on anti-diabetic drugs
2) Positive results of SARS CoV 2 RNA by real time PCR (polymerase chain reaction)
3) Patient with aged between 18-80 years
4) Patients in whom high resolution CT (HRCT) scan of thorax -and CT Severity Score (CTSS) was available
5) Availability of at least a complete single dataset of the inflammatory markers (C Reactive protein),ferritin, D-dimer and interleukin -6 done

Exclusion criteria

1) COVID-19 patients who were pregnant or lactating
2) Patients who were considered positive by imaging criteria or other methods without any confirmation by RTPCR
3) Patients who received steroids or Tocilizumab prior to admission

After taking the inclusion and exclusion criteria into account, data of 133 patients were available for analysis. Those patients who had multiple values of the inflammatory markers available, the highest value of that particular inflammatory marker during their hospitalization period was taken up for the purpose of statistical analysis. CTSS manual scoring on a scale of 25 was done in both the institutes not artificial intelligence driven score on a scale of [40] and patients who had their HRCT thorax and CTSS done elsewhere were not taken up for analysis. Similarly, for inflammatory markers, the four parameters were taken into account if done from the two institutional labs or outsourced to the same reference laboratory. IL 6 was outsourced to the same specialty laboratory from both the tertiary care institutes

Primary outcome studied was mortality and se we also looked at mean length of hospital stay, ICCU stay and requirement of ventilatory support (invasive or non-invasive modes of ventilation support used). Without analyzing the impact of the biomarkers on these items as no single SOP (standard operating procedure) was followed in executing the same. Hence the predictive impact of the inflammatory biomarkers on these three parameters were not assessed.

Statistical methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as Mean (SD) for parametric data or median (IQR) for non-parametric data and results on categorical measurements are presented in number (%). Significance is assessed at a level of 5 %. Normality of data tested by Anderson Darling test, Shapiro-Wilk, Kolmogorov-Smirnoff test and visually by QQ plot. With a type I error of 0.05, type II error of 0.20, and null hypothesis value of 0.5 with an expected ratio of positive to negative cases of seven, the minimum sample size required is 12 positive cases and 121 negative cases to construct a ROC curve for a variable with an anticipated AUC of 0.8 or more. Since we had 15 positive events (dead) and 118 negative events (recovered) within the study sample, and all the inflammatory markers having an AUC of more than 0.8, we calculated the optimum cut-off for all the inflammatory variables.

Statistical software: The Statistical software namely Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for windows, SPSS, Inc., Chicago, IL, USA, is used for data analysis with Microsoft Word and Excel being used to generate tables.

Results

After accounting for the inclusion and exclusion criteria, a total of 133 subjects' data (84 males 63.16% and 49 females 36.84%) with mean age of 55.96 ± 11.94 years was available for analysis. Nearly half of the individuals (46.6%) had an HbA1C of > 9% and only 18 % individuals in this cohort had an HbA1C < 7.5%. Age did not prove to be a predictor of outcomes, nor did BMI – however it is to be kept in mind that in majority of the sick patients the weight was derived from a calculation based on the length of the patient measured in ICU which can often be off target resulting in an erroneous BMI (Table 1A). The inflammatory markers are enumerated in Table 1B.

Table 1A Demographic characteristics of overall cohort with COVID-19, N= 133

Male, n (%)	84 (63.16)
Female, n (%)	49 (36.84)
Age (years), Mean ± SD	55.96 ± 11.94
HbA1c (mg/dL), Mean ± SD	8.79 ± 2.21
HbA1c < 7.5%, n (%)	24 (18)
HbA1c > 7.5% but <9%, n (%)	47 (35.3)
HbA1c > 9%, n (%)	62 (46.6)
BMI (kg/m^2), Mean ± SD	25.39 ± 1.98
SBP (mmHg), Mean ± SD	138.42 ± 16.9
DBP (mmHg), Mean ± SD	80.34 ± 10.67

Table 1B inflammatory markers of overall cohort with COVID-19, N= 133

D-dimer (ng/ml), Median (IQR)	384 (319.5– 435)
CRP (mg/L), Median (IQR)	29 (23 –36.5)
IL-6 (pg/mL), Median (IQR)	25 (18 – 30.5)
Serum Ferritin (ng/mL), Median (IQR)	417.5 (377.5 – 506)

Primary outcome viz. mortality was seen in 15 patients (10.9%), whereas the median hospital stays and ICU stay was 10 days and 4 days respectively and a large percentage of patients 47.37 % (63patients) required ventilatory support (either non-invasive ventilation via BiPAP or invasive mechanical ventilation after endotracheal intubation). (Table 2)

Table 2 primary and secondary outcome measures of overall cohort with COVID-19, N= 133

CT-SS Score, Median (IQR)	12 (10-14)
ICU stay (days), Median (IQR)	4 (2-6)
Hospital Stay (days), Median (IQR)	10 (8-12)
Ventilator support, n (%)	63 (47.37)
Mortality, n (%)	15 (10.9)

D dimer was the inflammatory marker which had the highest predictive value for mortality, the primary outcome,with an asymptotic significance of <0.001 and the area under the ROC (receiver operator curve) being1.00. Ferritin, Interleukin-6 and CRP all showed fair to excellent predictability for mortality with the asymptotic significance being < 0.05 for all. Although not a biochemical inflammatory backreacts also had an asymptotic significance of.003 and also came out as a fair to excellent marker for predicting the primary outcome that is mortality in COVID-19 infected diabetic patients. (Table 3 & 4) (Figure 1)

Discussion

The mortality rate arrived at in this study is quite high in comparison to the mortality being quoted by the agencies involved.[7] but it must always be kept in mind that this percentage is derived of a subset of diabetic patients and diabetes is an accepted comorbidity for COVID-19 infection.[6] The fact that these patients were taken from two tertiary care center data imply that their disease was moderate to severe and this cohort had no asymptomatic or mild cases which heavily contribute to the total number of cases and ultimately are instrumental in bringing down the mortality percentages.

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Table 3 Receiver-operating characteristic (ROC) analysis - Area under the Curve: Predictive ability for increased risk of mortality in hospitalized COVID-19 patients with Diabetes Mellitus, N= 133

Area Under the ROC Curve

Test Result Variable(s)	Area	Std. Error	Asymptotic Significance	Asymptotic 95% Confidence Interval		Predictive Ability for Mortality
				Lower Bound	Upper Bound	
Age	.597	.104	.354	.394	.800	Fail to predict
SBP	.341	.102	.130	.141	.542	Fail to predict
DBP	.491	.092	.931	.311	.671	Fail to predict
BMI	.731	.108	.027	.520	.942	Fail to predict
FERRITIN	.851	.062	.001	.729	.972	Fair to Excellent
D-DIMER	1.000	.000	<0.001	1.000	1.000	Excellent
CRP	.856	.048	.001	.761	.950	Fair to Excellent
IL-6	.881	.069	.000	.745	1.000	Fair to Excellent
CTSS Score	.806	.074	.003	.761	.951	Fair to Excellent

Table 4 Optimum cut-off value of inflammatory markers for predicting mortality, N=133

Test Result Variable(s)	Optimum cut-off value	Sensitivity for optimum cut-off value	Specificity for optimum cut-off value
D-dimer (ng/ml)	381	100	96.5
CRP (mg/L)	32.5	92.9	64.8
IL-6 (pg/mL)	24.5	78.6	95.3
Serum Ferritin (ng/mL)	429.5	85.7	59.8
CTSS			

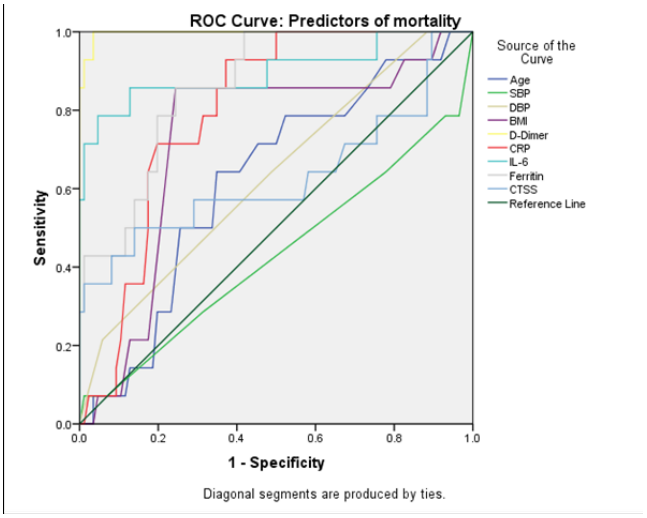

Figure 1 Receiver-operating characteristic (ROC) curve to identify predictive ability of study variables for increased risk of mortality in hospitalized COVID-19 patients with Diabetes Mellitus.

When fibrin is cleaved by plasmin to breakdown clots, D dimer is produced and the assay of D dimer is part of the routine algorithm to exclude the diagnosis of thrombosis. However any process that increases fibrin production or even its breakdown also increases the levels of D dimer.[8] Pathological processes that increase D dimer include pulmonary embolism, deep vein thrombosis, disseminated intravascular coagulation (DIC), vasculitis , post trauma , post-surgery etc. whereas physiological processes like inflammation and pregnancy also do the same.[9] Yumeng et al. also showed that amongst all the subjects in their study with high D dimer level only 3 had ISTH-DIC score of > 5 that established that high D dimer in COVID-19 is not related to DIC but rather is a salient feature of the disease itself.

D dimer turned out to be an excellent predictor for mortality in this subset of patients which is in complete agreement with the study by Yumeng Yao and colleagues[9] who showed that D dimer level > 2mg/L was the only variable associated with increased odds ratio of mortality. OR 10.17 (95% CI 1.10- 94.38) P=0.041. Zhou et al.[10] in a retrospective cohort study also reported that D dimer level > 1 microgram/ml in CoVID-19 patients was an indicator for increased risk of mortality. Hence D dimer can be used as a single clinically important biomarker to indicate the severity and also the in-hospital mortality of COVID-19 patients with diabetes.

In presence of active infection, elevated ferritin levels helps to protect the body system by restricting the availability of iron to pathogen – this is a hypothesis put forward by some studies.[11,12] This is further supported by the fact that iron supplementation during infection enhances the mortality rate in human beings.[13] Acutely elevated levels of ferritin in the bloodstream containing high levels of pathogenic organism produces a hypoferremia blood with low iron like state.[14] which restricts availability of iron to the pathogen. Elevated levels of serum Ferritin has been used as a biomarker for other viral infections like dengue.[15] where it has been labelled as a flagship sign for macrophage activation syndrome (MAS) which is a state of severe systemic inflammation due to activation of T-lymphocytes and macrophages that leads to hyperactivated dysregulated immune responses. COVID-19 infection initially leads to a primary cytokine storm mainly produced by epithelial cells, endothelial cells and alveolar macrophages.[16] however in the later stages there is evidence of a secondary cytokine storm induced by activated T cells and causes complications similar to that in MAS.[17] Hence the serum ferritin levels can be used as a biomarker to determine the severity of COVID-19 illness and also serves as a fair to excellent predictor of in-hospital mortality as also shown in the study of inflammatory markers by Abdul Rehman Rashid et al.[18]

CRP is an acute phase inflammatory protein produced by the liver that may be elevated in several conditions, such as inflammation, cardiovascular disease, and infection. In severe cases of COVID-19 infected patients persistently elevated CRP levels are found to be associated with an increased risk of DIC, ARDS and hypercoagulation.[16] DIC is a condition where there is systemic stimulation of coagulation of blood which leads to excess formation of fibrin and its accumulation causing microvascular thrombin the organ system {as was found in the autopsy specimen of the lungs of COVID-19 victims of Italy} leading to multi organ dysfunction syndrome.[MODS.19]. C reactive protein in our study, emerged as a biomarker with fair to excellent predictive value for mortality which again fell in lines with the study

of Abdul Rehman Rashid and colleagues.[18] who concluded that CRP at levels of > 45.5mg/l had a sensitivity of 86.36% and specificity of 88.89% for predicting mortality {somewhat higher than that found in our cohort}. A meta-analysis by Huang et al found three times increased risk of mortality amongst patients with CRP> 10 mg /L.[20] and Liu et al showed that a CRP of > 41.8 mg/ L was associated with severe complications.[21] which just reiterates our findings.

As the pandemic of COVID-19 progressed, building blocks of evidence became available that showed that pro inflammatory cytokines play a pivotal role in the pathophysiologic mechanism that precipitates the lung damage inpatients infected by the COVID-19virus.Ye Q et al published a mechanistic model and described the cytokine storm in the infected COVID-19 patients.[16] Many of the COVID-19 infected patients develop a fulminant and lethal immune reaction which is cytokine mediated and leads to macrophage and monocyte infiltration of the alveolar tissue, of the lung in particular. Interleukin 6.[IL-6] is a leading cause of inflammatory and immune response that is initiated by inflammation or injury and is found to be elevated in more than fifty percent of the patients infected by COVID-19.[22] Study by Herold T, et al.[23] showed that elevated levels of IL 6 predicted the need for mechanical ventilation and a meta-analysis of nine studies.[24] also reiterated that need for mechanical ventilation as well as mortality is predicted by the levels of IL 6. IL 6 in our study of the subset of diabetic patients also showed an area under the curve of 80.6% and hence came out as a fair to excellent predictor of mortality.

Although this study generated a significant suggestion of role of inflammatory markers as predictors of mortality in people with diabetes and COVID-19, several limitations should be addressed. First of all this is a retrospective observational study with small sample size. Second, our dataset did not include recognized comorbidities for death from COVID-19, such as hypertension or cardiovascular disease. Third, the authors were not able to capture information about various factors that could have adversely affected inflammatory markers, especially C reactive protein which is often lower in patients with cirrhosis or those on medications such as statins. Another limitation of this study includes the lack of differentiation between the types of diabetes. Lastly, absence of control arm with non- diabetic subjects with COVID-19 infection and / or diabetic subjects with non-COVID-19 viral infection as comparator are major drawbacks of the study.

Conclusion

COVID-19 infection shows significant mortality rate in hospitalized patient in which immune mediated lung injury plays a major role. We suggest that biomarkers like D-dimer, serum ferritin, C reactive protein and IL-6 are reliable predictors of mortality in hospitalized COVID-19 patients with diabetes with D dimer having the highest sensitivity and specificity. Hence they could be used as early predictors for case management before deterioration. On the other hand, these parameters cannot be used independently for initial diagnosis and physicians need to monitor the presence of other infections that may interfere with the elevation of these markers.

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None

Conflicts of Interest

The authors declare no conflict of interest.

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