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Original Research Article

Association of serum interleukin 6 levels with clinical outcome of COVID-19 associated mucormycosis

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ABSTRACT

Background: Interleukin 6 (IL6) is an inflammatory cytokine and hence used as a serological marker of inflammation. COVID-19 infections induces a state of hyperinflammation which makes it conducive for opportunistic infections like mucormycosis.
Methods: The prospective single-center study considered adults patients of both the gender, diagnosed with COVID-19 infection by RT-PCR technique and clinically, microbiologically or radiologically confirmed cases of mucormycosis. Necessary demographic, clinical data and serum IL6 level were collected and selected subjects were followed up until discharge or death. Subjects were classified as those who survived and succumbed to death. Chi-square test was used to analyse for categorical data between the groups.
Results: The study included 61 subjects, where in there was statistically significant association between serum IL6 levels with clinical outcome of COVID-19 associated mucormycosis (CAM). Serum IL6 levels were significantly higher in patients who died.
Conclusions: Higher serum IL6 levels is associated with poor clinical outcome in patients with CAM. Hence it can be used as a marker to predict prognosis of the disease.

Keywords: COVID-19, Mucormycosis, Interleukin 6

INTRODUCTION

Coronaviruses are non-segmented positive stranded RNA viruses with a roughly 30 kb genome surrounded by a protein envelope. Most coronaviruses cause diseases in their particular host species.[1] Those coronaviruses that can infect humans through cross-species transmission have become an important threat to public health. Two serious coronavirus disease outbreaks have happened in the past two decades: severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012.[2,3] Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been recognised as the causal factor in a series of severe cases of pneumonia originating in Wuhan in Hubei province, China.[4] This disease has been named coronavirus disease 2019 (COVID-19) by WHO. SARS-CoV-2 has been shown to cause disease via a mechanism analogous to the SARS coronavirus, with potential damage to vital organs such as lung, heart, liver and kidney and infection poses a considerable risk to patients by the high prevalence of pneumonia.[5]

Since May 2021, there has been a surge in CAM which has been having devastating complications on patients.[6] Mucormycosis is an invasive fungal infection which commonly manifests as an opportunistic disease in patients with immune suppression.[7] It typically starts with nasal involvement followed by the paranasal sinuses and palate, ultimately invading the orbit and brain which is

called as rhino-orbito-cerebral mucormycosis.[8] COVID-19 infection is known to produce a state of hyperinflammation with release of various cytokines including IL1, IL6, TNF (tumor necrosis factor) alpha among others.[9] This state of immune dysfunction is associated with development of opportunistic infections, of which mucormycosis is on the rise currently.[10] While numerous treatment options have been explored, corticosteroids remain one of the common drugs to treat COVID-19 with proven benefit. The widespread use of corticosteroids can cause secondary infections including mucormycosis.[11] Even then the exact mechanism of mucormycosis occurring in COVID-19 is yet to be elucidated.

This study was being done to clinically correlate an inflammatory marker, serum IL6 in patients with CAM.

METHODS

The prospective study was carried out between May 2021 and June 2021 at Victoria hospital attached to Bangalore medical college and research institute. Approval and clearance were obtained from the institutional ethics committee. The study included patients aged ≥18 years of both the gender, diagnosed with COVID-19 infection by RT-PCR technique and clinically, microbiologically or radiologically confirmed cases of mucormycosis. The study excluded patients <18 years and those not willing to provide signed informed consent prior to the study. Case record form with follow up chart was used to record the demographic data, clinical features of the disease and blood investigations.

The demographic and clinical data collected were age, sex, socioeconomic status, occupation, travel/contact history, blood group, vaccination details, clinical symptoms and incidence of co-morbidities like hypertension, diabetes and metabolic renal cardiac and respiratory disorders. Serum IL6 levels of the included subjects were measured and recorded in the case proforma. All the selected participants were followed up until discharge or death.

SPSS version 20 was used to perform the statistical analysis. Data was entered in the excel spread sheet. Inferential statistics like Mann-Whitney test was applied to check the statistical difference of Hb levels between the groups (discharged and death). The level of significance was set at 5%.

RESULTS

The study considered 61 patients admitted to our centre and was diagnosed positive for CAM. The demographic and clinical characteristics considered for the analysis are given in Table 1 and 2.

The co-morbid conditions of the patients have been depicted in Table 3. Diabetes mellitus was the most common co-morbid condition among the subjects enrolled in the study. The other significant co-morbid conditions were hypertension and ischemic heart disease.

Table 1: Distribution of the subjects based on age.

Age (in years)		Total
Less than 30	Count	4
	%	6.6
31 to 45	Count	11
	%	18.0
46 to 60	Count	35
	%	57.4
Above 60	Count	11
	%	18.0
Total	Count	61
	%	100.0

Table 2: Distribution of the subjects based on gender.

Gender		Total
Female	Count	22
	%	36.1
Male	Count	39
	%	63.9
Total	Count	61
	%	100.0

Table 3: Distribution of the subjects based on co-morbidities.

Co-morbidities		Total
Diabetes mellitus	Count	53
	%	75.4
Ischemic heart disease	Count	2
	%	3.3
Hypertension	Count	1
	%	1.6
Nil	Count	5
	%	8.2
Total	Count	61
	%	100.0

Table 4: Association of serum IL6 with outcome using Chi-square test.

Serum IL-6 (pg/ml)		Outcome-discharge or death		Total
		Death	Discharge	
Less than 70	Count	0	49	50
	%	0.0	80.3	82.0
70 to 140	Count	1	4	7
	%	1.6	6.6	11.5
More than 140	Count	3	4	4
	%	5.0	6.6	6.6
Total	Count	4	57	61
	%	6.6	93.4	100.0
Chi-square value=17.02				
P=0.00*				

*significant.

Out of the 61 patients included in the study, 57 patients got discharged while 4 patients died. Serum IL6 levels of the patients was correlated with their clinical outcome, discharge or death. There was significant association between serum IL6 levels and outcome of disease as shown in Table 4 ($p<0.05$). Among the 4 people who died, one was a female and other 3 were male patients. All were diabetic patients aged more than 50 years. Serum IL6 levels were more than 140 pg/ml in all these who died. And among the patients who got discharged, majority had an IL6 level less than 70 (N=49, 80.3%).

DISCUSSION

COVID-19 infection caused by SARS-CoV-2 is known to cause certain pathophysiologic changes that lead to secondary infections along with interplay of pre-existing illness like type 2 diabetes mellitus and immune-suppressive conditions, respiratory pathology.[12] Increased propensity of COVID-19 caused alveolo-interstitial disruption, increased the risk of fungal infections backed by alteration in innate immunity in the form of reduced CD4+ T cells and CD8+ T cells.[13] Moreover, the alteration in N:L ratio and persistent lymphopenia contributed to decreased immunity.[14] Cytokine storm in COVID-19, specifically increased in IL6 was known to decrease the iron transport thereby increasing free iron by increasing ferritin levels.[15] Hyperferritinemia, caused the pathogen of mucormycosis to grow profusely thereby accentuating the vicious cycle.[16] IL6 levels were elevated in the hyperinflammatory state of COVID-19 infection and was associated with increased mortality.[17] Out of the 61 patients included in our study, 57 patients got discharged and 4 patients expired. All the 4 patients who expired had an IL6 level more than 140 pg/ml while majority of the patients who were discharged had an IL6 level less than 70 pg/ml. A study done by Pal et al stressed on raised IL6 in severe COVID-19 illness to be the cause for dysglycemia in patients predisposing them to invasive molds.[18] Uncontrolled blood sugars increased the risk of mucormycosis infection.[19] Diabetes mellitus was a known risk factor for mucormycosis, with alteration of innate immunity and increased risk of infections in diabetes mellitus.[20] In our study 55 out of the 61 subjects were diabetic (75.4%) and all the patients who died were also diabetic. The limitations of the study were that study sample size was relatively small and the parameter (IL6) was recorded only at a single point after admission while serial measurement was not done. Further studies needed to be done to assess the association of serum IL6 levels in CAM and elucidate the exact mechanisms involved in affecting the clinical outcome of the disease.

CONCLUSION

In our study it was found that higher serum IL6 levels was associated with poor clinical outcome in patients with CAM. Hence it can be used as a marker to predict the prognosis of the disease.

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