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CORRELATION OF EOSINOPHIL COUNT AND LDH IN PREDICTING DISEASE SEVERITY IN COVID 19 PATIENTS WITH UNDERLYING CHRONIC AIRWAY DISEASE

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Abstract

Background: Patients with underlying COPD, asthma, and chronic bronchitis may have different inflammatory states after SARS-CoV-2 infection compared to patients without chronic airway inflammation. In this study, we aimed to identify the potential predictors like LDH and eosinophils count for the disease severity of COVID-19 patients with underlying chronic airway diseases including chronic bronchitis, COPD, and asthma. **Material and Methods:** A single centered Retrospective observational study conducted among patients admitted under medicine department between May to August 2021 at a Tertiary care hospital, Bangalore, Karnataka, India. **Results:** 39 patients with underlying chronic airway inflammation, including COPD (61.5%), asthma (17.1%) and chronic bronchitis (20.5%), were confirmed to have SARS-CoV-2 infection. Of the patients, 12 were classified as mild, 23 as moderate and 4 were classified as severe. The mean age of all patients was 62.2 years with male preponderance. When compared with non-severe patients, patients with moderate disease were more likely to have elevated LDH (330.2) as compared to severe (319.75) and mild (289.67). However it was not statistically significant. Statistically significant association was found for CRP where moderate patients had more elevated CRP levels in comparision to severe and mild disease. Eosinopenia (0.25%) was found in patients with severe disease which was statistically significant. **Conclusion:** Eosinopaenia and elevated LDH have been identified as risk factors for severe COVID-19 cases; however, it is noteworthy that in our study they were also associated with severity of COVID-19 in patients with chronic airway diseases.

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Keywords: Covid 19, Airway inflammation, inflammatory markers.

Introduction

COVID-19 infection which was first reported as a cluster of pneumonia from Wuhan, China, in December 2019, has rapidly emerged as a global pandemic and has endangered human lives.[1] During the early course of the pandemic, Italy had the highest infection burden and India remained much less affected with corresponding mortality rates of 14.24% and 3.03%.[2]

However, the recent trends from the country shows an exponential increase in daily spike and the total cases has crossed 20 million mark according to the Health Ministry data published on May 15, 2021.[3] The officially confirmed deaths from the disease is around 2,66,207. This condition is associated with high morbidity, leading to significant burden on health care infrastructure and resources. The associated fatality rate is also higher than other respiratory viral infections. Hence, it is necessary to identify reliable predictors of disease severity and mortality for careful allocation of health care resources and to enable earlier clinical intervention to improve clinical outcomes. SARS-CoV-2 is able to attack the respiratory system through binding the cell entry receptors angiotensin converting enzyme 2 (ACE2) on airway epithelial cells and results in pneumonia and respiratory failure in critically ill patients. Chronic bronchitis, chronic obstructive pulmonary disease (COPD), and asthma are common respiratory diseases with chronic airway inflammation.[4,5] Eosinophils, neutrophils, and macrophages in innate immune response significantly increase in the airway and lung during the initial phase of inflammation. Recently, circulating eosinophil counts were also reported to be decreased in COVID-19 patients, and associated with the severity of the disease.[6,7]

Therefore, patients with underlying COPD, asthma, and chronic bronchitis may have different inflammatory states after SARS-CoV-2 infection compared to patients without chronic airway inflammation.[8,9] In this study, we aimed to identify the potential predictors like LDH and eosinophils count for the disease severity of COVID-19 patients with underlying chronic airway diseases including chronic bronchitis, COPD, and asthma.

Material and Methods

This was Retrospective observational study conducted among patients admitted under medicine department between May to August 2021 at a Tertiary care hospital, Bangalore, Karnataka, India. Approval and clearance were obtained from the institutional ethics committee. The study included all the patients aged ≥ 18 years of both the gender, diagnosed with COVID-19 infection by RT-PCR technique using ABI/Thermo Fischer - Taqppath technique with underlying airway disease like chronic bronchitis, Bronchial asthma and COPD. Case record form with follow-up chart was used to record the demographic data, and duration and clinical features of the disease. Patient's data like clinical symptoms, duration of illness and prevalence and duration of co-morbidities like hypertension, diabetes, renal, cardiac and respiratory disorders were collected. All the selected participants were followed up until discharge or death. A blood sample was collected from all the patients and sent for laboratory investigations which included complete blood count, renal function test, liver function test and inflammatory markers like C-reactive protein, lactate dehydrogenase, serum

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ferritin and D-dimer levels. Patients were divided based on disease severity in mild, moderate and severe disease. LDH and eosinophil were compared among these groups as markers of severity of the disease.

Statistical Analysis: SPSS (Statistical Package for Social Sciences) version 20. (IBM SPASS statistics [IBM corp. released 2011] was used to perform the statistical analysis

Data was entered in the excel spread sheet. Descriptive statistics of the explanatory and outcome variables were calculated by mean, standard deviation for quantitative variables, frequency and proportions for qualitative variables.

- Inferential statistics like
  - Chi-square test was applied to associate the qualitative variables.
  - ANOVA test was applied to compare the lab parameters among the groups (based on severity).
- The level of significance is set at 0.05.

Results

Table 1: Mean Age Distribution of the Subjects

	N	Minimum	Maximum	Mean	S.D
Age	39	25	95	62.21	14.615

Table 2: Distribution of the Subjects Based on Gender

Gender	Frequency	Percent
Females	11	28.2
Males	28	71.8
Total	39	100.0

Table 3: Association with Co-Morbidities

			Severity			Total	Chi-square value	p value
			Mild	Moderate	Severe			
Co-morbidities	Absent	Count	7	9	3	19	2.39	0.302
		%	58.3%	39.1%	75.0%	48.7 %		
	Present	Count	5	14	1	20		
		%	41.7%	60.9%	25.0%	51.3 %		
DM	Absent	Count	9	20	4	33	1.67	0.43
		%	75.0%	87.0%	100.0 %	84.6 %		
	Present	Count	3	3	0	6		

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		%	25.0%	13.0%	0.0%	15.4 %		
HTN	Absent	Count	9	14	3	26	0.84	0.65
		%	75.0%	60.9%	75.0%	66.7 %		
	Present	Count	3	9	1	13		
		%	25.0%	39.1%	25.0%	33.3 %		
IHD	Absent	Count	11	21	4	36	0.37	0.83
		%	91.7%	91.3%	100.0 %	92.3 %		
	Present	Count	1	2	0	3		
		%	8.3%	8.7%	0.0%	7.7%		
CKD	Absent	Count	12	22	4	38	0.71	0.7
		%	100.0 %	95.7%	100.0 %	97.4 %		
	Present	Count	0	1	0	1		
		%	0.0%	4.3%	0.0%	2.6%		
PTB	Absent	Count	11	18	4	33	1.89	0.38
		%	91.7%	78.3%	100.0 %	84.6 %		
	Present	Count	1	5	0	6		
		%	8.3%	21.7%	0.0%	15.4 %		

Table 4: Comaprsion of the Lab Parameters Based On Severity Using Anova

Lab parameters	**Severity**	**N**	**Minimum**	**Maximum**	**Mean**	**S.D**	**p value**
LDH (U/L)	Mild	12	126	623	289.67	170.92	0.77
	Moderate	23	133	643	330.22	160.97	
	Severe	4	171	399	319.75	103.01	
CRP (mg/L)	Mild	12	0	116	12.83	32.56	0.037*
	Moderate	23	2	133	40.78	29.42	
	Severe	4	3	38	24.25	14.95	
D-DIMER (ng/ml)	Mild	12	178	1050	494.25	348.03	0.061

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	Moderate	23	248	1050	745.65	244.10	
	Severe	4	245	1050	588.75	375.36	
EOSINOPHILS (%)	Mild	12	1	6	2.92	1.38	0.001*
	Moderate	23	0	4	1.74	0.86	
	Severe	4	0	1	0.25	0.50	

Table 5: Association of Severity with Vaccination Status

Vaccination status		**Severity**			**Total**
		Mild	**Moderate**	**Severe**	
Fully vaccinated	Count	8	15	0	23
	%	66.7%	65.2%	0.0%	59.0%
Not vaccinated	Count	0	5	2	7
	%	0.0%	21.7%	50.0%	17.9%
Partially vaccinated	Count	4	3	2	9
	%	33.3%	13.0%	50.0%	23.1%
Total	Count	12	23	4	39
	%	100.0%	100.0%	100.0%	100.0%
Chi-square value- 10.06					
p value- 0.039*					

Table 6: Association of Severity with Outcome

Outcome		**Severity**			**Total**
		Mild	**Moderate**	**Severe**	
Death	Count	0	0	4	4
	%	0.0%	0.0%	100.0%	10.3%
Discharge	Count	12	23	0	35
	%	100.0%	100.0%	0.0%	89.7%
Total	Count	12	23	4	39
	%	100.0%	100.0%	100.0%	100.0%
Chi-square value- 39.00					
p value- 0.001*					

Demographics

A total of 671 patients were admitted. 39 patients with underlying chronic airway inflammation, including COPD (61.5%), asthma (17.1%) and chronic bronchitis (20.5%), were confirmed to have SARS-CoV-2 infection. Of the patients, 12 were classified as mild, 23 as moderate and 4 were classified as severe.

The mean age of all patients was 62.2 years. [Table 1] Majority (71.8%) of the patients were male. [Table 2]

Comorbidities [Table 3]

20 (51.3%) patients had one or more comorbidities besides the three chronic airway diseases, with Hypertension (33.3%) and Diabetes mellitus (15.4%) being the most common comorbidities. 15.4% of the patients had past history of pulmonary Tuberculosis. There were

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no significant differences in the presence of these comorbidities between patients with non-severe and severe COVID-19. Half of the patients had smoking histories or were current smokers.

Laboratory Parameters [Table 4]

Laboratory findings of patients with non-severe and severe COVID-19 with chronic airway diseases when compared with non-severe patients, patients with moderate disease were more likely to have elevated LDH (330.2) as compared to severe (319.75) and mild (289.67). However it was not statistically significant. Statistically significant association was found for CRP where moderate patients had more elevated CRP levels in comparision to severe and mild disease.

Eosinopenia (0.25%) was found in patients with severe disease which was statistically significant.

Association with Covid 19 Vaccinations [Table 5]

About 59% fully vaccinated of whom majority were patients with mild disease (66.7) followed by moderate disease (65.2%). None of the patients with severe disease were fully vaccinated. All patients with severe disease were either partially vaccinated or had not taken even a single dose of vaccination.

Clinical Outcome [Table 6]

All patients with severe disease succumbed. All patients with mild and moderate disease were discharged.

Discussion

The mean age of patients was 62.2 years with male preponderance which was similar to the study done by Chen D et al where most of the patients with chronic airway disease were aged 70 years with male preponderance.[10] Some of the hypothesis proposed was that male patients have higher expression of ACE 2 which may be partly because ACE 2 expression encoded by the ACE2 gene lies on the X chromosome where men are homozygous allowing them to be potentially high ACE2 expressor.[11] It is also postulated that older patients aged more than 50 years have higher expression of ACE2 gene contributing to higher mortality in this age group. It also may be related to high prevalence of comorbidities among elderly.

Hypertension was common comorbidity found followed by type 2 diabetes mellitus**.** A meta-analysis by Pieshan Qiu et al; showed higher incidence of Hypertension.[12] Hypertension has been repeatedly reported as the highest pre-existing comorbidity in COVID-19 patients. However, whether hypertension itself or the uses of hypertensive therapies are responsible for these statistics is currently unknown. Hypertensive patients are commonly treated with ACE inhibitors (ACEI) and angiotensin-receptor blockers (ARB) which can significantly increase ACE2 expression.[12] However there is a conflicting evidence and opinions among the scientific community, it remains unclear whether treatment with ACEI/ARB has a positive or negative impact on COVID-19 progression. In this retrospective cohort study, we found that eosinophil counts less than 0.02×10^9/L and LDH levels greater than 225U/L on admission were associated with severity of COVID-19 in patients with underlying chronic bronchitis, COPD and asthma. Moreover, eosinophil counts and LDH levels tend to return to normal range in severe and non-severe patients after treatment, suggesting their roles as indicators of disease progression and treatment efficacy. Circulating and tissue-resident eosinophils

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participate in the pathological process and play a potent proinflammatory role, such as COPD, asthma and chronic bronchitis. In view of elevated eosinophils in patients with chronic airway inflammation, COPD, asthma and chronic bronchitis have not yet been reported as major risk factors for severity of SARS-CoV-2 infections. It remains unclear how eosinopaenia takes place in COVID-19, but the most possible reason could be due to its depletion of antiviral reaction, since Th1 (Type 1 T helper) antiviral response was inhibited in those patients with chronic airway inflammation. LDH has been reported to be associated with chronic airway disease and identified as a potential marker of chronic airway inflammation.[13,14] Meanwhile, a large number of studies reported elevated LDH levels in COVID-19, which could be a risk factor for mortality. Study done by Zheng et al,[15] found that LDH was significantly higher in severe patients compared with non-severe patients. Elevated LDH in severe cases indicated diffuse lung injury and tissue damage; therefore, we hypothesised that LDH might be another predictor of chronic airway inflammation exacerbation in COVID-19.

Conclusion

Eosinopaenia and elevated LDH have been identified as risk factors for severe COVID-19 cases; however, it is noteworthy that in our study they were also associated with severity of COVID-19 in patients with chronic airway diseases.

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