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Original Research Article

Assessment of inflammatory markers and their association with disease mortality in atypical pneumonia patients of tertiary care hospital in Southern Rajasthan

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Abstract

Background: COVID-19 infection involves a complex interplay of the immunological and inflammatory responses. Low blood-oxygen levels have been a hallmark in COVID-19 patients. The lung tissue damage infiltered by the viral-mediated inflammation decreases oxygen saturation to cause silent hypoxia and cell death. This study aimed to evaluate the association of inflammatory biomarkers with oxygen saturation (SpO_2) and mortality in severe COVID-19 patients.

Methods: A total of 200 patients with atypical pneumonia in American international institute of medical sciences Bedwas and Pacific Medical College and Hospital Bhilon ka Bedla, Udaipur, Rajasthan were included in this study. The laboratory tests were performed for biochemical assessment. Serum levels of C-reactive protein (CRP), lactate dehydrogenase (LDH), and ferritin were determined and compared between survivors and nonsurvivors. The correlation of these inflammatory markers was studied using logistic regression**.**

Results: Out of 200 subjects, 117 (58.5%) were COVID ±ve and 83 (41.5%) wereCOVID -ve. The maximum number of atypical pneumonia cases belonged to age group of 65-74 years (35%) followed by 55-64 years (25.5%) and 45-54 years (22%). Mean age was 60.10±11.34 years. 61.5% were male and 38.5% were female. 43 (21.5%) had mild, 39 (19.5%) had moderate and 118 (59%) had severe pneumonia infection. The mean of inflammatory parameters such as IL-6, CRP, ferritin and LDH were significantly increased in COVID-19 +ve patients. The mean D-Dimer level between COVID +ve and -ve didn't show a statistically significant difference. Out of 200 subjects 33 (16.5%) died while the rest survived. Levels of inflammatory markers were significantly higher in pneumonia subjects who died compared to those who survived which can be seen in above tables (p value <0.001). Comparison of mean levels of IL-6, CRP, Serum ferritin and LDH among RT-PCR positive and negative tested patients in mild, moderate and severe classes showed significant differences. While the D-Dimer level didn't show significant difference between positive and negative tested patients in different severity of pneumonia.

Conclusion: In conclusion, COVID biomarkers can have a pivotal role in assisting physicians in the management plan and work as an indicator for disease severity and possible outcome. Covid biomarkers are positively correlated with disease severity and oxygen requirement in patients with atypical pneumonia infection. Our data show that covid biomarkers have prognostic value for atypical pneumonia. It can be used as an alternative triage tool in individuals with Atypical pneumonia symptoms.

INTRODUCTION

Pneumonia is an infection of pulmonary parenchyma. Separation of potential agents into typical bacterial pathogens or atypical organisms may be helpful. The former category includes S.pneumoniae, Haemophilus influenza, and S. aureus and gram negative bacilli such as klebsiella pneumoniae and pseudomonas aeroginosa. The atypical organisms include Mycoplasma pneumonia, Chlamydia pneumonia ,and legionella species as well as respiratory viruses such as influenza viruses, adenovirus, human meta pneumovirus, respiratory syncytial viruses and COVID 19[1] Since the onset of the new coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2)pandemic in December 2019 [2,3], confirmed cases have been reported in countries all over the world. The World Health Organization proclaimed the 2019 coronavirus disease (COVID-19) pandemic on March 11, 2020, mostly because of the disease's pervasive development [4]. COVID-19 inflammation has been linked to disease severity [1]. Accumulative evidence has demonstrated that cytokine storm by immune cells during the cell lysis stage of COVID-19 viral replication raises C-reactive protein (CRP)

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and lactate dehydrogenase (LDH) levels [2,3,4,5]. It has been demonstrated that the mortality is due to the severe multisystemic end-organ failure as a result of cytokine storm. Hence, measuring the inflammatory markers prove important for prognostication and management of these patients. CRP produced in a liver has been reported to be significantly associated with the higher risks of the COVID-19 infection. The proportion of patients with elevated CRP levels was significantly higher in severe COVID-19 patients than in nonsevere patients and CRP levels in the early stages correlates with the disease severity [6, 7], CRP can act as an early marker of COVID-19 infection and inflammation which could help health workers to enable earlier clinical intervention in high-risk population [8].

Pooled analysis by Henry et al. reported that LDH levels predict COVID-19 severity. Elevated LDH levels associated with 6-fold increase in odds of developing severe covid disease and 16-fold increase in odds of mortality in COVID-19 patients [9]. While fewer studies have reported the predictive role of CRP in COVID-19 mortality, there is a dearth in the study of the association of LDH and ferritin with mortality among severe COVID-19 patients. Hence, we conducted a cohort (survivors-non-survivors) study of ICU-admitted COVID-19 patients to study the association between inflammation and mortality.

METHODS

A cross-sectional study was carried out on atypical pneumonia patients admitted in American international institute of medical sciences Bedwas and Pacific Medical College and Hospital Bhilon ka Bedla, Udaipur, Rajasthan.This study has been approved by the Institutional ethics committee.

Subjects-

1.Subjects those who fulfill the following criteria for inclusion-

a) INCLUSION CRITERIA

1. Patients giving consent and willing to participate inthe study.
2. Patients presenting with atypical pneumonia testingboth COVID 19 RT PCR positive and negative.

a) EXCLUSION CRITERIA

1.Patients with increased level of IL-6, D-Dimer and serum ferritin due to causes other than atypical pneumonia

2.Patients not willing to participate in study.

1. STUDY PROCEDURE

We retrospectively collected the clinical and laboratory data of patients diagnosed with atypical pneumonia. This included epidemiological data, clinical manifestation, comorbidities of patients, laboratory parameters such as CRP, ferritin, interleukin-6 (IL-6), lactate dehydrogenase (LDH), D-dimer, along with the mode of oxygen supplementation, and final outcome. After collection of all required data and careful medical chart review, the clinical data of laboratory confirmed patients were compiled and tabulated.

Diagnosis of COVID-19 pneumonia was confirmed by nasopharyngeal swab for SARS-CoV-2 reverse transcription-polymerase chain reaction (RT PCR). According to AIIMS DELHI guidelines, patients were divided into mild (Upper respiratory tract infection and /or fever WITHOUT shortness of breath or hypoxia),moderate (Any one of either respiratory rate more than or equal to 24 minute or spo2 :90% to 93%) and severe(any one of either respiratory rate more than or equal to 30/minute or spo2 less than 90%on room air. The sample size was calculated using OpenEpi version3.03a.

Sample Size n = [DEFF*Np(1-p)]/ [(d^2/$Z^2_{1-\alpha/2}$*(N-1) +p*(1-p)]

Where N= Population size

n = sample size

z = confidence intervalp = probability

d =allowable error &DEFF = Design Effect

Population size (for finite population correction factor or fpc) (*N*):1000000

Hypothesized % frequency of outcome factor in the population (*p*):50%+/-8

Confidence limits as % of 100(absolute +/- %) (*d*): 8%Design effect (for cluster surveys-*DEFF*): 1

Sample Size(n) for Confidence Level of 95% = 151.With a non -response rate of 10% = 151 +15 = 166. This was rounded off to 170.

Our study included 200 patients.

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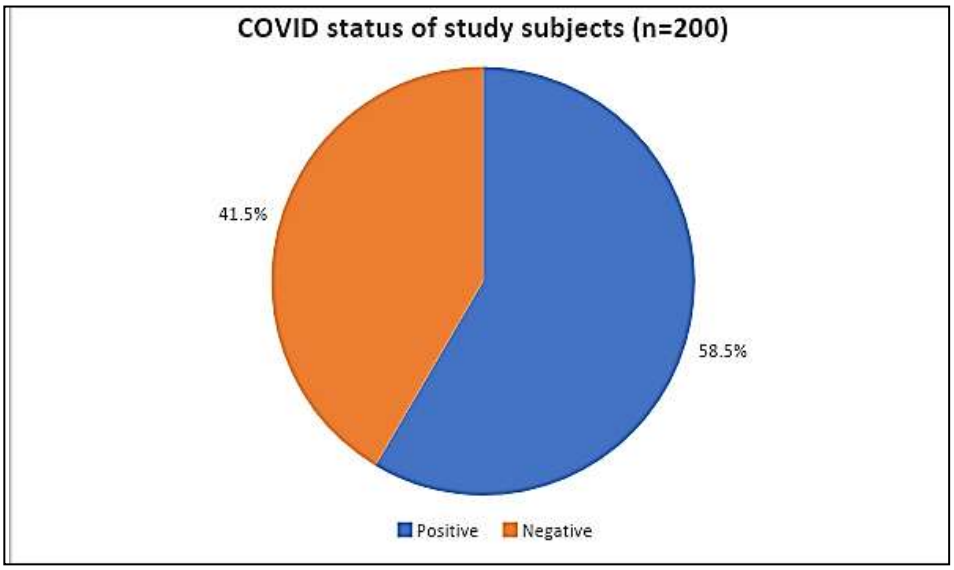
Statistical analysis: The data was compiled on MS Excel Sheet and will be analyzed by SPSSversion 16.0. Appropriate tests were applied to assess significance of correlationbetween unmet need and associated probable factors. The plan was submitted to the Ethics committee of the institute forapproval and got approved.



Graph 1: COVID status of study subjects (n=200) out of 2**00 subjects, (58.5%) were COVID**+ve and 83 (41.5%) were COVID-ve

Table1: Age wise distribution of study subjects (n=200)

Age group	COVID - 19					
	Negative		Positive		Total	
	No	%	No	%	No	%
<45 years	9	10.8	11	9.4	20	10.0
45-54 years	17	20.5	26	22.2	43	21.5
55-64 years	22	26.5	28	23.9	50	25.0
64-74 years	28	33.7	42	35.9	70	35.0
>74 years	7	8.4	10	8.5	17	8.5
Total	83	100.0	117	100.0	200	100.0

The maximum number of atypical pneumonia cases belonged to agegroup of 65-74 years (35%) followed by 55-64 years (25.5%) and 45-54 years (22%). Mean age was 60.10±11.34 years. Age wise distribution between COVID-19 positive and negative tested patients showed no significant differences between the groups (Table 1) as p value is more than 0.05.

Table 2: Gender wise distribution of study subjects (n=200)

	COVID – 19					
	Negative		Positive		Total	
Sex	No	%	No	%	No	%
Male	58	69.90	65	55.60	123	61.50
Female	25	30.10	52	44.40	77	38.50
Total	83	100.00	117	100.00	200	100.00

P value-0.04

Out of 200 pneumonia subjects 61.5% were male and 38.5% were female. Gender wise distribution between COVID-19 positive and negative tested patients showed significant differences as male populations are frequently tested positive than females. 58(69.90%) males and 25(30.10%) had RT PCR negative test results, while 65(55.60%) and 52(44%) had RT PCR positive results. And it is statistically significant as well.

Table 3: Severity of pneumonia in study subjects (n=200)

	COVID – 19		
	Negative	Positive	Total

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Severity of pneumonia	No	%	No	%	No	%
Mild	16	19.30	27	23.10	43	21.50
Moderate	16	19.30	23	19.70	39	19.50
Severe	51	61.40	67	57.30	118	59.00
Total	83	100.00	117	100.00	200	100.00

P value-0.789

Amongst 200 subjects, 43 (21.5%) had mild, 39 (19.5%) had moderate and 118 (59%) had severe pneumonia infection. Comparison of severity of pneumonia between COVID-19 positive and negative tested patients showed no significant differences between the groups (Table8) (p value- >0.05).

Table 4: Association of severity of pneumonia with inflammatorymarkers in study subjects (n=200)

	Mild	Moderate	Severe	p value
IL-6 (pg/ml)	58.16±21.98	63.91±23.66	99.47±44.04	<0.001
CRP (mg/L)	53.36±34.59	77.96±50.13	99.16±56.54	<0.001
S. Ferritin (ng/ml)	369.58±216.97	401.3±266.17	619.71±328.99	<0.001
D-dimer (µg/ml)	3.3±4.34	4.9±7.37	8.7±8.08	<0.001
LDH (IU/L)	372.34±212.28	416.83±253.95	548.25±251.27	<0.001

The mean of inflammatory parameters were significantly increased in patients with severe pneumonia infection and reached [99.47±44.04 pg/ml, 99.16±56.54 mg/L, 619.71±328.99ng/ml, 8.7±8.08_mcg/ml, and 548.25±251.27 IU/L] for IL-6, CRP, ferritin, D-dimer and Lactate Dehydrogenase (LDH) respectively, while in patients with mild pneumonia infection, the levels of IL-6, CRP, ferritin, D-dimer and Lactate Dehydrogenase (LDH) was [58.16±21.98 pg/ml, 53.36±34.59mg/L, 369.58±216.97ng/ml, 3.3±4.34 mcg/ml and 372.34±212.28 IU/L] respectively and in patient with moderate pneumonia infection the levels of IL-6, CRP, ferritin, D-dimer and Lactate Dehydrogenase (LDH) was [63.91±23.66 pg/ml, 77.96±50.13 mg/L, 401.3±266.17ng/ml, 4.9±7.37 mcg/ml, and 416.83±253.95 IU/L] respectively.

TABLE: 5 Comparison of the covid biomarkers between RT-PCR positive and negative tested patients in mild, moderate and severe classes.

Biomarker	Severity	COVID-19 Negative			COVID-19 Positive			Difference	SEd	t	df	P
		N	Mean	SD	N	Mean	SD					
IL6	Mild	16	51.31	23.958	27	62.23	20.091	-10.919	6.810	-1.603	41	.117
	Moderate	16	54.19	20.534	23	70.67	23.726	-16.486	7.320	-2.252	37	.030
	Severe	51	90.02	42.215	67	106.67	44.356	-16.654	8.074	-2.063	116	.041
CRP	Mild	16	38.25	27.757	27	62.32	35.565	-24.075	10.387	-2.318	41	.026
	Moderate	16	61.94	44.644	23	89.11	51.628	-27.176	15.925	-1.707	37	.096
	Severe	51	84.39	49.771	67	110.40	59.112	-26.009	10.273	-2.532	116	.013
Serum ferritin	Mild	16	291.562	199.2496	27	415.815	217.2164	-124.2523	66.5129	-1.868	41	.069
	Moderate	16	305.812	215.8756	23	467.726	281.7015	-161.9136	83.6825	-1.935	37	.061
	Severe	51	521.804	281.0080	67	671.851	305.3554	-150.0468	54.8401	-2.736	116	.007
DDZ	Mild	16	3.612	3.8206	27	3.233	4.6875	.3792	1.3851	.274	41	.786
	Moderate	16	5.181	7.1684	23	4.765	7.6632	.4160	2.4307	.171	37	.865
	Severe	51	8.498	7.5022	67	8.884	8.5606	-.3855	1.5092	-.255	116	.799
LDH	Mild	16	291.50	184.581	27	420.25	216.188	-128.747	64.736	-1.989	41	.053
	Moderate	16	301.06	142.328	23	497.37	284.699	-196.309	77.317	-2.539	37	.015
	Severe	51	449.37	217.078	67	623.52	250.845	-174.146	44.020	-3.956	116	.000

p value <0.001.

Table 6: Association of outcome with inflammatory markers in study subjects (n=200)

	Survived	Died	p value

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IL-6 (pg/ml)	76.22±35.61	121.26±48.33	<0.001
CRP (mg/L)	76.46±48.03	129.30±63.38	<0.001
S. Ferritin (ng/ml)	476.09±284.59	762.45±367.52	<0.001
D-dimer (µg/ml)	5.63±6.99	12.9±7.90	<0.001
LDH (IU/L)	455.35±246.13	633.87±249.65	<0.001

Level of inflammatory markers was significantly higher in pneumonia subjects who died compared to those survived which can be seen in abovetables (p value <0.001).

Table 6: Association of Type of O_2 supplementation withinflammatory markers in study subjects (n=200)

	Type of O_2supplement	Mean	SD	P value
IL-6 (pg/ml)	FM	73.644	14.81	<0.001
	NIV/MV	146.076	50.27	
	NP	73.171	21.46	
	NRBM	115.565	30.26	
	RA	60.899	22.83	
CRP (mg/L)	FM	77.259	40.23	<0.001
	NIV/MV	145.672	65.18	
	NP	63.743	31.97	
	NRBM	123.931	40.53	
	RA	65.065	44.18	
S.Ferritin(ng/ml)	FM	522.255	267.12	<0.001
	NIV/MV	821.693	391.51	
	NP	492.791	285.85	
	NRBM	689.535	243.06	
	RA	384.667	240.63	
LDH (IU/L)	FM	473.86	285.4	<0.001
	NIV/MV	636.00	216.45	
	NP	426.66	181.62	
	NRBM	722.91	201.79	
	RA	393.50	232.64	
		Median	IQR	
D-dimer level (µg/ml)	FM	3	2-7	<0.001
	NIV/MV	13	8.5-20.5	
	NP	2.5	2-4	
	NRBM	9	6-20	
	RA	2	1-4	

All the inflammatory markers were significantly higher in subjects where O_2 supplementation was NIV/MV compared to other mode of O_2 supplementation.

DISCUSSION

Present study was a hospital based descriptive epidemiological study done in 200 patients with atypical pneumonia coming to American international institute of medical sciences Bedwas and Pacific Medical College and Hospital Bhilon ka Bedla, Udaipur, Rajasthan. The study was aimed to assess the utility of various inflammatory markers in predicting severity mortality and their association with co morbidities. Out of 200 pneumonia subjects 61.5% were male and 38.5% were female. Gender wise distribution between COVID-19 positive and negative tested patients showed significant differences as male populations are frequently tested positive than females. 58(69.90%) males and 25(30.10%) had RT PCR negative test results, while 65(55.60%) and 52(44%) had RT PCR positive results and it is statistically significant as well. The maximum number of atypical pneumonia cases belonged to agegroup of 65-74 years (35%) followed by 55-64 years (25.5%) and 45-54 years (22%). Mean age was 60.10±11.34 years. Age wise distribution between COVID-19 positive and negative tested patients showed no significant differences between the groups Out of 200 subjects in our study, 43 (21.5%) had mild, 39 (19.5%) had moderate and 118 (59%) had severe pneumonia infection. In study by Marimuthu AK et al[10], 18 patients (8.1%) belonged to Category A (milddisease), 61 patients (27.6%) belonged to Category B1 (mild disease), 55 patients (24.9%) belonged to Category B2 (moderate disease), and 87 patients (39.4%) belonged to Category C (severe disease. In Vijaykumar V et al[11] study, 65% had the non-

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severe disease and only 22% had the critical disease as per clinical severity criteria by WHO. Hachim IY et al[240] also reported around 37% subjects in the severe category and 27% subjects as critical. In the present study, around 41% subjects were on room air, 17.5% needed nasal prongs, 13.5% needed non invasive ventilation, 15.5% were on face masks, 11.5% needed Nonrebreathing masks and 1% subjects were on mechanical ventilation. This is similar to a study by Marimuthu AK et al[236] . The mean of inflammatory parameters were significantly increased in patients with severe pneumonia infection and reached [99.47±44.04 pg/ml, 99.16±56.54 mg/L, 619.71±328.99ng/ml, 8.7±8.08 mcg/ml, and 548.25±251.27 IU/L] for IL-6, CRP, ferritin, D-dimer and Lactate Dehydrogenase (LDH) respectively, while in patients with mild pneumonia infection, the levels of IL-6, CRP, ferritin, D-dimer and Lactate Dehydrogenase (LDH) was [58.16±21.98 pg/ml, 53.36±34.59mg/L, 369.58±216.97ng/ml, 3.3±4.34 mcg/ml and 372.34±212.28 IU/L] respectively and in patient with moderate pneumonia infection the levels of IL-6, CRP, ferritin, D-dimer and Lactate Dehydrogenase (LDH) was [63.91±23.66 pg/ml, 77.96±50.13 mg/L, 401.3±266.17ng/ml, 4.9±7.37 mcg/ml, and 416.83±253.95 IU/L] respectively. Finding of our study were in concordance with Vijayakumari V et al study[11]. Conte G et al[13] also reported an increase in the value of the D-dimer as the most sensitive change in coagulation parameters in COVID-19 and postulated that this may indicate a greater risk for thrombosis. Thachil J et al[14] emphasized the importance of accurate D- dimer reporting in COVID-19. Ours is a pioneer study that reports persistently elevated D-dimer and not just admission D-dimer as a predictor for progression and severity in COVID-19. Our study aligned with the study by Bhandari S et al[15]. Another study by Hachim IY et al[12] also reported significant association of inflammatory markers with severity of COVID-19. Several studies have been conducted to ascertain the relationship betweenthese markers and the overall outcome of patients with COVID-19 disease. Inflammatory markers have been reported to be predictors of mortality in patients with COVID-19 disease [16]. The cytokine storm dueto the release of pro-inflammatory factors, akin to that reported in other infections, has been attributed to be a major cause of death in patients with severe COVID-19 disease [17]. Our study showed that high serum ferritin values were more significantly associated with death. High serum ferritin values at the time of admission have been independently associated with a severe disease course [18]. Hyperferritinemia has also been associated as an independent risk factor for acute respiratory distress syndrome (ARDS) in COVID-19 [19]. However, some reports have indicated that while hyperferritinemia is associated with a more severe course of the disease, it may not be associated with a worse prognosis [20]. Similarly, it was observed in our study that higher CRP levels were also associated with death. Earlier reports have also indicated that CRP levels at the time of admission and prior to discharge or death are markers of poor prognosis in patients with COVID-19 [21]. Finding was in concordance to study by Ruan Q et al. We observed that IL-6 was significantly higher amongst non-survivors as compared to survivors in our study group. These findings reiterate the fact that pneumonia is a hyperinflammatory state associated with an increase in pro-inflammatory cytokines and raised inflammatory markers are associated with a severe disease course and an adverse final outcome as suggested by earlier studies [22-24]. Elevated levels of D-dimer indicate increased risk of abnormal blood clotting, and D-dimer assays are commonly used in clinical practice to exclude a diagnosis of venous thromboembolism. Elevated levels of D-dimer were also found to be related with higher mortality rate ofcommunity acquired pneumonia.[25] Patients with severe community acquired pneumonia had significantly higher D-dimer levels, and D- dimer within normal range indicated low risk for complications.[26] Our study also reflected a similar finding showing D‑dimer to be a sensitive predictor of mortality. Marimuthu AK et al also reported similar observations in their study. A retrospective study of Huang Y et al[27] using a large sample size of 1751 Chinese patients showed that LDH is associated with higher mortality risk. In contrast, the meta-analysis of Martha JW et al[31] concluded that LDH was associated with poor prognosis in COVID-19 patients. Ahmeidi AA[28] showed that elevation in serum inflammatory marker CRP may be indicative of COVID- 19 infection severity and mortality and suggested that these parameters may predict COVID-19 severity Another study by Devang N et al[29] also reported positive correlation between level of inflammatory markers and mortality. Szarpak L et al[30]. reported a mean LDH of 154.49 U/L in COVID-19 and observed LDH as a COVID-19 severity marker and predictor for survival.

In our study, all the inflammatory markers were significantly higher in subjects where type of O_2 supplementation was NIV/MV compared to other modes of O_2 supplementation. Findings of our study were in concordance with the study of Marimuthu AK et al.[10] In our study The mean of inflammatory parameters such as IL-6, CRP, ferritin and LDH were significantly increased in COVID-19 +ve patients and reached [89.34±41.59 pg/ml, 95.12±56.29 mg/L, 585.45±331.09 ng/ml and 551.81±263.12 IU/L] respectively, while in patients with COVID -ve pneumonia infection, the levels of IL-6, CRP, ferritin and Lactate Dehydrogenase (LDH) were [75.65±40.03 pg/ml, 71.16±48.50 mg/L, 435.78±275.48 ng/ml and 390.35±210.47 IU/L] respectively. The mean D-Dimer level between COVID +ve and -ve didn't show a statistically significant difference. In contrast to our study, Sharma A et al did not find any significant difference in D-dimer level between COVID-19 positive and negative study subjects.

CONCLUSION

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Out of 200 subjects, 117 (58.5%) were COVID ±ve and 83 (41.5%) were COVID -ve. The maximum number of atypical pneumonia cases belonged to age group of 65-74 years (35%) followed by 55-64 years (25.5%) and 45-54 years (22%). Mean age was 60.10±11.34 years. 61.5% were male and 38.5% were female. 43 (21.5%) had mild, 39 (19.5%) had moderate and 118 (59%) had severe pneumonia infection. The mean of inflammatory parameters such as IL-6, CRP, ferritin and LDH were significantly increased in COVID-19 +ve patients. The mean D-Dimer level between COVID +ve and -ve didn't show a statistically significant difference. Out of 200 subjects 33 (16.5%) died while the rest survived. Levels of inflammatory markers were significantly higher in pneumonia subjects who died compared to those who survived which can be seen in above tables (p value <0.001). Comparison of mean levels of IL-6, CRP, Serum ferritin and LDH among RT-PCR positive and negative tested patients in mild, moderate and severe classes showed significant differences. While the D-Dimer level didn't show significant difference between positive and negative tested patients in different severity of pneumonia.

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