PREDICTORS OF MORTALTY IN COVID-19 PNEUMONIA: A RETROSPECTIVE STUDY

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ABSTRACT

The aim of the study was to evaluate the predictors of mortality in patients with COVID-19 pneumonia. The primary objective is to investigate the relationship between demographic, clinical and laboratory parameters on COVID -19 pneumonia related mortality and morbidity. A retrospective study was conducted among the in-patients admitted to SH medical centre hospital, a tertiary care hospital in Kerala, India for a period of 6 months in General Medicine & MICU. Case records of survivors and non-survivors were retrospectively reviewed for demographic data, clinical presentations, investigations, management, and outcome and these groups were compared to assess the risk factor of mortality. Out of 129 patients analysed, a significant association between age and risk for mortality was found. Majority of the patients among non survivors (53.12%) belongs to an age group of >75 years and 61-75 age group among survivors (32.30%). From the clinical manifestations, dyspnoea (p value 0.003) and fever (p value 0.024)   were found to be significant predictors of mortality. From the laboratory parameters, SpO_2, respiratory rate, Hb, WBC, platelet count, creatinine, serum ferritin and D-dimer were found to have a strong correlation with mortality. All the non survivors (100%) were observed with comorbidities when compared to survivors (81.54%). From this study we found that age> 75 years, clinical manifestations such as dyspnoea and fever, laboratory parameters such as elevated levels of D-dimer, serum ferritin, creatinine, WBC

count and decreased levels of platelet count, Hb, SpO_2 and presence of comorbidities to be independent predictors of mortality in COVID-19 PNEUMONIA. Early detection of symptoms and their proper management can reduce the risk for mortality.

KEY WORDS: Coronavirus disease of 2019(covid-19), The Indian Council of Medical Research(ICMR)

INTRODUCTION

The novel coronavirus disease (COVID-19) has drawn worldwide attention by causing the first pandemic by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Co V- 2) virus leading to international public health emergency. On the 3rd November, 2020, the World Health Organization (WHO) declared Corona virus outbreak as pandemic and public health emergency of international concern[1]

CORONAVIRUS

Corona viruses are spherical viruses with club-shape spikes projecting from the surface, giving a solar corona appearance. The helically symmetrical nucleocapsids, with a positive-sense RNA genome lying within the envelope makes them having the largest genome for RNA viruses. The SARS-CoV-2 belongs to order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae, genus Betacoronavirinae and subgenus Sarbecovirus. Genetic recombination within members of same or different genera leads to increased genetic diversity, causing spill over to other species and result in the emergence of novel viruses [2,3].
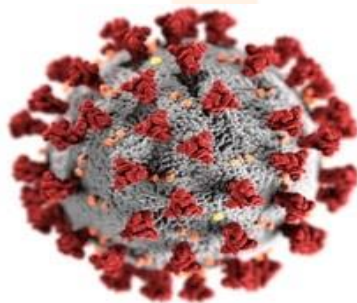

Figure 1- Coronavirus

CLINICAL PRESENTATION

The clinical presentation of SARS-COV-2 is rapidly evolving. Symptoms of coronavirus vary from person to person . The common symptoms include respiratory illness such as: fever, dry cough, fatigue, myalgia, and non-respiratory illness such as nausea, vomiting, loss of taste and smell, diarrhoea [4]
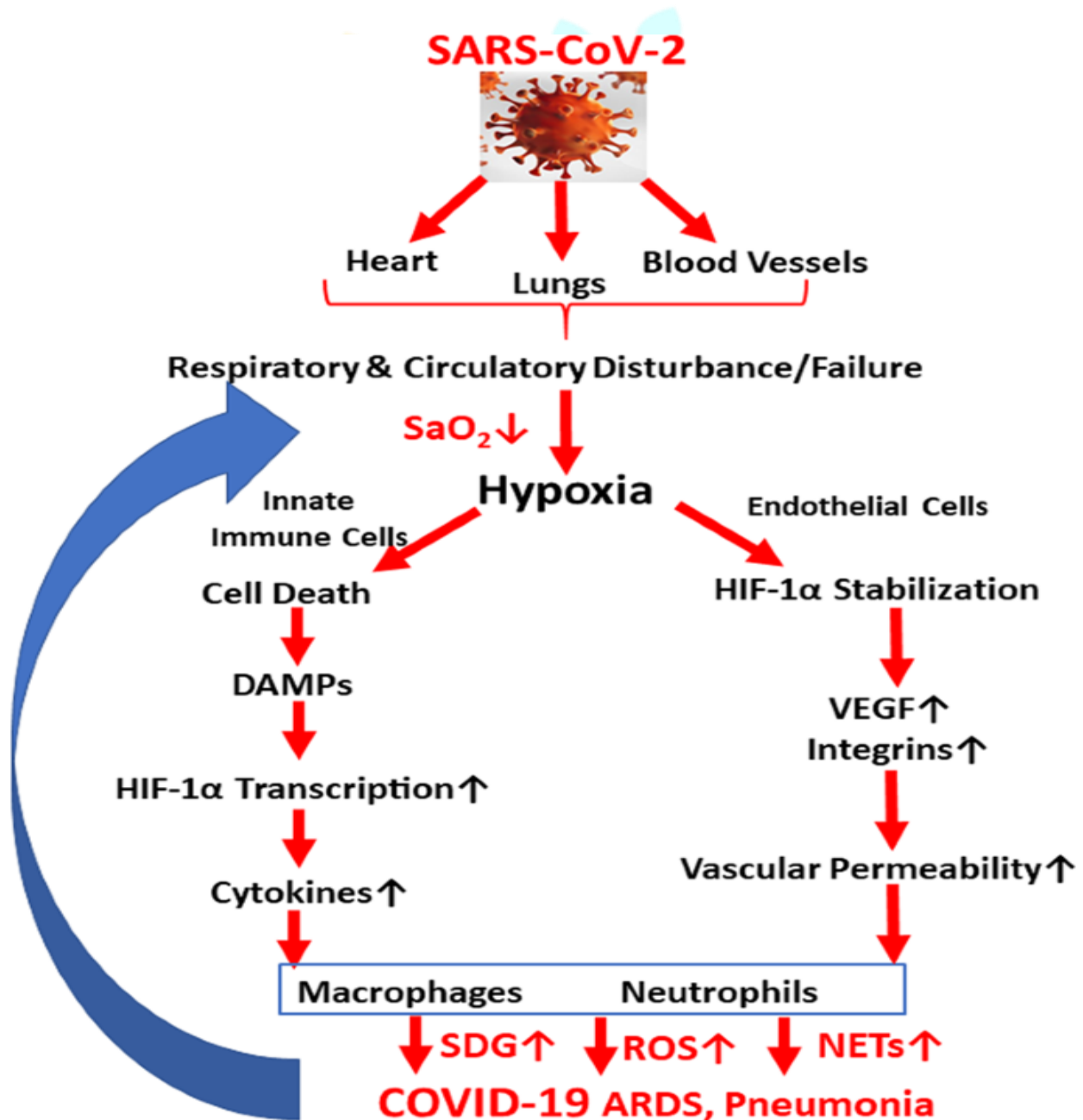
PATHOPHYSIOLOGY OF COVID-19 PNEUMONIA

Figure 5 : Pathogenesis of SARS COVID Pneumonia

Table 3 : Laboratory investigation for proven COVID 19 patients

TIME	TESTS
At Admission	CBC, RFT, LFT, CRP, RBS, S. electrolytes, ECG, Pulse oximetry.
If clinically Indicated	Portable CXR, HIV, HbsAg, HCV, D-Dimer, Ferritin, LDH, CPK, procalcitonin, Blood culture, TROP T/I, HRCT Thorax [only in case of worsening]
To repeat Every 48 hours if clinically deteriorating.	CBC, Creatinine, AST/ALT, CRP, LDH, CPK, Ferritin, D Dimer.
For Immunocompromised patients eg Transplant recipients, HIV	Tests to rule out opportunistic infections like Mycobacterium tuberculosis etc

DIAGNOSIS

A diagnostic test for the accurate decision of SARS-COV-2 was needed due to rapid spread of coronavirus in the people. As per Centres for Disease Control and Prevention (CDC) guidelines, by performing real-time fluorescence, a reverse transcriptase polymerase chain reaction (RT-PCR) test is the current standard of test to confirm COVID-2019. The specimen can be collected by two ways 1) From upper respiratory tract (nasopharyngeal and Oropharyngeal swab) 2) From lower respiratory tract (sputum, endotracheal aspirate, bronchoalveolar lavage), serum and urine and stool if possible [5]

From the laboratory investigation, there will be an increase in the white blood cell count in affected COVID-19 patients. Presence of leukopenia, leucocytosis and lymphopenia is also common. Elevated levels of lactate

dehydrogenase, ferritin, D-dimer, IL-6, CRP, WBC were seen in most patients. Presence of infection which lead to pneumonia are determined by doing radiological test such as Chest computed Tomography (CT scan) and chest X-ray: [6]

MATERIALS AND METHOD

A retrospective study was conducted among the in-patients admitted in General Medicine and MICU of SH medical centre hospital, a tertiary care hospital in Kerala, India for a period of 6 months from in General Medicine & MICU. The duration of oxygen treatment [positive pressure mask or mechanical ventilation] during hospitalization were collected. . Data such as demographic characteristics, clinical manifestations, comorbidities, and clinical parameters like blood pressure, respiratory rate, oxygen saturation, heart rate, and time to death & laboratory parameters such as baseline haemoglobin, white blood cell, thrombocyte, lymphocyte (%), monocyte (%), eosinophil (%), D-dimer, RBS, renal function test, liver function test, creatinine, urea, chest radiography were collected from patient medical records. The duration of oxygen treatment [positive pressure mask or mechanical ventilation] during hospitalization were collected. Data collected were evaluated for finding the relationship between demographic, clinical and laboratory parameters on COVID -19 related mortality and morbidity

STATICAL ANALYSIS

Data were coded and entered using Microsoft Excel and then transferred to IBM SPSS STATISTICS 22.0 version for analysis. Descriptive statistics, Chi-square test and t test were used for further analysis, in which P=<0.05 was taken as the significance value.

RESULT AND DISCUSSION

DEMOGRAPHIC DETAILS OF PATIENTS

Table 8: Gender distribution of patients with covid 19 pneumonia

(N=129)

GENDER	SURVIVORS (n=65)		NON SURVIVORS (n=64)	
	FREQUENCY (f)	PERCENTAGE (%)	FREQUENCY (f)	PERCENTAGE (%)
FEMALE	30	46.16%	31	48.44%
MALE	35	53.84%	33	51.56%
TOTAL	n=65	100%	n=64	100%

In our study, out of 65 COVID-19 Pneumonia survivors, 46.16% patients were females and 53.84% patients were male. In case of Non survivors, out of 64 COVID-19 Pneumonia patients, 48.44% patients were female and 51.56% were male.
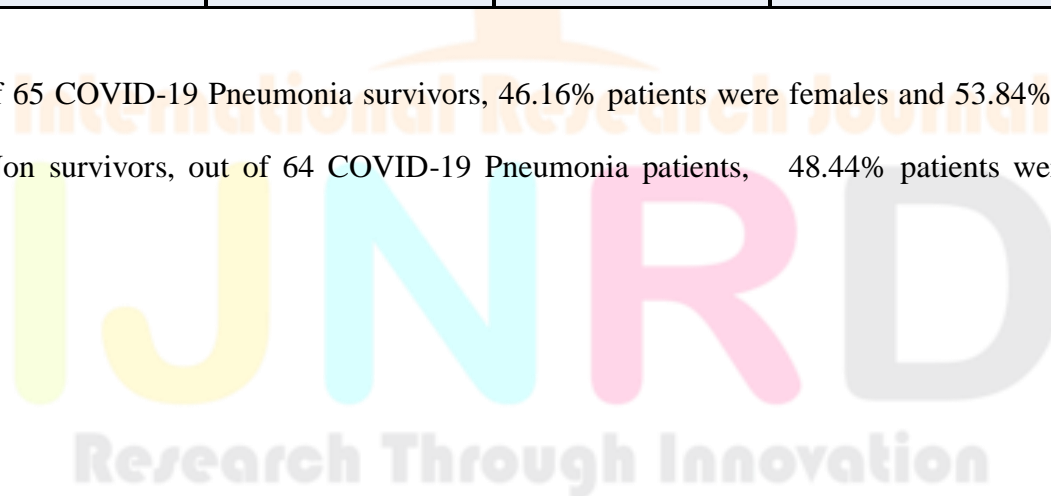
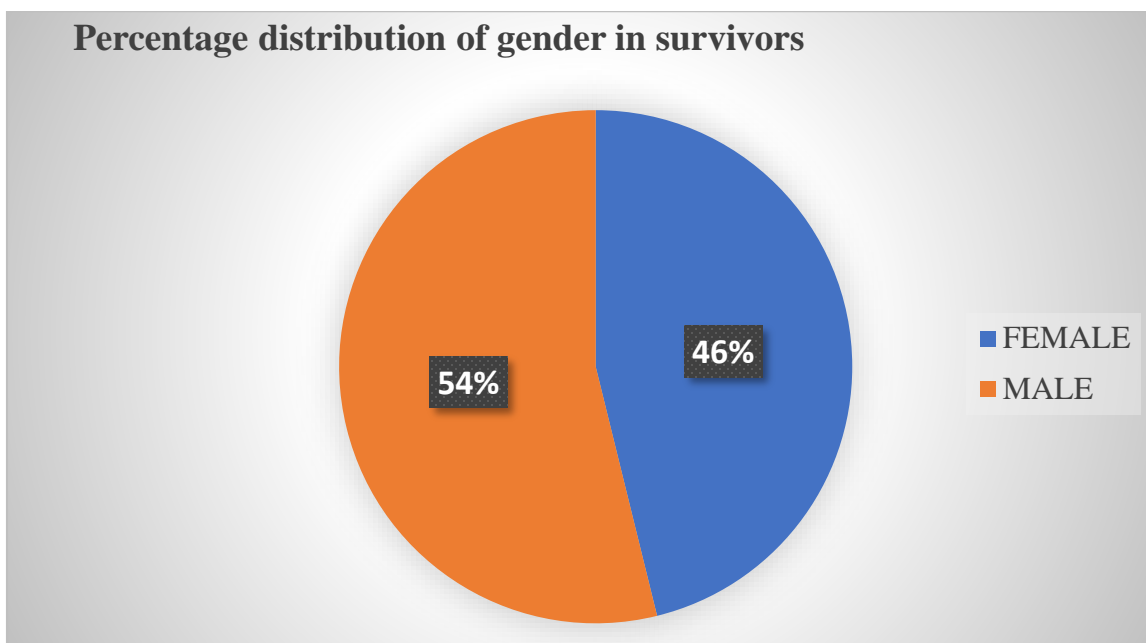**FIGURE 7: Percentage distribution of gender in survivors**

FIGURE8:Percentage distribution of gender in Non survivors
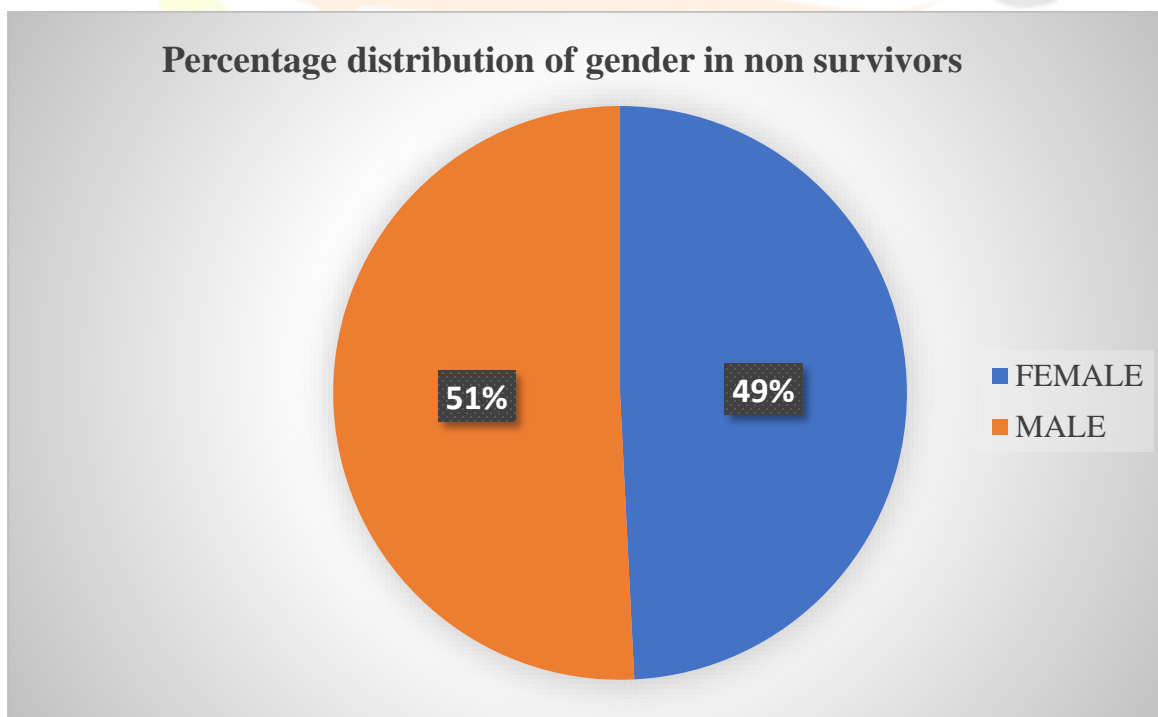
Table no. 9 : Distribution of age in patients with COVID 19 Pneumonia

AGE	SURVIVORS(n=65)		NON SURVIVORS(n=64)		[N=129]
	Frequency(f)	Percentage(%)	Frequency(f)	Percentage(%)	
18-25	3	4.62%	0	0%	Table 9 shows distribution of age in Covid-19 Pneumonia patients .In survivor group majority of patients were among 61-75
26-40	7	10.77%	0	0%	
41-60	15	23.07%	4	6.25%	
61-75	21	32.30%	26	40.63	
>75	19	29.24%	34	53.12%	
TOTAL	65	100%	64	100%	

years(32.30%) and in non survivor group majority of patients were >75 years (53.12%).

Figure 9 : <u>Frequency distribution of age in COVID-19 PNEUMONIA patients</u>

Frequency distribution of age in COVID-19 PNEUMONIA patients
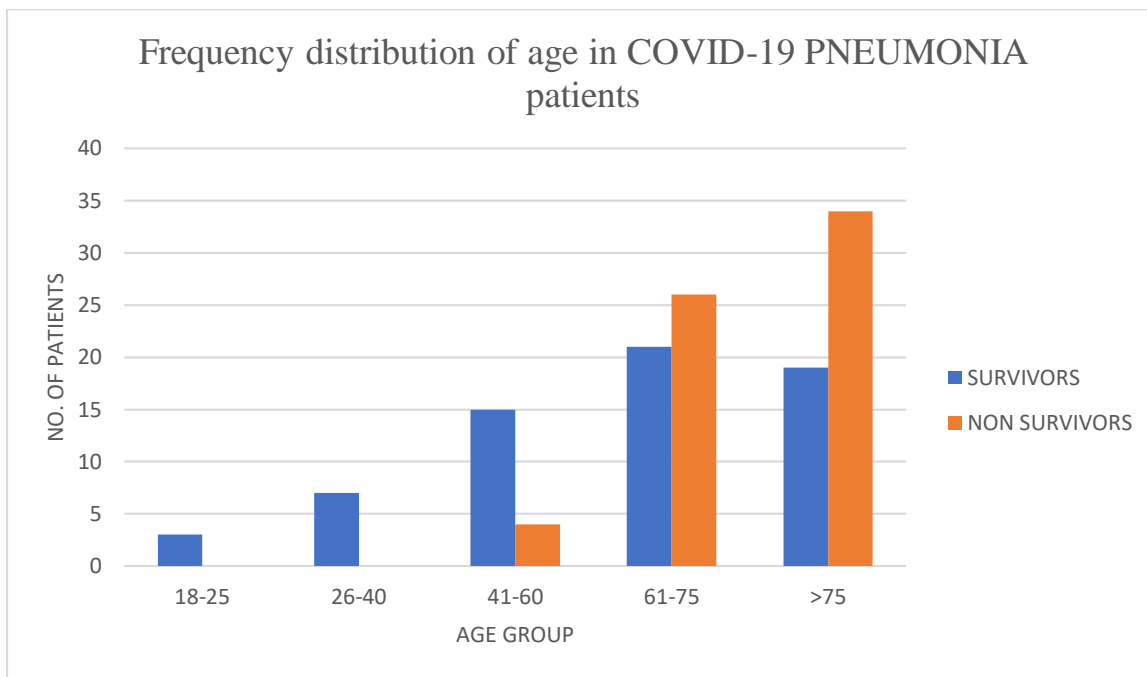
<u>RELATIONSHIP BETWEEN DEMOGRAPHIC PARAMETES WITH   MORTALITY   IN COVID-19</u>

<u>PNEUMONIA</u>

Table no.10 : <u>Association of age with Mortality in Covid 19 Pneumonia</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	76.06	10.16	13.58	5.193	<0.001***
Survivors (n=65)	62.48	18.34			

***Significant at 0.001 level

The above table shows association between age and mortality in Covid-19 Pneumonia. Since

the *p value is <0.001, were found to be statistically significant association between age and mortality.

Table no. 11 : Association of gender with mortality in Covid-19 Pneumonia

[N=129]

Gender	Non-Survivors (n=64)	Survivors (n=65)	Total	Odds Ratio	χ^2 test
Male	33	35	68		χ^2= 0.067
Female	31	30	61	1.096	df= 1, p= 0.795 (NS)

NS-Not Significant[Significant at 0.001 level]

The above table shows the association between gender and mortality in Covid-19 Pneumonia.

The p value is 0.795 which is not statistically significant. Association between gender and mortality was found to

be statistically not significant.

Table No 12 : Clinical manifestations in Covid-19 Pneumonia

[N=129]

SYMPTOMS	SURVIVORS (n=65)		NON SURVIVORS (n=64)	
	FREQUENCY[f]	PERCENTAGE[%]	FREQUENCY [f]	PERCENTAGE [%]
Cough	44	67.69%	40	62.5%
Dyspnea	37	56.92%	52	81.25%
Fever	32	49.23%	44	68.75%
Myalgia	20	30.76%	12	18.75%

Table 12 shows the clinical manifestations in Covid-19 Pneumon

ia patients. Among the survivors , the most prominent symptoms observed were cough (67.69%) followed by

dyspnea (56.92%) whereas in non survivors the most prominent symptoms were dyspnea (81.25%) followed by fever (68.75%).

RELATIONSHIP BETWEEN CLINICAL MANIFESTATION AND MORTALITY IN COVID-19 PNEUMONIA

Table13 : <u>Association of presence of cough among survivors and non-survivors</u>

[N=129]

Cough	Non-Survivors (n=64)	Survivors (n=65)	Total	Odds Ratio	χ^2 test
Present	40	44	84		χ^2= 0.383
Absent	24	21	45	0.795	df= 1, p= 0.536 (NS)

NS-Not Significant[significant at 0.05 level]

The above table shows association between cough and mortality in Covid-19 Pneumonia.

Since the p value is > 0.05, there is no statistically significant association between cough and mortality

.Table 14 : <u>Association of presence of dyspnea among survivors and non-survivors</u>

[N=129]

Dyspnea	Non-Survivors (n=64)	Survivors (n=65)	Total	Odds Ratio	χ^2 test
Present	52	37	89		χ^2= 8.921
Absent	12	28	40	3.28	df= 1, p= 0.003**

** Significant at 0.01 level

From the above table it is observed that the p value obtained from χ^2 test is 0.003 , which is statistically significant . Hence it shows a positive correlation between dyspnea and mortality

Table 15 : <u>**Association of presence of fever among survivors and non-survivors**</u>

[N=129]

Fever	Non-Survivors (n=64)	Survivors (n=65)	Total	Odds Ratio	χ^2 test
Present	44	32	76		χ^2= 5.076
Absent	20	33	53	2.269	df= 1, p= 0.024*

*Significant at 0.05 level

The above table shows the association between fever and mortality. Since the calculated p value is 0.024, association between fever and mortality was found to be statistically significant.

Table16 : <u>**Association of presence of myalgia among survivors and non-survivors**</u>

[N=129]

Myalgia	Non-Survivors (n=64)	Survivors (n=65)	Total	Odds Ratio	χ^2 test
Present	12	20	32		χ^2= 2.498
Absent	52	45	97	0.519	df= 1, p= 0.114 (NS)

NS-Not Significant [significant at 0.05 level]

The association between myalgia and mortality is observed from above table. The p value obtained from the χ^2 test is > 0.05 hence the association between myalgia and mortality was not found to be statistically significant.

Table 17 : <u>**Duration of clinical manifestations**</u>

[N=129]

Duration	Survivors(n=65)		Non survivor(n=64)	
	Frequency[f]	Percentage[%]	Frequency[f]	Percentage[%]
≤3 days	60	92.3%	52	81.25%
4-6 days	1	1.54%	8	12.5%
7-10 days	4	6.16%	4	6.25%

The above table shows the duration of clinical manifestations in Covid-19 Pneumonia patients. The survivor group and non survivor group shows majority of patients with a duration of clinical manifestations less than or equal to 3 days .

Table 18: <u>**Association of duration of symptoms and mortality**</u>

Duration of symptoms	Non-Survivors (n=64)	Survivors (n=65)	Total	Odds Ratio	χ^2 test
≤ 3 days	52	60	112		χ^2= 3.446
>3days	12	5	17	0.361	df= 1, p= 0.063 (NS)

[N=129]

NS – Not significant[significant at 0.05 level]

The above table shows association of duration of symptoms and mortality. No statistically significant association was found between duration of symptoms and mortality since the P value is >0.05

Table 19   : Length of hospital stay

[N=129]

No. of days	Survivors(n=65)		Non Survivors(64)	
	Frequency[f]	Percentage[%]	Frequency[f]	Percentage[%]
≤10 days	49	75.38%	52	81.25%
>10 days	16	24.62%	12	18.75%

The above table depicts the length of hospital stay. Majority of non survivors (81.25%) and survivors (75.38%) had spent less than 10 days at hospital.

Table 20 : Association of length of hospital stay and mortality

[N=129]

Length of hospital stay	Non-Survivors (n=64)	Survivors (n=65)	Total	Odds Ratio	χ^2 test
≤ 10 days	52	49	101		χ^2= 0.653
>10 days	12	16	28	1.415	df= 1, p=0.419 (NS)

NS- Not Significant [Significant at 0.05 level]

The above table shows the association of length of hospital stay and mortality. Since the p value > 0.05 there is no statistically significant association between length of hospital stay and mortality.

Table 21 :Distribution of comorbidities in COVID-19 PNEUMONIA patients

[N=129]

COMORBIDITIES	SURVIVORS(n=65)		NON SURVIVORS(n=64)	
	Frequency[f]	Percentage[%]	Frequency[f]	Percentage[%]
With comorbidities	53	81.54%	64	100%
Without comorbidities	12	18.46%	0	0%
Total	65	100%	64	100%

The above table depicts the percentage distribution of comorbidities in covid-19 pneumonia patients, in which all

non

Figure 10: **Frequency distribution of comorbidities in Covid-19 Pneumonia patients**
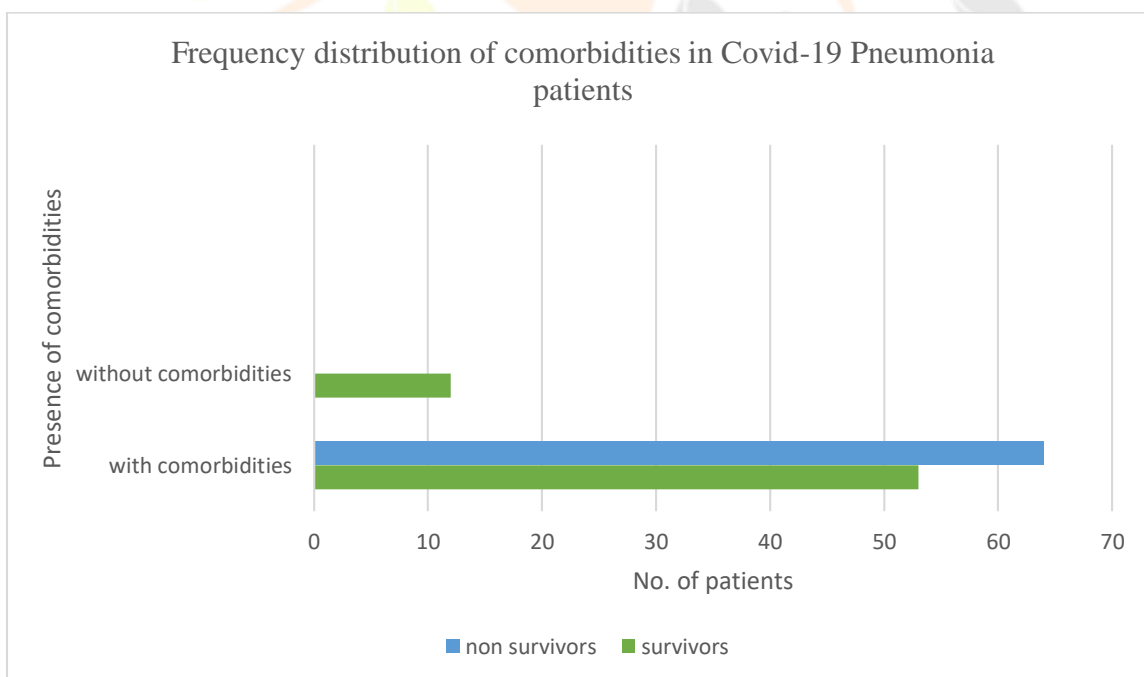
RELATIONSHIP BETWEEN COMORBIDITIES AND MORTALITY IN COVID-19 PNEUMONIA PATIENTS

Table 22 : <u>Association of presence of comorbidities and mortality</u>

[N=129]

COMORBIDITIES	Non-Survivors (n=64)	Survivors (n=65)	Total	χ^2 test
Present	64	53	117	χ^2= 13.027
Absent	0	12	12	df= 1, p<0.001***

*** Significant at 0.001 level

The association between comorbidities and mortality measured by using chi square test shows a statistically significant p value < 0.001 indicating a strong positive correlation between presence of comorbidities and mortality.

<u>RELATIONSHIP BETWEEN LABORATORY PARAMETERS AND RISK FOR MORTALITY IN COVID-19 PNEUMONIA</u>

VITALS (MEAN)	SURVIVOR (n=65)	NON SURVIVOR (n=64)
SpO2(%)	93.57%	87.86%
RESPIRATORY RATE[RR](breaths/min)	21.94	19.44
LAB FINDINGS (MEAN)		
Hb(g%)	12.62	11.10

WBC(cells/mm)	8232.30	10567.50
PLATELET(c/cu)	253000	193406
SERUM FERRITIN(microgram/L)	624.60	1274.77
D-dimer (ng/ml)	720.15	1323.14
SERUM CREATININE(mg/dL)	1.02	2.36
RBS(mg/dL)	208.38	372.58

Table 23 : <u>Mean distribution of Laboratory parameters in COVID-19 PNEUMONIA patients</u>

The above table shows the mean distribution of Laboratory parameters in Covid 19 pneumonia patients among survivors and non survivors. The mean SpO_2 value (87.86%) , mean respiratory rate (19.44 breaths/min) , Hb (11.10%) and platelet (193406c/cu) levels were decreased in non survivors compared to survivors. The WBC (10567.50cells/mm), serum ferritin level (1274.77microgram/L), D-dimer (1323.14ng/ml) and creatinine (2.36mg/dl) levels were elevated in non survivors compared to survivors.

Table 24 : <u>Comparison of SPO2 among survivors and non-survivors</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	87.86	5.10	5.71	6.019	<0.001***
Survivors (n=65)	93.57	5.65			

***Significant at 0.001 level

The above table shows the association between SpO_2 with mortality. The p value <0.001 indicates an extremely significant value of positive correlation between SpO_2 and mortality.

Table 25 : <u>**Comparison of RR among survivors and non-survivors**</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	19.44	4.15	2.50	4.827	<0.001***
Survivors (n=65)	21.94	0.50			

***Significant at 0.001 level

The relationship between Respiratory rate and mortality shows a positive association since the p value is statistically significant with a value< 0.001

Table 26 : <u>**Comparison of Creatinine level among survivors and non-survivors**</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	2.36	1.93	1.34	5.491	<0.001***
Survivors (n=65)	1.02	0.37			

***Significant at 0.001 level

The above table represents the relationship between Creatinine level and mortality in Covid-19 pneumonia. The p value obtained by using t test is 0.001 which is statistically significant indicating a strong association between creatinine level and mortality.

Table 27 : <u>Comparison of Haemoglobin level among survivors and non-survivors</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	11.10	1.81	1.52	4.468	<0.001***
Survivors (n=65)	12.62	2.05			

***Significant at 0.001 level

The above table shows the association of Hb level with mortality. The comparison among non survivor and survivors show a statistically significant p value <0.001.

Table 28 : <u>Comparison of WBC count among survivors and non-survivors</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	10567.50	5953.27	2335.20	2.7469	0.0069
Survivors (n=65)	8232.30	3370.37			

**significant at 0.001 level

This table shows comparison of WBC count among survivors and non survivors in predicting mortality in Covid-19 Pneumonia. Since the p value is 0.0069 the association between WBC count and mortality is statistically significant.

Table 29 : <u>Comparison of platelet count among survivors and non-survivors</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	193406.25	73343.44	50802.98	2.804	<0.006**
Survivors (n=65)	253000	125354.43			

**Significant at 0.001 level

The above table depicts the association of platelet count with mortality in Covid-19 Pneumonia. Since the p value is <0.006 there is a significant relation between platelet count and mortality .

Table 30 : <u>Comparison of D-Dimer among survivors and non-survivors</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	1323.14	829.48	602.99	4.888	<0.001***
Survivors (n=65)	720.15	544.39			

***Significant at 0.001 level

The above table shows a statistically significant association between D-dimer and mortality in Covid-19 Pneumonia, since the p value obtained is <0.001.

Table 31 : <u>**Comparison of Ferritin among survivors and non-survivors**</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	1274.77	829.48	650.17	4.1542	P<0.001**
Survivors (n=65)	624.60	943.49			

**significant at 0.001 level

The above table shows the association of ferritin and mortality in Covid-19 Pneumonia.

There is a strong relation between ferritin and mortality, since the p value is<0.001.

Table 32 : <u>**Comparison of RBS level among survivors and non-survivors**</u>

[N=129]

Group	Mean	Standard deviation	Mean difference	t value	p value
Non-survivors (n=64)	372.58	1410.13	164.19	0.936	0.351 (NS)
Survivors (n=65)	208.38	114.22			

NS- Not significant[Significant at 0.05 level]

The above table depicts the association of RBS and mortality in COVID -19 PNEUMONIA , since the p value is 0.351 , there is no statistically significant association between RBS and mortality.

CONCLUSION

This study was carried out for a period of 6 months in the general medicine & MICU department of a tertiary care hospital in Kerala. The study was conducted to evaluate the predictors of mortality in COVID-19 Pneumonia.

In the current study, out of 129 participants, we found that elderly patients were more commonly affected by moderate to severe pneumonia with very high mortality rates. Statistically significant association was found between age and mortality as the p value was <0.001. Elderly patients are commonly affected by severe pneumonia due to age-dependent decline in immunity. A Korean meta-analysis of COVID-19 pneumonia found old age to be the risk factor for increased mortality. Old age is an established risk factor for various infections, including viral infections and by far most significant predictor of mortality in COVID-19 pneumonia.

In our study we found that the most prominent symptoms were dyspnea [81.25%] with p value 0.003 followed by fever [62.5%] with p value 0.024 in non survivors and in survivors, prominent symptoms were cough (67.69%) followed by dyspnea (56.92%).

The presence of comorbidities is an established risk factor for mortality in patients with COVID-19 pneumonia in various studies done across the globe. In our study, we found that comorbidities are independent predictors of mortality (p value <0.001).

In the current study we noted SpO2 (87.86%) to be an independent predictor of mortality in severe COVID-19 pneumonia patients with a p value of <0.001. Laboratory parameters such as Hb (p value <0.001), WBC (p value 0.0069), platelet (0.006) & Creatinine (0.001) were found to be independent predictors of mortality. Ferritin is an intracellular protein that elevates during inflammation following SARS-CoV-2 infection as it is found to be secreted by alveolar macrophages in the lungs and also stimulated by various cytokines, including IL-6. Active ferritin in turn stimulates the immune system and activates macrophages leading to an increase in inflammatory process. Various single-center retrospective studies done in China found higher ferritin levels in patients who succumbed compared to survivors and discovered a decrease in ferritin levels with remission of the disease. We also found elevated ferritin levels with p value <0.001 in non-survivors compared to survivors. Using t test we

found that D dimer is an independent predictor of mortality with a p value of <0.001 which indicates the hypercoagulabe state occurring due to COVID-19.

We conducted this study on a total of 129 patients that included both survivors and non survivors of COVID-19 Pneumonia. From this study we observed that elderly patients with comorbidities had increased risk of mortality

Among the survivors , the most prominent symptoms observed were cough followed by dyspnea whereas among non survivors the most prominent symptoms were dyspnea followed by fever. Hence, cough ,dyspnea and fever were found to be more associated with mortality. Laboratory parameters like SpO_2,Hb, WBC, platelet, D dimer, ferritin were independent predictors of mortality.

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