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Research Paper: Clinical and Laboratory Predictors of Mortality in Patients With SARS-CoV-2 Infection in a Tertiary Care Center of Central Kerala, India - A Case control Study

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Running Title Predictors of Mortality of SARS Cov-2 Infection Among Hospitalized Patients

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ABSTRACT

Background: Since various studies indicate differences in the case fatality rate of SARS-CoV-2 in different settings, it is vital to elucidate the clinical and laboratory parameters. This would be helpful in identifying individuals who are susceptible to adverse outcomes, thereby targeting essential health interventions to resource poor settings. This study aimed to determine the clinical and laboratory predictors of mortality due to COVID-19.

Materials & Methods: In this case control study, we included 162 adult inpatients who died due to COVID-19 from May 2020 to February 2021, as cases (n=81) and those discharged as controls (n=81). Demographic, clinical, treatment, and laboratory data was extracted from medical records and electronic database and compared between survivors and non-survivors. Univariate analysis and multivariable logistic regression methods were used to identify the risk factors associated with in-hospital death.

Results: Comorbidities were present among 82 (50.6%) participants. Hypertension was the most common comorbidity 99(61.1%) followed by diabetes mellitus 92 (56.8%) and coronary artery disease 55(34%). Multivariable logistic regression model showed that cardiovascular disease (OR=5.80, 95%CI: 1.09–47.55, P=0.011), decreased oxygen saturation (OR=33.68, 95%CI: 2.81–403.80, P=0.006), elevated CRP (OR=1.16, 95%CI: 1.01–1.32, P=0.026), and serum creatinine (OR=3.26, 95%CI: 1.02–11.55, P=0.047) were the significant predictors of mortality.

Conclusion: This study found that comorbidities such as CAD, elevated serum creatinine, elevated inflammatory markers, and decreased O_2 saturation were independent predictors of mortality among COVID-19 patients.

Keywords: COVID-19, Mortality, Case-control study

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1. Introduction

Since the emergence of COVID-19 disease, it has rapidly become a worldwide threat. It was declared a pandemic by World Health Organization on 11th March, 2020 [1]. Since then, the disease has spread to 216 countries and territories, with 184,567,307 confirmed cases and 3,993,511 deaths as on July, 2021 [2]. The highest confirmed number of cases and deaths were reported in the United States of America with more than 34 million cases and over 600,000 deaths and India accounted for over 32 million cases and 402,758 deaths [2].

Global Case Fatality Rate of COVID-19 is estimated to be 3.6%. A study by Zhao et al., after analyzing 30 studies with 53000 patients, found a pooled Case Fatality Rate (CFR) of 3.1% [3]. Case fatality rate in India is 3.88%, whereas the state of Kerala has reported a lower-case fatality rate (adjusted CFR =1.12) [4].

The clinical spectrum of SARS-CoV-2 infection appears to be wide, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure and even death [5-7]. Majority of the COVID-19 infected patients recover after few days, but some deteriorate very rapidly with development of Acute Respiratory Distress syndrome (ARDS), acute respiratory failure, multi organ failure and death [5-7]. Factors found to be associated with above said complications, intensive care unit admissions and fatal outcomes included male gender, age above 60 years, presence of comorbidities, disease severity and laboratory parameters such as lymphocytopenia, elevated alanine aminotransferase, D-dimer, creatine kinase, high sensitivity cardiac troponin I, and prothrombin time [8].

COVID-19 and associated mortality poses a major public health threat especially in low and middle income countries. Prompt identification of the epidemiological, clinical and laboratory parameters would be helpful in identifying individuals more susceptible to severe disease and death, thereby targeting essential health interventions and resource allocation to focused areas, especially in resource poor settings. So, this study aimed to determine the clinical and laboratory predictors of mortality due to SARS-CoV-2 Infection.

2. Materials and Methods

Study design and participants

This case-control study was conducted at Jubilee Mission Medical College & Research institute, a tertiary care teaching hospital in Thrissur district of Kerala-a southern state of India. All adult patients who were diagnosed with SARS-CoV-2 infection either by Real-Time (RT) PCR (TeqPath COVID-19 CE-IVD RT-PCR kit, Thermo fisher scientific, USA) or Rapid Antigen Test (Meriscreen COVID-19 antigen detection test kit, Meril Diagnostics, India) during the period from May 2020 to February 2021 were included in the study. Among the admitted patients those with an outcome of death were considered as cases and those who were cured -that is, symptomatic relief, significant improvement in pulmonary radiology, and did not require supportive care or other treatments, negative SARS-CoV-2 Rapid antigen test and discharged from the hospital during the same time period were selected as controls. Patients, who's clinical and laboratory records were incomplete and those who died within one day of hospitalization were excluded from the study. Based on the clinical and laboratory values observed from an earlier publication [9], with 95% confidence interval and 80% power minimum sample size was calculated to be 59. From May 2020 to February 2021 we had 106 COVID deaths; 9 cases had incomplete clinical or laboratory records and 16 deaths occurred within 24 hours of admission and finally we enrolled 81 cases. For each case one control was selected, so 81 cases and 81 controls were included (Case: Control ratio= 1:1). Frequency matching was performed according to age, sex, and disease severity. The institute follows the Directorate of health services, Government of Kerala state, India guidelines on COVID management [10], which classifies disease severity to mild, moderate & severe.

Data collection and variables

Demographic characteristics, clinical and laboratory findings, treatment protocol, and outcome data were extracted from medical records and hospital computerized databases using a structured preformat. Pulse rate, blood pressure, respiratory rate, body temperature and comorbidities were collected from the patient's records. Tachycardia was defined as a pulse rate >100/minute, hypotension was defined as systolic blood pressure less than 90 mm Hg, tachypnea was considered as respiratory rate >24/minute, and fever was defined as body temperature >37.3°C.

Laboratory parameters were collected for a range of hematology, serology, inflammatory markers, general and special biochemistry indices. The parameters included total White Blood Cell (WBC) Count and differential, Platelet count, Neutrophil: Lymphocyte Ratio (NLR), Cardiac Troponins (Troponin I), Creatinine Phosphokinase (CPK), Arterial Blood Gases (ABG), blood sugar, D–Dimer, Ferritin, C-Reactive Protein (CRP), Liver Function Tests, Prothrombin Time (PT with INR), Sodium, Potassium, Creatinine, and Lactate Dehydrogenase (LDH). In-hospital management of the study subjects were assessed in terms of whether the patients were managed without oxygen therapy, requirement of high flow nasal cannula O_2 therapy, non-invasive ventilation and mechanical ventilation.

Statistical analysis

The measures of strength of associations between independent factors and outcome was calculated as crude odds ratio with 95% Confidence Interval (CI). Categorical variables were presented as number and percentages and compared applying Chi-square test. Continuous variables were presented as mean with Standard Deviation (SD) and median with interquartile range and compared applying t-test and Mann Whitney U test. Logistic regression model was constructed and adjusted odds ratios with 95% CI was calculated to estimate the strength of association in multivariate analysis. The statistical level of significance was set at $P<0.05$. SPSS version 25.0 (SPSS IBM, Armonk, NY) was used for data analysis. The study proposal was approved by the Institutional Ethics Committee (IEC) of Jubilee Mission Medical College & Research institute (67/21/IEC/JMMCRI).

3. Results

We report the findings from 81 patients who have died due to SARS-CoV-2 (cases) and 81 patients who have recovered from the disease (controls) from May 2020 to February 2021. Demographic and clinical characteristics of patients are summarized in Table 1.

Clinical characteristics

Cases and controls were similar with respect to age (mean age, 67.83 years vs 67.25 years; P=0.6) and sex (58.6% male vs. 41.4% male; P=0.87). Among the non-survivors, males, 47(58%) constituted a higher proportion than females 34(42%). Comorbidities were present among 82(50.6%) of the participants. Hypertension was the most common comorbidity 99(61.1%), followed by diabetes mellitus 92(56.8%) and coronary artery disease 55(34%). Fever, persistent cough, dyspnea and excessive fatigue were the most common reason for admission. On clinical examination, 35(21.6%) patients presented with tachycardia, 20(12.3%) with tachypnea, 4(2.5%) with hypotension and 46(28.4%) with a fall in oxygen saturation.

Laboratory parameters

The laboratory parameters of study participants are summarized in Table 2. Leucopenia was present in 9(5.7%) and leukocytosis in 51(32.1%) patients. There was significant difference between the median values of laboratory parameters including WBC, absolute Lymphocyte count, Neutrophil: Lymphocyte ratio, Creatinine, D-dimer, Lactate Dehydrogenase (LDH) and C-Reactive Protein (CRP) between the survivors and non-survivors (Table 2).

In-hospital management and outcome

Table 3 summarizes the in-hospital management and treatment outcomes of the study subjects. Invasive mechanical ventilation was required by 9(5.6%) patients; of whom 8(9.87%) did not survive the disease (OR=11.15, 95%CI: 1.33-93.50, P=0.026). Non-invasive ventilation was used in 19(11.73%) patients, of whom 4(4.93%) survived and 15(18.51%) did not survive (OR=10.00, 95%CI: 1.16-85.59, P=0.006).

Secondary infection was the most common complication observed, followed by pneumonia, sepsis and ARDS, and the frequency of complications was higher among non-survivors (Table 3). The mean duration (in days) from onset of symptoms to discharge was 13.90±7.60 days; whereas the mean duration from onset of symptom to death was 7.63±6.42 days (P<0.0001; Table 3). Mean duration from hospital admission to discharge was 15.35±7.60 days and that from admission to death was 10.42±10.48 days (P=0.001; Table 3). Thus, both these time intervals showed a significant difference between the survivors and non-survivors.

In univariate analysis, the odds of in-hospital mortality were higher in patients with coronary heart disease, chronic kidney disease, presence of tachycardia, and reduced oxygen saturation (Table 1). Leucocytosis, Lymphopenia, high neutrophil to lymphocyte ratio, elevated serum creatinine, d-dimer, and CRP were also associated with increased odds of mortality (Table 2).

Multivariable logistic regression model was constructed including data for all the variables found to be sig-

Table 1. Clinical characteristics of study participants

	Characteristics	No. (%)			OR (95%CI)	P
		Total (n=162)	Non-Survivors (n=81)	Survivors (n=81)		
	Age (years), Mean±SD	-	67.53±12.74	67.25±12.14	Not calculated	0.637
Gender	Males	95(58.6)	47(58.0)	48(59.2)	Not calculated	0.873
Gender	Females	67(41.4)	34(41.9)	33(40.7)	-	
Comorbidity	Hypertension	99(61.1)	49(60.5)	50(61.7)	0.9(0.5-1.7)	0.872
Comorbidity	Diabetes	92(56.8)	47(58)	45(55.6)	1.1(0.6-2.06)	0.751
Comorbidity	Coronary artery disease	55(34)	35(43.2)	20(24.7)	2.3 (1.1-4.5)	0.013
Comorbidity	Chronic Obstructive pulmonary disease	12(7.4)	4(4.9)	8(9.9)	0.4(0.13-1.64)	0.230
Comorbidity	Bronchial asthma	7(4.3)	2(2.5)	5(6.2)	0.38(0.07-2.04)	0.246
Comorbidity	CVA/Stroke	19(11.7)	11(13.6)	8(9.9)	1.4(0.57-3.77)	0.464
Comorbidity	Chronic kidney disease	36(22.2)	26(32.1)	10(12.3)	3.35(1.49-7.54)	0.002
Comorbidity	Dyslipidemia	25(15.4)	14(17.3)	11(13.6)	1.3(0.56-3.13)	0.514
Clinical parameters	Pulse rate >100/mt	35(21.6)	24(29.6)	11(13.6)	2.67(1.21-5.93)	0.013
Clinical parameters	Hypotension(SBP<90mmHg)	4(2.5)	2(2.5)	2(2.5)	1(0.13-7.27)	1.000
Clinical parameters	Respiratory rate(>24/mt)	20(12.3)	12(14.8)	8(9.9)	1.58(0.61-4.11)	0.339
Clinical parameters	Oxygen saturation (<94%)	46(28.4)	37(45.7)	9(11.1)	6.72(2.96-15.26)	0.0001
Clinical parameters	Presence of secondary infections	33(20.4)	18(22.2)	15(18.5)	1.257(0.584-2.708)	0.558

OR: Odds ratio; CI: Confidence interval CVA: Cerebrovascular Accidents; SBP: Systolic Blood Pressure.

nificant in univariate analysis. The results showed that presence of cardiovascular disease (OR=5.80, 95%CI: 1.09–47.55, P=0.011), decreased oxygen saturation (OR=33.68, 95%CI: 2.81–403.80, P=0.006), elevated CRP (OR=1.16, 95%CI: 1.01–1.32, P=0.026), and serum creatinine (OR=3.26, 95%CI: 1.02–11.55, P=0.047) were the significant independent predictors of mortality in patients with COVID-19.

The results of the baseline arterial blood gas analysis of the survivors and non-survivors are shown in Figure 1 and 2. The mean values of partial pressure of oxygen (PaO_2) was found to be 79.66±65.87 mm Hg among non- survivors and 75.29±34.47 mm Hg in survivors, but this difference was not statistically significant (P=0.715). The mean oxygen saturation level in survivors was 87.10±16.04 % and in non survivors was 81.77±22.68%. There was no significant difference between survivors and non surivors in terms of ABG indices

4. Discussion

Our study was a comprehensive analysis of baseline clinical and laboratory parameters of patients who died of Covid-19 as cases and those who were admitted and cured as the control arm. There was significantly increased odds for mortality in those who had coronary artery disease and chronic kidney disease compared to patients with no similar comorbidities, whereas those who had hypertension, Chronic Obstructive Pulmonary Disease (COPD), Type II diabetes or dyslipidemia had no increased odds for mortality. Laboratory investigations revealed a greater likelihood of mortality in patients with decreased oxygen saturation, elevated levels of serum creatinine and CRP.

The majority of our non-survivor patients were elderly (67.83 years) with a male preponderance (58.6 %). Common symptoms with which the patient presented were fever, cough, dyspnea and fatigue. The risk of mortality in

Table 2. Laboratory parameters of study participant

Parameters	Non-Survivors	Survivors	Mann-Whitney U Test	P
WBC count (x10^{3}cells/µL)	9.220(6.2625-12.9825)	7.280(5.980-10.760)	1.89	0.041
Absolute lymphocyte count (x10^{3}cells/µL)	1.3(0.7-1.925)	1.65(1-2.375)	2.38	0.017
Neutrophil: Lymphocyte ratio	6.23(4.0-11.73)	4.70(2.85-8.85)	2.36	0.018
Platelet count (cells/mm^3)	228000(151000-308000)	234000(190250-290250)	0.56	0.571
Albumin (mg/dl)	3.6(3.2-3.95)	3.7(3.2-4.1)	1.32	0.186
Globulin (mg/dl)	3.6(3.2-3.95)	3.5(3.3-3.9)	0.24	0.803
Albumin/Globulin ratio	0.97(0.885-1.12)	1.03(0.9-1.18)	1.33	0.183
CPK(MB), U/L	367(127.25-1206)	98(64-403)	1.23	0.218
Creatinine (mg/dl)	1.5(0.9-3.37)	1(0.72-1.4)	4.07	<0.001
Ferritin (ng/ml)	304(142-814)	283.5(107.75-837)	0.46	0.643
D-dimer (ng/ml)	641.5(307.25-1795)	396(207-991)	2.72	0.006
Cardiac troponin (ng/ml)	0.05(0.02-1.22)	0.11(0.025-2.53)	0.078	0.938
LDH (IU/L)	409(357-770)	312.5(224.25-477.75)	2.08	0.037
CRP (mg/l)	12.8(7.1-21.9)	7.9(1.65-13.95)	2.31	0.021
Sodium (mEq/L)	132(128-135.25)	133(129-136)	0.37	0.709
Potassium (mEq/L)	4(3.4-4.5)	3.9(3.5-4.3)	0.52	0.601
Bilirubin (mg/dl)	0.7(0.5-1.00)	0.8(0.5-1.00)	0.15	0.874
SGPT (IU/L)	28(16-40)	31(20.75-45.25)	1.16	0.245
SGOT (IU/L)	55(33-82)	42.5(31.75-62.75)	1.22	0.222

WBC: White Blood Cell; A: G ratio- Albumin globulin ratio; LDH: Lactate Dehydrogenase; CRP: C Reactive Protein; SGPT: Serum glutamic pyruvic transaminase; SGOT: Serum Glutamic Oxaloacetic Transaminase.

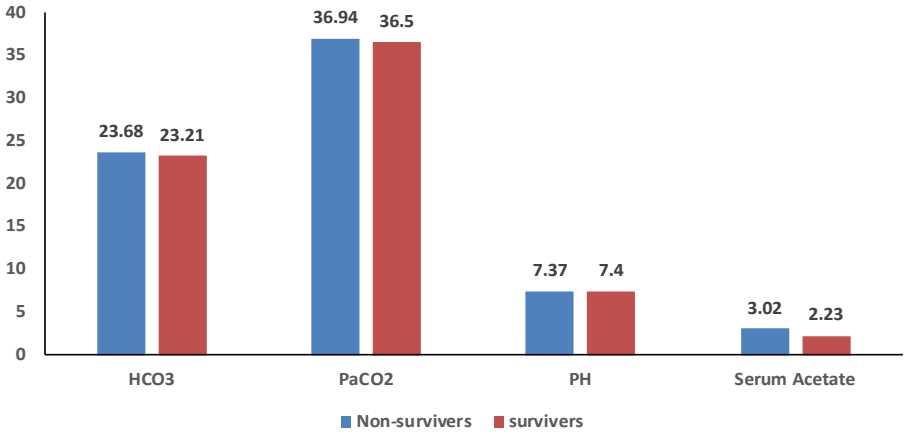

Figure 1. Mean values of arterial blood gas analysis between survivors and non survivors

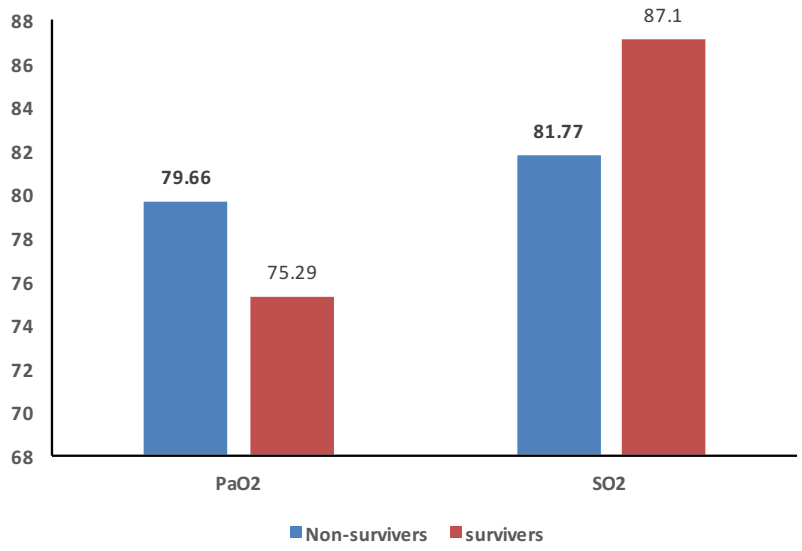

Figure 2. Mean values of partial pressure of oxygen and oxygen saturation between survivors and non survivors

Coronary Artery Disease (CAD) patients was found to be 2 times higher than patients without CAD. A study done by Shaobo Shi [11] in Wuhan found that patients with cardiac injury had higher mortality than those without (51.2% vs 4.5%, respectively) and the risk of mortality in patients with cardiac injury was higher both from time of symptom onset and from the time of hospital admission to endpoint. In contrast, a study done by Mattia Bellan et al. [12] in Italy showed that CAD is not a predictor of COVID-19 death. Although many studies have reported an increased risk of mortality due to Type II Diabetes mellitus, this study found no escalation of mortality in patients

Table 3. In-hospital management and outcomes of the study participants

	Treatment and Outcome	No. (%) / Mean±SD			OR (95%CI)	P
		Total (n=162)	Non-Survivors(n=81)	Survivors (n=81)		
Treatment	Room air without oxygen support	79(48.8)	33(40.8)	46(56.8)	(Ref)	
	High flow nasal cannula O_2 therapy	54(33.33)	24(29.6)	30(37.5)	2.133(0.20-22.44)	0.528
	Noninvasive ventilation	19(11.7)	15(18.5)	4(4.9)	10.00(1.16-85.59)	0.036
	Mechanical ventilation	9(5.5)	8(9.9)	1(1.2)	11.15(1.33-93.50)	0.026
Outcome	Sepsis	9(5.5)	6(7.4)	3(3.7)	1.6(0.08-5.12)	0.697
	Secondary infection	33(20.4)	18(22.2)	15(18.5)	1.25(0.58-2.71)	0.558
	Pneumonia	16(9.9)	8(9.8)	8(9.8)	1.3(0.22-7.9)	0.753
	ARDS	7(4.320)	3(3.7)	4(4.9)	1.35(0.29-6.23)	0.699
	Time interval from onset of symptoms to death/discharge		7.63±6.42	13.90±7.60		<0.001
	Time interval from admission to death/discharge		10.42±10.48	15.35±7.60		0.001

ARDS: Acquired Respiratory Distress Syndrome.

with diabetes, this may be due to limited sample size and retrospective nature of the study. The American College of Cardiology released a clinical bulletin in March 2020 [13] where they found that the fatality was higher in diabetes patients (7.3%). In a systematic review conducted by Ian Huang et al. [14] among the 6452 patients from 30 studies, showed that diabetes was associated with greater mortality (RR=2.12, 95%CI: 1.44, 3.11).

In the current study, 22.2% of the participants had Chronic Kidney Disease (CKD). This could be due to the fact that our institute is the largest center for dialysis in central Kerala. In concordance with many other studies our study showed a notable increase in mortality in CKD patients (OR=3.35, 95%CI: 49-7.54). In contrast, a study done by Chinnadurai et al in the UK established that there was no increased risk of mortality in CKD patients [15].

Our study showed that patients with tachycardia had about three times higher probability of mortality. A study done in Wuhan by Fei Zhou et al. [9] also inferred a similar finding. No significant association was found between in hospital death and presence of bradycardia, hypotension or tachypnea.

The likelihood of death was considerably higher among those who were managed with non-invasive ventilation and mechanical ventilation. We found that a decreased oxygen saturation on admission (SPO_2 <94%) is a strong predictor of mortality. A study done by Fernando Mejía et al found that oxygen saturation (SaO_2) values of less than 90% on admission correlated with mortality, presenting 1.86 (95%CI: 1.02–3.39), 4.44 (95%CI: 2.46–8.02) and 7.74 (95%CI: 4.54–13.19) times greater risk of death for SaO_2 of 89–85%, 84–80% and <80%, respectively, when compared to patients with SaO_2 >90% [16]. In resource poor settings, for the purpose of diagnosing hypoxemia at an early stage and referring to a tertiary care facility and avert mortality the directorate of health services, Government of Kerala state, India [10] has recommended 94% as the cut off value of SPO_2.

CRP and creatinine were found to be the independent predictor of mortality. In a systematic review by Izcovch et al, which included 207 studies of COVID-19 mortality, the above parameters were found to be predictors of mortality [17]. Kiss et al., in a meta-analysis observed similar findings. The baseline total White Blood Cell count (WBC), CRP, LDH, creatine kinase (CK), D-dimer and lower Absolute Lymphocyte Count (ALC) were associated with increased mortality. They also found that WBC, ALC, D-Dimer, CRP, LDH, and CK changes on admission could serve as poor prognostic outcome [18]. in accordance with our study, Victor et al, in their study on 2511 patients found that neutrophilia, lymphocytopenia, eosinopenia, decreased renal function, prior pulmonary disease and red blood cell abnormalities were associated with increased mortality [19]. We found that a high NLR more than 3.13 was a risk factor for increased mortality. Xiaoming Li et al, in a meta-analysis found that a high NLR has a good predictor for mortality in patients with COVID-19, which was similar to our finding [20]. The guidelines by Kerala Directorate of Health Services Kerala also stipulate to monitor these parameters [10]. High white cell count shows that secondary infection was common among the non survivors in our study. Severe lymphopenia seen among the deceased patients denotes a state of severe cellular immune deficiency which is a common finding among critically ill COVID-19 cases [21]. Even though COVID-19 is a viral disease, current study found that leukocytosis was more common than leucopenia (32.1% vs 5.7%) and it was also a significant predictor of mortality.

This study found some useful predictors of mortality such as CRP and creatinine that can be evaluated through laboratory investigations even in low resource settings. These investigations are economical and readily available even in remote areas of Kerala, which can guide treating physicians on initiating anticoagulants. In a low resource setting CRP can be an effective alternative to Interleukin - 6 which is an expensive investigation.

5. Conclusion

Patients with cardiovascular diseases, having clinical parameters such as low oxygen saturation and abnormal laboratory parameters such as elevated serum creatinine and CRP are likely to have a severe course and fatal outcome. Most of the clinical and laboratory parameters described in our study are inexpensive, easily available, accessible, reproducible and can be very easily applied in any level of healthcare, in resource poor settings.

This study suffers from some limitations including limited sample size, retrospective nature of the study design, data collection based on routinely hospital records which might result in measurement bias.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Institutional Ethics Committee (IEC) of Jubilee Mission Medical College & Research institute (67/21/IEC/JMMCRI).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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