ORIGINAL ARTICLE

A Retrospective Observational Study to Determine the Early Predictors of In-hospital Mortality at Admission with COVID-19

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Abstract

Introduction: Coronavirus disease-2019 (COVID-19) systemic illness caused by a novel coronavirus severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has been spreading across the world. The objective of this study is to identify the clinical and laboratory variables as predictors of in-hospital death at the time of admission in a tertiary care hospital in India.

Materials and methods: Demographic profile, clinical, and laboratory variables of 425 patients admitted from April to June 2020 with symptoms and laboratory-confirmed diagnosis through real-time polymerase chain reaction (RT-PCR) were studied. Descriptive statistics, an association of these variables, logistic regression, and CART models were developed to identify early predictors of in-hospital death.

Results: Twenty-two patients (5.17%) had expired in course of their hospital stay. The median age [interquartile range (IQR)] of the patients admitted was 49 years (21–77 years). Gender distribution was male — 73.38% (mortality rate 5.83%) and female—26.62% (mortality rate 3.34%). The study shows higher association for age (>47 years) [odds ratio (OR) 4.52], male gender (OR 1.78), shortness of breath (OR 2.02), oxygen saturation <93% (OR 9.32), respiratory rate >24 (OR 5.31), comorbidities like diabetes (OR 2.70), hypertension (OR 2.12), and coronary artery disease (OR 3.18) toward overall mortality. The significant associations in laboratory variables include lymphopenia (<12%) (OR 8.74), C-reactive protein (CRP) (OR 1.99), ferritin (OR 3.18), and lactate dehydrogenase (LDH) (OR 3.37). Using this statistically significant 16 clinical and laboratory variables, the logistic regression model had an area under receiver operating characteristic (ROC) curve of 0.86 (train) and 0.75 (test).

Conclusion: Age above 47 years, associated with comorbidities like hypertension and diabetes, with oxygen saturation below 93%, tachycardia, and deranged laboratory variables like lymphopenia and raised CRP, LDH, and ferritin are important predictors of in-hospital mortality.

Keywords: COVID pneumonia, COVID-19, COVID-19 mortality, Mortality predictors, SARS-CoV-2.

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Introduction

Coronavirus disease-2019 (COVID-19) pneumonia caused by a novel coronavirus severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has spread across the world very rapidly. COVID-19 is playing a major role in changing the economic and social order of the world. The clinical features of SARS-CoV-2 infection can vary from asymptomatic infection or mild acute respiratory infection symptoms. Symptoms such as fever, dry cough, fatigue, and loss of taste usually occur in the early stages of COVID-19, leading to acute respiratory failure, multiple organ failure, and other fatal complications in patients with underlying comorbidities and age.[1–16]

The course of the disease can be complicated with the deranged function of the various organs like lung, heart, brain liver, kidney, and the coagulation system. In addition to acute respiratory failure, common complications include acute kidney injury, liver dysfunction, myocardial damage, and septic shock.[5,17–20] Coagulation complications like venous and arterial thromboembolic events have also occurred in this illness. There are reports of acute cerebrovascular disease and encephalitis with severe COVID-19 illness.[7]

There are several risk factors associated with adverse outcomes, like diabetes mellitus, obesity, chronic kidney disease, and immunocompromised states. However, in certain instances without any apparently identified risk factors, mortality has been reported.[5,21,22]

No specific and effective treatment has been so far developed for COVID-19. In addition, details of the clinical and virological course of illness have not yet been well understood. So, early recognition of patients with poor prognosis may facilitate the early supportive treatment for such patients early and reduce mortality.

The early predictors for the COVID-19 mortality in most of the studies from China, Western Europe, and the US have stated that older age, male gender, comorbidities like hypertension, lymphopenia, bilateral patchy consolidation (ground-glass appearance) in chest images, and raised pro-inflammatory markers as predictors of mortality. However, these features had challenges

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in the Indian population due to—(a) dearth of research linking risk factors to a comprehensive group of variables and (b) additional variables important in Indian population linking middle-aged group with comorbidities and severity at presentation.

Materials and Methods

Study Design and Participants

This study included all adult (>17 years) patients of COVID-19 who were admitted at Indraprastha Apollo Hospitals New Delhi between April and June 2020. Only those patients were included in the study who are confirmed cases of COVID-19, that is, positive for COVID-19 by molecular methods—real-time polymerase chain reaction (RT-PCR) from respiratory samples (nasopharyngeal secretions/endotracheal secretions/bronchoalveolar lavage). The study was approved by the Research Ethics Committee of Indraprastha Apollo Hospitals and the requirement for informed consent was waived by the Ethics Committee as it was a retrospective study.

Data Collection

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were collected from medical records using a standardized data collection paper form and the electronic medical records. Data were cross-verified by another physician. The EMR records were coded with ICD-10 for diagnoses and LOINC coding for the laboratory variables. The variables including demographic details, symptoms and vitals at presentation, and history of comorbidities were collected for these patients. At admission, routine blood examinations performed included complete blood count, coagulation profile, serum biochemical tests, and pro-inflammatory markers. Chest radiographs were also done for all inpatients. The patient was considered febrile if the axillary temperature was above 98.6°F. Sepsis and septic shock were defined as per the Third International Consensus Definition for Sepsis and Septic Shock.[23]

Acute kidney injury was diagnosed as per KDIGO guidelines. The acute cardiac injury was diagnosed by high cardiac biomarkers. Coagulopathy was defined as a prolonged prothrombin time of 3 seconds or a 5-second extension of activated partial thromboplastin time.

Statistical Analysis (Methodology)

Out of over 100 clinical and laboratory variables observed for the study, the objective was to determine the clinically and statistically relevant continuous and categorical variables. We used the Mann–Whitney *U* test, χ^2 test, and Fisher's exact test for comparison between the expired and the discharged patients. The odds ratios (ORs) were calculated using the R Library to determine the association between the underlying factors and the outcome (expired patients). Threshold or cutoff values for the clinical factors (vitals) and laboratory variables were used to categorize by determining their interquartile range (IQR) (first or third quartile) and clinically relevant values. A binary fit logistic regression model, including a classification and regression tree, was built to determine the early predictors of the event taking into consideration 16 clinical and laboratory factors. Considering the number of expired patients ($n = 22$; 5.46%), we tried to avoid overfitting of the model and restricted our variables to 16. The variables were derived from three factors namely—(a) addressing the variables with missing values, (b) OR (adjusted), and finally, (c) the significance values including the weightage and *p* values. Owing to the low event rate (event per variable ratio), we used penalized regression with the use of lasso shrinkage methods and provide the corrected regression coefficients.

Results

Initial analysis of the data set included 425 patients admitted at Indraprastha Apollo Hospitals from April to June 2020 with symptoms of COVID-19 and had laboratory-confirmed diagnosis through RT-PCR. Twenty-two patients (5.17%) had expired in course of their hospital stay. The analysis was conducted by data for descriptive statistics, OR—determining the risk of mortality—using thresholds for continuous variables and by identifying the predictors for early mortality using regression models (logistic regression and classification and regression tree models). Thresholds for continuous variables were selected where the OR, *z*, and *p* value were statistically significant. The details of the mean and ORs of the variables are provided in Tables 1 and 2.

The median age of the patients admitted was 49 years (IQR 21–77). 73.38% of admitted patients were male (female 26.62%). The average weight of the patients was 74.68 kg, 5.24% of the patients had a history of smoking. The OR for age (>47 years) is significant at 4.52, male gender at 1.78, and body weight (>75 kg) at 1.94. 27.66% of patients gave a positive contact history, predominantly with household contacts like spouses, siblings, or children [Table 1 and Figure 1 (adjusted OR)].

Symptoms and Comorbidities at Admission

Fever was a predominant symptom of the patients at the time of admission. 63.76% of patients had provided a history of temperatures above 99°F at the time of admission. The fever was mostly continuous and the average duration of fever at the time of admission was around 5.13 days (IQR 1–9 days). Fever was mostly associated with cough in 40% of patients and sore throat in 18.35% among admitted patients. Other notable symptoms were myalgia/arthralgia (9.65%), headache (8.25%), nausea/vomiting (6.59%), whereas chills/rigor (1.64%), anosmia (0.7%), and nasal congestions (0.7%) were relatively rare. 23.53% of patients presented with shortness of breath at admission; however, only 1.17% had crepitations and wheezes on examination. Odds ratio for shortness of breath at admission is 2.02 and significantly, individuals who reported to the hospital >5 days is at 1.90. Hypertension (33.88%) and diabetes (29.41%) are the most common comorbidities among the patients admitted. Patients with concomitant diabetes and hypertension were around 18%. Chronic kidney disease (7.06%), coronary artery disease (5.66%), hypothyroidism (5.21%), asthma-COPD-ACO (asthma COPD complex) (2.82%), history of malignancy (1.65%), and pulmonary tuberculosis (1.65%) were the significant comorbidities and clinical conditions. There were no patients with pregnancy in this cohort. Fifty-one percent of patients in this cohort were taking medication for chronic conditions [Table 1 and Fig.1 (adjusted OR)].

Vitals and Chest X-ray at Admission

The mean temperature of patients at admission was 98°F. However, 21.17% of patients had temperatures above 100.4°F within the next 24 hours following admission. Mean pulse rate at admission (85/minute; 68–92/minute), systolic blood pressure (123.7 mm Hg;

Table 1: Demographics, symptoms and comorbidities, vitals at admission, and chest imaging findings [odds ratio (adjusted)]

Variables	*Mean*	*Odds ratio*	*95% CI*	*Significance*
Age	47.769	4.52	1.50–13.62	$p = 0.0104$
Gender: Male	73.38%	1.78	0.59–5.38	$p = 0.3300$
Weight	74.68	1.94	0.77–4.86	$p = 0.1801$
Travel	2.12%	7.52	1.37–41.18	$p = 0.0377$
Visit: Hotspots	2.59%	1.97	0.24–16.27	$p = 0.5590$
Contact	27.66%	0.55	0.18–1.65	$p = 0.3087$
Fever	63.76%	1.24	0.50–3.13	$p = 0.6585$
Symptoms (all)	69.88%	1.53	0.55–4.23	$p = 0.4405$
Duration of illness >5 days	4.708	1.90	0.77–4.68	$p = 0.1884$
Sore throat	18.35%	0.68	0.20–2.35	$p = 0.5594$
Cough	40.00%	0.84	0.35–2.06	$p = 0.7209$
Sputum production	3.77%	5.86	1.49–23.06	$p = 0.0226$
Shortness of breath	23.53%	2.02	0.82–4.98	$p = 0.1513$
Headache	8.25%	0.50	0.07–3.85	$p = 0.5253$
Nausea/vomiting	6.59%	0.65	0.08–5.03	$p = 0.6936$
Myalgia/arthralgia	9.65%	2.34	0.75–7.33	$p = 0.1738$
Comorbidities (all)	51.06%	3.68	1.33–10.17	$p = 0.0169$
Diabetes	29.41%	2.70	1.14–6.42	$p = 0.0347$
Hypertension	33.88%	2.12	0.90–5.03	$p = 0.1071$
Chronic kidney disease	7.06%	0.60	0.08–4.63	$p = 0.6397$
Coronary artery disease/Ischemic heart disease	5.66%	3.18	0.86–11.76	$p = 0.1102$
Malignancy	1.65%	3.58	0.40–32.05	$p = 0.2982$
Hypothyroidism	5.21%	2.02	0.44–9.30	$p = 0.4026$
Medication for chronic disease	50.94%	3.68	1.33–10.17	$p = 0.0169$
Systolic blood pressure	123.7	2.48	0.93–6.64	$p = 0.0917$
Diastolic blood pressure	78.0	1.04	0.34–3.18	$p = 0.9461$
Temperature	98.27	9.32	3.54–24.59	$p < 0.0001$
Respiratory rate	21.012	19.29	6.33–58.79	$p < 0.0001$
SpO_2	96.578	17.68	4.37–71.52	$p = 0.0001$
Pulse rate	85.689	2.82	0.98–8.09	$p = 0.0743$
Bilateral patchy shadows (GGO)	16.47%	14.12	5.60–35.65	$p < 0.0001$
Local patchy shadows (GGO)	2.12%	2.54	0.30–21.64	$p = 0.4303$
Effusions (uni/bilateral)	12.71%	1.10	0.31–3.84	$p = 0.8930$

109.5–130.5), and diastolic blood pressure (78.0 mm Hg; 70–90) were measured. The average respiratory rate was 21.01 (IQR 17–23/minute), whereas the mean oxygen saturation was at 96.58% (IQR 94–99) [Table 1 and Fig. 1 (adjusted OR)].

Laboratory Values within 24 Hours of Admission

Patients had undergone laboratory tests for complete blood count, coagulation profile (PT, APTT, INR), basic biochemistry (liver function, electrolytes, renal function) tests, proinflammatory markers [C-reactive protein (CRP), ferritin, procalcitonin, lactate dehydrogenase, D-dimer, etc.]. The significant associations in laboratory variables include the lymphocytes (<12%) 8.74 (95% CI 3.57–21.37), CRP (quantitative >48) 1.99 (95% CI 0.81–4.90), ferritin (>800) 3.18 (95% CI 1.28–7.93), and lactate dehydrogenase (>430) 3.37 (95% CI 1.38–8.20) (Table 2).

Selection of Features and Combined Model

Based on the available data and missing values, adjusted OR, *z* scores, the *p* values, and the individual weightage of these clinical and laboratory variables, the model included the patient's age, gender (male), weight (>75 kg); symptoms of fever, cough, shortness of breath; comorbidities like diabetes, hypertension and coronary artery disease; vitals at admission like respiratory rate (>24/minute), oxygen saturation (<93%), and pulse rate (>100/minute); and finally laboratory variables of lymphocyte (<12%), CRP (>48), ferritin (>800), and LDH (>430) for further analysis as early predictors of mortality at admission. Interestingly, the Forest Plot analysis (Fig. 1) shows heterogeneity with close relations with the overall fixed effect model and the random effects model with $I^2 = 46\%$ and the *p* value of 0.02, with the adjusted OR. Recovered patients were discharged following second and negative RT-PCR tests and their length of stay at the hospital was 12.17 days (6.46–17.87).

Using these 16 clinical and laboratory variables, we created a logistic regression model to determine the early predictors of mortality. The model used a logit function with 30% test data. The model summary includes 26.38% deviance R-Sq, AIC at 117.08, area under receiver operating characteristic (ROC) curve as 0.85 for

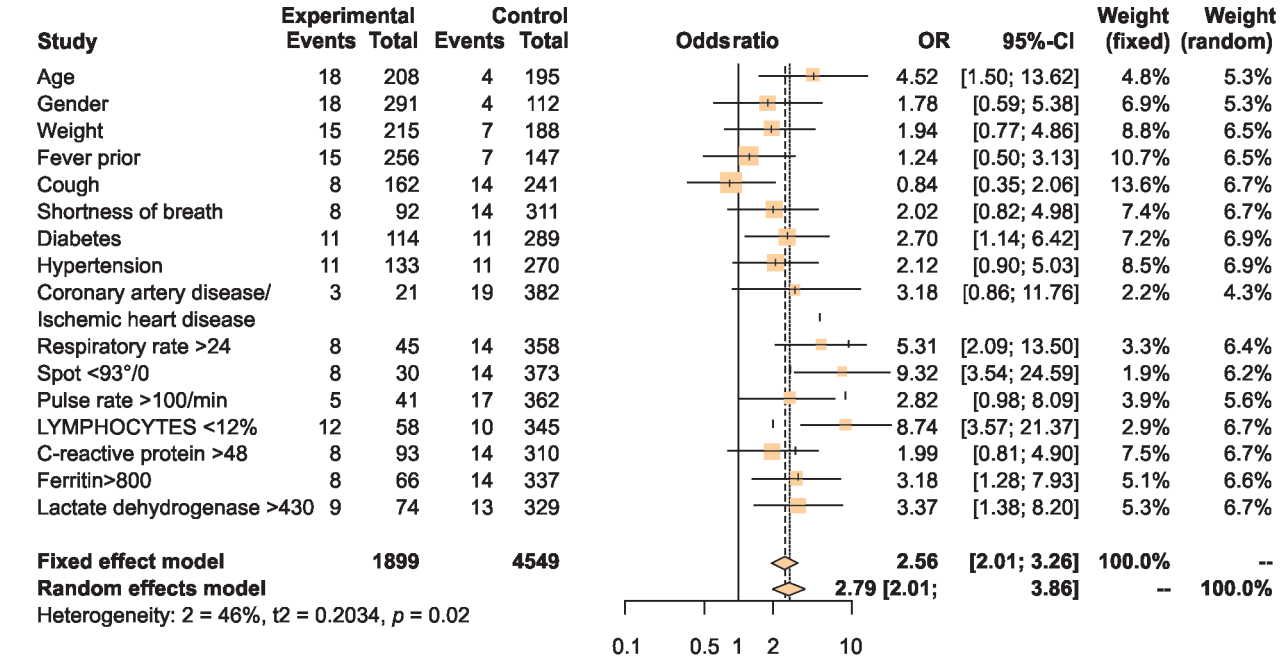

Fig. 1: Multivariate odds ratio of the 16 clinical and laboratory parameters with the forest chart

Table 2: Laboratory values within 24 hours [odds ratio (adjusted)]

Variables	*Mean*	*IQR*	*Threshold*	*Odds ratio*	*95% CI*	*Significance*
Hemoglobin (g%)	12.878	11.5–14.6	<11.5	1.20	0.43–3.36	$p = 0.7429$
Total leukocyte count	9.12	6–12	>8,000	2.18	0.89–5.39	$p = 0.1120$
Lymphocytes	26.235	12–40	<12%	8.74	3.57–21.37	$p < 0.0001$
Neutrophils	66.36	47–85	>85%	5.92	2.42–14.46	$p = 0.0003$
Eosinophils	1.419	0–3	<2%	6.21	0.82–46.86	$p = 0.0860$
Monocytes	6.006	3–9	<4%	2.60	1.08–6.31	$p = 0.0472$
Platelet	281	164–399	<200 K	0.67	0.28–1.61	$p = 0.4022$
Prothrombin time	13.541	11.4–15.6	>12.5	0.92	0.39–2.18	$p = 0.8592$
APTT	38.44	30–46	>38	0.59	0.25–1.43	$p = 0.2729$
INR	1.288	1.1–1.5	>1.3	0.60	0.23–1.59	$p = 0.3342$
Sodium (Na)	138.22	132–143	<135	6.63	2.65–16.59	$p = 0.0002$
Potassium (K)	4.3142	3.5–5	<3.5	0.96	0.12–7.54	$p = 0.9709$
Bilirubin total	0.6	0.2–1.0	>1.0	5.04	1.70–14.99	$p = 0.0081$
SGOT	38.00	19–57	>40	3.30	1.37–7.94	$p = 0.0121$
SGPT	45.65	25–70	>60	1.67	0.70–3.96	$p = 0.2751$
Blood urea	40.24	22–58	>40	6.20	2.55–15.06	$p = 0.0002$
Creatinine	1.459	1.2–1.8	>1.5	2.14	0.75–6.08	$p = 0.1819$
Protein	7.064	6.2–7.8	<6.5	5.52	2.29–13.31	$p = 0.0004$
Albumin	4.355	3.7–5	<3.5	7.80	3.00–20.29	$p = 0.0001$
C-reactive protein	40.27	0–80	>48	1.99	0.81–4.90	$p = 0.1601$
Ferritin	494.5	20–900	>800	3.18	1.28–7.93	$p = 0.0208$
LDH (lactate dehydrogenase)	327.22	171	>430	3.37	1.38–8.20	$p = 0.0129$
D-dimer	18.7	0.5		2.62	0.56–12.33	$p = 0.2601$

train and 0.74 for the test (Fig. 2). Similarly, we developed a 7-node classification and regression tree (Fig. 3) with a similar performance which classifies the step by step and sequential importance of the variables. In the penalized regression with lasso methods, we determined $\Lambda_{(min)}$ as 0.00448065 and $\Lambda_{(1se)}$ as 0.01035088, and their significance incorporated in the modified logistic regression equation. However, owing to the limited data size and lower event rate, the model is not expected to perform better in out of samples.

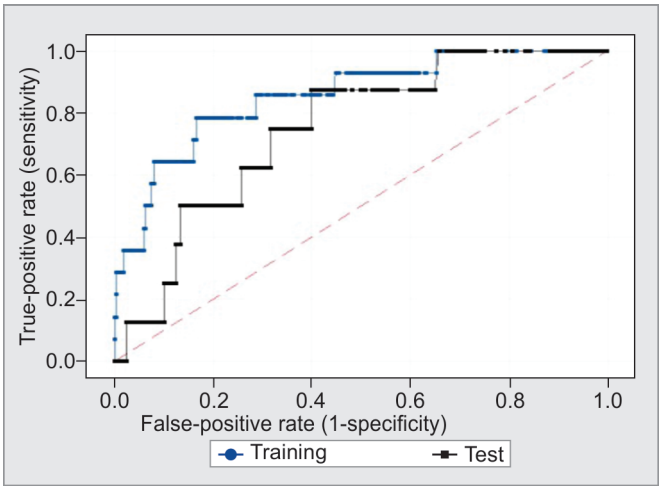

Fig. 2: Receiver operating characteristic curve showing the performance of the logistic regression model with the 16 parameters in the training and test mode

Discussion

The retrospective cohort study of 425 patients admitted at a tertiary care hospital determines the significant early clinical and laboratory variables of mortality and downhill course of events in COVID-19. We determine that individuals with age >47 years, comorbidities like hypertension and diabetes, with oxygen saturation below 93% (with or without supplemental support), tachycardia, and deranged laboratory variables like lymphocytes below 12% and raised ferritin are important early markers or predictors of in-hospital death. Additionally, male gender, weight above 75 kg (corresponding to higher BMIs >30 in Indian population), respiratory distress (shortness of breath) at admission, respiratory rate >24/minute, history of coronary artery diseases, and other laboratory markers like CRP and lactate dehydrogenase are other variables studied in the current model.

Elderly age has emerged as a significant predictor of mortality. However, in the current cohort of 425 patients, we see that the patients above 65 years, the OR (4.034; 95% CI 1.68–9.71; $p = 0.002$) of in-hospital mortality does not vary much with the threshold of age >47 years. This shows that the associated factors like comorbidities—diabetes, hypertension, coronary artery disease, etc., play a vital role in overall mortality.

Using these 16 predictors, the current logistic regression model (on logit) and the CART model (Fig. 3) was developed to identify early predictors of mortality to augment proper therapeutic interventions. From a comparative perspective, we looked at the SOFA score for the prediction of in-hospital mortality at the time of admission. However, the variables of the SOFA score like PaO_2, FiO_2, platelet counts, GCS (almost all patients at admission were conscious), blood pressure, and laboratory variables like bilirubin or creatinine were not statistically significant in the model. This signifies that there are needs for separate models with predictors with higher associations of variables for predicting COVID-19 outcomes at admissions.

The study looked at other significant variables like coagulation factors, hemodynamic derangements at admission, and other pro-inflammatory markers at admission. The coagulation factors (PT, INR, APTT) did not show significant odds for mortality, however,

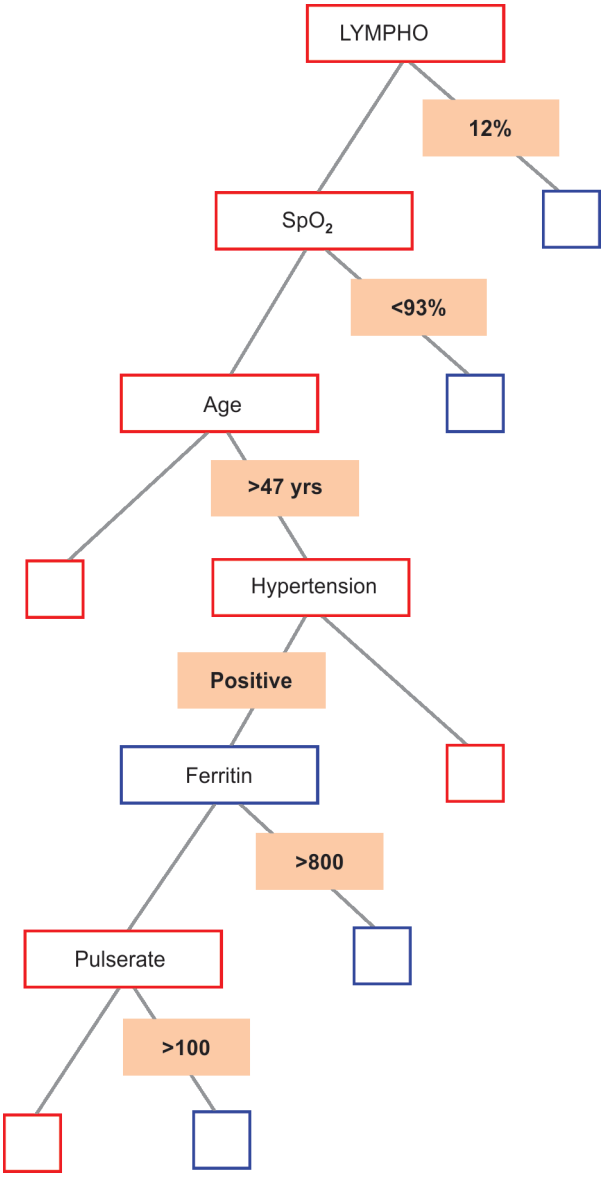

Fig. 3: Seven-node CART classification model with splits. Blue squares mortality events and red squares recovery discharge

it is being studied further for the subsequent changes during the course of the stay at the hospital for predisposing factors like thrombosis and secondary ischemia leading to cardiovascular sequelae or stroke. Furthermore, these variables shall be important in determining the risk of mortality in a low resource setting using the patient's history, comorbidities, vitals, and conventional laboratory parameters.

There are certain limitations of the paper. In the context of volume, we present only the initial cases admitted at our center and hence we acknowledge the need for continuing the study with further data. Second, not all patients had undergone all tests, like the high-end proinflammatory tests at admission, and hence their influence on the overall predicted model for mortality may be underestimated. Third and most importantly, the in-hospital mortality at our center does not reflect the overall COVID-19 mortality in the community or a tertiary care setting.

Conclusion

The major gain of this study is about determining the top 16 clinical and laboratory variables as predictors for in-hospital death and in process of developing an iterative model to predict accurately an individual's risk at the time of admission. It provides the care provider to determine the important risk factors of early and timely intervention. These predictors require further studies and their extensive validation with further in house data and out of sample data from other centers before extensive use.

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Statements

- Retrospective Research—The retrospective research has been approved Institutional Ethics Committee and had been deliberated with over five intensivists treating COVID-19 patients.
- Contributorship Statement—All authors have equally contributed to the research and writing of the paper.
- Competing interests—All authors declare that there are no competing/conflicting interests.
- Funding—There was no available or separate funding for this research.
- Data Sharing Statement—Data cannot be shared with any third party.

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