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An integrated approach-demographic, clinical, laboratory and radiological features in predicting mortality of sars-cov-2 patients in critical care medicine

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Abstract
Background: With the rapidly evolving new variants of SARS-Cov-2, the scientific community is still learning to identify patients with higher risks for effective triaging and better resource allocation as there is no effective specific therapeutics for COVID-19 patients.
Aim: To analyse the demographic, laboratory, clinical and radiological features in COVID -19 patients admitted in critical care medicine and to study their association with survivors and non survivors and to propose a model to predict mortality rate in critically ill COVID -19 patients.
Methods: The data of RT-PCR confirmed COVID-19 patients (age, gender, RR, PR, BP, SpO_2, DM, HTN, WBC, Hb, Platelet, CRP, LDH, D-dimer, Creatinine, Urea, CT Score, lung involvement pattern and distribution) was retrospectively evaluated and compared between survivors and non-survivors.
Results: Among the 91 enrolled patients, 65(71.42%) survived and 26 (28.58%) succumbed to death. In the non-survivors mean age was 61.42±13.24, male 18(69.23%), female 8(30.76%). Backward stepwise logistic regression is used to identify the significant predictors of mortality. These parameters were significant in our Backward logistic regression model: RR(*p*:0.008, OR1.164), spO_2(*p*:0.05, OR:0.928), WBC(*p*:0.001, OR:1.170), D-dimer (*p*: 0.005, OR:0.999), Urea (*p*:0.001, OR:0.916) and CT(*p*:0.000, OR:1.259). The sensitivity of the model is 80.00% (95% confidence interval is [59.30% 93.17%]), specificity is 92.68%. (95% CI is [80.08% 98.46%]). The overall accuracy is 87.88%. (95% CI is [77.51% 94.62%]). The positive predictive value is 86.96%. (95% CI is [68.79% 95.28%]). The negative predictive value is 88.37%. (95% CI is [77.55% 94.36%]).
Conclusion: Involving clinical, laboratory and radiological features has shown to be a good approach in mortality prediction of critically ill COVID-19 patients.

Keywords: D-dimer, creatinine, inflammatory markers, critically ill, COVID-19 mortality, CT score

Introduction
The Corona virus is from a large family of viruses that affects humans, livestock, bats and other wild animals. They can cause major health issues of respiratory system, central nervous system, gastrointestinal system and liver [1, 2]. This pandemic of Corona virus disease 2019 (COVID-19) caused by SARS-CoV-2 was first observed in Wuhan (China) in December 2019. Later it became a pandemic infecting millions of people worldwide. By January 30 2020, the WHO had to declare it a Global Sanitary Emergency because of its high contagiousness leading to a huge burden on the health care system [3, 4]. There were 23.1 million COVID-19 cases reported from South East Asia till date, out of which 86% are from India with confirmed death cases of 52 hundred thousand [5]. About one-third of the hospitalized patients eventually needed Critical Care admission and they have shown to develop Acute Respiratory Distress Syndrome (ARDS), multiple organ dysfunction, cardiac failure and pulmonary embolism [4].
It was noticed that nearly 14% of patients with COVID-19 associated pneumonia usually get severe and only 5% need critical care admission [5]. The mortality rate of COVID-19 patients in the ICU is very high ranging from 6% to 86% when compared to that of other causes of viral pneumonia that required intensive care [6].
With the arrival of new variants of Corona virus, the situation is rapidly evolving. Death rates show variations between countries depending on various risk factors [7]. Because of the poor health care system, low awareness of disease prevention, lack of health care professionals and complex medical gadgets and also inadequate critical care units, this COVID period has been detrimental in low and

middle income countries [8]. The scientific community is still learning to identify patients with higher risk for proper triaging and better resource allocation since no proven specific therapeutics are available as well as the disease is highly transmissible. A good understanding of the patterns of symptoms, signs, co-morbidities, epidemiology and other risk factors to find the association with severity of illness leading to death of the patient can provide a better outcome in COVID-19 cases [9]. By utilizing the basic information of COVID-19 patients, regularly monitored parameters, clinical features to define severity of covid infection, co-morbidities present in them and easily available and accessible investigations from Laboratory and Radiology departments of our hospital, we tried to assess adverse outcomes in them. After analyzing the risk factors, we proposed a model to predict mortality rate in critically ill COVID-19 patients so that our hospital's risk assessment and clinical management would be improved for aggressive treatment and intervention in COVID-19 patients.

Materials and Methods

This is a retrospective observational study done from May to July 2021 in the department of Biochemistry and Critical Care Medicine of a tertiary care hospital after obtaining Institutional Ethical clearance from Ethics Committee -1 with number: YEC-1/2020/085 on 22-12-2020. Written informed consent was waived off since it's a retrospective design. Ethical standards were maintained throughout the study. The data was stored in a private laptop which was password protected and only the principal investigator had access to the information. Strict confidentiality of the information collected was maintained. Trial Registration No: CTRI/2020/12/030070.

A total of 91 RT-PCR confirmed COVID-19 patients with a definite outcome (discharge/death) admitted in Critical Care Medicine were enrolled in this study. Case details were retrieved from institution's registry of COVID-19 patients including the outcome. Data collected were from the day of admission to critical care medicine which included: Demographic details – age, gender Clinical data-1) vitals: respiratory rate per minute (RR), blood pressure (BP, mmHg), oxygen saturation (SpO2), Pulse rate (PR) 2) co morbidities: hypertension (HTN), diabetes mellitus (DM) Laboratory tests - white blood cell count (WBC), haemoglobin (Hb), platelet count, lactate dehydrogenase (LDH), C-reactive protein (CRP), D-dimer, creatinine and urea. Laboratory tests for LDH, CRP were performed by immunoturbidimetry. *In vitros* 5600 Integrated system. D-dimer was estimated in Minividas instrument by Enzyme Linked Fluorescent Assay technique. Radiologic findings- CT score (computed tomography), predominant pattern of lung involvement and any additional findings like pleural effusion and parenchymal band were included. CT scoring was done by reviewing all the five lobes of lungs [10]. Considering and evaluating the presence of GGO and consolidation of lung, each lobe was given scores between 0 and 5. Score 0: no involvement, 1: <5%, 2: 6-25%, 3: 26- 50%, 4: 51-75%, 5: >76%. Total score ranges from 0-25 with maximum of 5 points to each lobe.

Statistical Analysis

Data entered in excel spread sheet were analysed using IBM SPSS Statistics for Windows, Version 23. Continuous variables are reported as means with standard deviation (SD) while categorical variables as percentage and counts. The two sample t tests and chi square test are used as tests of significance. P value less than 0.05 is considered as significant. The logistic regression is used to build the predictive model for mortality rate. The specificity, sensitivity and accuracy are used to assess model validity

Results

In our study, 91 RT-PCR confirmed COVID-19 patients admitted in Critical care Medicine were analyzed. Out of these, 58 (63.73%) were male and 33(36.26%) were females with a mean age of 57.57±14.679 years. Among the 65 (71.42%) survived, 40 (61.53%) were males and 25(38.46%) were females. 26 (28.57%) patients succumbed to death of which 18 (69.25%) males and 8(30.76%) females were present. There was no significant difference noticed in the mortality rates between male and female patients. The mean age of non survivors was 5.39 years more than who survived. But there was no significant difference noted in terms of age between both the categories. Table 1 summarizes the baseline characteristics of the 91 patients.

While analyzing the vitals of these patients, respiratory rate (RR), spO_2 and systolic blood pressure (SBP) were found to be significant while comparing survivors and non survivors. A higher diastolic blood pressure (DBP) was commonly found in non survivors, even though not significant. Pulse rate (PR) showed no significant difference among both the groups. Table 2 gives the details of co-morbidity in these patients.

In the Laboratory data, hemoglobin (Hb) and platelet count were comparatively lower in non survivors. White blood cell (WBC), lactate dehydrogenase (LDH), D-dimer, urea and creatinine have shown to be statistically significant when comparing survivors and non survivors. Comparatively lower level of C-reactive protein (CRP) was seen among the survived category (Table 3).

Radiological features on comparison have shown that multifocal ground glass opacity was the predominant pattern in the category of non survivors. Whereas, ground glass opacity with consolidation was more common in survivors. Other additional findings of CT scan were the presence of pleural effusion and fibrotic changes which were statistically significant while comparing survivors with non survivors (*p*: 0.0421) (Table 4).

With the help of backward logistic regression analysis incorporating the significant variables, we proposed a model to identify risk factors of mortality in the critically ill patients. . The parameters significant in our Backward logistic regression model are: RR (*p:*0.008, OR1.164), spO_2 (*p*:0.05, OR:0.928), WBC (*p*:0.001, OR:1.170), D-dimer(*p*: 0.005, OR:0.999), Urea (*p*:0.001, OR:0.916) and CT(*p*:0.000, OR:1.259). The Nagel kerke for the model is 74.3%. The sensitivity of the model is 80.00% (95% confidence interval is [59.30% 93.17%]), specificity is 92.68%. (95% CI is [80.08% 98.46%]). The overall accuracy is 87.88%. (95% CI is [77.51% 94.62%]). The positive predictive value is 86.96%. (95% CI is [68.79% 95.28%]). The negative predictive value is 88.37%. (95% CI is [77.55% 94.36%]). Figure: 1 shows the logistic regression model of mortality predictors

Table 1: Baseline characteristics of patients

Variable	All patients	Survivors	Non survivors	p-value
Male	58(63.73%)	40(61.53%)	18(69.25%)	0.23
Female	33(36.26%)	25(38.46%)	8(30.76%)	
Age (years)	57.57±14.679	56.03±15.035	61.42±13.243	0.11

Table 2: Details of underlying diseases of patients and their association to mortality

Co-morbidities		All patients	Survivors	Non survivors	p value
Hypertension	Present	36(39.6%)	25(69.4%)	11(30.6%)	0.919
	Not present	55(60.4%)	40(72.7%)	15(27.3%)	
Diabetes mellitus	present	31(34.4%)	19(61.3%)	12(38.7%)	0.213
	Not present	59(65.6%)	45(76.3%)	14(23.7%)	

Table 3: Clinical data and CT scoring of patients according to survival status

Variables	All patients			Survivors			Non-survivors			P value
	N	Mean	Std. deviation	N	Mean	Std. deviation	N	Mean	Std. deviation	
Vitals										
RR	81	26.30	9.431	55	24.40	8.37	26	30.31	10.376	0.008
SpO_2	88	87.80	11.442	62	89.32	10.302	26	84.15	13.308	0.053
SBP	86	128.95	27.569	60	124.83	23.106	26	138.46	34.490	0.034
DBP	86	79.07	13.602	60	77.50	12.299	26	82.69	15.889	0.104
PR	86	96.90	19.709	60	98.03	18.809	26	94.27	21.807	0.419
Laboratory variables										
Hb	90	12.13	2.409	64	12.241	2.3892	26	11.862	2.486	0.502
Platelet	90	260.18	117.099	64	262.41	114.716	26	254.69	124.934	0.779
WBC	90	10.94	5.777	64	9.650	4.900	26	14.1469	6.586	0.001
LDH	76	422.66	208.577	51	384.24	124.210	25	501.04	307.039	0.021
CRP	90	78.12	65.932	64	71.014	65.979	26	95.613	63.700	0.109
D-dimer	90	1141.75	1283.892	64	910.906	1104.5841	26	1710.00	1523.587	0.007
Creatinine	91	1.74	2.9313	65	1.357	1.7403	26	2.712	4.670	0.046
Urea	91	56.44	51.978	65	40.92	19.753	26	95.23	80.848	0.000
Radiological features										
CT score	91	16.62	4.024	65	15.63	3.818	26	19.08	3.486	0.000

Reported as mean with standard deviation (std. deviation). RR= respiratory rate, SBP= systolic blood pressure, DBP= diastolic blood pressure, PR= pulse rate, Hb= hemoglobin, WBC= white blood cell, LDH= lactate dehydrogenase, CRP= C- reactive protein

Table 4: Radiological findings and association with survival status

Radiological features		All patients	Survivors	Non survivors	p-value
Pattern	GGO and Consolidation	32(40.90%)	24(43.63%)	8(30.76%)	0.3884
	Multifocal GGO	49(59.03%)	31(56.36%)	18(69.76%)	
Additional features	No additional finding	76(83.51%)	58(89.23%)	18(69.23%)	0.0421
	Pleural effusion	10(10.98%)	4(6.15%)	6(23.07%)	
	Fibrotic changes	5(5.49%)	3(4.61%)	2(7.69%)	

Discussion

COVID-19 has become a great challenge to the whole world causing a significant impact on all aspects of life. Therefore, risk factors contributing to the development of disease severity have to be traced for optimizing hospital resources reallocation and proper public health recommendations. The main finding from our study is that, it helped to understand the importance for an integrated approach by combining different departments for prediction of outcome for this disease.

While analyzing the baseline characteristics of patients, many studies have shown that Male gender has a higher rate of hospitalization, ICU admission, other interventions and also death [11]. Still no significant difference was noticed in ICU mortality on gender basis in our study. But advanced age was more common in patients who succumbed to this disease. Even though, we could not associate age to be a mortality predictor, in previously published studies, age was a risk factor for mortality which may be due to the presence of underlying diseases and co-morbidities in them [12]. Also, older age was likely to develop complications due to the weak immune response [13].

On observing the vital signs, elevated RR, elevated SBP and decreased pulse oxygen saturation were significantly associated with mortality in critical care department. The lung's ability to oxygenate blood is lowered due to the damaged alveoli and edema, resulting in respiratory failure and ultimately death [14, 15]. Thus, these factors require a more vigilant monitoring.

Diabetes and Hypertension were shown to be the most common co morbidities in COVID-19 patients [16, 17]. Majority of the patients enrolled in this study were diabetic and hypertensive. Many studies have shown DM and HTN to have a higher risk of mortality in COVID-19 which may be due to the role of ACE2. Expression of ACE2 is substantially increased in patients with DM and those who are treated with ACE inhibitors and ARBs. Consequently, the increased expression of ACE2 would facilitate infection with COVID-19 [18]. Our model could establish DM as the predictor for mortality in these patients but not hypertension. A recent meta-analysis have shown that in severely ill COVID-19 patients, the Hb values are essentially reduced compared to those with milder forms [19]. In our study, the mean value of Hb and Platelet count were comparatively lower in non-survivors. In anemia, transport of oxygen to several organs get disrupted leading to hypoxia that ultimately results in multiple organ dysfunctions [20]. Further evidences from previous studies show that the inflammatory cytokine storm and lymphopenia were observed much higher in severe COVID-19 patients and has an association with disease severity. As a result of reduction of CD3+, CD4+ and CD8+ T cells, there is also a rise in CRP, in severely ill patients [21]. In this study, CRP level is seen higher among non-survivors

Among the Laboratory variables, WBC, LDH, D-dimer, creatinine and urea were shown to be significant in survivors and non-survivors. Literature suggests that leukocytosis, neutrophilia and lymphopenia are risk factors that help in predicting the outcomes of these patients [22]. LDH is considered as an independent risk factor for severely ill COVID patients. It usually gets elevated in cell death and injury. It is considered to be an indicator of poor immune response of the host and therefore is helpful in early recognition of lung injury [23].

Recently, in US and China, clinical as well as autopsy reports of COVID-19 patients have shown increased clotting and DIC. An increase in D-dimer and a low level in platelet can have poor prognosis. Since the innate immunity and coagulation pathways are closely linked, when the SARS-Cov-2 targets ACE2, there is angiotensin dysregulation, innate and adaptive immunity pathway activation as well as hyper coagulation that ends up in organ damage like acute kidney injury. So, monitoring of kidney function tests also prove helpful in early detection of poor outcome [24].

Respiratory illness in COVID-19 usually manifests as pneumonia. Usually, CT findings would be seen even before the onset of symptoms and it can provide a clear insight into the disease course [25]. Typical appearance of COVID-19 pneumonia on chest CT is ground glass opacities or areas of consolidation with lower lung distribution. Expansion of lung lesions is an alarm for disease worsening [26, 27]. Our study reported that CT scores are significantly different in survivors and non-survivors. Several other studies also have found out the correlation of the extent of lung

involvement in CT imaging and the need for mechanical ventilation [28], it is a predictor of mortality in this model.

To reduce mortality rate, it is critical to identify factors associated with greater complications in population. If we have a healthy collaboration and teamwork among different departments in the hospital, it may have a positive impact on quality of decision making and can help to deliver high standard care which eventually minimize the strain on healthcare system.

Conclusion

In this study, we found that the best approach to predict mortality in critically ill patients would be by integrating clinical, laboratory and radiological features. And we proposed a model by combining RR, SpO_2, DM, WBC, urea and CT scoring. We hope that this model would help Physicians in confident decision making in critically ill patients and providing them a better care. Further studies with larger sample, more variables and complete follow up is needed to confirm impact of COVID-19 and formulate a model that can be used by physicians in their daily practice.

Limitations

It was a single centre study with small sample size. Also we could not gather information on severity of co morbidities. Prior treatment received outside hospital was also not known. This model is applicable only in a tertiary care set up.

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Conflicts of Interest

The authors declare no conflicts of interest

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