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A Retrospective Study of Hospitalized COVID-19 Patients using the CIRC (COVID-19 Inpatient Risk Calculator) Score to Predict Mortality and Severe Disease Progression

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Abstract **Original Research Article**

The acute crisis with the coronavirus disease of 2019 (COVID-19) caused by the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) is the largest biomedical catastrophe of our lifetimes. The COVID-19 inpatient risk calculator (CIRC) scoring system was used to predict mortality in hospitalized patients so that it has applications in future outbreaks of the disease. ***Methods:*** The retrospective study included 200 adult patients, over the age of 18 years, who were admitted in a tertiary care center. Clinical and laboratory features were collected from the medical records and entered into the COVID-19 inpatient risk calculator. Predictability of the CIRC scoring system was analyzed using linear regression analysis. ***Result:*** There was a statistically significant difference between the means of the CIRC scores on days 2, 4 and 7 of admission, in subjects with different outcomes. The values of D-dimer, C-reactive protein and ferritin in the subjects showed a statistically significant association with the respective CIRC scores on days 2, 4 and 7. The areas under the curve for days 2, 4 and 7 were all greater than 0.9, indicating the high predictability of the CIRC scoring system, indicating that the higher is the CIRC score, higher is the possibility of mortality. ***Conclusion*:** In this large-scale retrospective study of COVID-19 patients in a tertiary care setting, we confirm the high predictive value of the CIRC scoring system in assessing the possible progression of the infection into severe disease and mortality. The application of CIRC scores may be confidently used in determining the probability of the patient progressing into severe disease and or death, within 7 days of arrival to the hospital.

Keywords: Covid 19, CIRC score, in-patient, inflammatory markers.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is defined as illness caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV), which was first identified amidst an outbreak of respiratory illness cases in Wuhan City, Hubei Province, China [1]. It was initially reported to the WHO on December 31st, 2019. On January 30st, 2020, the WHO declared the COVID-19 outbreak a global health emergency. On March 11th, 2020, the WHO declared COVID-19 a global pandemic, its first such designation since declaring H1N1 influenza a pandemic in 2009 [2]. The illness caused by SARS-CoV-2 was termed COVID-19 by the WHO, the acronym derived from "coronavirus disease 2019" [3].

The acute crisis with the coronavirus disease of 2019 (COVID-19) caused by the novel coronavirus Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) is the largest biomedical catastrophe of our lifetimes.

In India, the first case of COVID-19 was reported in Thrissur, Kerala, on 27th January in a 20-year old lady with a travel history to China [3]. The rapid movement of people from the global epicenters and between cities facilitated COVID-19 transmission in India, and infection started spreading to the major cities of India. In response to the increase in cases and to break the transmission chain, active government interventions like international travel suspension, contact tracing, containment, and mitigation strategies were initiated.

However, despite the proactive measures, the infection continued to rise in different parts of the country and the confirmed cases reached 4,25,86,544 as of February 12, 2022 [2].

From prehistory, we have known that many viruses that infect us are long lived, recurring with a frequency that is often unknown and indeed unexpected. When the pandemic began in the early months of 2020, almost 2 years ago, no one thought that it would continue as long as this. Vaccines would be found that would ensure most populations would become resistant to severe disease. India recorded a staggering number of cases in the second wave [3-5].

Looking into the near future, although COVID-19 is no longer a pandemic, controlling infection is likely to be a problem in the future as well. Since its initial occurrence, India has been plagued by a variety of different sub-variants of SARS-CoV-2. Since December 2023, we have seen an increasing number of cases affected by the JN.1 sub-variant. Public health interventions will be directed towards social distancing and improving hygienic practices. Testing, contact tracing, isolation of infected, and precautionary self-isolation of contacts is critical in reducing the number of new cases.

COVID-19 is a tricky illness in that some patients with COVID-19 worsen several days after initially developing symptoms, in a pattern uncharacteristic of other viral illnesses. Overall, nearly 5% of patients returned within 72 hours and needed admission to the hospital. For context, this rate may be 5-times higher than that described for all ED patients. An additional 3.5% of patients needed admission within 1 week [7]. The fact that patients were hospitalized on their second visit indicates that their illness and symptoms progressed to the point where they needed a higher level of support, such as oxygen or therapeutic medications, than they could receive at home [8].

Chronic comorbidities, complications, and demographic variables including acute kidney injury, COPD, diabetes, hypertension, CVD, cancer, increased D-dimer, male gender, older age, current smoker, and obesity are clinical risk factors for a fatal outcome associated with coronavirus.

The COVID Inpatient Risk Calculator (CIRC) uses factors on admission to the hospital to predict the likelihood that a patient admitted with COVID-19 will progress to severe disease.

MATERIALS AND METHODS

The study was conducted on patients admitted at Apollo Hospitals, Sheshadripuram. All of the patients with RT-PCR positive statuses for COVID-19 admitted between February 2021 to May 2021 who fulfilled the inclusion and exclusion criteria were included in the study. History of the patient was noted in terms of admission from a nursing home, respiratory symptoms, gastrointestinal symptoms and constitutional symptoms. Examination findings of temperature, respiratory rate and pulse rate were noted. At the time of admission, basic information was collected- such as the patients' demographics (age, sex, BMI), medical and social history, and pre-existing comorbidities. The investigations done were- albumin, GFR, WBC, CRP, troponin, absolute lymphocyte count, d-dimer and ferritin. Charlson comorbidity index was calculated separately for each patient.

INCLUSION CRITERIA

1. Adults> 18 years
2. Constitutional symptoms- Loss of smell or taste.
3. Vitals- Respiratory rate. temperature, RT-PCR COVID-19 positive status.
4. The availability of the relevant investigations required to calculate CIRC scores.

EXCLUSION CRITERIA

Patients not having the necessary investigations done in order to calculate their CIRC scores.

STATISTICAL ANALYSIS

The data was entered into the Covid 19 inpatient risk calculator. The data was then compiled into Microsoft Excel Sheets. The qualitative variables were expressed in terms of proportions and the difference between two proportions were tested by Chi square test. The quantitative variables were expressed in terms of percentage or expressed as mean and standard deviation. The difference between two means was tested using the Student t-test. For all analyses P value < 0.05 were considered statistically significant.

The compiled data was analyzed for correlation using Pearson's correlation coefficient. Predictability was assessed using linear regression analysis.

DISCUSSION

The COVID-19 inpatient risk calculator (CIRC) scoring system, developed by John Hopkins scientists, uses factors on admission to the hospital to predict the likelihood that the patient will progress to severe disease (requiring NIV support, HFNC, invasive ventilator support, ECMO, vasopressor support), or death within 7 days of arrival [10]. This retrospective study attempts to determine the applicability and accuracy of the scoring system. It predominantly includes patients of Indian origin, of ages 20 to 90, and of a different demographic than earlier studies, making it the first large scale study of its kind.

The current study was one of its kind collecting large retrospective data in a tertiary care center which

treated a significant number of patients burdening the metropolitan city of Bangalore. It used the hitherto unknown CIRC scoring system to assess morbidity and mortality.

The study consisted of 70.5% males and 29.5% females. The prime inclusion criteria was the evidence of COVID-19 infection in patients from September 2020 to May 2021. The study included patients from all age groups; the majority of the population included in this study was between the ages of 61 to 70 years. Of the comorbidities taken into account, the most frequently occurring one was type 2 diabetes mellitus, followed by heart disease. All of the blood parameters used to calculate the CIRC score in this study were within 48 hours of admission, and vital signs were an average of the first 24 hours after admission.

Sex

Our study consisted of predominantly male patients. Biological differences in the immune systems between men and women exist, which may impact our ability to fight an infection including SARS-2-CoV-2. Generally, females are more resistant to infections than men, and this is possibly mediated by several factors including sex hormones and the high expression of coronavirus receptors (ACE 2) in men; but also lifestyle, such as higher levels of smoking and drinking among men as compared to women. Additionally, women have a more responsible attitude towards the COVID-19 pandemic than men. This may reversibly affect the undertaking of preventive measures such as frequent hand washing, wearing face masks, and staying at home on order.

Age

The study consisted of patients from all age groups. The majority of subjects were in the age group of more than 50 years. Besides the impact of genetics and underlying comorbidities, aging causes numerous physiological changes within the immune system. These factors cause the progressive decline in the immune system's ability to fight latent and novel infections, and to mount adequate responses to vaccines therefore affecting individual's susceptibility to coronavirus infections but also determine the disease course and clinical outcomes.

Comorbidities

Comorbidities increase the chances of infection. Based on current information and clinical expertise, the elderly- especially those in long-term care facilities- and people of any age with serious underlying medical conditions are at a greater risk of getting COVID-19. The elderly, a vulnerable population, with chronic health conditions such as diabetes and cardiovascular or lung disease are not only at a higher risk of developing severe illness, but also at an increased risk of death if they become ill. People with underlying uncontrolled medical conditions such as diabetes, hypertension, lung, liver, and kidney disease, cancer patients on chemotherapy, smokers, transplant recipients, and patients taking steroids chronically are at increased risk of COVID-19 infection.

Multiple comorbidities are associated with the severity of COVID-19 disease progression. Many of the poorer outcomes for COVID-19 have been related to cardiovascular comorbid conditions. However, this may be a direct result of the cardiovascular condition itself or attributed to other comorbidities along with a cardiovascular condition. Patients with type 2 diabetes were also more likely to have increased severity of COVID-19. It was noted that poor blood glucose control resulted in a substantially increased risk of complications and death.

Symptoms

COVID-19 patients, as depicted in Fig 1, showed fever (88.8%) as the most common symptom, followed by dry cough (68%) and fatigue (33%) [10]. Other symptoms noted were productive cough (28.5%), SOB (17%), muscle pain (14.4%), sore throat (11.4%), and headache (10.2%) [10]. The least common symptoms were diarrhea (4.4%), nausea and vomiting (4.1%), rhinorrhea (3.2%), abdominal pain (0.16%), and chest pain (0.11%).

Inflammatory markers-

CRP

C-reactive protein is an acute-phase inflammatory protein produced by the liver and regulated at the transcriptional level by cytokines IL-6 and IL-1. It is an important index for diagnosing and evaluating severe pulmonary infectious diseases. SARS-CoV-2 shares similar clinical features with Middle East respiratory syndrome coronavirus and in patients with severe Middle East respiratory syndrome coronavirus pneumonia. An increasing C-reactive protein level is related to clinical deterioration.

D-Dimer

D-Dimer is a fibrinogen degradation product. Hyperinflammation and hypoxia-induced injury caused by SARS CoV-2 infection could cause the dysfunction of endothelial cells and stimulate thrombosis and elevation of D-Dimer. Elevated D-Dimer could cause the formation of pulmonary microthrombi, deep venous thrombosis and disseminated intravascular coagulopathy which are associated with poor prognosis.

Ferritin

Serum ferritin is an acute-phase protein, which can be used as a prognostic marker for tissue damage or acute infections. Patients with COVID-19 in the severe group had a higher level of serum ferritin than those in the non-severe group. It was noted that a higher serum ferritin level was associated with mortality in COVID-19

patients. Though the pathophysiological background responsible for the association of hyperferritinemia and disease severity in patients with COVID-19 is not clearly grasped, it is suggested that hyperferritinemia in COVID-19 patients is most likely due to the cytokine storm and a secondary hemophagocytic lymphohistiocytosis.

RESULT

Data Analysis and Interpretation

Data was entered into Microsoft Excel (Windows 7; Version 2007) and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 20.0; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequencies and percentages were calculated for categorical variables. Comparison between males and females were analyzed using Chi-Square test and unpaired T-test respectively for categorical and continuous variables. In this study, receiver operating characteristic (ROC) curve analysis was employed to determine optimal cutoff values. Pearson's S correlation coefficient was calculated between various quantitative variables in the study. Bar charts and pie charts were used for visual representation of the analyzed data. The level of significance was set to 0.05.

Table 1: Distribution of study subjects according to the gender (N = 200)

Gender	No.	Percent
Male	141	70.5
Female	59	29.5

Among the 200 subjects studied, 141 (70.5%) were male, and 59 (29.5%) were female.

Table 2: Distribution of study subjects according to the age (N=200)

Age (Years)	No.	Percent
≤ 30	**10**	**5.0**
31-40	**26**	**13.0**
41-50	**38**	**19.0**
51-60	**46**	**23.0**
61-70	**57**	**28.5**
>70	**23**	**11.5**
Mean (SD)	55.24 (14.41)	
Range	22-90	

The study population had different age groups. The majority of subjects was found to be in the age group of 61-70 years of age. The minority was <30 years of age. The mean age was 55.24.

Table 3: Distribution of Study Subjects according to the comorbidities (N=200)

Comorbidities	No.	Percent
Diabetes with Complication	30	15.0
Diabetes without Complication	81	40.5
Total Diabetes mellitus	111	55.5
Hypertension	20	10.0
Renal Disease	19	9.5
Chronic Pulmonary Disease	17	8.5
Cerebrovascular disease	6	3.0
Congestive Cardiac Failure	5	2.5
Hemiplegia/Paraplegia	2	1.0
Dementia	2	1.0
Peripheral Vascular Disease	1	0.5
Rheumatological Disease	1	0.5
Peptic Ulcer	1	0.5
Liver Disease	1	0.5
AIDS	-	-
Malignancy	1	0.5

Among the subjects studied, and the comorbidities taken into account, the most frequently occurring comorbidity was found to be type 2 diabetes mellitus, which was found in 111 (55.5%) of the subjects, of which 30 (15.0%) were with complications and 81 (40.5%) were without. While, on the other end of the

spectrum, only 1 (0.5%) of the subjects had peripheral vascular disease, a rheumatological disease, peptic ulcer disease, liver disease and malignancies, each. The incidence of a history of myocardial infarction, renal disease, chronic pulmonary disease and cerebrovascular disease were in 20 (10%), 19 (9.5%), 17 (8.5%), 6 (3%) of the subjects respectively. The occurrence of CCF, hemiplegia/ paraplegia and dementia was found to be in 5 (2.5%), 2 (1%) and 2 (1%) of the subjects respectively. None of the subjects studied had AIDS.

Table 4: Distribution of study subjects according to the outcome (N=200)

Outcome	No.	Percent
Death	37	18.5
Discharged	163	81.5
With Oxygen	16	8.0
Without Oxygen	147	73.5

Of the 200 subjects studied, 163 (81.5%) were discharged, out of which 147 (73.5%) were discharged without oxygen, and 16 (8%) were discharged with oxygen. 37 (18.5%) of the subjects studied, died.

Table 5: Association between CIRC score and outcome (N=200)

CIRC Mean (SD)	Death	Discharged with Oxygen	Discharged without Oxygen	P Value
Day 2	22.97 (14.96)	9.84 (6.96)	6.93 (7.71)	<0.001*
Day 4	32.18 (18.09)	13.92 (9.51)	9.70 (10.26)	<0.001*
Day 7	36.19 (18.93)	15.54 (10.58)	10.70 (11.30)	<0.001*
ANOVA Test, P Value *Significant				

There was a statistically significant difference between the means of the CIRC scores on days 2, 4 and 7 of admission, in subjects with different outcomes.

Table 6: Association between Outcome and Lab Parameters (N=200)

Mean (SD)	Death	Discharged with Oxygen	Discharged without Oxygen	P Value
D-Dimer	3.13 (4.22)	1.75 (2.37)	0.747 (1.000)	<0.001*
Ferritin	794.20 (609.02)	473.97 (328.05)	294.68 (320.13)	<0.001*
CRP	122.69 (62.33)	53.30 (39.53)	33.06 (39.76)	<0.001*
HB	12.21 (2.22)	13.01 (1.58)	13.40 (1.58)	
ANOVA Test, P Value *Significant				

Statistically significant association was found between the means of values of D-dimer, ferritin, C-reactive protein and hemoglobin in subjects with different outcomes.

Table 7: Correlation between CIRC Score and Lab Parameters (N=200)

	Day 2	Day 4	Day 7
HB	-0.018	-0.047	-0.070
P Value	0.798	0.504	0.322
D-Dimer	0.323	0.343	0.351
P Value	<0.001*	<0.001*	<0.001*
CRP	0.507	0.528	0.538
P Value	<0.001*	<0.001*	<0.001*
Ferritin	0.461	0.491	0.503
P Value	<0.001*	<0.001*	<0.001*

The values of D-dimer, C-reactive protein and ferritin in the subjects showed a statistically significant association with the respective CIRC scores on days 2, 4 and 7. However, the hemoglobin values showed no such statistically significant correlation.

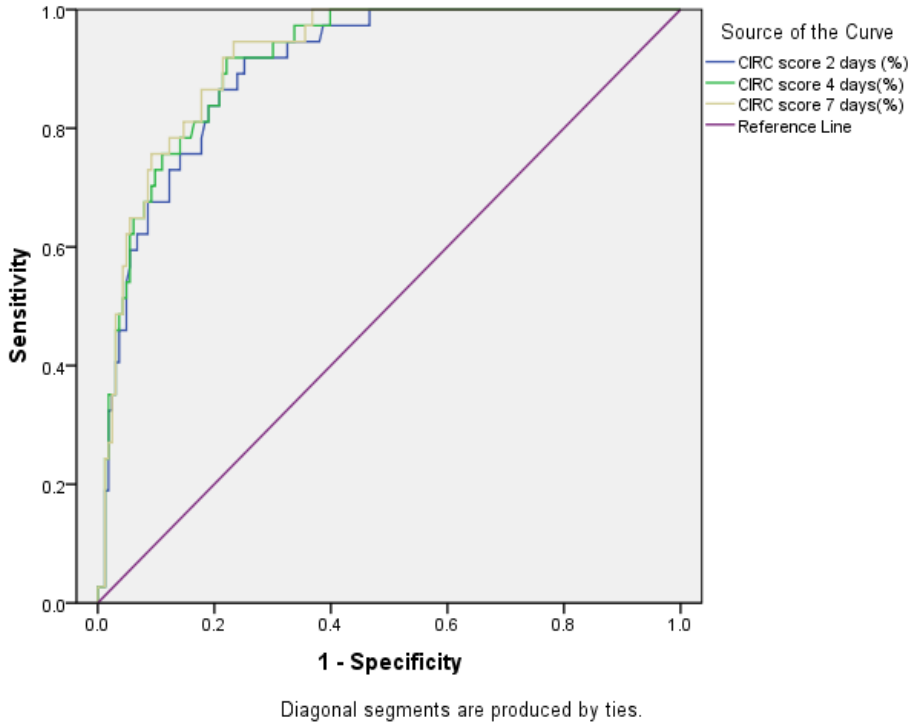

Table 8: ROC curve and area under the curve

Area Under the Curve					
Test Result Variable(s)	**Area**	**Std. Error[a]**	**Asymptotic Sig.[b]**	**Asymptotic 95% Confidence Interval**	
				Lower Bound	**Upper Bound**
CIRC score 2 days (%)	0.902	0.023	0.000	0.856	0.948
CIRC score 4 days(%)	0.913	0.021	0.000	0.871	0.955
CIRC score 7 days(%)	0.919	0.020	0.000	0.879	0.959

Area under the curve ranges from 0 to 1, where a higher number indicates a higher prediction. The areas under the curve for days 2, 4 and 7 are all greater than 0.9, indicating the high predictability of the CIRC scoring system. This indicates that the higher the CIRC score is, the higher is the possibility of mortality.

The cutoff values of the CIRC scores for days 2, 4 and 7 were 5.2, 8.45 and 10.18 respectively, as indicators of mortality; and were 4.76, 6.37 and 6.74 respectively, indicating the necessity for oxygen supplementation. The average cutoff for CIRC scores indicating mortality was found to be 7.94, and as an indicator for the necessity for oxygen supplementation was observed to be 5.95.

CONCLUSION

COVID-19 is a tricky infection with many complexities involved in its progression. It's very difficult to predict when the patient may progress to morbid states, or even mortality. Inflammatory markers like CRP, D-Dimer and ferritin, as well as CT scans of the thorax may give us some insight into the advancement of the disease, but are also highly unpredictable, and are only vague indicators, and not objective proof that may be used uniformly across care setups, and in multiple demographics.

The CIRC score, as demonstrated, is easily calculable, and has a progressive approach to assessing the worsening of patients' conditions. Our study had predominantly male elderly patients. The study indicated that the higher the CIRC score is, the higher is the possibility of mortality. The average cutoff (across 7 days) for the CIRC scores indicating mortality was found to be 7.94, and as an indicator for the necessity for oxygen supplementation was observed to be 5.95.

In our retrospective study, we confirm the high predictive value of the CIRC scoring system in assessing the possible progression of the infection into severe disease and mortality. The COVID-19 Inpatient Risk Calculator scores may be used with confidence in determining the probability of the patient progressing into severe disease and or death, within 7 days of arrival to the hospital.

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