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Original Article

Outcome Analysis of COVID 19 Patients Using ISARIC/WHO 4C Mortality Score in COVID Unit of Bangladesh Institute of Tropical and Infectious Diseases (BITID)

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Abstract

Background: *ISARIC/WHO 4C Mortality Score is a risk stratification tool that helps predict the in-hospital mortality of COVID-19 patients. However, this tool was developed and validated in a British population, and thus, the external validation of this tool in local populations is important. This study aimed to analyze the outcome of COVID 19 patients using 4C Mortality Score in the COVID unit of Bangladesh Institute of Tropical and Infectious Diseases (BITID) Chattogram.*

Materials and methods: *This hospital-based prospective observational study included 115 admitted adult patients with a confirmed diagnosis of COVID-19 by RT-PCR method. Patients under age of 18 and those with missing data in any of the components of ISARIC 4C score were excluded from study. Relevant sociodemographic and clinical data were collected, and the 4C mortality score was calculated at admission. Outcome measures were need for oxygen therapy, mode of oxygen therapy, and in-hospital mortality.*

Results: *Mean age of the patients was 50.6±18.4 years in the present study and 47.8% were male. The median ISARIC 4C mortality score was 7.0 (Interquartile range: 3-12) and at the time of admission 31 (27%), 34 (29.6%), 33 (28.7%), and 17 (14.8%) patients were in low, intermediate, high, and very-high risk groups, respectively. The mortality was 10.4%, the area under the curve of the score was 0.921 (95% Confidence Interval [CI]: 0.868-0.974, p < 0.001) and the cutoff value correctly classified 83.5% of the patients. The cutoff value of >11 had sensitivity, 91.67% (95% CI: 61.52-99.79); specificity, 82.52% (95% CI: 73.79-89.30), positive predictive value, 37.93% (95% CI: 20.69-57.74), and negative predictive value, 98.84% (95% CI: 93.69-99.97). There was a significant moderate positive correlation between admission 4C mortality score and length of stay in hospital for the surviving patients (Pearson correlation coefficient=0.514, p<0.001).*

Conclusion: *The ISARIC score was found to have excellent predictive ability for mortality in hospitalized COVID-19 patients in our Bangladeshi cohort. Despite recent advances in the treatment and management of adults hospitalized with COVID-19, 4C mortality score can continue to inform clinical decision making.*

Key words: COVID-19; ISARIC; Mortality; Survival; Sensitivity.

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INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) has been caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that declared as a global pandemic by the World Health Organization (WHO).[1] The disease potentially yields severe illnesses, such as Acute Respiratory Distress Syndrome (ARDS) and multi-organ dysfunction syndrome, with a high mortality rate in patients with various risk factors.[2] The underlying conditions for developing a fatal disease include age,

hypertension, diabetes mellitus, coronary heart disease, chronic obstructive lung disease, and chronic kidney disease.[3] Therapeutic strategies established over time are currently providing evidence-based treatment for COVID-19 patients.[4] Although the focus is on severe and fatal cases, most COVID-19 patients follow an asymptomatic or mild course without necessary admission management and specific treatment.[5]

Prediction models could help forecast outcomes when patients are admitted to the hospital and may assist in triaging patients when allocating healthcare resources. Some of these prediction models were not explicitly developed for patients with COVID-19, and models specifically designed for patients with COVID-19 are also available.[6,7] One of the most recently published prediction models specifically designed for patients with COVID-19 is the Coronavirus Clinical Characterization Consortium (4C) mortality score.[8]

The 4 C mortality score was recently developed to predict in-hospital mortality in a very large cohort of COVID-19 patients in the UK.[8] The score requires eight specific predictors of mortality, including age, sex, comorbidities, respiratory rate, peripheral oxygen saturation, Glasgow Coma Scale (GCS), blood urea nitrogen, and C-reactive Protein (CRP). Most of these items reflect the severity of illness in hospitalized patients and indicate sepsis, organ failure and shock. By incorporating such demographic, clinical and laboratory parameters, 4C mortality score shows good discriminatory performance.[7] To date external validation of 4C score to prognosticate in-hospital mortality took place in different populations and reported that the ISARIC 4C mortality score could stratify and predict mortality in COVID-19 patients on arrival in the hospital.[9-20]

Studies have yet to be available in the literature highlighting the utility of the 4C mortality score among Bangladeshi patients. As our population differs from the patients for whom the 4C mortality score was validated, this new scoring system must be validated first in our setting. If a positive correlation could be found in this pilot study, that would help us triage patients with severe disease at the outset and improve the standard of care.So, this study aimed to analyze the outcome of COVID 19 patients using ISARIC/WHO 4C Mortality Score in COVID unit of BITID, Chattogram.

MATERIALS AND METHODS

A Hospital-based prospective observational study was conducted in the COVID-19 unit of BITID Hospital, Chattogram, Bangladesh from August 2021 to December 2022. Ethical approval was obtained from the Ethical Review Committee of BITID and written informed consent was obtained from the patients or their caregivers.

Admitted patients with confirmed COVID19 (Positive Real-Time Reverse Transcriptase-Polymerase Chain Reaction [RT-PCR] assay of a nasopharyngeal swab) were included in the study. Those who failed to fulfil all the parameters of ISARIC 4C score were excluded.

Consecutively admitted 150patients were screened and after exclusion only 115 patients were included in analysis. Data regarding demographic, clinical, and biochemical parameters were collected at admission by a structured case record form. 4C mortality score were calculated and patients were observed during their hospital stay for outcome analysis. Outcome parameters were in-hospital mortality, length of stay, and need for supplementary oxygen. Patients were managed according to the National Guidelines for hospitalized COVID-19 patients (DGHS).[21]

Statistical analyses were performed with Statistical Package for the Social Sciences (SPSS, IBM) version 23.0 for Windows. Categorical variables were summarized as frequencies and percentages. Quantitative data were expressed as mean ± Standard Deviation (SD) or median and Interquartile Range (IQR). The Chi-square test was used to perform intergroup and categorical comparisons. Receiving Operating Characteristics (ROC) curves for 4C Mortality Score was constructed, and an appropriate cut-off value with the highest sensitivity and specificity was determined for discriminating survived from deceased patients. The UC with 95% CI was evaluated as follows: a value of less than 0.5 as no predictive ability, from >0.5 to 0.7 as insufficient, from >0.7 to 0.8 as acceptable, from >0.8 to 0.9 as excellent and >0.9 as outstanding.[22] The correlation between length of hospital stay and 4C mortality score was determined by Pearson Correlation coefficient and simple linear regression line was plotted to predict length of stay from admission 4C mortality score. $p < 0.05$ was considered as statistical significance.

RESULTS

Mean age of the patients was 50.6±18.4 years in the present study and 47.8% were male. More than half of the patients were unvaccinated and 35.36% were fully vaccinated (Table I). Out of 115 patients, around two-thirds (65.2%) had one or more comorbid conditions. The most frequent comorbidity was hypertension (47.8%), followed by diabetes mellitus (34.8%), ischemic heart disease (12.2%), and COPD (7%) (Table II).

Fever, cough, dyspnea, fatigue, body ache, vomiting, nausea, diarrhoea, headache, were the most frequent clinical symptoms with 107 (93%), 94 (81.7%), 69 (60%), 32 (27.8%), 25 (21.7%), 17 (14.8%), 15 (13%), 14 (12.2%), and 14 (12.2%) cases, respectively (Table III).

The clinical and biochemical variables incorporated in the 4C mortality scores are shown in Table IV. It depicted that respiratory rate was 20-29 per minutes in 65.2% of the participants, SPO_2 on room air was >92% for 67%, GCS was 15 in 62.2%, blood urea was >14 in 7.8%, CRP level was >100 mg/dl was in 40.9% of the patients.

The median ISARIC 4C mortality score was 7.0 (Interquartile Range [IQR]: 3-12) for the entire cohort. Based on the 4C Mortality Score Risk Group, at the time of admission 34

(29.6%) patients were in intermediate risk group, followed by 33 (28.7%) in high-risk group, 31 (27%) in low-risk group, and 17 (14.8%) were in very-high risk group (Figure 1).

Out of 115 patients, 56 (48.7%) need supplementary oxygen and most of them (24.3%) received oxygen through nasal cannula. Average length of stay in-hospital was 7.5±4.9 days. One-hundred (87%) patients recovered and discharged from hospital and 12 patients expired giving the in-hospital mortality rate of 10.4% (Table V).

The fitted ROC curve of ISARIC 4C score against in-hospital mortality had AUC of 0.921 (95% CI: 0.868-0.974, p < 0.001) [Figure 2]. Applying Youden index analysis it was found that the optimal cutoff value, the value providing the best tradeoff between sensitivity and specificity, for the identification of in-hospital mortality was 11.

The sensitivity and specificity with scores ≥11 were 91.67% (95% CI: 61.52-99.79) and 82.52% (95% CI: 73.79-89.30), respectively, the PPV and NPV was 37.93% (95% CI: 20.69-57.74) and 98.84% (95% CI: 93.69-99.97), respectively, and the cutoff value correctly classified 83.48% (95%CI:75.41-89.75) of the cohort (Table VI).

Figure 3 depicts that, none of the patients with low and intermediate risk group expired in-hospital, whereas 3 (9.1%), and 9 (52.9%) patients in the high and very-high risk groups, respectively, expired in-hospital.

There was a significant moderate positive correlation between admission 4C mortality score and length of stay in hospital for the surviving patients (Pearson correlation coefficient=0.514, p<0.001). Figure 4 suggests that the 4C mortality score can estimate the length of hospitalization for surviving patients, the higher the scores, the more extended the hospital stay.

Table I Age, sex, and vaccination status of the patients (n=115)

Variables		Frequency	Percentage
Age, Years			
	<50	45	39.1
	50-59	23	20.0
	60-69	23	20.0
	70-79	20	17.4
	≥80	4	3.5
	Mean ± SD	50.6±18.4	
Sex			
	Male	55	47.8
	Female	60	52.2
Vaccination status			
	Not vaccinated	60	52.2
	Partially vaccinated	14	12.2
	Fully vaccinated	41	35.6

Data were expressed as frequency (%) if not mentioned otherwise.

Table II Comorbidity status of the patients (n=115)

Variables	Frequency	Percentage
Comorbidity types		
Hypertension	55	47.8
Diabetes mellitus	40	34.8
Ischemic heart disease	14	12.2
COPD	8	7.0
Hypothyroidism	5	4.3
Pregnancy	4	3.5
Chronic liver disease	3	2.6
Chronic kidney disease	3	2.6
Asthma	3	2.6
Tuberculosis	2	1.7
Epilepsy	1	0.9
Obesity	1	0.9
Total no of comorbidity		
No comorbidity	41	35.6
One	33	28.7
Two	21	18.3
Three	16	16.9
Four	4	3.5

COPD: Chronic Obstructive Pulmonary Disease

Table III Presenting symptoms of the patients (n=115)

Symptoms	Frequency	Percentage
Fever	107	93.0
Cough	94	81.7
Dyspnoea	69	60
Fatigue	32	27.8
Bodyache	25	21.7
Vomiting	17	14.8
Nausea	15	13.0
Diarrhoea	14	12.2
Headache	14	12.2
Runny nose	9	7.8
Anosmia	8	7.0
Sore throat	6	5.2
Anorexia	5	4.3
Ageusia	3	2.6

Table IV Clinical and biochemical parameters of the patients at admission (n=115)

Variables		Frequency	Percentage
Respiratory rate, /min	<20	36	31.3
	20-29	75	65.2
	≥ 30	4	3.5
SPO2 on room air	≥92%	77	67.0
	<92%	38	33.0
GCS	15	106	92.2
	<15	9	7.8

Variables		Frequency	Percentage
Urea (mmol/L)	≤7	75	65.2
	>7-14	31	27.0
	>14	9	7.8
CRP (mglL)			
	<50	22	19.1
	50-99	46	40.0
	>100	47	40.9

GCS: Glasgow Coma Scale, CRP: C-Reactive Protein.

Table V In-hospital outcome of the patients (n=115)

Outcome parameters	Frequency	Percentage
Supplementary oxygen needed		
No	59	51.3
Yes	56	48.7
Oxygen delivery device		
Not require	59	51.3
Nasal cannula	28	24.3
Face mask	11	9.6
NRM	12	10.4
HFNC	3	2.6
CPAP	2	1.7
Length of hospital stay, days	7.5±4.9	
Final outcome		
Recovered	100	87.0
Death	12	10.4
Referred to higher center	3	2.6

NRM: Non Rebreathing Mask, HFNC: High Flow Nasal Cannula, CPAP: Continuous Positive Airway Pressure.

Table VI To determine the diagnostic accuracy (AUROC) of 4C morality score for discriminating survived patients from those who died in the hospital

ISARIC 4C mortality score	In hospital outcome		p value
	Expired	Survived	
≥11	11 (37.9)	18 (62.1)	<0.001
<11	1 (1.2)	85 (98.8)	
Statistic	**Value**	**95% CI**	
Sensitivity	91.67%	61.52% to 99.79%	
Specificity	82.52%	73.79% to 89.30%	
Positive Likelihood Ratio	5.25	3.33 to 8.25	
Negative Likelihood Ratio	0.10	0.02 to 0.66	
Positive Predictive Value	37.93%	20.69% to 57.74%	
Negative Predictive Value	98.84%	93.69% to 99.97%	
Accuracy	83.48%	75.41% to 89.75%	

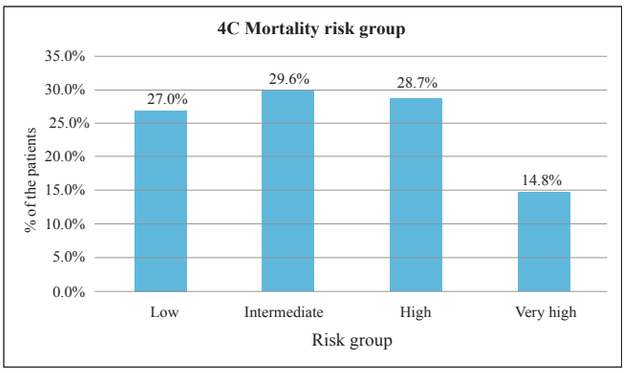

Figure 1 Distribution of the patients according to their 4C risk score

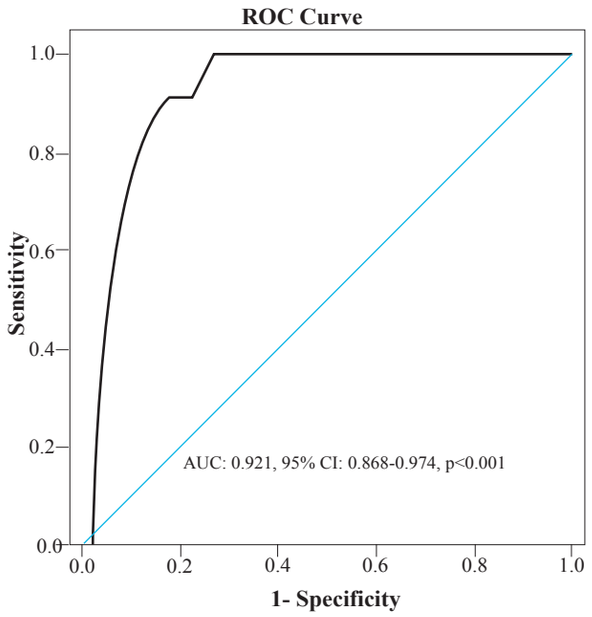

Figure 2 Receiver operating characteristic curves of ISARIC 4C mortality score's discriminatory ability for in-hospital mortality.

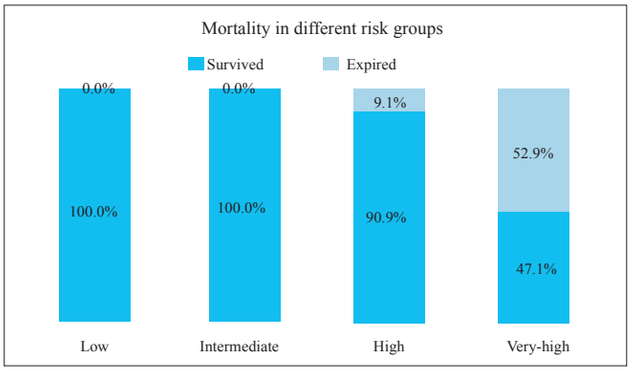

Figure 3 In-hospital mortality rates in different 4C mortality risk groups

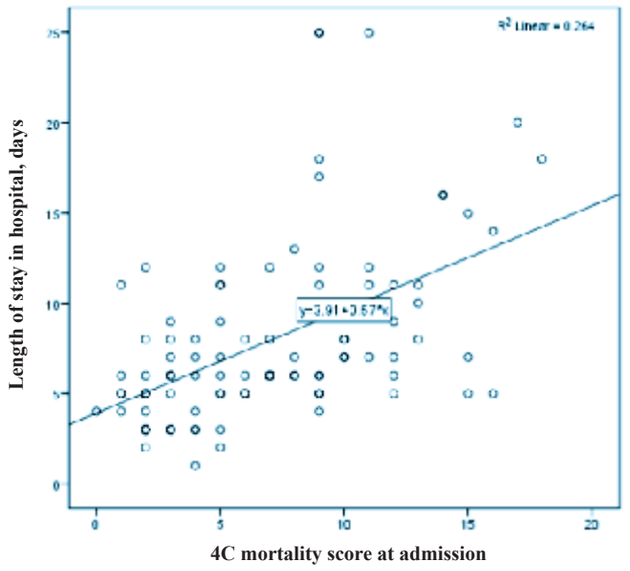

Figure 4 Scatter-dot plot showing correlation between admission 4C mortality score and length of stay in hospital among the surviving patients

Abbreviations: AUC: Area Under the Receiver Operating Characteristic Curve, CI: Confidence Interval, ISARIC: International Severe Acute Respiratory and Emerging Infections Consortium, ROC: Receiver Operating Characteristic Curve, 4C: Coronavirus Clinical Characterization Consortium.

DISCUSSION

The mortality rate among the studied patients was 10.4%, which is lower than the mortality rate (16.9%) reported in a previous article conducted at the COVID-19 unit of Chittagong Medical College Hospital in the first wave of COVID.[23] Studies in other counties also observed that the overall mortality rates were significantly lower in the second to fifth wave periods than in the first wave period.[24] Throughout the present study period, post-hospitalization treatment in Bangladesh evolved. As the understanding of the pathogenesis of COVID-19 improved, more effective treatments including corticosteroids, remdesivir, and anticoagulants were introduced after the first wave period.[21]

In the population of our study, the ISARIC score was found to have excellent predictive ability for mortality risk, with an AUC of 0.921 (95% CI: 0.868-0.974, $p < 0.001$).[22] The AUC in our study was slightly higher than that reported by the original development and validation study (AUC = 0.786; 95% CI: 0.781–0.79).[8] Although this is uncommon in external validation studies, higher AUCs were similarly reported by van Dam et al.[7] (AUC = 0.84; 95% CI: 0.79–0.88) and Wellbelove et al.[9] (AUC = 0.83; 95% CI: 0.71–0.95). Other studies have reported AUC values similar to the validation study or lower.[17,10] This variation among studies-although minimal-utilizing the same prediction model may reflect the variations in the studied populations, with regard to their demographic characteristics, clinical severity and sample size. Regardless of those variations, all studies in literature, including the present study, found the discriminatory ability of ISARIC score to be acceptable or excellent.

The present study, similar to the original study, showed rising mortality rates across groups of severity, that is, a directly proportional relationship between mortality risk and increase in score. The mortality rates of the Low, Intermediate, High, and Very High-risk groups on the 4C Mortality Score were 0.0%, 0.0%, 9.1%, and 52.2%, respectively. These are similar to those reported in the original study, which reported rates of 1.2%, 9.9%, 31.4%, and 61.5%, respectively.[8] This reflects that the model performs optimally, especially when considering that the higher mortality rates were higher within all groups in our study compared with the original study.[8] In the present study, the optimal cutoff value associated with Youden's index was a score >10, with this value correctly classifying 83.5% of the patients.

The diagnostic parameters (Sensitivity, specificity, PPV and NPV) of the cutoff of >10 in the present study were considerably higher compared to the same cutoff value in the British study.[8] This could possibly be due to inclusion of all patients irrespective of the severity. One of the most important diagnostic parameters is NPV, which indicates the probability of survival in patients with scores <11. In the present study, NPV was 98.84% (95% CI: 93.69-99.97), which provides an excellent risk probability to guide clinical decision making, this discrimination was supported by the present study finding of a significantly higher survival of patients with scores <11 and lower mortality.

There was significant moderate positive correlation between admission 4C mortality score and length of stay in hospital for the surviving patients, which suggested that the 4C mortality score can estimate the length of hospitalization for surviving patients; the higher the scores, the more extended the hospital stay. These findings agreed with the findings of Ocho et al.[16] These results indicated that the 4C mortality score can be used for bed management when the number of COVID-19 patients progressively increase, although the literature has not yet highlighted this point.

LIMITATIONS

Other than the limited sample size, the studied population comprised only hospitalized patients at a single center. So, these findings may thus not be applicable to other outpatient or community settings. The study did not incorporate other standard scores, including APACHE II, SOFA, A-DROP, or CURB-65 and pneumonia severity index, into the comparison.

Finally, emergence of genetic variants and the influence of the treatment that patients received were not analyzed in the study. During the study period, treatment strategies and guidelines had gradually changed and accordingly patients received appropriate therapies. This therapeutic change could have affected the results.

CONCLUSIONS

In summary, the present study validated the utility of the 4C mortality score for predicting the prognosis of our cohort. Similar to previous studies reported overseas, the 4C mortality score can be used to accurately estimate mortality and the length of hospital stay.

RECOMMENDATIONS

Based on the study findings, it could be proposed to adopt 4C mortality score for patient triage, treatment choice and duration, and discharge planning and to effectively predict each patient's admission duration to efficiently use limited hospital COVID-19 beds. Further multicenter studies with a larger sample size and including those with varied severities are required to validate the score in the larger Bangladeshi population and possibly explore predictors of mortality in COVID-19 patients.

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DISCLOSURE

All the authors declared no competing interest.

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