ORIGINAL ARTICLE

ISARIC 4C MORTALITY SCORE AS A PREDICTOR OF IN–HOSPITAL MORTALITY IN COVID-19 PATIENTS ADMITTED IN AYUB TEACHING HOSPITAL DURING FIRST WAVE OF THE PANDEMIC

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Background: Many factors have been identified which can predict severe outcomes and mortality in hospitalized patients of COVID-19. This study was conducted with the objective of finding out the association of various clinical and laboratory parameters as used by International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) World Health Organization (WHO)-ISARIC/WHO 4C Mortality score in predicting high risk patients of COVID-19. Ascertaining the parameters would help in triage of patients of severe disease at the outset, and shall prove beneficial in improving the standard of care. **Methods:** This cross-sectional study was carried out in COVID-19 Department of Ayub Teaching Hospital, Abbottabad. All COVID-19 patients admitted from 15th April to 15th July 2020 were included. **Results:** A total of 347 patients were included in the study. The mean age was 56.46±15.44 years. Male patients were 225 (65%) and female 122 (35%). Diabetes (36%) was the most common co-morbidity, followed by hypertension (30.8%). Two hundred & six (63.8%) patients recovered and 117 (36.2%) patients died. Shortness of breath (80%), fever (79%) and cough (65%) were the most common presenting symptoms. Patients admitted with a 4C Mortality score of 0–3 (Low Risk Category), the patients who recovered were 36 (90%) and those who died were 4 (10.0%). In patients admitted with a 4C Mortality score of more than 14 (Very High-Risk Category), the number of patients who recovered was 1 (20%), and those who died were 4 (80%). The difference in mortality among the categories was statistically significant (p<0.001). Hypertension was a risk factor for death in patients of COVID-19 (Odds ratio=1.24, 95% CI [0.76–2.01]). Lymphopenia was not associated with statistically significant increased risk for mortality. **Conclusion:** The ISARIC 4C mortality score can be used for stratifying and predicting mortality in COVID-19 patients on arrival in hospital. We propose that it should be used in every patient of COVID-19 presenting to the hospital. Those falling in Low and Intermediate Risk Category should be managed in ward level. Those falling in High and Very High Category should be admitted in HDU/ICU with aggressive treatment from the start.

Keywords: COVID-19; SARS-CoV-2; Risk factors; Mortality; Clinical Laboratory Tests

Citation: Ali R, Qayyum F, Ahmed N, Haroon MZ, Irshad R, Sajjad S, *et al*. ISARIC 4C Mortality score as a predictor of in–hospital mortality in COVID-19 patients admitted in Ayub Teaching Hospital during first wave of the pandemic. J Ayub Med Coll Abbottabad 2021;33(1):20–5.

INTRODUCTION

COVID-19 infection is caused by a novel coronavirus SARS-Co-V-2, which is the seventh member of the Human Coronaviruses (HCoV) family. Since emerging from a local seafood market in Hubei Province of China on December 8th 2019, COVID-19took the world by storm and is still playing havoc with the lives and lifestyles of the world population.[1] As of 2nd November 2020, more than 56 million people have been infected with it worldwide; at least 1.3 million people have been confirmed to have died from it.[2]

The disease was a new quandary, both for the general population as well as the health care providers. Data available so far suggests that the clinical course of this infection is different from seasonal flu, pneumonia, and even sepsis. The clinical picture of patients with severe COVID-19 infection is characterized by pneumonitis, profound hypoxia, and systemic inflammation affecting multiple organs.[3,4]

The transmission rate of SARS-Co-V-2 (R^0 2.4–3.8) has been observed to be much higher than previous coronavirus outbreaks. The genomic analysis discovered that it is 70% similar to SARS-Co-V. Both of them gain entry into the human cells by binding to ACE2 receptor. But the specific spike protein on the surface of SARS-Co-V-2 has 10 to 20 times higher affinity for the human ACE2 receptor

than SARS-Co-V. This has led to its rapid spread throughout the world in a very short time.[5]

Because of paucity of data in the initial months of the pandemic, there was also a lot of uncertainty about the factors affecting prognosis of hospitalized COVID-19 patients.[6] Meta-analyses were done to better understand these factors affecting the severity and prognosis of such patients. Till now various factors have been identified which can predict severe outcomes and risk of death in hospitalized patients, such as prolonged fever, co-morbidities, Vitamin D deficiency, and various blood markers.[7] Most of the studies are hospital based case-control analysis of COVID-19 patients, and they visualize risk based on ICU care and observed mortality.[8] A large scale study conducted in 35,463 hospitalized patients of COVID-19 in the UK used the ISARIC/WHO Clinical Protocol to predict mortality. This is an easy-to-use protocol as it requires parameters which are easily available on hospital presentation.[9]

As the global race to develop a human vaccine is rapidly making headway, many treatment options have also been studied. Remdesivir has now become standard of care in COVID-19patients.[10] Dexamethasone has been shown to reduce mortality in patients requiring oxygen support.[11] Tocilizumab has been studied for its role in cytokine storm.[12] Convalescent plasma therapy is also being studied in trials.[13]

Confirmed cases of COVID-19 started coming to our hospital in March, 2020. Like the rest of the world, it was a new experience for us. The knowledge regarding management of these patients was very scarce at that time. The need for pragmatic risk stratification was essential to allow early identification, and rigorous management of those patients who were at the highest risk of death. This study was conducted with the objective of finding out the association of various clinical and laboratory parameters in predicting high risk patients of COVID-19 admitted with us. The main outcome was in-hospital mortality. 4C Mortality score, an infographic that visualises risk, based on observed mortality among hospitalized patients with COVID-19 showed utility and effective validation in the UK patients was applied to our patients in order to determine its role in our population. A positive correlation would help us in triage of patients of severe disease at the outset, and prove beneficial in improving the standard of care.

MATERIAL AND METHODS

This cross-sectional study was carried out in COVID-19 Department of Ayub Teaching Hospital, Abbottabad. Prior approval from the Ethical Committee was sought. All COVID-19patients admitted from 15thApril to 15th July 2020 were included in the study. Age, gender, clinical features, co-morbidities, complications, length of stay, ICU requirement, laboratory abnormalities, in-hospital mortality; all were collected by using a pre-specified case report form from patients fulfilling the inclusion criteria admitted during this period. The data was analysed by using SPSS 21.

RESULTS

A total of 347 patients were included in the study. Mean age of the patients was 56.46±15.44 years, and the age ranged between 15–92 years (Figure-1). Male patients were 225 (64.8%) and female patients were 122 (35.2%). The mean time of symptom duration upon admission was 5.81±4.99 days. The mean oxygen saturation of patients on admission was 75.58%±15.90, ranging from 19% to 99%. The mean temperature on admission of our patients was 98.36°F±0.98.

Overall, 206 (63.8%) patients recovered and 117 (36.2%) patients died. A total of 95 (27.4%) patients required Low Flow Oxygen, and 192 (55.3%) required High Flow Oxygen. 31 (8.9%) patients required either BiPAP or CPAP. 29 (8.4%) patients were put on ventilator. Only 4 patients were healthcare workers 24 (6.9%) patients had no outcome (left hospital against medical advice). Demographic and clinical characteristics of patients are summarized in Table-1.

Diabetes (35.7%) was the most common co-morbidity, followed by hypertension (30.8%). The distribution of co-morbidities is shown in Table-2.

29.7% patients were received in critical condition. The condition of the patients on arrival is summarized in Table-3. The average number of days spent in hospital was 8.8±6.9 days.

In a total of 27 patients who were put on ventilator, the mortality was 100%. The outcome of patients with respect to the ventilatory support they received is summarized in Table-4.

Of the patients admitted with a 4C Mortality score of 0–3 (Low Risk Category), the patients who recovered were 36 (90.0%) and those who died were 4 (10.0%). And of the patients who presented with a 4C score of more than 14 (Very High Risk Category), the number of patients who recovered was 1 (20%), and those who died were 4 (80%). The difference in mortality among the categories was statistically significant (p<0.001) Table-5. The distribution of 4C Mortality Score in both genders and in different age categories is shown in Figures-2,3, and 4.

In patients who presented with Lymphopenia, mortality was 34.4% (22), whereas those who did not have Lymphopenia mortality was 33.5% (54). This was not statistically significant (Odds Ratio=0.98, 95% CI [0.52–1.8]). Table-6

The mortality in patients who had hypertension was 39.6% (40), whereas mortality in patients who did not have hypertension was 34.7% (77). Hypertension was a risk for death in patients of COVID-19(Odds ratio=1.24,95% CI [0.76–2.01]). Table-7. Shortness of breath (79.8%), fever (79%) and cough (65.3%) were the most common presenting symptoms in our patients. Table-8. Patients who presented within 7 days of onset of symptoms, mortality was 41.1% (92), whereas those who presented later than this mortality was 25.3% (25).

Table-1: Demographic and clinical characteristics of COVID-19 patients on admission

Characteristics	Number or Mean
Mortality	117 (36.2%)
Age	56.46±15.44 years
Gender Male Female	225 (64.8%) 122 (35.5%)
Mean SPO_2 on arrival	75.58%±15.90
Duration of symptoms on arrival	5.81±4.99 days
Temperature on arrival	98.36°F±0.98
Respiratory Rate (breath/min)	27±7
Systolic Blood Pressure (mmHg)	120±18
Diastolic Blood Pressure (mm Hg)	77±13.4
Hemoglobin (g/dL)	12.89±1.93
TLC (10^9/L)	11.18±5.79
Lymphocyte count 10^3/µL	1.66±1.04
Platelets (10^3/µL)	238.84±96.86
Creatinine (mg/dL)	1.2±0.9
Urea (mmol/L)	7±5.5
CRP (mg/L)	112±100
D-Dimers (ng/mL)	1937±2758
LDH (U/L)	566±262
Serum Ferritin (ng/mL)	1329±2644

Table-2: Co-morbidities in patients admitted in COVID-19 Department

Co-morbidity	Number (Percentage)
Diabetes Mellitus	124 (35.7)
Hypertension	107 (30.8)
Coronary Artery Disease	36 (10.4)
Cerebrovascular Disease	11 (3.2)
Chronic Kidney Disease	7 (2.0)
Hypothyroidism	2 (0.6)

Table-3: Condition of patients on arrival

Condition on Arrival	Number (Percentage)
Moderate	147 (42.4)
Severe	97 (28.0)
Critical	103 (29.7)

Table-4: Oxygen support and outcome in patients

Support	Total	Outcome	
		Recovered	Death
Low Flow O_2	88	87	1
High Flow O_2	179	112	67
CPAP	19	6	13
BiPAP	10	1	9
Ventilator	27	0	27

Table-5: Outcome of patients with respect to 4C Mortality Score

Score	Risk Group	Outcome		Total
		Recovered (%)	Death (%)	
0–3	Low	36 (90.0)	4 (10.0)	40
4–8	Intermediate	105 (73.4)	38 (26.6)	143
9–14	High	64 (47.4)	71 (52.6)	135
>14	Very High	1 (20.0)	4 (80.0)	5

Table-6: Lymphocyte count and Outcome in COVID-19 patients

Lymphocyte Count (µL)	Outcome	
	Recovered (%)	Deaths (%)
<1000	39 (60.9)	22 (34.4)
≥1000	99 (61.5)	54 (33.5)

Table-7: Hypertension and Outcome in COVID-19 patients

Hypertension	Outcome	
	Recovered (%)	Death (%)
Present	61 (60.4)	40 (39.6)
Absent	145 (65.3)	77 (34.7)

Table-8: Presenting symptoms of COVID-19 patients

Symptoms	Frequency (%)
Shortness of breath	79.8
Fever	79.0
Cough	65.3
Sore throat	5.8
Diarrhea	4.0
Vomiting	2.3
Anosmia	2.3
Headache	1.7

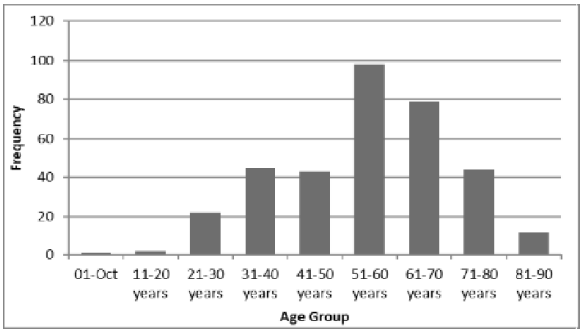

Figure-1: Age distribution of COVID-19 patients

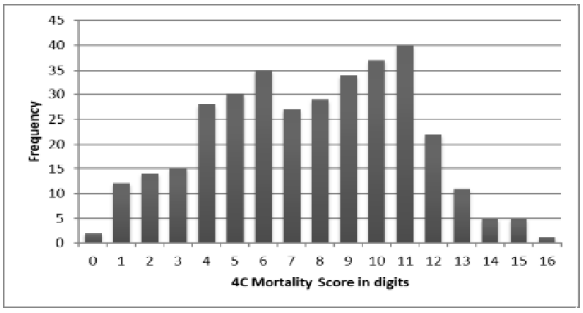

Figure-2: 4C Mortality score distribution in COVID-19 patients

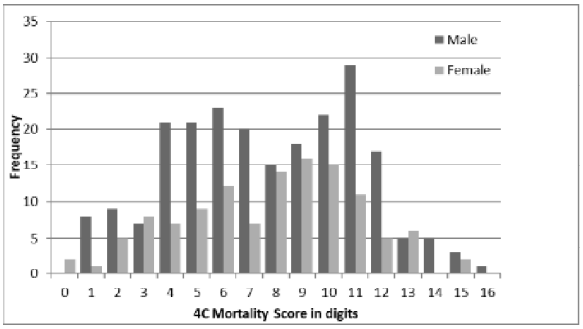

Figure-3: 4C Mortality score distribution in both genders

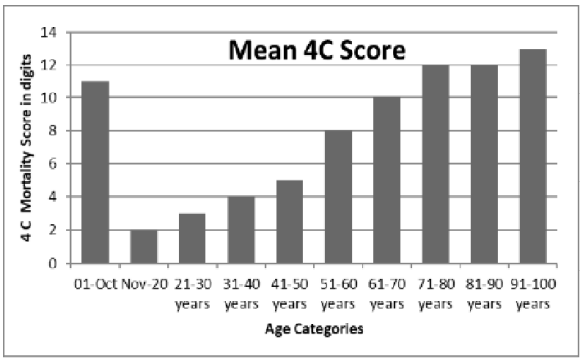

Figure-4: 4C Mortality score distribution in different age groups

DISCUSSION

COVID-19 has caught the world off-guard. It has left all health care systems over-burdened. The illness is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV 2) and named 'COVID-19', an acronym derived from 'coronavirus disease 2019'. The disease was declared a global pandemic by WHO on March 11, 2020.[14] Treatment is especially challenging as the world scrambles to find a cure for it.

When the pandemic started, we did not know the risk factors that lead to increased mortality. Over the period of time, risk factors and laboratory abnormalities were identified. Different protocols and risk scores were developed to quickly identify those at high risk for complications and mortality.[15–17] The ability to predict early about patients at risk of poor outcome could help initiate aggressive treatment right from the start. It is also going to be very helpful in using the resources wisely and combating the COVID-19 pandemic in a better way. This is particularly important in the light of a looming threat of a flare-up in cases in the winter and the 2nd wave of COVID-19 has already started surging.

One such protocol, the 4C Mortality Score, was developed by ISARIC/WHO Coronavirus Clinical Characterisation Consortium in the UK. A study was performed by SR Knight *et al*[9] on 35,463in 260 hospitals across England for validation and development of this protocol. The 4C Mortality Score includes eight variables which can be easily assessed on admission. These include age, gender, number of co-morbidities, peripheral oxygen saturation, respiratory rate, level of consciousness, C reactive protein, and urea level. The study group concluded that 4C Mortality Score was accurate at characterizing the patients at high risk for in-hospital death.

As this study was done in England, we needed to confirm the predictability of this score in our population. In our study the ISARIC 4C mortality score was highly predictive of in–hospital mortality. The mortality increased from 10% in the Low Risk category to 80% in the Very High Risk category in our study. It is comparable to the results of SR Knight, who found the mortality to increase from 1.7% in the Low Risk category to 66.2% in the High Risk category.[9]

In our study the overall mortality was 36.2%. This is comparable to studies done in other parts of the world. The in-hospital mortality was 32.3% in a retrospective study done in Illinois during March to May 2020.[18] The Clinical Characterization Protocol UK (CCP-UK) study found in-hospital mortality to be 32.2%.[9] In a study on 10,131 US veterans, the in-hospital mortality was 30.4%. However, mortality rates of hospitalized patients have ranged from 10.2% to 67% across the world.[19]

In our study hypertension was associated with increased risk of mortality in admitted patients of COVID-19 (Odds ratio=1.24, 95% CI [0.76–2.01]). Hypertension was the most common co-morbidity followed by diabetes mellitus among COVID-19 patients in many studies.[20] In our study diabetes was the most common co-morbidity followed by hypertension. Many studies have reported hypertension to be a risk factor for increased mortality in COVID-19 patients. A meta-analysis of 19 studies with 15,302 COVID-19 patients showed that hypertension was significantly associated with increased risk of adverse outcomes with an odds ratio of 1.44, 95% CI [1.24–1.66][21]. Similarly, a meta-analysis of thirteen studies with a total of 3027 patients of COVID-19 found that hypertension was statistically higher in critical/mortal patients compared with non-critical patients [OR = 2.72, 95% CI (1.60–4.64)].[22]

In our study we did not find an increased risk of mortality with lymphopenia. Many studies and meta-analysis have found a correlation of lymphopenia and poor outcome in patients of COVID-19.[23] Many explanations have been put forward to explain this phenomenon. A key factor could be the inflammatory cytokine storm and

increased levels of TNF-α and IL-6. Some have postulated that COVID-19 infection can lead to exhaustion of T cells.[24]

One reason for high mortality in our population could be Vitamin D deficiency. Despite being a sunny country, many studies have pointed out to an overall deficiency of Vitamin D in Pakistan. A local study conducted by Jadoon SA *et al*. in Abbottabad, found that 78.3% of the patients had Vitamin D deficiency or insufficiency.[25] A cross-sectional population survey conducted in Karachi found that 83.4% of respondents had a low level of Vitamin D.[26] Vitamin D deficiency has also been identified as a growing health problem in the Nutritional Health Survey of Pakistan.[27] An Italian study points to a possible protective effect of sunlight exposure against COVID-19 mortality.[28] A study conducted by Radujkovic *et al.* in Germany found that Vitamin D deficiency was associated with higher risk of invasive mechanical ventilation and death.[29] We consider that low levels of Vitamin D could also be a cause of poor prognosis in our population.

Our study has limitations in being a single centre study with a relatively small sample size. Further multi-centre studies are needed in Pakistan to better understand the risk factors for those patients who at higher risk for in-hospital complications and mortality.

CONCLUSION

The ISARIC 4C mortality score is a very easy to use and valuable tool for stratifying and predicting mortality in COVID-19 patients on arrival in hospital. The need for this risk stratification is to timely identify those patients of COVID-19 that are at high risk of death, and to improve medical management decisions. We propose that the 4C Mortality Score be used in every patient of COVID-19 presenting to the hospital. Those falling in Low and Intermediate Risk Category should be managed in ward level, whereas those falling in High and Very High Category should be admitted in HDU/ICU and aggressively treated right from the start.

AUTHORS' CONTRIBUTION

NA conceived the idea and set guidelines for the article. RA and FQ wrote the article and did literature search. MZ H analysed the data. UF and RI did critical appraisal and proof reading. All others contributed to acquisition of the data.

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Submitted: November 21, 2020	*Revised: November 24, 2020*	*Accepted: November 27, 2020*

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