

Utility of Age-adjusted Charlson Comorbidity Index as a Predictor of Need for Invasive Mechanical Ventilation, Length of Hospital Stay, and Survival in COVID-19 Patients

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ABSTRACT

Background: Multiple parameters may be used to prognosticate coronavirus disease-2019 (COVID-19) patients, which are often expensive laboratory or radiological investigations. We evaluated the utility of age-adjusted Charlson comorbidity index (CCI) as a predictor of outcome in COVID-19 patients treated with remdesivir.

Materials and methods: This was a single-center, retrospective study on 126 COVID-19 patients treated with remdesivir. The age-adjusted CCI, length of hospital stay (LOS), need for invasive mechanical ventilation (IMV), and survival were recorded.

Results: The mean and standard deviation (SD) of age-adjusted CCI were 3.37 and 2.186, respectively. Eighty-six patients (70.5%) had age-adjusted CCI ≤ 4 , and 36 (29.5%) had age-adjusted CCI > 4 . Among patients with age-adjusted CCI ≤ 4 , 20 (23.3%) required IMV, whereas in those with age-adjusted CCI > 4 , 19 (52.8%) required IMV ($p < 0.05$, Pearson's chi-square test). In those with age-adjusted CCI ≤ 4 , the mortality was 18.6%, whereas it was 41.7% in patients with age-adjusted CCI > 4 ($p < 0.05$, Pearson's chi-square test). The receiver operating curve (ROC) of age-adjusted CCI for predicting the mortality had an area under the curve (AUC) of 0.709, $p = 0.001$, and sensitivity 68%, specificity 62%, and 95% confidence interval (CI) [0.608, 0.810], for a cutoff score > 4 . The ROC for age-adjusted CCI for predicting the need for IMV had an AUC of 0.696, $p = 0.001$, and sensitivity 67%, specificity 63%, and 95% CI [0.594, 0.797], for a cutoff score > 4 . ROC for age-adjusted CCI as a predictor of prolonged LOS (≥ 14 days) was insignificant.

Conclusion: In COVID-19 patients, the age-adjusted CCI is an independent predictor of the need for IMV (score > 4) and mortality (score > 4) but is not useful to predict LOS (CTRI/2020/11/029266).

Keywords: Age-adjusted Charlson comorbidity index, Coronavirus disease 2019, Invasive mechanical ventilation, Length of hospital stay, Mortality, Remdesivir.

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INTRODUCTION

Various parameters to prognosticate the outcome of coronavirus disease-2019 (COVID-19) patients have been proposed. These include clinical parameters, laboratory parameters as well as radiological parameters.¹⁻³ However, for the laboratory and radiological reports to be available, time is an important factor. Many of the investigations like ferritin, procalcitonin, and computerized tomography (CT) scan of the thorax are expensive and cause a financial burden on the patients, especially in developing countries.⁴ Though various scoring systems for predicting the mortality in COVID-19 have been proposed, most include laboratory investigations like lymphocyte percentage, procalcitonin, and D-dimer.⁵ The age-adjusted Charlson comorbidity index (CCI) assimilates age and 19 medical comorbidities to calculate the total score, with a particular score assigned to each comorbid condition, without any requirement of investigation values.⁶ Precise prognostication during first counseling is especially important at a time when the physician—patient relation is often compromised in the presence of physical barriers in the COVID-19 situation.⁷ CCI score has been shown to have an independent prognostic value in COVID-19 patients, irrespective of the availability of laboratory or radiological investigations.⁸ Previous literature has validated the use of CCI in COVID-19 patients to predict the adverse outcomes in terms of disease severity as well as mortality.^{8,9} Each point increase in CCI score has also been validated to predict death in COVID-19 patients by an exponential increase in odds ratio.⁹ Advanced age more than 65 years has been validated

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to predict mortality in hospitalized COVID-19 patients.¹⁰ Thus, we aimed to evaluate the utility of the age-adjusted CCI as a prognostic parameter for mortality, length of hospital stay (LOS), and need for invasive mechanical ventilation (IMV) in COVID-19 patients treated with remdesivir and performed a utility study in Indian population. We evaluated the utility of age-adjusted CCI score to prognosticate the outcome of COVID-19 patients on admission, even without any of the expensive investigation reports being readily available.

MATERIALS AND METHODS

Study Design

It was a single-center, retrospective study done on COVID-19 patients treated with remdesivir who were admitted to the hospital between July 2020 and September 2020. After Institutional Ethical Committee clearance (IEC 654-2020) and Clinical Trial Registry-India (CTRI) registration (CTRI/2020/11/029266), 126 patients were included in the study. Since it was a retrospective study, informed consent was waived off by the IEC.

Study Participants

All patients aged between 18 and 90 years who had tested positive for COVID-19 as per reverse transcription-polymerase chain reaction or rapid antigen test and admitted to the hospital with moderate-severe COVID-19 were eligible for inclusion. All patients who had received remdesivir treatment for 5 days and corticosteroid as per the discretion of the treating physician were included. Following is the flowchart depicting the methodology of the study (Fig. 1).

Data Collection

Data of age, gender, and comorbidities were collected from both electronic database and manual database of the hospital. Each patient had a unique hospital identification number, and thus, duplication was avoided by checking the hospital identification number of each of the patients. Age-adjusted CCI was calculated for patients who received remdesivir for 5 days. The need for IMV, days of hospital stay, and in-hospital mortality were noted from the records. Laboratory parameters and chest radiograph findings were also noted. Chest radiograph findings were obtained from Picture Archiving and Communication System (InstaRISPCS) of the hospital.

Outcome Measures

The primary outcome was in-hospital mortality of the COVID-19 patients, whereas the secondary outcomes were LOS and requirement of IMV.

Statistical Analysis

Data were analyzed using EZR software, version 1.53, Japan.¹¹ The mean and SD of continuous variables were calculated. Median and interquartile range were calculated for continuous variables having skewed distribution. Shapiro-Wilk test was used for the skewness of data determination. Fischer's exact test and Pearson's Chi-square test were used to test the statistical significance between categorical data. A p -value <0.05 was considered significant. Reliability of age-adjusted CCI for predicting the outcomes in terms of mortality, need for invasive ventilation, and LOS was analyzed

by receiver operating curve (ROC) and area under the curve (AUC) along with cutoff values with sensitivity and specificity.

RESULTS

The data of 122 COVID-19 patients were used for statistical analysis.

The demographic variables are depicted in Table 1.

There was a significant difference in the mortality rates and requirement of IMV between those having age-adjusted CCI ≤ 4 and >4 as depicted in Table 2. However, LOS was not significantly different as depicted in Table 2.

Among patients with age-adjusted CCI ≤ 4 , 20 (23.3%) required IMV, whereas in those with age-adjusted CCI >4 , 19 (52.8%) required IMV ($p < 0.05$, Pearson's chi-square test).

A total of 91/122 patients survived (74.6%) and 31 patients expired (25.4%). In those with age-adjusted CCI ≤ 4 , the mortality was 18.6%, whereas it was 41.7% in patients with age-adjusted CCI >4 ($p < 0.05$, Pearson's chi-square test). The ROC of age-adjusted CCI for predicting the mortality had an AUC of 0.709, $p = 0.001$, and sensitivity 68%, specificity 62%, and 95% confidence interval (CI) (0.608, 0.810), for a cutoff score >4 (Fig. 2).

The ROC of age-adjusted CCI for predicting the need for IMV is depicted below (Fig. 3). It had an AUC of 0.696, $p = 0.001$, and sensitivity 67%, specificity 63%, and 95% CI (0.594, 0.797), for a cutoff score >4 .

However, the ROC of age-adjusted CCI as a predictor of prolonged LOS (≥ 14 days) was having AUC of 0.448, which was not significant, with $p = 0.319$, and sensitivity 38.7%, specificity 53.3%, and 95% CI (0.344, 0.551) (Flowchart 1).

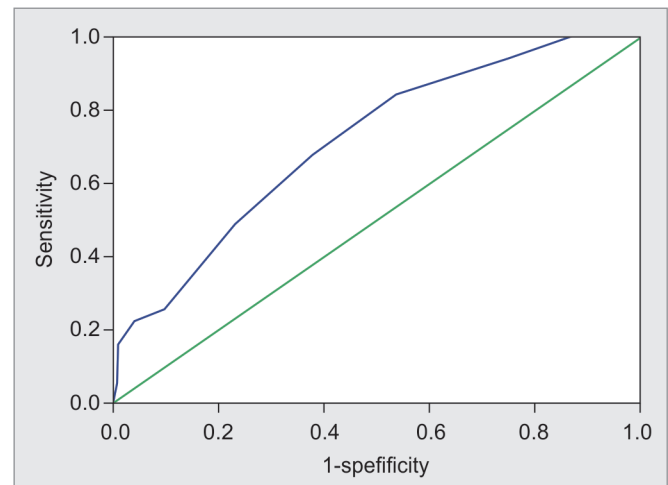


Fig. 1: ROC curve depicting the methodology of the study

Table 1: Demographic variables and clinical characteristics of the patients

N = 122	Values	
Age in years (mean \pm SD)	59.02 \pm 14.28	
Gender	Males 95	Females 27
Age-adjusted CCI (mean \pm SD)	3.37 \pm 2.18	
CCI score	$<3 = 47$ (38.5%)	$\geq 3 = 75$ (61.5%)
IMV	Yes = 39 (32%)	No = 83 (68%)
LOS in days (mean \pm SD)	14.79 \pm 6.46	
Outcome of hospital stay	Survived 91 (74.6%)	Expired 31 (25.4%)

Table 2: Differences in outcomes and ventilatory requirements between the low (≤ 4) and high (> 4) age-adjusted CCI groups

Outcomes	Age-adjusted CCI ≤ 4 (N = 86)	Age-adjusted CCI > 4 (N = 36)	p-value*
Mortality	16 (18.6%)	15 (41.7%)	0.008
LOS	15.1 \pm 6.2 (mean and SD)	13.8 \pm 7.1 (mean and SD)	0.3
IMV	20 (23.3%)	19 (52.8%)	0.001

CCI, Charlson comorbidity index; N, number of patients; SD, standard deviation; *Pearson's Chi-square test

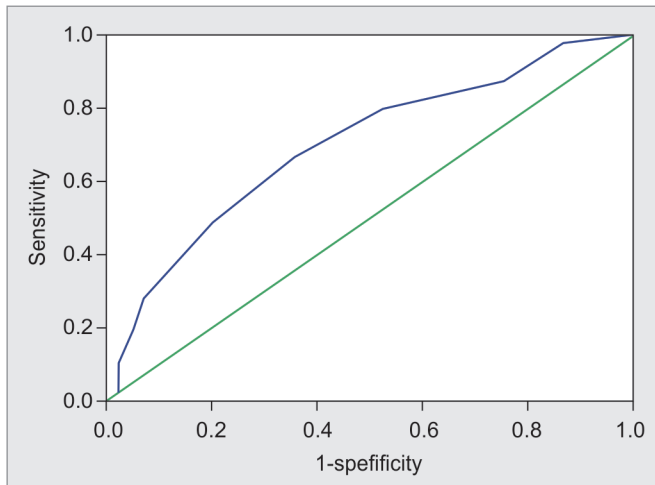


Fig. 2: ROC curve depicting the age-adjusted CCI for predicting the mortality (AUC of 0.709, $p = 0.001$, and sensitivity 68% and specificity 62%, for a cutoff score > 4)

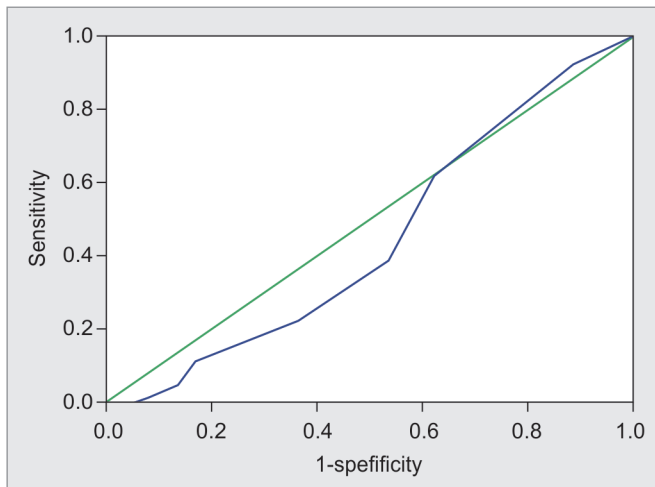
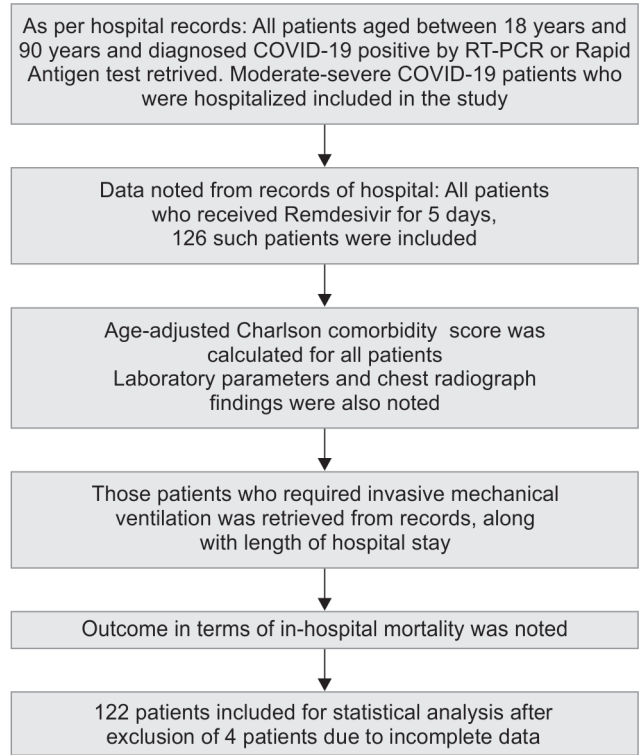


Fig. 3: ROC of age-adjusted CCI for predicting the need for IMV (AUC of 0.696, $p = 0.001$, and sensitivity 67% and specificity 63%, for a cutoff score > 4)

DISCUSSION

Conventionally, outcome in COVID-19 patients has been prognosticated using clinical, laboratory, and radiological investigations.^{1,5} Various nonspecific symptoms like fatigue, expectoration, hemoptysis, dyspnea, and chest tightness have been reported to be independent predictors of death.¹ Among laboratory

Flowchart 1: ROC curve of age-adjusted CCI for predicting the LOS (AUC of 0.448, $p = 0.319$)



parameters, high leucocyte count, lactate dehydrogenase, serum ferritin, D-dimer, and procalcitonin have been concluded to be poor prognostic indicators.^{1,5} Similarly, high c-reactive protein (CRP) and interleukin-6 were also concluded as a poor prognostic marker as well.^{12,13} Radiologically, CT of the thorax was reported to be a tool for predicting poor prognosis.² However, in many resource-limited setups, markers like CRP, procalcitonin, ferritin as well as CT of the thorax may not be readily available or are expensive investigations. Without any biochemical or radiological test, a comorbidity score that can be easily calculated would be of immense help to the clinician to assess the need for IMV, LOS, or mortality and thus prognosticate the patients on admission.

CCI score has been described to be a valid tool for the prediction of mortality.¹⁴ Age was said to be a risk factor for poor outcome in COVID-19.¹⁵ Age-adjusted CCI includes scores as per various age-groups, along with a summation of scores for various comorbidities.¹⁶

The scoring calculation allocates the various points to calculate the total age-adjusted CCI score as depicted in [Table 3](#).¹⁶

It has been recommended that CCI could be beneficial in prognostication of hospitalized COVID-19 patients.¹⁷ The systematic review and meta-analysis, which has validated the use of CCI as risk stratification to predict mortality in COVID-19 patients, have concluded that per point increment in CCI score in COVID-19 patients increased the chances of mortality by 16%.¹⁷ In a previous study, CCI score ≥ 3 has been shown to have a poor outcome in COVID-19 patients in terms of mortality and disease severity and may predict the need for ventilator support and even readmissions.¹⁷ However, in our study, as per statistical analysis, a cutoff score of > 4 was derived for age-adjusted CCI predicting the need for IMV and a higher chance of mortality. Thus, we classified the patients as those with low or high age-adjusted CCI

Table 3: Points allocated for different age-groups and comorbid conditions for the calculation of age-adjusted CCI

Score	Age and comorbid conditions
Age of the patient	1 point to total score for each decade after 40 years
1 point	50–59 years
2 points	60–69 years
3 points	70–79 years
4 points	≥80 years
1 point for each of these comorbidities	Diabetes mellitus without end-organ damage, cerebrovascular disease, myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, and mild liver disease
2 points for each of these comorbidities	Diabetes mellitus with end-organ damage, moderate/severe renal disease, hemiplegia solid tumor without metastasis (exclude if >5 years from diagnosis), leukemia, and lymphoma
3 points	Moderate/severe liver disease
6 points for each of these comorbidities	Metastatic solid tumor, AIDS (not just HIV-positive)

as ≤ 4 or >4 . Another new scoring system, COVID-19 lymphocyte ratio or lymphocyte percentage, age, CCI score, dyspnea (CoLACD), has been found beneficial and effective to predict the mortality in COVID-19 patients.¹⁸ The ROC in the study showed an AUC of 0.831 for predicting mortality, which was slightly higher than the AUC for age-adjusted CCI in our study (0.709). The cutoff CoLACD score of 2.5 in the study had a greater sensitivity (82%) and specificity (73%) than the cutoff score >4 in our study. However, the study did not use this CoLACD score to predict the possible need for IMV in patients. We wanted to use the age-adjusted CCI, since age has been shown to be an important risk factor in COVID-19, and the age-adjusted CCI can be calculated just on the basis of comorbidities, even without any investigation required as in the CoLACD score. We chose to evaluate the age-adjusted CCI as an independent risk factor for not only mortality, but also for the ability to predict the need for IMV and extended LOS (≥ 14 days), in patients who were treated with remdesivir. A median length of 14 days of hospital stay has been shown in COVID-19 patients; thus, we considered a stay ≥ 14 days as an extended LOS.¹⁹ CCI as a valid scoring for the prediction of outcome in various other clinical conditions like malignancy, acute coronary syndrome, and postsurgery has been validated, with different cutoff values proposed as predictors of adverse outcomes.^{6,20–22}

The cutoff value in our study was higher than that in the study done by Kim et al.²³ In the afore-mentioned study, an age-adjusted CCI ≥ 3 was found to be associated with adverse outcomes, higher mortality, lower hemoglobin, lymphocytes, and platelets.²³ However, the study was done on Korean population. In our patients, we found that those with an age-adjusted CCI score of only >4 had a higher risk of mortality.

Regarding the need for IMV, the ROC curve predicted the cutoff score of >4 for age-adjusted CCI as a predictor. This was a significant finding in our study, as the patient and relatives may be explained about intensive care unit requirements on the day of admission itself, and the clinician will be more sagacious while caring for such patients. To the best of our knowledge, there has been no other study depicting a high comorbidity score as a risk for IMV in COVID-19 patients in India. A study that predicted the need for IMV concluded three factors at admission as significant: heart rate >101.5 , oxygen saturation-to-fraction of inspired oxygen ratio (SpO₂/FiO₂ ratio) <4.4 , and a positive troponin I.²⁴ The advantage in our study is that the need for IMV may be predicted without any invasive investigations like arterial blood gas or serum troponin.

Another aspect of outcome in COVID-19 patients is LOS. Literature has depicted increased age, CRP, D-dimer, and high neutrophil count as factors leading to a longer LOS.²⁵ Trials have also shown that fever, bilateral pneumonia, and diabetes mellitus were the risk factors for prolonged hospital stay.²⁶ There were no studies concluding either CCI or age-adjusted CCI to be a predictor for LOS. In our study also, we did not find a significant cutoff value for age-adjusted CCI for predicting a longer LOS.

There are certain strengths in our study. We analyzed a parameter like age-adjusted CCI that may be used to prognosticate the outcome in COVID-19 patients in any setting anywhere in the country. We could determine a cutoff score >4 for age-adjusted CCI both for predicting the mortality and for the requirement of IMV. This could be used to prognosticate the patient outcome even without any investigation. We included only those patients who were administered remdesivir for all 5 days along with corticosteroids to ensure consistency among the patients being analyzed.

However, our study had few limitations. It was a single-center, retrospective study. The treatment protocol was not uniform in terms of the corticosteroid and the anticoagulant that were administered. Also, the investigators calculating the age-adjusted CCI were not blinded to the outcome, as they had to access the data from past medical records due to the retrospective nature of the study.

CONCLUSION

In COVID-19 patients, age-adjusted CCI is an independent predictor of need for IMV and outcome in terms of in-hospital mortality. A higher cutoff score >4 was found to be associated with higher risk of IMV and mortality. However, it was not a reliable predictor of LOS.

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