Clinical Research

Charlson comorbidity index to predict 28-day mortality in critically ill COVID-19 patients

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ABSTRACT

BACKGROUND Severe COVID-19 patients may become critically ill and require treatment in the intensive care unit (ICU). As intensive care resources are limited, mortality predictors should be used to guide resource allocation. This study aimed to validate the Charlson comorbidity index (CCI) as the mortality predictor of critical COVID-19 patients in the ICU.

METHODS A retrospective cohort study was done in adult patients admitted to the ICU with severe COVID-19 at Cipto Mangunkusumo Hospital and Universitas Indonesia Hospital from March to August 2020. We extracted the subject's CCI score from the medical records and the 28-day mortality after ICU admission. The CCI score was validated by the Hosmer–Lemeshow calibration test, determination of area under the curve (AUC), and optimal cut-off point for the critical patients in the ICU. We used the chi-square test to examine the association of comorbidities with mortality.

RESULTS Mortality was higher in CCI scores >4 (odds ratio [OR]: 8.83; 95% confidence interval [CI] = 1.81–43.01). The CCI score had moderate discrimination ability (AUC 76.1%; 95% CI = 0.661–0.881). Chronic kidney disease (CKD) (OR: 18.00, 95% CI = 2.19–147.51), congestive heart failure (CHF) (OR: 4.25, 95% CI = 1.23–14.75), and uncontrolled diabetes mellitus (DM) (OR: 18.429, 95% CI = 2.19–155.21) increased the risk of 28-day mortality.

CONCLUSIONS The CCI score could predict the 28-day mortality of critical COVID-19 patients. The coexistence of CKD, CHF, DM, peripheral vascular disease, and peptic ulcer in COVID-19 patients should be considered for patient management.

KEYWORDS Charlson comorbidity index, COVID-19, critical illness, mortality

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) on March 11, 2020;[1] it has since evolved into an unprecedented global health crisis. As of May 12, 2020, the global case fatality rate (CFR) of COVID-19 was 6.95%, and the corresponding Indonesian CFR was 6.93%.[2] COVID-19 is associated with high mortality rates in the intensive care units (ICUs). Considering the high demand for ICU beds and the impact on hospital capacity preparedness, it is important to establish a prediction tool for ICU mortality to enable early prognosis screening. Such a tool will help identify patients with better outcomes and lower mortality risks, which will subsequently benefit ICU admission screening and management.[3]

The most frequently used ICU scoring systems, Acute Physiology and Chronic Health Evaluation II and Simplified Acute Physiology Score II, have yielded unusually low scores in non-survivors and underestimated the actual disease severity and

mortality risk in critically ill COVID-19 patients.[1] The Charlson comorbidity index (CCI) is a well-known scoring system that considers 19 comorbidities, weighted 1–6 depending on their severity; from these, a single numerical score (ranging from 0 to 33) is obtained, which enables the prediction of the 1-year mortality. Christensen et al[4] reported that when controlled for age and sex, a CCI score of >0 was associated with an increased risk of severe COVID-19 and death. Although the CCI was initially used to predict long-term mortality, it has recently been used for ICU admission screening and to assess short-term mortality in high-risk patients.[4–6] In clinical practice, the CCI helps stratify patients into subgroups based on severity, develops care models, and targets resource allocation.[7] A mortality predictor can be used to assess the course of a particular disease and disease management strategies, including resource allocation. Therefore, this study aimed to validate the CCI as a predictor of mortality in critically ill COVID-19 patients admitted to the ICU.[7]

METHODS

Research design

This retrospective cohort study was conducted at Cipto Mangunkusumo Hospital, Jakarta, Indonesia and Universitas Indonesia Hospital, Depok, Indonesia from September to October 2020. The study population comprised COVID-19 patients admitted to the ICU between March and August 2020. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia (No: KET-745/UN2.F1/ETIK/PPM.00.02/2020). The minimum sample size for this study was estimated to be 95 patients with the following parameters: predefined type-1 error (α), 5%; precision, 10%; and expected area under the curve (AUC), 80%.

Inclusion and exclusion criteria

The inclusion criteria were aged >18 years, positive tests for COVID-19, and ICU admission. The exclusion criteria were death before admission to the ICU, incomplete medical records, and unknown mortality outcomes before 28 days of treatment.

Patient selection

Data of patients who met the criteria for the diagnosis and surveillance of COVID-19, according to the WHO COVID-19 case definition (updated in Public Health Surveillance for COVID-19 [December 16, 2020]), were collected from a registry book and electronic medical records maintained in the ICU. Confirmed case patients should be patients who fulfilled the following criteria: 1) COVID-19 diagnosis confirmed via positive nucleic acid amplification tests or reverse transcription-polymerase chain reaction assays; 2) presence of severe acute respiratory illness, chest imaging findings suggestive of COVID-19, recent onset of anosmia or ageusia in the absence of other etiologies, and respiratory distress prior to death; and 3) history of contact with a probable or confirmed case or of links with a COVID-19 cluster.[8]

Comorbidity diagnostic criteria

Data for CCI score analysis were extracted from electronic health records. Each comorbidity was defined based on the International Classification of Diseases codes. The comorbidities were diagnosed by the physician-in-charge after considering the laboratory findings obtained within the first 24 hours of ICU admission.[9]

Myocardial infarction was categorized as definite or probable with electrocardiogram changes and/or enzymatic changes. Congestive heart failure (CHF) was characterized by exertional dyspnea or paroxysmal nocturnal dyspnea. Peripheral vascular disease (PVD) was characterized by the presence of intermittent claudication or chronic arterial insufficiency, a history of gangrene or acute arterial insufficiency, or an untreated thoracic or abdominal aorta aneurysm (≥6 cm). Cerebrovascular disease was characterized by a cerebrovascular accident with minor or no residual symptoms and transient ischemic attacks. Dementia was defined as a chronic cognitive deficit. Chronic obstructive pulmonary disease was characterized by the presence of chronic respiratory disorder with a history of passive or active smoking. Peptic ulcer disease was characterized by a history of ulcer bleeding or any history of treatment for ulcer disease. Liver disease was categorized as severe (cirrhosis and portal hypertension with variceal bleeding history), moderate (cirrhosis and portal hypertension without a variceal bleeding history), and mild (chronic hepatitis or cirrhosis without portal hypertension). Diabetes mellitus (DM) was categorized as non-DM, controlled DM without complications, and uncontrolled DM with chronic complications. Hemiplegia was defined by the

presence of weakness as a sequela of a cerebrovascular accident. Chronic kidney disease (CKD) was categorized as moderate (creatinine >3 mg/dl) to severe (on dialysis therapy). Solid tumors were identified as with or without metastasis. Leukemia was classified as acute or chronic myelogenous leukemia, acute and chronic lymphocytic leukemia, and polycythemia vera. Lymphomas comprised Hodgkin's lymphoma, lymphosarcoma, Waldenstrom's macroglobulinemia, myeloma, and other lymphomas.[9] AIDS was defined as patients included with definite or probable AIDS. Connective tissue disease was included as systemic lupus erythematous, polymyositis mixed connective tissue disease, polymyalgia rheumatica, and moderate to severe rheumatoid arthritis.[9]

Mortality outcome

The survival or mortality outcomes within 28 days after ICU admission were recorded by a research assistant blinded to the comorbidity data. Data on patients discharged home before 28 days of hospitalization were obtained by contacting them directly. All of participants could be contacted, and the informed consents were complete. The participants were excluded if the data were incomplete or they could not be contacted.

Statistical analysis

All data were analyzed using SPSS software version 25.0 (IBM Corp., USA). The patient characteristics were subjected to a univariate analysis. Categorical data are expressed as proportions, whereas numerical data are expressed as means if normally distributed or as medians if non-normally distributed.

The CCI scores were classified into two groups (≤4 and >4 points) to predict 28-day mortality. The cut-offs are based on previous studies suggesting that patients with CCI scores of ≤4 points are at a lower risk of mortality.[10] A bivariate analysis was performed to evaluate the association of the CCI scores of ≤4 and >4 with the 28-day ICU mortality in patients with COVID-19. Categorical variables were analyzed using a chi-square test or Fisher's exact test. Numerical variables were analyzed using an unpaired or Mann–Whitney tests. $p<0.05$ was considered statistically significant. The predictive validity of the CCI score was evaluated using multivariate logistic regression analysis based on the discrimination and calibration values; the calibration values were calculated using the Hosmer–Lemeshow test.

RESULTS

Among the 213 patients isolated in the ICU, 2 and 3 patients were excluded for missing medical records and incomplete data, respectively. Among the remaining 208 patients, 95 (45.7%) were confirmed to have COVID-19. Table 1 shows the characteristics and CCI scores between the COVID-19 survivors and non-survivors.

The proportion of men was higher than that of women in both the survivor and non-survivor groups. The Hosmer–Lemeshow calibration test showed that the CCI score can predict the outcomes of COVID-19 (chi-square = 1.242 and $p = 0.743$). The AUC value was 76.1% (95% confidence interval [CI] = 0.661–0.881), showing that the CCI score has moderate discrimination quality in predicting the outcome of COVID-19 critically ill patients (Figure 1). The cut-off on the CCI score was 2.5 with sensitivity at 72.5% and specificity at 67.3% in predicting the 28-day mortality of COVID-19 patients in the ICU. Table 1 presents data on the association between CCI scores and patient outcomes. The mortality risk was higher in the group with CCI scores >4 than in the group with CCI scores ≤4.

Some comorbidities were significantly associated with mortality in COVID-19 patients; significant associations were found between mortality and patients with moderate-to-severe CKD (odds ratio [OR]: 18.00, 95% CI = 2.19–147.51, $p = 0.001$), CHF (OR: 4.25, 95% CI = 1.23–14.75, $p = 0.016$), DM (controlled DM OR: 1.86, 95% CI = 0.68–5.07; uncontrolled DM OR: 18.43, 95% CI = 2.19–155.21; $p = 0.003$), PVD (OR: 0.0402, 95% CI = 0.31–0.52, $p = 0.039$), and peptic ulcer (OR: not available [NA], 95% CI = NA, $p = 0.029$). These patients were at a relatively high risk of mortality; among patients with DM, the mortality risk was higher in those with uncontrolled DM than in those without DM (OR: 18.429, 95% CI = 2.19–155.21, $p = 0.003$).

DISCUSSION

We found a significant association between the CCI and short-term ICU mortality in patients with COVID-19. A higher CCI score was associated with poor outcomes in the acute setting. Moreover, the CCI score had good discrimination and calibration values for predicting the outcomes of patients with confirmed COVID-19 admitted to the ICU. With an AUC of 76.1%, the CCI can predict mortality in the ICU

Table 1. Outcomes on COVID-19 patients based on comorbid variables

Variables	Outcomes		OR (95% CI)	*p*
	Non-survivors, n (%) (N = 40)	Survivors, n (%) (N = 55)		
Age (years), mean (SD)	59.03 (14.07)	46.60 (15.05)	-	-
Male sex	27 (37)	45 (63)	-	-
Confirmed status	40 (42)	55 (58)	-	-
CCI score				**0.003**
Score ≤4	30 (32)	53 (56)	1.00	
Score >4	10 (11)	2 (2)	8.83 (1.81–43.01)	
CKD moderate–severe	10 (91)	1 (9)	18.00 (2.19–147.51)	**0.001**
DM				**0.003**
Non-DM	21 (33)	43 (67)	1.00	
Controlled DM	10 (48)	11 (52)	1.86 (0.68–5.07)	
Uncontrolled DM	9 (90)	1 (10)	18.43 (2.19–155.21)	
CHF	10 (71)	4 (29)	4.25 (1.23–14.75)	**0.016**
MI	12 (48)	13 (52)	1.39 (0.55–3.47)	0.487
COPD	11 (44)	14 (56)	1.11 (0.44–2.79)	0.823
Liver disease mild–severe	2 (40)	3 (60)	0.92 (0.15–5.73)	1.000
PVD	3 (100)	0 (0)	0.04 (0.31–0.52)	**0.039**
Solid tumor	2 (33)	4 (67)	0.67 (0.12–3.86)	1.000
CVA or TIA	2 (100)	0 (0)	NA*	0.175
Dementia	2 (67)	1 (33)	NA*	0.571
AIDS	0 (0)	1 (100)	NA*	1.000
Connective tissue disease	0 (0)	1 (100)	NA*	1.000
Peptic ulcer	4 (100)	0 (0)	NA*	**0.029**

CCI=Charlson comorbidity index; CHF=congestive heart failure; CI=confidence interval; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; COVID-19=coronavirus disease 2019; CVA=cerebrovascular accident; DM=diabetes mellitus; MI=myocardial infarction; NA=not available; OR=odds ratio; PVD=peripheral vascular disease; SD=standard deviation; TIA=transient ischemic attack

*Unable to be analyzed due to absence of patient in one or more cells. Categorical data were analyzed using chi-square or Fisher's exact test. There was no patient with leukemia, hemiplegia, and lymphoma in the survivor and non-survivor groups

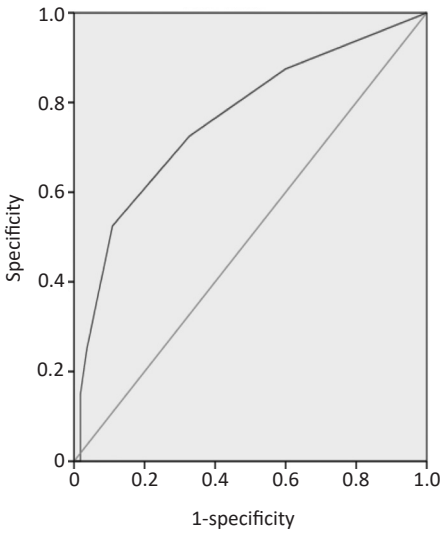

Figure 1. Charlson comorbidity index (CCI) score's receiving operating characteristic curve (ROC) in predicting outcome of confirmed case

with moderate quality and good match-model results using the Hosmer–Lemeshow goodness of fit test. This is in line with the findings reported by Zhou et al[11] who stated that with an AUC of 81.6%, the CCI score had a good discrimination ability to predict the outcome of confirmed COVID-19 patients in ICU. Our study revealed a predictive cut-off CCI score of 2.5 for mortality (sensitivity: 72.5%, specificity: 67.3%) and the risk of mortality increased by 1.89 times for every increase in the CCI score.

COVID-19 patients with comorbidities are believed to be at a higher risk of severe COVID-19. This study showed that compared to patients with COVID-19 but without CKD, those with both COVID-19 and CKD were at an 18-fold higher mortality risk. A previous meta-analysis also revealed a significant association between CKD and severe COVID-19, which affected the mortality

rate.[9] CKD modifies the immune system via persistent systemic inflammation and immunosuppression secondary to dysfunctional B cells and phagocytic T cells, along with increased proinflammatory cytokine production and monocyte activation. These changes are worsened by decreased kidney function. Neutrophil function decreases in patients before and on dialysis. In patients with CKD, impaired B and T cells undergo apoptosis; this causes T lymphopenia, progressive immunodeficiency, and a high risk of infection.[9,12]

CHF was significantly associated with mortality outcomes. Patients with COVID-19 and CHF were at a 4.25-fold higher risk of mortality than those without CHF. In a previous study, compared with patients with COVID-19 but without CHF, those with COVID-19 and CHF were associated with an approximately 2-fold higher risk of mortality, 3 times higher risk of the need of mechanical ventilation, and a longer hospital stay length despite controlling for relevant clinical factors.[13] CHF induces monocytes to produce many tumor necrosis factor alpha and lesser interleukin-10, thereby weakening immunity. Acute COVID-19 causes tissue damage and cardiac depression, leading to the onset of acute decompensated heart failure. The resultant decreased hemodynamic stability is more likely to fail to overcome the severe inflammation common in critically ill COVID-19 patients.[14,15] Moreover, coagulation dysfunction triggered by sepsis worsens CHF.[16]

PVD was significantly correlated with COVID-19-associated ICU mortality. A case study revealed PVD onset without a prior history; unfortunately, few studies have examined the association between peripheral arterial disease and COVID-19. However, inflammatory cells, such as polymorphonuclear neutrophils, T lymphocytes, histiocytes, and macrophages in the lining of blood vessels, are correlated with endothelial proliferation, angiogenesis with collagen deposition degree, myofibroblast proliferation, and thrombosis.[17]

DM is significantly associated with COVID-19 outcomes. It worsens the risk of COVID-19 through several mechanisms wherein the viral load and high angiotensin-converting enzyme 2 (ACE2) receptor expression serves as a gateway for viral infection in the lung tissues. Viral replication increases blood sugar levels.[18] Patients with DM present with mild-to-chronic elevations in inflammation-inducing macrophage, monocyte, and T-cell recruitment levels, which worsen the already excessive production of proinflammatory cytokines and further damage the lung tissues. This damage is associated with some structural changes in the lungs, including vascular permeability changes and alveolar dysfunction, which reduce gaseous exchange. These respiratory impairments complicate lung function and result in a higher risk of mechanical ventilator requirement.[18–20] Severe acute respiratory syndrome coronavirus 2 infects the endothelial cell directly via the ACE2 receptor. Patients with DM with highly elevated cytokine levels suffer from systemic hypercoagulation, tissue edema, and microcirculatory vasoconstriction, all of which worsen organ ischemia in severe COVID-19. Hypercoagulation, along with increased platelet activation and adhesion to the endothelial wall, promotes thromboembolic events in COVID-19.[18,21]

Only a few studies have evaluated the association between peptic ulcers and COVID-19. The present study revealed a significant association between peptic ulcer incidents and mortality in patients with COVID-19. A case study by Melazzini et al[22] revealed that gastrointestinal bleeding secondary to peptic ulcers was common in patients with severe COVID-19. The mechanism underlying COVID-19-associated peptic ulcer development may involve acute gastric mucosa inflammation, direct gastric epithelial damage by the causative virus, and cytokine-activated inflammation.[22]

This study had several limitations. Considering the urgent need for short-term mortality predictors to develop effective management strategies, this study was retrospective in nature and was conducted over a short duration. Secondary data were extracted from medical records, incurring a risk of selection, recall, or misclassification bias; furthermore, causation could not be determined. The included patients received multidisciplinary care; this increased the potential bias in establishing the operational definition of each comorbidity according to personal interpretation. Limited diagnostic test availability may have increased the bias in the determining confirmed cases, which may have influenced the patient's disease progression, prognosis, and mortality. Moreover, the small sample size for the CCI cut-off resulted in disproportionate data that affected its validity as a predictive tool. We suggest further prospective observational studies to assess the relationships between the risk factors (adjusted for comorbidities) and the CCI score for predicting disease severity and mortality in critically ill COVID-19 patients.

In conclusion, the CCI score could predict the 28-day mortality in patients with critical COVID-19. Critical

COVID-19-associated mortality rates remain high; thus, mortality risk stratification of patients with COVID-19 based on their underlying comorbidities may improve clinicians' ability to identify those who require more intensive care and greater hospital financial allocation for improved outcomes. Moreover, the presence of comorbidities, including CKD, CHF, DM, PVD, and peptic ulcers in these patients, should be considered during patient management.

Conflict of Interest

The authors affirm no conflict of interest in this study.

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