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Application of Charlson Comorbidity Index to assess prognosis of 18-month mortality in patients with acute myocardial infarction

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ABSTRACT

Aim. To evaluate the prognostic value of the Charlson Comorbidity Index (CCI) for predicting 18-month all-cause mortality and develop a nomogram for predicting 18-month mortality in acute myocardial infarction (MI) patients.

Materials and methods. The prospective, single-center, observational study included 712 consecutive patients with acute MI undergoing coronary angiography within 24 hours after hospitalization. The primary endpoint was 18-month all-cause mortality. The logistic regression analysis was adopted to identify independent prognostic factors. A nomogram for predicting the endpoint was developed using the multivariate analysis. The discriminative ability of the CCI and a nomogram were evaluated using the receiver-operating characteristic (ROC) curve analysis.

Results. Of the patients, 61% were male, median age was 65 years (interquartile range (IQR) was 56–74years). Median CCI was 4 (IQR: 3–6) points. The mortality rate was 12.1% at 18 months with the area under the curve (AUC) of 0.797 for CCI (95% confidence interval (CI): 0.746–0.849; p < 0.001). The multivariate analysis revealed that CCI (odds ratio (OR) 1.28; 95% CI 1.08–1.52; p = 0.004), age (OR 1.06; 95% CI 1.02–1.09; p = 0.002), and three-vessel coronary artery disease (OR 2.60; 95% CI 1.36–4.98; p = 0.004), incorporated into the nomogram, were independent predictive factors of an adverse outcome. The nomogram showed good discrimination in predicting 18-month mortality in patients with acute MI (AUC = 0.819; 95% CI: 0.767–0.870; p < 0.001; sensitivity 65.1%; specificity 88.2%.).

Conclusion. CCI was independently associated with and moderately predicted 18-month mortality in patients with acute MI. The proposed nomogram facilitated early identification of high-risk patients, allowing for the implementation of more effective treatment strategies and reducing acute MI mortality.

Keywords: Charlson Comorbidity Index, comorbidity, mortality, myocardial infarction, nomogram

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the Ethics Committee at the Institute of Medicine of RUDN University.

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Применение индекса коморбидности Чарльсона для оценки прогноза 18-месячной смертности у пациентов с острым инфарктом миокарда

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РЕЗЮМЕ

Цель. Оценить прогностическую способность индекса коморбидности Чарльсона (ИКЧ) для прогнозирования 18-месячной смертностиу пациентов с острым инфарктом миокарда (ИМ) с применением номограммы, разработанной на основе математического анализа.

Материалы и методы. В проспективное одноцентровое наблюдательное исследование были включены 712 последовательных пациентов с острым ИМ, которым выполняли коронарографию в течение 24 ч с момента госпитализации. Первичной конечной точкой исследования была принята смерть от всех причин в течение 18 мес наблюдения. Для выявления независимых прогностических факторов риска наступления смерти применялся логистический регрессионный анализ. На основе результатов многофакторного анализа была разработана номограмма для прогнозирования клинического исхода. Дискриминационная способность ИКЧ и номограммы была оценена с помощью логистической регрессии, в качестве инструмента оценки его диагностической способности применялся метод ROC-анализа (ROC-анализ).

Результаты. Среди пациентов доминировали мужчины (61%), медиана возраста составила 65 лет (интерквартильный размах [ИКР] 56–74 года). Медиана ИКЧ составила 4 (ИКР: 3–6) балла. Смертность в течение 18 мес составила 12,1%, с площадью под ROC-кривой для ИКЧ 0,797 (95%-й доверительный интервал [ДИ] 0,746–0,849; p<0,001). Многофакторный анализ показал, что ИКЧ (отношение шансов [ОШ] 1,28; 95%-й ДИ 1,08–1,52; p=0,004), возраст (ОШ 1,06; 95%-й ДИ 1,02–1,09; p=0,002), трехсосудистое поражение коронарных артерий (ОШ 2,60; 95%-й ДИ 1,36–4,98; p=0,004), включенные в номограмму, были независимыми предиктивными факторами неблагоприятного клинического исхода. Номограмма продемонстрировала хорошую дискриминационную способность прогнозирования 18-месячной смертности у пациентов с острым ИМ (площадь под ROC-кривой 0,819; 95%-й ДИ 0,767–0,870; p<0,001; чувствительность 65,1%; специфичность 88,2%).

Заключение. ИКЧ независимо ассоциировался и умеренно предсказывал смертность в течение 18 мес у пациентов с острым ИМ. Предложенная номограмма облегчила раннюю идентификацию пациентов с высоким риском событий, что позволило внедрить более эффективные стратегии лечения и снизить смертность при остром ИМ.

Ключевые слова: индекс коморбидности Чарльсона, инфаркт миокарда, коморбидность, смертность, номограмма

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено комитетом по этике Медицинского института РУДН.

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INTRODUCTION

Cardiovascular diseases (CVDs) are the most common cause of mortality worldwide, which substantially contributes to loss of good health and excessive healthcare costs [1, 2]. Acute myocardial infarction (MI) is one of the most common causes of death from CVDs. Despite improvements in the diagnostic, treatment, and preventive strategies, CVD remains the main cause of death in Europe, with coronary artery disease (CAD) being the most common cause of CVD mortality [2]. Growing aging population has resulted in higher prevalence of comorbidities, particularly among patients with acute MI [3] and is associated with an increased risk of mortality and future cardiovascular events [4, 5]. Therefore, determining key risk factors and implementing appropriate clinical recommendations can make a significant contribution to saving the lives of individuals with acute MI and comorbidities.

The Charlson Comorbidity Index (CCI) is a well-established surrogate marker of comorbidity, validated to predict a risk of adverse outcomes in patients with acute MI [6]. Despite frequent presence of comorbidities in MI patients, their role in the long-term prognosis after acute MI has been poorly studied.

The aim of the study was to evaluate the prognostic value of CCI for predicting 18-month all-cause mortality and develop a nomogram for predicting 18-month mortality in patients with acute MI.

MATERIALS AND METHODS

The present study is a prospective, single-center, observational study. It included all consecutive patients aged > 18 years admitted with acute MI to Vinogradov City Clinical Hospital (Moscow, Russia) from January 2017 to December 2018. The patients underwent coronary angiography (CAG) within 24 hours after hospitalization. The exclusion criteria were type 3, 4, or 5 MI. The diagnosis of acute MI was made according to the Third universal definition

of MI [7]. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at the Institute of Medicine, Peoples' Friendship University of Russia, and complied with the Declaration of Helsinki.

Data collection and clinical outcomes. Variables included clinical characteristics, interest cardiovascular risk factors, comorbidities, physical examination findings, blood test results, and imaging data (electrocardiography, echocardiography, and CAG). Cardiac troponin I levels were measured using the Access 2 Immunoassay System (Beckman Coulter, USA), with 99th percentile upper reference limit being 0.02 ng / l. The CCI was calculated using baseline data by summing all comorbidity scores (available online) [8, 9]. The Global Registry of Acute Coronary Events (GRACE) 2.0 score was used to stratify risks for MI patients [10]. Anemia was defined as a hemoglobin concentration of less than 120 g / 1 for men or less than 130 g / 1 for women [11]. Multivessel CAD was defined as the presence of ≥ 70 % stenosis in two or more major coronary arteries of ≥ 2.5 mm in diameter detected during direct subtraction angiography [12].

The primary endpoint was 18-month all-cause mortality, both in-hospital and out-of-hospital, that was recorded in patient electronic medical records and death registers.

Statistical analysis. Statistical analysis was performed using the IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, IL, USA) and R software (version 3.6.3) software. Quantitative variables were presented as the mean and the standard deviation for normally distributed data or as the median (*Me*) and the interquartile range (IQR) for non-normally distributed data. Qualitative variables were presented as absolute values and percentages. Categorical variables were compared using the Chi-square and Fisher's exact tests, while continuous variables were compared by the unpaired Student *t*-test and Mann – Whitney *U*-test. The logistic regression analysis was used to identify factors associated with 18-month

mortality. The odds ratios (OR) and 95% confidence intervals (CI) were presented. Based on the estimated factors from the multivariate logistic regression model, a nomogram was constructed to assess the risk of 18-month death (rms package in R). The ROC analysis was used to assess the discriminating ability of the CCI and the nomogram in relation to 18-month mortality [13]. A two-tailed *p* value of 0.05 was chosen as a threshold for statistical significance for all tests.

RESULTS

A total of 712 consecutive patients were included in the study; 434 patients (61%) were male. The median age of patients was 65 (IQR: 56–74) years; 47.8% of patients were hospitalized with ST elevation. The proportion of patients < 44 years, \geq 45 and < 59 years, \geq 60 and < 74 years, \geq 75 and < 90 and \geq 90 years was 8.84%, 5.8%, 28.1%, 42.6%, 23%, and 0.6%, respectively. During the follow-up period, 86 patients (12.1%) died.

The baseline characteristics of the patients are shown in Table 1. In the group of diseased patients, more elderly patients, female gender,

ST elevation, arterial hypertension, CAD, prior MI, prior heart failure (HF), prior stroke, atrial fibrillation, chronic kidney disease (CKD), anemia, Killip class II–IV acute heart failure, three-vessel CAD, and higher CCI and GRACE scores were more common. Values for systolic blood pressure (BP), hemoglobin, creatinine, and left ventricular ejection fraction (LVEF) were lower in the group of deceased patients. There were no significant differences between the groups in prior myocardial revascularization, peripheral artery disease (PAD), chronic lung disease (asthma and / or chronic obstructive pulmonary disease), gastric and duodenal ulcer, troponin level, and the frequency of percutaneous coronary intervention (PCI).

The median CCI score was 4 (IQR: 3–6, range 0–13). The distribution of CCI scores in all the participants was shown in Fig.1. Among components of CCI, past history of MI was the most frequent comorbidity (21.8%) followed by diabetes mellitus (21.1%), chronic lung diseases (asthma and chronic obstructive pulmonary disease) (16.2%), dementia (9.3%), gastric and duodenal ulcer (9.1%), and CKD (8.6%) (Table 2).

Basic characteristics of 712 patients with myocardial infarction

Table 1

Parameter	Patient population, $n = 712$	Survived patients, $n = 626$	Deceased patients, $n = 86$	p
Age, years, Me (IQR)	65 (56; 74)	64 (55; 71.2) 76.5 (67.7; 83.2)		< 0.001
Women, <i>n</i> (%)	278 (39)	227 (36.3)	51 (59.3)	< 0.001
ST elevation, n (%)	340 (47.8)	289 (46.2)	51 (59.3)	0.022
Arterial hypertension, n (%)	634 (89)	552 (88.2)	8.2) 82 (95.3)	
CAD, n (%)	328 (46.1)	267 (42.7)	267 (42.7) 61 (70.9)	
Prior MI, n (%)	155 (21.8)	125 (20)	125 (20) 30 (34.9)	
Prior myocardial revascularization, n (%)	85 (11.9)	77 (12.3) 8 (9.3)		0.483
Prior HF, n (%)	57 (8.0)	44 (7.0) 13 (15.1)		0.017
Diabetes, n (%)	150 (21.1)	125 (20) 25 (29.1)		0.066
Prior stroke, n (%)	51 (7.2)	36 (5.8) 15 (17.4)		< 0.001
History of atrial fibrillation, n (%)	73 (10.3)	57 (9.1)	.1) 16 (18.6)	
CKD, n (%)	61 (8.6)	44 (7.0)	44 (7.0) 17 (19.8)	
PAD, n (%)	26 (3.7%)	20 (3.2)	3.2) 6 (7.0)	
Chronic lung disease, n (%)	115 (16.2%)	95 (15.2)	20 (23.3)	0.062
Gastric and duodenal ulcer, n (%)	65 (9.1%)	57 (9.1)	57 (9.1) 8 (9.3)	
CCI, score, Me (IQR)	4 (3; 6)	4 (3; 5)	6 (5; 8)	< 0.001
Anemia, n (%)	189 (26.5)	145 (23.2)	44 (51.2)	< 0.001
Chest pain, n (%)	658 (92.4)	583 (93.1)	583 (93.1) 75 (87.2)	
Shortness of breath, n (%)	124 (17.4)	102 (16.3) 22 (25.6)		0.047
Killip class II–IV, HF n (%)	160 (22.5)	115 (18.4) 45 (52.3)		< 0.001
Systolic blood pressure, mm Hg., Me (IQR)	140 (120; 159)	140 (120; 160)	130 (110; 150)	0.019

Table 1 (continued)

Parameter	Patient population, $n = 712$	Survived patients, $n = 626$	Deceased patients, $n = 86$	p
Diastolic blood pressure, mm Hg., Me (IQR)	80 (76; 89)	80 (77; 90)	80 (70; 80)	0.021
Troponin I, ng / ml, Me (IQR)	0.39 (0.09; 2.85)	0.39 (0.09; 2.86)	0.42 (0.09; 2.50)	0.996
Hemoglobin, g / l, Me (IQR)	136 (123; 147)	138 (125; 148)	122 (105; 136.5)	< 0.001
Creatinine, mcmol / l, Me (IQR)	94 (80; 107)	69 (55; 84)	52.5 (41; 66.5)	0.014
LVEF, %, Me (IQR)	45 (40; 54)	45 (40; 54)	40 (34; 50)	< 0.001
No lesion / stenosis of CA < 50%, n (%)	73 (10.3)	69 (11)	4 (4.7)	0.086
Three-vessel CAD, n (%)	390 (54.8)	320 (51.1)	70 (81.4)	< 0.001
PCI, n (%)	566 (79.5)	499 (79.7)	67 (77.9)	0.671
GRACE, score, Me (IQR)	117 (98; 141)	113 (96; 134)	149 (128.5; 171.25)	< 0.001

Note. AIDS - acquired immunodeficiency syndrome

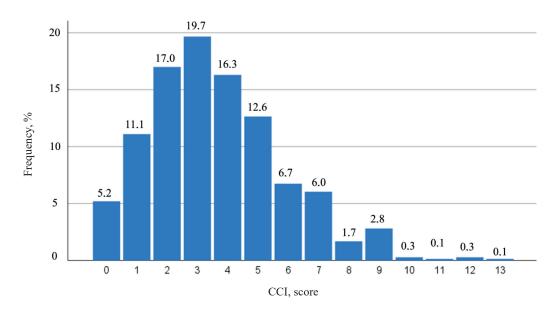


Fig. 1. Distribution of CCI scores among the patients

Frequency of comorbidities for each CCI category Comorbidity Number Frequency Prior MI 155 21.8 Diabetes (mild to moderate) 150 21.1 Chronic lung disease 115 16.2 Dementia 66 9.3 Gastric and duodenal ulcer 65 9.1 CKD 61 8.6 Prior hospitalization for HF 57 8.0 Stroke 51 7.2 Cancer 27 3.8 PAD 3.7 26 4 0.6 Liver disease 0.1 AIDS 1 0 0 Rheumatic disease Hemiplegia or paraplegia 0

Table 2

The univariate analysis showed that CCI score, age, female gender, ST elevation, systolic BP, diastolic BP, atrial fibrillation, anemia, Killip class HF, creatinine level, LVEF, and three-vessel CAD were associated with 18-month all-cause mortality (p < 0.05) (Table 3). The multivariate analysis revealed that CCI score (OR 1.28, 95% CI 1.08–1.52, p = 0.004), age (OR 1.06, 95% CI 1.02–1.09, p = 0.002), and three-vessel CAD (OR 2.60, 95%CI 1.36–4.98, p = 0.004) were independently associated with the primary endpoint.

The analysis of ROC curves for CCI predicting 18-month all-cause mortality showed that the area under the curve (AUC) for CCI was 0.797 (95% CI: 0.746-0.849, p < 0.001). The sensitivity and

specificity were 69.8% and 78.4%, respectively with the cut-off CCI value being >5 points (Fig. 2).

Based on the estimated variables in the multivariate model, a nomogram was developed to predict the risk of 18-month mortality in patients with acute MI (AUC = 0.819, 95% CI: 0.767–0.870, p < 0.001, sensitivity 65.1%, specificity 88.2%) (Fig. 3). The risk of death within 18 months in patients with acute MI was assessed according to the following equation:

Risk =
$$= \frac{1}{(1 + e^{-z})}$$
,

where Z = -7.984 + 0.341 x CCI + 0.051 x age + 0.967 x three-vessel CAD.

Instruction for use: a total score is summed from the score of each factor on the corresponding axis with drawing a vertical line to the "Points" axis. Summing scores of all factors and drawing a vertical line to the "Risk of 18-month mortality" line determine the individual's risk of death within 18 months.

Table 3

Univariate and multivariate analysis of the risk factors in predicting 18-month all-cause mortality							
Parameter	Univariate analysis		Multivariate analysis				
	OR (95% CI)	p	OR (95% CI)	р			
CCI, score	1.65 (1.47–1.84)	< 0.001	1.28 (1.08–1.52)	0.004			
Age, years	1.09 (1.07–1.12)	< 0.001	1.06 (1.02–1.09)	0.002			
Women	2.56 (1.62–4.06)	< 0.001	1.35 (0.73–2.51)	0.336			
ST elevation MI	1.70 (1.07–2.69)	0.023	1.33 (0.76–2.34)	0.318			
Systolic BP ≤ 115 mm Hg	2.37 (1.43–3.95)	0.001	2.84 (1.09–7.38)	0.032			
Diastolic BP ≤ 70 mm Hg	1.88 (1.45–3.10)	0.012	2.14 (0.82–5.61)	0.121			
History of atrial fibrillation	2.28 (1.24-4.19)	0.008	1.32 (0.64–2.75)	0.453			
Anemia	3.47 (2.19–5.51)	< 0.001	1.67 (0.93–2.99)	0.083			
Killip class II–IV ≥ 2	2.67 (2.05–3.45)	< 0.001	1.22 (0.66–2.26)	0.523			
Creatinine level ≥ 115 mcmol / 1	1.83 (1.08–3.08)	0.023	1.09 (0.55–2.13)	0.811			
LVEF ≤ 40%	3.16 (1.93–5.17)	< 0.001	1.79 (0.97–3.32)	0.063			
Three-vessel CAD	4.18 (2.38–7.36)	< 0.001	2.60 (1.36–4.98)	0.004			

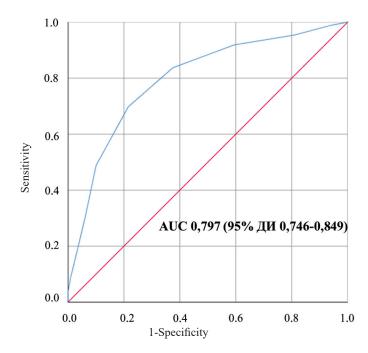


Fig. 2. The analysis of the ROC curve for CCI for predicting 18-month all-cause mortality in patients with acute MI

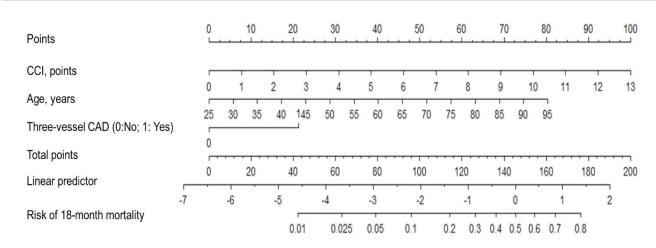


Fig. 3. Nomogram for predicting 18-month all-cause mortality in acute myocardial infarction: Charlson Comorbidity Index, age, and three-vessel coronary artery disease

DISCUSSION

The obtained results were used to build a predictive model for this population. In our study, male patients prevailed, which is consistent with the findings from previous studies [6, 14, 15]. Arterial hypertension had higher prevalence in our study (89%) than in the works by J. Sanchis et al. including 1,017 non ST-elevation acute coronary syndrome (NSTE-ACS) patients [16] and J.E. Núñez et al. in a cohort of 1,035 acute MI patients [17], where arterial hypertension accounted for 65 and 61.4% of the total population, respectively.

When analyzing the comorbidity profile in CCI, past history of MI (21.8%) and diabetes mellitus (21.1%) were the most frequent comorbidities, which is consistent with the results of the study by D. Radovanovic et al. including 30,711 patients with acute coronary syndrome (ACS) from 69 Swiss hospitals in the AMIS Plus registry [6]. In their study, prior MI and diabetes mellitus were reported in 18 and 14.7% of cases, which is concordant with the study by M. Hautamäki involving 1,576 patients in the MADDEC (Mass Data in Detection and Prevention of Serious Adverse Events in Cardiovascular Disease) study, where prior MI accounted for 22%. In contrast to the findings obtained by J.E. Núñez et al. [17], diabetes mellitus without target organ damage (21.5%) was the most common CCI category, followed by a history of acute MI (17.6%), chronic obstructive pulmonary disease (8.6%), stroke (6.6%), HF (6.4%), PAD (5.5%), and kidney disease (4.1%).

Previous studies have confirmed the positive correlation between CCI and adverse outcomes in patients with MI [3, 17–19]. In a prospective,

multicenter, observational study involving 29,620 acute MI patients, 46.8% had comorbidities [6]. CCI was an independent predictor of in-hospital mortality: CCI = 1 had OR of 1.36 (95% CI 1.16–1.60; p = 0.001), CCI = 2 had OR of 1.65 (95% CI 1.38–1.97; p < 0.001), and CCI \geq 3 had OR of 2.20 (95% CI 1.86–2.57; p < 0.001). With a combination of CCI, age, and gender in the ROC analysis, the AUC was 0.761 (95% CI 0.74–0.773) for predicting inhospital mortality. In contrast, using CCI alone yielded the AUC of 0.670 (95% CI 0.656–0.685) for in-hospital mortality. After adjustments for age, the AUC improved to 0.83 (95% CI 0.80–0.86) for predicting 12-month mortality.

M. Schmidt et al. examined the association between comorbidity and mortality in 234,331 patients with first-time hospitalization for MI from 1984 through 2008 [3]. The authors reported an association between comorbidity and 30-day mortality (adjusted hazard ratio (aHR) 1.35 (95% CI 1.26-1.45) for moderate (CCI = 1) and 1.96 (95% CI 1.83-2.11) for very severe comorbidity (CCI \geq 3)), as well as 12-month mortality (aHR 1.83 (95% CI 1.68-2.00) for moderate and 3.89 (95% CI 3.58-4.24) for severe comorbidity). In another study [19], the overall aHR for all-cause mortality was 1.39 (95% CI 0.90-2.14) and 2.33 (95% CI: 0.79-6.84) for mild comorbidity, 2.05 (95% CI: 0.69–6.06) for moderate comorbidity, and 1.07 (95% CI: 0.64–1.80) for severe comorbidity. In a study involving 1,035 consecutive acute MI patients, J.E. Núñez et al. found that a higher CCI score independently predicted mortality or acute MI within 30 days and one year [17].

The analysis of factors associated with fatal outcomes revealed that CCI, age, and three-vessel CAD were independent predictors of 18-month mortality in patients with acute MI. In our study, the proportion of the elderly accounted for two-thirds of all patients. The clinical significance of CCI in this patient cohort was demonstrated in previous studies [20–22]. Given that comorbidity burden increases with age, particularly in elderly patients who become more vulnerable and frailer, comorbidity indices become more significant for this age group [23].

In a prospective, cohort study including 520 elderly (\geq 80 years) patients hospitalized with NSTE-ACS, CCI was independently associated with mortality or readmissions (HR 1.15, 95% CI (1.06–1.26); p=0.001) within 6 months of follow-up [21]. In another prospective, cohort study involving 715 NSTE-ACS patients, CCI was a prognostic factor of readmission for HF after 2-year follow-up (OR = 1.2 (95%CI: 1.04–1.3) [24].

The severity of CAD detected by CAG also has a prognostic value in acute MI [25]. The prevalence of significant multi-vessel CAD was common in patient with acute MI, both with NSTE-ACS and ST elevation ACS, and accounted for 40–50% of cases [26–28]. Three-vessel CAD served as a prognostic factor within the CADILLAC risk score (the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications), predicting 30-day and 12-month mortality for acute MI after PCI [29]. This score integrated age, LEEF, renal insufficiency, three-vessel CAD, and post-procedural Thrombolysis in Myocardial Infarction (TIMI) flow.

For risk stratification after acute MI, CCI was incorporated in several scores for predicting adverse outcomes [30, 31]. In a study of 1,202 ACS patients, the addition of CCI to the GRACE score improved the prediction of future cardiovascular events and mortality [32], while CCI was shown to be one of the strongest predictors of non-cardiovascular mortality in patients undergoing PCI [33]. The results from the National Readmissions Database revealed that CCI ≥ 3 was the foremost predictor of 30-day readmission among patients with NSTE-ACS [34]. The current analysis calls attention to the synergistic prognostic impact of both comorbidities and angiographic variables that are potentially modifiable or that require specific intervention.

Our study has several limitations. Firstly, it is an observational study, and inherent limitations like non-randomization and unmeasured confounding factors cannot be eliminated. However, well-designed observational studies can still provide valid results without systematically overestimating outcomes, compared to randomized controlled trials. Secondly, a small sample size, single-center nature of the study, and a lack of nomogram validation reduce the power of our model for clinical implementation. Thirdly, CCI was designed over 30 years ago, and clinical definitions of certain conditions, like CKD, have evolved significantly. This may make it impractical to accurately assess their impact on comorbidity burden and prognosis using the traditional CCI format. Top of Form

CONCLUSION

CCI demonstrated a moderate predictive capacity for 18-month mortality in acute MI patients. Age, CCI, and three-vessel CAD were independently associated with 18-month mortality. The nomogram-based risk assessment model facilitated early identification of high-risk patients, allowing for the implementation of more effective treatment strategies and reducing acute MI mortality.

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