Impact of Charlson Comorbidity Index Score on Management and Outcomes after Acute Coronary Syndrome

Running title: Utility of Charlson Comorbidity Index in ACS

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Word Count: 5635

Abstract:

Patients presenting with acute coronary syndrome (ACS) are frequently comorbid. However, there is limited data on how comorbidity burden impacts their receipt of invasive management and subsequent outcomes. We analyzed all patients with a discharge diagnosis of ACS from the National Inpatient Sample (2004-2014), stratified by Charlson Comorbidity Index (CCI) into 4 classes (CCI 0, 1, 2 and ≥3). Regression analyses were performed to examine associations between comorbidity burden and receipt of invasive intervention and in-hospital clinical outcomes. Of all 6,613,623 ACS patients analyzed, the prevalence of patients with severe comorbidity (CCI≥3) increased from 10.8% (2004) to 18.1% (2014). CCI class negatively correlated with receipt of invasive management, with CCI≥3 group being the least likely to receive coronary angiography and PCI (odds ratio (OR): 0.42 95%CI 0.41-0.43 and OR 0.47, 95%CI 0.46-0.48, respectively). CCI class was independently associated with an increased risk of mortality and complications, especially CCI≥3 that was associated with significantly increased odds of MACCE (OR 1.70, 95%CI 1.66-1.75), mortality (OR 1.74, 95%CI 1.68-1.79), acute ischemic stroke (OR 2.35, 95%CI 2.23-2.46) and major bleeding (OR 1.64, 95%CI 1.59-1.69). Comorbidity burden has significantly increased amongst those presenting with ACS over an 11-year period and correlates with reduced likelihood of receipt of invasive management and increased odds of mortality and adverse outcomes. In conclusion, objective assessment of comorbidities using CCI score identifies high-risk ACS patients in whom targeted risk reduction strategies may reduce their inherent risk of mortality and complications.

Keywords: Acute Coronary Syndrome, Charlson Comorbidity Index score, Outcomes

Introduction

Cardiovascular disease remains the leading cause of death in the United States (US).[1] A significant proportion of patients with CAD have concurrent comorbid conditions.[2,3] While at an individual level, a patient's comorbidities affects treatment strategy, rehabilitation potential and prognosis; at a population level comorbid burden has a bearing on the utilization of healthcare resources.[4] Comorbidities rarely occur in isolation and should be considered in totality, considering both cardiovascular and non-cardiovascular conditions.[5,6] The Charlson Co-morbidity Index (CCI) is a measure of co-morbidity burden and provides a means of quantifying the prognostic impact of 22 comorbid conditions on the basis of their number and individual impact by means of a score that was developed as a prognostic indicator for patients with a variety of medical conditions and has been shown to predict mortality, morbidity, risk of repeat hospitalizations, length of stay and cost of treatment. [3,7,8] Previous studies evaluating the impact of CCI on outcomes in acute coronary syndrome (ACS) have generally been limited to single center studies [9], small sample sizes [10], specific cohorts of patients, such as first time hospitalization for acute myocardial infarction) [11], ST-segment elevation myocardial infarction (STEMI) [12], or focused only on incidence of ACS and not outcomes. [13] Furthermore, there is limited data on temporal trends and incidence of cardiovascular and non-cardiovascular comorbidities from a national perspective and their influence on the management and outcomes of ACS patients. As such, the present study examined temporal trends in comorbidity burden, as measured by CCI score, amongst patients with ACS, and evaluated its impact on utilization of invasive management and subsequent clinical outcomes in a nationwide cohort of US hospitalizations.

Methods

The data is extracted from the National Inpatient Sample (NIS)—the largest publicly available all-payer inpatient healthcare database in the United States. Further information on NIS dataset is available in **Supplementary Appendix A**.

The study period was from January 2004 to December 2014. All adults (≥18 years) with the principal diagnosis of ACS were eligible for inclusion and identified by International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM), diagnosis codes 410.xx (acute myocardial infarction) and 411.1 (Unstable Angina). Missing data were assumed to be missing at random: observations with missing data were removed if there were less than 10% data missing in that covariate **(Supplementary Figure 1)**. Baseline patient characteristics for each discharge includes age, gender, race, admission day (weekday or weekend), primary expected payer, median household income for patient's ZIP code, 17 comorbidities using Deyo modification of the Charlson comorbidity index [14] and other clinically relevant comorbidities (smoking, carotid disease, atrial fibrillation, long-term use of anticoagulants, prior percutaneous coronary intervention (PCI), and prior coronary artery bypass grafting (CABG)).

NIS database includes up to 30 diagnosis and 15 procedure codes, which were used to identify the specific conditions and each Charlson comorbidity. The components of Charlson comorbidity index are shown in Supplementary Table 1. A list of ICD-9-CM codes used to extract those diseases is provided in **Supplementary Table 1a** and **Supplementary Table 1b**. CCI score was calculated by summing individual scores and was analysed as a categorical variable and a continuous variable separately. CCI score was stratified according to severity of comorbidity burden into 4 groups: "0" (no comorbidity), "1" (mild comorbid burden), "2" (moderate comorbid burden), "≥3" (severe comorbid burden).

The primary outcomes of interest were in-hospital MACCE (Major Acute Cardiovascular & Cerebrovascular Events) and major bleeding. Secondary outcomes included

the receipt of invasive management (PCI or coronary angiography (CA)), length of stay and total hospitalization charges. In-hospital MACCE was defined as a composite of mortality, cardiac complications, acute ischemic stroke, and vascular complications (vascular injury). Cardiac complications were defined as any event of pericardial effusion, cardiac tamponade, coronary dissection or need for pericardiocentesis) Major bleeding included any gastrointestinal, intracranial, retroperitoneal and procedure-related hemorrhages.

Statistical analyses were performed using STATA version 14.0. Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were used to report the results of models. Multiple imputation with chained equations (MICE) [15] was used to manage the missing data where missing data was more than 10% of the covariate. 10 complete datasets were generated with any missing covariate date imputed. All outcomes and other covariates including age, gender, median ZIP income and year of hospitalization were included in the imputation model to ensure congeniality with the analysis model [16]. Further information on statistical methods is available in **Supplementary Appendix B**.

A sensitivity analysis was performed using CCI score as a continuous variable to assess the impact of per unit score of CCI on in-hospital outcomes (MACCE, mortality, acute stroke and major bleeding). The multivariable logistic regression models for each of the 4 outcomes were then performed separately for the STEMI subgroup.

Results

A total of 6,613,623 weighted hospitalizations for ACS were included in the analysis, with approximately 8.5% (n=123,344) of the raw dataset excluded **(Supplementary Figure 1)** due to missing data. The median age of ACS patients was 67 (56-79) years old and changed little over the study period while the proportion of women decreased during the 10 years from 41.8% to 38.5% (2004-2014) **(Table 1).** The percentage of patients with STEMI decreased

from 39% in 2004 to 28% in 2014. Amongst the Charlson comorbidities, the prevalence of both cardiovascular risk factors (previous MI, peripheral vascular disease (PVD), previous cerebrovascular disease (CVA), and diabetes) and non-cardiovascular comorbidities such as metastatic disease, liver disease and chronic pulmonary disease increased over the study years. **(Table 1). Table 2** demonstrates patient demographics stratified by CCI across all years. Patients with a higher comorbid burden (CCI≥2) were older compared to those with lower burden or no burden. Female patients were less prevalent than male patients in all the groups studied, however, females were more common in the severe comorbid burden cohort (45.7% in CCI≥3 vs. 33.9% in CCI=0). The percentage of patients without any comorbidities (CCI=0) declined from 37.3% in 2004 to 30.2% in 2014, whilst the percentage of patients with severe comorbid burden (CCI≥3) increased from 10.8% to 18.1%. **(Figure 1)**.

The rates of PCI and coronary angiography (CA) increased over years (32.9% in 2004 to 46.7% in 2014; 53.3% in 2004 to 69.3% in 2014, respectively) **(Figure 2)** although rates of utilization of CABG remained stable. **(Table 1)** Comorbidity burden negatively correlated with the rate of utilization of PCI and CA (PCI: 53.5% in CCI=0 to 24.0% in CCI≥3; CA: 72.0% in CCI=0 to 47.0% in CCI≥3). **(Table 2)** In comparison to patients with no comorbidities (CCI=0), patients in CCI=2 were 45% less likely in the odds of receiving a PCI whereas those with CCI≥3 were 53% less likely (OR 0.55, 95%CI 0.54-0.56 in CCI=2 and OR 0.47, 95%CI 0.46-0.48 in CCI≥3). A similar pattern was found in the receipt of CA. **(Table 3)**

The rates of MACCE, mortality and major bleeding decreased over the included years (2004-2014), while the prevalence of cardiac complications increased negligibly over time. The rates of acute ischemic stroke and vascular complications did not change. **(Table 4)** The rates for MACCE, mortality, acute ischemic stroke and major bleeding increased with increasing comorbid burden (MACCE: 5.4% in CCI=0 to 11.4% in CCI≥3; mortality: 3.3% in CCI=0 to

8.1% in CCI≥3; acute ischemic stroke: 0.9% in CCI=0 to 3.0% in CCI≥3; major bleeding: 3.9% in CCI=0 to 6.1% in CCI≥3). **(Figure 3, Table 5)**

The results of multivariable regression demonstrated increased comorbid burden was independently associated with increased odds of MACCE and mortality **(Table 3).** For example, compared with the reference category (CCI=0), CCI≥3 was significantly associated with a 70% increase in the odds of MACCE and 74% increase mortality (OR 1.70, 95%CI 1.66-1.75 and OR 1.74, 95%CI 1.68-1.79). CCI=2 was associated with a 35% increase in the odds of MACCE (OR 1.35, 95%CI 1.32-1.38) and an almost 50% increase in the odds of mortality (OR 1.45, 95% 1.41-1.50). Patients with CCI scores of 1, 2, ≥3 had increased odds of acute ischemic stroke and major bleeding compared to those patients with CCI=0, with CCI≥3 having about 2.5-fold in the odds of acute ischemic stroke (OR 2.35, 95%CI 2.23-2.46). The results of the sensitivity analysis by keeping CCI as a continuous variable are presented in **Supplementary Table 2** with similar findings to the main analysis. Each unit increase in CCI score was associated with increased odds of all outcomes (MACCE, mortality, acute ischemic stroke and major bleeding).

In a subgroup analysis of STEMI patients, similar findings were reported to the main analysis. (**Supplementary Table 3)** The prognostic impact of each individual Charlson comorbidity using multivariable models on clinical outcomes was presented in **Supplementary Table 4**.

Patients with a CCI score 0 and 1 had a similar median length of stay (3 days), which was up to 4 days for CCI=2 and 5 days for CCI≥3. **(Table 2)** A similar trend was also found in the association of hospital costs with increasing comorbid burden: median cost of hospitalization increased from $17,675 in CCI=0 to $21,139 in CCI≥3.

Discussion

We present the largest study to date analyzing the temporal trends in comorbidity burden (characterized by the CCI) and their impact on prognosis and treatment in patients with ACS. We report that the prevalence of severe comorbidity burden as defined by CCI doubled from one in ten patients to almost one in five over a period of eleven years (2004-2014). This was in the absence of any obvious change in the age distribution of admitted ACS patients and a slight reduction in the proportion of ACS patients who were female. We observed that ACS patients with severe comorbid burden (CCI≥3) are least likely to receive coronary angiography or PCI, and that increasing comorbidity burden was independently associated with an increased risk of MACCE, acute ischemic stroke, major bleeding complications and mortality. Finally, increasing comorbidity was associated with an increased hospitalization cost and length of stay.

Our analysis reveals that patients presenting with ACS are increasingly comorbid and complex with a multitude of cardiovascular and non-cardiovascular comorbidities. Previous studies have shown that among patients with acute MI, the prevalence of cardiovascular risk factors and comorbidities such as diabetes, hypertension, heart failure and atrial fibrillation increased during 1990 to 2007. [2,17] However these studies were either smaller in sample size [2,17] or community based study restricted to a particular geographic area [2]. When patient demographics were stratified by CCI score we found that ACS patients with severe comorbid burden were older and with greater percentage of women.

In this study we report that in-hospital mortality significantly increases with increasing comorbid burden. When patients with no comorbidities (CCI=0) were compared to patients with CCI=1, 2 and ≥3 comorbidities, the risk of mortality increased by 31%, 45% and 74% respectively. Previously our large meta-analysis [3] of studies [9-13,18-21] evaluating the impact of CCI score on cardiovascular diseases demonstrated that among ACS patients the risk of

mortality was significantly higher with an incremental increase in CCI score. Three studies [10,13,21] demonstrated that patients with any comorbidities (CCI>0) had nearly two times the risk of death (RR 1.93; 95%CI 1.67–2.24) compared to those with CCI=0 [3]. Whilst in our study only in-hospital mortality was evaluated, multiple other studies have shown CCI score to be a predictor of mortality even at 1 year. [10,11,20]

In our analysis the most notable of in-hospital complications that increased significantly with increase in CCI was the occurrence of acute ischemic stroke and major bleeding. The risk of acute ischemic stroke in CCI≥3 was almost 2.5-fold that in CCI=0. Additionally, post-PCI stroke was associated with a significantly higher mortality and increased length of stay. Our analysis also revealed that there was an increasing risk of occurrence of major bleeding complications with increase in CCI score. An expert consensus document on high bleeding risk recognizes several of the components of CCI such as advanced age, chronic kidney disease, liver disease, history of stroke or gastrointestinal bleed, as independent risk factors for bleeding following PCI [22], although does not consider measures of overall comorbid burden. [23]

Previous analyses have not been powered to study the prognostic impact of individual comorbid conditions that make up CCI. Our analysis suggests that the individual components of CCI with greatest prognostic impact are mainly non-cardiovascular comorbid conditions that are not routinely included in ACS prognoses scores such as cancer, moderate or severe liver diseases, peptic ulcer diseases and neurological deficits such as hemiplegia or paraplegia.

The adverse outcomes that we report to be associated with increasing CCI are likely to be multifactorial, with patients with severe comorbid burden at increased risk of both recurrent ischemic events and mortality. Paradoxically, a notable finding of our study is that ACS patients with severe comorbid burden are more likely to be conservatively managed as compared to their counterparts with lesser or no comorbidities. Previously the AMI Florence working group

reported that coronary reperfusion strategy was less frequently adopted in patients with increasing chronic comorbidity score based on data analysis of a population-based registry with a smaller sample size (N=740), which included only STEMI patients. [24] The same group also demonstrated that application of PCI was associated with a long-term survival advantage that increased progressively with increase in risk profile in ACS patients and hypothesized that a conservative approach in these multimorbid patients may not justified. [25] In a further study, Nunez et al. demonstrated that a higher CCI score was an independent predictor of 30 day and 1 year of the composite mortality or acute myocardial infarction endpoint. [9] Such patients at higher risk of ischemic complications are more likely to benefit from an early invasive approach, but this must be balanced against the increased risk of complications such as major bleeding, stroke and cardiovascular complications. [23] A previous study of 1202 ACS patients has shown that addition of CCI to the GRACE score improved the prediction of future cardiovascular events and mortality [18], whilst CCI has been shown to be one of the strongest predictors of non-CV mortality in patients undergoing PCI [26]. Incorporation of CCI into risk stratification tools may help guide the management of this complex group of patients. An analysis of the National Readmissions Database revealed that CCI≥3 was the foremost predictor of 30-day readmission among patients with non-ST elevation ACS. [27]

Finally, we also report that comorbidity burden may have an important health economic impact in patients with ACS, we observe an incremental increase in the median adjusted cost of hospitalization of ACS patients with increase in comorbidity burden ($17675 in CCI=0 to $21139 in CCI≥3). As expected, the median length of stay also increased with increasing comorbidity burden (5 days for CCI≥3 group as compared to 3 days for CCI=0). In general although length of stay for STEMI patients have been shown to have decreased over time [28],

those that do have a longer length of stay have been associated with higher morbidity and mortality [29,30].

Unlike our current study, previous studies have failed to comprehensively evaluate the impact of CCI on management strategy and occurrence of complications such as bleeding, stroke, vascular and cardiac complications. We acknowledge several limitations of our study, which are inherent to the NIS database. Like with any other administrative database, coding errors and underreporting of secondary diagnoses are a potential source of bias. The NIS database also does not capture the exact cause of death and lacks data regarding long term outcomes thereby limiting us to just in-hospital events. Additionally, the NIS database lacks formal adjudication of outcomes, and events such as bleeding are not defined based on standardized definitions used in cardiovascular trials. [31]

In conclusion, our temporal analysis of ACS hospitalizations suggests that comorbidity burden has significantly increased amongst in this population over an 11-year period, and correlates with reduced likelihood of receipt of invasive management and increased odds of mortality and adverse outcomes. Objective assessment of comorbidities using CCI score identifies high-risk ACS patients in whom targeted risk reduction strategies may reduce their inherent risk of mortality and complications.

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Figure Titles and Legends:

Figure 1. Distribution of the CCI groups across the study years (2004-2014).
Legend: CCI: Charlson comorbidity index.

Figure 2: Rates of PCI and CA according to CCI groups between 2004 and 2014.
Legend: PCI: percutaneous coronary intervention; CA: coronary angiography; CCI: Charlson comorbidity index.

Figure 3: Rates of MACCE, mortality, acute ischemic stroke and major bleeding according to CCI groups between 2004 and 2014.
Legend: MACCE: Major Acute Cardiovascular & Cerebrovascular Events; CCI: Charlson comorbidity index.

Table 1. Secular trends of baseline characteristics between 2004 and 2014 in ACS patients.

Variable	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
Patients demographics												
No. of unweighted discharges with ACS diagnosis	157,239	146,475	149,034	135,694	139,142	133,265	127,600	133,505	126,622	124,853	125,833	None
No. of weighted discharges with ACS diagnosis	647,068	611,467	677,163	612,637	594,553	585,658	547,855	549,441	602,020	594,590	589,860	None
No. of weighted discharges with STEMI diagnosis	252,357 (39%)	232,357 (38%)	250,550 (37%)	214,423 (35%)	202,148 (34%)	187,411 (32%)	169,835 (31%)	164,832 (30%)	174,586 (29%)	172,431 (29%)	165,161 (28%)	None
Median (IQR) age, y	68 (57-79)	68 (56-80)	67 (56-79)	67 (56-79)	68 (56-79)	67 (56-79)	67 (56-79)	67 (57-79)	67 (57-78)	67 (57-78)	67 (57-78)	648 (0.009%)
Female, %	41.8%	41.5%	40.6%	41.0%	40.9%	40.1%	40.0%	39.8%	38.4%	38.8%	38.5%	1035 (0.014%)
Race, %												
White	55.9%	57.3%	57.0%	55.9%	61.7%	63.3%	65.6%	66.9%	71.0%	70.7%	71.0%	1,255,683 (17.4%)
black	7.0%	5.5%	6.7%	7.5%	7.4%	7.8%	9.9%	9.7%	10.1%	10.1%	10.2%	
Hispanic	5.2%	5.5%	5.8%	5.6%	5.3%	6.1%	6.4%	7.4%	7.2%	7.6%	7.4%	
Asian/Pacific islander	1.5%	1.2%	1.4%	1.8%	1.9%	1.8%	2.0%	2.0%	2.1%	2.3%	2.3%	

Native American	0.2%	0.2%	0.4%	0.5%	0.7%	0.5%	0.4%	0.6%	0.5%	0.5%	0.5%	
other	2.0%	2.3%	2.0%	2.3%	2.9%	3.6%	2.4%	2.9%	3.2%	2.8%	3.0%	
Missing Race	28.1%	27.9%	26.7%	26.4%	20.1%	16.9%	12.8%	10.6%	5.9%	6.1%	5.5%	
Admission/weekend, %	25.0%	25.1%	24.9%	25.5%	26.3%	25.9%	26.4%	26.2%	25.9%	26.5%	26.3%	None
Median zip code income national quartile, %												
Frist	28.3%	28.4%	27.1%	28.6%	28.3%	29.0%	29.3%	29.2%	31.5%	30.0%	29.6%	172846 (2.4%)
Second	28.1%	26.5%	27.1%	26.1%	29.2%	28.0%	27.1%	25.7%	26.1%	27.7%	29.3%	
Third	22.4%	24.4%	24.3%	23.6%	22.6%	23.6%	23.8%	25.4%	23.0%	23.4%	22.7%	
Fourth	21.2%	20.7%	21.4%	21.7%	20.0%	19.4%	20.0%	20.0%	19.5%	19.0%	18.4%	
Resource utilization. (Median/IQR)												
Median (IQR) length of stay (LOS), d	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)	144 (0.002%)
Median (IQR) adjusted cost of hospitalization, $	11772.7 (5738-20739)	12514.8 (6143-21758)	13908.3 (6990-23544)	13749.3 (7195-23171)	14934.4 (7880-24589)	14934.4 (7797-24378)	15169.1 (8079-25077)	15659.6 (8537-25433)	14417.6 (8119-22483)	15026.6 (8373-23660)	15201 (8524-23743)	410508 (5.7%)
Charlson Comorbidities, %												
Previous Myocardial infarction	7.9%	7.9%	8.6%	9.1%	9.3%	10.3%	11.0%	11.7%	12.0%	12.4%	12.9%	None
Congestive heart failure	30.3%	30.1%	28.5%	28.7%	28.3%	28.7%	29.1%	30.2%	29.9%	30.5%	31.0%	None

Peripheral vascular disease	1.2%	1.2%	1.3%	1.3%	1.5%	1.7%	1.6%	1.6%	1.6%	1.6%	1.7%	None
Previous Cerebrovascular disease	1.8%	1.7%	1.7%	2.5%	6.0%	7.2%	7.7%	8.6%	8.8%	8.9%	9.4%	None
Dementia	0.7%	0.8%	0.8%	0.7%	0.7%	0.7%	0.6%	0.7%	0.6%	0.5%	0.5%	None
Chronic pulmonary disease	19.4%	20.5%	20.2%	20.5%	19.4%	20.1%	20.0%	21.0%	21.0%	21.1%	21.4%	None
Rheumatologic disease	1.6%	1.7%	1.7%	1.8%	1.9%	1.9%	2.0%	2.1%	2.3%	2.3%	2.3%	None
Peptic ulcer	1.2%	1.1%	1.0%	1.0%	1.0%	1.1%	1.0%	1.0%	1.0%	0.9%	0.9%	None
Mild liver disease	0.4%	0.4%	0.4%	0.4%	0.3%	0.4%	0.4%	0.5%	0.5%	0.5%	0.6%	None
Diabetes	25.6%	25.5%	26.1%	27.1%	27.4%	28.5%	29.1%	30.2%	31.1%	31.4%	31.8%	None
Diabetes with chronic complications	3.7%	3.7%	3.6%	4.2%	4.2%	4.6%	4.8%	5.6%	5.6%	5.8%	6.1%	None
Hemiplegia or paraplegia	0.4%	0.3%	0.3%	0.4%	0.5%	0.5%	0.5%	0.4%	0.4%	0.4%	0.5%	None
Renal Disease	1.4%	1.1%	0.4%	0.5%	0.8%	0.9%	1.2%	1.3%	1.2%	1.3%	1.4%	None
Any malignancy including leukaemia and lymphoma	2.4%	2.6%	2.4%	2.7%	2.8%	2.8%	2.7%	2.8%	2.8%	2.9%	3.0%	None
Moderate or severe liver disease	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.2%	0.2%	0.3%	0.2%	0.3%	None

Metastatic solid tumour	0.7%	0.8%	0.8%	0.9%	0.9%	0.9%	0.8%	0.9%	0.8%	0.8%	0.9%	None
AIDS	0.1%	0.1%	0.1%	0.1%	0.1%	0.2%	0.2%	0.2%	0.1%	0.1%	0.1%	None
Other conditions, %												
Smoking	24.7%	27.0%	28.9%	30.3%	31.7%	34.7%	36.0%	37.6%	39.6%	41.1%	43.8%	None
Carotid disease	1.0%	1.1%	1.2%	1.4%	1.6%	1.8%	1.9%	2.1%	2.2%	2.3%	2.3%	None
Atrial Fibrillation	15.9%	16.3%	16.3%	16.2%	15.4%	16.0%	16.2%	17.5%	17.5%	17.7%	18.3%	None
Long-term use of anticoagulants	1.4%	1.7%	1.9%	2.3%	2.4%	3.1%	3.4%	3.9%	3.9%	3.9%	4.4%	None
Previous PCI	6.5%	7.2%	8.4%	9.4%	10.2%	11.6%	12.5%	14.3%	14.8%	15.4%	16.2%	None
Previous CABG	6.7%	6.6%	6.7%	6.6%	7.0%	7.6%	7.7%	8.6%	8.3%	8.3%	8.5%	None
Charlson Comorbidity Index Score, %												
0 (CCI=0)	37.3%	37.0%	37.4%	36.2%	35.0%	34.2%	33.5%	32.1%	31.6%	31.0%	30.2%	None
1 (CCI=1)	33.1%	33.2%	33.6%	33.1%	33.1%	32.1%	32.0%	31.1%	31.4%	31.3%	31.1%	None
2 (CCI=2)	18.7%	18.9%	18.7%	19.0%	19.3%	19.4%	19.7%	19.9%	20.3%	20.5%	20.6%	None
3 (CCI≥3)	10.8%	10.9%	10.4%	11.7%	12.7%	14.2%	14.8%	16.8%	16.8%	17.2%	18.1%	None
Treatments/procedural characteristics, %												
PCI	32.9%	35.4%	38.6%	38.0%	40.0%	41.9%	42.2%	43.2%	45.2%	46.2%	46.7%	None
Coronary Angiography	53.3%	56.4%	58.2%	59.0%	60.3%	63.4%	64.2%	64.3%	67.6%	68.6%	69.3%	None

Infusion of thrombolytic agent	1.7%	1.7%	1.6%	1.3%	1.4%	1.2%	1.0%	1.2%	1.1%	1.1%	1.1%	None
CABG	8.8%	8.4%	9.0%	8.4%	8.2%	8.7%	7.9%	7.8%	8.2%	8.4%	8.4%	None
IABP use	4.1%	4.4%	4.6%	4.6%	5.0%	5.0%	4.7%	4.7%	4.6%	4.4%	4.2%	None

ACS: acute coronary syndrome; IQR: interquartile range; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CCI: Charlson Comorbidity index; IABP: intra-aortic balloon pump.

Table 2: Patient characteristics stratified by categorised Charlson Comorbidity Index Score (CCI).

	Charlson Comorbidity Index Score (CCI)			
Variables	CCI = 0	CCI = 1	CCI = 2	CCI ≥ 3
Patient demographics				
No. of weighted discharges with ACS diagnosis	2466301 (34.2%)	2328309 (32.3%)	1406418 (19.5%)	1000872 (13.9%)
Median (IQR) age, y	62(52, 74)	68(57, 80)	72(61, 82)	72(63, 81)
Female, %	33.9%	41.8%	44.6%	45.7%
Race, %				
White	63.5%	62.1%	63.0%	63.7%
black	6.8%	8.3%	9.1%	10.4%
Hispanic	5.5%	6.5%	6.6%	7.1%
Asian/Pacific islander	1.7%	1.8%	1.8%	2.1%
Native American	0.4%	0.4%	0.5%	0.5%
other	2.7%	2.7%	2.5%	2.4%
Missing Race	19.1%	17.9%	16.3%	13.4%
Primary expected payer, %				
Medicare	41.2%	57.4%	68.9%	74.8%
Medicaid	5.6%	6.5%	6.9%	6.7%
Private including HMO	40.7%	26.6%	17.8%	13.8%
Self-pay	8.3%	6.0%	4.0%	2.4%
No charge	0.8%7	0.6%	0.4%	0.2%
Other	3.4%	2.8%	2.2%	1.9%
Admission/weekend, %	26.0%	25.7%	25.7%	25.7%
Median zip code income national quartile, %				
Frist	26.2%	30.0%	31.4%	31.1%
Second	27.0%	27.7%	27.7%	27.2%
Third	24.4%	23.2%	22.8%	23.2%
Fourth	22.5%	19.4%	18.1%	18.5%

Resource utilization. (Median/IQR)				
Median (IQR) length of stay (LOS), d	3(2, 4)	3(2, 6)	4(2, 7)	5(3, 8)
Median (IQR) adjusted cost of hospitalization, $	$17675($14556, $22123)	$19660($14271, $23844)	$20611($13897, $24930)	$21139($13910, $25389)
Charlson Comorbidity, %				
Previous Myocardial infarction	N/A	9.1%	17.3%	28.0%
Congestive heart failure	N/A	26.7%	55.8%	72.2%
Peripheral vascular disease	N/A	1.2%	2.5%	4.4%
Previous Cerebrovascular disease	N/A	3.7%	9.6%	18.9%
Dementia	N/A	0.4%	1.2%	2.2%
Chronic pulmonary disease	N/A	19.0%	37.8%	49.6%
Rheumatologic disease	N/A	1.9%	3.4%	4.9%
Peptic ulcer	N/A	0.8%	1.8%	2.9%
Mild liver disease	N/A	0.2%	0.6%	1.9%
Diabetes	N/A	37.0%	49.2%	49.3%
Diabetes with chronic complications	N/A	N/A	6.1%	25.0%
Hemiplegia or paraplegia	N/A	N/A	0.5%	2.3%
Renal Disease	N/A	N/A	0.7%	6.5%
Any malignancy including leukaemia and lymphoma	N/A	N/A	2.9%	15.4%
Moderate or severe liver disease	N/A	N/A	N/A	1.3%
Metastatic solid tumour	N/A	N/A	N/A	6.0%

AIDS	N/A	N/A	N/A	1.0%
Other conditions, %				
Smoking	38.0%	33.0%	30.5%	30.5%
Carotid disease	0.9%	1.6%	2.3%	3.0%
Atrial Fibrillation	10.4%	17.2%	21.9%	23.4%
Long-term use of anticoagulants	1.8%	2.8%	3.8%	4.5%
Previous PCI	7.3%	12.0%	14.1%	15.6%
Previous CABG	4.1%	7.3%	10.3%	12.3%
Treatments/procedural characteristics, %				
PCI	53.5%	40.7%	30.3%	24.0%
Coronary Angiography	72.0%	62.5%	54.2%	47.0%
Infusion of thrombolytic agent	1.8%	1.3%	1.0%	0.8%
CABG	7.2%	9.2%	9.4%	7.8%
IABP use	3.8%	5.1%	5.2%	4.1%

ACS: acute coronary syndrome; IQR: interquartile range; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; IABP: intra-aortic balloon pump.

Table 3: Association between categorised Deyo Charlson index scores and recipient of treatments, in-hospital clinical outcomes with ACS diagnosis (adjusted odds ratio, 95% confidence intervals † §).

	Charlson Comorbidity Index Score (CCI)		
Outcomes*	CCI = 1	CCI = 2	CCI ≥ 3
PCI†	0.74 (0.72, 0.74)	0.55 (0.54, 0.56)	0.47 (0.46, 0.48)
CA†	0.77 (0.75, 0.78)	0.59 (0.57, 0.60)	0.42 (0.41, 0.43)
MACCE§	1.23 (1.20, 1.25)	1.35 (1.32, 1.38)	1.70 (1.66, 1.75)
Mortality§	1.31 (1.29, 1.34)	1.45 (1.41, 1.50)	1.74 (1.68, 1.79)
Acute ischemic stroke§	1.26 (1.21, 1.31)	1.48 (1.41, 1.55)	2.35 (2.23, 2.46)
Major Bleeding§	1.16 (1.13, 1.18)	1.33 (1.29, 1.37)	1.64 (1.59, 1.69)

*Reference is CCI=0; ACS: acute coronary syndrome; PCI: percutaneous coronary intervention; CA: coronary angiography; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications; PCI: percutaneous coronary intervention; CA: coronary angiography.

† Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, type of ACS, If the patient smokes, carotid disease, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

§ Adjustment for age, gender, ethnicity, day of admission (weekday/weekend), median income, type of ACS, If the patient smokes, carotid disease, diagnosis of atrial fibrillation, long-term use of anticoagulants, previous procedure of percutaneous coronary intervention, previous procedure of coronary artery bypass graft, use of percutaneous coronary intervention, coronary angiography, coronary artery bypass graft, use of intra-aortic balloon pump, infusion of thrombolytic agent and year of hospitalisation.

Table 4. Secular trends of in-hospital clinical outcomes between 2004 and 2014 in ACS patients.

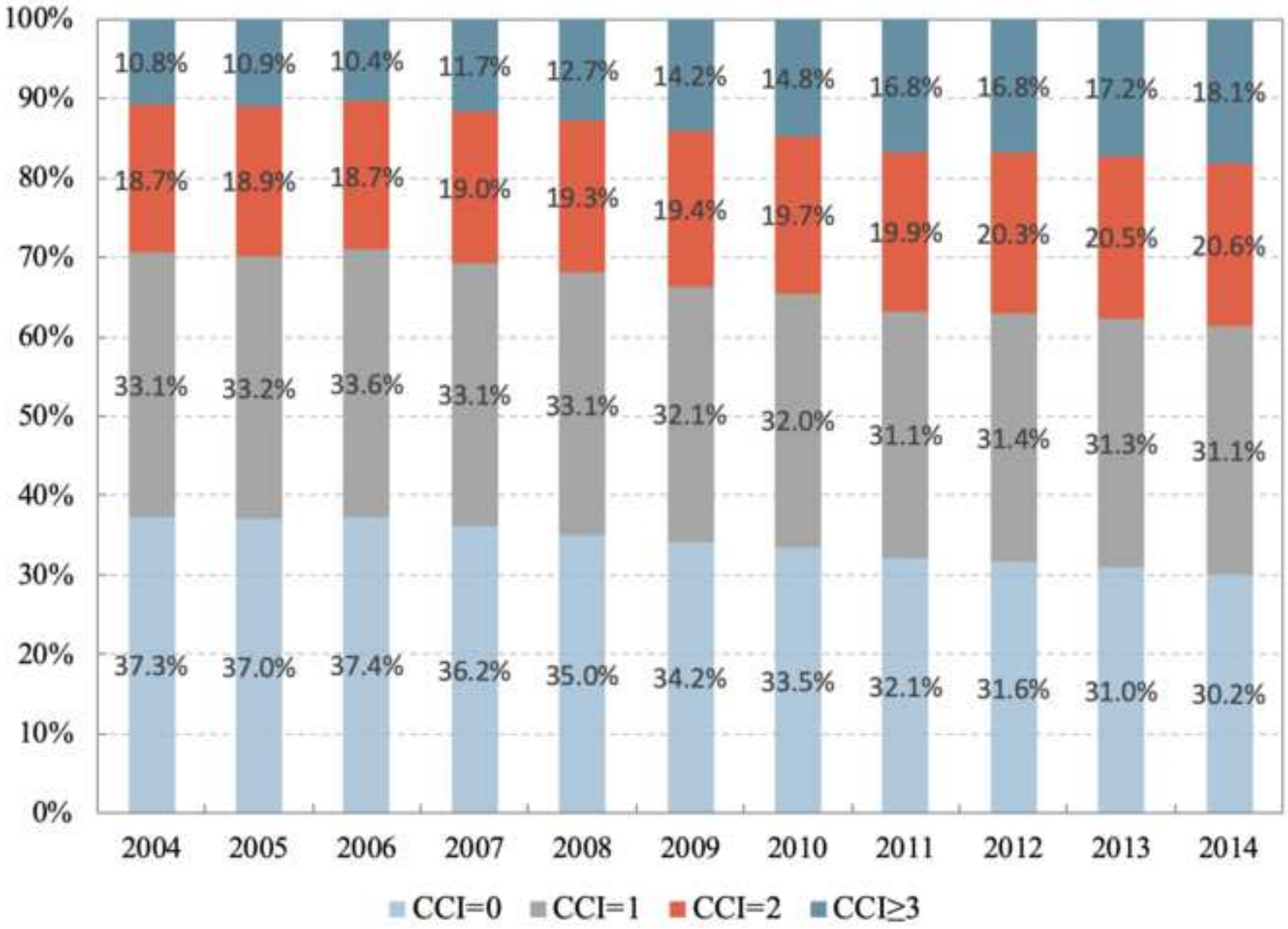
Variable	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
Clinical outcomes/ complications, %												
MACCE	8.7%	8.6%	8.2%	8.1%	8.4%	8.0%	7.5%	7.3%	7.2%	7.2%	7.2%	None
Mortality	6.6%	6.3%	5.8%	5.7%	5.7%	5.3%	5.1%	5.1%	5.0%	4.8%	4.8%	2881 (0.04%)
Cardiac complications	0.3%	0.4%	0.5%	0.5%	0.8%	0.8%	0.8%	0.7%	0.8%	0.8%	0.8%	None
Acute ischemic stroke	1.6%	1.6%	1.7%	1.6%	1.8%	1.6%	1.6%	1.5%	1.4%	1.4%	1.6%	None
Vascular complications	0.7%	0.8%	0.8%	0.8%	0.8%	0.8%	0.6%	0.6%	0.5%	0.6%	0.5%	None
Major Bleeding	5.7%	5.3%	5.3%	5.4%	5.4%	5.1%	4.5%	4.2%	4.0%	3.8%	3.6%	None

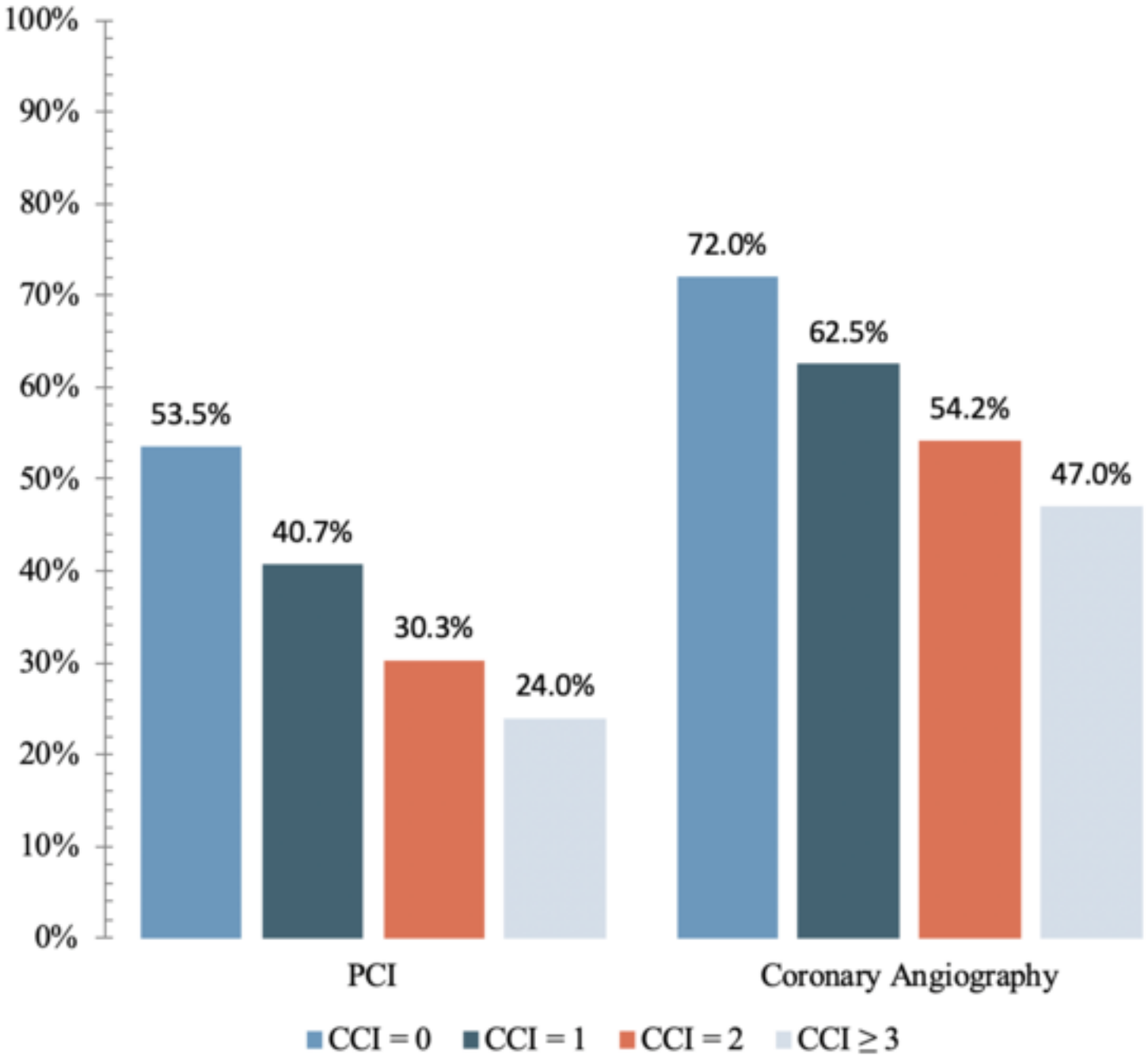
ACS: acute coronary syndrome; MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.

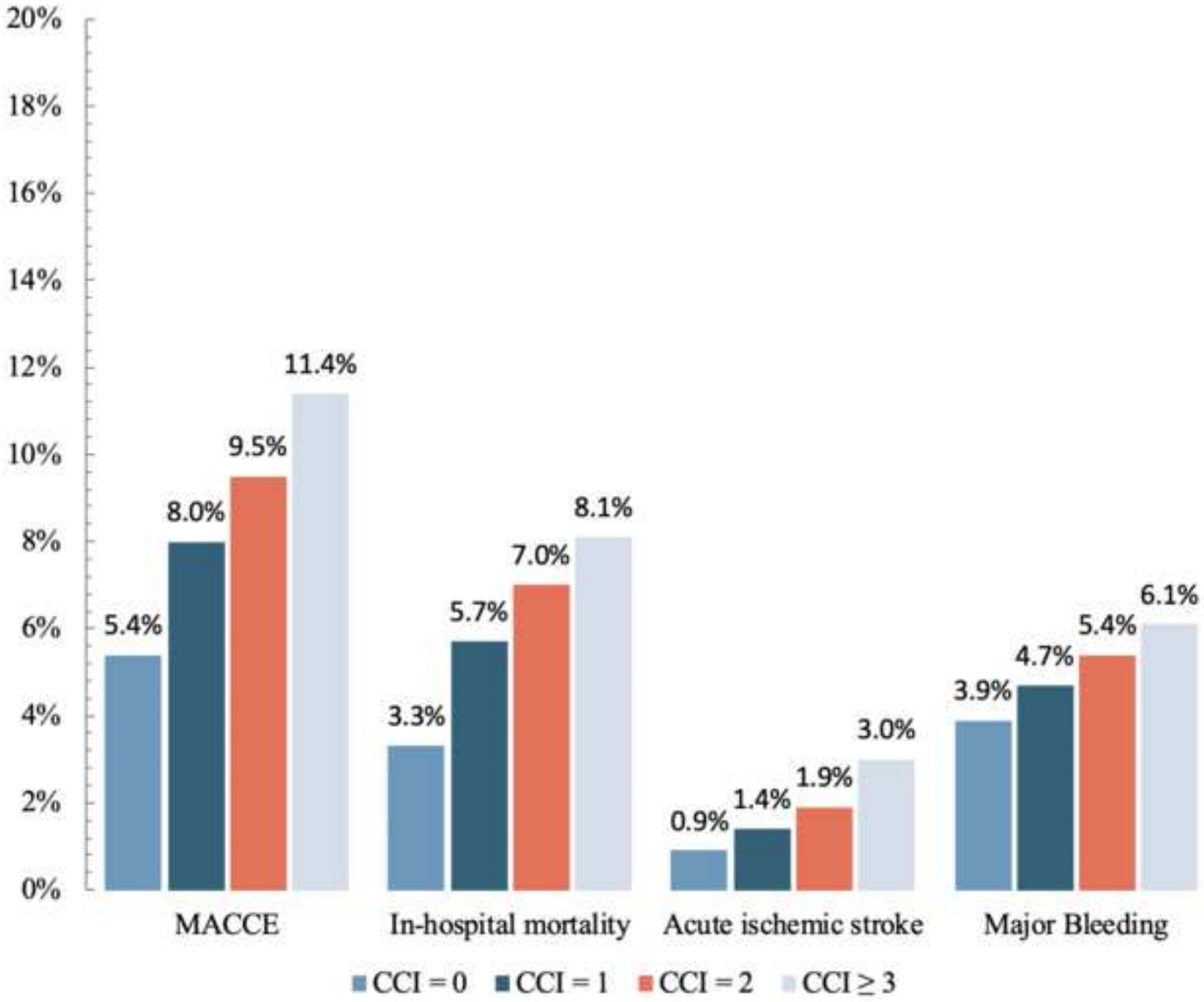
Table 5: In-hospital clinical outcomes by categorised Charlson Comorbidity Index Score (CCI).

	Charlson Comorbidity Index Score (CCI)			
Outcomes	CCI = 0	CCI = 1	CCI = 2	CCI ≥ 3
MACCE	5.4%	8.0%	9.5%	11.4%
Mortality	3.3%	5.7%	7.0%	8.1%
Cardiac complications	0.8%	0.6%	0.5%	0.4%
Acute ischemic stroke	0.9%	1.4%	1.9%	3.0%
Vascular complications	0.6%	0.7%	0.7%	0.6%
Major Bleeding	3.9%	4.7%	5.4%	6.1%

MACCE: major acute cardiovascular and cerebrovascular events: composite of death, cardiac complications, stroke, and vascular complications.







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