Impact of Charlson Co-Morbidity Index Score on Management and Outcomes After Acute Coronary Syndrome

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Patients presenting with acute coronary syndrome (ACS) are frequently co-morbid. However, there is limited data on how co-morbidity 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 to 2014), stratified by Charlson Co-morbidity Index (CCI) into 4 classes (CCI 0, 1, 2, and ≥3). Regression analyses were performed to examine associations between co-morbidity 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 co-morbidity (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 percutaneous coronary intervention (odds ratio (OR) 0.42 95% confidence interval [CI] 0.41 to 0.43 and OR 0.47, 95% CI 0.46 to 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 Major Acute Cardiovascular & Cerebrovascular Events (OR 1.70, 95% CI 1.66 to 1.75), mortality (OR 1.74, 95% CI 1.68 to 1.79), acute ischemic stroke (OR 2.35, 95% CI 2.23 to 2.46), and major bleeding (OR 1.64, 95% CI 1.59 to 1.69). Co-morbidity 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 co-morbidities using CCI score identifies high-risk ACS patients in whom targeted risk reduction strategies may reduce their inherent risk of mortality and complications. **(Am J Cardiol 2020;130:15−23)**

Cardiovascular disease remains the leading cause of death in the United States (US).[1] A significant proportion of patients with CAD have concurrent co-morbid conditions.[2,3] Although at an individual level, a patient's co-morbidities affects treatment strategy, rehabilitation potential, and prognosis; at a population level co-morbid burden has a bearing on the utilization of healthcare resources.[4] Co-morbidities rarely occur in isolation and should be considered in totality, considering both cardiovascular and noncardiovascular 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 co-morbid 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 noncardiovascular co-morbidities from a national perspective and their influence on the management and outcomes of ACS patients. As such, the present study examined temporal trends in co-morbidity 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 are 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

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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 co-morbidities using Deyo modification of the CCI[14] and other clinically relevant co-morbidities (smoking, carotid disease, atrial fibrillation, long-term use of anticoagulants, previous percutaneous coronary intervention (PCI), and previous 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 co-morbidity. The components of CCI 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 analyzed as a categorical variable and a continuous variable separately. CCI score was stratified according to severity of co-morbidity burden into 4 groups: "0" (no co-morbidity), "1" (mild co-morbid burden), "2" (moderate co-morbid burden), and "≥3" (severe co-morbid burden).

The primary outcomes of interest were in-hospital Major Acute Cardiovascular & Cerebrovascular Events (MACCE) 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. Ten complete datasets were generated with any missing covariate data 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 to 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 to 2014; Table 1). The percentage of patients with STEMI decreased from 39% in 2004 to 28% in 2014. Among the Charlson co-morbidities, the prevalence of both cardiovascular risk factors (previous MI, peripheral vascular disease, previous cerebrovascular disease, and diabetes) and noncardiovascular co-morbidities 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 co-morbid burden (CCI ≥2) were older compared with those with lower burden or no burden. Female patients were less prevalent than male patients in all the groups studied, however, women were more common in the severe co-morbid burden cohort (45.7% in CCI ≥3 vs 33.9% in CCI = 0). The percentage of patients without any co-morbidities (CCI = 0) declined from 37.3% in 2004 to 30.2% in 2014, whereas the percentage of patients with severe co-morbid 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). Co-morbidity 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 co-morbidities (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 to 0.56 in CCI = 2 and OR 0.47, 95% CI 0.46 to 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 to 2014), whereas 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 co-morbid 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 and Table 5).

The results of multivariable regression demonstrated increased co-morbid 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 to 1.75 and OR 1.74, 95% CI 1.68 to 1.79). CCI = 2 was associated with a 35% increase in the odds of MACCE (OR 1.35, 95% CI 1.32 to 1.38) and an almost 50% increase in the odds of mortality (OR 1.45, 95% CI 1.41 to 1.50). Patients with CCI scores of 1, 2, ≥3

Table 1
Secular trends of baseline characteristics from 2004 to 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
black	7.0%	5.5%	6.7%	7.5%	7.4%	7.8%	9.9%	9.7%	10.1%	10.1%	10.2%	(17.4%)
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
Second	28.1%	26.5%	27.1%	26.1%	29.2%	28.0%	27.1%	25.7%	26.1%	27.7%	29.3%	(2.4%)
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

(*continued on next page*)

Table 1 (*Continued*)

Variable	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Missing
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 co-morbidity index; IABP = intra-aortic balloon pump.

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 to 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 co-morbidity 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 co-morbid 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 co-morbidity burden (characterized by the CCI) and their impact on prognosis and treatment in patients with ACS. We report that the prevalence of severe co-morbidity burden as defined by CCI doubled from one in ten patients to almost 1 in 5 over a period of 11 years (2004 to 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 co-morbid burden (CCI ≥3) are least likely to receive coronary angiography or PCI, and that increasing co-morbidity burden was independently associated with an increased risk of MACCE, acute ischemic stroke, major bleeding complications, and mortality. Finally, increasing co-morbidity was associated with an increased hospitalization cost and length of stay.

Our analysis reveals that patients presenting with ACS are increasingly co-morbid and complex with a multitude of cardiovascular and noncardiovascular co-morbidities. Previous studies have shown that among patients with acute MI, the prevalence of cardiovascular risk factors, and co-morbidities such as diabetes, hypertension, heart failure, and atrial fibrillation increased during 1990 to 2007.[2,17] Although, 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 co-morbid burden were older and with greater percentage of women.

In this study we report that in-hospital mortality significantly increases with increasing co-morbid burden. When patients with no co-morbidities (CCI = 0) were compared with patients with CCI = 1, 2, and ≥3 co-morbidities, 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

Table 2
Patient characteristics stratified by categorized Charlson co-morbidity index score (CCI)

	Charlson co-morbidity 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.

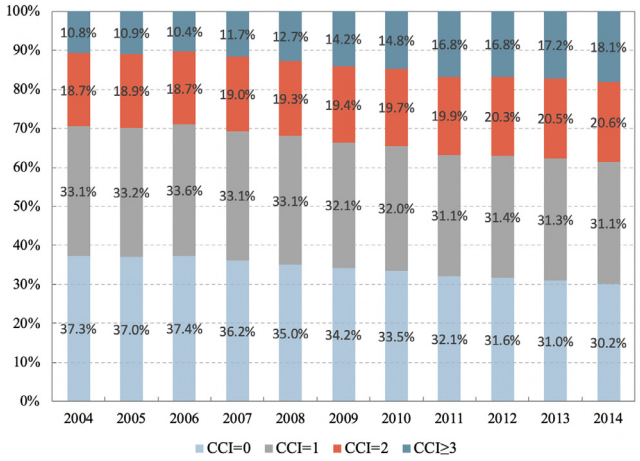

Figure 1. Distribution of the CCI groups across the study years (2004 to 2014). CCI = Charlson co-morbidity index.

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 co-morbidities (CCI >0) had nearly 2 times the risk of death (relative risk 1.93; 95% CI 1.67 to 2.24) compared with those with CCI = 0.[3] Although 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

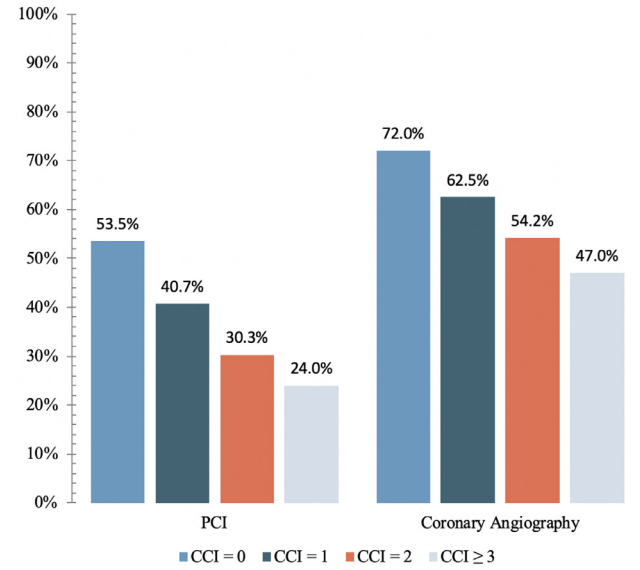

Figure 2. Rates of PCI and CA according to CCI groups from 2004 to 2014. PCI = percutaneous coronary intervention; CA = coronary angiography; CCI = Charlson co-morbidity index.

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

	Charlson co-morbidity 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.

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 co-morbid burden.[23]

Previous analyses have not been powered to study the prognostic impact of individual co-morbid conditions that make up CCI. Our analysis suggests that the individual components of CCI with greatest prognostic impact are mainly non-cardiovascular co-morbid 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 co-morbid burden at increased risk of both recurrent ischemic events and mortality. Paradoxically, a notable finding of our study is that ACS patients with severe co-morbid burden are more likely to be conservatively managed as compared to their counterparts with lesser or no co-morbidities. Previously the AMI Florence working group reported that coronary reperfusion strategy was less frequently adopted in patients with increasing chronic co-morbidity score based on data analysis of a

Table 4
Secular trends of in-hospital clinical outcomes from 2004 to 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.

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 end point.[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 1,202 ACS patients has shown that addition of CCI to the GRACE score improved the prediction of future cardiovascular events and mortality,[18] whereas 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]

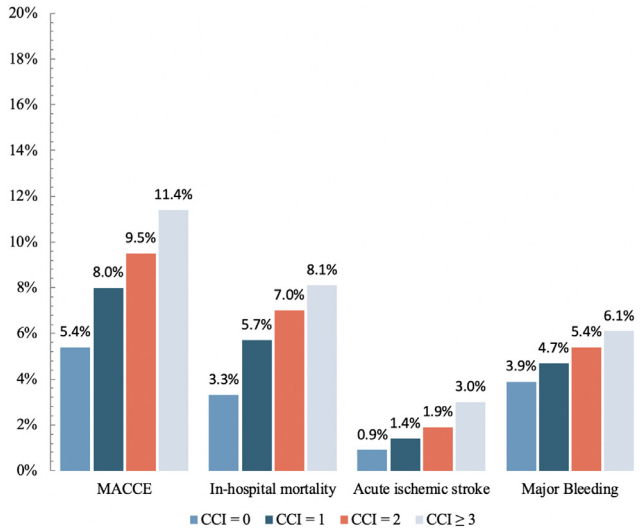

Figure 3. Rates of MACCE, mortality, acute ischemic stroke, and major bleeding according to CCI groups from 2004 to 2014. MACCE = Major Acute Cardiovascular & Cerebrovascular Events; CCI = Charlson co-morbidity index.

Table 5
In-hospital clinical outcomes by categorized Charlson co-morbidity index score (CCI)

	Charlson co-morbidity 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.

Finally, we also report that co-morbidity 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 co-morbidity burden ($17,675 in CCI = 0 to $21,139 in CCI ≥3). As expected, the median length of stay also increased with increasing co-morbidity burden (5 days for CCI ≥3 group as compared with 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 co-morbidity 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 co-morbidities 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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FZ- Data curation, Formal Analysis, Writing initial draft, **AB**−Writing initial draft (lead), **MOM -** Writing initial draft, Supervision, **JE-** Supervision, Writing - Review & Editing, **GP-** Supervision, Writing - Review & Editing, **MAM-**Conceptualization, Supervision, Writing - Review & Editing.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.06.022.

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