**Temporal Trends in Comorbidity Burden and Impact on Prognosis in Patients with Acute Coronary Syndrome Using the Elixhauser Comorbidity Index Score**

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# Abstract

Despite current evidence, little is known about the impact of comorbidity burden on invasive management strategies and clinical outcomes in the context of acute coronary syndrome (ACS). All ACS hospitalizations between 2004 and 2014 from the National Inpatient Sample were included, stratified by Elixhauser Comorbidity Score (ECS) and number of Elixhauser Comorbidities (NEC) to compare the receipt of invasive management and clinical outcomes between different ECS and NEC classes to the lowest class of either measure. A total of 6,613,623 records with ACS were included in the analysis. Overall comorbidity burden increased over the 11-year period, with higher comorbidity classes (ECS≥14 and NEC≥5) increasing from 2.1% to 4.6% and 4% to 16%, respectively. Higher ECS and NEC classes negatively correlated with the rates of utilization of coronary angiography (CA) and percutaneous coronary intervention (PCI) (ECS ≥14 vs. <0: CA: 38.2% vs. 69.3%, PCI: 18.6% vs. 45.3%; NEC ≥5 vs. 0: CA: 49.3% vs. 73.4%, PCI: 24.4% vs. 57.4%). Overall, higher ECS and NEC classes were independently associated with significantly increased odds of all complications, including MACCE, mortality, stroke and bleeding. In conclusion, among patients hospitalized for AMI, a higher comorbidity number or severity is associated with lower rates of receipt of CA and PCI, but not CABG, and worse clinical outcomes. Comorbidity burden assessment using ECS can help stratify patient groups at greatest risk of adverse outcomes in which invasive management is currently underutilized.

**Key Words:** acute coronary syndrome, comorbidity, Elixhauser, outcomes, management

# Introduction

Increased life expectancy and advancements in medical care have led to a rise in the number of patients living with comorbidities, who represent a significant proportion of those presenting with acute coronary syndrome (ACS).1 Comorbidities rarely occur in isolation and many patients presenting with AMI have several comorbidities. However, only a few studies examined the association between comorbidity and ACS outcomes, and their findings were limited by single center analyses, small sample size and the analysis of specific cohorts (e.g. first time MI), geographical regions or outcomes (e.g. mortality). 2 3 4 5 6 7 Therefore, the current evidence does not inform physicians of the patterns of comorbidity burden in this high-risk group, and whether this burden has changed over time in line with the shift in patient socio-demographics. Furthermore, it is unclear whether there is a difference in the management strategy offered to patients based on comorbidity burden, and whether the latter has an impact on clinical outcomes.

The modified Elixhauser Comorbidity Score (ECS) is a well validated measure of comorbidity using administrative datasets that has been shown to be superior to CCI in cardiovascular and surgical cohorts. 2,8 9,10 The present study was designed to examine national estimates of the prevalence and temporal trends of comorbidity burden in patients presenting with AMI in the US, and the associations between comorbidity burden and in-hospital management strategy and clinical outcomes.

# Methods

The National Inpatient Sample (NIS) is the largest publicly available all-payer of hospitalized patients in the United States and is sponsored by the Agency for Health Research and Quality (AHRQ) as a part of the Healthcare Cost and Utilization Project (HCUP) 11. NIS includes anonymized data on discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset constitutes a 20% stratified sample of US community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population. The NIS database has 15 diagnoses codes and 15 procedures codes for each hospital discharges record from the year 2004- 2008. The number of diagnoses codes have been extended to 25 from the year 2009-2013 and to 30 in 2014. The first diagnosis in the NIS is introduced as the “principal diagnosis”.

All individuals ≥18 years with a principal diagnosis of ACS between 2004 and 2014 were eligible for inclusion, as identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 410.0x, 410.1x, 410.2x, 410.3x, 410.4x, 410.5x, 410.6x, 410.8x, 4109x (STEMI), 4107x (NSTEMI), and 4111 (Unstable Angina Pectoris). (**Supplementary table 1**)

Patient-level variables were already available in the NIS database including age, gender, race, primary source of payment, admission day (weekday versus weekend), median household income, and patient Elixhauser comorbidities described by Van Walraven et al.**8** It comprises 30 conditions, each weighted in to a single numeric score based on their association with in-hospital mortality in the original cohort by Van Walraven et al. Other clinically relevant comorbidities (smoking, dementia, and atrial fibrillation, long-term use of anticoagulants, previous myocardial infarction (MI), previous stroke, previous percutaneous coronary intervention (PCI), and prior coronary artery bypass grafting (CABG)) were extracted from secondary diagnoses fields using ICD-9-codes **(Supplementary Table 1),** as were procedural characteristics such as PCI, coronary angiography (CA), thrombolysis, CABG, use of intra-aortic balloon pump (IABP).

ECS was calculated for each patient using the weights provided in **Supplementary Table 2**, with a possible range of scores between -19 and +89. Only 29 of the 30 ECS variables were included since cardiac arrhythmias, the excluded variable, may have been present on admission (i.e. comorbidity) or occurred as a result of ACS (i.e. outcome). Total ECS was stratified in to 5 groups for the purpose of analysis; <0, 0, 1-5, 6-13, ≥14. The number of Elixhauser comorbidities (NEC) was also calculated by summing individual comorbidities and stratified in to 6 groups; 0, 1, 2, 3, 4 and ≥5 comorbidities.

The main clinical outcome was in-hospital MACCE (major acute cardiovascular and cerebrovascular events: composite of mortality, cardiac complications, vascular complications and acute ischemic stroke) and major bleeding. In-hospital major bleeding included gastrointestinal, intracranial hemorrhage, retroperitoneal hemorrhage and procedure-related hemorrhage.

Other outcomes were analyzed included the receipt of invasive management (coronary angiography (CA) or percutaneous coronary intervention (PCI)) the length of in-hospital stay and the total charge of hospitalization. A charge to cost conversion ratio was used to calculate the total charge into the real cost of hospital services since the data given in the NIS is not representative of the actual amount billed for the payer.

Continuous variables are expressed as median with their corresponding interquartile range as they did not follow a normal distribution pattern while categorical variables are presented as percentages. Missing data was assumed to be missing at random: observations with missing data less than 10% of the covariate data were deleted from the dataset as these were unlikely to affect the statistical inferences from this nationally representative cohort **(Supplementary Figure 1).** Multiple imputation with chained equations was performed to impute the missing data in “Race” variables, which had more than 10% missing data, prior to fitting models. Model estimates were produced from those imputed datasets and then combined together using Rubin’s Rules.**12**

Survey statistics (survey estimation commands) were applied to all analyses to produce national estimates, which is also recommended by AHRQ. Since the records from NIS were sampled by hospitals instead of individuals and represent collections from hospital clusters across the United States community hospitals, analyses were conducted with a consideration of this multistage, probability sampling. Because the design of the hierarchical structure of NIS dataset means that different records may be drawn with different probabilities, each hospital discharge is linked to a “sampling weight” that was used in all analyses to calculate national estimates.

Multivariable logistic regression models were utilized to explore the association between the Elixhauser comorbid burden and the aforementioned in-hospital adverse outcomes. The lowest score group (ECS<0) has been used as the reference category for all comparisons. Models were adjusted for age, gender, race, median income, day of admission, if the patient smokes, diagnosis of dementia, diagnosis of atrial fibrillation, long-term use of anticoagulants, prior MI, prior stroke, prior PCI, prior CABG, use of PCI, use of coronary angiography, use of CABG, infusion of thrombolytic agent, year of hospitalization. Exploratory analyses based on medians were conducted to see the impact of comorbid burden on length of in-hospital stay and total charge. All the analysis was performed on Stata/MP version 14.0.

A sensitivity analysis was conducted by analyzing the ECS and NEC as continuous variables compared to the categorical ECS and NEC. In addition, a subgroup analysis of primary outcomes in STEMI patients was performed in comparison to the entire ACS cohort.

# Results

A total of 6,613,623 records with a principal diagnosis with ACS were included in the final dataset with approximately 8.5% of the original dataset removed due to missing data. **(Supplementary Figure 1)** The median age of the total cohort was 67 (56-79) years old with 40% females. The distribution of ECS and NEC groups is illustrated in Figure 1. ECS=0 category had the highest proportion of patients (37.6%), while only 3.5% of the patients had an ECS≥14. Within the NEC groups, more than a quarter of patients had 2 comorbidities (25.2%), closely followed by patients with 1 comorbidity (23.1%).

Several differences in patient characteristics were observed between ECS groups as well as the NEC groups. (**Tables 1a and 1b**) The average age increased with comorbidity burden in both the ECS and NEC groups. A minimal difference in sex distribution was observed within the ECS groups, with males being more prevalent across all groups. In contrast, males were more prevalent in the lower NEC groups whereas an equal sex distribution was observed in those with 5 or more comorbidities (NEC≥5). The prevalence of some cardiovascular risk factors increased in parallel to NEC class (NEC 1 to 5: hypertension 57.8% to 89.8%, diabetes uncomplicated 8.1% - 48.4%, diabetes with complications 0.8% to 21.8%, obesity 3.2% - 27.0%). In contrast, in the ECS groups the highest prevalence of cardiovascular comorbidities was in ECS<0 group while the lowest was in ECS=0.

The overall comorbidity burden increased over the 11-year period, with higher ECS (ECS=6-13, ECS≥14) and NEC (NEC 3, 4 and 5) groups becoming more prevalent in later years (ECS: 2004 to 2014: 13.1% to 19.2%, and 2.1% to 4.6%, respectively; NEC=3: 17% to 20%, NEC=4: 8% to 14%, and NEC≥5: 4% to 16%). **(Figures 2a and 2b)** Despite a modest change in median age over the years (2004 vs 2014: 68 vs. 67 years), the prevalence of women has declined over the study period (2004 vs 2014: 41.5% vs. 38.5%).(**Supplementary Table 3a**) The proportion of STEMI patients also declined over the same period (2004 to 2014: 39% to 28%). We also observe a significant rise in the prevalence several cardiovascular risk factors such as diabetes (complicated and uncomplicated), hypertension, smoking and renal failure.

The overall rates of utilization of invasive management (CA and PCI) have significantly increased over the study period (2004 vs. 2014; CA: 53.3% vs. 69.3% and PCI: 32.9% vs. 46.7%) while no change was observed in the rates of CABG (2004 vs. 2014: 8.8% vs. 8.4%). (**Supplementary Table 3a**) Patients in higher ECS and NEC groups were less likely to receive CA or PCI. **(Tables 1a and 1b)** In contrast, there was no difference in rates of CABG between ECS groups whereas the CABG rates were significantly higher in patients with a greater number of comorbidities.

The overall incidence of MACCE and mortality decreased over the study period (2004 to 2014: 6.6% to 4.8% and 8.7% to 7.3%, respectively). **(Supplementary Table 3b)** However, there was an incremental rise in MACCE and mortality events with increasing ECS and NEC classes (MACCE: 3.8% in ECS<0 to 22.2% in ECS≥14, 5.6% in NEC=0 to 12.2% in NEC≥5; mortality: 2.0% in ECS<0 to 15.8% in ECS≥14, 3.8% in NEC=0 to 8.5% in NEC≥5). **(Table 2a, Table 2b)** The lowest incidence of complications (acute stroke, vascular complications and major bleeding) was observed in the lowest ECS group (ECS=0) with a rise in complication rates with increasing ECS. A similar pattern was observed in NEC groups.

In multivariable analysis, higher ECS was independently associated with increased odds of MACCE and mortality compared to ECS<0 group **(Table 3)**. ECS≥14 had over 4-fold increase in the odds of MACCE and mortality (OR 4.65, 95% CI 4.49-4.82 and OR 4.81, 95% CI 4.60-5.02, respectively), compared to ECS<0 group, with groups similarly associated with increased odds of MACCE and mortality (ECS 0, ECS 1-5 and ECS 6-13). The odds of acute ischemic stroke and major bleeding increased with rising ECS, except ECS=0 group where there was no increased risk of stroke (OR 0.98, 95% CI 0.92-1.03) or major bleeding (OR 0.61, 95% CI 0.59-0.63) compared to those with a score of <0. Within the NEC groups, a higher NEC count was associated with increased odds of MACCE and in-hospital mortality compared to those without comorbidities (NEC=0), with the exception of patients with only one comorbidity (NEC=1) who were at no increased risk of either event. **(Table 4)** Higher NEC count was also associated with increased odds of acute ischemic stroke and major bleeding in all groups compared to those without comorbidities, with NEC≥5 being associated with 2-3 fold higher odds of either complication (stroke: OR 2.98 95% CI 2.73-3.24 and major bleeding: OR 2.59 95% CI 2.46-2.72). The adjusted odds of adverse events in the STEMI subgroup were similar to those of the whole cohort. **(Supplementary Table 4a and 4b)** The prognostic association of each individual Elixhauser component on clinical outcomes was given in **Supplementary Table 5.**

As a sensitivity analysis, the association between in-hospital outcomes and ECS and NEC scores as continuous variables was undertaken. We observed that 1-unit increase in either score was independently associated with increased odds of all adverse outcomes (MACCE, mortality, acute ischemic stroke and major bleeding). **(Supplementary Table 6**)

Then median length of stay increased within increasing ECS class (ECS>0: (ECS <0 and ECS=0: 3 days, ECS=1-5: 4 days, ECS=6-13: 5 days, ECS≥14: 6 days) **(Table 1a)** and number of comorbidities **(Table 1b).** Patients with ECS=0 had the lowest median adjusted cost of hospitalization ($16,762). Adjusted cost of hospitalization increased gradually with increasing number of comorbidities ($17362 in NEC=0 vs. $25924 in NEC≥5).

# Discussion

We present the largest study to examine temporal trends of comorbidity burden in patients with ACS from a national perspective and report several important findings. First, we show an increasing burden of comorbidity in patients presenting with ACS over an 11-year period, with close to one in five patients presenting with an ACS having 5 or more comorbid conditions. We demonstrate an association between the number and severity of comorbid burden and ACS-related adverse outcomes, including MACCE, mortality, acute ischemic stroke and major bleeding, which persisted despite adjustment for differences in receipt of invasive management. Finally, our analysis also highlights the economic implications of comorbidity burden as evidence by longer admissions and higher hospitalization charges in more comorbid patients.

Only a few studies have examined the impact of comorbidity burden on receipt of invasive management in patients with ACS. A study of 740 patients with ST-elevation myocardial infarction reported lower rates of coronary reperfusion (primary PCI or thrombolysis) in those with a higher chronic comorbidity score.13 While this study provides us with insights in to the invasive management (or lack thereof) of a specific subgroup of AMI, in a modest number of patients, our analysis confirms that this finding is consistent nationwide in both STEMI and NSTEMI subgroups. We observe an inverse relationship between comorbidity severity (ECS) and number (NEC) and receipt of CA and PCI, especially in patients with ECS≥14 and NEC≥5 who were 30-50% less likely than ECS<0 and NEC=0 groups, respectively, to receive either procedure. Interestingly, while the severity of comorbidity burden had no impact on the rates of receipt of CABG, the number of comorbidities positively correlated with receipt of CABG. The latter is likely due to the characteristics of patients with multiple comorbidities, who were older and had a higher prevalence of diabetes, both of which favoring CABG over PCI.14,15

Previous studies have examined the association between comorbidity burden and ACS outcomes. 2 3 4 5 6 7,16 However, their findings have been subject to limitations as previously described, making them less generalizable to the target population. Furthermore, the majority of studies have assessed comorbidity using CCI instead of ECS, despite the latter being more superior in predicting mortality in cardiovascular cohorts2, and did not examine outcomes other than mortality in the ACS population. A two-center study of 5275 AMI patients hospitalized in Spain between 2003 and 2009 reported an rise in the incidence of AMI and number of comorbidities over the study period, as well as increased odds of mortality per unit score of Elixhauser (OR 1.14, 95% CI 1.07-1.22) and Charlson indices (OR 1.17, 95% CI 1.11-1.23).16 However, they did not examine the impact of comorbidity on management strategy and clinical outcomes such as bleeding, vascular and cardiac complications, and stroke. In a meta-analysis of studies examining the effect of comorbidity, as measured by CCI, on ACS outcomes, each additional unit of CCI score was associated with 33% increased risk of mortality (RR 1.33, 95% CI 1.15-1.54) and a higher CCI score was shown to correlate with increased odds of in-hospital, 30-day and 6-month mortalities.17 We highlight the impact of comorbidity burden, including severity and number, on all major ACS-related outcomes and report a “dose-response” relationship between comorbidity burden and these outcomes. Higher ECS and NEC groups were associated with a significantly increased risk of mortality, acute ischemic stroke, major bleeding and MACCE. Moreover, each additional ECS unit score or comorbidity count (NEC) was associated with an increased risk of all complications. Although these findings may in part be due to lower rates of coronary revascularization in these patients, comorbidity itself was shown to be an independent predictor of adverse outcomes.

Although the NIS is an administrative dataset that is subject to potential selection bias resulting from any coding inaccuracies or missing data, the use of ICD-9 codes have been previously validated for cardiovascular outcomes research.18-22 Although the NIS database contains many variables of interest, data on antiplatelet regime type and duration, medical therapy and left ventricular function are not routinely collected and may provide additional information to better stratify risk and procedural outcomes.23 Furthermore, the lack of certain laboratory data and cause of death precluded the classification of major bleeding according to standardized definitions such as BARC (Bleeding Academic Research Consortium) or TIMI (Thrombosis in Myocardial Infarction). Additionally, NIS only captures in-hospital outcomes and it is possible that mortality and other adverse events such as major bleeding and further ischemic events in the long term may be even greater in patients with greater comorbid burden. Finally, in keeping with all observational registry work, the possibility of unmeasured or unrecognized confounders may contribute to the adverse outcomes, although capture of a wide range of comorbid conditions in the NIS may help to mitigate this bias.

 In conclusion, our nationwide analysis of more than 6.5 million ACS hospitalizations demonstrates an inverse relationship between the number and severity of comorbidities and receipt of invasive strategies such as coronary angiography and PCI, but not CABG, which was more utilized in patients with a higher number of comorbidities. Furthermore, we show that a greater comorbidity burden as measured by either Elixhauser score or number of comorbidities correlates with worse clinical outcomes, including mortality, bleeding and stroke. The present study emphasizes the importance of objective comorbidity burden assessment to guide to management strategy and reliably assess prognosis at an individual patient level.

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**Figure titles and captions**

**Figure 1. Distribution of comorbidity burden according to ECS and NEC categories.**

Caption: ECS: Elixhauser comorbidity score; NEC: Number of Elixhauser comorbidities.

**Figure 2a. Distribution of the ECS groups across the study years (2004-2014).**

Caption: ECS: Elixhauser comorbidity score; NEC: Number of Elixhauser comorbidities; p-value for trend < 0.0001.

**Figure 2b. Distribution of the NEC groups across the study years (2004-2014).**

Caption: ECS: Elixhauser comorbidity score; NEC: Number of Elixhauser comorbidities; p-value for trend < 0.0001.