**The influence of Elixhauser comorbidity index on percutaneous coronary intervention outcomes**

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**Abstract**

**Background**

Clinical outcomes with respect to the evolution of comorbidity burden in national cohorts of patients undergoing PCI have not been reported.

**Objectives**

We sought to explore the association between comorbidity burden and peri-procedural outcomes in patients treated with PCI in the National Inpatient Sample (NIS).

**Methods**

6,601,526 PCI procedures were identified between 2004 and 2014 and comorbidities were defined by the Elixhauser classification system (ECS) consisting of 30 comorbidity measures. Endpoints included in-hospital mortality, periprocedural complications, length of stay and cost. Patients were classified based on their ECS in five categories (ECS I<0, ECS II=0, ECS III=1-5, ECS IV=6-13, ECS V ≥ 14).

**Results**

Patients with a score over 13 had a 5-fold increase in the odds of mortality (OR:5.13, 95 % CI:4.76-5.54), major bleeding (OR:11.46, 95% CI: 10.66-12.33). and doubled the hospitalisation costs ($31,452 vs $17.566).

**Conclusions**

Our study of over 6 million PCI procedures demonstrates that patients with the greatest comorbid burden (as defined by an ECS of >13) have a 5-fold increase risk of in-hospital mortality, a 4-fold increase in in-hospital peri-procedural complications and an 11-fold increase in major bleeding events once differences in baseline patient characteristics are adjusted for. In addition, ECS significantly impacts the length of stay and doubles the healthcare costs. Comorbid burden is an important predictor of poor outcomes after PCI and should be considered as part of the decision-making processes in patients undergoing PCI.

**Condensed Abstract**

Our study of over 6 million PCI procedures demonstrates that only one in eight patients undergoing PCI in the United States are free from significant comorbid disease and suggests that patients with the greatest comorbid burden (as defined by an ECS of >13) have a 5-fold increase risk of in-hospital mortality, a 4-fold increase in in-hospital peri-procedural complications and an 11-fold increase in major bleeding events. In addition, ECS significantly impacts the length of stay and doubles the healthcare costs. Comorbid burden is an important predictor of poor outcomes after PCI and should be considered as part of the decision-making processes in patients undergoing PCI.

**Key Words**

PCI, Elixhauser classification system, peri-procedural complications, healthcare costs

**Introduction**

The average age of patients undergoing percutaneous coronary intervention (PCI) in contemporary practice has increased over time with more complex disease encountered.(1) This aging population has an increasing burden of co-morbid conditions, with registry studies suggesting that at least 75% of patients undergoing PCI have at least one coexisting major comorbid condition.(2) The influence of individual cardiovascular comorbid conditions(3-5) on post PCI outcomes are well described in the literature, although less so for non-cardiovascular conditions.(6-9) Comorbidities rarely occur in isolation, with patients having multiple comorbid conditions that may impact on a patient’s clinical course synergistically, rather than in isolation. Data on the influence of global measures of comorbid burden and their impact on clinical outcomes are relatively limited, and mainly derived from small cohorts limited to single centres.(2, 4) In the Nobori-2 study, the risk of cardiac mortality post PCI in patients with a high global comorbid burden as defined by the Charlson comorbidity score was quadruple compared to cohorts with no comorbid conditions.(2)

The Elixhauser classification system (10) (ECS) is one of the most commonly used measures of comorbid burden and comprises 30 comorbidity measures used to derive a weighted comorbidity score (van Walraven Elixhauser comorbidity score) to assess global comorbid burden.(11) The ECS is superior in comparison to the individual comorbidities in predicting death across medical subspecialties (12, 13) as well as demonstrating marginal improvement in predicting in-hospital mortality after orthopaedic surgery.(14)

Clinical outcomes with respect to the evolution of comorbidity burden in national cohorts of patients undergoing PCI have not been reported. We therefore sought to evaluate the prevalence and temporal trends of co-morbid conditions that comprise the ECS, and their association with clinical outcomes and healthcare costs through analysis of over 6 million PCI procedures performed in the United States through analysis of the United States Nationwide Inpatient Sample (NIS).

**Methods**

**Data source**

The data are derived from hospital discharges in the United States between 2004 and 2014, as part of the National Inpatient Sample (NIS). This is the largest all – payer inpatient health care database in the United States and was developed by the Healthcare Cost and Utilization Project (HCUP) which is sponsored by the Agency for Healthcare Research and Quality (AHRQ). Since 2012, the NIS approximates a 20% stratified sample of all discharges from all US community hospitals participating in HCUP. Prior to 2012, the NIS, known as the Nationwide Inpatient Sample, was a sample of all discharge records from a sample of hospitals.

**Study design**

Individuals over the age of 18 with a PCI performed between January 2004 and December 2014 were identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes of one or a combination of 00.66 (*Percutaneous Transluminal Coronary Angioplasty),*36.06 (*Insertion of non-drug-eluting coronary artery stent(s))* or 36.07 (*Insertion of a drug-eluting coronary artery stent(s))*. Before a revision of the codes in 2005 the codes 36.01 (*Single vessel percutaneous transluminal coronary angioplasty or coronary atherectomy without mention of thrombolytic agent),* 36.02 (*Single vessel percutaneous transluminal coronary angioplasty or coronary atherectomy with mention of thrombolytic agent)* and 36.05 (*Multiple vessel percutaneous transluminal coronary angioplasty [PTCA] or coronary atherectomy performed during the same operation, with or without mention of thrombolytic agent)* were also used, and these codes were included when identifying procedures in discharges from 2004 and 2005.

Patient demographics are recorded for each hospital discharge including age, gender, race, admission type (elective or emergent), admission day (weekday or weekend), median household income according to ZIP code, expected primary payer, and patient comorbidity conditions using the Elixhauser comorbidity index were collected. ICD-9 CM codes were used to identify a primary diagnosis of an acute myocardial infarction or a diagnosis of cardiogenic shock, ST-elevated myocardial infarction or non-ST-elevated myocardial infarction during index hospitalisation. These diagnosis codes were also used to identify other patient comorbidities including smoking, hypercholesterolemia and historical patient information.

The Elixhauser comorbidities were used to calculate a score using the method and weightings proposed by van Walraven.(10, 11) This value was analysed as a continuous and categorical value as defined in the original paper (Supplementary table 3). The number of Elixhauser comorbidities was also considered as a sum of the number of individual comorbidities and was also categorised into patients with 0, 1, 2, 3 and 4 or more comorbidities.

Information regarding the PCI procedure was determined from the procedure codes, including whether the PCI was conducted on single or multiple vessels, whether it involved bifurcation stenting. The use of adjunctive devices including intracoronary pressure wire, intravascular ultrasound or a mechanical assist device (such as an intra-aortic balloon pump) were also recorded. Where available, we also included the stent type deployed (bare metal or drug-eluting).

**Clinical Outcomes**

In-hospital clinical outcomes of mortality and procedural-related complications, were identified. Length of stay on the discharge record and the total charge of hospitalisation for each individual discharge were also captured. The total charge is calculated using a chare-to cost conversion ratio of the amount billed for services.

Detailed procedural complications, identified using ICD-9-CM codes, included vascular injuries, iatrogenic cardiac and pericardial complications, need for emergency coronary artery bypass grafting and a post-operative stroke or transient ischaemic attack. Bleeding complications included: gastrointestinal, retroperitoneal, intracranial, intracerebral haemorrhage, unspecified haemorrhage, and whether a blood transfusion was required. Complications were identified by ICD-9-CM codes in any secondary diagnosis field (Supplementary Table 1).

**Statistical analysis**

Statistical analysis was performed on STATA/MP version 14.0. Continuous variables are presented as median and interquartile range, due to skewed data, and categorical data are presented as number and percentage. Where missing data was less than 10% of the covariate data, the observations with missing data were removed. Data was assumed to be missing at random.

For all analyses, the survey estimation commands were used (by using the svy prefix in analyses conducted in Stata), following the recommendations from AHRQ to account for the complex survey design of the NIS database. Because the design of our study from 2004-14 means that different observations may have different probabilities of selection, calculation of national estimates and correct variances, used sampling weights provided for each individual discharge by the AHRQ. Due to records being sampled by hospitals rather than individuals, clustering of records within hospitals was taken into account in the survey estimation. This was done by defining each hospital to be the primary sampling unit.

Several multivariable analyses were conducted to investigate the association between the Elixhauser comorbidities with (a) in-hospital mortality, (b) any defined complication (c) a composite of any of the considered complications. Logistic regression models were fitted in order to investigate the impact on the van Walraven Elixhauser score, the number of Elixhauser comorbidities on record, and the impact of individual comorbidities on in-hospital mortality or an in-hospital complication (post-operative bleeding, vascular complication, cardiac complication or a stroke/TIA). No formal analysis was conducted to look at the impact of current cancer diagnosis on length of stay and total cost of treatment. Both the van Walraven score and the number of comorbidities were categorised for the analysis, with a sensitivity analysis looking at keeping the covariates as continuous.

**Results**

A total of 7,121,387 PCI procedures were performed between 2004-2014 in the US. Discharges with less than 10% missing data for included outcomes as well as covariates were removed. 6,601,526 procedures were included in the final analysis with approximately 7% of the original dataset removed due to missing data. (Supplementary Figure 1)

Just over 50% of the patients had an Elixhauser score of 0 (Figure 1). Twenty-five percent of the dataset had an Elixhauser score between 0 and 5 and less than 2% of records had an Elixhauser score of greater than 13. With respect to the distribution of categorized number of Elixhauser comorbidities, 29% had at least 1 comorbidity closely followed by the number of patients with 2 comorbidities (27%) with only 13% of patients having no comorbid conditions (Figure 2).

Clinical demographics stratified by categorised Elixhauser score are described in Table 1. Patients in the higher score categories were older and more likely to be female compared to the lower score categories. They were also more likely to receive a bare metal stent (35.3% vs 22.6%) and require the use of an assist device or IABP (10.8% vs 2.0%) during the procedure compared to lower categories. During the time course of this analysis between 2004 and 2014 the proportion of patients with an Elixhauser score >13 or with more than 5 different comorbid conditions increased, accounting for 3.2% and 12.4% of patients undergoing PCI in 2004 and 2014, respectively. Similarly, the proportion of patients undergoing PCI with no comorbid conditions declined from 18.2% in 2004 to 8.6% in 2014 (Figure 3 and Supplementary Figures 3).

An increasing number of comorbidities was noted with an increase in the median age (68 for 5 or more comorbidities vs 60 for patients with no comorbidities). Females were more likely to have more comorbidities. 78.3% of patients with no comorbidities were male which decreased to 50.9% when there were more than 5 recorded comorbidities. Across all the categories hypertension was the most common comorbidity and was present in 68.9% of patients with a single comorbidity. This increased to 91.5% patients with 5 or more comorbidities.

*Clinical Outcomes*

In-hospital mortality increased with increasing Elixhauser score, from 0.7% for a score of 0 and less than 0 to 10.2% with a score of 13 or more (Table 2). A similar pattern was observed with respect to complications. Patients with a score of 0 had the lowest complication rate (5.2%) whilst the rate of complications was 30.3% for patients with a score of more than 13.

In hospital mortality was similar in patients with 0, 1 or 2 comorbidities (approximately 1%), with a two-fold increase in patients with 3(1.9%) or 4 comorbidities (2.8%). Patients with 5 or more comorbidities had an in-hospital mortality rate nearly 5 times greater (4.7%) compared to those patients with no comorbidities. Similarly, the incidence for complications increased with the number of Elixhauser comorbidities.

Multivariable logistic regression analysis for categorised Elixhauser reveal that compared to the reference category (ECS score of 0), patients with a score of <0 have a 10% decrease in the odds of mortality (OR:0.91, 95% CI: 0.86-0.97), patients with a score between 0 and 5 have almost a 2-fold increase (OR:1.94, 95% CI: 1.85-2.03), individuals with a score between 6 and 12 have over a 3-fold increase (OR:3.42, 95% CI: 3.25-3.60) and patients with a score over 13 have a 5-fold increase in the odds of mortality (OR:5.13, 95 % CI:4.76-5.54) (Table 3). Similarly, categorised Elixhauser score was an independent predictor of peri-procedural complications. The most profound impact was seen in the context of major bleeding (OR:11.46, 95% CI: 10.66-12.33) between the cohorts with high comorbid burden and minimal comorbidity. The results of the multivariable regression keeping the score as a continuous variable are given in Supplementary Table 2.

Furthermore, multivariable logistic regression results for categorised number of Elixhauser comorbidities reveal that in hospital mortality gradually increased with an increasing number of Elixhauser comorbidities with an odds ratio of 1.16 (95% CI:1.08-1.24) for 2 comorbidities up to 2.41 (95% CI:2.22-2.60) for 5 or more comorbidities compared to those who have none (Supplementary Table 4). There was a profound increase in the odds of a bleeding complication with a 14-fold increase in those with 5 or more comorbidities compared to 0 (13.92 95% CI 12.79,15.15). The results of the multivariable regression keeping the number of Elixhauser comorbidities as a continuous variable are given in Supplementary Table 3.

*Length of stay and cost*

For patients with a van Walraven Elixhauser score of less than 0, 0 and between 0 and 5 there was a similar median length of stay of approximately 2 days. This increased to 4 days for those with a score between 6 and 12 and to 8 days with a score greater than 13 (Table 1). Increases in the van Walraven Elixhauser score were also associated with an increase on the cost of hospitalisation, with patients who have a score over 13 having near double the hospitalisation costs ($31,452 vs $17.566 for a score <0 and $16,260 for a score of 0). If we consider the number of Elixhauser comorbidities, changes in median length of stay are not as substantive, with a median of 2 days for those with 0,1,2 or 3 comorbidities, 3 days for those with 4 comorbidities and 5 days for those with 5 or more comorbidities. The median cost of hospitalisation ranges from $16,169 for patients with no comorbidities to $24,594 for patients with 5 or more comorbidities.

**Discussion**

Our analysis, the first to systematically study changes in global comorbid burden as defined by the ECS in a national cohort of over 6 million patients undergoing PCI reveals that comorbid burden has significantly increased over the past decade in the United States. By 2014, only a minority of patients undergoing PCI have no comorbid conditions (8.6%). In addition, we demonstrate that ECS is independently associated with an increased risk of in hospital mortality, in hospital complications, length of stay and healthcare costs. Patients with the greatest comorbid burden (as defined by an ECS of >13) have a 5-fold increase risk of in-hospital mortality, a 4-fold increase in in-hospital peri-procedural complications, and an 11-fold increase in major bleeding events once differences in baseline patient characteristics are adjusted for.

An increasingly elderly population of patients with significant comorbid burden and complex coronary disease are undergoing coronary revascularisation due to more effective treatments, better stent designs, and advancements in interventional techniques and coronary imaging..(15-19) Whilst the association between individual cardiovascular comorbid conditions and clinical outcomes following PCI has been extensively studied, non-cardiovascular comorbidity is often not captured in PCI datasets. This is particularly relevant given that many non-cardiovascular comorbid conditions such as cancer (20) or chronic liver disease (21) may have a more important prognostic impact on longer term outcomes than co-existing cardiovascular disease. Most current reports examining contemporary trends have focused on conventional cardiovascular risk factors and have not considered either non-cardiovascular comorbidities or more global measures of comorbid burden.(22, 23) Patients enrolled into clinical trials are often younger with low comorbidity burden. Many comorbid conditions frequently encountered in clinical practice are formal exclusion criteria in the randomised trials. Our analysis of over 6 million individuals is the first of its kind assessing ECS and its association with clinical outcomes and peri-procedural complications including length of stay and healthcare costs. This analysis suggests that only one in 8 patients undergoing PCI in the United States are free from comorbidities, and that comorbid burden was greatest in women and older individuals. Chronic pulmonary disease, anaemia and hyperthyroidism represent the most common non-cardiovascular comorbid conditions encountered whilst the most common cardiovascular conditions were hypertension. diabetes, hypercholesterolemia and peripheral vascular disease. Patients with higher comorbid burden were more likely to experience life threatening complications and had a fivefold increase in in-hospital mortality. This study adds evidence to literature that assessment of global comorbid burden is important and provides independent prognostic information to patient outcomes. We have previously published an analysis in the same cohort of PCI patients looking at the prognostic impact of another measure of global comorbid burden, the Charlson score (24). In this analysis we showed that comorbidity burden (as measured with Charlson score) was independently associated with a variety of clinical outcomes following PCI, with the highest risk score category (Charlson score ≥3) independently associated with mortality (OR1.96 95% CI 1.86-2.07), bleeding (OR 4.26, 95% CI 4.09-4.42) and stroke (OR 2.40, 95% CI 2.30-2.51). The highest comorbidity burden category in the Elixhouser scale (van Walraven Elixhauser score ≥13) appeared to have greater prognostic impact on these endpoints, and was independently associated with mortality (OR 5.13, 95% CI 4.76-5.54), bleeding (OR 11.46 95%CI 10.66-12.33) and stroke (OR 4.04 95% CI 3.78-4.31).

Our cohort of 6,601,526 patients undergoing PCI is the largest study to formally assess comorbid burden and its relationship with clinical outcomes to date, considering both cardiovascular and non-cardiovascular comorbidities. Additionally, our study provides an insight into how comorbid states influence health economics and hospital stay. This confirms a smaller Spanish study of 434,108 PCIs(15) demonstrating that another measure of comorbid burden, the Charlson comorbidity index, was an independent predictor of mortality, stent thrombosis and major adverse cardiovascular events

Additional findings include: decreased odds of in-hospital mortality associated with obesity, hypertension and hyperthyroidism and increased odds of in-hospital mortality associated with fluid and electrolyte disorders, anaemia, and coagulopathy. These findings are hypothesis generating. The obesity paradox has been well documented in literature(25-30). A post hoc analysis of the 345,192 participants undergoing PCI from the British Cardiovascular Intervention Society Registry(29) demonstrated that obese patients had a short and long-term survival advantage over individuals with normal body mass index. Similarly, patients with anaemia undergoing PCI are known to be at increased risk of major bleeding complications, major adverse cardiovascular events and mortality(31). We also observe that patients with a coagulopathy are at increased risk of major bleeding complications and mortality.

With an increasing prevalence of comorbid conditions encountered in PCI practice, global comorbid burden represents an important consideration in the clinical decision-making process in the management of these individuals. The addition of comorbid burden measurement to contemporary risk stratification tools may provide an added dimension to patient assessment and management plans. Previously, the inclusion of Charlson comorbidity index to Mayo Clinic Risk Score resulted in a net reclassification improvement of 34% (p<0.001), modest improvement in integrated discrimination index, as well as C-statistic.(7) This is particularly pertinent given that the primary aetiology of death post PCI has transitioned from a cardiac one to malignancy and chronic diseases.(32) Non-cardiac comorbidities were amongst the strongest independent predictors of non-cardiac mortality in this study,(32) further supporting integration of comorbid burden into contemporary risk scores to more accurately predict mortality post PCI. The performance of several PCI risk models have declined over time as a result of new technology, changes in clinical practice guidelines as well as profile of the patients undergoing PCI. Hence, it is important to update such scores to maintain their performance and prevent calibration drift. (34) Inclusion of measures of global comorbid burden such as ECS may improve their performance, particularly at a time when comorbidity burden in patients undergoing PCI is increasing. During admission and review of an individual undergoing PCI an ECS could be calculated and could be helpful in risk stratification and utilise the information to explain the risks of the procedure during informed consent. Furthermore, ECS is independently associated with major bleeding complications, with the highest ECS category (ECS>13) independently associated with an 11-fold increase in the risk of bleeding complications (OR 11.46 95%CI 10.66-12.33). Bleeding avoidance strategies in this cohort of patients is particularly relevant, such as the use of less potent anti-thrombotics either during / post PCI procedure, use of stent platforms that only require abbreviated DAPT durations, shortened DAPT and radial access to reduce access site related bleeding complications.

This work is subject to a number of limitations that are inherent to the post hoc analysis of large administrative databases. The NIS dataset does not capture information regarding antiplatelet and anticoagulation regimes, procedural details (e.g. angiographic and lesion specific data, type of stent) or frailty. Differences in these parameters between groups may in part contribute to some of the relationships reported. Frailty is an important factor and has been considered as an independent predictor of poor outcomes.(35-37) A meta-analysis(35) of 2332 patients suggested that frailty was a predictor of all-cause mortality after PCI (hazard ratio: 2.97, 95% confidence interval: 1.56 to 5.66). Unfortunately, the timing of the PCI during the course of the admission is unknown in the PCI dataset and hence it is difficult to ascertain the complexity of the patient’s admission. Lastly, coding errors and selection bias are inherent to the retrospective large administrative database analysis.

In summary, our study of over 6 million PCI procedures demonstrates that a wide range of comorbid conditions are increasingly encountered in contemporary PCI practice and that only one in eight patients undergoing PCI in the United States are free from significant comorbid disease. Our analysis suggests that patients with the greatest comorbid burden (as defined by an ECS of >13) have a 5-fold increase risk of in-hospital mortality, a 4-fold increase in in-hospital peri-procedural complications and an 11-fold increase in major bleeding events once differences in baseline patient characteristics are adjusted for. In addition, ECS significantly impacts the length of stay and doubles the healthcare costs. Comorbid burden is an important predictor of poor outcomes after PCI and should be considered as part of the decision-making processes in patients undergoing PCI. Further research in this arena should assess both ECS’s incremental value to conventional PCI risk model, but also those patients that may be better managed through alternative means such as medical management.

**Figure legends**

Figure 1: Distribution of categorised van Walraven Elixhauser score for included records

Figure 2: Distribution of included records for the categorised number of Elixhauser comorbidities

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Supplementary figure 1: Flow diagram of included/excluded records

Supplementary Figure 2: Distribution of categorised number of Elixhauser comorbidities for each included year of the study.

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