Influence of Comorbid Conditions on One-Year Outcomes in Non-ST-Segment Elevation Acute Coronary Syndrome

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OBJECTIVE: To investigate comorbid conditions with prognostic influence in non-ST-segment elevation acute coronary syndrome (NSTEMACS).

PATIENTS AND METHODS: The study group consisted of a derivation cohort of 1017 patients (admitted from October 1, 2002, through October 1, 2008) and an external validation cohort of 652 patients (admitted from February 1, 2006, through September 30, 2009). Comorbid conditions, including risk factors and components of the Charlson comorbidity index (ChCI) and coronary artery disease-specific index, were recorded. The main outcome was one-year mortality.

RESULTS: During follow-up, 103 patients died. After adjusting for variables associated with NSTEMACS characteristics (base model), 5 comorbid conditions predicted mortality: severe or mild renal failure (hazard ratio [HR], 2.9 and HR, 1.6, respectively), dementia (HR, 3.1), peripheral artery disease (HR, 2.0), previous heart failure (HR, 2.6), and previous myocardial infarction (HR, 1.4). A simple comorbidity index (SCI) was developed using these variables, (per point: HR, 1.6; 95% confidence interval, 1.4-1.8; $P=.0001$). Adding the SCI, Charlson comorbidity index, or coronary artery disease-specific index to the base model resulted in a gain of 6.58%, 5.00%, and 4.04%, respectively, in discriminative ability ($P=.001$), without significant differences among the 3 indices. In patients with comorbid conditions, the highest risk period was in the first weeks after NSTEMACS. The strength of the association between SCI and mortality rate was similar in the external validation cohort (HR, 1.3; 95% confidence interval, 1.1-1.6; $P=.001$).

CONCLUSION: Renal dysfunction, dementia, peripheral artery disease, previous heart failure, and previous myocardial infarction are the comorbid conditions that predict mortality in NSTEMACS. A simple index using these variables proved to be as accurate as the more complex comorbidity indices for risk stratification. In-hospital management of patients with comorbid conditions merits further investigation.

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CAD = coronary artery disease; ChCI = Charlson comorbidity index; CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio; IDI = integrated discrimination improvement; LVEF = left ventricular ejection fraction; NSTEMACS = non-ST-segment elevation acute coronary syndrome; SCI = simple comorbidity index

Patients of advanced age constitute a high proportion of the population hospitalized for an acute coronary syndrome.¹ Many of them have comorbid conditions that could have a profound effect on their management and prognosis. The Charlson comorbidity index (ChCI) and the coronary artery disease (CAD)-specific index based on the ChCI are the comorbidity indices used in cardiac patients.²⁻⁴ Both indices have been shown to predict mortality in a variety of ischemic heart disease scenarios⁵⁻⁹; however, the ChCI was

derived from patients admitted to an internal medicine service with a wide spectrum of diseases other than acute coronary syndrome.² However, despite the known importance of comorbid conditions, they are rarely documented, and consequently not used, in clinical trials and registries.¹⁰⁻¹⁵ One of the reasons could be the complex scoring system of the mentioned indices, which involve many variables with different assignation of points. Conceivably, patients with acute coronary syndromes could show a more restrictive range of comorbid conditions.

The current study included consecutive patients with non-ST-segment elevation acute coronary syndrome (NSTEMACS) from 2 centers, defined as the derivation and external validation cohorts. Its aim was to identify the comorbid conditions that were more prevalent and had greater prognostic relevance in patients with NSTEMACS. The ultimate goal was to provide clinicians a tool with which they could evaluate the effect of given comorbid conditions on the prognosis of patients hospitalized with NSTEMACS. Conceivably, further studies could test different therapeutic approaches across comorbidity status.

PATIENTS AND METHODS

DERIVATION COHORT

This prospective cohort consisted of 1017 consecutive patients admitted to the Hospital Clínic Universitari (Valèn-

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cia) with an NSTEACS, from October 1, 2002, to October 1, 2008. All patients presented to the emergency department with acute chest pain. The diagnosis of NSTEACS was made by meeting at least 1 of the following criteria: (1) ST-segment depression (≥ 1 mm) on initial or subsequent electrocardiography; (2) troponin I elevation at any determination (>0.20 ng/mL; Dimension assay, Dade Behring, Newark, DE); or (3), in the absence of the 2 previous criteria, evidence of ischemia on noninvasive stress tests or of significant stenosis on coronary angiography.¹⁶⁻¹⁸ The only exclusion criteria were persistent ST-segment elevation or previous known heart disease other than CAD (eg, cardiac valve disease or cardiomyopathy).

During hospitalization, invasive management was recommended at our institution once the diagnosis was established; however, the final decision on cardiac catheterization was left up to the attending cardiologist. Measurement of left ventricular ejection fraction (LVEF) using echocardiography was also recommended.

DATA COLLECTION

The following data were collected at admission: demographic data, such as age and sex; acute coronary syndrome presentation characteristics, such as admission heart failure, ST-segment depression, troponin elevation, and admission white blood cell count; and the presence of comorbid conditions, defined as previous medical conditions that could influence outcome, including coronary risk factors and all components of the ChCI.³ The ChCI and the CAD-specific index were calculated using the appropriate weights.^{3,4} The definitions of the variables were those used in the ChCI.^{2,3} The presence of dementia (defined as a long-standing cognitive defect) was determined using information from the physician and a questionnaire administered by a trained nurse. Anemia was defined as a hemoglobin concentration of less than 12 g/dL for men or less than 13 g/dL for women (to convert to g/L, multiply by 10).

OUTCOMES

The main outcome was total mortality at one-year follow-up. The secondary end point was death or acute myocardial infarction. All except 4 patients completed follow-up.

EXTERNAL VALIDATION COHORT

This cohort consisted of 652 consecutive patients with NSTEACS admitted to the Hospital Clínic of Barcelona from February 1, 2006, to September 30, 2009. The primary and secondary end points were recorded at 6-month follow-up.

STATISTICAL ANALYSES

Categorical variables are reported as absolute values (percentages). Age was scaled to years divided by 10. White

blood cell count was dichotomized using the threshold at the fourth quartile ($>10 \times 10^9/L$); moreover, this cut point provided prognostic value in a previous study.¹⁹ Three categories of renal function status were considered depending on the glomerular filtration rate (GFR)²⁰: greater than 50, 20-50, and less than 20 mL/min/1.73 m². The GFR was estimated using the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology equations.²¹

Univariate analysis was performed to investigate the association between the collected data and outcome. Variables that were significant at $P < .05$ were introduced in a Cox regression model (backward conditional method with removal criterion if $P > .15$). The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A simple comorbidity index (SCI) was created using the comorbidity variables that were independently associated with the outcome by assigning 1 or 2 points according to the weight of their HR (1 point: HR, 1-2; 2 points: HR, 2-3).

The added prognostic value of each of these comorbidity indices was calculated and compared against the base model. Likewise, the SCI model's performance was tested in the external validation cohort. The base model included age, sex, admission heart failure, ST-segment depression, and white blood cell count greater than $10 \times 10^9/L$. Models' performances were evaluated using the following discrimination and calibration measures: Brier score and scaled Brier score, Nagelkerke R^2 , C-statistic, integrated discrimination improvement (IDI) index, calibration slope, and Hosmer-Lemeshow test for goodness of fit. Adjustment for multiple comparisons was performed for the IDI indices comparisons among models. The patient population was divided into 3 groups according to SCI score, and the cumulative rate of mortality was compared among them using Kaplan-Meier curves.

Left ventricular ejection fraction was measured in 955 patients, and its role in prognosis was analyzed. Three subgroups were distinguished: normal LVEF ($>55\%$), moderately depressed LVEF ($<55\%$ but $>40\%$), and severely depressed LVEF ($<40\%$).

Because invasive management could have influenced the outcome in a sensitivity analysis, the predictive value of the SCI was additionally adjusted to take into consideration those who underwent cardiac catheterization at the index hospitalization.

All statistical analyses were performed using STATA 11.1 (STATA Corp, College Station, TX) and R 2.11.1 (R Foundation for Statistical Computing, Vienna, Austria) with Hmisc, version 3.8-3 (available at <http://biostat.mc.vanderbilt.edu/wiki/Main/Hmisc>) and Design, version 2.3-0 (available at <http://biostat.mc.vanderbilt.edu/s/Design>) packages from Harrell's library.

RESULTS

The mean $\pm$ SD age of patients in the derivation cohort was 68 ± 13 years, and 668 (66%) were men. Admission heart failure was observed in 12% of the patients, ST-segment depression in 38%, troponin elevation in 68%, and white blood cell count greater than $10 \times 10^9/L$ in 31%. Table 1 summarizes the comorbid conditions of the patient population. Some of the comorbid conditions that are components of the ChCI had very low prevalence: acquired immunodeficiency syndrome, 6 patients; mild liver disease, 7 patients; severe liver disease, 8 patients; and metastatic solid tumor, 2 patients.

Of the 1017 patients in the derivation cohort, 725 patients (71%) underwent coronary angiography, and 450 (44%) were revascularized. At discharge, 88% of the patients received aspirin; 44%, clopidogrel; 68%, statins; 75%, β -blockers; and 63%, angiotensin-converting enzyme inhibitors.

During follow-up, 103 patients (10%) died, and 197 (19%) died or experienced an acute myocardial infarction.

MULTIVARIATE ANALYSIS

Table 2 shows the results of the multivariate analysis. Age, male sex, heart failure, ST-segment depression, and white blood cell count greater than $10 \times 10^9/L$ were independently associated with mortality. Furthermore, renal failure (severe dysfunction [GFR <20 vs >50 mL/min/1.73 m²]: HR, 2.9; 95% CI, 1.5-5.9; $P=.01$; mild dysfunction [GFR 20-50 vs >50 mL/min/1.73 m²]: HR, 1.6; 95% CI, 1.1-2.6; $P=.04$), dementia (HR, 3.1; 95% CI, 1.2-8.2; $P=.01$), peripheral artery disease (HR, 2.0; 95% CI, 1.2-3.3; $P=.01$), previous history of heart failure (HR, 2.6; 95% CI, 1.6-4.3; $P=.0001$), and previous myocardial infarction (HR, 1.4; 95% CI, 0.9-2.1; $P=.10$) emerged as the most important and independent comorbid factors predicting mortality. These 5 variables were used to construct an SCI, assigning 2 points to severe renal dysfunction, dementia, previous history of heart failure, and peripheral artery disease, and 1 point to mild renal failure or previous myocardial infarction.

COMPARISON OF THE COMORBIDITY INDICES

All 3 comorbidity indices predicted outcome in the multivariate models: the SCI (per point: HR, 1.6; 95% CI, 1.4-1.8; $P=.0001$), the ChCI (per point: HR, 1.3; 95% CI, 1.2-1.4; $P=.0001$), and the CAD-specific comorbidity index (per point: HR, 1.2; 95% CI, 1.1-1.2; $P=.0001$). Table 3 shows all performance measures (overall, discrimination, and calibration) for each final model. All 3 multivariate models that included one of the comorbidity indices (SCI, ChCI, or the CAD-specific index) showed higher discriminative ability than the base model, as judged by the IDI indices (6.58%,

TABLE 1. Comorbid Conditions Among Patients in the Derivation Cohort (N=1017)^a

Current smoker	243 (24)
Hypertension	656 (65)
Hypercholesterolemia	494 (49)
Diabetes	404 (40)
Family history of ischemic heart disease	60 (6)
Previous myocardial infarction	249 (24)
Previous coronary stenosis	197 (19)
Previous coronary angioplasty	85 (8)
Previous coronary surgery	74 (7)
Previous admission for heart failure	75 (7)
Peripheral artery disease	93 (9)
Cerebrovascular disease	81 (8)
Chronic pulmonary disease	85 (8)
Diabetes with end-organ damage	59 (6)
Mild renal failure ^b	218 (21)
Severe renal failure ^b	27 (3)
Cancer	59 (6)
Rheumatic disease	65 (6)
Peptic ulcer disease	42 (4)
AIDS	6 (0.6)
Mild liver disease	7 (0.7)
Severe liver disease	8 (0.8)
Hemiplegia	15 (1.5)
Dementia	14 (1.4)
Metastatic solid tumor	2 (0.2)
Anemia ^c	195 (19)

^a Data are provided as number (percentage) of patients. Definitions of variables (comorbid conditions) are the same as those used in the Charlson comorbidity index.^{2,3}

^b Mild renal failure is defined as a glomerular filtration rate of 20-50 mL/min/1.73 m², and severe renal failure is defined as a glomerular filtration rate of <20 mL/min/1.73 m².

^c Anemia is defined as a hemoglobin concentration of <12 g/dL for men or <13 g/dL for women (to convert to g/L, multiply by 10).

5.00%, and 4.04%, respectively; $P<.001$ for all comparisons). Nevertheless, no statistically significant differences in the IDI indices were found among their comparisons (SCI vs ChCI, 1.57%; $P=.16$; SCI vs CAD-specific index, 2.25%; $P=.10$; ChCI vs CAD-specific index, 0.68%;

TABLE 2. Multivariate Analysis for One-Year Mortality^a

Variable	Hazard ratio (95% CI)	P value
Age (y/10)	1.7 (1.4-2.2)	.0001
Male sex	1.6 (1.0-2.5)	.06
Heart failure at admission	2.4 (1.5-4.0)	.0001
ST-segment depression	1.6 (1.1-2.5)	.01
White blood cell count $>10 \times 10^9/L$	1.9 (1.2-2.8)	.01
Comorbid conditions		
Previous MI	1.4 (0.9-2.1)	.10
Previous heart failure	2.6 (1.6-4.3)	.0001
Peripheral artery disease	2.0 (1.2-3.3)	.01
Dementia	3.1 (1.2-8.2)	.01
Renal failure ^b		
Mild	1.6 (1.1-2.6)	.04
Severe	2.9 (1.5-6.0)	.01

^a CI = confidence interval; MI = myocardial infarction.

^b Mild renal failure is defined as a glomerular filtration rate of 20-50 mL/min/1.73 m², and severe renal failure is defined as a glomerular filtration rate of <20 mL/min/1.73 m².

TABLE 3. Comparison of the Performance of Comorbidity Indices in the Derivation (N=1017) and Validation Cohorts (N=652)^{a,b}

Performance measure	Derivation cohort				External validation of SCI model
	Base model	ChCI	CAD-SI	SCI	
Overall					
Brier	7.6	7.0	7.1	6.9	6.3
Brier-scaled	16.4	22.4	21.3	23.6	12.2
R ² (Nagelkerke)	26.1	31.1	30.0	33.0	24.4
Discrimination					
C-statistic	82.3	83.7	83.3	84.8	83.1
Discrimination slope	17.1	22.1	21.1	23.6	16.4
IDI (P value)	NA	5.00 ^c (.0001)	4.04 ^c (.01)	6.58 ^c (.0001)	NA
Calibration					
Calibration slope	1	1	1	1	1.023
H-L test (P value)	.87	.70	.47	.80	.60

^a CAD-SI = coronary artery disease-specific index; ChCI = Charlson comorbidity index; H-L = Hosmer-Lemeshow statistics for goodness of fit; IDI = integrated discrimination improvement; NA = not applicable; SCI = simple comorbidity index.

^b Data are provided as percentages unless indicated otherwise.

^c Compared with the base model.

$P=.45$.) The SCI also predicted death or myocardial infarction (per point: HR, 1.3; 95% CI, 1.2-1.5; $P=.0001$).

RISK STRATIFIED BY COMORBID CONDITIONS

The distribution of the SCI scores for the patient population was as follows: 0 points, 560 patients; 1 or 2 points, 327 patients; and 3 or more points, 130 patients. Mortality progressively increased as the number of points increased, from 3.6% in the lowest-comorbidity category to 11% (HR, 1.7; 95% CI, 1.0-3.1; $P=.06$) and 36% (HR, 4.8; 95% CI, 2.7-8.5; $P=.0001$) in the intermediate- and high-comorbidity categories. The Figure depicts the Kaplan-Meier curve for each category. The greatest separation between

the curves occurs within the first weeks after NSTEMACS. The same pattern was observed for the end point of death or acute myocardial infarction: 11%, 22% (HR, 1.6; 95% CI, 1.1-2.2; $P=.02$), and 49% (HR, 2.9; 95% CI, 1.9-4.3; $P=.0001$).

PROGNOSTIC INFLUENCE OF LVEF

The influence of LVEF was investigated in the 955 patients in whom it was measured. Moderate (HR, 1.7; 95% CI, 1.0-2.9; $P=.04$) and severe (HR, 2.5; 95% CI, 1.5-4.3; $P=.001$) LVEF depression predicted mortality. After adjusting for LVEF, the SCI maintained its prognostic value (per point: HR, 1.6; 95% CI, 1.4-1.8; $P=.0001$).

FIGURE. One-year mortality (left) and one-year mortality or acute myocardial infarction (MI) (right), stratified by the simple comorbidity index (SCI).

INVASIVE MANAGEMENT

Cardiac catheterization use decreased as comorbidity increased, from 83% in the low-comorbidity category to 67% and 36% in the intermediate- and high-comorbidity categories ($P=.0001$). After management strategy was introduced in the predictive model, however, both invasive management (HR, 0.5; 95% CI, 0.3-0.8; $P=.01$) and the SCI (per point: HR, 1.5; 95% CI, 1.3-1.7; $P=.0001$) were associated with mortality.

VALIDATION COHORT

In the validation cohort, 51 patients (8%) died and 72 (11%) died or experienced myocardial infarction. Patient distribution according to the SCI showed a gradient of risk from the subgroup at low risk (3% mortality) to those at intermediate (8%) and high (20%) risk ($P=.0001$). Table 3 shows the performance of the SCI model in the derivation and validation cohorts. As expected, the model's performance in the validation cohort was less good than in the derivation cohort, according to R^2 (24.4% vs 33.0%) and scaled Brier scores (12.2% vs 23.6%). Furthermore, the C-statistic slightly decreased (from 0.848 to 0.831), indicating lower discriminative ability when this prediction model is refitted in a population different from the one in which it was developed. The calibration slope was close to 1, which precludes the need for shrinkage of the regression coefficients in the prediction model (to correct for overfitting). The Hosmer-Lemeshow test was not significant. Overall, and on the basis of these external validation parameters, the generalizability and transportability of our prediction model is credible and robust. Moreover, when the SCI model was refitted in the validation cohort, it was independently associated with mortality (per point: HR, 1.3; 95% CI, 1.1-1.6; $P=.001$) and death or myocardial infarction (per point: HR, 1.3; 95% CI, 1.1-1.5; $P=.0001$).

DISCUSSION

Our findings suggest that renal failure, dementia, and history of cardiovascular disease, such as peripheral artery disease, previous heart failure, or previous myocardial infarction, are the comorbid conditions with the greatest effect on prognosis in NSTEMI. A simple index constructed with these variables proved to be as accurate as wider previously reported comorbidity indices, such as the ChCI and the CAD-specific index,^{2,4} for patient reclassification purposes.

COMORBIDITY INDICES

The ChCI, created in 1987 and adapted to code diagnosis data in 1993, is the best-known comorbidity index^{2,3}; however, its complexity discourages its use. It includes 17 variables, each of which is scored on a range of 1 to 6 points,

and has demonstrated prognostic value in acute coronary syndromes.^{5,6} More recently, the CAD-specific index was introduced to facilitate the application of the ChCI.⁴ Based on the ChCI, the CAD-specific index reduced the number of variables to 10 and used a scoring system that ranged from 1 to 7 points. Our index represents a further simplification. The superior simplicity can be explained by the population on which each of the indices is based. The ChCI was based on a general medicine population with many comorbid conditions that are rarely observed in patients with acute coronary syndromes. In contrast, the CAD-specific index was calculated from patients with stable CAD referred for cardiac catheterization. Our index was derived from an NSTEMI population, which is very different from the populations of both ChCI and of the CAD-specific index.

COMORBIDITY VARIABLES

Comorbidity variables are not considered in any of the scores derived from clinical trials,¹⁰⁻¹² which typically have included young persons with a lower-risk profile,²² and are scantily represented in registries including nonselected patients admitted with acute coronary syndromes.¹³⁻¹⁵ In a recent study, renal failure proved to be a powerful predictor of mortality in NSTEMI.²³ Previous myocardial infarction or heart failure signals the impairment of ventricular function, whereas peripheral artery disease implies wide atherosclerotic involvement. Dementia was a strong predictor of mortality in patients hospitalized for heart failure.²⁴ The impairment of functional status, measured by urinary incontinence and assisted mobility, has also been associated with one-year mortality after acute myocardial infarction.²⁵ All of these conditions could be markers of frailty and are associated with decreased resistance and increased vulnerability to stressors.²⁶ Because the number of patients of advanced age admitted with an acute coronary syndrome is increasing, evaluation of geriatric conditions should be incorporated into the prognosis assessment.

INVASIVE MANAGEMENT

The cardiac catheterization rate was lower in patients with higher comorbidity, and this could have influenced the results. The paradox of applying maximum resources to lower-risk patients is a constant in national and international registries of NSTEMI.^{15,27,28} This attitude may be rooted in the perception that patients with comorbid conditions do not benefit from invasive management or are poor candidates for revascularization. As observed in the Figure, most events occurred early after NSTEMI in patients with comorbid conditions, suggesting that therapeutic management during hospitalization could be of key importance. Although the predictive value of comorbid conditions persisted after adjusting for cardiac catheterization use, the

poor short-term prognosis of patients stratified as high risk because of comorbid conditions leads us to speculate that an invasive approach could have potential benefit in this population.

STUDY LIMITATIONS

This study has some limitations. First, we did not collect admission systolic blood pressure and heart rate, and these indicators of hemodynamic impairment have prognostic value in NSTEMACS.¹¹ This limitation was overcome in part by adjusting the predictive models for admission heart failure and LVEF. Second, this is an observational study from 2002 to 2008, and the medical treatment at discharge does not reflect the current guidelines for NSTEMACS. This sub-optimal adherence to the guidelines has also been observed in other registries, especially in older people.¹⁴

CONCLUSION

Predictive models that include comorbidity indicators have the greatest discriminative accuracy for risk stratification after NSTEMACS. The current study shows that a simple comorbidity assessment using 5 variables improves patient risk classification. The optimal management of NSTEMACS patients with comorbid conditions warrants further investigation.

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