Clinical risk scoring beyond initial troponin values: Results from a large, prospective, unselected acute chest pain population

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BACKGROUND: Risk stratifying the diverse group of patients who present to hospital with chest discomfort remains challenging. Current clinical risk models, typically derived from selected populations, are limited by their relative complexity and the absence of a well-defined role of troponin.

OBJECTIVE: To derive a simple clinical risk score from a large, unselected population of patients with chest discomfort and to delineate the prognostic value of an initial troponin measurement.

METHODS: Prospective, consecutive data were collected from patients who presented to a tertiary care hospital. Multivariate analysis was used to identify variables predictive of the primary end point: death, nonfatal myocardial infarction or revascularization at 30 days. Integer values were assigned, generating a risk score to quantify individual patient risk.

RESULTS: Among 1054 patients, predictor variables included ST-segment deviation (strongest predictor – assigned two points), male sex, prior congestive heart failure, three or more cardiac risk factors and prior acetylsalicylic acid use (one point each). There was a progressive increase in events with increasing total score ($P < 0.0001$), with a 15-fold gradient from scores of 0 to 4 and greater. Although a negative troponin measurement was associated with fewer events for all scores, patients with higher scores remained exposed to substantial risk. A negative initial troponin measurement conferred a negative predictive value of 97.3% (95% CI 93.7% to 99.1%) among patients with a risk score of 0.

CONCLUSION: Significant 30-day events occurred in patients with elevated risk scores, despite negative initial troponin measurements, emphasizing the importance of clinical risk stratification. This simple clinical risk score, in conjunction with a single troponin I measurement, facilitates triage of patients who present to hospital with chest discomfort.

Key Words: Coronary disease; Enzymes; Patients; Prognosis; Risk factors

Patients with cardiac ischemia have heterogeneous symptoms and clinical presentations in hospital emergency departments, with a wide range of clinical outcomes. Risk stratification is of critical importance in making appropriate triage decisions and determining which patients warrant admission to hospital for hemodynamic, electrocardiographic and clinical monitoring, and which patients may safely be discharged home. It is estimated that 2% to 4% of patients with

Évaluation du risque clinique au-delà des valeurs de départ de la troponine : Résultats d'une vaste étude prospective, menée dans une population non sélectionnée de patients souffrant de douleur thoracique aiguë

CONTEXTE : La classification du risque, dans le groupe très diversifié de patients qui se présentent à l'hôpital pour des malaises à la poitrine, reste toujours difficile. Les modèles actuels de risque clinique, tirés la plupart du temps de populations sélectionnées, sont limités par leur complexité relative et l'absence d'une valeur bien établie de la troponine.

BUT : La présente étude avait pour buts de produire un score simple de risque clinique à partir d'une large population non sélectionnée de patients qui présentaient des malaises à la poitrine et de fixer une valeur pronostique à la mesure de la troponine au départ.

MÉTHODE : Il y a eu collecte prospective et consécutive de données chez des patients qui se sont présentés dans un centre hospitalier de soins tertiaires. Nous avons procédé à une analyse plurifactorielle pour repérer les variables prédictives de mort, d'infarctus du myocarde non mortel et de revascularisation au bout de 30 jours, principaux critères d'évaluation de l'étude. Des valeurs entières leur ont été attribuées, ce qui a produit un score de risque permettant de quantifier le risque individuel d'événement cardiaque.

RÉSULTATS : Chez les 1054 patients participants, les variables prédictives comprenaient le décalage du segment ST (prédicteur le plus puissant : 2 points), le sexe masculin, les antécédents d'insuffisance cardiaque congestive, la présence d'au moins trois facteurs de risque de maladie cardiaque et la prise antérieure d'acide acétylsalicylique (1 point chacun). Nous avons noté une augmentation progressive du nombre d'événements en fonction du score total ($p < 0,0001$); un gradient de facteur 15 séparait les scores de 0 à 4 et plus. Bien que la mesure négative de la troponine fût associée à un nombre réduit d'événements pour tous les scores, les patients qui obtenaient des scores élevés connaissaient malgré tout un risque important. Une mesure négative de la troponine au départ a été associée à une valeur prédictive négative de 97,3 % (intervalle de confiance à 95 % : 93,7-99,1 %) chez les patients qui avaient un score de risque de zéro.

CONCLUSION : Des événements importants ont été notés au bout de 30 jours chez des patients qui avaient enregistré des scores élevés de risque, malgré une mesure négative de la troponine au départ, d'où l'importance de la classification du risque clinique. Ce score simple de risque clinique, associé à une seule mesure de la troponine, facilite le triage des patients qui se présentent au service d'urgence pour des malaises à la poitrine.

an acute coronary syndrome are mistakenly sent home from the emergency department, and this misdiagnosis results in significantly increased morbidity and mortality (1-5). Moreover, previous research suggests that more than 50% of patients admitted with the diagnosis of an acute coronary syndrome are subsequently discharged with a diagnosis of noncardiac chest pain, which may contribute unnecessary economic strain to the health care system (5-7).

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Previous efforts toward effectively triaging patients with chest discomfort have yielded an array of predictive models that aim to identify patients at high risk for cardiac ischemia and related complications (8-13). While current risk factor models can aid in decision making regarding admission to critical care beds, they offer little explicit guidance in the selection of low-risk patients, who may be safely discharged home from the emergency department (8,11,14). In recent years, sensitive biomarkers of myocardial injury, such as serial serum troponin T and troponin I levels, have been shown to independently predict adverse outcome from cardiac events among patients with chest pain syndromes (15-19). In this manner, they have added to the armamentarium of available strategies for making triage decisions. However, despite their widespread use, the use of troponin measurements as part of a more comprehensive risk factor model is not well established for the broad spectrum of patients who present to hospitals with chest pain (1,11,14,20). Moreover, emerging data suggest that although a negative troponin measurement is associated with lower short-term risk, it does not necessarily identify a 'low-risk' patient subset (21).

Using a consecutive, unselected cohort of patients who presented to hospital with symptoms suggestive of ischemic heart disease, the primary aim of the present study was to develop a simple risk score derived from clinical characteristics to reliably predict major cardiac events (death, nonfatal myocardial infarction [MI] or revascularization) at 30 days from initial assessment. We also sought to determine the additive value of an initial troponin I measurement to such a model. Ultimately, a simple risk score may be used to stratify the broad group of patients who present to the emergency department into those who require admission to hospital, those who require further risk stratification or those who may be appropriate for early discharge.

PATIENTS AND METHODS

Patients

All patients older than 18 years of age with nontraumatic chest pain or symptoms suggestive of ischemic heart disease were identified for enrolment on presentation to the emergency department, in conjunction with the University of Alberta (Edmonton, Alberta) chest pain assessment program. These patients were identified prospectively by a single data analyst; clinical and demographic data were subsequently collected via chart review by two trained data extractors. A total of 1628 patients were enrolled. Data for the first 805 patients were collected between May 2000 and August 2000; data for the following 823 patients were collected between January 2001 and March 2001, after the introduction of a chest pain assessment program, and all consecutive patients were included, irrespective of their enrolment in this program. Assessment demonstrated no significant heterogeneity in these two patient populations, and thus, they were combined for our analysis. Patients with an admission diagnosis of acute ST-elevation MI or cardiac arrest were subsequently excluded from the analysis. Patients were also excluded if they did not consent to follow-up or if they were transferred from the emergency department to another institution. Finally, for those patients with multiple presentations during the study period, only the index assessment was included in the analysis. All patients provided informed consent for the present study, and the University of Alberta Research Ethics Committee approved the research protocol.

Outcome measures

The primary outcome evaluated in the study was a composite end point, including any of death, nonfatal MI or revascularization at

30 days from initial presentation. Secondary outcomes included the individual components of the primary end point at 30 days. Patients admitted to hospital from the emergency department and those discharged home were followed in the present study. Patients who were sent home from the emergency department had a 12-lead electrocardiogram (ECG) and serum troponin I measurement performed within five to seven days after emergency department discharge. Follow-up at 30 days (all patients) was performed by structured telephone interview, and patient-reported outcomes were corroborated through computerized records and chart review. An MI was defined as new Q waves or other diagnostic ECG changes, creatine kinase elevation with a creatine kinase (muscle-brain) fraction greater than 0.05 or troponin I elevation greater than 0.20 µg/L in the absence of an alternative diagnosis. At the five- to seven-day follow-up visit in patients discharged directly from the emergency department, the diagnosis of MI was made if there were diagnostic ECG changes and/or if a repeat troponin I elevation was greater than 0.20 µg/L. Revascularization was defined as percutaneous coronary intervention or coronary artery bypass grafting.

Statistical analysis

A range of demographic and clinical variables with potential predictive capacity were selected for study and arranged in dichotomous fashion. All comparisons between groups were performed by χ^2 analysis. Predictive variables were tested using univariate logistic regression, and those achieving a level of significance of $P < 0.20$ were selected for entry into a multivariate logistic regression model that used forward stepwise elimination. Ultimately, covariates significant at the $P < 0.05$ level were retained for the final model. A simple risk-scoring system was subsequently generated by assigning an integer value to each predictor variable based on the magnitude of the parameter estimates in the multivariate model. The total risk score was therefore derived from the arithmetic sum of the values assigned for the risk factors present in each patient. Because serum troponin I levels have been shown previously (22) to be strong, independent predictors of major cardiac events, troponin measurement variables were excluded from the final multivariate predictive model. The additive value of serum troponin I was assessed by comparing outcomes among patients with positive and negative initial troponin I values for various risk scores, and by calculating the sensitivity, specificity, and positive and negative predictive values of troponin for various risk scores. All analyses were performed using SAS software, version 8.2 (SAS Institute Inc, USA).

RESULTS

Patient characteristics

A total of 1054 patients were included in the final analysis (Figure 1). Of the 1628 patients eligible for study, 477 were excluded from analysis due to lack of consent for follow-up or transfer to another institution. Of the remaining 1151 patients, complete follow-up data were obtained for 1130 patients (98%). A further 56 patients with an admission diagnosis of acute ST-elevation MI or cardiac arrest were excluded, as were 20 patients with multiple presentations during data collection.

Complete demographic and clinical characteristics on presentation are shown in Table 1. The primary outcome (death, nonfatal MI or revascularization) occurred in 141 patients (13.4%) at 30 days. Overall, there were 41 deaths (3.9%),

Figure 1) Study cohort derived from total eligible population of unselected patients who presented to the emergency department with non-traumatic chest pain or symptoms suggestive of ischemic heart disease. STEMI ST-segment elevation myocardial infarction

63 nonfatal MIs (6.0%) and 59 patients who underwent revascularization (5.6%) at 30 days. The primary outcome at 30 days occurred in 27.1% of patients admitted to hospital, compared with 7.2% of patients discharged from the emergency department ($P<0.0001$). Among discharged patients, the five- to seven-day event rate was 4.4%.

Predictive model

Multivariate analysis demonstrated the powerful, independent predictive value of an initial troponin measurement ($P<0.0001$; OR estimated at 8.4 [95% CI 5.3 to 13.3]). Subsequent analysis, including remaining predictive variables exclusive of troponin, yielded eight significant univariate predictors ($P<0.20$) of the primary end point at 30 days, and these were subsequently entered into multivariate logistic regression analysis. Ultimately, only five variables remained independent predictors ($P<0.05$) (Table 2). The C statistic for the multivariate linear regression model was 0.74, indicating good overall predictive capacity.

The risk score was thus derived using the five independent predictor variables; ST-segment deviation on the initial ECG was the strongest predictor and was assigned a value of 2. The

TABLE 1
Baseline clinical and demographic characteristics of study patients (n=1054)

Characteristics	
Age in years, mean $\pm$ SD	61 $\pm$ 16
Age >65 (years)	485 (46.0)
Sex, n (%)	
Male	590 (56.0)
Female	464 (44.0)
Cardiac history, n (%)	
Prior myocardial infarction or angina	327 (31.0)
Prior coronary artery bypass grafting	95 (9.0)
Prior percutaneous coronary intervention	78 (7.4)
History of congestive heart failure	101 (9.6)
Cardiac risk factors, n (%)	
Diabetes mellitus	173 (16.4)
Smoking	175 (16.6)
Hyperlipidemia	172 (16.3)
Hypertension	404 (38.3)
Family history coronary artery disease	209 (19.8)
≥ 3 of above risk factors	116 (11.0)
ECG on presentation to emergency department, n (%)	
ECG normal	411 (39.0)
ST-segment deviation on initial ECG	106 (10.1)
ECG abnormal*	478 (45.4)
Troponin I measurement on presentation to emergency department, n (%)	
Troponin I measurement on presentation	765
Initial troponin I measurement >0.20 μ g/L	109/765 (14.2)
Medications given before or on presentation to emergency department, n (%)	
Acetylsalicylic acid (before presentation)	116 (11.0)
Acetylsalicylic acid (before or on presentation)	369 (35.0)
Nitroglycerin	316 (30.0)
Unfractionated heparin/LMWH	136 (12.9)
Beta-blocker	112 (10.6)
Disposition, n (%)	
Admitted	329 (31.2)
Discharged	725 (68.8)

Clinical and demographic characteristics of 1054 patients included in analysis. *An abnormal electrocardiogram (ECG) on presentation showed Q waves, nondiagnostic ST-segment changes, left bundle branch block or paced rhythm. LMWH Low-molecular-weight heparin

parameter estimates for the other variables were more homogeneous, and each was therefore assigned a value of 1. The total risk score then represents the sum of the values for a patient's corresponding risk factors (Table 3). Because of the small number of patients with a risk score of more than 4, those with scores of 4 or greater were collapsed into a single cohort. The event rates for patients with different risk scores are shown in Figure 2. There is a progressive increase in event rates with increasing risk score ($P<0.0001$ by χ^2 for trend), with an almost 15-fold increase in events in patients with a risk score of 0 to a risk score of 4 or greater.

Additive contribution of troponin

The prognostic contribution of the initial troponin measurement was assessed by comparing events between patients with

TABLE 2
Results of univariate and multivariate logistic regression analyses

Variables	Univariate logistic regression			Multiple logistic regression		
	Beta coefficient	P	Unadjusted OR (95% CI)	Beta coefficient	P	Adjusted OR (95% CI)
Age ≥65 years	0.46	0.01	1.59 (1.11–2.27)			
Male sex*	1.16	<0.0001	3.20 (2.10–4.87)	1.27	<0.0001	3.56 (2.29–5.54)
Prior myocardial infarction or angina	0.62	0.0008	1.86 (1.29–2.67)			
Prior congestive heart failure*	0.8	0.002	2.23 (1.35–3.66)	0.67	0.01	1.96 (1.15–3.35)
Prior coronary artery bypass grafting	0.46	0.10	1.59 (0.92–2.74)			
≥3 risk factors for coronary artery disease*	0.9	<0.0001	2.46 (1.55–3.91)	0.69	0.006	2.00 (1.21–3.29)
ASA taken before presentation to emergency department*	0.73	0.003	2.07 (1.28–3.34)	0.72	0.006	2.06 (1.23–3.46)
ST deviation on electrocardiogram*	1.52	<0.0001	4.59 (2.93–7.17)	1.56	<0.0001	4.74 (2.94–7.64)

*Variables that maintained significance in the multivariate model. ASA Acetylsalicylic acid

TABLE 3
Clinical risk score

Predictor variable	Risk score value
Male sex	1
Prior history of congestive heart failure	1
≥3 risk factors for coronary artery disease	1
ASA taken before presentation to emergency department	1
ST-segment deviation on electrocardiogram	2
Total risk score	x/6

Risk score predicting the combined end point of death, nonfatal MI or need for revascularization at 30 days. An individual's risk score represents the sum of the values assigned for the clinical variables listed above. ASA Acetylsalicylic acid

Figure 2) Overall 30-day event rates (death, myocardial infarction or revascularization) by risk score category

positive and negative initial troponin I values for different risk scores. The initial troponin I measurement was drawn a median of 6.0 h from symptom onset (interquartile range 3.0 h to 16.5 h); patients with a negative troponin measurement at presentation had lower 30-day event rates among all risk score cohorts (Figure 3). The progressive increase in events with increasing risk score was maintained in both troponin-negative and troponin-positive subgroups ($P < 0.0001$ by χ^2 for trend in both subgroups). At the lowest end of the risk spectrum,

Figure 3) Impact of initial troponin measurement on risk model. Event rate at 30 days (death, myocardial infarction or revascularization) for patients with a negative initial troponin I measurement compared with patients with a positive initial troponin I measurement by risk score category

patients with a risk score of 0 and a negative initial troponin measurement had a 2.7% event rate at 30 days, corresponding to a negative predictive value for troponin of 97.3% (95% CI 93.7% to 99.1%). There were five patients with a risk score of 0 and a negative initial troponin measurement in whom the composite outcome occurred, including two nonfatal MIs six days after emergency department discharge. Patients with risk scores greater than 0 had non-negligible event rates, irrespective of the initial troponin measurement. Table 4 summarizes the sensitivity, specificity, and positive and negative predictive values of the initial troponin I measurement among the different risk score cohorts.

DISCUSSION

Results from our prospective study of unselected patients who presented to hospital with chest pain suggest that a simple clinical risk score can be used to assist in risk stratification and triage. In the absence of predictive risk factors, a single negative troponin measurement on presentation may identify a very low risk subgroup of patients. However, significant 30-day events occurred in patients with elevated risk scores despite negative initial troponin measurements, which emphasizes the

TABLE 4
Performance of initial troponin I measurement as a diagnostic test

Risk score	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)*
0	50.0 (18.7–81.3)	93.7 (89.2–96.7)	29.4 (10.3–56.0)	97.3 (93.7–99.1)
1	36.4 (20.4–54.9)	91.6 (87.9–94.4)	31.6 (17.5–48.7)	93.1 (89.6–95.7)
2	33.3 (18.6–51.0)	90.5 (83.7–95.2)	52.2 (30.6–73.2)	81.4 (73.6–87.7)
3	63.2 (38.4–83.7)	81.1 (64.8–92.0)	63.2 (38.4–83.7)	81.1 (64.8–92.0)
≥4	62.5 (35.4–84.8)	80.0 (44.4–97.5)	83.3 (51.6–97.9)	57.1 (28.9–82.3)

*Sensitivity, specificity, and positive and negative predictive values of the initial troponin measurement by risk score level. *The negative predictive value diminishes in patients with progressively higher risk scores*

importance of clinical risk assessment and the inherent potential risk in these patients, irrespective of the troponin measurement. Our risk score can be easily derived at the bedside from clinical information available after initial emergency department assessment, following a similar approach to other risk stratification models, including the Thrombolysis In Myocardial Infarction (TIMI) risk score for unstable angina (23).

In our model, ST-segment deviation on the initial ECG was the strongest predictor variable in the multivariate analysis and was accordingly given greater weight than the other four clinical predictors. Therefore, patients presenting with chest pain and ST-segment deviation on ECG were considered to be part of a moderate- to high-risk subgroup, irrespective of other clinical risk factors or initial troponin measurements. This finding is consistent with results from previous studies, which have demonstrated an association between ST-segment depression and adverse prognosis in patients with acute coronary syndromes (24,25). Other independent predictors of 30-day events in our study included male sex, prior acetylsalicylic acid use, history of congestive heart failure and three or more cardiac risk factors. Clinically, these variables may reflect a greater burden of underlying disease when present in an individual patient; indeed, two of these predictor variables (prior acetylsalicylic acid use and three or more cardiac risk factors) have been shown to have prognostic importance in the TIMI risk score for patients with established unstable angina or acute coronary syndromes (23).

Patients with a risk score of 0 and a single negative troponin I measurement represented the lowest risk cohort and had a 30-day event rate of 2.7%. In this group, the early (five- to seven-day) event rate was 1.1% based on follow-up 12-lead ECG and troponin measurements mandated by the study protocol; this may approximate the rate of discharge of patients with unstable coronary syndromes from the emergency department. By comparison, the 30-day event rate was 7.2% for all patients discharged following emergency department assessment in our study, with a five- to seven-day event rate of 4.4%, which suggests the potential benefit of risk stratification in the triage of patients according to our risk factor model.

In addition to the characteristics identified in our model, patients may have other clinically important features that may impact overall prognosis. Optimal assessment of chest pain therefore requires good clinical judgement in conjunction with models such as ours when selecting patients for safe discharge. In our study protocol, for example, we identified two patients with a risk score of 0 and a negative initial troponin measurement who suffered nonfatal MIs six days following emergency department discharge. These patients may typify a small subset of individuals who would benefit from early noninvasive evaluation with exercise or pharmacological stress testing.

One approach being used with increasing frequency in the triage of chest pain is the implementation of hospital- or emergency department-based chest pain assessment units (1,6,7,11,26,27). These units usually serve to rule out acute coronary syndromes in patients at low or intermediate risk for ischemic chest pain and aim to further risk stratify with timely noninvasive evaluation. In our model, patients with risk scores of 1 and 2, and a negative initial troponin measurement could be classified as being at intermediate risk, with 30-day event rates of 6.9% and 18.6%, respectively. Our proposed risk factor model may therefore have potential use in the selection of patients for evaluation in dedicated chest pain assessment units. By extension, patients with risk scores of 3 to 6 may represent the highest risk subgroup, in which more aggressive management strategies are warranted.

Limitations

Consideration must be given to the limitations inherent in our study. A number of patients were not included in the analysis because informed consent for follow-up could not be obtained. These patients may represent a clinically important subgroup of either high- or low-risk patients, whose impact on the final predictive model remains indeterminate. The list of candidate variables chosen for analysis in the derivation of the risk score was not exhaustive and did not include other variables that have previously been shown to predict adverse cardiac events associated with acute chest pain syndromes (8,9,21,28,29). However, we sought to capture those characteristics with the greatest clinical relevance and potential predictive capacity. In addition, the variables used in the final risk factor model, as well as the troponin measurements, were analyzed in a dichotomous rather than a continuous fashion. While allowing for greater simplicity as a bedside prognostic tool, the model may have been more refined by taking into consideration the magnitude of ST-segment deviation on ECG, as well as the magnitude of the positive initial troponin measurement.

CONCLUSION

We have proposed a simple clinical risk scoring system derived from a large, prospective, unselected population that can be used to facilitate risk stratification and triage of patients with acute chest pain. Although prospective validation is required, this risk model may be used to risk-stratify a broad group of patients who present to the emergency department into those who require admission to hospital, those who require further risk stratification within dedicated chest pain assessment units and those who may be appropriate for early discharge.

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