Simple Laboratory Test-Based Risk Scores in Coronary Catheterization: Development, Validation, and Comparison to Conventional Risk Factors

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Background: We developed and validated laboratory test–based risk scores (i.e., *lab risk scores*) to reclassify mortality risk among patients undergoing their first coronary catheterization.

Methods: Patients were catheterized between 2009 and 2015 in Calgary, Alberta, Canada (n = 14 135, derivation cohort), and in Edmonton, Alberta, Canada (n = 12 143, validation cohort). Logistic regression with group LASSO (least absolute shrinkage and selection operator) penalty was used to select quintiles of the last laboratory tests (red blood cell count, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular volume, red cell distribution width, platelet count, total white blood cell count, plasma sodium, potassium, chloride, CO_2, international normalized ratio, estimated glomerular filtration rate) performed <30 days before catheterization and by age and sex that were significantly associated with death ≤60 and >60 days after catheterization. Follow-up was until 2016. Risk scores were developed from significant tests, internally validated in Calgary among bootstrap samples and externally validated in Edmonton after recalibration using coefficients developed in Calgary. Interaction tests were performed, and net reclassification improvement vs conventional demographic and clinical risk factors was determined.

Results: Lab risk scores were strongly associated with mortality (29–40× for top vs bottom quintile, *P* for trends <0.01), had good discrimination and were well calibrated in Calgary (C = 0.80–0.85, slope = 0.99–1.01) and Edmonton (C = 0.80–0.82; slope = 1.02–1.05)—similar to demographic and clinical risk factors alone. Associations were attenuated by several comorbidities; however, scores appropriately reclassified 11%–20% of deaths (both follow-up periods) and 6%–9% of survivors (>60 days) after catheterization vs demographic and clinical risk factors.

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Received June 27, 2019; accepted November 19, 2019.
DOI: 10.1093/jalm/jfaa008

Conclusions: In 2 populations of patients undergoing their first coronary catheterization, risk scores based on simple laboratory tests were as powerful as a combination of demographic and clinical risk factors in predicting mortality. Lab risk scores should be used for patients undergoing coronary catheterization.

IMPACT STATEMENT

Our study will benefit cardiologists, internists, intensive care physicians and laboratories seeking to provide more accurate, objective and convenient risk assessments of patients undergoing coronary catheterization. We used rigorous methods to show that risk scores based on common laboratory tests provide similar predictive power as a series of demographic and clinical risk factors, and incrementally improve risk assessments when used in conjunction with them. Our study also presents novel findings on the performance of these scores in a different population they were derived in, and how demographic and clinical risk factors modify their performance

INTRODUCTION

Appropriate treatment of patients with coronary artery disease requires accurate risk estimation. To simplify prognostication, algorithms have been developed to transform predictive demographic and clinical data (e.g., age, sex, electrocardiogram variables, vital signs, presence of traditional risk factors for coronary artery disease) into risk scores *(1–5)*. Simple laboratory tests such as complete blood count (CBC), electrolytes, and creatinine are also strongly predictive of cardiovascular events *(6–18)* and mortality *(19, 20)*. However, laboratory data are obtained more easily, are relatively free of error, and make up a large portion of the electronic medical record. Despite these benefits, simple laboratory data remain underutilized. It is unclear whether these data can provide prognostic information above and beyond standard risk assessments.

The objectives of this study were *(1)* to develop and internally and externally validate laboratory test–based risk scores (i.e., *lab risk scores*) for mortality in patients undergoing coronary catheterization, *(2)* to examine variations in these associations according to conventional demographic and clinical risk factors, and *(3)* to determine whether lab risk scores improve prognostication above and beyond demographic and clinical risk factors.

MATERIALS AND METHODS

Ethics Statement

This study was approved by the University of Calgary Conjoint Research Ethics Board (Ethics ID: E25065). Patient consent was obtained at catheterization.

Population

Our study included patients from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH; www.approach.org). Established in 1995, APPROACH is cardiac registry that captures detailed information on patients undergoing coronary catheterization and revascularization in Alberta, Canada. Only patients who underwent their first coronary

catheterization between November 16, 2009, and September 21, 2015, at either of the 2 catheterization sites (Calgary, n = 23 636; Edmonton, n = 28 441) were eligible for inclusion. Data from Calgary were used for model development and internal validation. Data from Edmonton were used for external validation. At the time of analysis, follow-up was available until September 6, 2016.

Outcomes

Outcomes used in this study were death occurring ≤60 or >60 days after catheterization. Patients who died on the day of catheterization were excluded. Mortality information was provided by linkage of APPROACH to Alberta Vital Statistics.

Laboratory Variables

Laboratory data were extracted along with verification date and time and healthcare number from the provincial laboratory information systems of Alberta Precision Laboratories. Laboratory tests were candidate predictors if ≥1 result was present in >80% of patients' laboratory records. These tests included CBC (red blood cell count, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular volume, red cell distribution width, hemoglobin, platelet count, and total white blood cell), plasma sodium, potassium, chloride, CO_2, creatinine and whole blood international normalized ratio (INR). Hematocrit was excluded because of its high correlation with red blood cell count ($r = 0.86$) and hemoglobin ($r = 0.96$). White blood cell count differential was not included because it was not routinely reported in Calgary. Estimated glomerular filtration rate (eGFR) was calculated from plasma creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation *(21)*, and it was assumed that all patients were white because in 2011, Alberta was 82% white *(22)*. Laboratory data were merged with APPROACH data by personal healthcare number. The last tests performed ≤30 days before the first recorded catheterization were included in this analysis.

Demographic and Clinical Risk Factors

Demographic and clinical risk factors in APPROACH were age, sex, body mass index (BMI; kg/m^2), smoking status (current, prior, never), presence of renal disease, hypertension, hyperlipidemia, type 2 diabetes, congestive heart failure, prior history of myocardial infarction (MI), family history of heart disease, ejection fraction (<20%, 20%–34%, 35%–50%, >50%, missing), diagnoses of ST-segment elevation MI (STEMI) or non-STEMI (NSTEMI), and coronary artery disease severity defined by a modified 5-unit Duke severity score based on the number of coronary vessels affected and the extent of occlusion as well as catheterization priority (emergency, urgent, planned, and unknown). All variables were assessed at the time of catheterization. Differences in demographic and clinical risk factors were assessed among patients with and without laboratory data.

Statistical Analysis

Model selection, discrimination, and calibration. Continuous variables except for age were coded into quintiles and treated as 4 dummy variables to help account for nonlinear relationships. Age and sex were included because they are used frequently to interpret laboratory data. Logistic regression was used to select variables in the Calgary data set after applying a group LASSO (least absolute shrinkage and selection operator) penalty based on a tuning parameter that penalizes the number of variables in a model *(23–25)*. All quintile dummy variables were included in the model regardless of their significance if at least 1 dummy variable was a significant predictor. The ability to discriminate between deaths and survivors was calculated as the C statistic, and

calibration metrics were slope, intercept, and associated *P* values from linear regression of the observed probability (number of deaths within deciles of predicted probability to number of patients in deciles) vs expected probability (mean predicted probability within deciles). A score with perfect discrimination and calibration would yield a C statistic of 1.0, slope of 1.0 (and $P > 0.05$ for comparison to a slope of 1.0), and intercept of 0 (and $P > 0.05$ for comparison to an intercept of 0) *(26)*. Models with the highest C statistic (best discrimination) and highest slope *P* value (no difference between predicted and observed probabilities) were selected for lab risk score development and validation.

Lab risk scores. Regression coefficients were multiplied by an integer and rounded to the nearest whole number to make them large and easy to work with. A continuous lab risk score (log odds of death) was generated for each patient after adding together products of coefficients and patient values. Separate models were then fitted with the lab risk score as the sole predictor. Discrimination and calibration metrics were contrasted with models containing demographic and clinical risk factors.

Internal validation. Bootstrapping was used to internally validate models containing continuous lab risk scores in the Calgary data set. In each iteration, a C statistic from the bootstrap sample and a C statistic from the original sample were calculated using coefficients estimated in the bootstrap sample. The mean difference of the C statistics across 100 bootstrap subsamples was then subtracted from the C statistic of the lab risk score in the original sample to obtain optimism-adjusted C statistics *(27)*. Average calibration metrics were also calculated from the bootstrap samples.

External validation and recalibration. Quintile ranges and coefficients estimated using the Calgary data set were used to create lab risk scores in the Edmonton data set. Discrimination and calibration metrics were determined and then recalculated after a global recalibration factor was applied to regression coefficients using methods described by Janssen et al. *(28)*.

Lab risk scores, patient characteristics, outcomes, and interactions. Patient characteristics were tabulated by lab risk score quintiles. An ordinal variable for lab risk score quintile was used to test for linear trends across patient characteristics using linear regression (continuous variables) and logistic regression (dichotomous variables). Logistic regression coefficients representing associations between quintiles of lab risk scores and mortality outcomes were plotted for illustrative purposes.

Discrimination and calibration of models were determined containing *(1)* only continuous lab risk scores, *(2)* demographic and clinical risk factors, and *(3)* both *(1)* and *(2)*, and model improvement attributed to using lab risk scores in addition to demographic and clinical risk factors was evaluated using log-likelihood ratio tests of nested models.

Interactions between lab risk scores and demographic and clinical risk factors were evaluated using multiplicative terms in a combined Calgary and Edmonton data set to maximize sample size. Stratified associations between lab risk scores and mortality end points were shown for significant interactions.

Net reclassification improvement. Net reclassification improvement *(29)* was calculated for deaths, survivors, and overall to evaluate the ability of lab risk scores to correctly reclassify mortality risk when added to a model containing established demographic and clinical risk factors. Patient probability estimates were stratified into categories frequently used for cardiovascular risk assignment (0% to <5%, 5% to <10%, 10% to <20%, and ≥20%) *(30)*.

Net reclassification improvement estimates were also calculated following the addition of

demographic and clinical risk factors to a model initially containing only the lab risk score.

Statistical analyses were performed using R (3.2.4; R Foundation for Statistical Computing) and SAS version 9.4 (SAS Institute). Analyses were considered statistically significant at $\alpha < 0.05$.

RESULTS

The Calgary development data set initially contained 14 135 patients (mean age, 63 years; 69% male) catheterized between November 2009 and October 2015. Patients were followed for a median of 3.5 years (51 038 person-years) from the time of catheterization until death or censoring (see online Supplemental Fig. 1). There were 1157 deaths (23 per 1000 person-years), among which 216 occurred ≤60 days after catheterization and 941 afterward. The median time from catheterization until death was 1.3 years, and the median time between laboratory testing and catheterization was 1 day. Among those with complete demographic and clinical info (n = 13 072), patients excluded because of missing laboratory data (n = 8514; 36% of original APPROACH data) were more likely to have high BMI; to be current smokers; or to have had STEMI, low ejection fraction, a high modified 5-unit Duke severity score, or an emergency catheterization but were less likely to be prior smokers or to have hypertension; hyperlipidemia; prior MI; congestive heart failure; or planned, urgent, or unknown catheterization priority (see Supplemental Table 1).

The Edmonton validation data set initially contained 12 394 patients (mean age, 62 years; 68% male) catheterized between November 2009 and November 2015. Patients were followed for a median of 3.4 years (44 127 person-years) from the time of catheterization until death or censoring (see Supplemental Fig. 1). There were 1420 deaths in total (32 per 1000 person-years), 347 occurring ≤60 days from catheterization and 1073 afterward. The median time from catheterization until death was 0.83 year, and the median time between laboratory testing and catheterization was 1 day. Among those with complete demographic and clinical info (n = 10 416), patients who were excluded because of missing laboratory data (n = 13 542; 48% of original APPROACH data) were more likely to be older and to have higher BMI, hypertension, family history of heart disease, prior MI, and planned catheterization but were less likely to be current smokers and to have renal disease, hyperlipidemia, STEMI, NSTEMI, congestive heart failure, low ejection fraction, missing ejection fraction, lower modified 5-unit Duke severity score, and urgent catheterization priority (see Supplemental Table 1).

Compared with Calgary, higher proportions of Edmonton patients were current smokers (30% vs 21%) and had renal disease (6.5% vs 3.5%), STEMI (26% vs 15%), NSTEMI (36% vs 20%), or urgent (14% vs 7%) and emergency (84% vs 56%) procedures, but a lower proportion had planned procedures (3% vs 34%) (Table 2, Supplemental Table 2).

For ≤60 days after catheterization, the final model selected (Table 1, Supplemental Fig. 2) in the Calgary data set showed that increasing age, total white blood cell count, INR, and decreasing CO_2, sodium, and eGFR were significantly associated with increased mortality risk—with evidence of nonlinear associations (Table 1). For >60 days after catheterization, the final model selected (Table 1, Supplemental Fig. 3) showed that increasing age, male sex, increasing hemoglobin, increasing red cell distribution width, increased INR, low and high CO_2, and decreasing chloride, eGFR, and red blood cell count were significantly associated with increased mortality risk—also with some showing evidence of nonlinear associations (Table 1).

Laboratory risk scores were created after multiplying regression coefficients and intercepts by 32 and rounding to the nearest whole number,

Table 1. Models selected in the Calgary (development) data set.

	Follow-up ≤60 days after catheterization				Follow-up >60 days after catheterization			
Predictor	**Stratification[a]**	**Odds ratio (95% CI)**	***P* value**	***P* for linear trend**	**Stratification**	**Odds ratio (95% CI)**	***P* value**	***P* for linear trend**
Age (per year)	Per 1 year increase	1.04 (1.02–1.05)	<0.01		Per 1 year increase	1.05 (1.04–1.05)	<0.01	
Male sex	…	…	…		vs female	1.48 (1.26–1.74)	<0.01	
CO_2 (mmol/L)	Q1 (5–22)	1.0 (reference)		<0.01	Q1 (5–22)	1.0 (reference)		0.81
	Q2 (23–24)	0.43 (0.28–0.63)	<0.01		Q2 (23–24)	0.74 (0.59–0.92)	0.01	
	Q3 (25–26)	0.34 (0.22–0.51)	<0.01		Q3 (25–26)	0.79 (0.65–0.98)	0.03	
	Q4 (27–27)	0.44 (0.26–0.72)	<0.01		Q4 (27–27)	0.63 (0.48–0.83)	<0.01	
	Q5 (28–48)	0.43 (0.27–0.66)	<0.01		Q5 (28–48)	0.98 (0.79–1.22)	0.88	
Sodium (mmol/L)	Q1 (117–136)	1.0 (reference)		<0.01	…	…	…	
	Q2 (137–138)	0.38 (0.25–0.57)	<0.01		…	…	…	
	Q3 (139–140)	0.46 (0.32–0.66)	<0.01		…	…	…	
	Q4 (141–141)	0.18 (0.08–0.36)	<0.01		…	…	…	
	Q5 (142–157)	0.41 (0.26–0.63)	<0.01		…	…	…	
Chloride (mmol/L)	…	…	…		Q1 (74–101)	1.0 (reference)		<0.01
	…	…	…		Q2 (102–103)	0.79 (0.64–0.97)	0.03	
	…	…	…		Q3 (104–105)	0.66 (0.54–0.81)	<0.01	
	…	…	…		Q4 (106–106)	0.70 (0.54–0.90)	0.01	
	…	…	…		Q5 (107–128)	0.59 (0.48–0.72)	<0.01	
eGFR (mL/min)	Q1 (2–60)	1.0 (reference)		<0.01	Q1 (2–60)	1.0 (reference)		<0.01
	Q2 (61–73)	0.42 (0.27–0.63)	<0.01		Q2 (60–73)	0.70 (0.57–0.86)	<0.01	
	Q3 (74–84)	0.46 (0.30–0.70)	<0.01		Q3 (74–84)	0.45 (0.64–0.51)	<0.01	
	Q4 (85–95)	0.33 (0.20–0.53)	<0.01		Q4 (85–95)	0.33 (0.69–0.55)	<0.01	
	Q5 (95–279)	0.32 (0.18–0.55)	<0.01		Q5 (95–279)	0.86 (0.66–1.12)	0.27	
Hb (g/L)	…	…	…		Q1 (67–128)	1.0 (reference)		<0.01
	…	…	…		Q2 (129–139)	0.85 (0.68–1.06)	0.15	
	…	…	…		Q3 (140–147)	0.74 (0.55–1.00)	0.05	
	…	…	…		Q4 (148–155)	0.92 (0.66–1.29)	0.64	
	…	…	…		Q5 (156–202)	1.28 (0.87–1.89)	0.22	

Continued

Table 1. (continued)

	Follow-up ≤60 days after catheterization				Follow-up >60 days after catheterization			
Predictor	**Stratification[a]**	**Odds ratio (95% CI)**	***P* value**	***P* for linear trend**	**Stratification**	**Odds ratio (95% CI)**	***P* value**	***P* for linear trend**
RBC (10^{12}/L)	…	…	…		Q1 (2–4.1)	1.0 (reference)		<0.01
	…	…	…		Q2 (4.2–4.4)	0.63 (0.50–0.78)	<0.01	
	…	…	…		Q3 (4.5–4.7)	0.58 (0.44–0.76)	<0.01	
	…	…	…		Q4 (4.8–5.0)	0.41 (0.29–0.57)	<0.01	
	…	…	…		Q5 (5.1–7.8)	0.29 (0.20–0.42)	<0.01	
RDW (%)	…	…	…		Q1 (10.3–12.9)	1.0 (reference)		<0.01
	…	…	…		Q2 (13.0–13.3)	1.10 (0.79–1.53)	0.58	
	…	…	…		Q3 (13.4–13.8)	1.47 (1.10–1.98)	0.01	
	…	…	…		Q4 (13.9–14.5)	2.15 (1.63–2.87)	<0.01	
	…	…	…		Q5 (14.6–34.6)	3.83 (2.93–5.06)	<0.01	
WBC (10^9/L)	Q1 (1.3–5.77)	1.0 (reference)		<0.01	…	…	…	
	Q2 (5.80–6.90)	1.24 (0.70–2.23)	0.46		…	…	…	
	Q3 (6.91–8.18)	1.28 (0.71–2.33)	0.41		…	…	…	
	Q4 (8.20–10.00)	1.43 (0.82–2.55)	0.22		…	…	…	
	Q5 (10.01–120.40)	4.73 (2.97–7.90)	<0.01		…	…	…	
INR (units)	Q1 (0.8–0.9)	1.0 (reference)		<0.01	Q1 (0.8–0.9)	1.0 (reference)		<0.01
	Q2 (1–1)	0.75 (0.48–1.20)	0.22		Q2 (1–1)	0.98 (0.79–1.23)	0.87	
	Q3 (1.1–1.1)	1.38 (0.86–2.24)	0.19		Q3 (1.1–1.1)	1.43 (1.12–1.82)	<0.01	
	Q4 (1.2–4.9)	2.36 (1.52–3.74)	<0.01		Q4 (1.2–4.9)	1.62 (1.27–2.07)	<0.01	

[a]Q, quintile/quartile with range in parenthesis; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; RBC, red blood cells; RDW, red cell distribution width; WBC, white blood cells; INR, international normalized ratio.

INR values were divided into quartiles due to sparse data. The model for ≤60 days of follow-up had a C statistic of 0.85, calibration slope of 1.00 ($P = 0.99$), and intercept of 0.00 ($P = 0.99$) using a tuning parameter value of 0.005 (see Supplemental Fig. 2). The model for >60 days of follow-up had a C statistic of 0.80, calibration slope of 0.99 ($P = 0.74$), and intercept of 0.00 ($P = 0.99$) using a tuning parameter value of 0.005 (see Supplemental Fig. 3).

Table 2. Patient characteristics by lab risk score in the Calgary (development) data set.

	Follow-up ≤60 days after catheterization					Follow-up >60 days after catheterization				
	Overall	Q1	Q3	Q5	*P* for trend	Overall	Q1	Q3	Q5	*P* for trend
Patients, n	14 135	2735	2805	2812		13 919	2729	2619	2700	
Median score (range)	−181 (−274 to −8)	−221 (−274 to −210)	−181 (−190 to −170)	−122 (−144 to −8)		−136 (−212 to −23)	−169 (−212 to −160)	−136 (−143 to −128)	−85 (−103 to −23)	
Age, year, mean (SD)	63 (12)	54 (10)	64 (11)	70 (11)	<0.01	63 (12)	53 (10)	63 (10)	73 (10)	<0.01
Men, % (n)	69 (9667)	72 (1959)	70 (1975)	66 (1868)	<0.01	69 (9525)	68 (1869)	72 (1882)	66 (1775)	<0.01
BMI, kg/m^2, mean (SD)	28.8 (7.8)	28.7 (6.4)	29.1 (9.4)	28.3 (6.7)	0.03	28.8 (7.9)	29.0 (8.2)	28.8 (6.9)	28.2 (7.9)	<0.01
Current smoker, % (n)	21 (2995)	23 (641)	22 (624)	19 (534)	<0.01	22 (2961)	25 (695)	24 (618)	15 (398)	<0.01
Prior smoker, % (n)	29 (3994)	26 (713)	30 (847)	28 (783)	0.18	29 (3955)	24 (653)	28 (739)	33 (904)	<0.01
Renal disease, % (n)	3.5 (485)	0.3 (9)	1.5 (43)	11.0 (308)	<0.01	3.2 (432)	0.3 (8)	1.2 (31)	11.2 (303)	<0.01
Hypertension, % (n)	67 (9326)	58 (1588)	67 (1889)	74 (2073)	<0.01	67 (9197)	55 (1513)	67 (1761)	77 (2086)	<0.01
Hyperlipidemia, % (n)	65 (9016)	66 (1815)	67 (1890)	58 (1628)	<0.01	65 (8925)	66 (1799)	67 (1764)	59 (1595)	<0.01
Type 2 diabetes, % (n)	24 (3367)	17 (463)	24 (681)	31 (870)	<0.01	24 (3297)	15 (401)	24 (635)	34 (906)	<0.01
Family history of heart disease, % (n)	33 (4622)	43 (1172)	33 (923)	22 (629)	<0.01	33 (4592)	43 (1180)	35 (917)	21 (558)	<0.01
Prior myocardial infarction, % (n)	5.5 (768)	4.2 (115)	5.5 (155)	6.9 (194)	<0.01	5.5 (752)	3.0 (83)	5.3 (138)	8.7 (235)	<0.01
STEMI, % (n)	15 (2132)	9 (234)	14 (395)	26 (723)	<0.01	15 (2030)	17 (451)	16 (422)	11 (309)	<0.01
NSTEMI, % (n)	20 (2849)	19 (517)	21 (584)	23 (654)	<0.01	20 (2808)	19 (517)	21 (539)	21 (571)	0.20
Congestive heart failure, % (n)	13 (1885)	5 (138)	11 (313)	28 (795)	<0.01	13 (1796)	4 (114)	9 (229)	32 (861)	<0.01
Low ejection fraction (<50%), % (n)	29 (4042)	24 (663)	29 (817)	32 (911)	<0.01	29 (3963)	28 (752)	30 (779)	30 (821)	<0.01
Ejection fraction missing, % (n)	18 (2520)	11 (312)	15 (428)	29 (803)	<0.01	18 (2440)	12 (339)	15 (402)	31 (828)	<0.01
Duke5 score, mean (SD)[a]	1.9 (1.0)	1.6 (1.1)	2.0 (1.0)	2.2 (1.0)	<0.01	1.9 (1.0)	1.6 (1.1)	1.9 (1.0)	2.1 (1.0)	<0.01
Catheterization priority										
Emergency, % (n)	7 (966)	4 (112)	6 (168)	12 (348)	<0.01	7 (893)	8 (207)	7 (181)	5 (126)	<0.01
Urgent, % (n)	56 (7837)	50 (1380)	54 (1517)	66 (1849)	<0.01	56 (7716)	52 (1414)	54 (1425)	67 (1812)	<0.01
Planned, % (n)	34 (4746)	43 (1176)	37 (1043)	20 (551)	<0.01	34 (4735)	38 (1031)	36 (933)	26 (691)	<0.01
Unknown, % (n)	2.7 (370)	2.5 (67)	2.8 (77)	2.3 (64)	0.69	2.7 (370)	2.8 (77)	3.1 (80)	2.6 (71)	0.90

[a]Duke5, modified 5-unit Duke severity score. Sample sizes are smaller than the original data sets because not all patients with laboratory data had complete demographic and clinical data. A small number of patients also died or were censored before 60 days and thus were excluded from this table.

Table 3. Internal and external validation of lab risk scores.

	Original model (Calgary)	Internal validation (Calgary)[a]	External validation (Edmonton)	
			Original	Recalibrated
≤60 days after catheterization				
C statistic	0.85	0.85 (0.01)	0.82	
Calibration slope	1.00	1.01 (0.03)	1.16	1.05
Calibration slope *P* value	0.99	0.55 (0.24)	0.01	0.18
Intercept	0.00	0.00 (0.00)	0.00	0.00
Intercept *P* value	1.00	0.75 (0.19)	0.06	0.38
>60 days after catheterization				
C statistic	0.80	0.80 (0.01)	0.80	
Calibration slope	0.99	0.99 (0.01)	1.11	1.02
Calibration slope *P* value	0.74	0.71 (0.17)	0.00	0.06
Intercept	0.00	0.00 (0.00)	0.00	0.00
Intercept *P* value	0.83	0.80 (0.12)	0.01	0.18

[a] Mean (SD) optimism-adjusted C statistics are shown for 100 bootstrap samples.

yielding mostly negative values, as higher laboratory results were generally protective. For ≤60 days after catheterization, increasing lab risk score quintile was significantly associated with greater age and modified 5-unit Duke severity score, as well as greater prevalence of renal disease, hypertension, type 2 diabetes, prior MI, STEMI or NSTEMI diagnoses, congestive heart failure, and low ejection fraction (<50%) (Table 2). It was also associated with a greater proportion of missing ejection fraction and higher emergency or urgent priority for catheterization. Conversely, increasing lab risk score quintile was associated with lower BMI and proportions of men, current smokers, hyperlipidemia, family history of heart disease, and planned catheterization. (Table 2) For >60 days after catheterization, trends were identical for increasing lab risk score except for prior smoking (increasing prevalence), STEMI (decreasing prevalence), and emergency priority for catheterization (decreasing prevalence). Trends were identical in the Edmonton data set except for BMI (no relationship at ≤60 days of follow-up), hyperlipidemia (increasing prevalence at >60 days follow-up), NSTEMI (no relationship), urgent catheterization (decreasing prevalence at <60 days follow-up), and planned catheterization (increasing prevalence at >60 days follow-up) (see Supplemental Table 2).

Lab risk scores had good discrimination and calibration (Table 3), which did not change substantially during internal validation. Although risk scores initially overestimated risk by 11%–16% in the Edmonton data set, this proportion was reduced through recalibration to 2%–5% *(28)*.

Increasing lab risk score quintile was significantly associated with increased risk of death (Fig. 1). Lab risk scores in the top quintiles were associated with 29- to 40 times greater odds of death. Adjusting for demographic and clinical risk factors weakened relationships by 60%–86%; however, associations remained significant (Fig. 1). Similar results were observed in the Edmonton data set (data not shown).

In a data set containing both Calgary and Edmonton data (adjusted for each site), lab risk scores were significantly more strongly associated

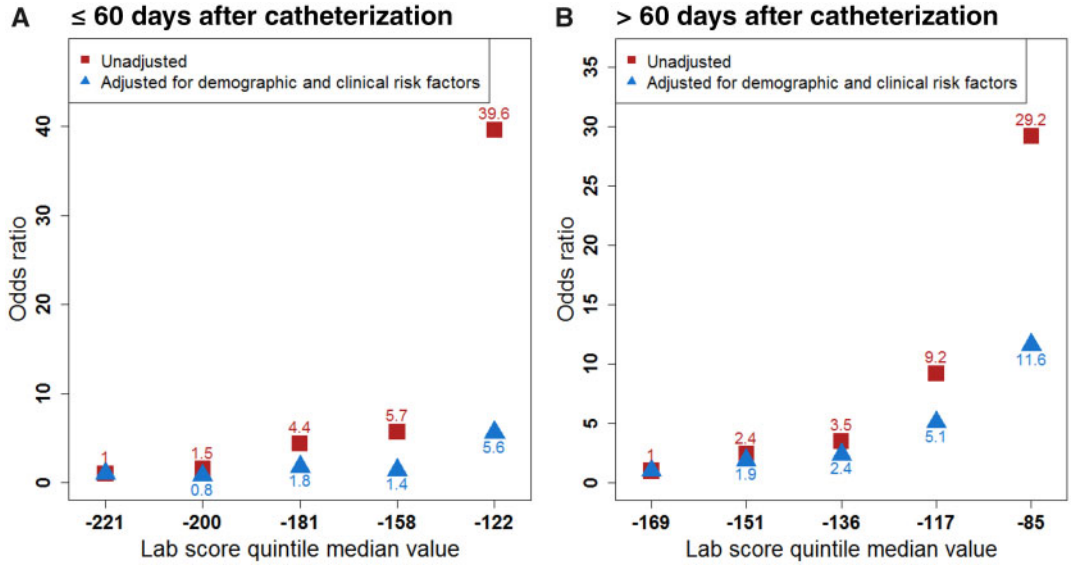

Fig. 1. Lab risk score quintiles and mortality risk in the Calgary (development) data set. Number of deaths/survivors in each quintile, ≤60 days: Q1, 4/2881; Q2, 6/2699; Q3, 18/2803; Q4, 30/2825; Q5, 158/2495; >60 days: Q1, 24/2730; Q2, 61/2803; Q3, 86/2723; Q4, 208/2517; Q5: 562/2205. Demographic and clinical risk factors: age, sex, BMI, smoking status, renal disease, hypertension, hyperlipidemia, type 2 diabetes, family history of heart disease, prior MI, congestive heart failure, whether ejection fraction was measured, ejection fraction (<20%, 20%–34%, 35%–50%, >50%), NSTEMI, STEMI, modified 5-unit Duke severity score, and catheterization priority. Each series exhibited a significant (*P* <0.01) positive linear trend between lab score quintile and log-odds of each outcome.

with mortality at ≤60 days after catheterization among patients who were free of renal disease, prior MI, or congestive heart failure (see Supplemental Table 3). Lab risk scores were more strongly associated with mortality >60 days after catheterization among patients free of type 2 diabetes or congestive heart failure or those who had NSTEMI or were above the median age (63 years) (Supplemental Table 3).

Compared with demographic and clinical risk factors, lab risk scores alone had slightly better discrimination in both follow-up periods and data sets except for ≤60 days in Calgary (Table 4). Calibration slopes for lab risk scores were within 3% of those for demographic and clinical risk factors. Models containing all predictors had the best discrimination and had calibration slopes that were almost universally the highest. (Table 4). Furthermore, addition of lab risk scores to the models significantly improved fit by the likelihood ratio test.

Compared with demographic and clinical risk factors, lab risk scores appropriately reclassified 11%–20% of deaths in Calgary and Edmonton to higher risk categories at both follow-up periods and 6%–9% of survivors to lower risk categories >60 days after catheterization (Table 5, Supplemental Tables 4–6).

DISCUSSION

In patients undergoing their first coronary catheterization in 2 large urban centers, risk scores based on simple laboratory tests, age, and sex classified patient risk nearly as well a combination of demographic and clinical risk factors but improved risk estimation when used with them. Lab risk scores

Table 4. Lab risk scores vs demographic and clinical risk factors.[a]

		Lab risk score	Demographic and clinical risk factors	Lab risk score + demographic and clinical risk factors[b]
≤60 days after catheterization				
Calgary	**C statistic (95% CI)**	0.85 (0.82–0.88)	0.89 (0.87–0.91)	0.91 (0.89–0.93)
	Calibration slope (*P* value)	1.00 (0.86)	1.00 (0.27)	1.00 (0.88)
	Calibration intercept (*P* value)	0.0 (0.99)	0.00 (0.60)	0.00 (0.95)
Edmonton (recalibrated)	**C statistic (95% CI)**	0.81 (0.78–0.83)	0.80 (0.77–0.83)	0.84 (0.81–0.86)
	Calibration slope (*P* value)	1.05 (0.78)	1.02 (0.64)	1.04 (0.38)
	Calibration intercept (*P* value)	0.00 (0.99)	0.00 (0.77)	0.00 (0.62)
>60 days after catheterization				
Calgary	**C statistic (95% CI)**	0.80 (0.78–0.81)	0.78 (0.76–0.80)	0.82 (0.81–0.84)
	Calibration slope (*P* value)	0.99 (0.79)	1.00 (0.98)	1.00 (0.92)
	Calibration intercept (*P* value)	0.00 (0.85)	0.00 (0.99)	0.00 (0.95)
Edmonton (recalibrated)	**C statistic (95% CI)**	0.79 (0.78–0.81)	0.78 (0.76–0.80)	0.82 (0.80–0.83)
	Calibration slope (*P* value)	1.02 (0.06)	1.03 (0.27)	1.00 (0.98)
	Calibration intercept (*P* value)	0.00 (0.99)	0.00 (0.43)	0.00 (0.99)

[a] Sample size and number of deaths varied across models because of missing demographic and clinical data. A calibration slope close to 1.0 and intercept close to 0 were desirable. Demographic and clinical risk factors were age, sex, BMI, smoking status, renal disease, hypertension, hyperlipidemia, type 2 diabetes, family history of heart disease, prior MI, congestive heart failure, whether ejection fraction was measured, ejection fraction (<20%, 20%–34%, 35%–50%, >50%), NSTEMI, STEMI, modified 5-unit Duke severity score, and catheterization priority. Lab risk scores calculated in the Edmonton data set were recalibrated.

[b] Models containing the lab risk score in addition to demographic and clinical risk factors fit data significantly better than demographic and clinical risk factors alone according to the likelihood ratio test.

Table 5. Net reclassification improvement (NRI) of mortality risk by lab risk scores vs demographic and clinical risk factors.[a]

	NRI for deaths, %	NRI for survivors, %	Overall NRI
≤60 days after catheterization			
Calgary	14.0	0.14	0.14
Edmonton (recalibrated)	20.3	−0.55	0.20
>60 days after catheterization			
Calgary	14.1	5.9	0.20
Edmonton (recalibrated)	11.0	9.3	0.20

[a] Demographic and clinical risk factors were age, sex, BMI, smoking status, renal disease, hypertension, hyperlipidemia, type 2 diabetes, family history of heart disease, prior MI, congestive heart failure, whether ejection fraction was measured, ejection fraction (<20%, 20%–34%, 35%–50%, >50%), NSTEMI, STEMI, modified 5-unit Duke severity score, and catheterization priority. Lab risk scores calculated in the Edmonton data set were recalibrated.

generally had stronger associations with mortality among patients with fewer comorbid conditions.

Mortality risk scores such as the Global Registry of Acute Coronary Events (GRACE) are recognized in treatment guidelines for patients presenting with acute coronary syndromes *(1–5)*. C statistics for these scores are typically >0.8 for assessing short-term (e.g., <30-day) risk but rely mostly on clinical characteristics, which can take significant time and effort to assess, and some may not be objective *(31)*. Although some scores contain limited laboratory data such as cardiac markers (e.g., troponin) *(1, 3, 4)* and markers of kidney function (creatinine), tests such as the CBC and electrolytes are not included. Simple tests such as a CBC can provide information on inflammation, infection, anemia, and hemostasis, whereas an electrolyte panel provides information on water balance, acid–base status, and renal function *(32)*. Other tests such as INR provide further information on hemostasis, and eGFR allows chronic kidney disease to be staged. As such, risk scores based on simple laboratory data can stratify patient mortality risk equally well (C = 0.8–0.9) *(19, 20, 33)* but are more conveniently calculated in laboratory information systems and are based on objective and precise assessments.

Some of the most well-known laboratory data–based risk scores have been developed by Intermountain Healthcare and have C statistics of 0.8–0.9 for predicting short- and long-term mortality in a variety of patients *(19, 20)*. These scores contain components of the CBC and complete metabolic panel (sodium, potassium, bicarbonate, calcium, glucose, and creatinine) as well as age and sex. Although C statistics are similar in different populations, calibration has not been reported. Calibration is particularly important because risk scores may correctly rank patient risk but incorrectly estimate actual risk. Similarly, risk reclassification, which measures prognostic ability above and beyond conventional risk factors, has not been reported. All metrics are needed to define practical utility *(34)*.

In our study, lab risk scores measured before catheterization were significantly associated with mortality risk and were similar (C ± 0.03) in their ability to discriminate between deaths and survivors in both development and validation data sets. Lab risk scores were similarly calibrated to actual risk in the validation data set after a recalibration procedure reduced risk overestimation. Interestingly, individuals in the validation data set had a higher mortality rate, likely related to a higher prevalence of serious conditions (e.g., renal disease, smoking, NSTEMI and STEMI) that resulted in more urgent procedures.

Although lab risk scores were strongly associated with outcomes, associations were attenuated but remained significant after adjusting for demographic and clinical risk factors. This finding confirms that lab risk scores capture some independent information about risk. However, this may be partially due to imperfect measurement and overly simplistically representation (presence vs absence) of some clinical risk factors.

In support of these findings, lab risk scores improved risk prediction of 11%–20% of deaths in both follow-up periods when considered in addition to demographic and clinical risk factors. Risk prediction slightly improved among patients who survived; however, this was only over follow-up >60 days. Our findings indicate that lab risk scores improve risk assessment of catheterization patients and could even replace some conventional assessments. Interestingly, we found that associations were attenuated in the presence of several serious conditions, and that attenuation may reduce the predictive power of lab risk scores in part because they affect mortality risk through different pathways (e.g., increased plaque burden). Another possibility is that they drive changes in laboratory parameters within the risk scores themselves, reducing score variability and attenuating associations. The strengthening of lab risk score associations among patients with NSTEMI was unexpected but may reflect the smaller initial effect of incomplete coronary artery blockage,

leaving other important effects to be detected in tests that are part of lab risk scores.

Despite our findings, it is unclear how clinicians should respond to an elevated lab risk score other than by increasing vigilance and initiating earlier and more aggressive "usual" therapies. Conversely, patients with lower risk scores could be treated more conservatively. In a pilot implementation of the Intermountain risk score combined with data from dictated reports, heart failure patients identified as high risk were entered into a care pathway with enhanced assessment, home care, and close follow-up, which lowered 30-day mortality risk by 69% after adjusting for age and sex *(35)*. It is unclear whether a similarly effective pathway could be implemented for patients undergoing coronary catheterization.

Our study has some strengths. First, we utilized a long-running registry of all coronary catheterization patients in a large region (Alberta, Canada) to develop strongly predictive risk scores based on simple laboratory data. Second, we used the robust group LASSO selection method to identify clusters of laboratory variables while accounting for nonlinear associations. Third, we developed and validated risk scores within different geographic areas, which enhanced generalizability. Fourth, we tested for interactions of scores with conventional risk factors and quantified additional predictive power gained by using them. Fifth, we used laboratory tests from a narrow window immediately preceding first catheterization; this approach eliminates the effect of catheterization itself and reduces the impact of other therapies that could be initiated following previous catheterizations.

Our study also has some limitations. The most significant is its observational design. We could not control when and what tests were ordered for catheterization patients, which led to missing data and some bias. Patients in Calgary without complete laboratory data were more likely to undergo emergency catheterization for STEMI, whereas those in Edmonton were more likely to undergo planned (scheduled in advance) catheterization for non-MIs. Because the reason behind these practice differences is not described by our data, using multiple imputation to re-generate missing laboratory data may lead to further bias *(36)*. Therefore, we performed complete case analysis and recalibrated scores developed in Calgary for use in Edmonton. As such, prospective implementation of scores may require temporal validation and recalibration. We also could not determine whether lab risk scores were causally related to mortality risk, markers of underlying causal conditions, or reflective of medical management, which could explain U-, L-, or J-shaped associations between individual laboratory tests and mortality risk. However, because lab risk scores have been successful in improving patient outcomes, the exact causal relationships may be irrelevant. Second, we used a relatively small number of laboratory tests as candidate predictors, and this may have limited predictive power. However, considering a greater number of rarer tests would have reduced the sample size and generalizability of our study. Third, clinical variables evaluated in the models were dichotomized and could not capture the full spectrum of disease states (e.g., hypertension vs blood pressure; hyperlipidemia vs LDL [low-density lipoprotein] cholesterol). However, clinicians routinely consider comorbidities as either present or absent during clinical risk assessments. Fourth, we did not contrast lab risk scores with clinical prognostic scores such as GRACE mainly because of missing data needed to compute these scores. Finally, we could not use proportional hazards modeling because the assumption of proportional hazards was violated for several analyses.

CONCLUSIONS

In 2 populations of patients undergoing their first coronary catheterization, risk scores based on simple laboratory tests yielded predictive power similar to conventional risk factors and improved identification of high-risk patients as well as some low-risk

patients. Lab risk score associations were somewhat attenuated among patients with comorbidities. Our findings support the use of lab risk scores in patients undergoing coronary catheterization.

SUPPLEMENTAL MATERIAL

Supplemental material is available at *The Journal of Applied Laboratory Medicine* online.

Nonstandard Abbreviations: lab risk score, laboratory test-based risk score; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; BMI, body mass index; MI, myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, nonST-segment elevation myocardial infarction; CBC, complete blood count.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.*

M. Gerling, statistical analysis; Y. Dong, statistical analysis; B. Abdalla, statistical analysis, M.T. James, project design support, S.B. Wilton, project design support, C.T. Naugler, project design support, D.A. Southern, project design support, administrative support, P.D. Galbraith, administrative support, B. O'Neil, project design support, M. Knudtson, project design support, administrative support, provision of study material or patients; L. de Koning, project design, statistical analysis financial support, administrative support.

Authors' Disclosures or Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest:* **Employment or Leadership:** C. Naugler, Alberta Precision Laboratories; L. de Koning, Alberta Precision Laboratories. **Consultant or Advisory Role:** None declared. **Stock Ownership:** None declared. **Honoraria:** None declared. **Research Funding:** Grant (#871) from the MSI Foundation of Alberta (Medical Services Research Foundation of Alberta). **Expert Testimony:** None declared. **Patents:** None declared.

Role of Sponsor: The funding organization played no role in the design of study, choice of enrolled patients, review and interpretation of data, preparation of the manuscript, or final approval of the manuscript.

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