

# Exceptional Mortality Prediction by Risk Scores from Common Laboratory Tests

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## ABSTRACT

**BACKGROUND:** Some components of the complete blood count and basic metabolic profile are commonly used risk predictors. Many of their components are not commonly used, but they might contain independent risk information. This study tested the ability of a risk score combining all components to predict all-cause mortality.

**METHODS:** Patients with baseline complete blood count and basic metabolic profile measurements were randomly assigned (60%/40%) to independent training (N = 71,921) and test (N = 47,458) populations. A third population (N = 16,372) from the Third National Health and Nutrition Examination Survey and a fourth population of patients who underwent coronary angiography (N = 2558) were used as additional validation groups. Risk scores were computed in the training population for 30-day, 1-year, and 5-year mortality using age- and sex-adjusted weights from multivariable modeling of all complete blood count and basic metabolic profile components.

**RESULTS:** Area under the curve c-statistics were exceptional in the training population for death at 30 days (c = 0.90 for women, 0.87 for men), 1 year (c = 0.87, 0.83), and 5-years (c = 0.90, 0.85) and in the test population for death at 30 days (c = 0.88 for women, 0.85 for men), 1 year (c = 0.86, 0.82), and 5 years (c = 0.89, 0.83). In the test, the Third National Health and Nutrition Examination Survey, and the angiography populations, risk scores were highly associated with death ( $P < .001$ ), and thresholds of risk significantly stratified all 3 populations.

**CONCLUSION:** In large patient and general populations, risk scores combining complete blood count and basic metabolic profile components were highly predictive of death. Easily computed in a clinical laboratory at negligible incremental cost, these risk scores aggregate baseline risk information from both the popular and the underused components of ubiquitous laboratory tests.

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**KEYWORDS:** Basic metabolic profile; Complete blood count; Risk assessment

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Trial Registration: Database registry of the Intermountain Heart Collaborative Study: NCT00406185 ([ClinicalTrials.gov](http://ClinicalTrials.gov)).

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Complete blood count and basic metabolic panel are inexpensive, common laboratory tests containing clinically important health information, although only a few of their components are used routinely in clinical care. Components including glucose, creatinine, white blood cell count, platelet count, and hematocrit are commonly used in clinical care for risk management, but the complete blood count and basic metabolic profile have about a dozen other components that may contain independent risk information that is often unused because of the clinical complexity and the lack of an evidence base to guide implementation of protocols to use the data.

A risk score is a useful tool for evaluating future risk for an individual patient on the basis of outcomes from large

populations to aid in guiding further diagnostic testing and treatment. Those used today include disease severity indices,<sup>1,2</sup> clinical acuity scores,<sup>3-5</sup> and long-term outcomes scores.<sup>6</sup> Unfortunately, such risk scores often have extensive data-collection needs, require results from expensive tests, apply only to highly selected populations or end points, or are difficult to compute or apply clinically. No risk score is currently available that applies to the general medical population, does not require specialty-specific predictors, and is easily computed from inexpensive quantitative data.

We previously developed a Complete Blood Count Risk Score for stratification of higher-risk patients with coronary disease.<sup>7</sup> Combining data from both the complete blood count and basic metabolic profile should improve death prediction because they provide distinct information regarding physiologic and metabolic pathways. Such simultaneous consideration at baseline before other more expensive or invasive tests or procedures should improve clinical risk prediction.

MATERIALS AND METHODS

Study Populations and End Points

This study’s primary aim was to develop and validate risk scores for mortality that aggregate all of the independent risk information contained within the complete blood count and the basic metabolic profile into a useful and intuitive metric for clinicians.

The primary outcome of this study was incident all-cause mortality. Death outcomes were determined from Intermountain Healthcare electronic records (covering an integrated delivery system of 22 hospitals and many clinics and employed physician offices), State of Utah death certificates, and the Social Security death master file. Patients not

listed as deceased in any registry were considered to be alive. The study cohort was evaluated for all-cause mortality at 30 days, 1 year, and 5 years.

Study patients in training and test populations were aged 18 years or more and had a complete blood count and basic metabolic profile measured by an Intermountain Healthcare core laboratory between January 1999 and September 2005. This study was approved by the Intermountain Healthcare Institutional Review Board. An external validation population from the Third National Health and Nutrition Examination Survey (NHANES III) also was used to test the risk scores in an independent, geographically distinct population (details on this representative general US population have been described<sup>8</sup>). A fourth population of patients undergoing coronary angiography between October 2005 and December 2007 at Intermountain Healthcare and enrolled in the database registry of the Intermountain Heart Collaborative Study were evaluated to test the 30-day and

1-year risk scores in a higher-risk group.

CLINICAL SIGNIFICANCE

- Complete blood count and basic metabolic profile are routinely obtained blood tests, but their prognostic abilities are underused.
- A risk score based on those tests, derived locally and validated externally, was shown to be highly predictive of mortality.
- This risk score, easily computed in a clinical laboratory at negligible incremental cost, can affect risk assessment by targeting high-risk patients for intensified surveillance and intervention.

Complete Blood Count

Baseline complete blood count testing used an automated Coulter Instrument method (COULTER Gen-S Hematology Analyzer, Beckman Coulter Corp, Hialeh, Fla) with low intra- and inter-run variability. Complete blood count components included hematocrit, hemoglobin, red cell distribution width, mean corpuscular volume, red blood cell count, platelet count, mean platelet volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and total white blood cell count. Hemoglobin, red blood cell count, and mean corpuscular hemoglobin were excluded because of multicollinearity. Component categorizations used quintiles of similar sample size. Complete blood count testing in NHANES III used similar methods.<sup>8</sup>

**Table 1** Sample Sizes for the Training, Test, NHANES III, and Coronary Angiography Populations Studied in the Development and Validation of the Intermountain Risk Score  
Data Are Presented as: N (Number of Deaths)

Death	Training Population	Test Population	NHANES III	Coronary Angiography
30-d	71,921 (1039)	47,458 (679)	16,372 (3)	2558 (66)
1-y	63,190 (3408)	41,774 (2284)	16,372 (239)	1396 (196)
5-y	14,214 (7146) <sup>a</sup>	9421 (4837) <sup>a</sup>	16,372 (1497)	—

NHANES III = Third National Health and Nutrition Examination Survey.  
<sup>a</sup>At the time of follow-up, only those seen between January 1999 and September 2000 had 5-year follow-up available.

**Table 2** Sex-specific Values<sup>a</sup> Are Used to Calculate the Intermountain Risk Score as the Sum of an Individual's Corresponding Values from Each Component at a Given Time Point

Component	Female			Male		
	30-d	1-y	5-y	30-d	1-y	5-y
Hematocrit ≤ 34.6	1	1	2	2	3	3
34.7-38.2	0	0	1	2	2	3
38.3-41.0	0	0	0	1	1	2
41.1-44.1	0	0	0	0	1	1
≥44.2	0	0	1	0	0	0
White blood cell count						
≤5.9	0	0	0	0	1	0
6.0-7.3	0	0	0	0	0	0
7.4-8.9	1	0	0	0	1	1
9.0-11.2	2	1	1	2	2	1
≥11.3	4	3	2	4	3	2
Platelet count ≤ 183	2	1	2	2	1	1
184-220	1	0	0	1	0	0
221-254	1	0	1	0	0	0
255-300	0	0	1	1	1	0
≥301	0	0	1	1	1	1
Mean corpuscular volume						
≤86.3	0	0	0	0	0	0
86.4-89.1	0	0	0	0	0	0
89.2-91.4	1	0	0	0	0	0
91.5-94.0	0	0	1	0	0	0
≥94.1	1	1	1	1	1	1
Mean corpuscular hemoglobin concentration						
≤33.3	1	1	0	1	1	0
33.4-33.8	0	0	0	0	1	0
33.9-34.2	1	0	0	0	0	0
34.3-34.6	0	0	0	0	0	1
≥34.7	0	0	0	0	0	1
Red cell distribution width						
≤12.5	0	0	0	0	0	0
12.6-13.0	2	1	1	1	0	0
13.1-13.5	1	1	2	1	1	2
13.6-14.3	3	2	2	2	2	3
≥14.4	4	4	5	3	3	4
Mean platelet volume						
≤7.5	1	1	1	1	1	0
7.6-8.0	1	0	1	1	0	0
8.1-8.4	1	0	0	2	0	0
8.5-9.1	0	0	0	0	0	0
≥9.2	0	0	0	1	0	0
Sodium ≤ 138	1	1	2	1	1	2
139	0	0	1	1	0	0
140-141	0	0	1	0	0	0
142	0	0	0	1	0	0
≥143	1	1	0	2	1	0
Potassium ≤ 3.7	1	1	1	2	0	0
3.8-3.9	0	0	0	1	0	0
4.0-4.1	0	0	1	1	0	0

**Table 2** Continued

Component	Female			Male		
	30-d	1-y	5-y	30-d	1-y	5-y
4.2-4.4	0	0	0	0	0	0
≥4.5	1	0	1	1	0	0
Bicarbonate ≤ 23	3	1	1	4	2	1
24-25	1	0	0	2	0	0
26	1	0	0	1	0	0
27-28	0	0	0	0	0	0
≥29	2	1	1	1	1	1
Calcium ≤ 8.5	4	3	3	1	2	2
8.6-8.9	2	2	2	0	1	2
9.0-9.2	2	1	1	0	0	1
9.3-9.5	0	0	0	0	1	0
≥9.6	1	1	0	0	0	0
Glucose ≤ 85	1	0	0	1	1	0
86-94	0	0	0	0	0	0
95-104	1	0	1	1	1	0
105-125	1	1	1	2	1	1
≥126	3	2	2	3	2	1
Creatinine ≤ 0.8	0	1	1	2	3	2
0.9	0	0	1	1	1	1
1.0	0	0	0	0	1	0
1.1-1.2	1	1	1	0	0	0
≥1.3	2	2	3	2	2	1
Age (y)						
18-29	-3	-5	-5	1	0	0
30-39	-2	-1	-1	1	-1	0
40-49	0	0	0	0	0	0
50-59	1	1	1	1	1	1
60-69	2	2	3	1	1	2
70-79	2	3	4	2	2	3
≥80	5	6	8	4	5	7
Sex						
Female	0	0	0	—	—	—
Male	—	—	—	0	0	0

<sup>a</sup>Risk models and component values are Copyright © 2006-2008, IHC Health Services, Inc (freely available for academic use).

## Basic Metabolic Profile

Basic metabolic profile testing used an automated VITROS 950 (Ortho Clinical Diagnostics, Raritan, NJ) with low intra- and inter-run variability. Basic metabolic profile components included sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, and calcium. Chloride and blood urea nitrogen were collinear with other components and excluded. Components were categorized into quintiles. Basic metabolic profiles in NHANES III used similar methods.<sup>8</sup>

## Risk Modeling

Intermountain patients seen between January 1999 and September 2005 were randomly assigned to 1 of 2 populations using an indicator variable created by a pseudo-random number generator using a long-period Mersenne Twister. The first population (training population) was used to fit the risk models and create risk scores among 60% of patients.

The risk scores were then applied to the other 40% (ie, test population), the NHANES III population, and the angiography population to independently validate the initial results by internal and external replication.

Surviving patients with less than 1 or 5 years of follow-up were excluded from 1- and 5-year end points, respectively (Table 1). Day 0 was the day of clinic visit or of hospital discharge, and 1- and 5-year end points included all those dying up to that time. Logistic regression was used to model the risk prediction equations with adjustment for age and sex. Dummy variables modeled each category, with the referent defined as the lowest risk group (except for age categories: 18-29, 30-39, 40-49 [referent], 50-59, 60-69, 70-79, and  $\geq 80$  years). A scalar score value was derived for each variable category by multiplying its  $\beta$ -coefficient by 3 and rounding to the nearest integer (referent value = zero). Each patient's risk score became the sum of the score values based on his or her individual data.

Receiver operator characteristic curves were used to determine the area under the curve c-statistic from risk score data. The c-statistic measures the ability of a predictive variable to correctly classify those with and without a study outcome (eg, cases and controls) as true positives and true negatives, and it ranges from 0.5 (no predictive ability, ie, random like a coin flip) to 1.0 (exact prediction). The accuracy of the risk score-predicted mortality was compared with the actual mortality (determined by life table methods) using Pearson's correlation coefficient. Analyses were performed in SPSS (v.15.0, SPSS Inc, Chicago, Ill) for Intermountain Healthcare patients, and analyses of NHANES III data used SUDAAN (because of limitations of SUDAAN, no c-statistic could be computed).

## Further Statistical Methods

Variables are summarized as mean  $\pm$  standard deviation for continuous variables and frequencies for discrete variables. Simple comparisons used Student *t* test or Pearson's chi-square test. Two-tailed *P* values are presented with .05 designated as nominally significant.

In clinical setting subpopulations (inpatient, outpatient, emergency), overall risk scores were simply applied to compare c-statistics. For sex-specific analyses, new risk scores were fit and c-statistics were calculated, and sensitivity, specificity, positive-predictive value, and negative predictive value calculations were used to determine risk thresholds where the sensitivity or specificity exceeded 90%. These thresholds were used to establish clinical categorizations of low risk (less than high-sensitivity threshold [referent]), moderate risk (high-sensitivity threshold or greater and less than high-specificity threshold), and high risk (high-specificity threshold or greater). Thresholds were applied to the test, NHANES III, and angiography populations where, once sex-specific categorizations were assigned, population-specific testing included all participants in a single analysis.

In addition to modeling them together, risk models were evaluated for the complete blood count alone and the basic metabolic profile alone. Comparison risk scores were devel-

oped for models entering only age and sex variables (without complete blood count or basic metabolic profile components) and models entering only the tests' components (without age or sex) to determine relative contributions to risk prediction.

In the patients who underwent angiography, logistic regression adjusted for age, sex, body mass index, blood pressure, lipid levels, smoking status, diabetes, family history of early coronary disease, renal failure, heart failure, presentation (stable chest pain, unstable chest pain, acute myocardial infarction), number of significantly diseased coronary vessels ( $\geq 70\%$  stenosis), type of treatment (medical, percutaneous coronary intervention, coronary bypass surgery), and medications prescribed at hospital discharge (statin, beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, diuretic), although c-statistics were calculated from univariate analysis.

**Table 3** Receiver Operating Characteristic Curve Results for the Intermountain Risk Score Sex-specific Models and for Overall, Overall Reduced Parameter Models, and Subgroups

Risk Model	Area Under the Curve (c-statistic)		
	30-d	1-y	5-y
Training population			
Female-specific	0.90	0.87	0.90
Male-specific	0.87	0.83	0.85
Overall	0.88	0.85	0.88
Complete Blood Count and Basic Metabolic Profile model (no age or sex)	0.87	0.81	0.83
Age and sex model	0.72	0.75	0.80
Models applied to:			
inpatients	0.83	0.81	0.86
outpatients	0.90	0.85	0.86
emergency patients	0.83	0.86	0.88
Test population			
Female-specific	0.88	0.86	0.89
Male-specific	0.85	0.82	0.83
Overall	0.87	0.84	0.87
Complete Blood Count and Basic Metabolic Profile model (no age or sex)	0.85	0.80	0.82
Age and sex model	0.72	0.75	0.78
Inpatients	0.82	0.80	0.85
Outpatients	0.85	0.84	0.85
Emergency patients	0.88	0.84	0.87
Angiography population			
Female-specific	0.86 <sup>a</sup>	0.78 <sup>a</sup>	—
Male-specific	0.87 <sup>a</sup>	0.79 <sup>a</sup>	—

Test and angiography population results are also provided (C-statistics for the NHANES III population were not available because of software limitations).

<sup>a</sup>Not including cardiac risk factors, comorbidities, or treatment variables.

RESULTS

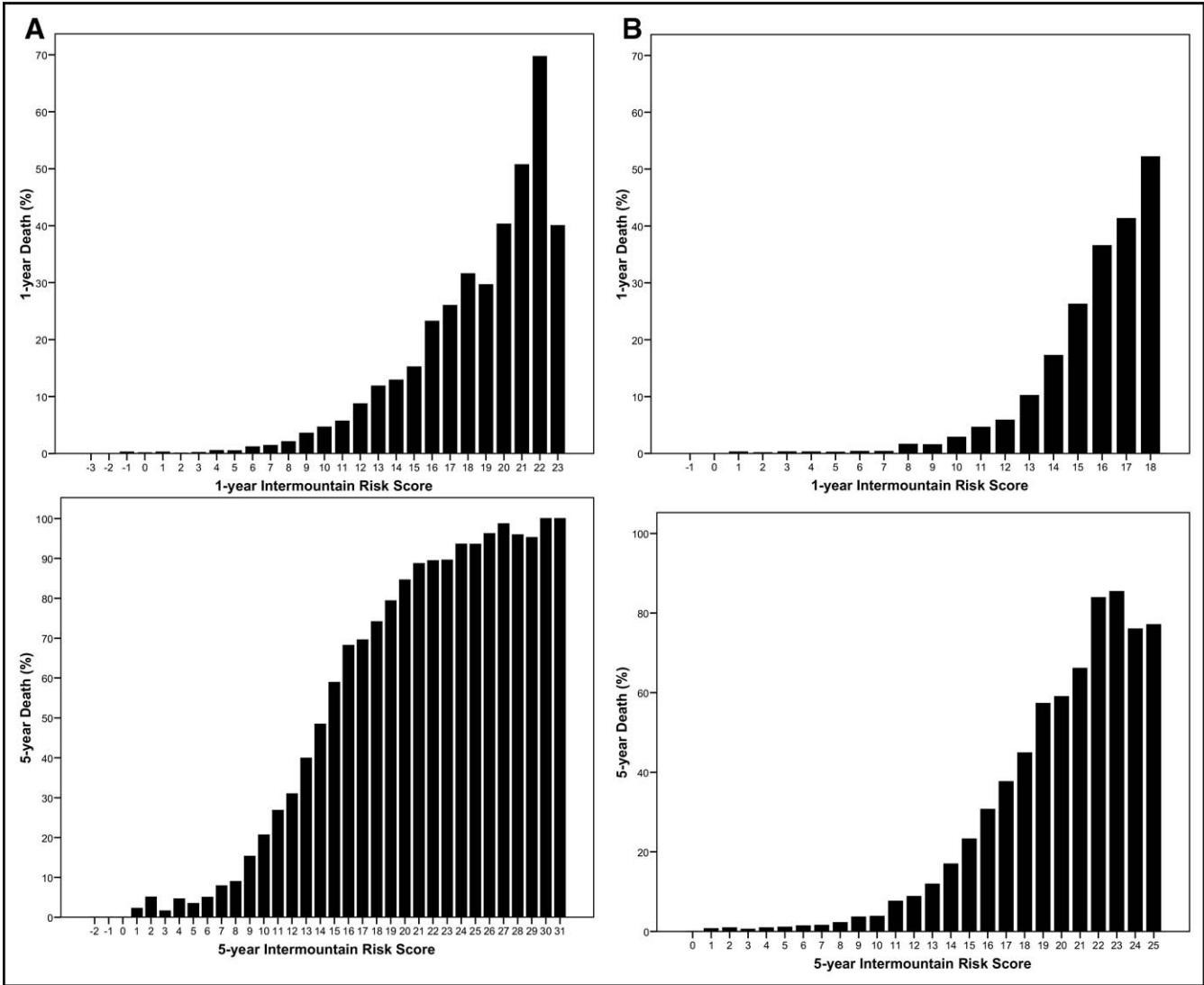
Training and Test Populations

Demographics of the training population were as follows: age,  $55.0 \pm 20.0$  years (range: 18-103 years); female, 58.4%; inpatient, 48.5%; outpatient, 40.3%; and emergency, 11.2%. Results were similar for the test population for age ( $55.2 \pm 19.9$  years), sex (58.0% were female), patient care setting, and laboratory test component values (all  $P > .12$  compared with the training population).

Sex-specific risk score values are provided in Table 2 (overall values are in Supplemental Table 1, available online from authors). C-statistics for the Intermountain (ie, complete blood count/basic metabolic profile) Risk Score in the training population were exceptional for all-cause death (Table 3). Risk scores better predicted risk among women, with the lower 95% confidence limit

of the c-statistic for women not overlapping the upper limit of the men’s c-statistic at any time point. Predicted and actual death showed excellent correlation (Supplemental Figure 1, available online from authors). Results were similar in the test population for correlations of predicted and actual survival (Supplemental Figure 2, available online from authors), predictive ability (Figure 1, Supplemental Figures 3 and 4, available online from authors), and high c-statistics (Table 3).

Predictive ability was lower for inpatients, as is expected because additional risk determinants often exist for higher disease-acuity patients. Comparison of risk scores (Table 3) with models entering age + sex only or entering only the laboratory test components suggested that the majority of the predictive ability arose from the complete blood count and basic metabolic profile, not age and sex.



**Figure 1** Risk stratification for death in the test (A) and NHANES III (B) populations by the 1- and 5-year Intermountain Risk Scores. Sample sizes across the risk scores approximated the normal distribution.



NHANES III

Average age in the non-health care NHANES III population was 47.6 years, and 53.6% were female. Analysis was impossible at 30 days (3 deaths total). Risk scores were associated with death ( $P < .001$ ) at 1 and 5 years (Figure 1, Supplemental Figure 5, available online from authors), although absolute risk was lower in this general US population.

Patients Who Underwent Angiography

The average age among patients who underwent angiography was 61.0 years, and 45.6% were female. Five-year follow-up was not available, but c-statistics were high (Table 3) and risk scores were associated with death ( $P < .001$ ) at 30 days and 1 year (Supplemental Figure 6, available online from authors). Correlation of actual to predicted death was high (Supplemental Figure 7, available online from authors).

Risk Thresholds

Sex-specific risk score thresholds from the training population (Table 4) produced similar sensitivity and specificity results in the test and angiography populations (Table 5) but appeared to be less precise for the NHANES III population. Relative risks of death for low-, moderate-, and high-risk categories are shown for the test, NHANES III, and angiography populations in Figure 2. The sample size and proportions dying in the 3 populations are provided in Supplemental Table 2 (available online from authors). For a general non-health care population such as NHANES III, the thresholds may need adjustment (Supplemental Table 3, available online from authors), although relative risks were not as high using those thresholds (Supplemental Table 4, available online from authors).

Laboratory Test-specific Models

Results for the Complete Blood Count Risk Score (modeled with age and sex, but excluding the basic metabolic profile) are found in Supplemental Tables 5 and 6 (available online from authors), and it also was highly predictive of death in NHANES III (data not shown). For the Basic Metabolic Profile Risk Score, results are shown in Supplemental Tables 7 and 8 (available online from authors), and it also significantly stratified risk of death in NHANES III (data not shown).

DISCUSSION

Optimally, a general medical risk score would be intuitive to clinicians, would apply to any patient, group, or individual, and would not complicate (by time or expense) the care-delivery process—being computed outside of the clinical setting and provided on standard clinical reports. The components of this ideal risk score would not have qualitative or subjective measures, would be simple to obtain, would use commonly obtained well-characterized tests, and would not use specialty-specific risk predictors. The ideal risk score also would be inexpensive to providers and patients, and would trigger attempts by providers to modify disease processes that, left unchecked, increase morbidity, decrease quality of life, and cause premature death.

A variety of risk scores have been proposed for the estimation of clinical acuity,<sup>3-5</sup> prediction of disease severity,<sup>1,2</sup> and prevention of disease.<sup>6</sup> Unfortunately, such risk scores often require considerable data collection, use results from expensive tests, apply to specific populations, address intermediate outcomes or short-term end points, or introduce too many calculation difficulties for application to the clinical care process. Difficulties that arise with such risk scores also include complications of missing data and prob-

Table 4 Sex-specific Intermountain Risk Score Thresholds for Use in Patient Testing and Clinical Decision Making

Population	Death End Point	Risk Score Threshold	Predicted Death	Sensitivity/Specificity	PPV/NPV	Proportion of Population with Risk Score above the Threshold
High Sensitivity						
Females	30-d	≥15	≥1%	93%/69%	3%/99.9%	0.31
	1-y	≥9	≥3%	93%/59%	10%/99.5%	0.44
	5-y	≥11	≥31%	90%/74%	73%/89%	0.59
Male	30-d	≥15	≥2%	90%/69%	5%/99.7%	0.33
	1-y	≥11	≥4%	91%/55%	13%/99%	0.48
	5-y	≥9	≥36%	93%/52%	73%/83%	0.74
High Specificity						
Female	30-d	≥20	≥4%	63%/92%	8%/99.6%	0.09
	1-y	≥15	≥14%	57%/91%	22%/98%	0.12
	5-y	≥16	≥67%	69%/90%	85%/78%	0.36
Male	30-d	≥19	≥6%	57%/90%	10%/99%	0.11
	1-y	≥17	≥22%	41%/93%	28%/96%	0.10
	5-y	≥15	≥84%	55%/92%	90%/59%	0.35

PPV = positive predictive value; NPV = negative predictive value.

**Table 5** Sensitivity and Specificity Results for the Test, NHANES III, and Angiography Populations Based on the Thresholds in Table 4

				Proportion of Population with Risk Score above the Threshold	
Population	Death End Point	Risk Score Threshold	Sensitivity/ Specificity		
Test Population					
Female	30-d	≥15	89%/69%	0.31	
		≥20	57%/92%	0.08	
	1-y	≥9	93%/58%	0.44	
		≥15	51%/91%	0.11	
	5-y	≥11	91%/66%	0.60	
		≥16	36%/97%	0.18	
	Male	30-d	≥15	87%/68%	0.33
			≥19	54%/90%	0.11
1-y		≥11	90%/54%	0.49	
		≥17	39%/92%	0.10	
5-y		≥9	92%/50%	0.75	
		≥15	52%/89%	0.35	
NHANES III Population					
Female	1-y	≥9	87%/80%	0.21	
		≥15	47%/97%	0.03	
	5-y	≥11	84%/75%	0.29	
		≥16	53%/94%	0.10	
Male	1-y	≥11	76%/85%	0.16	
		≥17	24%/99.5%	0.01	
	5-y	≥9	79%/80%	0.27	
		≥15	31%/99%	0.05	
Angiography Population					
Female	30-d	≥15	81%/70%	0.65	
		≥20	63%/94%	0.15	
	1-y	≥9	84%/56%	0.42	
		≥15	32%/95%	0.13	
Male	30-d	≥15	89%/65%	0.49	
		≥19	61%/90%	0.08	
	1-y	≥11	84%/56%	0.38	
		≥17	32%/95%	0.13	

NHANES III = Third National Health and Nutrition Examination Survey.

lems of accurate data quantification or interpretation. Most risk scores also do not apply specifically to the long-term prediction of death.

### Clinical and Epidemiologic Insights

The complete blood count and basic metabolic profile are commonly ordered, relatively inexpensive laboratory tests that contain potentially important health information and are readily accessible in almost all practice settings. The elements of the tests are quantitative and easily electronically encoded, have international standards for measurement, and are essentially always determined when the panels are mea-

sured; thus, the Intermountain Risk Score is an almost ideal metric for application to existing clinical laboratory processes. Further, the Intermountain Risk Score encapsulates familiar and useful clinical data with little or no additional expenditure of time or money, and because a physician or other caregiver does not have to order special tests, does not have to collect the data elements, and does not have to calculate the risk score, it might provide a natural enhancement to the clinical care process.

In the present study, the Intermountain Risk Score was predictive of death among a general patient population and the results were reproducible in 3 separate test populations (a general patient population, a representative US population sample [NHANES III], and a high-risk coronary angiography population). The predicted death outcomes closely mirrored actual results; thus, the Intermountain Risk Score should be considered for clinical application. With reimbursement increasingly tied to performance and patient outcomes ratings, better and inexpensive approaches to risk assessment are needed. This risk score may represent such a tool and deserves prospective testing for clinical use by randomized intervention trials.

### Biological Insights

Risk factors for death include age, sex, tobacco use, hyperglycemia, dyslipidemia, pulse rate, and hypertension, as well as previous cancer, myocardial infarction, peripheral vascular disease, cerebrovascular accident, chronic obstructive pulmonary disease, and coronary heart disease.<sup>9-12</sup> Although patient history is not typically available in a clinical laboratory and some laboratory tests, such as for lipid levels, are less frequently measured than the complete blood count and basic metabolic profile, the Intermountain Risk Score's excellent risk prediction ( $c \geq 0.82$ ) suggests that such other information would add little to a general risk score for death, except perhaps in high-risk populations. In this study's higher-risk angiography population, risk score associations were statistically independent of comorbidities and treatments.

Age and sex are generally available to a laboratory and are strong risk predictors. A surrogate for many underlying physiologic processes, age is the strongest contributor to the Framingham Risk Score.<sup>6</sup> Sex-specific differences are well known. In this study, however, the complete blood count and basic metabolic profile components not only added substantial information beyond age and sex, but models entering them first showed minimal additional predictive ability from age and sex (improvement of only  $c = 0.01$  at 30 days and  $c = 0.05$  at 5 years). It is unclear whether the physiologic factors that the complete blood count and basic metabolic profile measure cause aging or whether they are simply better markers of age-related changes in health. Given the roles of the blood components and metabolic processes in human health, the former appears likely—at least in part. Regardless, the predictive ability of the complete blood count's and basic metabolic profile's elements is noteworthy and clinically useful beyond age, sex, and even

other risk factors (eg, as in the patients who underwent angiography).

This study also raises basic questions regarding the underlying pathophysiology of human disease. For example, although not often used clinically, a high red cell distribution width indicated a level of risk at all 3 study time points that was similar in magnitude to that of being 80 years of age or older

and stronger than hematocrit, platelets, or white blood cell count, as we have previously shown.<sup>7</sup> The strength and consistency of the findings also suggest that some components are clinically underused, as do recent replications of our red cell distribution width finding.<sup>13,14</sup> In addition, differences in risk score results between women and men may aid in understanding sex-related differences in disease and survival (eg, calcium level contributed more to risk in women than in men, perhaps because of osteoporosis risk).

STUDY STRENGTHS AND LIMITATIONS

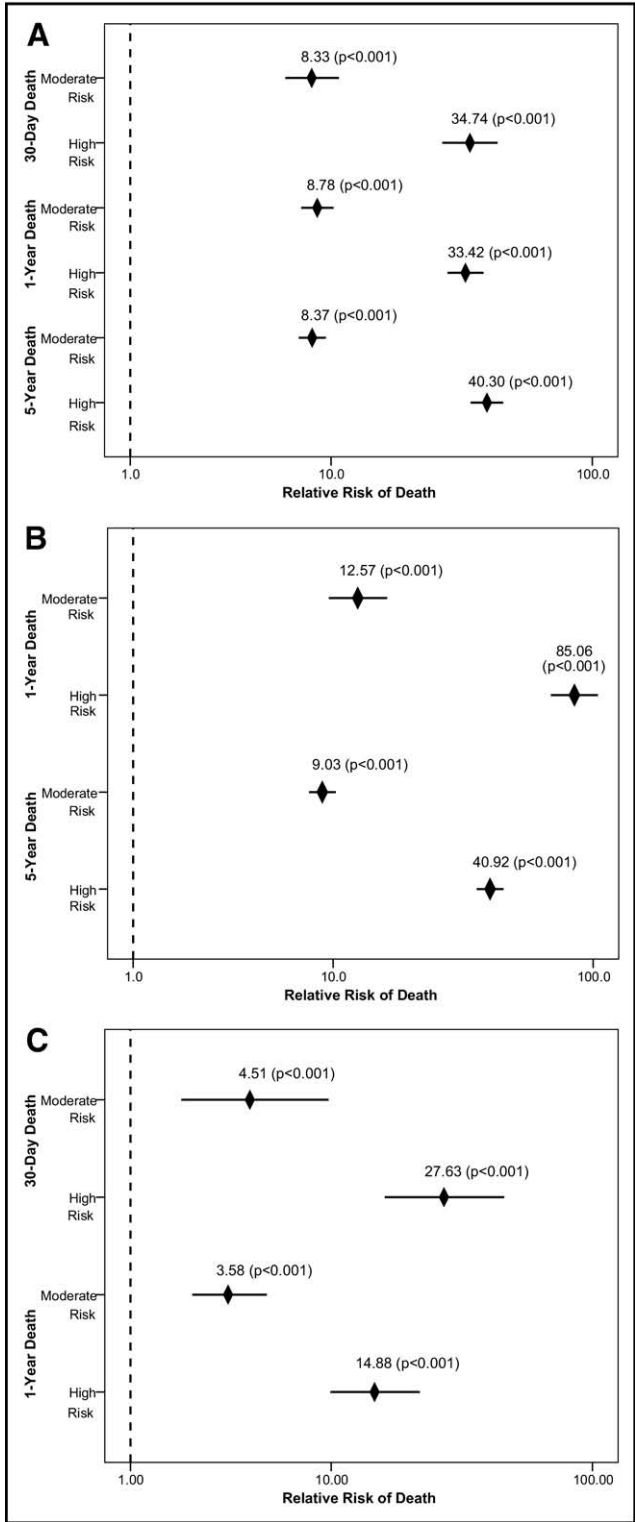
Because the study was observational, it might be limited by confounders and unmeasured variables may have influenced study findings. The study used only a baseline measurement of complete blood count and basic metabolic profile, so repeated measurement over time may provide additional research ability to stratify risk and clinical opportunities to ameliorate risk. Use of quintiles of component measures instead of other statistical methods of categorization may have made the risk scores more applicable to multiple populations, but also likely caused a loss in some information; thus, further validation of the risk scores may be useful.

The study adjusted the effect of the complete blood count and basic metabolic profile components for patient age and sex, and many other covariables were included in the modeling for patients with coronary disease. Further, the replication of results in multiple separate populations provided independent validation of risk score results with little loss of effect. Although this study was performed on large populations without regard to test indication or disease acuity or type, and findings were replicated, these risk scores remain to be applied prospectively for actual clinical use.

Finally, several time points for the training, test, and coronary angiography populations did not include the full population samples because of incomplete follow-up data for those times; thus, sample sizes in those groups were smaller and more susceptible to the effects of statistical variation. Cause of death information also was not available; thus, the 5-year death rate in the training and test populations might reflect a higher than average risk population.

CONCLUSIONS

In large, independent patient populations across a large integrated health care system and in a nationally represen-



**Figure 2** Relative risks of death based on risk categories from Table 4: low risk (less than high-sensitivity threshold), moderate risk (high-sensitivity threshold or greater and less than high-specificity threshold), and high risk (high-specificity threshold or greater). Test (A), NHANES III (B), and angiography (C) populations. When fully adjusted for risk factors, comorbidities, and treatments, angiography patient relative risks were as follows: 30 days, 3.24 ( $P = .030$ ) and 13.80 ( $P < .001$ ); 1 year, 2.02 ( $P = .017$ ) and 8.62 ( $P < .001$ ). The low-risk category is the referent, and the x-axes are on a logarithmic scale.



tative general US population, the Intermountain Risk Score provided exceptional stratification of mortality by simultaneously modeling the components of the complete blood count and basic metabolic profile together with age and sex. Although only a few of the components of these panels are routinely used clinically, each component provided meaningful contribution to risk, including less used components that had a similar or greater contribution to risk as hematocrit, glucose, and creatinine. Risk scores from such baseline laboratory tests could improve identification of at-risk individuals in both the hospital setting and the outpatient clinic. Differences between the level of risk imparted by individual complete blood count and basic metabolic profile components also might provide insight on disease pathophysiology and the opportunity for earlier and more specific diagnostic and therapeutic interventions.

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