BMJ Open

Association of the Intermountain Risk Score with major adverse health events in patients positive for COVID-19: an observational evaluation of a US cohort

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ABSTRACT

Objectives The Intermountain Risk Score (IMRS), composed using published sex-specific weightings of parameters in the complete blood count (CBC) and basic metabolic profile (BMP), is a validated predictor of mortality. We hypothesised that IMRS calculated from prepandemic CBC and BMP predicts COVID-19 outcomes and that IMRS using laboratory results tested at COVID-19 diagnosis is also predictive.

Design Prospective observational cohort study.

Setting Primary, secondary, urgent and emergent care, and drive-through testing locations across Utah and in sections of adjacent US states. Viral RNA testing for SARS-CoV-2 was conducted from 3 March to 2 November 2020.

Participants Patients aged ≥18 years were evaluated if they had CBC and BMP measured in 2019 and tested positive for COVID-19 in 2020.

Primary and secondary outcome measures The primary outcome was a composite of hospitalisation or mortality, with secondary outcomes being hospitalisation and mortality separately.

Results Among 3883 patients, 8.2% were hospitalised and 1.6% died. Subjects with low, mild, moderate and high-risk IMRS had the composite endpoint in 3.5% (52/1502), 8.6% (108/1256), 15.5% (152/979) and 28.1% (41/146) of patients, respectively. Compared with low-risk, subjects in mild-risk, moderate-risk and high-risk groups had HR=2.33 (95% CI 1.67 to 3.24), HR=4.01 (95% CI 2.93 to 5.50) and HR=8.34 (95% CI 5.54 to 12.57), respectively. Subjects aged <60 years had HR=3.06 (95% CI 2.01 to 4.65) and HR=7.38 (95% CI 3.14 to 17.34) for moderate and high risks versus low risk, respectively; those ≥60 years had HR=1.95 (95% CI 0.99 to 3.86) and HR=3.40 (95% CI 1.63 to 7.07). In multivariable analyses, IMRS was independently predictive and was shown to capture substantial risk variation of comorbidities.

Conclusions IMRS, a simple risk score using very basic laboratory results, predicted COVID-19 hospitalisation and mortality. This included important abilities to identify risk in younger adults with few diagnosed comorbidities and to predict risk prior to SARS-CoV-2 infection.

Strengths and limitations of this study

► The Intermountain Risk Score (IMRS) is computed using weighted values of each independent parameter in the complete blood count and basic metabolic profile to encapsulate prognostic risk information, including both improvements and declines in health, and is widely validated.

► A simple decision-support tool, IMRS uses standardised, quantitative, objective, clinically familiar, frequently ordered, low-cost, electronically available parameters used frequently in medical care throughout the world and can be computed automatically in the background by an electronic health record and delivered seamlessly to caregivers and patients.

► Limitations include the potential for residual or uncontrolled confounding, although risk scores like IMRS are intended to be used without systematic consideration of other variables; however, IMRS remained the dominant predictor of outcomes when controlling for comorbidities.

► The study was conducted in a population from the same geographical area in which IMRS was derived; thus, regional variation in risk and risk predictors should be considered.

► The study populations were less racially diverse than in some other geographies; thus, evaluation of the ability of IMRS to predict COVID-19-related outcomes in other populations would be informative.

INTRODUCTION

The novel coronavirus, SARS-CoV-2, was described first in Wuhan, China,[1 2] in late 2019. The ensuing global pandemic[3–8] has caused greater than 1 million deaths, from pneumonia[9] and respiratory failure often associated with multiorgan failure.[9–12] The multiorgan involvement of the SARS-CoV-2 virus in the clinical COVID-19 syndrome

includes a hyperinflammatory disorder[13] that activates macrophages[14 15] and induces cytokine release,[16 17] as in sepsis.[18 19] Because of the high mortality[20 21] and prolonged hospital stay[3 22] associated with COVID-19, great interest exists in identifying the patients who are at highest risk of mortality and hospitalisation in the setting of limited medical resources.

The predictive ability of biomarkers[23–27] and clinical characteristics[28] for severe COVID-19 are being actively sought, and mortality prediction models have been described.[24 29–31] The Intermountain Risk Score (IMRS) is a sex-specific clinical decision tool that predicts all-cause mortality using age and the complete blood count (CBC) and basic metabolic profile (BMP), which are reflexive of the function of organs and systems.[32] IMRS has exhibited good predictive validation when applied across a wide range of disease states and external patient populations.[32–45] While those studies have focused on use of IMRS for prediction of major adverse health events primarily in people with chronic diseases, IMRS also predicted mortality after emergency admission for acute trauma.[45] Because IMRS uses standardised, objective data from only two universally available and commonly collected laboratory panels, IMRS could provide an easy and generalisable strategy for prognostic stratification of patients with COVID-19.

The primary objective of this study was to evaluate the predictive ability of IMRS—calculated from preinfection laboratory values—for the composite endpoint of COVID-19 hospitalisation and mortality. This objective was chosen because hospitals and health systems often have CBC and BMP results of many people stored in their electronic health records. Secondary objectives were to assess predictive ability for other major adverse outcomes including need for mechanical ventilation, need for intensive care and thromboembolic events. We also report the performance of IMRS calculated for patients with laboratory tests performed at the time of COVID-19 diagnosis.

MATERIALS AND METHODS
Objective and study populations
The primary hypothesis of this study was that IMRS, generated based on CBC and BMP weightings published in 2009 and using laboratory results obtained in 2019, predicts hospitalisation or mortality in patients diagnosed with COVID-19 in 2020.

Subjects for this observational cohort study were drawn from the set of all individuals with COVID-19 diagnostic testing at any Intermountain Healthcare facility from 3 March 2020 to 2 November 2020 (online supplemental figure S1), among whom the vast majority of viral testing was conducted by PCR. Subjects included all adult patients aged ≥18 years who had testing in healthcare facilities or at drive-up specimen collection locations due to symptoms or exposure, or for routine testing prior to procedures or surgeries. Subjects tested for COVID-19 more than once were only included in the study at the time of their first

positive test. The primary study population included individuals who tested positive for COVID-19 in 2020 and had CBC and BMP panels obtained in 2019 (the 2019 cohort). Electronic data warehouse records were searched to identify candidates for study by matching COVID-19 testing records with laboratory results. Overall, n=3883 COVID-19-positive patients with a CBC and BMP available in 2019 were identified. For subjects with multiple relevant laboratory tests in 2019, the closest to 2020 was selected. The vast majority of CBC and BMP panels (90.1%) were tested either on the same day or within 30 days of each other (82.6% were same day, an additional 7.5% were up to 30 days apart). Subjects with missing CBC or BMP were excluded.

Secondary analyses were performed in an additional sample of people positive for COVID-19. This 2020 cohort included subjects whose CBC and BMP were tested at the time of COVID-19 diagnosis, defined as the closest test to the date of COVID-19 diagnosis that was within 30 days preceding and up to 7 days after.

Patient and public involvement
Patients or the public were not involved in the design, conduct, reporting or dissemination plans of this research study.

Predictor variables
IMRS was calculated using previously published sex-specific weightings[32] for the 1-year mortality IMRS, which was previously shown to be the most predictive version of IMRS and to be superior to comorbidity scores.[33] IMRS computation used measured values of laboratory parameters from the CBC and BMP panels: hematocrit, white blood cell (WBC) count, platelet count, mean corpuscular volume, mean corpuscular haemoglobin (MCH) concentration, red cell distribution width, mean platelet volume, sodium, potassium, calcium, bicarbonate, glucose and creatinine (see http://intermountainhealthcare.org/IMRS), and the published weightings for computation of IMRS are provided in the online supplemental appendix.[32] Possible IMRS values range from −5 to 28 for women and −1 to 28 for men, and were categorised into risk groups (low/moderate/high) per the original IMRS derivation thresholds.[32] Given the large number of patients in the low-risk group, this category was split into two subgroups of roughly equal size: 'low risk' (women: IMRS ≤5, men: IMRS ≤6) and 'mild risk' (women: 6–8, men: 7–10). Components of the CBC and BMP parameters excluded from IMRS—haemoglobin, red blood cell count, MCH, chloride, blood urea nitrogen—were included in the study in analyses where components of the laboratory panels were evaluated instead of IMRS.

The age-adjusted Charlson Comorbidity Index (CCI) was also calculated,[33] with component comorbidities defined based on International Classification of Disease, 10th Revision, Clinical Modification (ICD-10-CM) diagnosis codes (or International Classification of Disease, Ninth Revision (ICD-9) codes for records available from

1999 to 30 September 2015) present at or before the time of COVID-19 diagnosis. The CCI was categorised into tertiles of similar sample size for analyses (Charlson values of 0–1, 2–3 and 4–22).

Other study variables included age, sex, race, ethnicity, body mass index (BMI), obesity (defined as BMI ≥30 kg/m²), history of coronary artery disease (CAD), history of atrial fibrillation (AF), prior coronary artery bypass graft, prior percutaneous coronary intervention, hypertension history, history of hyperlipidaemia, history of smoking and prior diagnosis of depression. Risk factors were defined based on ICD-9 and International Classification of Disease, 10th Revision, codes, and the patient's social history was also used for smoking data.

Study endpoints

The primary study outcome was a composite endpoint of COVID-19 hospitalisation and all-cause mortality. Hospitalisation was determined from healthcare use records in the Intermountain electronic data warehouse that contains the data of the 24 hospitals and 215 outpatient care centres in the health system. Mortality was determined from electronic death records available in the Intermountain electronic medical record, from Utah death certificates, and through the US Social Security Administration death master file. Follow-up was through 2 November 2020. These electronic passive surveillance methods have been found to consistently capture >90% of deaths and hospitalisations (data unpublished). COVID-19 hospitalisation and mortality were also evaluated separately as secondary endpoints. Other secondary endpoints included need for treatment in the intensive care unit for subjects who were hospitalised, need for mechanical ventilation, incident coronary heart disease (including new diagnosis of CAD, unstable angina and myocardial infarction), incident stroke, incident deep vein thrombosis (DVT), admission for AF, and admission for new diagnosis or exacerbation of heart failure. These secondary non-fatal outcomes were defined based on ICD-10-CM codes.

Statistical considerations

Analysis of covariables across IMRS categories of low, mild, moderate and high risks for covariables and IMRS components was performed using the χ^2 test or analysis of variance for discrete and continuous variables, respectively. To test the primary hypothesis, survival analyses evaluated the association of IMRS with the composite endpoint. Other analyses were of secondary interest.

Survival analyses used Kaplan-Meier methods to graphically display univariable associations of IMRS with the study composite endpoint and its hospitalisation and mortality components. The log-rank test was used to assess statistical significance of these results. Cox regression was used to analyse the univariable association of IMRS with the composite of hospitalisation or mortality and its components to calculate HRs and 95% CIs. To explore the relationship of IMRS with clinical variables,

Cox models were also constructed that entered IMRS, age decade, sex, cardiac risk factors, the time from 2019 IMRS measurement to COVID-19 testing and an indicator variable for each comorbidity included in the CCI (see table 1 for a detailed list of the a priori selected covariables). Note that age and sex are figured into IMRS but are not collinear, so adjustments for these remove their risk information from IMRS. In additional analyses, the Charlson Index replaced its component factors in Cox regression analysis. Comparisons of Cox models entering IMRS alone, other variables or both IMRS with other variables were conducted by examining the −2 log likelihood of each model. The proportional hazards criterion was checked using a time-dependent covariate in Cox regression and was satisfied in each analysis.

Substratified analyses of the association of IMRS with study endpoints were conducted in subpopulations defined by age, sex, the Charlson index tertiles, and the other comorbidities and risk factors (see table 1 for covariables). Similar Cox regression analyses were also used to evaluate associations of IMRS with the secondary study endpoints. The area under the receiver operator characteristic curve, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were also calculated. SPSS V.26.0 was used for statistical analyses and significance for the primary endpoint was defined as p≤0.05 using two-sided tests of hypothesis.

RESULTS

Among n=3883 eligible subjects in the 2019 cohort, age averaged 47.5±18.2 years, 40.0% were male, BMI averaged 31.3±8.3 kg/m², and 38.7%, 32.3%, 25.2%, and 3.8% had low, mild, moderate, and high-risk IMRS, respectively. A greater proportion of subjects identified as Hispanic/Latinx ethnicity (29.5%) or Native Hawaiian/Pacific Islander (4.1%) compared with the general Utah population (14.2% and 1.6%, respectively). Other baseline characteristics of the primary study population are shown in table 1. Baseline values of CBC and BMP components overall and across IMRS categories are shown in online supplemental table S1.

IMRS calculated using 2019 CBC and BMP panels was strongly associated with the composite endpoint of COVID-19 hospitalisation or mortality in Kaplan-Meier survival analysis (figure 1). Absolute risks of the composite outcome were 3.5%, 8.6%, 15.5% and 28.1% in low-risk, mild-risk, moderate-risk and high-risk IMRS categories, respectively (table 2). In Cox regression, IMRS in the mild-risk group had HR=2.33 (95% CI 1.67 to 3.24); the moderate-risk group had HR=4.01 (95% CI 2.93 to 5.50); and the high-risk group had HR=8.34 (95% CI 5.54 to 12.57) when compared with low-risk IMRS for the primary composite endpoint (table 3). This predictive ability was due to an ability of IMRS to stratify both the risk of hospitalisation and the risk of mortality (figure 2 and tables 2 and 3). C-statistics were calculated for each sex separately because IMRS weightings are sex-specific, with c=0.700 for

Table 1 Baseline characteristics of the primary study population, consisting of subjects who tested positive for COVID-19 in 2020 and whose IMRS was calculated from complete blood count and basic metabolic profile components that were tested in 2019, prior to COVID-19

Characteristics	Overall	Low IMRS	Mild IMRS	Moderate IMRS	High IMRS
Age (years)	47.5±18.2	35.6±13.1	49.6±15.1	59.3±16.1	73.4±13.9*
Sex (male, %)	40.00	32.20	49.90	38.70	43.8*
Race (%)†					
Native American	1.30	0.60	1.50	1.70	2.70
Asian	1.50	1.60	1.90	1.10	0.00
Black	1.80	1.50	1.70	2.60	1.40
Pacific Islander	4.10	2.80	5.20	4.50	6.20
White	84.00	87.10	81.50	82.60	81.50
Other/unavailable	4.90	4.40	5.50	5.00	6.20
Declined	2.40	2.10	2.80	2.50	2.10
Ethnicity (Hispanic, %)	29.50	30.50	31.50	26.60	21.7‡
BMI	31.3±8.3	30.0±7.3	32.3±8.8	32.3±8.9	29.5±7.6*
Obesity (BMI >30 kg/m^2) (%)	42.10	36.50	45.20	47.80	34.9‡
CCI and constituent comorbidities					
CCI	3.26±3.56	1.35±1.85	2.99±2.85	5.25±4.01	8.80±4.22*
MI history (%)	6.10	1.70	5.10	10.80	21.0*
Heart failure history (%)	10.00	2.90	6.40	19.10	39.9*
Cancer history (%)	9.50	4.70	8.80	13.80	27.3*
Metastatic cancer (%)	2.20	0.70	2.30	2.90	8.4*
Cerebrovascular dz (%)	10.60	4.10	9.80	17.20	28.0*
Chronic pulmonary dz (%)	42.10	38.60	41.90	45.60	51.7*
Diabetes without complications (%)	25.80	8.40	26.60	43.60	51.7*
Diabetes with complications (%)	10.80	1.70	8.70	21.60	35.0*
CKD history (%)	12.30	3.30	7.90	24.30	46.2*
PVD history (%)	10.20	2.50	7.80	19.20	35.0*
Mild liver dz (%)	18.90	12.80	19.50	24.60	28.0*
Moderate/severe liver dz (%)	1.30	0.30	0.50	2.80	5.6*
Dementia history (%)	3.10	0.30	1.50	6.40	17.5%*
HIV/AIDS history (%)	0.10	0.10	0.20	0.00	0.00
Paralysis history (%)	2.70	1.80	2.20	4.10	5.6*
Peptic ulcer dz (%)	7.10	5.00	6.60	8.90	17.5*
Connective tissue dz (%)	5.30	3.50	4.10	8.40	9.1*
Other comorbidities and risk factors (%)					
CAD history	14.30	3.70	13.70	26.80	45.9*
AF history	6.60	1.60	4.40	14.60	24.7*
Hypertension	41.80	18.90	46.30	64.40	86.3*
Hyperlipidaemia	36.40	18.00	40.70	53.60	72.6*
Smoking history	28.40	23.90	29.90	32.80	32.2*
Prior CABG	1.30	0.30	1.30	2.50	3.4*
Prior PCI	3.00	0.50	3.50	5.40	8.9*
Depression history	36.00	35.50	33.50	38.20	46.6‡

*P trend <0.001 across IMRS categories.
†P=0.010 among IMRS categories.
‡P trend ≤0.05 across IMRS categories (and p trend ≥0.001).
§Categories of low, mild, moderate and high risk were IMRS ≤5, 6–8, 9–14 and ≥15 for women and IMRS ≤6, 7–10, 11–16 and ≥17 for men, respectively.
AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; dz, disease; IMRS, Intermountain Risk Score; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.
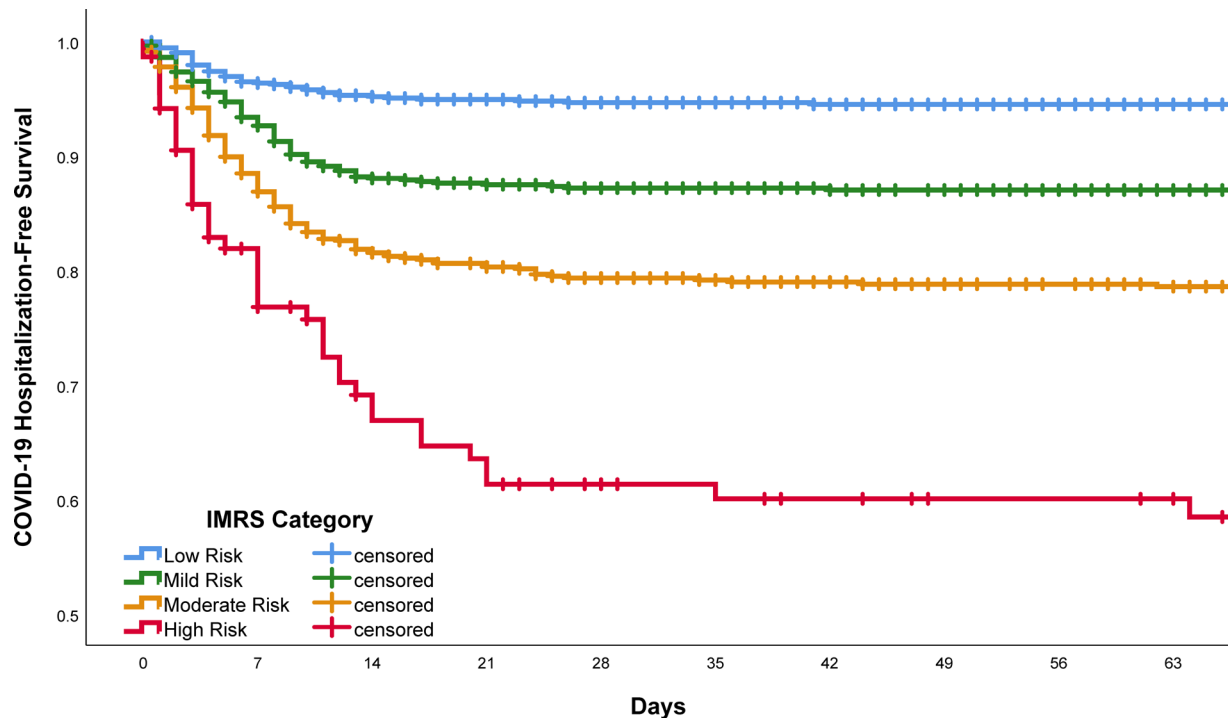
Figure 1 Kaplan-Meier survival curves stratified by IMRS with the composite endpoint of hospitalisation or mortality during the acute phase of the first 2 months after subjects tested positive for COVID-19. IMRS was calculated from complete blood count and basic metabolic profile panels tested in 2019, prior to the advent of COVID-19. Categories of low, mild, moderate and high risk correspond, respectively, to IMRS ≤5, 6–8, 9–14 and ≥15 for women, and IMRS ≤6, 7–10, 11–16 and ≥17 for men. IMRS, Intermountain Risk Score.

women and c=0.715 for men. For individual outcomes, c-statistics in women and men were, respectively, c=0.687 and c=0.692 for hospitalisation and c=0.841 and c=0.792 for mortality.

Although the magnitude of the associations decreased, IMRS remained an independent predictor of the composite endpoint in analyses adjusted for comorbidities and other potential confounders (table 3). Other variables retained as predictive in the model included the CCI (tertile 3 vs 1: HR=2.85, 95% CI 1.97 to 4.12, p<0.001; tertile 2 vs 1: HR=1.49, 95% CI 1.01 to 2.20, p=0.046), male gender (HR=1.55, 95% CI 1.25 to 1.92), obesity (HR=1.35, 95% CI 1.09 to 1.68, p=0.007), history of hypertension (HR=1.30, 95% CI 0.97 to 1.73, p=0.08) and smoking history (HR=0.74, 95% CI 0.58 to 0.93, p=0.010). Adjustment for the time from the 2019 IMRS measurement to the time of COVID-19 testing did not affect the result for IMRS (table 3). Further, in strata based on the median time from IMRS measurement to COVID-19 (10.4 months), high-risk versus low-risk IMRS was similar for those with ≤10.4 (HR=8.02, 95% CI 4.82 to 13.33) and >10.4 (HR=8.69, 95% CI 4.36 to 17.34).

Subgroup analysis revealed that IMRS predicted COVID-19 hospitalisation or mortality across groups defined by age, sex and CCI (table 3 and online supplemental tables S2,3). In older subjects (age ≥60 years, n=1087), 11.1%, 12.6%, 20.9% and 29.2% experienced the composite outcome in the low-risk, mild-risk, moderate-risk and high-risk IMRS categories, respectively

(p trend <0.001). Age-stratified associations in Cox regression are shown in table 3. Among younger subjects (<60 years of age, n=2796), the composite endpoint occurred in 3.0%, 6.9%, 9.7% and 23.1% of subjects in low-risk, mild-risk, moderate-risk and high-risk IMRS groups, respectively (see table 3). Importantly, subjects had substantially fewer comorbidities in the younger group (the Charlson index for those aged 18–49 years was 1.2±1.8, and that for 50–59 years was 3.3±2.7), in contrast to the significantly higher comorbidity burden for subjects aged ≥60 years (the Charlson index for those aged 60–69 years was 5.3±3.3 and that for ≥70 years was 8.1±3.5). Charlson Index, subpopulation and secondary analyses (eg, 2020 cohort) are provided in the online supplemental results, figure S2, and tables S4–S6.

DISCUSSION

Summary of study findings

IMRS, a laboratory-based prognostic decision tool, was highly associated with the combination endpoint of COVID-19 hospitalisation or mortality. Successful risk stratification existed using laboratory test results ascertained in the year prior to COVID-19. Secondary analyses also showed risk prediction ability at the time of COVID-19 diagnosis. IMRS had the highest predictive ability when calculated using laboratory findings from 2019, with absolute risk of COVID-19 hospitalisation or mortality of 3.5% in the low-risk category and 15.5% (HR >4.0) for

Table 2 Absolute risk across IMRS categories for the composite endpoint of hospitalisation or mortality and for other secondary study outcomes of patients testing positive for COVID-19 in 2020 who had complete blood count and basic metabolic profile laboratory panels measured in 2019 (prior to the advent of COVID-19)

Endpoint	Overall outcome	Low IMRS	Mild IMRS	Moderate IMRS	High IMRS
	Outcome stratified by IMRS risk categories*				
Primary study endpoint					
Hospitalisation or mortality	9.1% (353/3883)	3.5% (52/1502)	8.6% (108/1256)	15.5% (152/979)	28.1% (41/146)
Components of the primary endpoint (secondary outcomes)					
Hospitalisation only	8.2% (318/3883)	3.5% (52/1502)	7.9% (99/1256)	13.6% (133/979)	23.3% (34/146)
Mortality only	1.6% (62/3883)	0.1% (2/1502)	1.2% (15/1256)	3.2% (31/979)	9.6% (14/146)
Other secondary outcomes					
ICU† (hospitalised subjects)	33.3% (106/318)	17.3% (9/52)	28.3% (28/99)	41.4% (55/133)	41.2% (14/34)
Ventilation‡ (hospitalised subjects)	20.4% (65/318)	9.6% (5/52)	19.2% (19/99)	23.3% (31/133)	29.4% (10/34)
CHD§	2.2% (84/3883)	0.3% (5/1502)	1.7% (21/1256)	4.5% (44/979)	9.6% (14/146)
Stroke	0.4% (14/3883)	0.1% (2/1502)	0.2% (3/1256)	0.8% (8/979)	0.7% (1/146)
Deep vein thrombosis	0.7% (26/3883)	0.1% (1/1502)	0.5% (6/1256)	1.6% (16/979)	2.1% (3/146)
Atrial fibrillation admission	2.5% (96/3883)	0.6% (9/1502)	1.4% (18/1256)	5.5% (54/979)	10.3% (15/146)
HF¶ diagnosis or exacerbation	2.9% (112/3883)	0.4% (6/1502)	1.8% (22/1256)	6.4% (63/979)	14.4% (21/146)

All comparisons across IMRS categories in this table had p trend <0.001 except for ICU care (p trend=0.001), mechanical ventilation (p trend=0.015) and stroke (p trend=0.008).
*Categories of low, mild, moderate and high risk were IMRS ≤5, 6–8, 9–14 and ≥15 for women and IMRS ≤6, 7–10, 11–16 and ≥17 for men, respectively.
†Need for admission to the ICU among subjects who were hospitalised.
‡Mechanical ventilation among subjects who were hospitalised.
§CHD, including n=65 stable coronary artery disease, n=15 unstable angina and n=4 acute myocardial infarction.
¶HF, including new diagnoses and admissions for exacerbations of previously diagnosed HF.
CHD, coronary heart disease; HF, heart failure; ICU, intensive care unit; IMRS, Intermountain Risk Score.

the moderate-risk strata and 28.1% (HR >8.0) for the high-risk strata. IMRS predicted the composite endpoint for women and men, for younger and older individuals, and for people with both lower and higher comorbidity indices while also predicting the need for intensive care and mechanical ventilation. Further, IMRS predicted postdischarge stroke, DVT and ischaemic heart disease events.

Historical context

One of the legacies of the COVID-19 pandemic will be the collection of massive amounts of electronic data on millions of people during acute infection and long-term postinfection periods. The applicable data include patient demographics and health status, major adverse health events, preventive approaches and therapeutic options. Having mechanisms in place to collect large datasets has allowed the rapid proliferation of risk prediction tools.[24 29–31] COVID-19 risk prediction scores primarily focus on the prediction of severe health outcomes such as hospitalisation and mortality using predictors available at the time that a patient was acutely infected. While useful for clinical decision-making, such scores may have limited applicability for people not currently infected.

It is well recognised that acute infection alters various laboratory biomarkers, not the least of which is WBC count. Further, acute infection by a pathogen that is as deleterious as SARS-CoV-2 may also lead to the diagnosis of pre-existing subclinical comorbidities. People who have not been infected with SARS-CoV-2 or have not developed symptoms may not experience such biomarker changes or express symptoms of undiscovered morbidities. Only a few studies have evaluated a risk tool for use in COVID-19 risk prediction that employed a previously derived score,[46 47] and in neither of these studies were the scores based primarily on laboratory tests nor did the studies evaluate subjects based on health status prior to COVID-19 diagnosis.

IMRS is widely validated[32–45] and was previously found to be superior to comorbidity-based scores for prediction of mortality while providing additional independent and complementary risk information when comorbidities were known.[33] The results of this study support those prior findings,[33] including that IMRS adds important additional information beyond comorbidities. In these analyses of subjects with COVID-19, IMRS also captured a substantial amount (≈42%) of the comorbidities' predictive ability for hospitalisation/mortality. It is likely that IMRS captures risk information regarding undiagnosed illness in addition to those diagnoses that are known. The findings do suggest that IMRS does not capture all of the predictive ability of comorbidities; thus, if both IMRS and a comorbidity score are available, the overall

Table 3 Relative hazards (HRs, 95% CIs) for the association of the IMRS with the composite endpoint of hospitalisation or mortality (and with each endpoint separately) for patients (n=3883) who tested positive for COVID-19 in 2020 and had complete blood count and basic metabolic profile panels measured in 2019 (pre-COVID-19)

Outcome/population	Mild risk versus low risk	Moderate risk versus low risk	High risk versus low risk
Overall population			
Hospitalisation/mortality: Univariable	2.33 (1.67 to 3.24)*	4.01 (2.93 to 5.50)*	8.34 (5.54 to 12.57)*
Multivariable model 1	1.47 (1.04 to 2.08)†‡	1.87 (1.31 to 2.67)*†	3.21 (2.03 to 5.06)*†
Multivariable model 2	2.33 (1.68 to 3.25)*§	4.02 (2.94 to 5.51)*§	8.36 (5.55 to 12.59)*‡
Hospitalisation only	2.14 (1.53 to 2.99)*	3.51 (2.55 to 4.84)*	6.86 (4.45 to 10.57)*
Mortality only	8.15 (1.86 to 35.66)‡	19.65 (4.70 to 82.10)*	69.01 (15.68 to 303.74)*
Population subgroups (all subgroup analyses are for the composite hospitalisation/mortality outcome)			
Age <60 years (n=2796)	2.24 (1.51 to 3.30)*	3.06 (2.01 to 4.65)*	7.38 (3.14 to 17.34)*
Age ≥60 years (n=1087)	1.18 (0.58 to 2.40)	1.95 (0.99 to 3.86)	3.40 (1.63 to 7.07)*
Women (n=2329)	1.83 (1.17 to 2.88)‡	3.40 (2.26 to 5.10)*	6.81 (3.88 to 11.94)*
Men (n=1554)	2.70 (1.60 to 4.54)*	4.69 (2.81 to 7.83)*	10.04 (5.38 to 18.73)*
Charlson tertile 1 (n=1433)	1.92 (1.04 to 3.55)‡	2.06 (0.91 to 4.66)	25.15 (3.37 to 187.89)‡
Charlson tertile 2 (n=803)	1.43 (0.73 to 2.78)	1.90 (0.95 to 3.82)	4.05 (0.91 to 17.99)
Charlson tertile 3 (n=1143)	1.30 (0.75 to 2.26)	1.66 (0.99 to 2.79)	2.61 (1.45 to 4.68)‡

Analyses of the association of IMRS with the composite endpoint in subpopulations are also provided.
*P<0.001.
†IMRS results adjusted for age, sex, cardiac risk factors and the component comorbidities of the Charlson Comorbidity Index.
‡P≤0.05 (and p≥0.001).
§IMRS results adjusted for the number of days from the 2019 measurement of IMRS until the date of COVID-19 diagnosis.
IMRS, Intermountain Risk Score.

predictive ability is greater when combining both tools, which further replicates prior findings.[33]

IMRS provides added value beyond its predictive ability by being readily available through simple calculation and electronic delivery, by empowering precision application for health improvement. The c-statistic is traditionally used to assess risk prediction models because prediction was historically used primarily for diagnostic purposes. In the diagnostic paradigm, prediction was assessing the value of a test to identify if a patient had disease or other health endpoint that had already occurred. In the present application, though, IMRS is used for prognostic purposes, and PPV and NPV are the most relevant predictive values. This reasoning is described in more detail in previous work.[35] Notably, no prognostic risk prediction score with which we are familiar has a high or even moderate PPV when thresholds of risk are delineated at meaningful levels. Thus, a high NPV is arguably the most relevant value for choosing a score and many scores achieve NPV >90%, including IMRS and the CCI. While IMRS is not necessarily unique in its ability to achieve high NPV, due to its efficiencies, it may be superior to other scores to provide systematic risk assessment across large populations. These efficiencies include computerised computation from reliable, repeatable, widely available, objective, standardised, quantitative laboratory parameters that are ubiquitous in medical records and may be surfaced with relative ease to healthcare professionals and to patients.

Unlike clinical comorbidity-based COVID-19 scores, IMRS informs risk that is based on comorbidities that may not even yet be diagnosed, which is especially applicable in younger people. A significant limitation of a comorbidity score in a general population is that risk will be underestimated among people with undiagnosed conditions. While computerised databases of health systems capture diagnosed comorbidities for those who have been assessed medically, those with an asymptomatic undiagnosed condition cannot accurately report all pertinent risk information. Furthermore, variable adherence by patients and variable response to treatments are not represented in comorbidity scores that are especially incapable of reflecting the spectrum of improved health. In contrast, this study suggests that IMRS may capture such information. IMRS strongly stratified risk for people aged <60 years, which in part may be the consequence of undiagnosed comorbidities. This is of specific interest for identifying at-risk individuals during this COVID-19 era who may be overlooked by comorbidity scores because they have no history of disease.

This study examined all adult patients at Intermountain who were positive for COVID-19 and had CBC and BMP laboratory panel data in 2019 or at the time of COVID-19 diagnosis in 2020. It may be that large numbers of additional patients with CBC and BMP results stored electronically from 2018 or earlier could also have their risk of poor COVID-19 outcomes evaluated by IMRS, which should be investigated. Further, a modified IMRS can be
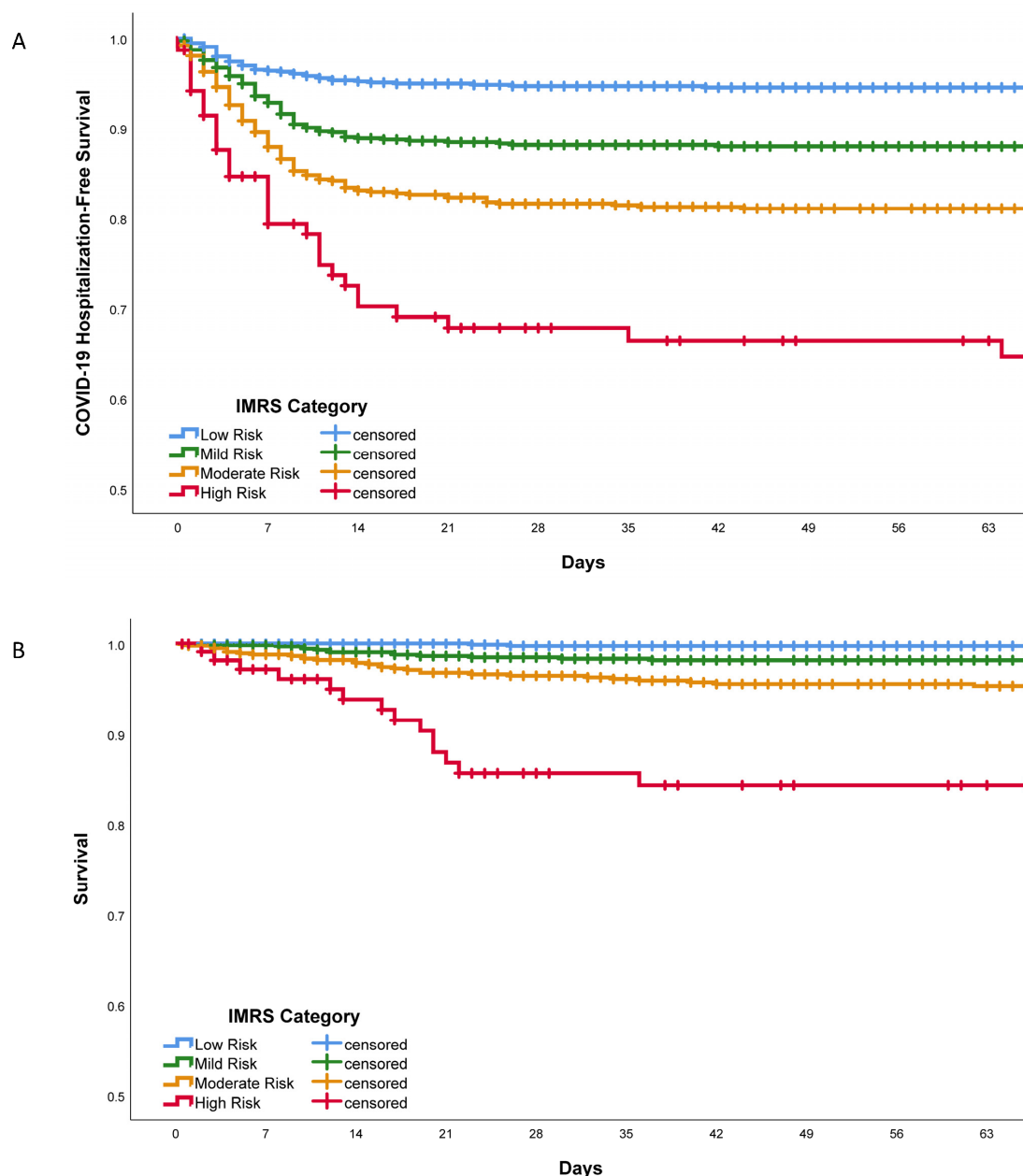
Figure 2 Kaplan-Meier survival curves showing the association of the IMRS with (A) hospitalisation and (B) mortality. IMRS was calculated from complete blood count and basic metabolic profile panels tested in 2019 prior to the advent of COVID-19. Categories of low, mild, moderate and high risk correspond, respectively, to IMRS ≤5, 6–8, 9–14 and ≥15 for women, and IMRS ≤6, 7–10, 11–16 and ≥17 for men. IMRS, Intermountain Risk Score.

calculated from just CBC parameters or just BMP components,[32] and 3.7-fold additional patients beyond those studied here have data from only one of the laboratory panels. If this data availability translates to other health systems, sufficient data to calculate IMRS and use it to risk stratify a large proportion of community-dwelling people may exist. Overall, only about 8% of COVID-19-positive adults had available laboratory data from 2019; thus, the current study may represent people who had a clinical reason for CBC and BMP testing, and these results may not generalise to the general population that is at risk of COVID-19. Further investigation of IMRS as a predictor

of COVID-19 severity and COVID-19 health outcomes should be conducted.

CONCLUSIONS

IMRS, a well-validated general health decision tool, predicted COVID-19 hospitalisation and mortality outcomes in people who tested positive for COVID-19. This finding was particularly prescient when IMRS was calculated prior to COVID-19 infection and was most profound for younger adults with few, if any, symptomatic comorbidities. One implication is that IMRS

may help to risk stratify people in the population who would especially benefit from earlier COVID-19 vaccination/booster to reduce both individual and population risk of death, morbidity and healthcare use as the manufacturing and distribution of vaccines continue now and in a postpandemic world when booster shots are anticipated to remain relevant. IMRS may also be useful for clinical decision-making to triage people who are at higher risk and for patients to self-identify their risk level (online calculator, http://intermountainhealthcare.org/IMRS) to guide personal decision-making, such as how careful they are with regard to infection-prevention measures. Further, more general messages can be derived from these data regarding (1) the meaningful differences in risk stratification ability when predictors are collected at a non-acute baseline timepoint compared with during an acute infection or other event, and (2) the superiority of objective laboratory biomarkers over comorbidities in younger people who have not yet developed symptoms of a comorbidity but for whom laboratory panels may identify risk well before an acute health event.

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