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Prospective Validation of the Emergency Heart Failure Mortality Risk Grade for Acute Heart Failure: The ACUTE Study

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Citation of this paper:
Lee, Douglas S.; Lee, Jacques S.; Schull, Michael J.; Borgundvaag, Bjug; Edmonds, Marcia L.; Ivankovic, Maria; McLeod, Shelley L.; Dreyer, Jonathan F.; Sabbah, Sam; Levy, Phillip D.; O'Neill, Tara; Chong, Alice; Stukel, Therese A.; Austin, Peter C.; and Tu, Jack V., "Prospective Validation of the Emergency Heart Failure Mortality Risk Grade for Acute Heart Failure: The ACUTE Study" (2019). *Paediatrics Publications*. 1201.
https://ir.lib.uwo.ca/paedpub/1201

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Circulation

ORIGINAL RESEARCH ARTICLE

Prospective Validation of the Emergency Heart Failure Mortality Risk Grade for Acute Heart Failure

The ACUTE Study

Editorial, see p 1157

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BACKGROUND: Improved risk stratification of acute heart failure in the emergency department may inform physicians' decisions regarding patient admission or early discharge disposition. We aimed to validate the previously-derived Emergency Heart failure Mortality Risk Grade for 7-day (EHMRG7) and 30-day (EHMRG30-ST) mortality.

METHODS: We conducted a multicenter, prospective validation study of patients with acute heart failure at 9 hospitals. We surveyed physicians for their estimates of 7-day mortality risk, obtained for each patient before knowledge of the model predictions, and compared these with EHMRG7 for discrimination and net reclassification improvement. We also prospectively examined discrimination of the EHMRG30-ST model, which incorporates all components of EHMRG7 as well as the presence of ST-depression on the 12-lead ECG.

RESULTS: We recruited 1983 patients seeking emergency department care for acute heart failure. Mortality rates at 7 days in the 5 risk groups (very low, low, intermediate, high, and very high risk) were 0%, 0%, 0.6%, 1.9%, and 3.9%, respectively. At 30 days, the corresponding mortality rates were 0%, 1.9%, 3.9%, 5.9%, and 14.3%. Compared with physician-estimated risk of 7-day mortality (PER7; c-statistic, 0.71; 95% CI, 0.64–0.78) there was improved discrimination with EHMRG7 (c-statistic, 0.81; 95% CI, 0.75–0.87; *P*=0.022 versus PER7) and with EHMRG7 combined with physicians' estimates (c-statistic, 0.82; 95% CI, 0.76–0.88; *P*=0.003 versus PER7). Model discrimination increased nonsignificantly by 0.014 (95% CI, –0.009–0.037) when physicians' estimates combined with EHMRG7 were compared with EHMRG7 alone (*P*=0.242). The c-statistic for EHMRG30-ST alone was 0.77 (95% CI, 0.73–0.81) and 30-day model discrimination increased nonsignificantly by addition of physician-estimated risk to 0.78 (95% CI, 0.73–0.82; *P*=0.187). Net reclassification improvement with EHMRG7 was 0.763 (95% CI, 0.465–1.062) when assessed continuously and 0.820 (0.560–1.080) using risk categories compared with PER7.

CONCLUSIONS: A clinical model allowing simultaneous prediction of mortality at both 7 and 30 days identified acute heart failure patients with a low risk of events. Compared with physicians' estimates, our multivariable model was better able to predict 7-day mortality and may guide clinical decisions.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02634762.

Key Words: decision making ■ emergency departments ■ heart failure ■ hospitalization ■ mortality ■ risk assessment ■ treatment outcome

Sources of Funding, see page 1155

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Clinical Perspective

What Is New?

- In this prospective, multicenter, real-world study of 1983 acute heart failure patients presenting to the emergency department, we found that the Emergency Heart failure Mortality Risk Grade (EHMRG7) stratified the risk of 7-day mortality, and was better able to predict risk than physicians' estimates.
- Seven-day mortality rates were 0%, 0%, 0.6%, 1.9%, and 3.9% in those at very low, low, intermediate, high, and very high risk.
- The EHMRG30-ST model was able to simultaneously predict 30-day risk in heart failure patients, enabling identification of a very low risk patient subgroup at both time points.

What Are the Clinical Implications?

- Paradoxically, physicians estimated that lower-risk patients would have higher mortality, and that the highest-risk group would have better survival than was observed.
- This may explain, in part, our earlier observations that reliance on clinically judged risk estimates alone may result in a potential mismatch, whereby many low-risk patients are hospitalized or, conversely, potentially unsafe discharges from the emergency department might occur.
- The EHMRG models provide physicians important prognostic information that complements clinical judgment in the decision to admit or perform early discharge of patients from the hospital or the emergency department.

Heart failure (HF) is a leading cause of hospitalization in North America, with substantial health economic impacts.[1] Patients with acute HF often present to the emergency department for care, and in some cases patients are admitted to hospital based not on symptoms but rather because of the unknown risk of clinical instability.[2] There has been a slight decline in hospitalizations for HF in recent decades; however, emergency department visits for this condition have not decreased significantly.[3–5] Up to 15% of acute HF patients who present to an emergency department in the United States are discharged home directly, but this proportion has not changed appreciably over time and varies between academic and community hospitals partly because of patient complexity.[5,6] However, in the absence of validated methods for risk stratification, some high-risk patients will be discharged home and may subsequently die despite having been considered safe to discharge.[7] Conversely, many-low risk patients are admitted to hospital, leading to inefficient use of scarce healthcare resources and exposure to adverse events related to hospitalization.[2]

Accurate prognostic information may enhance our ability to predict outcomes, thus informing disposition decisions for patients with acute HF after presentation to the emergency department.[8] Specifically, higher-risk patients would be hospitalized to facilitate more timely investigations and medical optimization, whereas lower-risk patients could be discharged earlier than routinely performed. Similar approaches to hospitalization decisions for pneumonia have resulted in increased early discharge rates and patient satisfaction, with no change in mortality.[9] However, few similar risk models have been prospectively validated in acute HF, and none have been compared with physicians' estimates of risk.

We previously derived and internally validated the Emergency Heart failure Mortality Risk Grade (EHMRG7) for prediction of 7-day risk.[10] Furthermore, we extended the model to predict 30-day mortality (EHMRG30-ST) by inclusion of one additional variable, the presence of ST-segment depression on the 12-lead ECG.[11] The primary objectives of this study were to (1) prospectively evaluate the performance of EHMRG7 in a new cohort of patients seeking care in the emergency department, and (2) compare the model with physicians' estimates of 7-day mortality risk. Our secondary objective was to examine the performance of EHMRG30-ST in the same prospective cohort. We hypothesized that the multivariable risk score would have superior predictive accuracy compared with physician-estimated risk.

METHODS

Patients

At 9 hospitals in Ontario, Canada from July 2010 to March 2015, patients presenting to the emergency department with HF were recruited (Table I in the online-only Data Supplement). We included those with acute HF diagnosed clinically as suggested by national guidelines published by the Canadian Cardiovascular Society and the Framingham criteria (90% sensitivity for acute HF). Acute HF was confirmed using (1) final primary diagnosis of ICD-10 code I50 in the discharge abstracts of the hospital or the emergency department (95% specificity for acute HF) and (2) entry into the Ontario HF Cohort, which has been validated against electronic medical records (84.8% sensitivity, 97.0% specificity). B-type natriuretic peptide was not required for diagnosis, but could be used if deemed clinically necessary. Research Ethics Board approval was obtained from all participating sites before study initiation. Participating Research Ethics Boards waived the requirement for informed consent for this study because it posed minimal risk to participants and challenges in obtaining consent from acutely ill HF patients in the emergency setting. Therefore, we were able to include all patients irrespective of language spoken and ethnicity. Those who were palliative or had do not resuscitate orders on arrival were also excluded, as they were not included in the aforementioned studies. We also excluded patients who were dialysis dependent because the pathophysiology and management of acute HF is different in these patients. The methodology of the ACUTE study (Acute Congestive Heart

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Failure Urgent Care Evaluation) and details of the physician survey have been previously published and registered (URL: www.clinicaltrials.gov. Unique identifier: NCT02634762).[12] The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, because of privacy laws.

Data Entry and Physician Survey

During the study period, the variables needed to determine the EHMRG7 risk score were entered into a computer-based calculator by a physician, nurse, or research assistant in the emergency department. Data entry and the survey were performed after the necessary laboratory tests were completed and after reassessing the patient's response to diuretic therapy, but before the physician rendered a disposition decision about admission or discharge from the emergency department (see Table 1 for list of variables). Before the EHMRG7 risk score was displayed, the physician responsible for emergency department disposition was required to estimate the probability that the patient would die within 7 days and enter their proposed management plan for the patient. They were required to enter their physician-estimated risk both as a percentage (from 0–100%) and as a category of risk: very low, low, intermediate, high, or very high risk as previously described.[12] The EHMRG7 score could not be calculated unless the physician-estimated risk survey was completed, so that their estimates could not be influenced by the results display. Information about the ACUTE study was presented at departmental meetings and in the emergency department (eg, data entry, calculation of risk score), but individual physician participation in patient recruitment was voluntary. The treating physicians were encouraged to make admission/discharge decisions as per usual, and not base any admission or treatment decisions on the EHMRG7 score. In addition to the above, we collected the unique hospital medical record number, date of visit, and sex of the patient for probabilistic linkage. All data were then securely transferred using a virtual private network connection to the ICES for storage.

Risk Prediction

The EHMRG7 risk score was determined using previously published methods, and was available to the emergency department physician.[10] We also determined the EHMRG30-ST risk probability in patients who had a 12-lead ECG performed, as previously published (see Table 1).[11] The 12-lead ECG was abstracted using a standardized data collection form as described previously.[13] The 7-day risk score was not modified in this study and the previously-published 30-day EHMRG30-ST coefficients were used, without further refitting or recalibration, to determine how the originally published models performed.[10,11] Consequently, we used previously published thresholds to divide patients into 5 risk groups, and subdivided the highest risk group into 2 highest risk deciles based on previous decile thresholds (groups 5a and 5b).

Data Sources and Linkage

Data linkage techniques have been reported elsewhere.[12] In summary, we cross-indexed the prospectively-identified patient's medical record number with the National Ambulatory Care Reporting System, which contains records of all emergency department visits in the Province of Ontario, to determine their unique encoded health card number. We subsequently linked each patient with the Registered Persons Database to determine mortality and the Canadian Institute for Health Information Discharge Abstract Database to determine (1) admission to hospital or discharge home from the emergency department, (2) intubation or noninvasive positive pressure ventilation in hospitalized patients, and (3) hospital length-of-stay.[14–16]

Outcomes

The primary outcome was death within 7 days after presentation to the emergency department. Mortality within 30 days after emergency presentation was a secondary outcome. We considered mortality prediction to be important because it forms the foundation for future studies of nonfatal outcomes (eg, hospital readmissions and return emergency visits) as a competing risk.

Statistical Analysis

Continuous variables were summarized as medians with interquartile ranges. Categorical variables were presented as proportions and compared using the χ^2 statistic. To compare physician-estimated risk and EHMRG7, we (1) calculated the Spearman rank correlation, and (2) standardized both scores to have a mean of 0 and variance of 1 and examined the β-coefficient from a logistic regression model for the outcome of death for 1 SD increase in the standardized scores. Using previously-published thresholds for different quintiles of risk, odds ratios and 95% confidence intervals (CIs) for 7-day and 30-day mortality were determined for each increasing risk category or score. We also used logistic regression to determine the effect on mortality of increasing physician-estimated and EHMRG-predicted risks of death. Shrinkage estimators were used to determine that there was no model overfit.

We compared the EHMRG7 and physician-estimated risk using areas under the receiver operating characteristic curves and compared predicted rates using the sign test. We examined the impact of EHMRG7 in 2 ways. First, we identified the proportion of patients in whom the physician-judged decision to admit or discharge would have been changed if EHMRG7 was used to guide decisions. Specifically, we counted the

Table 1. Variables in the EHMRG 7-Day and 30-Day Risk Models

Age*
Arrival by ambulance*
Systolic blood pressure (triage)†
Heart rate (triage)†
Oxygen saturation (triage)†
Potassium concentration*
Creatinine concentration*
Troponin*
Active cancer*
Metolazone use prior to ED arrival*
ST-depression on 12-lead ECG (30-day model only)*

*Obtained from the electronic medical record in the emergency or face sheet.

†Obtained from nurse at initial triage on arrival to emergency.

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number of additional discharges from the emergency department if all low-/very low–risk patients were discharged, and the number of excess hospital admissions if all high-/very high–risk patients were admitted, compared with the physicians' original management plan before knowledge of the EHMRG risk result. Second, we examined continuous and categorical net reclassification improvement of the EHMRG model and physician-estimated risk combined compared with physician estimation alone for 7- and 30-day outcomes.[17]

We examined factors associated with hospital admission using univariate and multiple logistic regression analyses. The following factors were included in the model: age, sex, diuretic given in the emergency department, symptomatic improvement with diuretic, and 1 SD increase in physician-estimated risk and EHMRG7 scores. Although ACUTE was a single-arm study, to provide context and estimate how our study cohort compared with the general population of HF patients who visited the emergency department, we examined those with a primary International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) diagnosis code I50 using the National Ambulatory Care Reporting System during similar years of the study at participating hospitals. Comorbidities, including previous HF or myocardial infarction, diabetes mellitus, hypertension, ischemic heart disease, atrial fibrillation, and other noncardiac comorbidities, were identified using published methods.[14,18–20] In our logistic regression models, calibration was assessed using the Hosmer–Lemeshow statistic. Model performance was evaluated using the c-statistic and the Brier score. Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). *P* values < 0.05 were considered statistically significant.

RESULTS

Patient Characteristics and Outcomes

Characteristics of the 1983 unique patients enrolled in this prospective study are shown in Table 2. A flow diagram of exclusion criteria for the study cohort is shown in Figure 1. Among the study cohort, 88.5% met ICD-10 discharge criteria for acute HF and 94.6% met the HF entry criteria into the Ontario HF Cohort.[20,21] Characteristics of nonstudy HF patients in the population are shown in Table II in the online-only Data Supplement. Variables for determination of the 7- and 30-day risk models are shown in Table 3. Among the study cohort, 1566 (79%) were admitted from the emergency department. There were 39 deaths at 7 days and 138 deaths (121 in-hospital and 17 out-of-hospital) at 30 days. Intubation or noninvasive positive pressure ventilation occurred in 83 (5.3%) hospitalized patients.

Risk of Death According to Physician-Estimated Risk or Model Predictions

Stratifying by risk categories, there were no deaths in the 2 lowest EHMRG7 risk groups at 7-day follow-up (Figure 2). There were also no deaths in the lowest risk

Table 2. Cohort Characteristics

Characteristic	Study Cohort
N	1983
Demographics	
Age, median (IQR)	81 (71, 87)
Men, n (%)	1032 (52.0%)
Previous HF diagnosis*	1422 (71.7%)
Risk factors	
Diabetes mellitus*	1050 (53.0%)
Hypertension*	1784 (90.0%)
Cardiac etiologic conditions	
Previous MI‡	418 (21.1%)
Previous ischemic heart disease†	1015 (51.2%)
Valvular heart disease	211 (10.6%)
Previous atrial fibrillation†	776 (39.1%)
Noncardiac comorbidities	
CVD‡	236 (11.9%)
COPD‡	502 (25.3%)
Dementia‡	147 (7.4%)
Renal disease‡	386 (19.5%)
Any cancer‡	173 (8.7%)

COPD indicated chronic obstructive pulmonary disorder; CVD, cardiovascular disease; HF, heart failure; and MI, myocardial infarction.

*Ambulatory or inpatient diagnoses from the Ontario diabetes mellitus, hypertension, or heart failure databases.[20]

†Ambulatory or inpatient diagnoses for ischemic heart disease[18] or atrial fibrillation[19] within 3 years before emergency presentation

‡Comorbidity diagnosis based on Charlson classification system within 3 years before emergency presentation using the Canadian Institute for Health Information or National Ambulatory Care Reporting System databases.

EHMRG30-ST risk group at 30-day follow-up (Figure 2). The median EHMRG7 scores were 46 (interquartile range [IQR], –6 to 96) and –11 (IQR, –46 to 32) among those who were admitted and discharged, respectively. Median predicted risks of 30-day death were 8% (IQR, 4% to 17%) for admitted and 4% (IQR, 2% to 7%) for patients discharged from the emergency department (*P*<0.001). Observed mortality rates were 2.4% (7-day) and 7.7% (30-day) for admitted, and <1.5% (7-day) and 3.3% (30-day) for discharged patients. The odds ratio for 7-day mortality was 1.41 (95% CI, 1.21–1.60) for a 1-SD (1-SD = 7.9%) increase in the physician-estimated risk and 1.54 (95% CI, 1.28–1.81) for a 10% increase in physician-estimated risk. The odds ratio for 7-day death was 2.94 (95% CI, 2.17–4.03) for a 1-SD (1-SD = 73.3 points) increase in the unstandardized EHMRG7 score and 2.48 (95% CI, 1.87–3.27) for a 10% (equivalent to 61.7 points) increase in the predicted risk of 7-day death.

When the cohort was stratified by the 5 EHMRG30-ST risk strata (with the highest stratum being further divided into 2 substrata), there was early separation of survival curves over 30 days of follow-up, with partic-

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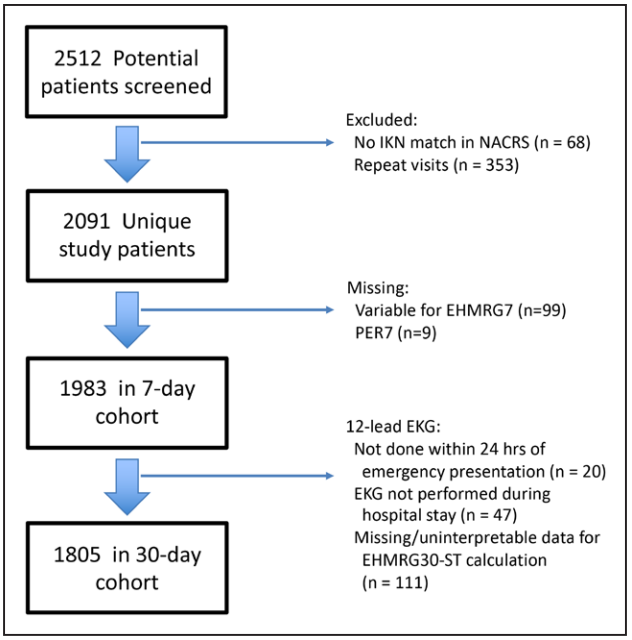

Figure 1. Patient flow diagram.
EHMRG7 indicates Emergency Heart failure Mortality Risk Grade for 7-day mortality; EHMRG30-ST, Emergency Heart failure Mortality Risk Grade for 30-day mortality with ST-segment depression; IKN, ICES Key Number; NACRS, National Ambulatory Care Reporting System; and PER7, physician-estimated risk of 7-day mortality.

ularly high risk observed in categories 5a and 5b (Figure 3). The EHMRG30-ST model demonstrated nonlinearity for the outcome of the log odds of 30-day mortality, therefore a logit transformation was performed. After logit transformation, the odds ratio for 30-day death was 2.93 (95% CI, 2.39–3.63) for a 1-SD (1-SD = 1.21) increase and 2.43 (95% CI, 2.05–2.89) for a 1-unit increase in the logit EHMRG30-ST.

Model Performance

The c-statistic for prediction of 7-day mortality using the physician-estimated risk was 0.71 (95% CI, 0.64–0.78). EHMRG7 demonstrated superior discrimination with a c-statistic of 0.81 (95% CI, 0.75–0.87), which was significantly improved compared with physician-estimated risk (P=0.022). When both physician-estimated risk and EHMRG7 were combined together in the same model, the c-statistic was 0.82 (95% CI, 0.76–0.88), which was superior to physician-estimated risk alone (P=0.003), but was not significantly different from EHMRG7 alone (P=0.242). Receiver operating curves are shown in Figure I in the online-only Data Supplement. Prediction of 30-day mortality for logit-transformed EHMRG30-ST exhibited a c-statistic of 0.77 (95% CI, 0.73–0.81). There was no lack of model fit as demonstrated by Hosmer–Lemeshow statistic P values > 0.1 for all EHMRG models with or without physician estimated risk. The Brier scores were 0.019 and 0.059 for the 7- and 30-day models, respectively. The shrinkage estimators for the 7-day and 30-day models were 0.98 and 0.99, indicating no model overfit. Calibration plots of observed versus predicted 7-day and 30-day mortality are shown in Figures II and III in the online-only Data Supplement, respectively.

Net Reclassification Improvement

Using a category-free approach, the net reclassification improvement was 0.763 (95% CI, 0.465–1.062) for EHMRG7 combined with physician-estimated risk compared with PER7 alone. Using categories of risk based on groups 1, 2, 3, 4, 5a, and 5b, categorical net reclassification improvement was 0.820 (95% CI, 0.560–1.080) when using EHMRG7 score combined with physician-estimated risk compared with PER7 alone (Table III in the online-only Data Supplement). Net reclassification improvement was 0.308 (95% CI, 0.050–0.566) for those with events and 0.512 (95% CI, 0.480–0.545) for those without events (Tables IV and V in the online-only Data Supplement, respectively). The integrated discrimination improvement was 0.030 overall, 0.029 for events, and –0.001 for nonevents. Comparing EHMRG7 alone to PER7 alone, overall net reclassification improvement was similarly high: 0.718 (95% CI, 0.453–0.984). The improvement in reclassification was high in those without events: 0.462 (95% CI, 0.428–0.496), as shown in Table IV in the online-only Data Supplement.

Table 3. EHMRG Variables

Variable	Median (IQR) or n (%)
N	1983
Age, y	81 (71, 87)
Arrival by ambulance	864 (43.6%)
Triage SBP, mm Hg	136 (119, 155)
Triage heart rate, bpm	84 (72, 101)
Triage O_2 saturation, %	96 (93, 98)
Creatinine concentration, mg/dL	1.18 (0.89, 1.69)
Potassium concentration	
< 4.0 mEq/L	583 (29.4%)
4.0 to 4.5 mEq/L	787 (39.7%)
> 4.5 mEq/L	613 (30.9%)
Troponin, >ULN	686 (34.6%)
Active cancer	142 (7.2%)
Metolazone	69 (3.5%)
ST-depression on ECG*	
Absent	928 (51.4%)
Present	225 (12.5%)
Other (LBBB, paced, LVH)	652 (36.1%)

EHMRG indicates Emergency Heart failure Mortality Risk Grade; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; IQR, interquartile range; and ULN, upper limit of normal.
*Based on n=1805.

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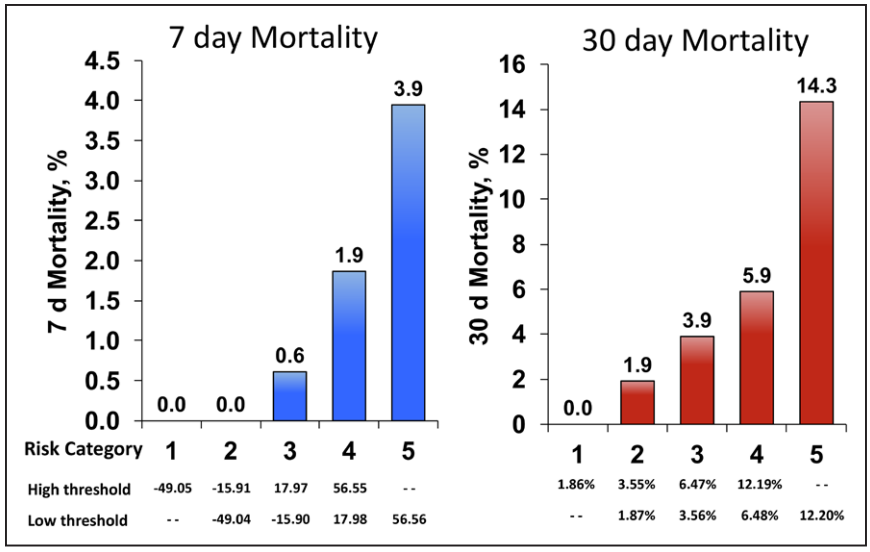

Figure 2. Mortality rates by EHMRG7 or EHMRG30-ST risk categories.
Risk categories: 1 = very low, 2 = low, 3 = intermediate, 4 = high, and 5 = very high. EHMRG7 indicates Emergency Heart failure Mortality Risk Grade for 7-day mortality; and EHMRG30-ST, Emergency Heart failure Mortality Risk Grade for 30-day mortality with ST-segment depression.

Comparison of Physician-Estimated Risk With EHMRG7

As shown in the scatterplot, there was low correlation between the predicted probability of 7-day death using the EHMRG7 and physician-estimated risk (Figure IV in the online-only Data Supplement). Physician-estimated risk was higher than the mean predicted risk across the deciles of the EHMRG7 model for the lowest 9 deciles of risk (Figure 4). In contrast, physician estimates underestimated risk in the highest EHMRG7 decile (6.4 versus 10.4%). In the lowest 4 deciles, physician-estimated risk ranged from 2.1% to 3.1%, and was 2.5% to 3.2% in deciles 5 to 7 (Figure 4). With the exception of decile 8 (P=0.455), comparisons were statistically significant for all deciles comparing physician-estimated risk with EHMRG7 (all P<0.001).

Physician Survey

The response rate to the physician survey was 100% because it was required before entering the risk score (Table 4). The majority of patients were given furosemide, and approximately one-third were considered to have improved while being observed in the emergency department. In 1561 (78.7%) patients, the plan was to admit the patient either directly or after specialist referral (Table 4). Physicians preferred outpatient follow-up with a cardiologist or the heart function clinic in the majority of cases.

Results of the survey stratified by the EHMRG7 score, and the ultimate disposition of patients from the emergency department, are shown in Table VII in the online-only Data Supplement. Of the 400 patients in whom the plan was to ultimately discharge home, 131 were high or very high risk according to the EHMRG7 score, but only 24 were admitted to hospital. Conversely, although 186 of the patients initially planned for discharge were very low or low risk, 20 were still admitted to hospital. Of the 1571 patients in whom the plan was to admit to hospital from the emergency department, 332 were low or very low risk. Of these, 310 (93.4%) were admitted to hospital. If decisions to admit or discharge were purely guided by EHMRG7 such that all high-/very high–risk patients were admitted and all low-/very low–risk patients were discharged, hospital admissions could have been reduced by as much as 9.8% (Table VII in the online-only Data Supplement).

Predictors associated with hospital admission are shown in Table 5. On multivariable analysis, use of diuretics was associated with increased odds of admission, whereas perceived improvement with furosemide was associated with decreased odds of hospital admission. Higher physician-estimated risk and EHMRG7 scores were associated with higher likelihood of hospitalization per 1-SD increment. Among those who were admitted to hospital, higher-risk patients had significantly longer lengths of hospital stay: 7 (IQR, 4–13) days for very high (P<0.001) and 6 (IQR, 3–12) days for high risk (P=0.044) compared with 5 days for intermediate risk (IQR, 3–9 days). Length of hospital stay for low- (6 [IQR, 3–11] days) and very low– (5 [IQR, 3–8] days) risk groups did not differ from those who were at intermediate risk (P=0.135 and P=0.213, respectively).

Estimation of Simultaneous 7-Day and 30-Day Mortality Risks

Simultaneous 7-day risk scores (x axis) and 30-day risk (y axis) are shown in Figure V in the online-only Data Supplement for the current prospective validation cohort (red x). For comparison, a similar scatterplot is presented for the previously published original derivation cohort (background, blue square), demonstrating that the risk distributions of the 2 cohorts overlap, without a systematically higher or lower risk in the validation cohort.[10]

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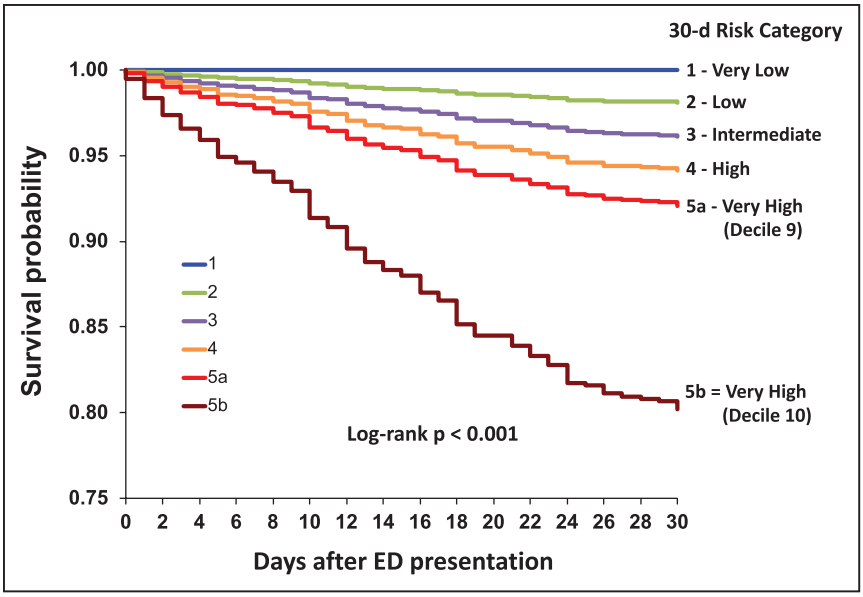

Figure 3. Survival curve for time to 30-day death by EHMRG30-ST risk category (1, 2, 3, 4, 5a, and 5b).
ED indicates emergency department; and EHMRG30-ST, Emergency Heart failure Mortality Risk Grade for 30-day mortality with ST-segment depression.

Figure VI in the online-only Data Supplement divides our prospective validation cohort according to tertiles of 7- and 30-day risks simultaneously. Low risk patients are low risk at both 7 and 30 days. Those considered high risk could be at increased risk at either 7- or 30-day time points (Figure VI in the online-only Data Supplement).

DISCUSSION

In this study, we prospectively and externally validated a model for simultaneous prediction of both 7-day and 30-day mortality for acute HF patients presenting to the emergency department. We found that the EHMRG demonstrated high discrimination for both 7-day and 30-day mortality. One of the strengths of the model was its ability to identify low-risk patients, with no deaths at 7 days in the lowest 2 quintiles and no deaths at 30 days in the lowest risk quintile. The models were also able to identify high-risk patients, with mortality rates of 20% by 30 days after emergency department presentation. Physicians' estimates of 7-day mortality risk were assessed before any risk scores were calculated, and these were modestly discriminative, but EHMRG7 was superior to these estimates. When compared using net reclassification analysis, we found that EHMRG7 substantially improved reclassification of risk compared with physician estimates alone. Interestingly, although EHMRG7 was superior to physician-estimated risk alone, discrimination was numerically increased, albeit nonsignificantly, when EHMRG7 and physician-estimated risk were combined.

The emergency department is the final common pathway where patients with acutely decompensated HF present. The decision to admit or discharge the patient with acute HF is critically important; however, these decisions have been made based on clinical judgment without the routine use of predictive risk models.[22] Although physician-estimated risk has not been

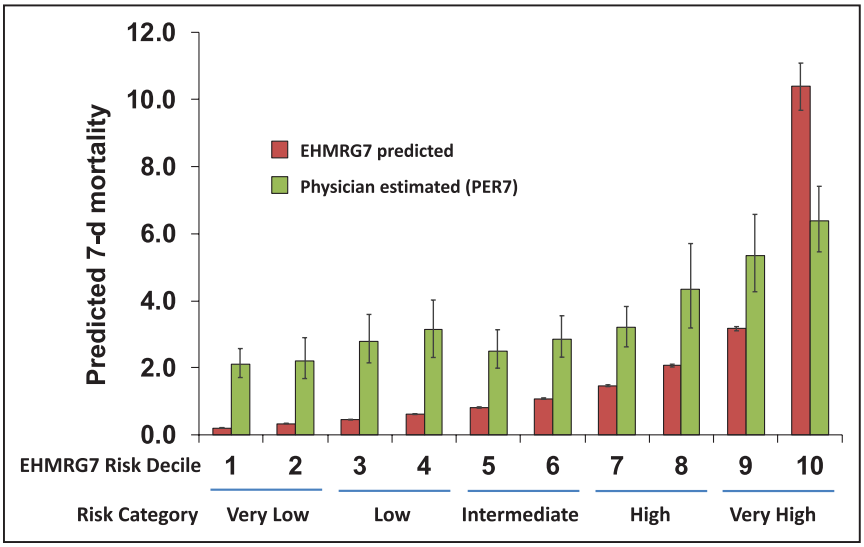

Figure 4. Physician estimated risk vs EHMRG7 risk score deciles.
EHMRG7 indicates Emergency Heart failure Mortality Risk Grade for 7-day mortality; and PER7, physician-estimated risk of 7-day mortality.

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Table 4. Survey Results

Survey Question	Option	n (%)
N		1983
Was furosemide provided in ED?	Yes	1648 (83.1%)
Did patient improve with treatment?*	Yes	567 (34.4%)†
Plan for patient	Admit to hospital	615 (31.0%)
	Admit after specialist referral	956 (48.2%)
	Discharge after specialist referral	74 (3.7%)
	Discharge home	326 (16.4%)
If patient is discharged, what type of follow-up would you suggest?	Cardiologist	829 (41.8%)
	HF clinic	681 (34.3%)
	Internal medicine clinic	140 (7.1%)
	Family physician	441 (22.2%)

HF indicates heart failure.
*Denominator = those who received furosemide.
†Judged clinically.

formally studied in the acute hospital setting, a previous report found that physicians overestimated the risk of ambulatory patients with advanced, chronic HF and were unable to differentiate survival of perceived low- versus high-risk patients in the clinic setting.[23] Inaccuracies in physicians' predictions of prognosis have also been reported in patients in whom outcomes occur stochastically, including acute stroke[24] and length of stay in the intensive care unit.[25] Inaccuracies in prognostication by physicians could potentially lead to low-risk hospital admissions and high-risk hospital discharges, which could lead to postdischarge mortality.[7]

From the perspective of risk stratification, the present study provides real-world emergency department–based clinical validation of the EHMRG models for 7-day and 30-day mortality risk, which were originally derived using large-scale chart review by highly trained nurse abstractors.[10,11] The EHMRG is distinct from other risk assessment methods for acute HF. Many methods for risk estimation have been published for chronic stable HF patients in the ambulatory clinical setting.[26–28] Relatively few prognostic scores have been validated in the acute setting where patients present to the emergency department and acute care decisions must be made quickly, often without the availability of left ventricular functional assessment or advanced cardiac imaging. A recently published systematic review reported on other models for acute HF, and found that they were limited because of modest discriminative ability, high event rates in the lowest-risk group, and exclusion of a large proportion of potential patients.[29–32] Furthermore, other models included composite nonfatal events, which did not account for competing risks.[29–32] One model that examined 30-day mortality was the MEESI-AHF (Multiple Estimation of risk based on the Emergency department Spanish Score in patients with AHF), a complex model requiring knowledge of >20 variables including a separately calculated Barthel index.[33] Although the Barthel index was the most important part of the MEESI-AHF model, the accuracy of self-report to determine the score has been questioned in the elderly,[34] and it is not routinely assessed in the acute setting as demonstrated by 28% missingness of this variable in the MEESI-AHF cohort.[33] Finally, with the exception of the Ottawa Heart Failure Risk Scale,[31] none of the above models have been validated externally and prospectively, nor have they been shown to perform better than physician judgment.

The biological mechanisms conferring increased mortality risk for predictors such as blood pressure, heart rate, and renal function have been previously described.[10,11,35] Since the publication of our original derivation models, studies have provided further links between the covariates in our models with acute HF mortality. Specifically, the prognostic value of serum potassium concentrations and the U-shaped association with risk, over the continuum of time, was demonstrated in Spanish and Danish cohorts.[36,37] The chronic use of metolazone was associated with in-hospital hypotension in the ASCEND-HF trial (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) and is indicative of relative diuretic resistance, which are both predictors of later mortality.[38,39] Finally, troponin elevation has been confirmed as a predictor of mortality in acute HF.[40–42] The current study also provides insights potentially contributing to the

Table 5. Predictors of Admission to Hospital (Versus Discharge From ED)

Variable	Odds Ratio (95%CI)	*P* Value
Univariate predictors		
Men	1.14 (0.92, 1.42)	0.225
Diuretics		
None	reference	n/a
Given, no improvement or uncertain	2.17 (1.57, 2.97)	<0.001
Given, improved	0.46 (0.34, 0.63)	<0.001
PER (%), per 1-SD	3.90 (2.55, 6.32)	<0.001
EHMRG7 score, per 1-SD	2.21 (1.94, 2.53)	<0.001
Multivariable predictors		
Men	1.25 (0.99, 1.59)	0.065
Diuretics		
None	reference	n/a
Given, no improvement or uncertain	2.00 (1.43, 2.79)	<0.001
Given, improved	0.40 (0.28, 0.55)	<0.001
PER (%), per 1-SD	2.47 (1.71, 3.83)	<0.001
EHMRG7 score, per 1-SD	2.08 (1.81, 2.40)	<0.001

EHMRG7 indicates Emergency Heart failure Mortality Risk Grade for 7-day mortality; and PER, physician-estimated risk.

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observation that low-risk patients are often hospitalized and high-risk patients are sometimes discharged.[2,43] Specifically, physicians tended to overestimate the probability of 7-day mortality in low-risk patients, while paradoxically underestimating the probability in those at highest risk.

These findings have implications for the many patients with acute HF who present to emergency departments worldwide because estimation of prognosis underlies many clinical decisions. Since EHMRG does not rely on advanced imaging and biomarkers with limited accessibility, it enables prognostication in a wide range of healthcare systems. A determination of low risk may be an important consideration when deciding to discharge patients early if they improve symptomatically with diuretic administration. Such patients could be followed rapidly in an ambulatory HF clinic where further investigations and medical optimization could occur.[44] Intermediate- or high-risk patients will likely require hospital admission, and those at highest risk may potentially require more intensive monitoring during their hospital stay.[45] Our findings suggest that reliance on clinically judged risk estimates alone may result in a potential mismatch, whereby many low-risk patients are hospitalized or potentially unsafe discharges from the emergency department might occur. Although the EHMRG provides important prognostic information, it does not supplant clinical decision-making. Instead, EHMRG is 1 factor that complements other pragmatic aspects of the decision to admit or discharge patients from hospital. These clinical factors include (but are not limited to) ability for self-care, availability of social supports, multiple active medical issues requiring treatment simultaneously, comorbidities, functional status, and excessive congestion or limited mobility necessitating in-hospital care provision. Finally, our study highlights the insights gained by examining and comparing physician-estimated risk against prediction models, and provides an approach that investigators can use in the validation of risk scores and algorithms in the future.

Limitations of our study should be noted. Since the current study was not an explicit clinical validation, physicians were not directed to use the EHMRG score to make admission decisions. Therefore, we could not determine physician compliance with using the score or its impact on hospitalization. Our study could not capture the complex thought processes and patient-physician exchanges that were involved in recommending hospital admission or discharge, of which physician-estimated risk is but 1 component of the decision, nor could we rule out the possibility that physicians subconsciously used the score to make decisions despite being instructed otherwise. Thus, the analyses of physician management plan in relation to patients' risk scores should be considered hypothesis-generating, and the actual reduction of hospitalizations may be less pronounced than our estimates. Both of the above limitations would require an implementation trial, recruiting patients prospectively where admission–discharge decisions are based on the EHMRG, to test the hypothesis of a beneficial effect on decision-making and outcomes. This hypothesis will be tested in the COACH trial (Comparison of Outcomes and Access to Care for Heart failure) (URL: www.clinicaltrials.gov. Unique identifier: NCT02674438).[44] EHMRG was not designed to predict repeat emergency visits or postdischarge hospitalizations, which occurred in 586 (29.6%) and 424 (21.4%) patients overall within 30 days after hospital separation. Because death is a competing risk for these nonfatal outcomes, our study may represent the basis for future efforts to predict these nonfatal outcomes. Because the EHMRG models were designed for HF patients, the performance of the models could be adversely affected if applied to those without an emergency department diagnosis of HF. Finally, our study excluded patients who were palliative and had an advanced directive of a do-not-resuscitate order before arrival in the emergency department; these patients are known to have higher mortality risk.[46] Although palliative patients were never included in the original derivation of EHMRG7, they were included in a Spanish prospective validation study, which found that risk was stratified even among this higher-risk patient group.[47]

In conclusion, clinical characteristics at emergency department presentation are highly predictive of 7-day and 30-day mortality among patients with acute HF. A mathematical combination of these predictors was superior to physician estimate of mortality, demonstrating improved discrimination and risk reclassification. Although it has now been validated prospectively, EHMRG should not be used alone to decide whether to admit or discharge patients, but should still be used alongside clinical judgment. Implementation testing followed by broad use of the prospectively validated EHMRG risk algorithm may improve care efficiency of those at lower risk and enhance safety by decreasing inappropriate discharge of high risk patients.

ARTICLE INFORMATION

Received April 18, 2018; accepted October 11, 2018.

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Acknowledgments

This manuscript is dedicated to the memory of Dr. Jack V. Tu (March 1, 1965–May 30, 2018).

Sources of Funding

ICES is supported in part by a grant from the Ontario Ministry of Health and Long Term Care. The opinions, results and conclusions are those of the authors and no endorsement by the Ministry of Health and Long-Term Care or by ICES is intended or should be inferred. Parts of this material are based on data and information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors, and not necessarily those of CIHI. This study was supported by a Strategy for Patient-Oriented Research (SPOR) grant from the Ontario SPOR Support Unit (OSSU) and a Foundation Grant from the Canadian Institutes of Health Research (grant # FDN 148446). Dr D. Lee is supported by a midcareer investigator award from the Heart and Stroke Foundation and the Ted Rogers Chair in Heart Function Outcomes, a joint Hospital-University Chair of the University Health Network and the University of Toronto. Dr Austin is supported by a Mid-Career investigator award from the Heart and Stroke Foundation. Dr Tu is a Tier 1 Canada Research Chair in Health Services Research and an Eaton Scholar of the Department of Medicine, University of Toronto. Dr J. Lee is supported by a Merit Award from the Department of Medicine, University of Toronto.

Disclosures

Dr Levy reports having been a consultant for or received honoraria from Novartis, Trevena, Roche Diagnostics, Astra Zeneca, Sciex, and Siemens. He has also received research support from Roche, Novartis, Gilead, Edwards Lifesciences, Amgen, BCBSMF, GE/EMF, PCORI, NHLBI, and AHRQ. The other authors report no conflicts.

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