

Prospective Validation of the Emergency Heart Failure Mortality Risk Grad for Acute Heart Failure: The Acute Congestive Heart Failure Urgent Care Evaluation (ACUTE) Study

Running Title: *Lee et al.; Validation of EHMARG for Acute Heart Failure*

Douglas S. Lee, MD, PhD^{1,2,3}; Jacques S. Lee, MD, MSc^{3,4}; Michael J. Schull, MD, MSc^{1,3,4};
Bjug Borgundvaag, MD, PhD^{3,5}; Marcia L. Edmonds, MD, MSc⁶; Maria Ivankovic, MD⁷;
Shelley L. McLeod, MSc^{3,5}; Jonathan F. Dreyer, MD⁶; Sam Sabbah, MBBS, MSc^{2,3};
Phillip D. Levy, MD, MPH⁸; Tara O'Neill, BES¹; Alice Chong, BSc¹;
Therese A. Stukel, PhD^{1,3}; Peter C. Austin, PhD^{1,3}; Jack V. Tu, MD, PhD^{1,3,4}

¹ICES, Toronto, Ontario, Canada; ²Peter Munk Cardiac Centre and University Health Network,
Toronto, Ontario, Canada; ³University of Toronto, Toronto, Ontario, Canada; ⁴Sunnybrook
Health Sciences Centre, Toronto, Ontario, Canada; ⁵Schwartz/Reisman Emergency Medicine
Institute, Sinai Health System, Toronto, Ontario, Canada; ⁶University of Western Ontario,
London, Ontario, Canada; ⁷Trillium Health Partners, Mississauga, Ontario, Canada;
⁸Wayne State University Department of Emergency Medicine and Integrative Biosciences
Center, Detroit, MI

Address for Correspondence:

Douglas S. Lee, MD PhD
Senior Scientist, Institute for Clinical Evaluative Sciences
Division of Cardiology, Peter Munk Cardiac Centre
Professor of Medicine, University of Toronto
Institute for Clinical Evaluative Sciences
2075 Bayview Ave, Rm G-106
Toronto, ON, Canada M4N 3M5
Tel: 416-480-4700
Email: dlee@ices.on.ca

Abstract

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 prior to 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 electrocardiogram.

Results: We recruited 1983 patients seeking emergency department care for acute heart failure. Mortality rates at 7 days in the five 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 to physician-estimated risk of 7-day mortality (PER7, c-statistic 0.71; 95% confidence interval [CI] 0.64, 0.78) there was improved discrimination with EHMRG7 (c-statistic 0.81; 95% CI 0.75, 0.87, $p = 0.022$ vs. PER7) and with EHMRG7 combined with physicians' estimates (c-statistic 0.82; 95% CI 0.76, 0.88, $p = 0.003$ vs. PER7). Model discrimination increased non-significantly, by 0.014 (95% CI -0.009, 0.037) when physicians' estimates combined with EHMRG7 were compared to 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 non-significantly 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 to 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 to physicians' estimates, our multivariable model was better able to predict 7-day mortality, and may guide clinical decisions.

Clinical Trial Registration: URL: <https://clinicaltrials.gov> Unique Identifier: NCT02634762

Key Words: heart failure; acute heart failure; emergency department; hospitalization; risk prediction; risk assessment; outcomes; mortality; decision support

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 30-day model 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.

Introduction

Heart failure (HF) is a leading cause of hospitalization in North America, with substantial health economic impacts.¹ Patients with acute heart failure often present to the emergency department for care, and in some cases patients are admitted to hospital based not on symptoms, but because of the unknown risk of clinical instability.² There has been a slight decline in hospitalizations for heart failure in recent decades, however emergency department visits for this condition have not decreased significantly.³⁻⁵ Up to 15 percent of acute heart failure 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 due partly to 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 heart failure after presentation to the emergency department.⁸ Specifically, higher risk patients would be hospitalized to facilitate more timely investigations and medical optimization, while 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 heart failure 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 electrocardiogram.¹¹ The primary objectives of this study were to: a) prospectively evaluate the performance of EHMRG7 in a new cohort of patients seeking care in the emergency department, and b) 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 to physician-estimated risk.



Methods

Patients

At 9 hospitals in Ontario, Canada from July 2010 to March 2015, patients presenting to the emergency department with heart failure were recruited (**Supplemental Table 1**). We included those with acute heart failure diagnosed clinically as suggested by national guidelines published by the Canadian Cardiovascular Society and the Framingham criteria (90% sensitivity for acute HF). Acute heart failure was confirmed using: (i) 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 (ii) 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 employed if deemed clinically necessary. Research Ethics Board approval was obtained from all participating sites prior to 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 heart failure 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 (DNR) orders upon arrival were also excluded, as they were not included in the aforementioned studies. We also excluded patients who were dialysis dependent since the pathophysiology and management of acute heart failure is different in these patients. The methodology of the ACUTE study and details of the physician survey have been previously published and registered (ClinicalTrials.gov NCT 02634762).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, due to 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 prior to the physician rendering a disposition decision about admission or discharge from the emergency department (see **Box** 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 to 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 (e.g., 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 Institute for Clinical Evaluative Sciences 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 electrocardiogram (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 employed, without further re-fitting 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 two highest risk deciles based on prior 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: a) admission to hospital or discharge home from the emergency department, b) intubation or non-invasive positive pressure ventilation in hospitalized patients, and c) 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 non-fatal outcomes (e.g., 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: a) calculated the Spearman rank correlation, and b) standardized both scores to have a mean of zero and variance of one, and examined the beta-coefficient from a logistic regression model for the outcome of death for one standard deviation increase in the standardized scores. Using previously-published thresholds for different quintiles of risk, odds ratios and 95% confidence intervals 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 two 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 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 to the physicians' original management plan prior to 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 to 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 one standard deviation increase in physician-estimated risk and EHMRG7 scores. While ACUTE was a single-arm study, to provide context and estimate how our study cohort compared to the general population of heart failure patients who visited the emergency department, we examined those with a primary ICD-10-CA diagnosis code I50 using the National Ambulatory Care Reporting System during similar years of the study at participating hospitals. Comorbidities, including prior heart failure or myocardial infarction, diabetes, 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, USA). 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 non-study HF patients in the population are shown in **Supplemental Table 2**. 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 non-invasive positive pressure ventilation occurred in 83 (5.3%) of hospitalized patients.

Risk of death according to physician-estimated risk or model predictions

Stratifying by risk categories, there were zero deaths in the two lowest EHMRG7 risk groups at 7 day follow-up (**Figure 2**). There were also zero deaths in the lowest risk EHMRG30-ST risk group at 30 day follow-up (**Figure 2**). The median EHMRG7 scores were 46 (IQR: -6, 96) and -11 (IQR: -46, 32) among those who were admitted and discharged, respectively. Median predicted risks of 30-day death were 8% (IQR: 4%, 17%) for admitted and 4% (IQR: 2%, 7%) for patients discharged from the emergency department ($p < .001$). 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 one

standard deviation (1-SD = 7.9%) increase in the physician-estimated risk and 1.54 (95% CI; 1.28, 1.81) for a 10-percentage point increase in physician-estimated risk. The odds ratio for 7-day death was 2.94 (95% CI; 2.17, 4.03) for a one standard deviation (1-SD = 73.3 points) increase in the unstandardized EHMRG7 score and 2.48 (95% CI; 1.87, 3.27) for a 10-percentage point (equivalent to 61.7 points) increase in the predicted risk of 7-day death.

When the cohort was stratified by the five EHMRG30-ST risk strata (with the highest stratum being further divided into two substrata), there was early separation of survival curves over 30 days of follow-up, with particularly high risk observed in categories 5a and 5b (**Figure 3**). The EHMRG30-ST model demonstrated non-linearity 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 one-standard deviation (1-SD = 1.21) increase and 2.43 (95% CI; 2.05, 2.89) for a one-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 to 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 than EHMRG7 alone ($p = 0.242$). Receiver operating curves are shown in **Supplemental Figure 1**. 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-and-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 vs. predicted 7-day and 30-day mortality are shown in **Supplemental Figures 2 and 3**, 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 to 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 to PER7 alone (**Supplemental Table 3**). 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 (**Supplemental Tables 4 and 5**, respectively). The IDI was 0.030 overall, 0.029 for events, and -0.001 for non-events. 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 **Supplemental Table 6**.

Comparison of physician-estimated risk to 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 (**Supplemental Figure 4**). 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 vs. 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 to EHMRG7 (all $p < .001$).

Physician survey

The response rate to the physician survey was 100% since 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 **Supplemental Table 7**. 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, while 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% (**Supplemental Table 7**).

Predictors associated with hospital admission are shown in **Table 5**. On multivariable analysis, use of diuretics was associated with increased odds of admission, while 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 one standard deviation 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 ($p < .001$) and 6 (IQR: 3, 12) days for high risk ($p = 0.044$) compared to 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 **Supplemental Figure 5** 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 distribution of the two cohorts overlap, without a systematically higher or lower risk in the validation cohort.¹⁰ **Supplemental Figure 6** 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 timepoints (**Supplemental Figure 6**).

Discussion

In this study, we prospectively and externally validated a model for simultaneous prediction of both 7-day and 30-day mortality for acute heart failure 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 two 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 to physician estimates alone. Interestingly, while EHMRG7 was superior to physician-estimated risk alone, discrimination was numerically increased, albeit non-significantly, when EHMRG7 and physician-estimated risk were combined.

The emergency department is the final common pathway where patients with acutely decompensated heart failure present. The decision to admit or discharge the patient with acute heart failure is critically important, however, these decisions have been made based on clinical judgment without the routine use of predictive risk models.²² While physician-estimated risk has not been formally studied in the acute hospital setting, a prior report found that physicians overestimated the risk of ambulatory patients with advanced, chronic heart failure 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 where outcomes occur stochastically, including acute stroke²⁴ 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 that could lead to post-discharge mortality.⁷

From the perspective of risk stratification, this 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 heart failure. Many methods for risk estimation have been published for chronic stable heart failure

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 heart failure, and found that they were limited due to 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 non-fatal events, which did not account for competing risks.²⁹⁻³² One model that examined 30-day mortality was the Multiple Estimation of risk based on the Emergency department Spanish Score in patients with AHF (MEESI-AHF), a complex model requiring knowledge of over 20 variables including a separately calculated Barthel index.³³ While 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 judgement.

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 heart failure 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 Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, 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 heart failure.⁴⁰⁻⁴² The current study also provides insights potentially contributing to the 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 heart failure 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 heart failure 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. While the EHMRG provides important prognostic information, it does not supplant clinical decision-making. Instead, EHMRG is one 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 employ 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 one 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 Comparison of Outcomes and Access to Care for Heart failure (COACH) trial (ClinicalTrials.gov NCT02674438).⁴⁴ EHMRG was not designed to predict repeat emergency visits or post-discharge hospitalizations, which occurred in 586 (29.6%) and 424 (21.4%) patients overall within 30 days after hospital separation. As death is a competing risk for these non-fatal outcomes, our study may represent the basis for future

efforts to predict these non-fatal outcomes. Since 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 prior to arrival in the emergency department; These patients are known to have higher mortality risk.⁴⁶ While 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 amongst 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 heart failure. A mathematical combination of these predictors was superior to physician estimate of mortality, demonstrating improved discrimination and risk reclassification. While 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 judgement. 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.

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Disclosures

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Table 1. Variables in the EHMARG 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 upon arrival to emergency



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Table 2. Cohort characteristics

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

* Ambulatory or inpatient diagnoses from the Ontario diabetes, hypertension, or heart failure databases²⁰

[†] Ambulatory or inpatient diagnoses for ischemic heart disease¹⁸ or atrial fibrillation¹⁹ within 3 years prior to emergency presentation

[§] Comorbidity diagnosis based on Charlson classification system within 3 years prior to emergency presentation using the Canadian Institute for Health Information or National Ambulatory Care Reporting System databases

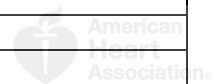


Table 3. EHMARG variables

Variable	Units	Median (IQR) or n(%)
N		1983
Age	years	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%)

* based on n=1805



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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%)

* Denominator = those who received furosemide

[†] Judged clinically



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Table 5. Predictors of admission to hospital (vs. discharge from ED)

Univariate predictors			
Variable	Units	Odds ratio (95%CI)	p-value
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)	<.001
	Given, improved	0.46 (0.34, 0.63)	<.001
PER (%)	per 1-SD	3.90 (2.55, 6.32)	<.001
EHMRG7 score	per 1-SD	2.21 (1.94, 2.53)	<.001
Multivariable predictors			
Variable	Units	Odds ratio (95%CI)	p-value
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)	<.001
	Given, improved	0.40 (0.28, 0.55)	<.001
PER (%)	per 1-SD	2.47 (1.71, 3.83)	<.001
EHMRG7 score	per 1-SD	2.08 (1.81, 2.40)	<.001



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Figure Legends

Figure 1. Patient flow diagram

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

Figure 3. Survival curve for time to 30-day death by EHMRG30-ST risk category (1, 2, 3, 4, 5a, and 5b)



Figure 4. Physician estimated risk vs. EHMRG7 risk score deciles

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2512 Potential patients screened



Excluded:
No IKN match in NACRS (n = 68)
Repeat visits (n = 353)

2091 Unique study patients



Missing:
Variable for EHMRG7 (n=99)
PER7 (n=9)

1983 in 7-day cohort



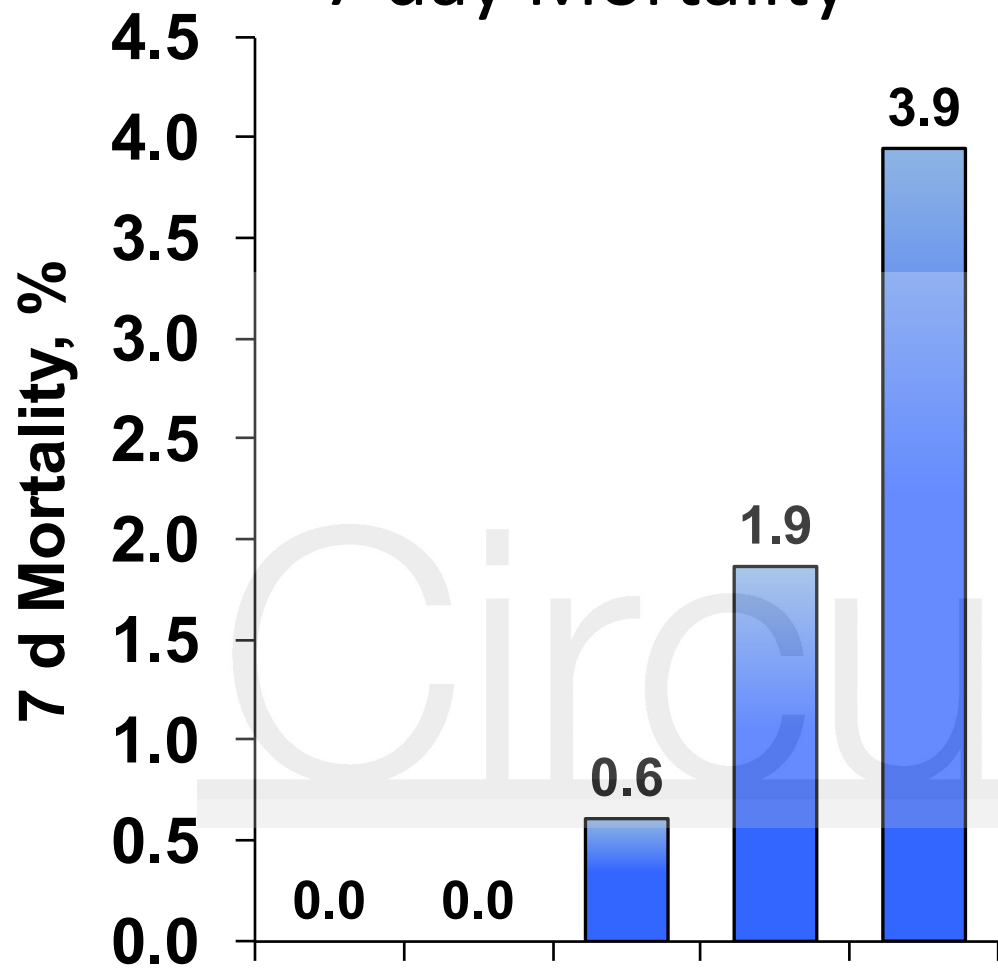
12-lead EKG:
Not done within 24 hrs of emergency presentation (n = 20)
EKG not performed during hospital stay (n = 47)
Missing/uninterpretable data for EHMRG30-ST calculation (n = 111)

1805 in 30-day cohort

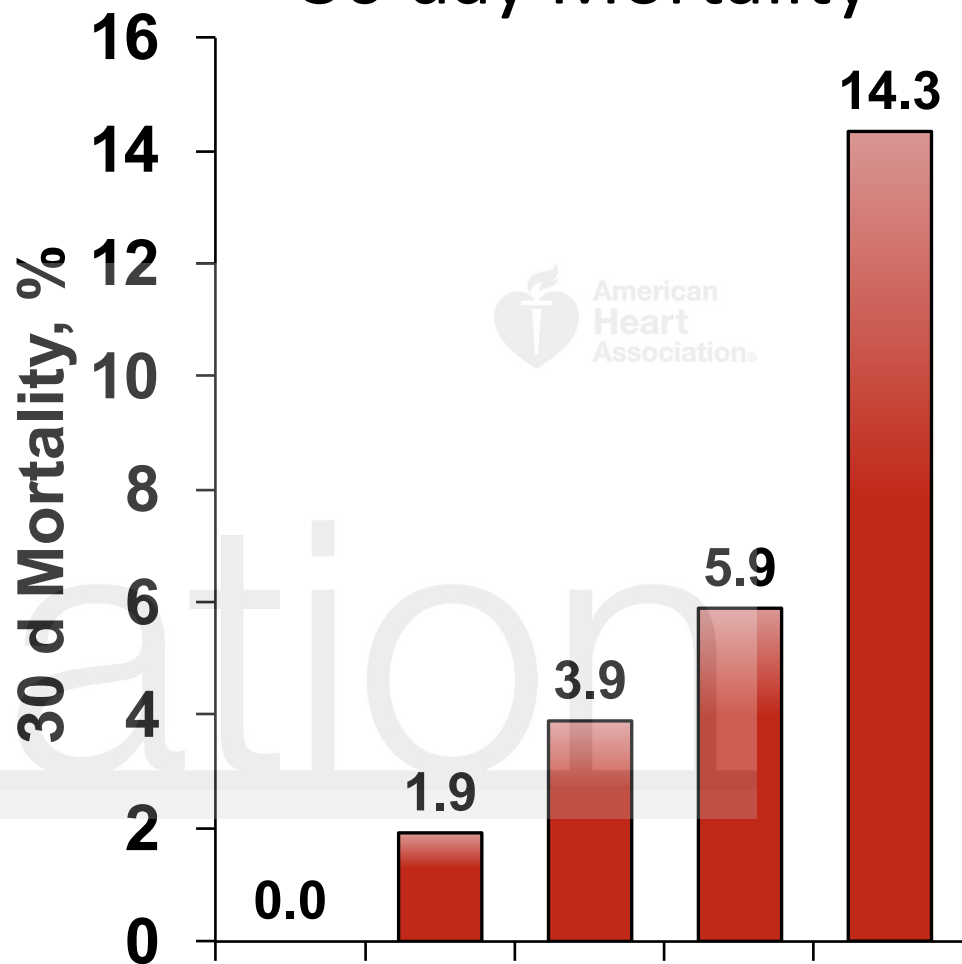


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7 day Mortality



30 day Mortality



Risk Category

1

2

3

4

5

High threshold

-49.05

-15.91

17.97

56.55

--

Low threshold

--

-49.04

-15.90

17.98

56.56

1

2

3

4

5

1.86%

3.55%

6.47%

12.19%

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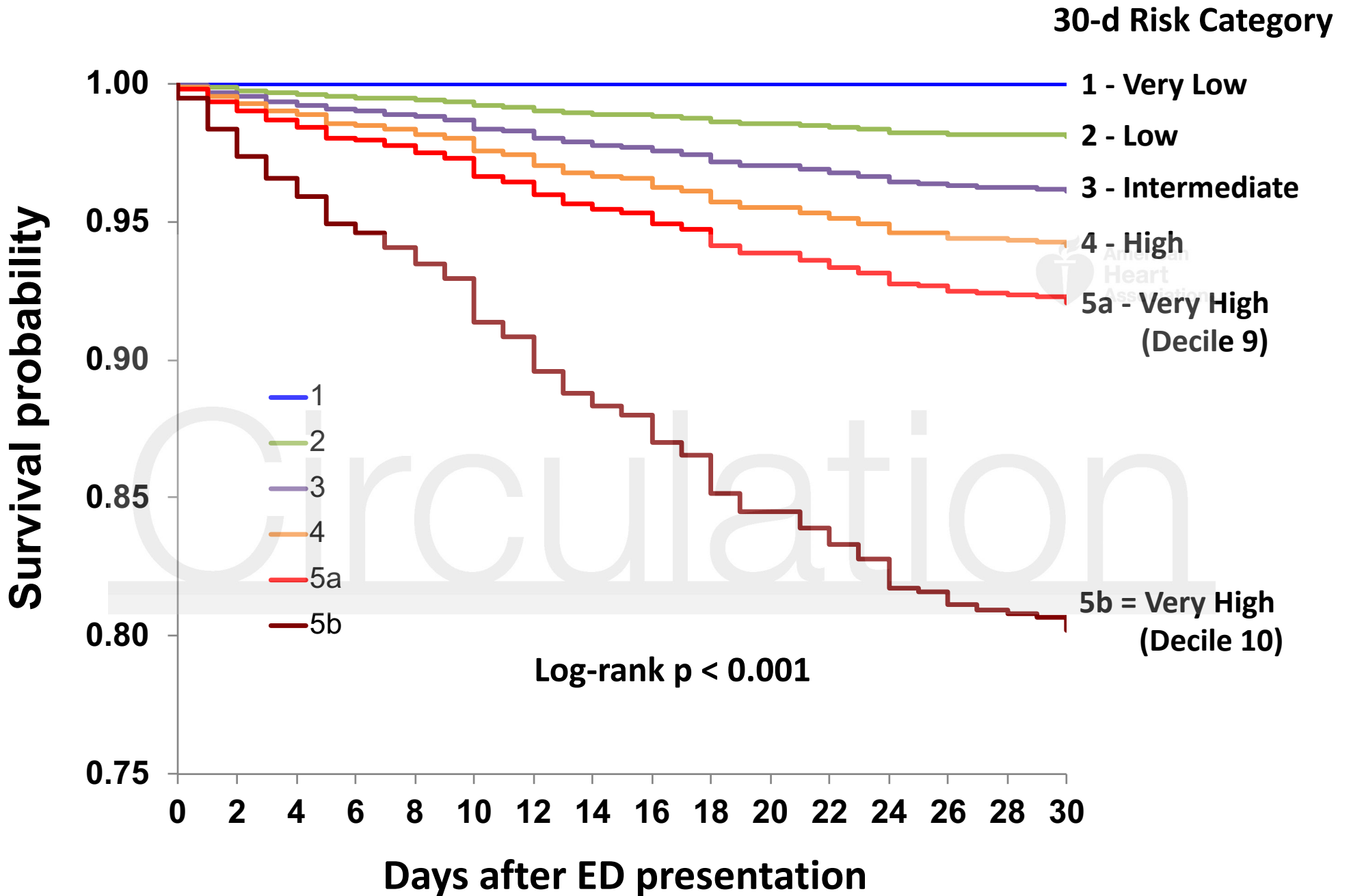
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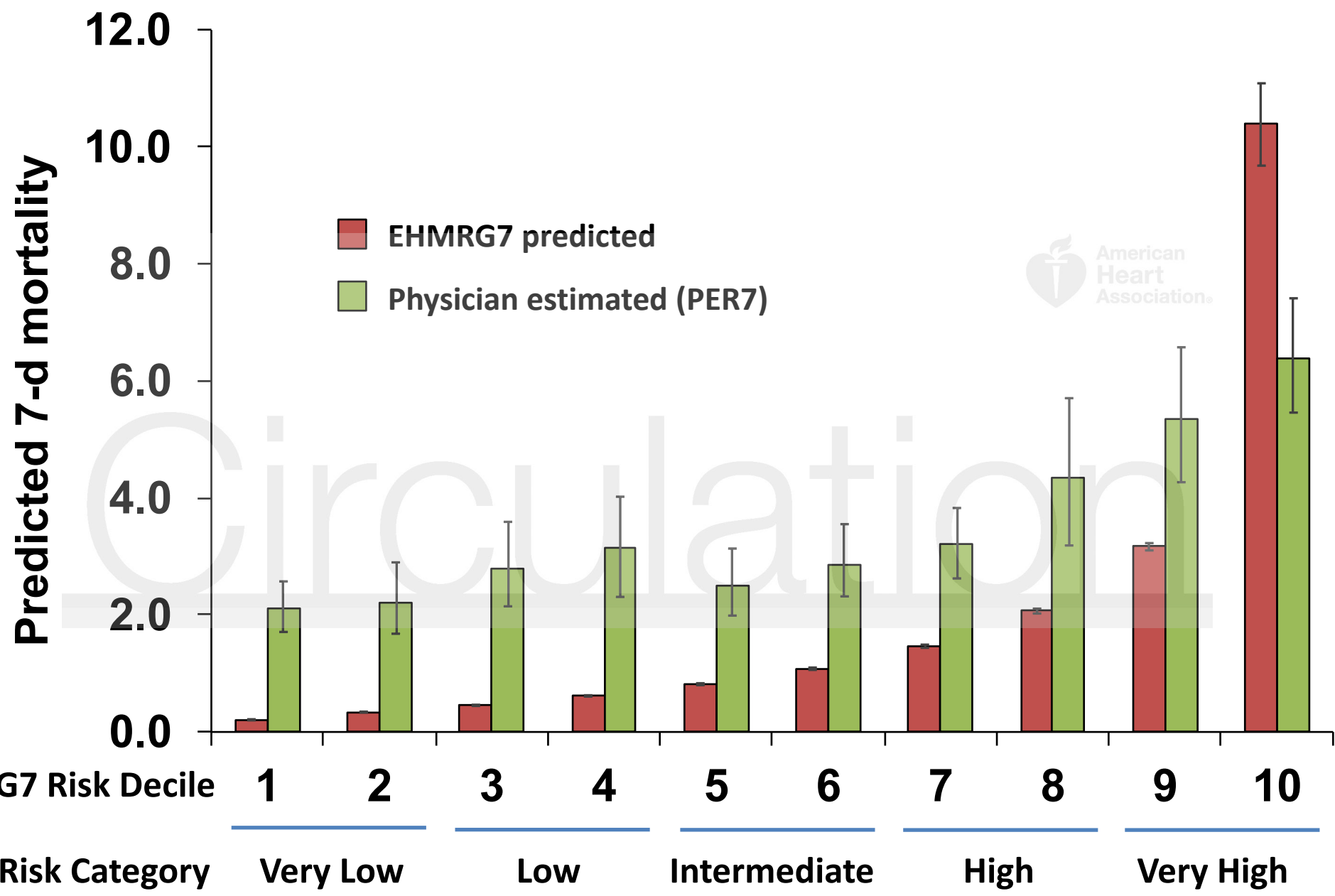
1.87%

3.56%

6.48%

12.20%





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