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2       **Predicting 30-day Mortality for Patients with Acute Heart Failure Who Are in the**  
3                   **Emergency Department: A Cohort Study**

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19

20      Word count for abstract: 272

21      Word count for text: 3289

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29

30 **Abstract**

31 **Background:** Physicians in the emergency department (ED) need additional tools to stratify patients with acute  
32 heart failure (AHF) according to risk.

33 **Objective:** To predict future mortality from data readily available on ED admission.

34 **Design:** Prospective cohort study.

35 **Setting:** 34 Spanish EDs

36 **Participants:** 4867 consecutive ED patients admitted during 2009-2011 for the derivation cohort and 3229  
37 patients admitted in 2014 for the validation cohort.

38 **Measurements:** Candidate risk factors and 30-day mortality.

39 **Results:** We found 13 independent risk factors in the derivation cohort and combined them to form an overall  
40 score, which we call the MEESSI-AHF (Multiple Estimation of risk based on the Emergency department Spanish  
41 Score In patients with AHF) score. This score predicted 30-day mortality with excellent discrimination (c-  
42 statistic=0.836) and calibration (Hosmer-Lemeshow P = 0.99), and it provided a steep gradient in 30-day  
43 mortality across risk groups (<2% mortality for patients in the 2 lowest risk quintiles and 45% mortality in the  
44 highest risk decile). We confirmed these characteristics in the validation cohort (for example, c-  
45 statistic=0.828). Multiple sensitivity analyses failed to find important amounts of confounding or bias.

46 **Limitations:** The study was confined to a single country. Participating EDs were not selected randomly. Many  
47 patients had missing data. Measuring some risk factors was subjective.

48 **Conclusion:** This tool has excellent discrimination and calibration, and it was validated in patients different  
49 from the patients used to develop it. We think physicians can consider using this tool to inform clinical  
50 decisions as we conduct further studies to determine whether the tool enhances physician decisions and  
51 improves patient outcomes.

52      **Primary Funding Source:** Spanish Ministry of Health, Catalonia Govern, Fundació Marató-TV3.

53      **Keywords:** acute heart failure, risk score, outcomes.

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57     **Introduction**

58     Annual hospital admissions due to acute heart failure (AHF) in Europe and the USA exceed 1 million in each  
59     region and account for most of the costs of heart failure-related care (1, 2). The emergency department (ED)  
60     has a central position in the management of AHF, since about 90% of patients with this condition attend an ED  
61     to improve their symptoms (3, 4). Once initial treatments have been administered in the ED and their effects  
62     checked, decisions are made regarding subsequent patient management: specifically does the patient need to  
63     be hospitalized or can they be discharged home with proper treatment and follow-up. As a result of a mainly  
64     subjective, empirically-driven assessment, a highly variable proportion of AHF patients is currently being  
65     directly discharged to home from ED: 16.3% in US (5), 23.9% in Spain (4), and 36.2% in Canada (6).

66     Although decision-making in the ED is of critical importance, emergency physicians currently are not stratifying  
67     patient by risk during this process. Some biomarkers, for example, heart-specific markers like natriuretic  
68     peptides and troponin or non-specific markers like glucose or creatinine, are associated with prognosis, but  
69     cannot by themselves predict outcomes with sufficient reliability to aid decision-making (7,8). Alternatively,  
70     several AHF risk scores have been developed (9,10), but these scores have been based on hospitalized patients  
71     thus ignoring the many AHF patients, more than a third in certain countries (6), who are entirely managed in  
72     the ED and discharged home. To our knowledge, only 3 risk scores have been developed specifically for use in  
73     the ED: 2 in Canada (the Ottawa Heart Failure Risk Scale, OHFRS, and the Emergency Heart Failure Mortality  
74     Risk Grade, EHMRG) (11,12) and 1 in United States (The Improving Heart Failure Risk Stratification in the  
75     Emergency Department, STRATIFY, scale) (13). However, some were not externally validated (OHFRS,  
76     STRATIFY), some were constructed from administrative data (OHFRS, EHMRG), some excluded a substantial  
77     portion of patients (EHMRG: palliative patients excluded; OHFRS: non-consecutive sample with multiple  
78     exclusion criteria), and some were derived from databases of limited size (OHFRS: 557 patients; STRATIFY:  
79     1033 patients). Therefore, we believe there is a need for additional tools to help physicians in the ED stratify  
80     patients with acute heart failure (AHF) according to risk.

81     **Methods**

82     The Acute Heart Failure in Emergency Departments (EAHFE) Registry

83 The EAHFE Registry collects detailed information on consecutive patients attending 34 Spanish EDs with a final  
84 diagnosis of AHF (14,15). Hospitals participate in the EAHFE Registry voluntarily, and they include university  
85 and community hospitals, EDs with high, medium or low volume of attendances (>300, 200-300, or <200/day,  
86 respectively), and hospitals from all areas of the country. Attending emergency physicians use Framingham's  
87 clinical diagnostic criteria (16) to identify patients for the registry. Thereafter, the diagnosis is double-checked  
88 by the principal investigator of each centre, who makes the final adjudication of AHF diagnosis based on the  
89 review of medical charts and all complementary tests done during the ED stay and any hospitalization. The  
90 diagnosis was confirmed by natriuretic peptide determinations or echocardiography (17) **in** the 92% of  
91 patients **included in the EAHFE Registry. The only exclusion criteria to be included in the EAHFE Registry is a**  
92 diagnosis of ST-elevation myocardial infarction, which occurred in approximately 3% of patients.

93 For every patient, data on demographics, clinical history, presentation and treatments were routinely collected  
94 on specific case record forms. Interventions, treatments and patient placements (hospital admission or  
95 discharge) were entirely based on the decision-making of the attending emergency physician. Subsequent  
96 follow-up, through telephone contact and consultation of medical records, was performed between day 31  
97 and 90. The EAHFE Registry complies with the Declaration of Helsinki and was approved by the Ethical  
98 Committees of all participating centres, and all patients gave informed consent. Around 2% of patients fulfilling  
99 inclusion and exclusion criteria refused to participate.

100 Study design

101 During the design of the EAHFE Registry, we planned to develop a model that could stratify patients according  
102 to their risk of experiencing adverse outcomes. We wanted this model to be used as soon as possible after  
103 arrival in the ED by the first emergency physician who saw the patient using variables routinely available in  
104 most EDs. We named this model MESSI-AHF (Multiple Estimation of risk based on the Emergency department  
105 Spanish Score In patients with AHF).

106 When developing the model, we selected registry patients from May 2009 **and November-December 2011** for  
107 the derivation cohort and patients from January-February 2014 for the validation cohort (**Figure S1**). We used  
108 patients in the derivation cohort to generate a 30-day mortality risk model and we used patients from the  
109 validation cohort to measure how stable the model was.

110 Data analysis

111 We first identified over 88 candidate predictor variables (Supplemental Table S1) that described baseline  
112 demographics, medical history and status at admission and could potentially have prognostic implications. To  
113 develop the risk score, we used logistic regression (without interaction terms) with checks for non-linearity  
114 and forward stepwise variable selection with an entry criterion of  $p < 0.010$ . We used multiple imputation with  
115 chained equations (18) to produce 50 imputed data sets for estimating missing values. Once we identified a  
116 predictor, we then identified a cut-off value based on our clinical information about the predictor's value (e.g.,  
117 serum potassium) or about the linear trend (e.g., serum creatinine and systolic blood pressure). In the final  
118 model, we formed each continuous variable into ordered categories to facilitate their use in practice. We  
119 measured the model's discrimination with the c-statistic, and we measured the model's calibration by  
120 comparing observed- versus model-derived mortality risk with the Hosmer-Lemeshow statistic. We conducted  
121 sensitivity analyses by type of hospital (university vs community), by daily ED census (low-medium vs high  
122 volume), and for alternative models that did not include values for Barthel index, NT-proBNP, or troponin (in  
123 any combination) **because they can be those more frequently be lacking in certain ED or in certain**  
124 **circumstances.** We compared our model with the EHMRG model (12) in a merged data set of both derivation  
125 and validation cohorts by comparing the areas under the ROC curves for 30-day mortality with the DeLong  
126 test. We used STATA software, version 13.1 (Stata Corp, College Station, TX, USA) for all analyses.

127 Role of the funding source

128 This study was partially supported by competitive grants from the Institute de Salud Carlos III supported with  
129 funds from Spanish Ministry of Health, (PI10/01918, PI11/01021, PI15/01019 and PI15/00773), Fundació La  
130 Marató de TV3 (20152510), and Catalonia Govern (GRC 2009/1385 and 2014/0313). The funding source had no  
131 role in the design, conduct, and analysis of this study or in the decision to submit the manuscript for  
132 publication.

133

134 **Results**

135 The study derivation cohort comprises 4897 consecutive patients admitted to an ED with AHF during May 2009  
136 and Nov-Dec 2011 (**Figure S1**). Thirty patients were excluded from analysis due to lack of follow-up, while  
137 those with censored data (48 patients with <30 days of follow-up) were included. Patients had a mean age  
138 79.7 years, 57.1% were females, comorbidities were very frequent (83.4% had hypertension, 42.2% diabetes  
139 mellitus, 39.4% dyslipidemia, 29.9% ischemic cardiomyopathy), 89.5% had New York Heart Association (NYHA)  
140 class III-IV and 56.5% had some dependency (Barthel index <100 points) at ED arrival, and 41.5% patients had  
141 LVEF below 50%, with 52.4% of them receiving beta-blockers, 62.9% angiotensin-converter enzyme inhibitor or  
142 angiotensin-II receptor blocker, and 29.1% mineralocorticoid-receptor antagonist. Patients subsequently  
143 hospitalized (75.6%) had a median length of stay of 7 days. The rest of the characteristics of the study  
144 population are presented in Table 1.

145 Within 30 days of admission, 500 patients (10.3%) had died. From all of the candidate predictors, a logistic  
146 regression model was used with forward stepwise variable selection to identify the final 13 highly significant  
147 independent death predictors included into the MESSI-AHF risk score. These variables are listed in Table 1  
148 ordered by their statistical strength of prediction (i.e. Barthel index at admission is the most highly significant)  
149 and each odds ratio is adjusted for all the other variables. Figure S2 displays the independent impact of each  
150 predictor on mortality risk based on the model in Table 1, and Table S2 shows comparison in key predictor  
151 variables in patient with and without missing values.

152 For any patient, one adds together their relevant risk coefficients plus the intercept coefficient in Table 1 to  
153 determine the multivariable risk score, which is the patient's predicted log (odds) of dying within 30 days. The  
154 distribution of this risk score for all 4867 patients is shown in Figure 1. Also, the curve in Figure 1 relates a  
155 patient's risk score to the probability of dying within 30-day of admission, which ranges from 0.005 to 0.898  
156 with a median of 0.051. To facilitate the calculation of any patient's risk of dying within 30 days, we have set  
157 up a website <http://bernalte.cat/calculadora/>: for a specific patient one enters the relevant 13 items and  
158 immediately their predicted % risk of dying within 30 days is provided.

159 Figure 2 shows the cumulative mortality over 30 days for patients classified into 6 risk groups: the bottom 4  
160 quintiles and the top two deciles of the risk score's distribution in this derivation cohort. Good discrimination  
161 of the model was achieved, with c-statistic 0.836 (95% CI 0.818 -0.853). There was a steep gradient in 30-day

162 mortality across risk groups: with 45% mortality for the top decile of risk and around 0.7% for the bottom  
163 quintile of risk. Similar discrimination capacity was observed in either university or community hospitals, as  
164 well as in low-medium or high-volume ED (Table 2). In this derivation cohort Figure 3(a) depicts the model  
165 goodness-of-fit, comparing observed and model-predicted 30-day mortality risk across the 6 risk groups. A  
166 useful nomenclature is as follows: low risk (first and second quintiles), intermediate risk (third and fourth  
167 quintiles), high risk (next decile) and very high risk (top decile). Sensitivity and specificity of the every risk  
168 threshold for each category plotted on a ROC curve is presented in Figure S3. Reduced models lacking Barthel  
169 index, troponin or NT-proBNP (in any combination) also showed good discriminatory capacity, ranging from  
170 0.829 and 0.784 (Table S3). **Accordingly, they have been incorporated in the website calculator.**

171 Finally, we used 3229 patients recruited during Jan-Feb 2014 to validate our risk score on an external  
172 population of patients, 299 (9.26%) dying within 30 days of ED admission. Five patients of the validation cohort  
173 were excluded from analysis due to lack of follow-up, while six patients with less than 30 days follow-up were  
174 included. Comparisons for key predictor variables between derivation and validation cohorts are shown in  
175 Table S4. Distribution of the MESSI-AHF scores is presented in Figure S4. In this validation cohort, Figure 3(b)  
176 compares the observed and model-predicted mortality in six risk groups (from lowest quintile to top decile).  
177 The model fit and extent of risk discrimination is very similar to what was found in the derivation cohort. The c-  
178 statistic in the validation cohort is 0.828 (95% CI 0.802-0.853), very similar to that achieved in model  
179 development. To check goodness of model fit, the Hosmer-Lemeshow test for the derivation cohort was  
180 P=0.99, and for the validation cohort P= 0.122. When compared with the previously developed risk score  
181 EHMRG intended for 7-day mortality prediction (12) **using a same sample of patients of the present study**, the  
182 MESSI-AHF had superior discrimination overall (c-statistic, 0.830 vs. 0.750; P<0.001; Figure S5).

183

#### 184 **Discussion**

185 The findings we present in this study are based on a large prospective population-based cohort of consecutive  
186 AHF patients admitted to 34 hospital EDs across Spain. Patients with many types of AHF were included, except  
187 for those developing AHF during an ST-elevation myocardial infarction, and all data were recorded shortly after  
188 arrival in the ED. The 13 predictors of 30-day mortality we identified should all be promptly available in routine

189 clinical practice worldwide; and we have provided a web calculator (<http://bernalte.cat/calculadora/>) to  
190 make it easier for physicians to calculate the risk for a specific patient. Using such a calculator, emergency  
191 physicians will now be able to determine whether a patient is at high (or low) risk of dying within 30 days  
192 which, in turn, might allow for better patient management. Our score may be particularly useful in the 10% of  
193 patients at very high risk for 30-day mortality (around a 45%), as well as in the 40% of patients at low risk for  
194 30-day mortality (<2%). Identification of both groups has important management implications. For a patient  
195 with very high risk, special attention has to be focused on ensuring that the patient and relatives are aware of  
196 the severity and, assuming they are appropriate, on prompt aggressive treatments with an emphasis on early  
197 admission to an intensive care unit. For a patient with low risk, attention should be focused on treatment that  
198 will lead to early discharge from the ED to home, which is consistent with a recent consensus about patients  
199 with <2% all-cause mortality as long as they are observed long enough in the ED (19).

200 In the US, the overall incidence rate of heart failure hospitalizations has declined 29.5% between 1998 and  
201 2007 (20). We suggest that this decline could be due to better ambulatory care that avoids patient  
202 decompensation and allows proper treatment of less severe AHF episodes without hospital admission. In this  
203 sense, there is an increasing perception that more AHF patients at low risk of adverse outcomes should avoid  
204 hospitalization (4, 21), and recent consensus opinions by clinical experts advocate that approach (19,22).  
205 Specifically, one group recommends rates of 20% to 40% direct ED discharge for patients being diagnosed with  
206 AHF (depending whether the ED lacks or possesses, respectively, a specific observation area) (19). These  
207 figures match well to patients in our low risk category (40%). Avoiding hospital admission is not only a matter  
208 of health care system efficiency improvement that could save substantial costs. Hospitalization itself could  
209 imply some potential hazards: nosocomial infection, increased errors in patient with polypharmacy, acute  
210 reactive psychosis and deteriorating functional status are quite common amongst the elderly being  
211 hospitalized. AHF patients are typically of advanced age, with a median age around 80 years in most series  
212 (4,12) (median 80 years in our cohort). However, we are not aware of any formal tools that are currently being  
213 used to aid ED risk stratification for AHF patients. Thus, some authors have argued that direct discharge of  
214 patients without objectively-based risk stratification is putting some patients at an unacceptably high risk of  
215 adverse events (6,23). This situation contrasts with improvements achieved in other high prevalent ED  
216 conditions, such as community-acquired pneumonia and acute coronary syndromes, where risk scores have

217 been developed (24,25) and are being widely applied to discharge less severe patients who previously would  
218 have been admitted to hospital. We believe that the **MEESSI-AHF risk score** can provide similar help in the  
219 management of patients with AHF, especially for elderly patients who are more challenging to evaluate (15).

220 All 13 variables we found to be predictive have been repeatedly reported as influencing the prognosis of  
221 patients with AHF (1,11-13,15,26-28). However, in our study 4 of these variables had more than 25% missing  
222 values. We adjusted for these missing values using a multiple imputation technique. Moreover, in order to  
223 match our score to what happens when real patients are in EDs, our website calculator provides a risk score  
224 even when values for Barthel index, troponin levels, and NT-ProBNP are not available and we have shown that  
225 these risk scores perform as well as the regular risk scores (Table S4).

226 Our model compares favourably with other risk models. For example, our model had a c-statistic of 0.836 in  
227 the derivation cohort and 0.828 in the validation cohort, which were higher than the comparable value when  
228 we calculated the EHMRG score in 2137 patients who had all the data necessary to calculate an EHMRG score.  
229 The EHMRG model focused on a shorter-term perspective (7-day mortality) (12). We feel a longer perspective  
230 (30-day mortality) provides a better framework to create a model to aid emergency physicians. Moreover,  
231 EHMRG score excluded palliative patients (who have a higher risk of adverse events), and that could limit its  
232 generalizability. **Certainly**, patients only receiving palliative care are not uncommon: e.g. 10.2% of our patient  
233 had a Barthel index of 0 to 20 points (indicating complete dependence) and an additional 32.8% had a Barthel  
234 index between 21 and 60 points (indicating severe dependence) and, although not directly recorded in our  
235 study, for many of them palliative care could apply. However, we have previously demonstrated that the  
236 exclusion patients for whom palliative care could potentially apply did not significantly change the  
237 discriminatory capacity of the model (only decreased from 0.741 to 0.729) (29). Our findings, in line with  
238 previous works in this field (30), affirm that the Barthel index is a key outcome predictor, adding value to  
239 previously developed risk scores. Thus, it is important to recognize that patient frailty and dependence are key  
240 aspects that should be considered in every disease impacting on an elderly population, as it comes about AHF  
241 patients. Finally, our model has been developed using data prospectively recorded using a standardised pro  
242 forma at the time of admission to the ED, instead of using retrospective extraction from administrative  
243 reports, as was done for the EHMRG model. The latter strategy could limit reliability and completeness of data.  
244 All the above-mentioned limitations, even with more extensive patient exclusion criteria and smaller sample,

245 also apply for the OHFRS model, which obtained a c-statistic of 0.77 (11). On the other hand, although the  
246 STRATIFY score (13) was developed using data recorded prospectively, it was derived with a limited number of  
247 cases, no external validation was done, and got moderate discriminatory capacity (c-statistic: 0.68) (13).  
248 Therefore, for the first time, we offer a risk-model with robust data from a large-scale population-based study  
249 to quickly assess patient prognosis.

250 Our study has important limitations. Some important predictors had a high number of missing values, which  
251 we have addressed with multiple imputation techniques and sensitivity analyses. There is a possibility of a  
252 “false positive” predictor entering the risk model after testing 88 candidate predictor variables, although use  
253 of  $p < 0.01$  as entry criterion has minimised this risk. Some variables, e.g. Barthel index, NYHA class, association  
254 with ACS, or low cardiac output, are partially based on subjective interpretation, but we tried to reduce this  
255 problem by providing all research centers with a dictionary for all variables and holding meetings with all  
256 researchers just before each recruitment phase in an attempt to minimize inconsistency. Additionally, the  
257 precision of our model might change in the future, especially if new treatments for heart failure were able to  
258 modify mortality, such as angiotensin II receptor blocker neprilysin inhibitors, which were not available when  
259 this study was performed. Finally, as for any study in a single country, caution should be taken in extrapolating  
260 findings internationally. Moreover, EDs were not randomly selected but were participants of the EAHFE  
261 Registry, with special interest in AHF, so it is possible results could differ when applied to other EDs. Thus, we  
262 encourage others to explore validation of our risk model in other countries/regions. Nonetheless, we believe  
263 that our model has the potential for being used widely.

264 In conclusion, our study demonstrates that physicians can use 13 readily available items to estimate individual  
265 risk of 30-day mortality for patients with AHF who are admitted to the ED. With strong risk discrimination,  
266 good model fit and external validation, this tool is now ready for clinical use. Further study is needed to  
267 elucidate the real potential of the MESSI-AHF risk score for enhancing physician behaviour and improving  
268 patient outcomes. We have provided user-friendly access to a way of calculating scores for specific patients  
269 (<http://bernalte.cat/calculadora/>). This tool has excellent discrimination and calibration, and it was validated  
270 in patients different from the patients used to develop it. We think physicians can consider using this tool to  
271 inform clinical decisions as we conduct further studies to determine whether the tool enhances physician

272 decisions and improves patient outcomes. We believe that this tool will be especially useful for identifying  
273 individuals at lower risk for whom further hospitalization may be not required.

274     **Acknowledgements:** All participants in the ICA-SEMES Research Group.

275     **Conflict of interests:** The authors state that they have no conflict of interests with the present work. The ICA  
276     SEMES Research Group has received unrestricted support from Otsuka, Orion Pharma and Novartis, and the  
277     present work was designed, performed, analysed and written exclusively by the authors independently of  
278     these pharmaceutical laboratories.

279

280    **References**

- 281    1. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. ADHERE Scientific  
282    Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure  
283    in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute  
284    Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; **149**:209–16. PMID: 15846257.
- 285    2. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, et al. Study Group on Diagnosis of  
286    the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey  
287    programme—a survey on the quality of care among patients with heart failure in Europe. Part 1: patient  
288    characteristics and diagnosis. *Eur Heart J* 2003; **24**:442–63. PMID: 12633546.
- 289    3. Weintraub NL, Collins SP, Pang PS, Levy PD, Anderson AS, Arslanian-Engoren C, et al. American Heart  
290    Association Council on Clinical Cardiology and Council on Cardiopulmonary, Critical Care, Perioperative and  
291    Resuscitation. L, American Heart Association Council on Clinical Cardiology and Council on Cardiopulmonary,  
292    Critical Care, Perioperative and Resuscitation. Acute heart failure syndromes: emergency department  
293    presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the  
294    American Heart Association. *Circulation* 2010; **122**:1975–96. PMID: 20937981.
- 295    4. Llorens P, Escoda R, Miró O, Herrero-Puente P, Martín-Sánchez FJ, Jacob J, et al. Characteristics and clinical  
296    course of patients with acute heart failure and the therapeutic measures applied in Spanish emergency  
297    departments: based on the EAHFE registry (Epidemiology of Acute Heart Failure in Emergency Departments).  
298    *Emergencias* 2015; **27**:11–22.
- 299    5. Storrow AB, Jenkins CA, Self WH, Alexander PT, Barrett TW, Han JH, et al. The burden of acute heart failure  
300    on U.S. Emergency departments. *JACC Heart Fail* 2014; **2**:269–77. PMID: 24952694.
- 301    6. Brar S, McAlister FA, Youngson E, Rowe BH. Do outcomes for patients with heart failure vary by emergency  
302    department volume? *Circ Heart Fail* 2013; **6**:1147–54. PMID: 24014827.

- 303 7. Mebazaa A, Gayat E, Lassus J, Meas T, Mueller C, Maggioni A, et al. Association between elevated blood  
304 glucose and outcome in acute heart failure: results from an international observational cohort. *J Am Coll*  
305 *Cardiol* 2013; **61**:820–9. PMID: 23333145.
- 306 8. Maisel A, Mueller C, Nowak R, Peacock WF, Landsberg JW, Ponikowski P, et al. Mid-region pro-hormone  
307 markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart  
308 Failure) trial. *J Am Coll Cardiol* 2010; **55**:2062–76. PMID: 20447528.
- 309 9. Passantino A, Moitillo F, Iacoviello M, Scrutinio D. Predicting mortality in patients with acute heart failure:  
310 role of risk scores. *World J Cardiol* 2015; **7**:902–11. PMID: 26730296.
- 311 10. Lee DS, Ezekowitz JA. Risk stratification in acute heart failure. *Can J Cardiol* 2014; **30**:312–9. PMID:  
312 24565256.
- 313 11. Stiell IG, Clement CM, Brison RJ, Rowe BH, Borgundvaag B, Aaron SD, et al. A risk scoring system to identify  
314 emergency department patients with heart failure at high risk for serious adverse events. *Acad Emerg Med*  
315 2013; **20**:17–26. PMID: 23570474.
- 316 12. Lee DS, Stitt A, Austin PC, Stukel TA, Schull MJ, Chong A, et al. Prediction of heart failure mortality in  
317 emergent care: a cohort study. *Ann Intern Med* 2012; **156**:767–75. PMID: 22665814.
- 318 13. Collins SP, Jenkins CA, Harrell FE Jr, Liu D2, Miller KF, Lindsell CJ, et al. Identification of Emergency  
319 Department Patients with Acute Heart Failure at Low Risk for 30-Day Adverse Events: The STRATIFY Decision  
320 Tool. *JACC Heart Fail* 2015; **3**:737–47. PMID: 26449993.
- 321 14. Miró Ò, Gil V, Müller C, Mebazaa A, Bueno H, Martín-Sánchez FJ, et al. How does a clinical trial fit into the  
322 real world? The RELAX-AHF study population into the EAHFE registry. *Clin Res Cardiol* 2015; **104**:850–60. PMID:  
323 25903109.
- 324 15. Herrero-Puente P, Martín-Sánchez FJ, Fernández-Fernández M, Jacob J, Llorens P, Miró Ò, et al. Differential  
325 clinical characteristics and outcome predictors of acute heart failure in elderly patients. *Int J Cardiol* 2012;  
326 **155**:81–6. PMID: 21397963.

- 327 16. Ho KKL, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart  
328 failure in Framingham heart study subjects. *Circulation* 1993; **88:107-15**. PMID: 8319323.
- 329 17. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Committee for  
330 Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012:  
331 The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European  
332 Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur  
333 Heart J* 2012; **33:1787-847**. PMID: 22611136.
- 334 18. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for  
335 practice. *Stat Med* 2011; **30:377-99**. PMID: 21225900.
- 336 19. Miró O, Levy PD, Möckel M, Pang PS, Lambrinou E, Bueno H, et al. Disposition of emergency department  
337 patients diagnosed with acute heart failure: an International emergency medicine perspective. *Eur J Emerg  
338 Med.* 2017; **24:2-12**. PMID: 27254376.
- 339 20. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization  
340 and mortality rates for Medicare beneficiaries, 1998-2007. *JAMA* 2011; **306:1669-78**. PMID: 22009099.
- 341 21. Ezekowitz JA, Kaul P, Bakal JA, Quan H, McAlister FA. Trends in heart failure care: has the incident diagnosis  
342 of heart failure shifted from the hospital to the emergency department and outpatient clinics? *Eur J Heart Fail  
343* 2010; **13:142-7**. PMID: 20959343.
- 344 22. Miró O, Peacock FW, McMurray JJ, Bueno H, Christ M, Maisel AS, et al. Acute Heart Failure Study Group of  
345 the ESC Acute Cardiovascular Care Association. European Society of Cardiology - Acute Cardiovascular Care  
346 Association position paper on safe discharge of acute heart failure patients from the emergency department.  
347 *Eur Heart J Acute Cardiovasc Care* 2016 Feb 21; (Epub ahead of print). DOI: 10.1177/2048872616633853.  
348 PMID: 26900163.
- 349 23. Lee DS, Schull MJ, Alter DA, Austin PC, Laupacis A, Chong A, et al. Early deaths in patients with heart failure  
350 discharged from the emergency department: a population-based analysis. *Circ Heart Fail* 2010; **3:228-35**.  
351 PMID: 20107191.

- 352 24. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-  
353 risk patients with community-acquired pneumonia. *N Engl J Med* 1997; **336**:243-50. PMID: 8995086.
- 354 25. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and  
355 myocardial infarction in the six months after presentation with acute coronary syndrome: prospective  
356 multinational observational study (GRACE). *BMJ* 2006; **333**(7578):1091. PMID: 17032691.
- 357 26. Ouwerkerk W, Voors AA, Zwinderman AH. Factors influencing the predictive power of models for  
358 predicting mortality and/or heart failure hospitalization in patients with heart failure. *JACC Heart Fail* 2014;  
359 **2**:429-36. PMID: 25194294.
- 360 27. Le Corvoisier P, Bastuji-Garin S, Renaud B, Mahé I, Bergmann JF, Perchet H, et al. Functional status and co-  
361 morbidities are associated with in-hospital mortality among older patients with acute decompensated heart  
362 failure: a multicentre prospective cohort study. *Age Ageing* 2015; **44**:225-31. PMID: 25313242.
- 363 28. Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, et al. CardShock Study Investigators; GREAT  
364 network. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail* 2015;  
365 **17**:501-9. PMID: 25820680.
- 366 29. Gil V, Miró O, Schull MJ, Llorens P, Herrero P, Jacob J, et al. Emergency Heart Failure Mortality Risk Grade  
367 score performance for 7-day mortality prediction in patients with heart failure attended at the emergency  
368 department: validation in a Spanish cohort. *Eur J Emerg Med* 2016; Sep 10 (Epub ahead of print) DOI:  
369 10.1097/MEJ.0000000000000422. PMID: 27622896.
- 370 30. Martín-Sánchez FJ, Gil V, Llorens P, Herrero P, Jacob J, Fernández C, et al. Acute Heart Failure Working  
371 Group of the Spanish Society of Emergency Medicine Investigation Group. Barthel Index-Enhanced Feedback  
372 for Effective Cardiac Treatment (BI-EFFECT) Study: contribution of the Barthel Index to the Heart Failure Risk  
373 Scoring System model in elderly adults with acute heart failure in the emergency department. *J Am Geriatr Soc*  
374 2012; **60**:493-8. PMID: 22329408.