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RESEARCH ARTICLE

Incremental value of C-reactive protein to the MEESSI acute heart failure risk score

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Aims We hypothesized that the current gold standard for risk stratification of patients with acute heart failure (AHF), the Multiple Estimation of risk based on the Emergency department Spanish Score In patients with AHF (MEESSI-AHF) risk score, can be further improved by adding systemic inflammation as quantified by C-reactive protein (CRP).

Methods and results In a prospective multicentre diagnostic study (BASEL V), AHF was centrally adjudicated by two independent cardiologists. The MEESSI-AHF risk score was calculated using an established reduced and recalibrated model containing 12 independent risk factors. Model extension was performed by refitting and adding CRP in the logistic regression model with 30-day mortality as binary outcome. Discrimination, calibration and clinical usefulness were used to assess the performance of the extended Multiple Estimation of risk based on the Emergency department Spanish Score In patients (MEESSI) model. Validation was performed in an independent, retrospective and single-centre AHF cohort. Among 1208 AHF patients with complete data allowing calculation of the recalibrated MEESSI and the extended MEESSI models, the prognostic accuracy for 30-day mortality of the extended MEESSI model (c-statistic 0.83, 95% confidence interval [CI] 0.79–0.87) was significantly higher compared to the recalibrated model (c-statistic 0.79, 95% CI 0.75–0.83, $p = 0.013$). The extended model allowed to stratify a higher percentage of patients into the lowest risk group compared to the recalibrated model (33.1% vs. 20.3%). Demonstrating a calibration plot's slope of 1.00 (95% CI 0.81–1.19) and an intercept of 0.0 (95% CI −0.22 to 0.22), the extended MEESSI model achieved excellent and improved calibration. Results were confirmed in the independent validation cohort ($n = 575$).

Conclusions Quantifying inflammation using CRP concentration provided incremental value in AHF risk stratification using the established MEESSI model.

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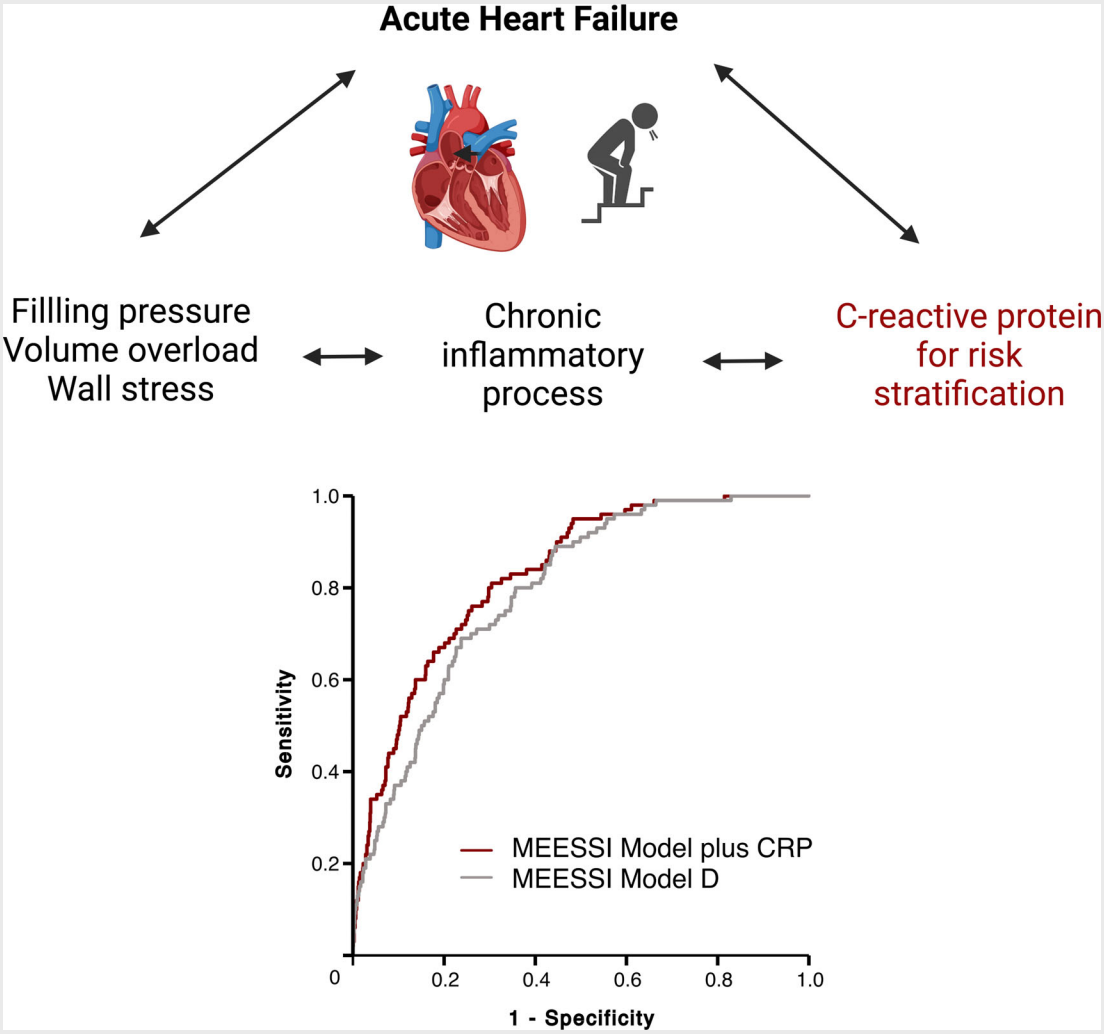
Graphical Abstract



Quantifying systemic inflammation using C-reactive protein (CRP) concentration provided incremental value in acute heart failure (AHF) risk stratification using the established Multiple Estimation of risk based on the Emergency department Spanish Score In patients (MEESSI) model.

Keywords Acute heart failure • C-reactive protein • Emergency department • Heart failure risk scores • Mortality • Risk stratification • Systemic inflammation

Introduction

Acute heart failure (AHF) is a complex and heterogeneous clinical syndrome associated with a concerning rise in incidence.[1] Equally, it is a growing social and economic burden in terms of inacceptable high rates of mortality and morbidity, as well as healthcare costs.[2] By 2030, costs for AHF hospitalizations are estimated to surpass $50 billion per year in the United States alone.[3] As these poor prospects can at least in part be attributed to a mismatch between AHF severity and the intensity of management both in-hospital and immediately after discharge, early, accurate and standardized risk prediction could contribute to an efficient and more cost-effective risk-adjusted management.[4–6]

The Multiple Estimation of risk based on the Emergency department Spanish Score In patients with AHF (MEESSI-AHF) risk score is a validated tool enabling early risk stratification of patients presenting with AHF to the emergency department (ED).[7,8] As it demonstrated high accuracy in the prediction of 30-day mortality in the derivation as well as in an external validation cohort, it may be considered the current gold standard for risk prediction in AHF.[7,8]

In addition to clinical variables and vital signs, the MEESSI-AHF risk score includes three widely used biomarkers quantifying pathophysiological processes central to the development and progression of AHF: natriuretic peptides corresponding to intracardiac pressures and myocardial stretch, cardiac troponin to cardiomyocyte injury, and creatinine to renal dysfunction.[6] As also systemic inflammation seems to have an important role in AHF, it is of note that this parameter as additional and easy to quantify pathway using for example, C-reactive protein (CRP) concentration has not been considered in the MEESSI-AHF score yet.[9–14]

We therefore aimed to test the hypothesis that the addition of CRP to the MEESSI-AHF risk score could further improve the model's operating characteristics in a large cohort study of unselected AHF patients.

Methods

Derivation cohort

Basics in Acute Shortness of Breath EvaLuation (BASEL V) (NCT01831115) was a prospective, multicentre, diagnostic study enrolling adults presenting to the ED with acute dyspnoea. Patients were recruited at two university hospitals (Basel and Zurich) and two non-university tertiary care centres (Aarau, Lucerne) in Switzerland.[8,15] Inclusion was irrespective of renal function, whereas patients with end-stage kidney disease on chronic haemodialysis were excluded. For this analysis, we only included patients with an adjudicated final diagnosis of AHF, a complete set of variables necessary for calculation of the MEESSI score and measurements of CRP at presentation. Details on variables of the MEESSI score, adjudication of the final diagnosis and follow-up can be found in online supplementary *Appendix S1*.

The study was carried out according to the principles of the Declaration of Helsinki and was approved by the local ethics committees. Written informed consent was obtained from all patients. The authors designed the study, and gathered and analysed the data according to the TRIPOD statement (online supplementary *Table S1*).

Independent validation cohort

Heart Failure-USB (University Hospital Basel) was a single-centre, retrospective cohort study including adult patients with the diagnosis of acute coronary syndrome and/or AHF based on ICD-10 coding and search in electronic records. Identified patients underwent detailed medical review by cardiologists to verify patients' diagnosis according to the European Society of Cardiology guidelines.[16] For this analysis, the diagnosis of AHF at presentation to the ED was mandatory and patients with acute coronary syndrome only were excluded (online supplementary Methods in *Appendix S1*).

Calculation and extension of the MEESSI-AHF risk score

In this analysis, a novel extended MEESSI model was compared to an established reduced and recalibrated MEESSI model (Model D with intercept adjustment) described in a previous study externally validating the original MEESSI-AHF risk score[8] and in the online supplementary *Appendix S1*.

C-reactive protein fulfilled the entry criterion of <0.010 in an univariable logistic regression analysis with 30-day mortality as binary outcome which was determined during devolvement of the MEESSI score (*p* for CRP <0.001; online supplementary *Table S2*).[7] Model extension was performed by adding CRP as novel marker as previously described.[17] In summary, the natural logarithm of CRP level at presentation was added in addition to the established reduced MEESSI model (Model D) in the logistic regression model with 30-day mortality as binary outcome and checks for multicollinearity between Model D and CRP (variance inflation factor <5).

According to the nomenclature in previous described updating methods,[17] the established alternative and recalibrated MEESSI model is referred to as recalibrated MEESSI model and the MEESSI model updated by CRP as extended MEESSI model in the following paragraphs.

Quantification of the added prognostic value of C-reactive protein

We summarized the added prognostic value of CRP as fraction of new information which is the proportion of explainable variation that is explained by CRP. This was calculated as one minus the ratio of variances of probability before (recalibrated model) and after (extended model) adding CRP.[18] In addition, a scatterplot of probability of 30-day mortality from the extended (*y*-axis) versus recalibrated model (*x*-axis) was generated and from this the median absolute change of predictions was calculated.

Measures of model performance

Established key measures in the validation of prediction models related to discrimination, calibration and clinical usefulness were used to assess the performance of the extended MEESSI model.[19] The model's calibration was quantified by Hosmer–Lemeshow test as well as graphical assessment by calibration plot. The calibration plot's slope and intercept were calculated using the R package 'rms'. Thereby logistic and flexible calibration curves and related statistics were generated using 'val.prob.ci.2', an established R function.[20] According to their predicted probability of 30-day mortality, patients were classified into the equivalent risk groups defined in the original MEESSI publication.[7] These risk groups were displayed in the calibration plot.

The model's discrimination was quantified by the c-statistic. Areas under the curves (AUC) for 30-day mortality were compared as proposed by DeLong *et al.*[21] Discrimination and calibration were assessed utilizing continuous risk prediction from the investigated model. Decision curve analysis was used to estimate clinical usefulness of the extended MEESSI model.[22,23] Details on this analysis are found in online supplementary *Appendix S1*.

Model extension of further reduced MEESSI models not including Barthel index score, cardiac troponin or N-terminal pro-B-type natriuretic peptide (NT-proBNP) level in different combinations was performed as described for Model D.

Further statistical methods as well as statistics applied in the independent validation cohort are displayed in online supplementary Methods in *Appendix S1*.

Sensitivity analysis

For sensitivity analysis, the operating characteristics of the extended MEESSI model were once more analysed after inclusion of patients

primarily excluded due to missing values. Therefore, we performed multiple imputation with chained equations to produce 20 imputed data sets for estimation of missing values. Besides all 12 variables used to calculate the MEESSI-AHF risk score, CRP as additional marker as well as 30-day mortality as binary and continuous variable were included in the imputation model. The extended MEESSI model, its c-statistics and Hosmer–Lemeshow *p*-value were calculated in every data set. Results were combined by using the Rubin rules.[24]

Results

Patient characteristics

Patients were enrolled at ED presentation between April 2006 and December 2013. Among 1578 patients with an adjudicated final diagnosis of AHF, 1572 patients (99.6%) had complete follow-up. Of these, 1208 (76.6%) were eligible for the primary analysis as they had complete data on the 12 candidate predictor variables needed for Model D and CRP measurements at presentation (online supplementary *Figure S1*).

Patients median age was 79 years, 42.1% were female, and median body mass index was 26.4 kg/m^2. Comorbidities included hypertension in 81.9%, coronary artery disease in 50.8%, previous history of AHF hospitalization and myocardial infarction in 50.1% and 30.1%, respectively (*Table 1*). Within 30 days of presentation, 100 patients (8.3%) died. Serum creatinine, potassium, cardiac troponin T, NT-proBNP and CRP concentrations were significantly higher in patients dying within 30 days of presentation versus survivors.

Quantification of the added prognostic value of C-reactive protein

C-reactive protein was not only statistically significant in an univariable logistic regression analysis but also in the multivariable logistic regression analysis with 30-day mortality as binary outcome and including all 12 independent predictor variables of the original MEESSI model (Model D) (online supplementary *Table S3*).

The fraction of new information resulting from adding CRP to the recalibrated MEESSI model was 17% (1−[variance of predicted probability of the recalibrated/variance of predicted probability of the extended MEESSI model]). The median absolute change of predictions (median probability of 30-day mortality from extended minus recalibrated MEESSI model) was −0.009. Therefore, the addition of CRP to the recalibrated MEESSI model resulted in an overall reduction of the predicted probability of 30-day mortality (online supplementary *Figure S2*).

Performance of the extended MEESSI model

The risk score distribution of the extended MEESSI model as well as the predicted probability of 30-day mortality are shown in online supplementary *Figure S3*. According to their predicted probability of death from the extended MEESSI model, patients were stratified into six risk groups/categories (bottom quintile to top decile) as pre-defined in the original MEESSI publication.[7] *Figure 1* shows the number of patients belonging to each group and their cumulative mortality rate over 30 days. There was a pronounced difference in 30-day mortality between risk groups: in the lowest risk group (bottom quintile) with a predicted probability of death from 0.5% to 2.1%, only two patients (0.5%) died within 30 days of presentation. In contrast, in the highest risk group (top decile) with a predicted probability of death from 25.8% to 89.9%, 34 patients (37.7%) died within 30 days of presentation. In addition, it was possible to stratify a higher percentage of patients into the lowest risk group when applying the extended MEESSI model compared to the recalibrated model (online supplementary *Figure S4*) (33.1% vs. 20.3%) while keeping the number of patients dying within 30 days of admission comparable (two patients vs. one patient). With regard to patients classified into the highest risk group by the extended MEESSI model, a higher percentage of patients died within 30 days of presentation when compared to patients classified into the equivalent risk group by the recalibrated model (37.7% vs. 31.0%).

The prognostic accuracy based on continuous risk prediction of the extended MEESSI model (c-statistic 0.83, 95% confidence interval [CI] 0.79–0.87) was significantly higher compared to the recalibrated MEESSI model (c-statistic 0.79, 95% CI 0.75–0.83; $p = 0.013$) (*Figure 2*). Further MEESSI models also extended by CRP and not including Barthel index score, cardiac troponin or NT-proBNP concentrations in different combinations, showed a similar discrimination (c-statistic 0.826–0.828), which was again significantly higher when compared to the pertaining recalibrated MEESSI model (online supplementary *Table S4*).

The calibration plot showed a high degree of agreement between the predicted probability of death according to the extended MEESSI model and the observed proportions (*Figure 3* and *Graphical Abstract*). This was indicated by the calibration curve mimicking the dotted line of optimal calibration. Regarding the overall goodness-of-fit, the calibration plot's slope was 1.00 (95% CI 0.81–1.19) and the intercept 0.0 (95% CI −0.22 to 0.22) whereby excellent calibration was achieved. Compared to the recalibrated MEESSI model (online supplementary *Figure S5*) having a slope of 0.98 (95% CI 0.78–1.18) and an intercept of −0.04 (95% CI −0.26 to 0.18) calibration was further improved.

The Hosmer–Lemeshow test for the extended MEESSI model comparing the actual risk prediction from the whole model to the observed outcome frequency, yielded a *p*-value of 0.84. Therefore, no significant lack of agreement between the predicted risk by the extended MEESSI model and observed outcome was observed.

Figure 4 shows a decision curve analysis calculating the clinical 'net benefit' for the extended and recalibrated MEESSI modelcompared to default strategies which are intervention for all or for none. The MEESSI model extended by CRP (net benefit 0.033) predicted 12 more true positives per 1000 patients, compared to the recalibrated MEESSI model (net benefit 0.021) at a threshold probability of 0.1. Furthermore, the extended MEESSI model kept

Table 1 Baseline characteristics in patients with an adjudicated final diagnosis of acute heart failure grouped by 30-day mortality in BASEL V[a]

	All patients ($n = 1208$)	Alive at 30 days ($n = 1108$)	Deceased within 30 days ($n = 100$)	*p*-value*
Demographics				
Age, years, median [IQR]	79.0 [71.0–85.0]	79.0 [70.0–85.0]	82.0 [75.0–86.0]	0.003
Female sex, *n* (%)	508 (42.1)	466 (42.1)	42 (42.0)	1.000
Body mass index, kg/m^2, median [IQR]	26.4 [23.3–30.1]	26.5 [23.4–30.2]	25.0 [21.1–28.8]	0.004
Recent history, *n* (%)				
Chest pain	383 (32.2)	357 (32.7)	26 (26.8)	0.279
Cough	632 (54.2)	575 (53.8)	57 (59.4)	0.344
Sputum production	425 (36.4)	380 (35.5)	45 (46.9)	0.035
Clinical parameters at ED				
Systolic BP, mmHg, median [IQR]	136.0 [119.0–155.0]	138.0 [120.8–155.0]	122.5 [105.0–143.2]	<0.001
Diastolic BP, mmHg, median [IQR]	78.0 [67.0–92.0]	78.0 [67.0–93.0]	76.0 [63.0–88.0]	0.094
Heart rate, bpm, median [IQR]	88.0 [72.0–106.5]	88.0 [72.0–106.0]	91.0 [76.0–112.0]	0.095
Temperature, °C, median [IQR]	37.0 [36.5–37.5]	37.0 [36.5–37.5]	37.0 [36.5–37.5]	0.950
Pulse oximetry, %, median [IQR]	96.0 [93.0–98.0]	96.0 [93.0–98.0]	95.0 [90.0–97.0]	0.001
Respiratory rate, breaths/min, median [IQR]	21.0 [17.0–27.0]	21.0 [17.0–27.0]	24.0 [20.0–30.0]	<0.001
Hypertrophy on electrocardiogram, *n* (%)[b]	169 (14.0)	156 (14.1)	13 (13.0)	0.883
Rales, *n* (%)	734 (62.5)	673 (62.4)	61 (62.9)	1.000
Elevated JVP, *n* (%)	505 (46.0)	454 (45.0)	51 (56.0)	0.056
Oedema, *n* (%)	743 (63.0)	681 (63.0)	62 (63.3)	1.000
NYHA class IV at presentation, *n* (%)	527 (43.6)	465 (42.0)	62 (62.0)	<0.001
Low-output symptoms, *n* (%)[c]	139 (11.5)	82 (7.4)	57 (57.0)	<0.001
Episode associated with ACS, *n* (%)[d]	78 (6.5)	70 (6.3)	8 (8.0)	0.658
Prior history, *n* (%)				
Hypertension	976 (81.9)	909 (83.1)	67 (68.4)	<0.001
Dyslipidaemia	646 (54.9)	596 (55.3)	50 (50.5)	0.412
Diabetes mellitus	353 (29.5)	328 (29.8)	25 (25.3)	0.398
CAD	606 (50.8)	558 (51.0)	48 (49.0)	0.787
MI	357 (30.1)	324 (29.8)	33 (33.3)	0.533
Hospitalization for HF	598 (50.1)	546 (49.8)	52 (53.6)	0.536
COPD	296 (24.7)	266 (24.2)	30 (30.3)	0.224
Tobacco use (past or present)	409 (36.2)	385 (36.9)	24 (27.3)	0.089
Laboratory values, median [IQR]				
Haemoglobin, g/L	127.0 [113.0–140.0]	127.0 [114.0–141.0]	120.0 [106.5–136.5]	0.003
Creatinine, µmol/L	104.0 [80.0–145.0]	103.0 [80.0–142.0]	130.5 [89.8–178.8]	<0.001
Sodium, mmol/L	139.0 [136.0–141.0]	139.0 [136.0–141.0]	138.0 [135.0–141.0]	0.081
Potassium, mmol/L	4.2 [3.8–4.5]	4.2 [3.8–4.5]	4.3 [3.9–4.9]	0.026
hs-cTnT, ng/L	37.0 [22.0–67.0]	35.0 [21.0–61.0]	75.0 [35.5–140.0]	<0.001
Fourth-generation cTnT, ng/L	10.0 [10.0–42.5]	10.0 [10.0–40.0]	70.0 [30.0–170.0]	<0.001
NT-proBNP, pg/ml	5052.5 [2372.0–10 092.0]	4837.0 [2267.2–9498.8]	10 168.0 [4922.0–18 394.5]	<0.001
CRP, mg/dl	11.5 [4.2–31.7]	10.1 [3.8–27.0]	34.8 [17.3–70.5]	<0.001

Percentages may deviate from the total column number in the first column line due to missing values. This table is independent of the assignment of a patient to a specific risk group.

AHF, acute heart failure; ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; cTnT, cardiac troponin T; ED, emergency department; HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; JVP, jugular venous pressure; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

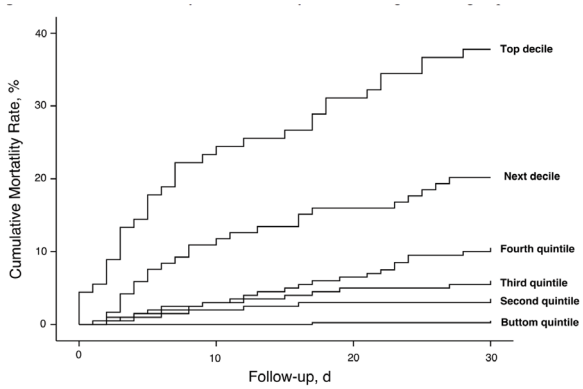
[a]Comparisons were performed by Mann–Whitney U or χ^2 test as appropriate.

[b]Defined using the Sokolow–Lyon index for left ventricular hypertrophy on the admission electrocardiogram.

[c]Defined as confusion, weakness, cold periphery, and ≥1 of the following: poor peripheral perfusion, anuria or oliguria.

[d]Defined according to the final diagnosis by the adjudicating physician.

*For comparison between survival and death within 30 days.



Original Risk groups	Original Intervals†	Median (IQR) CRP mg/dl	Patients, %	Numbers at risk, n Day 0	Day 10	Day 20	Day 30	Predicted probability of death within 30 d, %	Deaths within 30d per interval, n (%) Predicted	Observed
Low	Bottom quintile	4.4 (2.5-9.0)	33.1	400	399	398	397	0.5-2.1	4 (1.0)	2 (0.5)
	Second quintile	8.1 (3.8-16.8)	16.5	199	195	193	193	2.1-3.9	6 (3.0)	7 (3.5)
Intermediate	Third quintile	15.7 (5.9-35.4)	16.6	200	194	190	189	3.9-7.0	11 (5.5)	12 (6.0)
	Fourth quintile	22.9 (11.8-46.1)	16.6	200	194	187	180	7.0-14.5	20 (10.0)	21 (10.5)
High	Next decile	35.4 (16.0-89-6	9.9	119	106	100	95	14.5-25.7	24 (20.2)	24 (20.2)
Very high	Top decile	61.0 (33.2-135.0)	7.5	90	69	62	56	25.8-89.8	35 (38.9)	34 (37.7)

Figure 1 Cumulative mortality rate over 30 days for the six original risk groups in the extended MEESSI model in BASEL V. Division into risk groups was performed according to the predicted probability of 30-day mortality as specified in the original MEESSI model.[7]. One patient in the bottom quintile was censored. †Original intervals are not in accordance with the percentage of patients assigned to each group as patients were grouped according to the predicted probability of 30-day mortality. CRP, C-reactive protein; IQR, interquartile range.

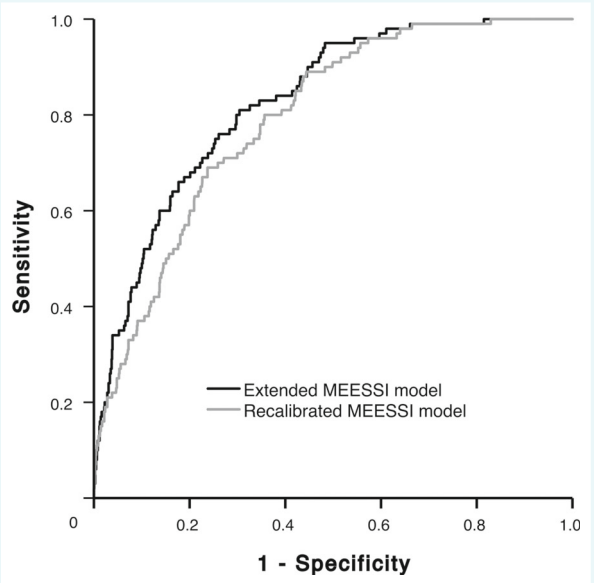


Figure 2 Direct comparison of the extended and recalibrated MEESSI model in BASEL V using receiver operating characteristic curves. The c-statistic was 0.79 (95% CI 0.75–0.83) for the recalibrated MEESSI model and 0.83 (95% CI 0.79–0.87) for the extended MEESSI model (DeLong test, $p = 0.013$). This figure is independent of the assignment of a patient to a specific risk group.

the highest net benefit over the full range of probability thresholds when compared to the recalibrated model.

Sensitivity analysis

Baseline characteristics of patients included in and those excluded from the main analysis are displayed in online supplementary *Table S5*. Besides significant differences in clinical parameters such as median heart rate at presentation, there were also significant differences in the MEESSI model's candidate predictor variables such as New York Heart Association class IV and low-output symptoms. After performing multiple imputation, the extended MEESSI score was calculated in additional 364 patients initially excluded due to missing values. When computing the operating characteristic in all 1572 patients with available follow-up, a c-statistic of 0.83 (95% CI 0.80–0.87) and a Hosmer–Lemeshow *p*-value of 0.35 were achieved.

Independent validation

A total of 575 patients presenting with AHF between January 2015 and February 2022 were included in the independent validation cohort. Thirty-day mortality rate was 9.2%. In comparison to the BASEL V cohort, patients in the independent validation cohort had a higher cardiovascular risk profile and were more often male. Further details on baseline characteristics, risk score distribution, comparisons to the BASEL V cohort and patient flow are shown in online supplementary *Tables S6–S8*, *Figures S6–S8* and Results in *Appendix S1*.

When applying the extended MEESSI model in the independent validation cohort results obtained in the main cohort were confirmed: the difference in 30-day mortality between six risk

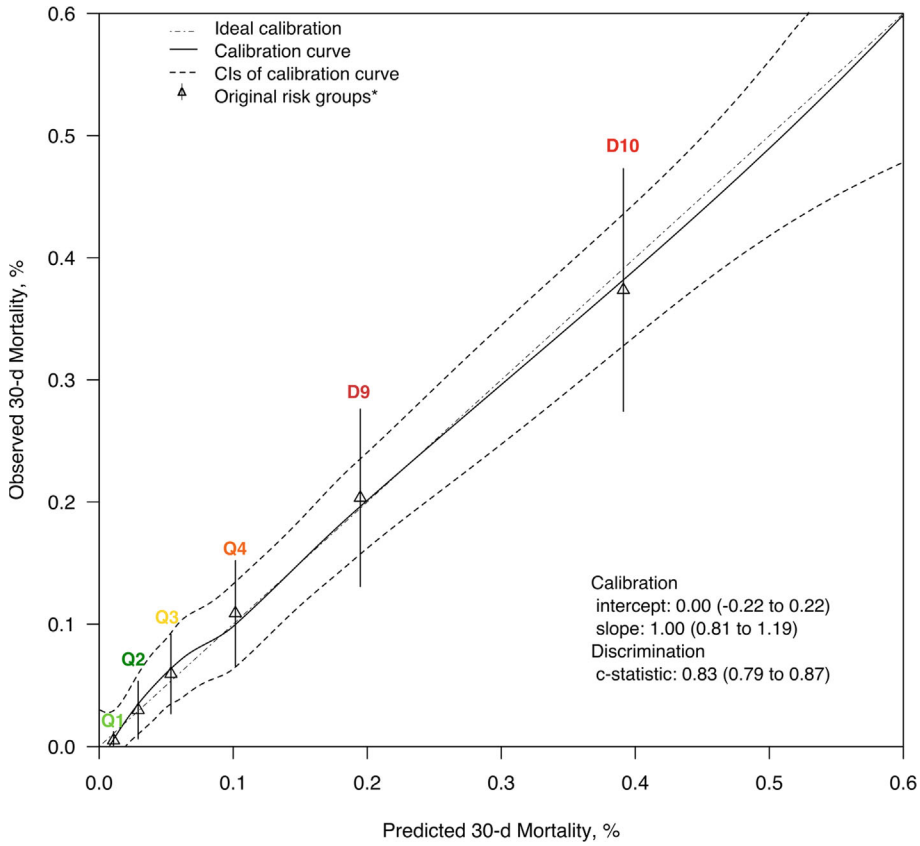


Figure 3 Calibration plot of the extended MEESSI model with the six original risk groups in BASEL V. Division into risk groups was performed according to the predicted probability of 30-day mortality as specified in the original MEESSI model.[7] The intercept, slope and c-statistic represent all patients, regardless of risk group. D, decile; Q, quintile. *Whiskers indicate 95% confidence intervals.

groups specified in the original MEESSI publication[7] was more pronounced in the extended compared to the recalibrated MEESSI model (online supplementary *Figures S9* and *S10*). In addition, calibration was improved by model extension with CRP (online supplementary Results in *Appendix S1*). Furthermore, the prognostic accuracy of the extended MEESSI model (c-statistic 0.77, 95% CI 0.72–0.83) was significantly higher compared to the recalibrated MEESSI model (c-statistic 0.70, 95% CI 0.63–0.77; $p = 0.006$) (*Figure 5*). The extended MEESSI model also had a higher net benefit when compared to the recalibrated model as indicated by the prediction of 11 more true positives per 1000 (online supplementary *Figure S11*).

Discussion

This secondary analysis from a large, prospective, multicentre, diagnostic study using central adjudication was performed to test the hypothesis that adding CRP, quantifying systemic inflammation, to the MEESSI-AHF risk score, further improves its performance. We report six major findings. First, after stratifying patients into the original risk groups, a pronounced difference in 30-day mortality was found when the MEESSI score extended by CRP was applied. In addition, compared to the recalibrated MEESSI score, it was possible to stratify more patients into the lowest risk group while keeping the absolute number of patients dying within 30 days of follow-up low and comparable. Second, the extended MEESSI-AHF score showed an excellent and significantly higher discrimination for every applied MEESSI model (Model D and F–H) when compared to the recalibrated MEESSI score (p for comparison 0.01–0.014). Third, the extended MEESSI score showed a near ideal calibration with an improved slope and intercept compared to the recalibrated MEESSI score. Fourth, in a decision curve analysis as method aiming to overcome limitations of traditional statistical metrics, which do not directly provide information on clinical value, the extended MEESSI score showed the highest net benefit over the full range of probability thresholds when compared to the recalibrated score.[23] Therefore, the extended MEESSI score would be the preferable approach regardless of a physician's individual value represented by a fixed probability threshold as level of prognostic certainty, which would determine the intensity of further treatment. In general, a low threshold probability would imply a lower burden of unnecessary treatment as the corresponding weighting factor (= threshold probability/1−threshold probability) would minimize the effect of false positives in the resulting net

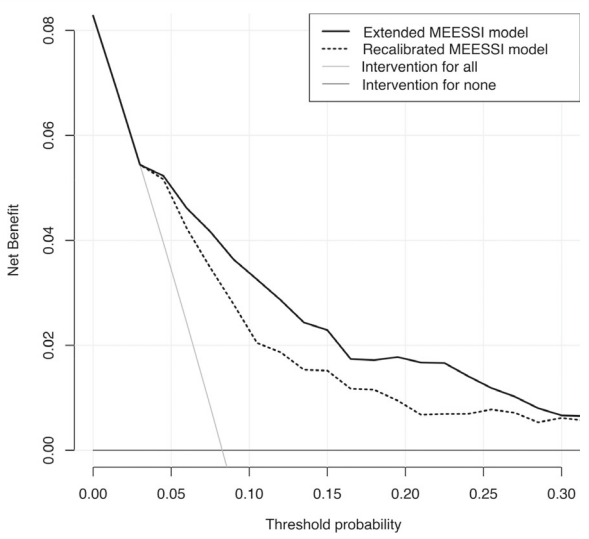


Figure 4 Decision curve analysis for the prediction of 30-day mortality of the recalibrated and extended MEESSI model in BASEL V. This decision curve analysis calculates the clinical 'net benefit' for the MEESSI models compared to default strategies which are intervention for all or none. The unit of net benefit is true positives (true-positive counts minus false-positive counts) weighted by the respective threshold probability. For a specific threshold probability, a larger net benefit indicates a greater number of true positive predictions without increase in the rate of false positives. For a threshold probability, a larger net benefit indicates a greater number of true positive versus false positive predictions for the specific model. One might also say that missing one high-risk patients is nine times worse than one unnecessary treatment or hospitalization. This figure is independent of the assignment of a patient to a specific risk group.

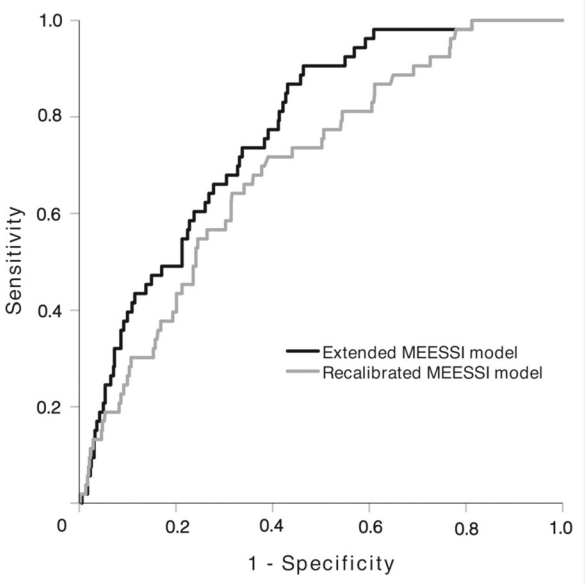


Figure 5 Direct comparison of the extended and recalibrated MEESSI model in Heart Failure-USB (independent validation cohort) using receiver operating characteristic curves. The c-statistic was 0.70 (95% CI 0.63–0.77) for the recalibrated MEESSI model and 0.77 (CI, 0.72–0.83) for the extended MEESSI model (DeLong test, $p = 0.006$). This figure is independent of the assignment of a patient to a specific risk group.

benefit (= true positives − [false positives × weighting factor]). Conversely, when facing a higher burden of unnecessary treatment, a higher threshold probability would increase the effect of false positive results.[25] In general, the improvement of a models' operating characteristics is also possible due to simple refitting to a novel dataset by re-estimation of beta coefficients regardless of the added value of a newly included marker. However, on the basis of a fraction of new information of 17% resulting from the addition of CRP, this is unlikely for our analysis and supports the incremental value of CRP.[17] Fifth, findings concerning the extended MEESSI score's operating characteristics were confirmed in a sensitivity analysis using multiple imputation for missing values in the overall cohort. Sixth, the incremental value of systemic inflammation in AHF risk stratification quantified by using CRP concentration was confirmed in an independent validation cohort.

These findings corroborate and extend previous studies on AHF risk stratification by using risk scores including cardiac and inflammatory biomarkers in general and those related to the MEESSI-AHF score in particular.[6–8,26] Natriuretic peptides, cardiac troponin and creatinine as biomarkers quantifying myocardial stretch, cardiomyocyte injury and renal dysfunction represent important pathophysiologic pathways involved in the development and progression of AHF and have already been incorporated in the original MEESSI score.[27,28] This study was built on prior evidence suggesting that even in the absence of an acute infection, systemic inflammation is common in AHF and associated with disease severity and adverse outcome.[6] The interaction between inflammation and AHF seems complex and mutually amplifying. The combination of arterial hypoperfusion and increased venous pressure in mesenteric vessels may result in bacterial translocation from the bowel to the bloodstream. This pathophysiological aspect characterizes the positive correlation of AHF severity expressed by low cardiac output and increased congestion with the extent of inflammation.[29] In this context several studies have documented increased mortality in AHF patients with continuously increasing CRP concentrations as a widely available quantitative marker of systemic inflammation.[10–13,30] Given this scientific background, our analysis confirmed the hypothesis that adding CRP provides incremental value and allows to obtain a more holistic characterization of AHF.[9,31] The absolute increase in c-statistic (from 0.79 to 0.83) and improvement of calibration after adding CRP seem modest at first sight. However, they represent a statistically significant incremental value of CRP on a combination of 12 clinical symptoms, vital signs and also biomarkers. Therefore, also in a synopsis of prior evidence our study supports a routine measurement of CRP in AHF patients for risk stratification on hospital admission.

In this study, the prognostic accuracy of the MEESSI-AHF score without Barthel index and extended by CRP (c-statistic, 0.83) was similar to the accuracy of the full model in the original

Spanish derivation cohort (c-statistic, 0.84).[7] Therefore, CRP can be discussed as a potential alternative to the Barthel index score in EDs not recording the latter. In addition, CRP could also be used in other reduced MEESSI models, for instance models which do not include Barthel index score, cardiac troponin or NT-proBNP concentrations in different combinations. As until now, the MEESSI model was only applied in Switzerland and Spain, and recalibration of the intercept or refitting of beta coefficients may also be needed when the score is introduced to a new population or when outcome frequencies change due to novel therapies and consecutive improved outcomes.

These findings may have profound clinical implications as improved risk stratification in AHF patients is desperately needed. In most institutions decisions regarding the intensity of treatment including admission to hospital, to an intermediate care unit or to an intensive care unit are mainly subjective. This results in high hospitalization rates with an enormous economic burden of about $50 billion per year in the United States alone[32] on one hand and patients' exposure to nosocomial infections, social deprivation and delirium on the other. As the application of the extended MEESSI score helped to stratify more patients in the lowest risk group without increase in the number of false negatives, the extended MEESSI score could particularly help to identify patients at low risk, who could be safely discharged home with appropriate outpatient management.

Some limitations could merit consideration when interpreting our findings. First, our findings are based on AHF patients presenting to the ED, whose condition was stable enough to provide informed consent. Accordingly, we cannot comment on the performance of the extended MEESSI-AHF score in a minority of patients haemodynamically too unstable for providing consent. However, decision making regarding the intensity of care usually is straight forward in these patients. Second, we also cannot generalize the performance of the extended MEESSI score to patients with end-stage kidney failure on chronic dialysis, since these patients were excluded. Third, this study only assessed the incremental value of CRP to several reduced MESSI model as Barthel index score was not prospectively recorded in this study. Therefore, we cannot comment on the incremental value of CRP to the full MEESSI model including Barthel index. Fourth, patients from the derivation (BASEL V) and validation cohort (Heart Failure-USB) were from the same country leading to reduced interregional generalizability of our findings. Fifth, although we used a very stringent methodology to adjudicate AHF, including central adjudication of two independent cardiologists/internists with open label measurements of natriuretic peptides, a misclassification of a small number of patients may still have occurred.

This study also has several important methodological strengths such as a largely unselected patient population recruited in the ED and highly representative for AHF. Furthermore, the diagnosis of AHF was centrally adjudicated by two independent and experienced cardiologists/internists. In addition, findings were validated in an independent AHF cohort.

In conclusion, quantifying systemic inflammation using CRP concentration provided incremental value in AHF risk stratification using the established MEESSI model. The extended MEESSI-AHF risk score seemed a highly promising, simple, inexpensive and widely available tool for standardized risk stratification of AHF patients.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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