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Implications of Alternative Hepato-Renal Prognostic Scoring Systems in Acute Heart Failure (From DOSE-AHF and ROSE-AHF)

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Abstract

Because hepatic dysfunction is common in patients with heart failure, the Model for End-Stage Liver Disease (MELD) may be attractive for risk-stratification. Although alternative scores such as the MELD-XI or MELD-Na may be more appropriate in heart failure populations, the short-term clinical implications of these in patients with acute heart failure (AHF) are unknown. The MELD-XI and MELD-Na were calculated at baseline in 453 patients with AHF in the DOSE-AHF and ROSE-AHF trials. The correlations and associations for each score with cardiorenal biomarkers, short-term endpoints at 72 hours including worsening renal function and clinical events to 60 days were determined. The median MELD-XI and MELD-Na was 16 and 17, respectively. Both were correlated with baseline cystatin C, NT-proBNP, and plasma renin activity ($P < 0.003$ for all). MELD-XI 16 and MELD-Na 17 were associated with a slight increase in cystatin C ($P < 0.02$ for both), higher diuretic efficiency ($P < 0.001$ for both), but not with change in global VAS scores ($P > 0.05$ for both) at 72 hours. Neither score was associated with CRS or worsening heart failure ($P > 0.05$ for all). Similarly, both the MELD-XI and MELD-Na were not associated with 60-day death/any re-hospitalization and 60-day death/heart failure re-hospitalization in adjusted analyses when analyzed as a dichotomous or continuous variable ($P > 0.05$ for all). The alternative MELD scores correlated with baseline cardiorenal biomarkers. In conclusion, lower baseline MELD scoring was associated with higher diuretic efficiency and a slight increase in cystatin C through 72 hours. However, MELD-Na and MELD-XI were not predictive of 60-day clinical events.

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Keywords

Acute heart failure; cardiorenal; MELD scoring

The Model for End-Stage Liver Disease (MELD) score, designed to risk-stratify cirrhotic patients awaiting liver transplantation, incorporates 3 variables: serum creatinine, bilirubin, and INR.^{1,2} These non-cardiac variables can identify liver dysfunction in patients with advanced heart failure and MELD scoring can provide strong risk assessment in heart failure patients independent of more traditional heart transplantation evaluation models.³ Alternative MELD scoring models, perhaps more attractive in patients with HF, offer prognostic information in patients taking chronic anticoagulation (MELD-XI: excludes INR)⁴⁻⁶ and in patients with hyponatremia (MELD-Na: includes sodium).⁷ Hepatic dysfunction may independently also alter loop diuretics responsiveness,^{8,9} and may be associated with renal dysfunction in heart failure.¹⁰ Therefore, we hypothesized that alternative MELD scores may be associated with treatment response and prognosis in acute heart failure (AHF). Because prior analyses have not adjusted for renal function in their multivariable models,⁵ a strong prognostic factor in AHF,¹¹ we also aim to incorporate this into our analysis. The Diuretic Strategies in Patients with Acute Decompensated Heart Failure (DOSE-AHF) and the Low-dose Dopamine or Low-dose Nesiritide in Acute Heart Failure with Renal Dysfunction (ROSE-AHF) together provide a well-characterized cohort, well-suited to study the clinical implications of these alternative MELD scores in AHF.

METHODS

The DOSE-AHF and ROSE-AHF studies conducted within the NHLBI-sponsored Heart Failure Clinical Trials Network were included in this analysis. Each protocol was approved by the Institutional Review Boards at each site and written informed consent was obtained from all patients prior to randomization. Both trials were conducted in the United States and Canada. DOSE-AHF and ROSE-AHF were prospective double-blinded trials testing the decongestive efficacy and renal consequences of different decongestive strategies (DOSE-AHF) or renal protective therapies (ROSE-AHF) in hospitalized AHF patients with clinical evidence of congestion and have been previously described.^{12,13}

All randomly assigned patients with available creatinine, bilirubin, and sodium levels checked locally at the enrolling sites (N=453) were included in this analysis. If there were patients enrolled in both trials, only the observations from DOSE-AHF were included as this was the first trial enrollment.

Baseline laboratory values were used to calculate MELD-XI [$5.11 \times (\ln \text{ total bilirubin}) + 11.76 \times (\ln \text{ creatinine}) + 9.44$],⁴ and a modified MELD-Na [MELD-XI – serum sodium – $(0.025 \times \text{MELD-XI} \times (140 - \text{serum sodium})) + 140$].⁷ The MELD modifications adopted by the United Network for Organ Sharing were applied: to avoid negative scores, the lower limit for all variables will be set at 1.0 and the upper limit for creatinine set at 4.0 mg/dL.

All outcomes were assessed from randomization. Worsening renal function (WRF) was defined as an increase in serum creatinine of >0.3 mg/dl from baseline until 72 hours.

Worsening heart failure (WHF) was defined as the need for rescue therapy (vasoactive therapy, ultrafiltration, or mechanical circulatory or respiratory support from baseline until 72 hours). The WHF definition for DOSE included additional open label loop diuretic or addition of a thiazide. Change in GVAS and cystatin C were also included as short term outcomes. The effectiveness of decongestive therapies was determined by improvement in symptoms, as measured by global well-being analogue scales and diuretic efficiency (net fluid loss produced per 40 mg of furosemide equivalents) until 72 hours.¹⁴

Cardiorenal biomarkers included plasma renin activity, cystatin C, and amino terminus pro-B-type natriuretic peptide (NT-proBNP) and were evaluated by a central laboratory. We analyzed these biomarkers at baseline and 72 hours. Plasma renin activity was only measured in DOSE-AHF. Mid-term clinical outcomes included investigator reported death and re-hospitalization to 60 days.^{12,13}

Continuous variables were expressed as medians with the 25th and 75th percentile. Categorical variables were expressed as frequencies with percentages. Statistical comparisons were made determined by the Wilcoxon rank sum test or Pearson's chi square test where appropriate. Spearman correlation coefficients were calculated for either MELD-XI or MELD-Na scores and plasma renin activity, NT-proBNP, and cystatin C. Logistic regression models were used to test the association between MELD-XI and MELD-Na scores with WRF or WHF by 72 hours. Cox-proportional hazards models were used to test the association between baseline dichotomized MELD-XI and MELD-Na and mid-term clinical outcomes. The proportional hazards assumption was validated via cumulative martingale residuals. Multivariable models were adjusted for baseline age, BUN, systolic blood pressure, beta blocker and ACE Inhibitor/ARB use at randomization. Cubic splines were used for non-linear variables. Two-sided P-values <.05 were considered statistically significant. Statistical analyses were completed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

The distribution of MELD-XI is shown in Figure 1 and the baseline characteristics by MELD-XI score dichotomized at the median of 16 are shown in Table 1. There were no statistically significant differences in age or white vs. non-white race but there was a larger percentage of males, lower body mass index (BMI), and a trend towards lower left ventricular ejection fraction in MELD-XI > 16 vs <= 16. Higher MELD-XI was not associated with other metrics of hepatic function such as aspartate aminotransferase or alanine aminotransferase.

The distribution of MELD-Na is shown in Figure 2 and the baseline characteristics by MELD-Na score dichotomized at median of 17 are shown in Table 2. The following associations were similar to MELD-XI: There were no statistically significant differences in age or white vs non-white race, but there was a larger percentage of males and a lower LVEF in MELD-Na > 17 vs <= 17. Higher MELD-Na was not associated with other metrics of hepatic function such as aspartate aminotransferase or alanine aminotransferase. Unlike MELD-XI, however, there was no association between higher MELD-Na and BMI.

Higher MELD-XI and MELD-Na scores were associated with higher NT-proBNP at baseline ($P<0.001$ for both). The relationship between both MELD scores and baseline cystatin C, NT-proBNP, and plasma renin activity are graphically shown in Figures 3 and 4. Both alternative MELD scores showed a statistically significant association with evidence of higher neurohormonal activation (cystatin C, NT-proBNP, and plasma renin) at baseline ($P<0.001$ for all).

As shown in Table 3, there was no association between MELD scoring and symptomatic change during treatment for acute decompensated heart failure as measured by changing global visual assessment scores (GVAS) could be detected. However, higher MELD scores by both scoring systems were associated with changes in renal function and diuretic response. Higher MELD-XI and MELD-Na was associated with less change in cystatin C ($P=0.005$ and $P=0.016$, respectively) and lower diuretic efficiency through 72 hours ($P<0.001$ for both).

By 72 hours, 99/444 (22.3%) subjects developed WRF and 59/444 (13.2%) subjects developed persisting or WHF (Table 4). However, neither MELD-XI or MELD-Na were associated with WRF ($P=0.13$ and $P=0.49$, respectively). Similarly, there was no association between MELD-XI or MELD-Na and persisting or WHF ($P=0.84$ and $P=0.49$, respectively).

The rate of death or re-hospitalization was 35.3% (159/450) and the rate of death or HF re-hospitalization was 23.7% (106/447) by 60-days. In unadjusted analyses, there was a trend towards decreased hazard of death or re-hospitalization (HR=0.77, 95% CI 0.56–1.05, $P=0.10$ and death or heart failure (HF) re-hospitalization (HR=0.72, 95% CI 0.49–1.05, $P=0.09$) for MELD-XI <16 vs ≥ 16 . However, after multivariable adjustment, there was no association between MELD-XI <16 vs ≥ 16 and either composite outcome (Table 4, $P=0.69$ and $P=0.56$, respectively). Results were no different when MELD-XI was analyzed as a continuous variable in unadjusted or adjusted analyses ($P=0.69$ and $P=0.55$, respectively). In comparison to a MELD-Na >17 , a MELD-Na ≤ 17 was associated with an approximate 30% reduction in the risk of death or re-hospitalization (HR 0.69, 95% CI 0.50–0.94, $P=0.019$). The association was stronger for death or HF re-hospitalization as MELD-Na ≤ 17 was associated with an approximate 44% risk reduction (HR 0.56, 95% CI 0.38–0.83, $P=0.004$) when compared to MELD-Na >17 . However, this was nullified after multivariable adjustment (Table 4, $P=0.87$ and $P=0.44$, respectively). Furthermore, MELD-Na was not associated with death or re-hospitalization when analyzed as a continuous variable in unadjusted or adjusted analyses ($P=0.87$ and $P=0.44$, respectively).

DISCUSSION

This analysis has several key observations which add to interpretation and utility of alternative MELD scores in patients with AHF. First, both the MELD-XI and MELD-Na scores were more closely associated with baseline cardiorenal biomarkers compared to more traditional markers of hepatic function such as albumin or transaminase levels. Second, and along similar lines, MELD-XI and MELD-Na scores were associated with renal function changes and diuretic efficiency during decongestive therapies, but were not associated with any short-term clinical endpoints (i.e. WRF and WRF by 72 hours). Third, the MELD-Na

score was more closely associated with the mid-term clinical outcomes than the MELD-XI and is likely representative of the addition of serum sodium levels to the score. Importantly, neither was associated with mid-term outcomes in adjusted analyses, diminishing the prognostic role of these scores for patients with AHF. Although these findings clarify the clinical relevance of these alternative MELD scores in AHF, they suggest that the primary clinical utility of MELD scoring in this population may be more reflective of renal comorbidity than hepatic comorbidity.

The MELD score was originally created to estimate survival in patients with end-stage liver disease, and is the major disease-specific severity score for liver allocation.¹⁵ Because patients with heart failure may have evidence of hepatic dysfunction,^{16–20} it is not surprising that liver-related risk-prediction is valid in heart failure populations.^{3,18} The prognostic relevance of higher MELD scoring in pre-transplant or pre-ventricular assist device heart failure populations even extends to the post-operative short-term and mid-term periods.^{6,21,22} However, the etiologies of the components of the MELD scoring (e.g. serum creatinine, bilirubin, and international normalized ratio) in heart failure are likely reflections of different pathological mechanisms. In contrast to primary hepatic dysfunction, bilirubin and creatinine elevation are closely associated and perhaps secondary to both elevations in central venous pressure and low cardiac output in heart failure.^{16,18,23}

Not surprisingly, the MELD and alternative MELD scores are prognostically informative in heart failure populations.^{3,18,21,22} In a cohort of patients with advanced heart failure, the MELD, MELD-Na, and MELD-XI scores were all associated with death, heart transplant, and ventricular assist device placement.³ Similar findings were seen in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.¹⁸ As expected, higher alternative MELD scores had either a trend (in the case of MELD-XI) or were associated (in the case of MELD-Na) with adverse clinical events in the present analysis. Worth noting, however, the MELD-Na was more closely associated with adverse clinical events which is likely related to the addition of sodium to the MELD-Na score – an established heart failure prognostic marker.²⁴ The MELD-Na may therefore be more clinically meaningful in heart failure other than MELD scoring. Importantly however, the lack of association with mid-term outcomes for both scores after multivariable adjustment conflicts with previous findings,^{5,18} and does not support their prognostic utility in patients with AHF apart from more transitional markers. Interestingly, there was a modest correlation between alternative MELD scoring and the cardiorenal axis: cystatin C, NT-proBNP, and plasma renin activity; suggesting that the prognostic use of MELD scoring in heart failure may be, in part, its representation of renal comorbidity – but that it may be less prognostically informative than these markers individually.

Lower diuretic responsiveness and ineffective decongestion during treatment for AHF are associated with adverse clinical events.^{14,25,26} Therefore, *a priori* identification of these patients is warranted. This analysis supports the utility of MELD scoring to forecast decongestive responsiveness in AHF with the association between higher MELD scores and lower diuretic responsiveness in AHF. The likeliest explanation is the contribution of baseline serum creatinine to the MELD scores, as renal function is a large contributor to the MELD calculation. Indeed, components of renal function such as BUN have been previously

associated with diuretic responsiveness.^{27,28} The close correlation with heightened cardiorenal interactions supports this as well as these markers also track with clinical response and poor outcomes.^{11,29} On the other hand, this observation may also represent the tendency for patients with hepatic impairment to have a diminished natriuretic response when given loop diuretics despite their renal function.⁸ Lower serum albumin levels, commonly seen in hepatic dysfunction, may represent diminished diuretic response as a result of reduced albumin-mediated loop diuretic delivery.⁹ Arguing against this, however, is the lack of association of the alternative MELD scores and serum albumin levels and that a previous analysis of these cohorts showed no association between albumin levels and diuretic efficacy.³⁰

There are several limitations inherent to the design of this study. First, formal coagulation studies were not collected as part of DOSE-AHF and ROSE-AHF. As a result, these findings are speculative towards the clinical impact of the standard MELD score in AHF.¹⁵ Second, this is an observational analysis of data from two clinical trials which were not adequately powered to detect clinical endpoints according to MELD-XI or MELD-Na scores. However, this analysis was conducted within the confines of carefully selected AHF populations with prospectively collected outcomes. This minimizes unintentional biases and other factors that may have confounded the MELD-risk relationship, but may create the untoward bias of excluding populations causing a differential impact on the observed relationships.

In conclusion, the alternative MELD scores, MELD-XI and MELD-Na, were associated with cardiorenal markers of neurohormonal activation. Although higher scores were associated with lower diuretic response, these findings do not support their prognostic role for short-term (e.g. WRF and WHF) and mid-term adverse clinical outcomes. These findings extend the clinical utility of alternative MELD scoring to AHF, but also suggest that it is mainly driven by the incorporation of renal function into these scores.

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Figure 1.
Distribution of MELD-XI Scores

Figure 2.
Distribution of MELD-Na Scores

Figure 3a–c. Correlations Between the MELD-XI Scores and Cardiorenal Biomarkers
 Spearman correlation coefficients are cystatin C (N=433), 0.59, $P<0.0001$; NT-proBNP (N=432), 0.30, $P<0.0001$; and plasma renin activity (N=172), 0.23, $P=0.0028$.

Figure 4a–c. Correlations Between the MELD-Na Scores and Cardiorenal Biomarkers
 Spearman correlation coefficients are cystatin C (N=433), 0.48, $P<0.0001$; NT-proBNP (N=432), 0.27, $P<0.0001$; and plasma renin activity (N=172), 0.33, $P<0.0001$

Table 1

Baseline Characteristics by Baseline MELD-XI Score

	MELD-XI > 16 (N=233)	MELD-XI 16 (N=220)	P-value*
Variable			
Age (years)	68.0 (60.0, 78.0)	68.0 (57.5, 77.0)	0.523
Men	193/233 (82.8%)	145/220 (65.9%)	< 0.001
White	158/233 (67.8%)	164/220 (74.5%)	0.114
BMI (kg/m ²) (N=433)	30.5 (26.4, 34.9) n=220	32.3 (26.6, 38.9) n=213	0.025
Ejection Fraction (%) (N=446)	28.0 (20.0, 50.0) n=230	33.0 (20.0, 54.5) n=216	0.072
Ischemic HF etiology	128/233 (54.9%)	120/220 (54.5%)	0.934
Diabetes	127/233 (54.5%)	124/220 (56.4%)	0.691
ICD	111/233 (47.6%)	81/220 (36.8%)	0.020
Sodium (mg/L) (N=453)	138.0 (135.0, 140.0)	139.0 (136.0, 141.0)	0.005
Creatinine (mg/dL)	2.0 (1.8, 2.4)	1.3 (1.1, 1.5)	< 0.001
Cystatin C (g/dL)	1.8 (1.5, 2.3) n=225	1.4 (1.1, 1.6) n=208	<0.001
NT-pro BNP (pg/mL) (N=432)	6655 (3039, 12751) n=224	3851 (1897, 7825) n=208	< 0.001
Plasma renin activity (ng/mL/hr)	5.8 (1.3, 16.6) n=71	2.0 (0.5, 8.8) n=101	0.005
Total Bilirubin (mg/dL) (N=453)	1.2 (0.7, 1.8)	0.8 (0.6, 1.2)	< 0.001
Albumin (g/dL) (N=427)	3.5 (3.2, 3.9) n=220	3.5 (3.1, 3.9) n=207	0.608
AST (IU/L) (N=444)	27.0 (22.0, 39.0) n=230	28.0 (21.0, 40.0) n=214	0.783
ALT (IU/L) (N=426)	23.0 (17.0, 33.0) n=222	23.0 (16.0, 35.5) n=204	0.922
ACE inhibitor or ARB	108/233 (46.4%)	142/220 (64.5%)	0.001
Beta Blockers	194/233 (83.3%)	179/220 (81.4%)	0.596
Warfarin	103/233 (44.2%)	97/220 (44.1%)	0.980
Digoxin	64/233 (27.5%)	62/220 (28.2%)	0.865
Aldosterone antagonist	65/233 (27.9%)	62/220 (28.2%)	0.946

* P-value: Wilcoxon Rank Sum test for continuous variables. Pearson Chi-square test for categorical variables. Continuous variables displayed as median (25th, 75th)

n's are only displayed for incomplete data.

Table 2

Baseline Characteristics by Baseline MELD-Na Score

Variable	MELD-Na > 17 (N=224)	MELD-Na ≤ 17 (N=229)	P-value*
Age (years) (N=453)	67.0 (58.5, 77.0)	69.0 (59.0, 78.0)	0.257
Men	184/224 (82.1%)	154/229 (67.2%)	<0.001
White	153/224 (68.3%)	169/229 (73.8%)	0.197
BMI (kg/m ²) (N=433)	30.6 (26.3, 35.0) n=215	32.3 (26.6, 38.2) n=218	0.065
Ejection Fraction (%) (N=446)	25.0 (20.0, 49.0) n=222	35.0 (23.0, 55.0) n=224	0.002
Ischemic HF etiology	122/224 (54.5%)	126/229 (55.0%)	0.905
Diabetes	126/224 (56.3%)	125/229 (54.6%)	0.722
ICD	112/224 (50.0%)	80/229 (34.9%)	0.001
Sodium (mg/L) (N=453)	137.0 (134.0, 139.0)	140.0 (138.0, 142.0)	< 0.001
Creatinine (mg/dl)	2.0 (1.6, 2.4)	1.4 (1.1, 1.5)	< 0.001
Cystatin C (g/dL)	1.8 (1.5, 2.3) n=216	1.4 (1.2, 1.7) n=217	<0.001
NT-pro BNP (pg/ml) (N=432)	6660 (2837, 12794) n=215	3926 (1949, 7872) n=217	< 0.001
Plasma renin activity (ng/mL/hr)	7.6 (1.3, 23.3) n=75	1.7 (0.5, 6.1) n=97	<0.001
Total Bilirubin (mg/dL) (N=453)	1.2 (0.7, 1.9)	0.8 (0.5, 1.2)	< 0.001
Albumin (g/dL) (N=427)	3.5 (3.1, 3.9) n=211	3.5 (3.2, 3.9) n=216	0.201
AST (IU/L) (N=444)	27.0 (22.0, 40.0) n=221	29.0 (21.0, 39.0) n=223	0.929
ALT (IU/L) (N=426)	23.0 (16.0, 33.0) n=214	23.0 (16.0, 35.0) n=212	0.919
ACE inhibitor or ARB	109/224 (48.7%)	141/229 (61.6%)	0.006
Beta Blockers	187/224 (83.5%)	186/229 (81.2%)	0.528
Warfarin	99/224 (44.2%)	101/229 (44.1%)	0.984
Digoxin	60/224 (26.8%)	66/229 (28.8%)	0.629
Aldosterone antagonist	70/224 (31.3%)	57/229 (24.9%)	0.132

* P-value: Wilcoxon Rank Sum test for continuous variables. Pearson Chi-square test for categorical variables. Continuous variables displayed as median (25th, 75th)

n's are only displayed for incomplete data.

Table 3

Short-term Continuous Outcomes

	MELD-XI > 16 (N=233)	MELD-XI 16 (N=220)	P-value*
Global Visual Assessment Score (N=377)	18.0 (1.0, 38.5) n=196	21.0 (2.0, 39.0) n=181	0.509
Cystatin C (mg/L) (N=382)	0.04 (−0.12, 0.26) n=200	0.11 (0.0, 0.26) n=182	0.005
Diuretic Efficiency through 72 h (ml/IV 40 mg furosemide eq.) (N=393)	545.8 (350.9, 815.0) n=205	708.7 (443.4, 1051) N=188	<0.001
	MELD-Na > 17 (N=224)	MELD-Na 17 (N=229)	P-value*
Global Visual Assessment Score (N=377)	18.0 (1.0, 37.0) n=195	20.0 (1.0, 40.0) n=182	0.503
Cystatin C (mg/L) (N=382)	0.04 (−0.12, 0.28) n=194	0.11 (−0.01, 0.25) n=188	0.016
Diuretic Efficiency through 72 h (ml/IV 40 mg furosemide eq.) (N=393)	553.7 (334.0, 847.2) n=202	682.9 (449.7, 1034) n=191	<0.001

* P-value: Wilcoxon Rank Sum test

Displayed as median (25th, 75th)

Table 4

Short- and Mid-term Outcomes by MELD-XI/Na Score

Outcome	N	Events	Hazard/Odds Ratio (95% CI)*	P-value
MELD-XI				
Worsening Renal Function [†]	444	99	1.41 (0.9, 2.21)	0.132
Persisting or Worsening Heart Failure [‡]	444	59	1.06 (0.61, 1.83)	0.844
Death/any re-hospitalization	449	159	0.99 (0.94, 1.04)	0.686
Death/HF re-hospitalization	446	106	1.02 (0.96, 1.08)	0.555
MELD-Na				
Worsening Renal Function [†]	444	99	1.17 (0.75, 1.83)	0.486
Persisting or Worsening Heart Failure [‡]	444	59	1.22 (0.70, 2.11)	0.486
Death/any re-hospitalization	449	159	1.00 (0.96, 1.05)	0.869
Death/any HF re-hospitalization	446	106	1.02 (0.97, 1.07)	0.436

* Odds ratios for worsening renal function/persisting or worsening heart failure and adjusted hazard ratios for all other outcomes are for either MELD-XI 16 vs. MELD-XI >16 or MELD-Na 17 vs. MELD-Na > 17. All hazard ratios are adjusted for Models adjusted for baseline age, BUN, SBP, beta blocker and ACE Inhibitor/ARB use at randomization. SBP was not linear so a cubic spline was used for adjustment of SBP

[†] Increase in creatinine by >0.3 mg/dl by 72 hours.

[‡] Persisting or worsening heart failure is defined as the need for rescue therapy (additional open label loop diuretic dose, addition of a thiazide diuretic, addition of a vasoactive agent, ultrafiltration, or mechanical circulatory support or ventilation for heart failure).