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Diamond–Forrester classification using echocardiography haemodynamic assessment in cardiac intensive care unit patients

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Abstract

Aims   We sought to determine whether the Diamond–Forrester classification using non-invasive haemodynamic measurements by 2-D and Doppler echocardiography would predict hospital mortality in cardiac intensive care unit (CICU) patients.
Methods and results   We retrospectively analysed unique patients admitted to the CICU at Mayo Clinic Rochester from 2007 to 2018. Doppler-derived cardiac index (CI) and ratio of mitral valve E velocity to medial mitral annulus e′ velocity (E/e′ ratio) were used to classify patients into four profiles: Profile I (warm/dry), Profile II (warm/wet), Profile III (cold/dry), and Profile IV (cold/wet). Logistic regression was used to determine predictors of hospital mortality, and Cox proportional-hazards analysis was used to determine predictors of mortality during one year of follow-up. We included 4563 patients with a mean age of 68.3 ± 14.3 years, including 36.2% female patients. The distribution of each profile was as follows: I, 47.4%; II, 36.2%; III, 7.9%; IV, 8.5%. A total of 5.8% patients died during hospitalization, and 18.1% died by 1 year. Patients with either low CI or elevated E/e′ ratio had higher in-hospital and 1 year mortality. Patients with elevated E/e′ ratio (i.e. Profiles II and IV) had an increased risk of death during hospitalization and at 1 year after multivariate adjustment (adjusted hazard ratio 1.72 and 2.17 for 1 year mortality, respectively, compared with Profile I, $P < 0.01$).
Conclusions   Simple Doppler echocardiographic assessment can be used to identify haemodynamic profiles defined by the Diamond–Forester classification in patients admitted in CICU. These profiles predict outcomes and may be used to guide therapy in critically ill patients.

Introduction

Critically ill patients require close haemodynamic monitoring to titrate treatment during and after their hospitalization.[1] This allows parsimonious administration of fluid and careful adjustment of inotropes and other vasoactive drugs when necessary. Although invasive haemodynamic monitoring is considered the 'gold standard' method, Doppler echocardiography is an alternative non-invasive and risk-free monitoring tool, which has matured sufficiently to be able to manage critically ill patients in the cardiac intensive care unit (CICU).[2]

In 1976, using right heart catheterization, Forrester *et al.*[3] identified four haemodynamic profiles among patients who had an acute myocardial infarction, based on the presence or absence of pulmonary congestion [pulmonary artery wedge pressure (PAWP) > or ≤ 18 mmHg] and adequacy of perfusion [cardiac index (CI) >2.2 L/min/m²]. Profile I represented no congestion or hypoperfusion (warm and dry); Profile II, congestion without hypoperfusion (warm and

wet); Profile III, hypoperfusion without congestion (cold and dry); and Profile IV, both congestion and hypoperfusion (cold and wet). These invasive haemodynamic profiles predicted short-term survival, with increased mortality when congestion was present, and even worse outcomes when both congestion and hypoperfusion were evident (Profile IV).

Over the last 40 years, the use of invasive haemodynamic assessment in critically ill patients has been replaced by non-invasive assessment using Doppler echocardiography, which can provide an estimate of PAWP through the ratio of the mitral early diastolic filling velocity (E-wave) to the annular early diastolic tissue Doppler velocity (E/e′) and calculate CI using the hydraulic orifice formula, which calculates stroke volume as a product of the left ventricular outflow tract (LVOT) area and time-velocity integral (TVI).[4,5]

Accordingly, we sought to determine whether the Diamond–Forrester classification, based on non-invasively obtained haemodynamic data by Doppler echocardiography, would predict hospital and 1 year mortality in CICU patients.

Methods

Study population

This study was approved by the Institutional Review Board of Mayo Clinic (IRB # 16-000722) and was performed under a waiver of informed consent. We retrospectively analysed a previously constructed database of consecutive unique adult patients aged ≥18 years admitted to the CICU at Mayo Clinic Rochester between 1 January 2007 and 30 April 2018 to identify patients with a clinically indicated echocardiogram performed within 1 day of CICU admission who had provided consent for their medical records to be used for research.[6,7] We excluded patients who did not have available data for either of our primary echocardiographic variables of interest (CI and E/e′ ratio).

Data sources

We recorded demographic, vital sign, laboratory, clinical, and outcome data, as well as procedures and therapies performed during the CICU and hospital stay.[8–12] All relevant data were extracted electronically from the medical record using the Multidisciplinary Epidemiology and Translational Research in Intensive Care Data Mart, a repository storing clinical data from all intensive care unit admissions at the Mayo Clinic Rochester.[13] The admission value of all vital signs, clinical measurements, and laboratory values was defined as either the first value recorded after CICU admission or the value recorded closest to CICU admission.[11] Admission diagnoses were defined as all International Classification of Diseases-9 diagnostic codes on the day of CICU admission

and 1 day before or after, including cardiac arrest (CA), cardiogenic shock (CS), acute coronary syndrome (ACS, including all subtypes), heart failure (HF), respiratory failure, and sepsis.[14]

Severity of illness scores

The Acute Physiology and Chronic Health Evaluation (APACHE)-III score, APACHE-IV predicted hospital mortality, and Sequential Organ Failure Assessment score were automatically calculated for all patients using data from the first 24 h of CICU admission using previously validated electronic algorithms, with missing variables imputed as normal as the default.[9–12] The Charlson Comorbidity Index and individual comorbidities were extracted from the medical record using a previously-validated electronic algorithm.[15]

Echocardiographic data

The transthoracic echocardiogram performed closest to the data of CICU admission (either before or after) was identified. Variables of interest included left ventricular ejection fraction (LVEF), LVOT peak spectral Doppler velocity, LVOT systolic spectral Doppler TVI, mitral valve early diastolic (E) spectral Doppler velocity, mitral valve atrial diastolic (A) spectral Doppler velocity and medial mitral annulus early diastolic tissue Doppler (e′) velocity. One best LVEF value for each patient was determined using a hierarchical approach: volumetric LVEF calculated using the 3D Simpson's biplane method was preferred, followed by other calculated LVEF methods, followed by visual estimation if these other methods were unavailable. The LVOT TVI was used to calculate the stroke volume (SV), SV index (SVI), cardiac output, and CI. The ratio of mitral valve E velocity and medial mitral annulus e′ velocity (E/e′ ratio) was used to reflect PAWP. Right ventricular systolic pressure was calculated as $4 * (TR \text{ velocity})^2 + RAP$, in mmHg.

Patients were classified as 'warm' or 'cold' based on CI > 2.2 L/min/m^2 or ≤ 2.2 L/min/m^2, respectively.[16,17] Patients were classified as 'wet' or 'dry' based on medial mitral E/e′ > 14 or ≤ 14, respectively.[18–20] Patients were grouped according to echocardiographic CI and estimated E/e′ according to the Diamond–Forrester classification, as follows: Profile I—warm and dry (CI > 2.2 L/min/m^2 and E/e′ ≤ 14); Profile II—warm and wet (CI > 2.2 L/min/m^2 and E/e′ > 14); Profile III mdash;cold and dry (CI ≤ 2.2 L/min/m^2 and E/e′ ≤ 14); or Profile IV—cold and wet (CI ≤ 2.2 L/min/m^2 and E/e′ > 14).

Survival estimates

The co-primary endpoints were hospital and 1 year mortality, determined using electronic review of health records.

Statistical analysis

Categorical variables are reported as number (percentage) and the Pearson χ^2 test was used to compare groups. Continuous variables are reported as mean (±standard deviation), and the Wilcoxon rank-sum test was used to compare groups. Receiver-operator characteristic curves were constructed by univariable logistic regression for prediction of hospital mortality and used to determine area under the receiver-operator characteristic curve values and the optimal cut-off for predicting hospital mortality was defined as the highest value of Youden's J index (sensitivity + specificity − 1). Logistic regression was used to determine odds ratio (OR) and 95% confidence interval values for prediction of hospital mortality, before and after adjustment for age, gender, comorbidities, APACHE-III score, invasive ventilator, vasoactive drugs, IABP, LVAD/transplant and admission diagnoses; the final model area under the receiver-operator characteristic curve value was 0.91 suggesting excellent discrimination. One-year survival was evaluated using Kaplan-Meier survival analysis, with groups compared using the log-rank test. Cox proportional-hazards analysis was used to determine hazard ratio (HR) and 95% confidence interval values for prediction of one-year mortality, before and after adjustment for age, comorbidities and Day 1 Sequential Organ Failure Assessment score. Two-tailed P values <0.05 were considered statistically significant. Statistical analyses were performed using JMP Pro version 14.1.0 (SAS Institute, Cary, NC, USA).

Results

Study population

Out of 12 428 potentially eligible unique CICU patient admissions, 3922 were excluded due to lack of an appropriately-time echocardiogram (352 without an echocardiogram and 3570 with an echocardiogram more than 1 day before or after CICU admission), leaving 8506 patients with an echocardiogram within 1 day of CICU admission. We subsequently excluded 3943 patients without measured CI or mitral E/e/ ratio. The final cohort included 4563 patients (*Supporting information, Figure S1*).[11] The echocardiogram was done on the day of CICU admission in 42.9% of patients, the prior in 3.9%, and following day in 53.2%.

The mean age of the population was 68.3 ± 14.3 years, and 36.2% were female (*Table 1*). Admission diagnoses (not mutually exclusive) included ACS in 61.6%, HF in 46.1%, CS in 10.8%, and CA in 11.3%. Patients with HF differed substantially from the remaining patients without HF, with greater illness severity and use of critical care therapies (*Table 1*). The mean LVEF was 48.1 ± 15.5%, the mean CI was

2.86 ± 0.72 L/min/m^2, and the mean E/e/ was 15.7 ± 8.8 (*Table 3*). LVEF (39.8% vs. 55.1%) and CI (2.7 vs. 3.0 L/min/m^2) were lower in patients with HF, and E/e/ was higher (19.3 vs. 12.8); all P < 0.001. A total of 16.0% of patients were classified as 'cold' (CI ≤ 2.2 L/min/m^2), including 23.8% with HF and 9.4% without HF. A total of 44.9% of patients were classified as 'wet' (E/e/ > 14), including 63.9% with HF and 28.8% without HF.

Hospital mortality

A total of 5.8% patients died in the hospital, including 3.6% who died in the CICU; both CICU and hospital mortality were higher in patients with HF, who accounted for the majority of deaths (*Table 1*). Patients with (CI ≤ 2.2 L/min/m^2 had higher hospital mortality (12.7% vs. 6.1%, unadjusted OR 2.23, 95% confidence interval 1.78–2.78, P < 0.001) compared with CI > 2.2 L/min/m^2. Patients with E/e/ > 14 had higher hospital mortality (9.2% vs. 3.7%, unadjusted OR 2.63, 95% confidence interval 2.06–3.37, P < 0.001) than those with E/e/ ≤ 14. When included together in a multivariate logistic regression model, both CI and E/e/ remained significantly associated with hospital mortality (both P < 0.001). When this analysis was performed in patients with HF, both CI < 2.2 (OR 2.02, 95% confidence interval 1.47–2.78, P < 0.001) and E/e/ > 14 (OR 1.76, 95% CI 1.25-2.48, P = 0.001) remained associated with hospital mortality. In patients without HF, only E/e/ > 14 was associated with mortality (OR 2.22, 95% confidence interval 1.40–3.53, P < 0.001), whereas CI < 2.2 was not (OR 1.30, 95% confidence interval 0.64–2.66, P = 0.46). Hospital mortality rose incrementally with lower CI (*Figure 1A*) or higher mitral E/e/ ratio (*Figure 1B*), including among patients with ACS or HF.

Diamond–Forrester classification

Using the Diamond–Forrester classification, patients were classified as follows: Profile I (warm/dry) 47.4%, Profile II (warm/wet) 36.2%, Profile III (cold/dry) 7.9%, and Profile IV (cold/wet) 8.5% (*Table 2*). Hospital mortality varied with Diamond–Forrester profile across admission diagnosis groups (*Figure 2A*). Patients with HF had higher hospital mortality in each Diamond–Forrester profile (*Figure 2A*, all P < 0.05), and the observed mortality varied based on the presence or absence of ACS (*Figure 2B*). Hospital mortality (*Table 2, Figure S2*) was higher in warm/wet patients (Profile II), as compared with warm/dry patients (Profile I); likewise, cold/wet patients (Profile IV) had higher hospital mortality than cold/dry patients (Profile III). Profile IV (cold/wet) patients had higher mortality than all other groups, while the Profile III patients (cold/dry) had similar mortality to Profile II patients (P = 0.97) and higher mortality than

Table 1 Baseline characteristics and outcomes of the final study population, including patients with and without an admission diagnosis of heart failure

| Variable	All patients (n = 4563)	Patients with heart failure (n = 2081)	Patients without heart failure (n = 2434)	P value
Age	68 ± 14	71 ± 13.6	66 ± 14	<0.001
Female (%)	1652 (36%)	827 (39.7%)	815 (33.5%)	<0.001
White race (%)	4235 (93%)	1922 (92.4%)	2267 (93.1%)	0.31
DM (%)	1281 (28%)	726 (34.9%)	548 (22.6%)	<0.001
Prior myocardial infarction (%)	850 (18.6%)	467 (22.4%)	377 (15.5%)	<0.001
Admission diagnosis, ACS	2779 (61.5%)	1124 (54.0%)	1655 (68.0%)	<0.001
Admission diagnosis, cardiac arrest	514 (11.3%)	289 (13.9%)	225 (9.2%)	<0.001
Admission diagnosis, shock	590 (13.0%)	457 (22.0%)	133 (5.5%)	<0.001
Admission diagnosis, sepsis	228 (5.0%)	173 (8.3%)	55 (2.3%)	<0.001
ICU length of Stay	2.40 ± 4.0	3.0 ± 5.7	1.9 ± 1.6	<0.001
Apache3 score SAS: 24 h	57.8 ± 23.1	65.8 ± 23.5	51.3 ± 20.6	<0.001
SOFA score	3.0 ± 2.8	4.0 ± 3.2	2.1 ± 2.2	<0.001
Charlson Comorbidity Index (CCI)	2.1 ± 2.5	2.8 ± 2.7	1.6 ± 2.2	<0.001
Invasive ventilation use	593 (13%)	417 (20.0%)	172 (7.1%)	<0.001
Dialysis during ICU	136 (3%)	115 (5.5%)	21 (0.9%)	<0.001
Vasoactive drugs	814 (17.8%)	593 (28.5%)	215 (8.8%)	<0.001
IABP	377 (8.3%)	262 (12.6%)	111 (4.6%)	<0.001
Haemoglobin	12.4 ± 2.0	12.0 ± 2.2	12.8 ± 2.0	<0.001
Platelet	217.6 ± 81.5	215.9 ± 85.3	218.9 ± 78.1	0.03
Sodium	137.8 ± 4.2	137.4 ± 4.8	138.3 ± 3.7	<0.001
Bicarbonate	23.5 ± 4.0	23.6 ± 4.6	23.6 ± 3.4	0.20
BUN	24.7 ± 17.0	30.8 ± 20.4	19.6 ± 11.3	<0.001
Creatinine	1.3 ± 1.0	1.6 ± 1.2	1.1 ± 0.8	<0.001
eGFR (MDRD)	68.2 ± 30.4	57.2 ± 29.4	76.7 ± 28.4	<0.001
Cath but no PCI	1142 (25.0%)	642 (30.8%)	489 (20.1%)	<0.001
PCI	1951 (42.8%)	710 (34.1%)	1376 (56.5%)	<0.001
LVAD/transplant	81 (1.8%)	77 (3.7%)	3 (0.1%)	<0.001
Diamond–Forrester classification				<0.001
I-warm/dry	2139 (47.4%)	564 (27.1%)	1575 (64.7%)	
II-warm/wet	1651 (36.6%)	1021 (49.1%)	630 (25.9%)	
III-cold/dry	347 (7.7%)	188 (9.0%)	159 (6.5%)	
IV-cold/wet	378 (8.4%)	308 (14.8%)	70 (2.9%)	
ICU death	165 (3.6%)	116 (5.6%)	49 (2.0%)	<0.001
Hospital discharge death	263 (5.8%)	188 (9.0%)	75 (3.1%)	<0.001
30 days mortality	326 (7.1%)	236 (11.2%)	85 (3.5%)	<0.001
1 year mortality	702 (15.4%)	513 (24.6%)	189 (7.8%)	<0.001

ACS, acute coronary syndrome; BP, blood pressure; CABG, coronary artery bypass graft; DM, diabetes mellitus; HF, heart failure; ICU, intensive care unit; LVAD, left ventricular assist device; PCI, percutaneous coronary intervention.
P value represents the comparison of patients with and without heart failure. Note that 48 patients did not have data on admission diagnoses.

Profile I (warm/dry) patients. After multivariate adjustment (*Figure S2*), Profile II (warm/wet, *P* = 0.01) and Profile IV (cold/wet, *P* = 0.002) patients had higher hospital mortality than Profile I (warm/dry) patients. No difference was observed between Profile III (cold/dry) patients and either Profile I or Profile II patients (*P* > 0.05), while Profile IV patients had higher mortality than Profile III patients (*P* = 0.01) but not Profile II patients (*P* = 0.25).

The Diamond–Forrester profile was more strongly associated with mortality in patients with HF than patients without HF (*Figure S3*). In the subgroup of patients with an admission diagnosis of HF, all other patients had higher mortality than Profile I, and patients in Profile IV also had higher mortality than Profile II (*Figure S3*). By contrast, the only difference observed in patients without HF was higher morality in Profile II vs. I (*Figure S3*). The Diamond–Forrester classification appeared to provide more robust mortality risk-stratification in patients with sinus rhythm vs. atrial fibrillation (*Figure S4A*) and in patients with LVEF ≥50% vs. LVEF <50% (*Figure S4B*).

One-year mortality by Forrester classification (central illustration)
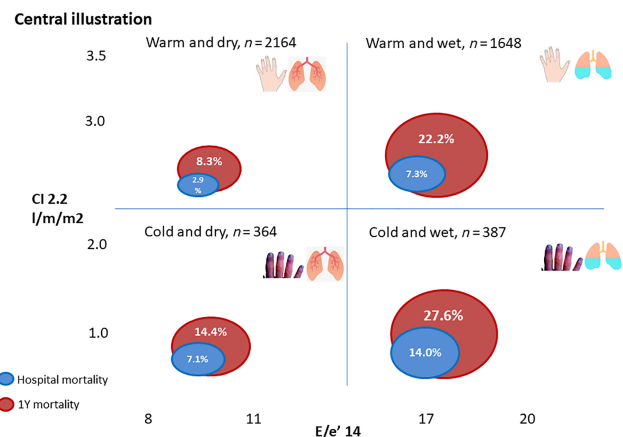
Central illustration
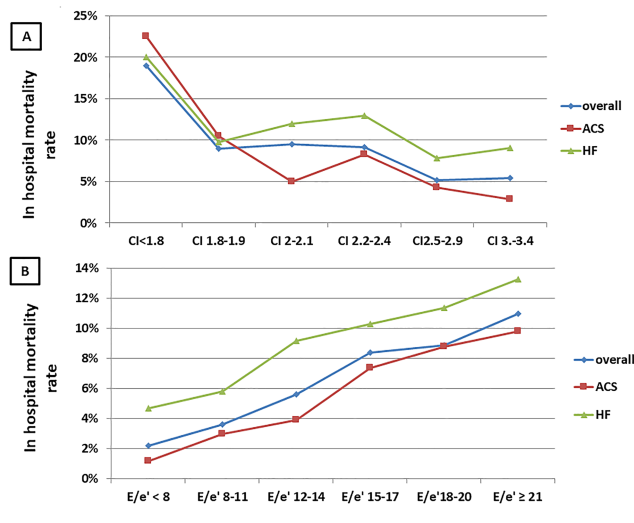
A total of 18.1% of patients died by 1 year, including hospital deaths; patients with HF had higher 1 year mortality (*Table 1*). Patients with CI < 2.2 had lower 1 year survival by Kaplan–Meier analysis (unadjusted Cox HR 1.72, 95% confidence interval 1.47–2.03, *P* < 0.001); this relationship was present for patients with HF (*P* = 0.003), but not those without HF (*P* = 0.19). Similarly, patients with estimated E/eʹ > 14 had lower 1 year survival by Kaplan–Meier analysis (unadjusted Cox HR 2.70, 95% confidence interval 2.32–3.15, *P* < 0.001); this relationship was present for patients with and without HF (both *P* < 0.001). The Forrester classification provided risk stratification for survival out to 1 year (*Figure 3*; *P* < 0.001 by log-rank); this relationship was present for patients with and without HF (both *P* < 0.001). One-year survival was significantly different between the haemodynamic profiles (all *P* < 0.01), with the highest unadjusted survival in Profile I, followed by Profile III, Profile II and the lowest survival in Profile IV. After multivariate adjustment, Profile IV remained significantly associated with higher 1 year mortality than Profile I or Profile III (*Figure 4*), and Profile II remained associated with higher 1 year mortality than Profile I.

Discussion

In this study, we used non-invasive Doppler-derived CI and mitral E/eʹ ratio to revisit the Forrester classification in CICU patients. The non-invasive haemodynamic classification, which can be easily obtained at the bedside, was found to provide in-hospital and long-term prognostic information. We demonstrated that non-invasive Diamond–Forrester classification using echocardiography is feasible in patients who are admitted to the CICU. More importantly, we demonstrated that patients with elevated mitral E/eʹ > 14 (wet profiles) have the worst short and long-term prognosis, which was further worsened by the presence of low CI (Profile IV). This study highlights the importance of Doppler echocardiography for risk stratification of CICU patients and adds to a growing evidence base underlining the importance of the mitral E/eʹ ratio as a prognostic marker in critically ill patients. We found that a low CI, a high mitral E/eʹ ratio and the non-invasive Diamond–Forrester classification provided more robust mortality risk stratification among patients with HF, whereas the CI in particular was less relevant among patients without HF.

The original Diamond–Forrester classification was based on the evaluation of 200 patients admitted with MI to one of the earliest coronary care units. Patients were assigned to four categories based on invasive haemodynamic data reflecting cardiac output and pulmonary congestion using on right heart catheterization-derived cut-off values of CI < 2.2 L/min/m^2, and pulmonary wedge pressure ≥18 mmHg, respectively.[3,17] This classification system has enjoyed a wide clinical application for management as well as for prognosis, but invasive haemodynamic monitoring has been waning gradually, and non-invasive echocardiography can provide similar estimates.[17,21] The use of right heart catheterization for invasive haemodynamic monitoring has fallen out of favour for most populations of critically ill patients, but CICU patients often have complex haemodynamic states where haemodynamic monitoring can still be useful. Therefore, non-invasive haemodynamic monitoring options such as Doppler echocardiography carry a substantial advantage, provided that they can be performed safely and serially at the bedside.[22–24]

Echocardiography has matured to be a reliable diagnostic tool at the patient's bedside, not only for defining the structural abnormalities of the heart, but also providing intracardiac haemodynamics thanks to the advent of blood flow Doppler, tissue Doppler, colour flow, and strain imaging. Skilled intensivists can use echocardiography to evaluate various aspects of shock states, fluid responsiveness, myocardial contractility, intracavitary pressures, heart–lung interaction, and biventricular interdependence. Because echocardiography can recreate the original Forrester classification, we decided to assess the prognostic power of the non-invasively obtained classification.

In this study, non-invasive Diamond–Forrester classification was re-created using E/eʹ and LVOT TVI for unselected patients admitted to the CICU, recognizing the potential limitations of these measurements. Most patients were classified as 'warm' (CI ≥ 2.2 L/min/m^2), consistent with accepted normal values.[16,25] A strength of our analysis is our inclusion of patients with a variety of admission diagnoses in addition

Table 2 Baseline characteristics and outcomes as a function of non-invasive Diamond–Forrester group

Variable	Profile I warm and dry (n = 2164)	Profile II warm and wet (n = 1648)	Profile III cold and dry (n = 364)	Profile IV cold and wet (n = 387)
Age	64 ± 14	74 ± 12	66 ± 14	71 ± 13
Female (%)	603 (28%)	795 (48%)	104 (28%)	150 (38%)
White race (%)*	2020 (93%)	1525 (92%)	337 (93%)	353 (91%)
DM (%)	443 (21%)	627 (38%)	70 (19%)	141 (36%)
Prior myocardial infarction (%)	287 (13.2%)	411 (24.8%)	61 (17.3%)	91 (24.1%)
Admission diagnosis, HF	558 (26%)	1017 (62%)	194 (54%)	312 (80%)
Admission diagnosis, ACS	1442 (68%)	943 (57%)	217 (60%)	177 (46%)
Admission diagnosis, both HF and ACS	332 (16%)	555 (34%)	106 (30%)	131 (34%)
Admission diagnosis, cardiac arrest	205 (6.9%)	168 (10.2%)	73 (20.3%)	68 (17.5%)
Admission diagnosis, shock	187 (8.7%)	216 (13.1%)	75 (20.9%)	112 (28.9%)
Admission diagnosis, sepsis	76 (3.5%)	99 (6.0%)	19 (5.3%)	34 (8.7%)
ICU length of stay	1.99 ± 1.9	2.59 ± 6.0	3.0 ± 2.6	3.3 ± 3.2
Apache3 score SAS: 24 h	49.9 ± 21.0	64.2 ± 20.9	62.8 ± 26.5	70.4 ± 24.7
SOFA score	2.3 ± 2.4	3.5 ± 2.8	3.8 ± 3.4	4.6 ± 3.5
Charlson Comorbidity Index (CCI)	1.57 ± 2.2	2.81 ± 2.6	1.68 ± 2.2	2.79 ± 2.7
Invasive ventilation use	192 (8.8%)	217 (13.1%)	91 (25%)	93 (24%)
Dialysis during ICU	27 (1%)	60 (4%)	13 (4%)	36 (9%)
Vasoactive drugs	246 (11.3%)	310 (18.7%)	109 (30.9%)	149 (39.4%)
IABP	129 (5.9%)	135 (8.2%)	46 (13.0%)	67 (17.7%)
Haemoglobin	12.8 ± 1.9	11.6 ± 2.0	13.1 ± 1.9	12.3 ± 2.0
Platelet	223.6 ± 81.9	214.9 ± 83.2	210.8 ± 70.9	203.0 ± 78.7
Sodium	138.1 ± 3.8	137.7 ± 4.5	138.0 ± 4.6	136.6 ± 4.9
Bicarbonate	23.6 ± 3.6	23.8 ± 4.2	23.0 ± 4.0	22.7 ± 4.6
BUN	19.1 ± 11.2	29.8 ± 19.8	24.0 ± 15.2	34.7 ± 21.2
Creatinine	1.1 ± 0.7	1.5 ± 1.2	1.3 ± 1.0	1.6 ± 1.3
eGFR (MDRD)	78.4 ± 28.1	58.7 ± 29.8	68.1 ± 27.5	53.9 ± 29.4
Cath but no PCI	487 (22.5%)	424 (25.7%)	100 (27.5%)	131 (33.9%)
PCI	1097 (50.7%)	590 (35.8%)	159 (43.7%)	105 (27.1%)
LVAD/transplant	5 (0.23%)	25 (1.52%)	11 (3.02%)	40 (10.34%)
Other heart surgery	360 (16.6%)	490 (29.7%)	104 (28.5%)	148 (38.2%)
ICU death	35 (1.6%)	72 (4.4%)	16 (4.4%)	42 (10.9%)
Hospital discharge death	62 (2.9%)	121 (7.3%)	26 (7.1%)	54 (14.0%)
30 days mortality	78 (3.6%)	155 (9.4%)	30 (8.2%)	63 (16.3%)
1 year mortality	179 (8.3%)	363 (22%)	53 (14%)	107 (27.6%)

ACS, acute coronary syndrome; BP, blood pressure; CABG, coronary artery bypass graft; DM, diabetes mellitus; HF, heart failure; ICU, intensive care unit; LVAD, left ventricular assist device; PCI, percutaneous coronary intervention.
All *P* values are <0.05 except*
P value 0.45.

to ACS (which was the patient population in the original Forrester study), showing that the echocardiographic Forrester classification predicted prognosis across the spectrum of CICU patients. Expectedly, most of the ACS patients were classified as warm/dry, while most of the HF patients were warm/wet. Similar to prior reports, the cold/dry profile was uncommon in this HF cohort.[26]

It is remarkable that a simple Doppler echocardiographic assessment within 1 day of CICU admission could provide mortality risk-stratification out to one year. One year survival differed significantly among each of the four Diamond–Forrester classification groups, with the highest survival among patients classified as warm/dry and the lowest survival among those classified as cold/wet. Mortality across groups differed between patients with ACS and HF, potentially reflecting differences in the relative prevalence and prognostic importance of these haemodynamic groups in these populations. Mortality was similar for all patients classified as 'dry' (i.e. E/e′ ratio ≤14) regardless of CI, emphasizing the primacy of diastolic dysfunction (as defined by elevated E/e′ ratio) over systolic dysfunction (as defined

by low CI) as a determinant of outcomes in this cohort. By contrast, low CI was associated with higher mortality among patients classified as 'wet' (E/e′ ratio >14)—this conditional probability risk likely reflects differences in pathophysiology, with patients displaying a low CI despite elevated filling pressures having more severe cardiac compromise. Our findings are consistent with prior studies emphasizing the association between an elevated E/e′ ratio and adverse outcomes in patients with ACS or CA.[27,28] The presence of an elevated mitral E/e′ ratio is a consistent predictor of adverse outcomes across populations of patients with acute and chronic cardiac disease, likely reflecting an impairment in the left ventricle's diastolic function that represents clinically important underlying heart disease.[29–32]

Future directions

We propose that these non-invasive echocardiographic profiles may be used to guide therapy and may provide a means for the identification of suitable patient populations for

Table 3 Echocardiographic data

Variable	All patients (n = 4563)	Profile I warm and dry (n = 2164)	Profile II warm and wet (n = 1648)	Profile III cold and dry (n = 364)	Profile IV cold and wet (n = 387)
AF at echo	501 (11.6%)	127 (6.1%)	239 (15.4%)	50 (14.7%)	85 (24.3%)
LVEDD (2D,mm)	51.5 ± 7.8	50.2 ± 6.0	52.2 ± 8.4	51.6 ± 8.8	56.3 ± 10.5
LVESD (2D,mm)	37.3 ± 9.9	34.7 ± 7.1	38.4 ± 10.5	39.4 ± 11.2	46.3 ± 13.1
LVESVI (biplane)	75.8 ± 28.9 (n = 1448)	67.6 ± 19.0 (n = 650)	81.9 ± 31.3 (n = 526)	72.8 ± 26.5 (n = 160)	91.7 ± 42.0 (n = 160)
LVEDVI (biplane)	44.8 ± 27.0 (n = 1442)	35.1 ± 16.4 (n = 647)	50.5 ± 28.2 (n = 525)	44.5 ± 23.6 (n = 112)	66.4 ± 33.7 (n = 158)
LVEF (%)	48.1 ± 15.5	53.0 ± 12.4	46.6 ± 15.5	41.0 ± 15.9	33.5 ± 17.0
LA volume index (mL/m^2)	38.4 ± 15.5 (n = 679)	32.7 ± 11.3 (n = 331)	44.5 ± 16.0 (n = 234)	37.1 ± 16.8 (n = 54)	46.4 ± 19.8 (n = 60)
MV E wave velocity (m/s)	0.82 ± 0.28	0.6 ± 0.20	1.00 ± 0.27	0.63 ± 0.21	0.91 ± 0.27
MV annulus e/ velocity (m/s)	0.06 ± 0.02	0.07 ± 0.02	0.05 ± 0.01	0.02 ± 0.04	0.041 ± 0.013
E/e' ratio	15.7 ± 8.8	10.0 ± 2.5	22.6 ± 8.6	10.3 ± 2.4	23.9 ± 9.6
LVOT diameter (mm)	2.2 ± 0.2	2.3 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.2
LVOT velocity (m/s)	1.01 ± 0.19	1.05 ± 0.17	1.03 ± 0.18	0.86 ± 0.17	0.85 ± 0.2
LVOT TVI (cm)	19.9 ± 4.9	20.6 ± 3.9	20.8 ± 4.9	16.1 ± 4.6	15.4 ± 5.2
LV CO (L/min)	5.61 ± 1.54	6.12 ± 1.38	5.79 ± 1.35	3.89 ± 0.74	3.62 ± 0.78
LV CI (L/min/m^2)	2.85 ± 0.72	3.04 ± 0.60	3.05 ± 0.64	1.90 ± 0.26	1.82 ± 0.30
TV velocity (m/s)	2.73 ± 0.49 (n = 3628)	2.58 ± 0.44 (n = 1581)	2.91 ± 0.48 (n = 1418)	2.61 ± 0.51 (n = 285)	2.82 ± 0.52 (n = 344)
Mean TV PG (mmHg)	30.8 ± 11.8 (n = 3628)	27.4 ± 10.6 (n = 1581)	34.8 ± 11.7 (n = 1418)	28.2 ± 11.8 (n = 285)	32.8 ± 12.2 (n = 344)
eRVSP (mmHg)	40.3 ± 14.0 (n = 3600)	35.2 ± 12.5 (n = 1572)	44.7 ± 13.7 (n = 1407)	39.4 ± 13.6 (n = 280)	46.2 ± 13.5 (n = 341)

AF; atrial fibrillation, LVEDD; left ventricular end diastolic dimension, LVESD; left ventricular end systolic dimension, LVESVI; left ventricular end systolic volume index, LVEDVI; left ventricular end diastolic volume index, EF; ejection fraction, MV; mitral valve, CO; cardiac output, CI; cardiac index, TV; tricuspid valve, PG; pressure gradient, eRVSP; estimated right ventricular systolic pressure.
All P values are <0.05.

Figure 2 (A) Hospital mortality varied with Diamond–Forrester profile across admission diagnosis (B): Hospital mortality varied with Diamond–Forrester profile groups based on the presence or absence of ACS. ACS, acute coronary syndrome; HF, heart failure; CA, cardiac arrest.
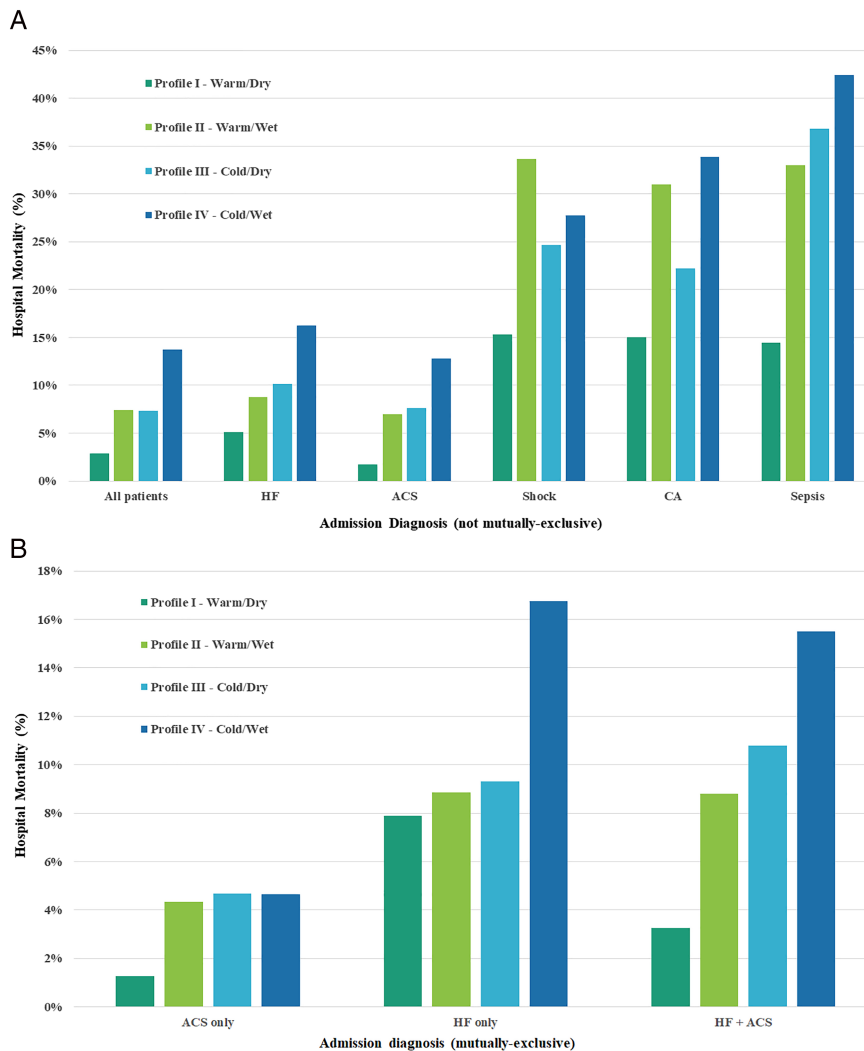

Figure 3 Kaplan–Meier survival rate according to clinical profile.
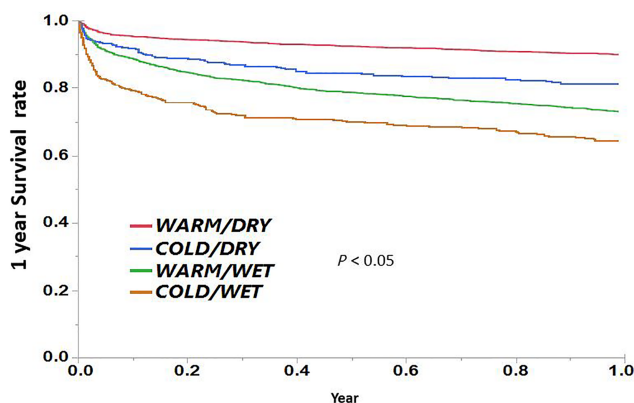
future therapies. The consistent identification of an elevated E/e′ ratio with adverse outcomes among patients with ACS in particular suggests that this group might benefit from more intensive guideline-directed medical therapy. Currently, medical therapy for patients with ACS depends on the presence or absence of reduced LVEF (<40%), but it is possible that patients with elevated E/e′ ratio could potentially benefit from additional therapies such as spironolactone, which are typically reserved for patients with LVEF and clinical heart failure.[33–35]

Indeed, the echocardiographic Diamond–Forrester classification could provide an objective way to clinically operationalize the Killip classification, which has proven useful in prognostication and clinical decision-making among patients with ACS. Among patients with HF, it is conceivable that vasoactive therapies and diuretics could be titrated using

Figure 4 Unadjusted and adjusted 1 year mortality according to profile.
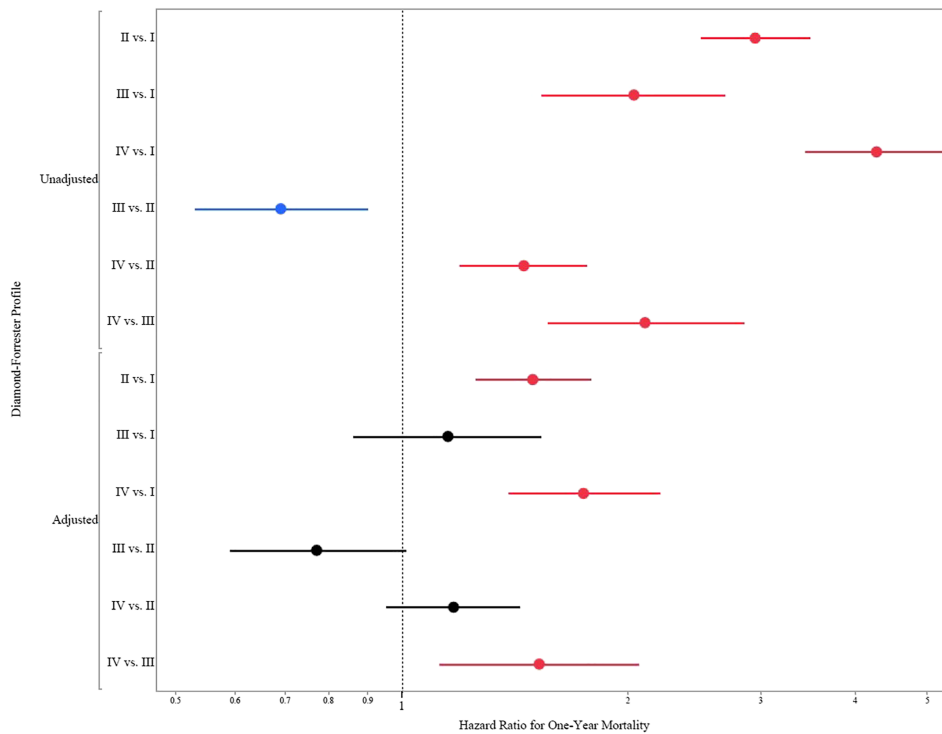
serial echocardiography to ensure that patients return to a warm/dry profile during hospitalization prior to discharge. Indeed, Doppler echocardiography could be used to screen patients with ACS or HF for inclusion in clinical trials, by targeting those patients with the most significant haemodynamic compromise for new or intensified medical therapies that might be less effective when applied to the broader population as a whole.

Limitations

This retrospective cohort analysis carries a number of limitations that make the results hypothesis-generating and prevent determination of causation. Not all patients in the original database had available echocardiogram data, and not all echocardiograms had all relevant variables reported, leading to potential selection bias in who underwent echocardiography that could have influenced the results. In particular, the observed hospital mortality in this cohort was lower than the overall CICU population from which it was derived.[7] We suspect that each patient's acuity of illness and other prognostically important factors influenced whether they underwent an echocardiogram and what echocardiographic data could be obtained. Although many patients likely underwent bedside transthoracic echocardiogram by the CICU team, we only included data from formal

echocardiograms which were performed by a cardiology fellow or sonographer, read by a staff cardiologist and entered into the database. Therefore, while measurement errors (e.g. in the LVOT diameter) may have occurred and potentially been amplified when calculating the CI, these data reflect those collected and reported in routine clinical practice. We were unable to determine whether patients were mechanically ventilated or on vasoactive drugs at the time of echocardiography, and these factors could have influenced the echocardiogram findings and therefore the study results. Furthermore, these echocardiographic data are merely a snapshot at a single time point in a patient's course, and fail to capture the inherent variability and changing nature of haemodynamics, particularly after ACS. Finally, significant controversy exists within the literature regarding the use of the mitral E/eʹ alone as a marker of diastolic dysfunction and elevated left ventricular filling pressures.[36,37] There are numerous clinical variables that can degrade the association between the E/eʹ ratio and the left ventricular filling pressures, and we could neither identify the presence of these factors in our cohort nor could we confirm the presence of elevated left ventricular filling pressures via invasive haemodynamics assessment.[29] We did not have adequate data to formally grade diastolic dysfunction in this cohort according to current guidelines, which might have greater accuracy for elevated left ventricular filling pressures.[38] Rather, we chose to use a simplified approach relying on the mitral

E/eʋ ratio, as this is easier to apply at the bedside in critically ill patients, as previously advocated for patients with sepsis and septic shock.[39] Despite the limitations of using E/eʋ in unselected CICU patients, we observed a strong association between E/eʋ and outcomes validating our approach. Likewise, estimation of SV and CI from the LVOT VTI may not be accurate in the presence of aortic valve disease or LVOT obstruction, and we did not have data regarding these findings.

Conclusions

Doppler echocardiography can be used to classify CICU patients according to their haemodynamics into the four profiles originally described by Forrester. Mortality during hospitalization and out to one year increased in a stepwise fashion for patients classified as warm/dry, cold/dry, warm/wet and cold/wet, with better performance of the Diamond–Forrester classification among patients with HF. Our data suggest that congestion and left ventricular diastolic dysfunction, as defined by an elevated E/eʋ ratio, is a more prognostically important finding than low output, as defined by a low CI calculated from the LVOT TVI. Haemodynamic

Doppler echocardiography is an important test for CICU patients, both to define prognosis and potentially guide supportive therapy. Further study is needed to compare the clinical utility of Doppler echocardiography vs. other modalities for haemodynamic monitoring in CICU patients.

Supporting information

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

Figure S1. Study population selection.
Figure S2. Odds ratio for hospital mortality according to clinical profile.
Figure S3. Odds ratio for hospital mortality in patients with HF than patients without HF according to clinical profile.
Figure S4A. Mortality risk-stratification in patients with sinus rhythm versus atrial fibrillation according to the Diamond-Forrester classification.
Figure S4B. Mortality risk-stratification in patients with LVEF ≥50% versus LVEF <50%.

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