ORIGINAL RESEARCH ARTICLE

Age and shock severity predict mortality in cardiac intensive care unit patients with and without heart failure

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Abstract

Aims   Age is an important risk factor for mortality among patients with cardiogenic shock and heart failure (HF). We sought to assess the extent to which age modified the performance of the Society for Cardiovascular Angiography and Interventions (SCAI) shock stage for in-hospital and 1 year mortality in cardiac intensive care unit (CICU) patients with and without HF.

Methods and results   We retrospectively reviewed unique admissions to the Mayo Clinic CICU during 2007–2015 and stratified patients by age and SCAI shock stage. The association between age and in-hospital mortality was analysed using multivariable logistic regression, and 1 year mortality was analysed using Cox proportional hazards analysis, both in the entire cohort and among patients with an admission diagnosis of HF or acute coronary syndrome (ACS). The final study population included 10 004 unique patients with a mean age of 67 ± 15 years, including 46.1% with HF and 43.1% with ACS. Older patients more frequently had HF and had more extensive co-morbidities, higher illness severity, more organ failure, and differential use of critical care therapies. The percentage of patients with SCAI shock stages A, B, C, D, and E were 46%, 30%, 16%, 7%, and 1%, respectively. Patients with HF were older, had greater severity of illness and higher SCAI shock stage, and had higher rates of death at all time points. In-hospital mortality occurred in 908 (9%) patients, including 549 (12%) patients with HF (61% of all hospital deaths). Age was independently associated with hospital mortality (adjusted odds ratio per 10 years 1.3, 95% confidence interval 1.2–1.4, $P < 0.001$) and 1 year mortality (adjusted hazard ratio per 10 years 1.2, 95% confidence interval 1.2–1.3, $P < 0.001$) in the overall cohort. The associations of age with both hospital mortality (adjusted odds ratio 1.6 vs. 1.3 per 10 years older) and 1 year mortality (adjusted hazard ratio 1.5 vs. 1.3 per 10 years older) were higher for patients with ACS compared with patients with HF. Older age was associated with higher adjusted hospital mortality and 1 year mortality in each SCAI shock stage (all $P < 0.05$). Additive increases in both hospital mortality and 1 year mortality were observed with increasing age and SCAI shock stage.

Conclusions   Age is an independent risk factor for mortality that modifies the relationship between the SCAI shock stage and mortality risk in CICU patients, providing robust risk stratification for in-hospital and 1 year mortality. Although patients with HF had a higher risk of dying, age was more strongly associated with mortality among patients with ACS.

Introduction

Older age is an established non-modifiable risk factor for mortality and other adverse outcomes in hospitalized patients with cardiovascular disease or critical illness, including cardiac intensive care unit (CICU) patients.[1,2] Age has been integrated into multiple clinical scoring systems designed for mortality risk stratification, and higher age has consistently been associated with an increased risk of mortality in both cardiovascular and non-cardiovascular conditions.[1,3–5] Cardiogenic shock (CS) is associated with significant morbidity and mortality, particularly among older patients.[5–8] Among patients with CS, older age has been identified as a major risk factor for mortality and has been potentially linked with a decreased response to certain therapies.[9–15]

Recently, the Society for Cardiovascular Angiography and Interventions (SCAI) published a CS severity classification system, allowing more consistent grading of CS acuity across studies.[16] The SCAI shock stages classification provides robust mortality risk stratification in unselected CICU patients and patients with CS.[5,17–19] One stated purpose of the SCAI shock stages classification is to standardize communication between providers to streamline inter-facility transfers in health systems utilizing the recommended "hub-and-spoke" model.[16] There are few available data regarding whether age influences the severity of CS or whether age modifies outcomes across the acuity spectrum of CS. Understanding the intersection of age and shock severity for mortality risk stratification could facilitate CICU patient triage and clinical decision-making.

The aim of this study was to determine the effect of age on in-hospital and 1 year mortality in unselected CICU patients as a function of shock severity (defined by the SCAI shock stage) and to provide further insights about how older age contributes to worse outcomes.

Methods

Study population

This study was approved by the Institutional Review Board of Mayo Clinic (IRB # 16-000722) as posing minimal risk to patients and was performed under a waiver of informed consent. The investigation conforms with the principles outlined in the Declaration of Helsinki. We retrospectively analysed a previously constructed database including data from the index CICU admission of consecutive unique adult patients aged ≥18 years admitted to the CICU at Mayo Clinic Hospital, St. Mary's Campus between 1 January 2007, and 31 December 2015.[1,4–6,17,18,20–26] To minimize bias associated

with CICU readmission, only data from the first CICU admission during the study period were analysed.

Data sources

Using the Multidisciplinary Epidemiology and Translational Research in Intensive Care Data Mart, we recorded demographic, vital signs, laboratory, clinical, and outcome data, as well as procedures and therapies performed during the CICU and hospital stay.[1,4–6,17,18,20–27] The admission vital signs, clinical measurements, and laboratory values were defined as either the first value recorded after or closest to the index CICU admission. Vital signs were recorded every 15 min during the first hour after CICU admission. Admission diagnoses were defined as all International Classification of Diseases-9 diagnostic codes within 1 day before or after CICU admission; admission diagnoses were not mutually-exclusive.[5,6,18,21]

Maximum vasopressor and inotrope doses during the CICU stay were quantified using the peak vasoactive–inotropic score.[22] Non-cardiovascular organ failure was defined as a score ≥3 on any of the non-cardiovascular Sequential Organ Failure Assessment (SOFA) organ sub-scores on CICU Day 1.[21] The Acute Physiology and Chronic Health Evaluation (APACHE) III score, APACHE IV predicted hospital mortality, and SOFA scores were automatically calculated using data from the first 24 h of CICU admission using previously validated electronic algorithms.[1,4,20,21,25] The non-cardiovascular SOFA score was calculated by summing the other five SOFA organ sub-scores.[4,25] Individual co-morbidities used to calculate the Charlson Co-morbidity Index were extracted from the medical record using a previously validated electronic algorithm.[28] The Braden Skin Score at the time of CICU admission was used as a surrogate marker of frailty.[1,26] When available, echocardiographic data were extracted for patients with an echocardiogram within 1 day before or after hospitalization; left ventricular systolic dysfunction (LVSD) was defined using left ventricular ejection fraction (LVEF) according to current guidelines.[29]

Definition of Society for Cardiovascular Angiography and Interventions shock stages

As per our previously published definitions, we defined hypotension/tachycardia, hypoperfusion, deterioration, and refractory shock using data from CICU admission through the first 24 h in the CICU (Supporting Information, *Table S1*).[5,17,18] We mapped the five SCAI shock stages with increasing severity (A through E) using combinations of these variables (Supporting Information, *Table S2*).[5,16–18] Late deterioration was defined as an increasing number or dose of

vasopressors after 24 h, independent of the initial SCAI shock stage.[5,17,18]

Statistical analysis

All-cause CICU, hospital, and 1 year mortality were determined using an electronic review of medical records for notification of patient death and last follow-up date. Mortality data were extracted from Mayo Clinic electronic databases, the state of Minnesota electronic death certificates, and the Rochester Epidemiology Project database.[30] Variables of interest were compared across age groups. Categorical variables are reported as number (percentage), and the Pearson χ^2 test was used to compare groups; trends across age groups and SCAI stages were determined using the Cochran–Armitage trend test. Continuous variables are reported as mean (± standard deviation), and the Wilcoxon rank-sum test was used to compare groups. Odds ratio (OR) and 95% confidence interval (CI) values for hospital mortality were determined using logistic regression, before and after adjusting for gender, Charlson Co-morbidity Index,

non-cardiovascular SOFA score, Braden Skin Score, SCAI shock stage, and late deterioration; admission diagnosis of cardiac arrest (CA); and the use of vasoactive medications, coronary angiography, percutaneous coronary intervention, dialysis, in-hospital cardiopulmonary resuscitation, and invasive mechanical ventilation. Kaplan–Meier survival analysis was used to determine 1 year mortality, with groups compared using the log-rank test. Hazard ratio (HR) values for 1 year mortality were determined using Cox proportional hazards models, before and after adjusting for these same variables. 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).

Results

Study population

The database included 10 004 unique CICU patients. The mean age was 67 ± 15 years, 3746 (37.4%) were female,

Table 1 Baseline characteristics, co-morbidities, and admission diagnoses of the study population, divided by age group

	Age (years)				P value
	<50 (n = 1290)	50–64 (n = 2733)	65–79 (n = 3734)	≥80 (n = 2257)	
Demographics and outcomes					
Age	42.6 (34.9, 47.2)	58.5 (54.7, 61.9)	72.6 (68.9, 76.2)	85.3 (82.6, 88.6)	<0.001
Female gender	464 (36%)	797 (29.2%)	1384 (37.2%)	1101 (48.8%)	<0.001
White race	1105 (85.7%)	2458 (89.9%)	3481 (93.5%)	2192 (97.1%)	<0.001
Body mass index	28.7 (24.5, 34.4)	29.6 (25.7, 34.4)	28.8 (25.3, 33.2)	26.9 (23.8, 30.3)	<0.001
ICU length of stay	1.7 (0.9, 2.8)	1.8 (1.0, 2.9)	1.8 (0.9, 3.0)	1.7 (0.9, 2.8)	0.0258
Hospital length of stay	3.9 (2.3, 8.5)	4.1 (2.5, 9)	4.9 (2.8, 9.6)	4.8 (2.8, 8)	<0.001
CICU mortality	32 (2.5%)	122 (4.5%)	228 (6.1%)	188 (8.3%)	<0.001
Hospital mortality	56 (4.3%)	196 (7.2%)	374 (10%)	282 (12.5%)	<0.001
Overall 1 year survival	1152 (89.3%)	2310 (84.5%)	2848 (76.5%)	1443 (63.9%)	<0.001
Co-morbidities					
Charlson Co-morbidity Index	0 (0, 2)	1 (0, 3)	2 (1, 4)	3 (1, 4)	<0.001
Prior myocardial infarction	109 (8.5%)	449 (16.5%)	872 (23.5%)	550 (24.4%)	<0.001
Prior congestive heart failure	169 (13.2%)	408 (15%)	814 (21.9%)	562 (24.9%)	<0.001
Prior stroke	65 (5%)	194 (7.1%)	513 (13.8%)	457 (20.3%)	<0.001
Prior chronic kidney disease	140 (10.9%)	410 (15%)	843 (22.7%)	638 (28.3%)	<0.001
Prior diabetes mellitus	186 (14.5%)	715 (26.2%)	1294 (34.8%)	642 (28.5%)	<0.001
Prior cancer	94 (7.3%)	369 (13.6%)	926 (24.9%)	746 (33.1%)	<0.001
Prior lung disease	171 (13.4%)	424 (15.6%)	820 (22.1%)	529 (23.4%)	<0.001
Prior dialysis	76 (5.9%)	171 (6.3%)	229 (6.2%)	95 (4.2%)	0.004
Admission diagnoses[a]					
Cardiac arrest	145 (11.4%)	351 (13.1%)	476 (12.9%)	221 (9.8%)	0.001
Respiratory failure	210 (16.5%)	514 (19.1%)	828 (22.5%)	527 (23.4%)	<0.001
Congestive heart failure	460 (36.1%)	1089 (40.5%)	1784 (48.4%)	1231 (54.7%)	<0.001
Acute coronary syndrome	449 (35.3%)	1226 (45.6%)	1622 (44.0%)	970 (43.0%)	<0.001
Atrial fibrillation/supraventricular tachycardia	232 (18.2%)	679 (25.3%)	1323 (35.9%)	986 (43.8%)	<0.001
Ventricular tachycardia/ventricular fibrillation	256 (20.1%)	459 (17.1%)	618 (16.8%)	275 (12.2%)	<0.001
Sepsis	91 (7.2%)	146 (5.4%)	219 (5.9%)	149 (6.6%)	0.13

CICU, cardiac intensive care unit; ICU, intensive care unit.
For categorical variables, data are presented as number (per cent), with P value representing trends across age groups using the Cochran–Armitage trend test. For continuous variables, data are presented as median (interquartile range), with P value representing between-groups comparisons using the Wilcoxon rank-sum test.
[a]Admission diagnosis data were missing for 106 patients, and admission diagnoses are not mutually exclusive.

and 9236 were White. Admission diagnoses included heart failure (HF) in 46.1%, acute coronary syndrome (ACS) in 43.1%, CA in 12.1%, and sepsis in 6.1%. The source of admission included catheterization/procedural laboratory in 40.0%, inter-facility transfer in 27.2%, emergency department in 14.0%, hospital ward in 16.0%, and others in 2.9%. Patients were grouped based on age: <50 years, 1290 (12.9%) patients; 50–64 years, 2733 (27.3%) patients; 65–79 years, 3724 (37.2%) patients; and ≥80 years, 2257 (22.6%) patients (*Table 1*). Baseline characteristics (*Tables 1* and *2*) varied as a function of age group: older patients had more co-morbidities, higher severity of illness, more organ failure (including acute kidney injury), and different patterns of admission diagnoses and use of critical care therapies. The use of critical care therapies was higher among patients aged 50–79 years but was lower among patients ≥80 years (*Table 2*). Admission vital signs and laboratory variables differed across age groups (*Table 3*), with lower heart rate, higher systolic blood pressure, lower haemoglobin, and worse renal function among older patients. Among patients with available echocardiographic data, the prevalence of LVSD increased, and LVEF decreased, with increasing age (*Table 2*).

Age and shock severity

The distribution of SCAI shock stages was as follows: A, 4602 (46.0%) patients; B, 2998 (30.0%) patients; C, 1575 (15.7%) patients; D, 732 (7.3%) patients; and E, 97 (1.0%) patients. The distribution of SCAI shock stages varied minimally across

Table 2 Baseline severity of illness and therapies and procedures of the study population, divided by age group

	Age (years)				P value
	<50 (n = 1290)	50–64 (n = 2733)	65–79 (n = 3734)	≥80 (n = 2257)	
Severity of illness					
Braden Skin Score	19 (17, 21)	18 (16, 21)	18 (15, 20)	17 (15, 19)	<0.001
APACHE III score	40 (30, 54)	48 (37, 63)	61 (50, 75)	70 (59, 82)	<0.001
APACHE IV predicted mortality	0.04 (0.02, 0.08)	0.05 (0.02, 0.12)	0.11 (0.05, 0.23)	0.18 (0.1, 0.3)	<0.001
SOFA score	2 (1, 4)	2 (1, 5)	3 (1, 5)	3 (2, 5)	<0.001
Non-cardiovascular SOFA	1 (0, 3)	1 (0, 3)	2 (0, 4)	2 (1, 4)	<0.001
Single organ failure	216 (16.7%)	439 (16.1%)	732 (19.7%)	485 (21.5%)	<0.001
Multi-organ failure	113 (8.8%)	334 (12.2%)	501 (13.4%)	282 (12.5%)	0.001
SCAI shock stages					
A	571 (44.2%)	1372 (50.2%)	1700 (45.6%)	959 (42.5%)	<0.001
B	450 (34.8%)	817 (29.9%)	1100 (29.5%)	631 (28%)	<0.001
C	185 (14.3%)	329 (12%)	576 (15.5%)	485 (21.5%)	<0.001
D	70 (5.4%)	199 (7.3%)	299 (8%)	164 (7.3%)	<0.001
E	14 (1%)	16 (0.6%)	49 (1.3%)	18 (0.8%)	<0.001
Late deterioration	93 (7.2%)	227 (8.3%)	268 (7.2%)	120 (5.3%)	0.001
Therapies and procedures					
RBC transfusion	98 (7.6%)	255 (9.3%)	514 (13.8%)	306 (13.6%)	<0.001
Use of any ventilator	267 (20.7%)	704 (25.8%)	1126 (30.2%)	629 (27.9%)	<0.001
Invasive ventilator	182 (14.1%)	450 (16.5%)	635 (17.1%)	340 (15.1%)	0.04
Noninvasive ventilator	118 (9.2%)	359 (13.1%)	638 (17.1%)	374 (16.6%)	<0.001
Pulmonary artery catheter	128 (9.9%)	255 (9.3%)	266 (7.1%)	72 (3.2%)	<0.001
Dialysis	99 (7.7%)	185 (6.8%)	173 (4.6%)	30 (1.3%)	<0.001
Continuous renal replacement therapy	27 (2%)	66 (2.4%)	59 (1.6%)	15 (0.7%)	<0.001
Vasoactive medications	312 (24.2%)	736 (26.9%)	961 (25.8%)	459 (20.3%)	<0.001
Vasopressor medications	234 (18.1%)	574 (21%)	848 (22.8%)	434 (19.2%)	0.001
Inotrope medications	171 (13.3%)	335 (12.3%)	323 (8.7%)	99 (4.4%)	<0.001
Coronary angiogram	656 (50.8%)	1605 (58.7%)	2053 (55.1%)	970 (43%)	<0.001
Percutaneous coronary intervention	334 (25.9%)	1041 (38.1%)	1307 (35%)	745 (33%)	<0.001
Intra-aortic balloon pump	82 (6.4%)	292 (10.7%)	348 (9.3%)	143 (6.3%)	<0.001
Impella®	5 (0.4%)	5 (0.2%)	7 (0.2%)	4 (0.2%)	0.6
ECMO	23 (1.8%)	29 (1.1%)	18 (0.5%)	2 (0.1%)	<0.001
In-hospital CPR	26 (2%)	83 (3%)	136 (3.7%)	68 (3%)	0.02
Inpatient echocardiogram	1028 (83.2%)	2286 (86.7%)	3135 (86.5%)	1770 (80.8%)	0.005
LVEF (%)	53 (35, 61)	51 (34, 60)	50 (34, 60)	50 (35, 62)	0.005
LVSD	408 (48.8%)	988 (51.0%)	1466 (55.2%)	831 (52.9%)	0.009
Mild	150 (17.9%)	352 (18.2%)	465 (17.5%)	271 (17.2%)	
Moderate	106 (12.7%)	302 (15.6%)	489 (18.4%)	334 (21.3%)	
Severe	152 (18.2%)	334 (17.2%)	512 (19.3%)	226 (14.4%)	

APACHE, Acute Physiology and Chronic Health Evaluation; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; RBC, red blood cell; SCAI, Society for Cardiovascular Angiography and Interventions; SOFA, Sequential Organ Failure Assessment.
For categorical variables, data are presented as number (per cent), with *P* value representing trends across age groups using the Cochran–Armitage trend test. For continuous variables, data are presented as median (interquartile range), with *P* value representing between-groups comparisons using the Wilcoxon rank-sum test.

Table 3 Vital signs and laboratory values closest to cardiac intensive care unit admission as a function of age group

	Age (years)				P value
	<50 (n = 1290)	50–64 (n = 2733)	65–79 (n = 3734)	≥80 (n = 2257)	
Vital signs					
Temperature (Celsius)	36.7 (36.5, 36.9)	36.7 (36.4, 36.9)	36.6 (36.4, 36.9)	36.6 (36.4, 36.9)	<0.001
Heart rate (b.p.m.)	86 (72, 101)	79 (67, 93)	78 (66, 93)	78 (64.8, 93)	<0.001
Systolic blood pressure	117 (102, 134)	119 (104, 136)	121 (105, 140)	127 (108, 146)	<0.001
Diastolic blood pressure	71 (62, 82)	71 (62, 82)	67 (57, 77)	65 (55, 76.2)	<0.001
Respiratory rate (respirations per minute)	18 (15, 21)	17 (14, 21)	18 (15, 21)	18 (15, 22)	<0.001
Shock index	0.72 (0.6, 0.9)	0.65 (0.5, 0.8)	0.64 (0.5, 0.8)	0.62 (0.5, 0.8)	<0.001
Oxygen saturation	98 (95, 99)	98 (95, 99)	97 (94, 99)	97 (94, 99)	<0.001
Mean arterial pressure	82 (73, 94)	84 (74, 95)	81 (71, 92)	81 (70, 93)	<0.001
Urine output in the first 24 h (mL)	1964 (1200, 2989)	1915 (1175, 2823)	1649 (1000, 2524)	1420 (835, 2141)	<0.001
Laboratory values					
Haemoglobin (g/dL)	13 (11.2, 14.4)	12.9 (11.2, 14.2)	11.9 (10.4, 13.4)	11.5 (10.1, 12.8)	<0.001
White blood cell count (× 10^9/L)	9.9 (7.6, 13.1)	9.8 (7.4, 12.8)	9.4 (7.2, 12.4)	9.4 (7.3, 12.5)	0.001
Platelets (× 10^9/L)	211 (166, 266)	208 (166, 259)	196 (154, 241)	195 (153, 244)	<0.001
Sodium (mmol/L)	138 (135, 140)	138 (136, 140)	138 (136, 141)	139 (136, 141)	<0.001
Potassium (mmol/L)	4.1 (3.8, 4.5)	4.2 (3.9, 4.6)	4.2 (3.9, 4.6)	4.3 (3.9, 4.7)	<0.001
Chloride (mmol/L)	103 (100, 106)	104 (100, 106)	103 (100, 106)	103 (100, 106)	0.47
Bicarbonate (mmol/L)	24 (21, 26)	24 (21, 26)	24 (21, 26)	24 (21, 27)	0.08
Anion gap	11 (9, 14)	11 (9, 13)	11 (9, 14)	11 (9, 14)	0.28
Blood urea nitrogen (mg/dL)	15 (11, 21)	18 (13, 26)	22 (16, 34)	26 (19, 38)	<0.001
Creatinine (mg/dL)	0.9 (0.7, 1.2)	1 (0.8, 1.3)	1.1 (0.8, 1.5)	1.2 (0.9, 1.6)	<0.001
Estimated GFR (MDRD)	87.4 (64.9, 104.8)	75.2 (52.3, 89.1)	60.5 (40.4, 81.5)	52.1 (35.4, 68.6)	<0.001
Aspartate aminotransferase (U/L)	46 (28, 111)	49 (29, 125)	44 (27, 100)	43 (27, 95)	0.003
Alanine aminotransferase (U/L)	38 (22, 69)	35 (22, 66)	30 (20, 58.2)	26 (17, 49)	<0.001
Lactate (mmol/L)	1.5 (1.1, 2.8)	1.8 (1.2, 3.1)	1.8 (1.1, 3.2)	1.8 (1.2, 3)	0.09
Arterial pH	7.38 (7.3, 7.4)	7.37 (7.3, 7.4)	7.36 (7.3, 7.4)	7.37 (7.3, 7.4)	0.11

GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
Data are presented as median (interquartile range), with P value representing between-groups comparisons using the Wilcoxon rank-sum test.

age groups (*Table 2* and Supporting Information, *Figure S1A*), without a definite trend (*P* = 0.23 for trend). The use of vasoactive drugs and the peak vasoactive–inotropic score varied across age groups, without significant trends (*Table 2*). There was lower use of all mechanical support devices (particularly intra-aortic balloon pump and extracorporeal membrane oxygenation) and pulmonary artery catheter in patients in the older age groups (*Table 2* and Supporting Information, *Figure S1B*). The prevalence of late deterioration varied across age groups and was lowest among patients ≥80 years (*Table 1*).

Hospital mortality

Hospital mortality occurred in 908 (9.1%) patients, including 570 (5.7%) who died in the CICU. Both CICU and hospital mortality were higher in older patients (*P* < 0.001 for trends). Hospital mortality rose with increasing age in each SCAI shock stage except stage D (all other *P* < 0.01 for trend; *Figure 1*). Hospital mortality rose with increasing SCAI shock stage in each age group (all *P* < 0.001 for trends; *Figure 1*). Similar findings were observed in patients with admission diagnoses of ACS (Supporting Information, *Figure S2A*) or HF (Supporting Information, *Figure S2B*). Age was significantly associated with unadjusted hospital mortality in each SCAI shock stage (all *P* < 0.05), and the SCAI shock stage was significantly associated with unadjusted hospital mortality in each

age group (all *P* < 0.001). Adding age to the SCAI shock stages increased the area under the receiver-operator characteristic curve for hospital mortality (0.790 vs. 0.765, *P* < 0.001 by DeLong test).

After multivariable adjustment, increasing age was associated with higher hospital mortality (adjusted OR per 10 years 1.324, 95% CI 1.234–1.420, *P* < 0.001). After adjustment, older age remained associated with higher hospital mortality in each SCAI shock stage (all *P* < 0.05; *Figure 2A*). As shown in Supporting Information, *Figure S2*, each older age group was associated with incrementally higher adjusted hospital mortality than each of the younger age groups (all *P* < 0.05).

One year mortality

A total of 2251 (22.5%) patients died by 1 year (including hospital deaths), and 954 (9.5%) patients had <1 year of follow-up. One year mortality increased progressively with rising age group (*Figure 3*; *P* < 0.001 by log-rank test). Age remained associated with 1 year mortality after multivariable adjustment (adjusted HR per 10 years 1.243, 95% CI 1.200–1.288, *P* < 0.001). After adjustment, older age was associated with higher 1 year mortality in each SCAI shock stage (all *P* < 0.05; *Figure 2B*). *Figure 4* demonstrates 1 year survival as a function of age and SCAI shock stage using the Kaplan–Meier method, showing gradations in 1 year mortality as

Figure 1 Crude hospital mortality as a function of Society for Cardiovascular Angiography and Interventions (SCAI) shock stage and age group. All *P* < 0.001 for age trend across each SCAI stage and all *P* < 0.001 for SCAI stage trend across each age group.
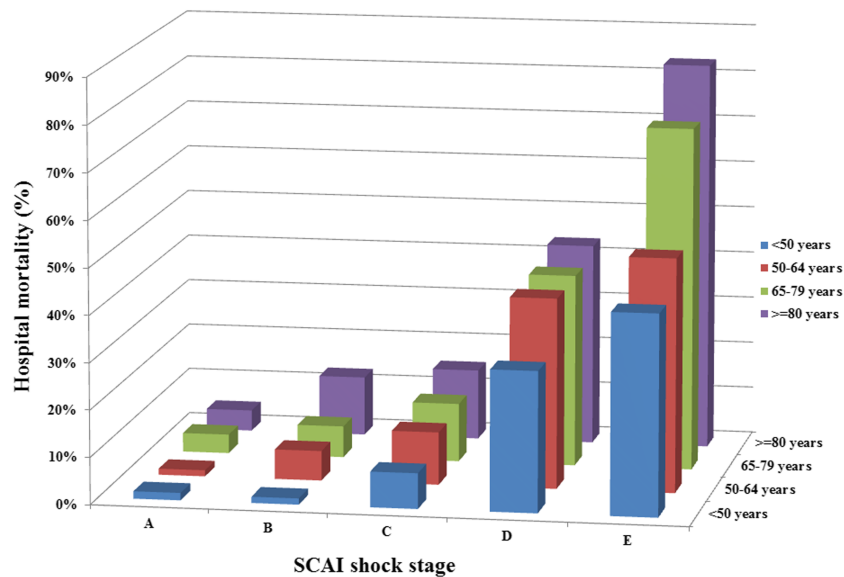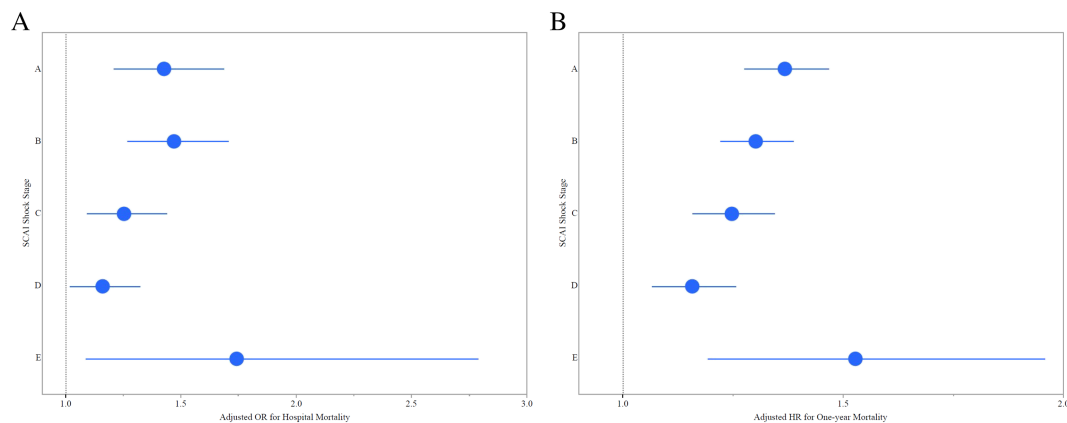

Figure 2 (A and B) Forest plot demonstrating (A) adjusted odds ratio (OR) values for hospital mortality using multivariable logistic regression and (B) adjusted hazard ratio (HR) values for 1 year using Cox proportional hazards analysis for increasing age (per 10 years higher) in each Society for Cardiovascular Angiography and Interventions shock stage.
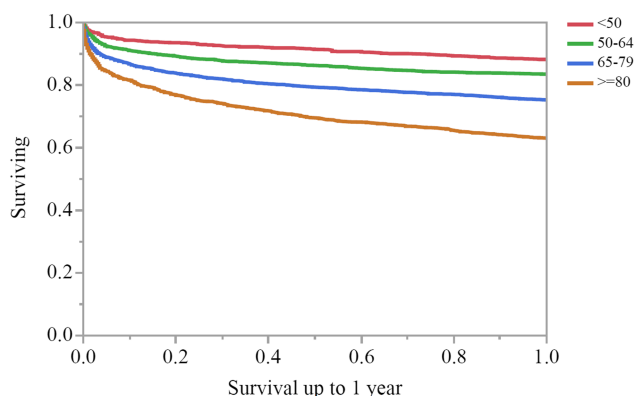

either age or SCAI shock stage increased. As shown in Supporting Information, *Figure S3*, each older age group was associated with incrementally higher adjusted 1 year mortality than each of the younger age groups (all *P* < 0.01).

Patients with heart failure

Subgroup analysis was performed in 4564 (46.1%) patients with an admission diagnosis of HF. Both a prior history of HF and an admission diagnosis of HF became more prevalent with increasing age (*Table 1*). Among patients with available

echocardiographic data, the prevalence of LVSD among patients with HF was 72.1%, with a median LVEF of 36% (interquartile range: 25, 55); 13.6% had mild LVSD, and the remainder had moderate or severe LVSD (*Table 4*). Patients with an admission diagnosis of HF were older (71.2 vs. 67.0 years, *P* < 0.001) and had higher illness severity, greater use of critical care therapies, and higher length of stay (*Table 4*); patients with HF had higher SCAI shock stages and a higher risk of late deterioration (all *P* < 0.001). Patients with HF had a higher risk of dying at all time points, accounting for 60.6% of all hospital deaths and 67.0% of all 1 year deaths. Although an admission diagnosis of HF was not

Figure 3 Kaplan–Meier curves demonstrating 1 year survival across age groups. *P* < 0.001 between groups by log-rank test.

per 10 years 1.311, 95% CI 1.202–1.430, *P* < 0.001). Similarly, age was more strongly associated with adjusted 1 year mortality in patients with an admission diagnosis of ACS (adjusted OR per 10 years 1.506, 95% CI 1.409–1.609, *P* < 0.001) than patients with an admission diagnosis of HF (adjusted OR per 10 years 1.279, 95% CI 1.225–1.336, *P* < 0.001). SCAI shock stage was a strong (*P* < 0.001) predictor of both hospital mortality and 1 year mortality in patients with ACS or HF, although the adjusted OR/HR values were modestly higher for patients with ACS.

Discussion

In this analysis of 10 004 CICU patients, we demonstrated the additive effects of older age and rising shock severity on short-term and long-term mortality. Older patients had higher overall illness severity, more co-morbidities, and more critical care needs but did not have greater shock severity based on SCAI shock stage. Older patients had higher in-hospital and post-discharge mortality even after adjusting for shock severity, early non-cardiovascular organ dysfunction, and frailty. Expectedly, older individuals with more severe shock had worse outcomes compared with younger patients or those with less severe shock. We observed relevant interactions between age and SCAI shock stage, and the effect of age on adjusted mortality varied by SCAI stage. Older patients in SCAI shock stages D and E had particularly

associated with hospital mortality after adjustment (*P* = 0.85), patients with HF were at higher risk of 1 year mortality (adjusted HR 1.456, 95% CI 1.321–1.606, *P* < 0.001). One year mortality by the Kaplan–Meier method increased incrementally as a function of higher SCAI shock stage and higher age among patients with HF (Supporting Information, *Figure S4*).

Age was more strongly associated with adjusted hospital mortality in patients with an admission diagnosis of ACS (adjusted OR per 10 years 1.589, 95% CI 1.393–1.813, *P* < 0.001) than patients with an admission diagnosis of HF (adjusted OR

Figure 4 Heat map demonstrating crude 1 year survival (by Kaplan–Meier method) as a function of age group and Society for Cardiovascular Angiography and Interventions (SCAI) shock stage. Darker colours represent a lower rate of survival.
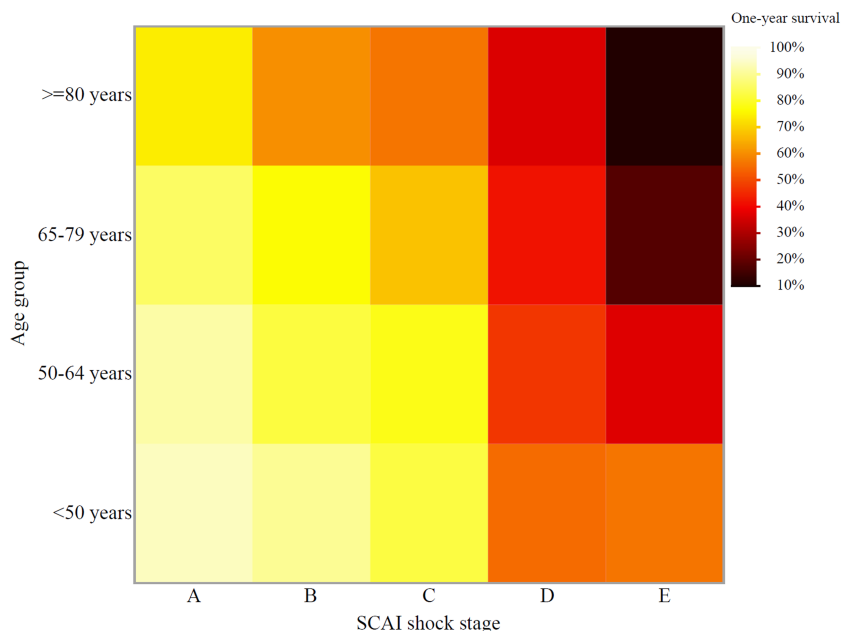
Table 4 Baseline characteristics of patients with and without and admission diagnosis of HF

	Patients with HF (*n* = 4564)	Patients without HF (*n* = 5334)	*P* value
Demographics and outcomes			
Age	71.2 (60.6, 80.8)	67.0 (55.7, 77.4)	<0.001
<50 years	460 (10.1%)	813 (15.2%)	<0.001
50–64 years	1089 (23.9%)	1598 (30.0%)	
65–79 years	1784 (39.1%)	1902 (35.7%)	
≥80 years	1231 (27.0%)	1021 (19.1%)	
Female gender	1757 (38.5%)	1954 (36.6%)	0.06
White race	4187 (91.7%)	4948 (92.8%)	0.06
Body mass index	28.4 (24.7, 33.3)	28.4 (25.0, 32.8)	0.35
ICU length of stay	2.0 (1.0, 3.7)	1.4 (0.9, 2.4)	<0.001
Hospital length of stay	7.0 (3.9, 12.3)	3.2 (2.1, 5.9)	<0.001
CICU mortality	311 (6.8%)	257 (4.8%)	<0.001
Hospital mortality	549 (12.0%)	357 (6.7%)	<0.001
Overall 1 year survival	3056 (67.0%)	4593 (86.1%)	<0.001
Co-morbidities			
Charlson Co-morbidity Index	2 (1, 5)	1 (0, 3)	<0.001
Prior myocardial infarction	1098 (24.1%)	870 (16.4%)	<0.001
Prior congestive heart failure	1701 (37.4%)	243 (4.6%)	<0.001
Prior stroke	700 (15.4%)	517 (9.7%)	<0.001
Prior chronic kidney disease	1371 (30.1%)	649 (12.2%)	<0.001
Prior diabetes mellitus	1615 (35.5%)	1199 (22.5%)	<0.001
Prior cancer	1066 (23.4%)	1057 (19.9%)	<0.001
Prior lung disease	1100 (24.2%)	837 (15.7%)	<0.001
Prior dialysis	388 (8.5%)	179 (3.4%)	<0.001
Admission diagnoses[a]			
Cardiac arrest	597 (13.1%)	596 (11.2%)	0.004
Respiratory failure	1503 (32.9%)	576 (10.8%)	<0.001
Acute coronary syndrome	1637 (35.9%)	2630 (49.3%)	<0.001
Atrial fibrillation/supraventricular tachycardia	1831 (40.1%)	1389 (26.0%)	<0.001
Ventricular tachycardia/ventricular fibrillation	977 (21.4%)	631 (11.8%)	<0.001
Sepsis	401 (8.8%)	204 (3.8%)	
Severity of illness			
Braden Skin Score	17 (15, 20)	18 (16, 20)	<0.001
APACHE III score	65 (52, 80)	52 (39, 52)	<0.001
APACHE IV predicted mortality (%)	14.1 (6.5, 29.2)	6.4 (2.7, 14.4)	<0.001
SOFA score	4 (2, 6)	2 (1, 4)	<0.001
Non-cardiovascular SOFA	3 (1, 5)	1 (0, 2)	<0.001
Single organ failure	1106 (24.2%)	746 (14.0%)	<0.001
Multi-organ failure	780 (17.1%)	436 (8.2%)	<0.001
SCAI shock stages			
A	1675 (36.7%)	2871 (53.8%)	<0.001
B	1562 (34.2%)	1414 (26.5%)	
C	758 (16.6%)	799 (15.0%)	
D	513 (11.2%)	213 (4.0%)	
E	56 (1.2%)	39 (0.7%)	
Late deterioration	566 (12.4%)	140 (2.6%)	<0.001
Therapies and procedures			
RBC transfusion	658 (14.4%)	506 (9.5%)	<0.001
Use of any ventilator	1817 (39.8%)	884 (16.6%)	<0.001
Invasive ventilator	989 (21.7%)	603 (11.3%)	<0.001
Noninvasive ventilator	1108 (24.3%)	369 (6.9%)	<0.001
Pulmonary artery catheter	622 (13.6%)	97 (1.8%)	<0.001
Dialysis	385 (8.4%)	102 (1.9%)	<0.001
Continuous renal replacement therapy	139 (3.0%)	28 (0.5%)	<0.001
Vasoactive medications	1685 (36.9%)	764 (14.3%)	<0.001
Vasopressor medications	1321 (28.9%)	750 (14.1%)	<0.001
Inotrope medications	789 (17.3%)	135 (2.5%)	<0.001
Coronary angiogram	2070 (45.4%)	3133 (58.7%)	<0.001
Percutaneous coronary intervention	1151 (25.2%)	2226 (41.7%)	<0.001
Intra-aortic balloon pump	568 (12.4%)	288 (5.4%)	<0.001
Impella®	16 (0.4%)	5 (0.1%)	0.006
ECMO	59 (1.3%)	13 (0.2%)	<0.001
In-hospital CPR	163 (3.6%)	147 (2.8%)	0.02
Inpatient echocardiogram	3864 (85.5%)	4283 (84.2%)	0.07
LVEF (%)	36 (25, 55)	55 (48, 63)	<0.001
LVSD	2397 (72.1%)	1267 (35.1%)	<0.001

(*Continues*)

Table 4 (continued)

	Patients with HF (n = 4564)	Patients without HF (n = 5334)	P value
Mild	452 (13.6%)	773 (21.4%)	
Moderate	655 (25.7%)	364 (10.1%)	
Severe	1090 (32.8%)	130 (3.6%)	

APACHE, Acute Physiology and Chronic Health Evaluation; CICU, cardiac intensive care unit; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; HF, heart failure; ICU, intensive care unit; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; RBC, red blood cell; SCAI, Society for Cardiovascular Angiography and Interventions; SOFA, Sequential Organ Failure Assessment.
For categorical variables, data are presented as number (per cent), with P value representing trends across age groups using the Pearson χ^2 test. For continuous variables, data are presented as median (interquartile range), with P value representing between-groups comparisons using the Wilcoxon rank-sum test.
[a]Note that admission diagnosis data were missing for 106 patients, who were not included in this analysis.

high crude in-hospital and 1 year mortality, despite age being more strongly associated with mortality in lower SCAI shock stages. This study adds to the growing body of evidence highlighting older age and greater shock severity as major mortality risk factors among CICU patients.

Age has been consistently found to be an independent risk factor for mortality in multiple prior studies of hospitalized and critically ill cardiac patients, including CICU populations, patients with CS, and patients with ACS.[9,15,31–33] Age is a critical variable in most mortality prediction risk scores, including those specifically designed for patients with CS as well as standard scoring systems such as APACHE.[1,3,11,12,20,24] Illness severity scores have lower discrimination of mortality in older CICU patients, raising important questions about how best to risk-stratify older CICU patients given their higher risk of adverse outcomes than younger patients.[1] Even though age is an important risk factor for mortality in both ACS and HF, we unexpectedly observed that the relationship between age (and to a lesser extent SCAI shock stage) and mortality was weaker for patients with HF compared with ACS patients.([24,34]) While this could reflect the lower overall discrimination for hospital mortality that we have previously observed in CICU patients with HF (who have a higher baseline mortality risk), this could suggest that standard risk factors for mortality do not adequately categorize CICU patients with HF and imply a need to identify novel risk factors within this cohort.([6,24]) Indeed, age itself may be a less relevant risk factor in patients with HF than illness duration, co-morbidity burden, and frailty (i.e. biological age vs. chronological age).

Our study demonstrates additively higher mortality as both age and SCAI shock stage increased, contributing to the growing literature validating the SCAI shock stages paradigm for risk stratification of critically ill cardiac patients.[5,17–19] We observed incremental increases in hospital mortality with rising age in SCAI shock stages A, B, and C, with a notable step-up in hospital mortality for patients aged ≥65 years in SCAI shock stage E. One year mortality was high for older patients with severe shock—fewer than half of SCAI shock stage D patients aged ≥50 years were alive at 1 year, as were fewer than one

in five SCAI shock stage E patients aged ≥65 years. Overall, these data help to provide mortality estimates to guide triage and transfer of older CICU patients with shock, particularly in resource-limited settings.

We observed trends suggesting less aggressive care strategies among patients ≥80 years, which suggests that the application of critical care therapies in older patients may be modified by age-related co-morbidities, frailty, perceived benefits, and individual goals of care. Importantly, the efficacy of standard therapies for CS has not been systematically examined in older patients, and older age may be an exclusion criterion for advanced HF therapies. The stronger association that we observed between age and mortality for patients with ACS when compared with HF patients could reflect the effects of older age on the clinical efficacy of revascularization in ACS. Notably, a *post hoc* subgroup analysis of the SHOCK trial suggested a decreased benefit of early revascularization among acute myocardial infarction-related CS patients aged ≥75 years.[14] In contrast, the majority of observational studies have demonstrated meaningful survival benefits with early revascularization and aggressive critical care therapies in older acute myocardial infarction-related CS patients attributable to their higher baseline risk.[9,35,36] Furthermore, older patients with ACS and CS may have subtle symptoms and non-cardiac co-morbidities leading to delays in diagnosis and management with resultant worse outcomes.[37] Despite poor outcomes, care was not necessarily futile among our older patients with severe shock, and individualized decision-making should take into account prognostically relevant factors such as organ failure severity and baseline health status.

The proposed pathophysiological basis for the relationship between age and outcomes is multifactorial, including decreased tissue regenerative capacity, limited physical reserve, co-morbidities, frailty, and psychosocial factors.[1,37–39] Frailty has gained recent interest as a predictor of poor outcomes in hospitalized patients with cardiac disease, including CICU patients.[39] Nguyen *et al*. recently demonstrated that frailty was associated with increased adverse outcomes in ACS patients.[40] In the present study, we

adjusted for the Braden Skin Score as a marker of frailty, as this has been previously demonstrated to predict worse outcomes in CICU patients.[1,26] Age remained associated with mortality even after adjusting for the Braden Skin Score, which itself was a strong predictor of hospital and 1 year mortality; this implicates both frailty and other age-related factors as contributors to worse outcomes. Future studies are needed to better understand the physiological underpinnings of the relationship between age and adverse outcomes in CICU patients, accounting for frailty and patient care preferences.

Limitations

This study has relevant limitations that apply to similar retrospective cohort analyses, particularly the potential for the results to have been influenced by unmeasured confounding variables. The CICU population at Mayo Clinic may differ from other populations in terms of baseline demographics (particularly a low prevalence of racial and ethnic minorities), case mix, and procedure utilization; although the observed hospital mortality in our cohort was lower than some prior CICU studies, it is generally in line with other reported academic tertiary-care CICU populations.[2,3,8,33,41] This was an all-comers CICU cohort including a heterogeneous group of patients with an array of admission diagnoses and a wide spectrum of illness severity including fewer than one-quarter of patients who met SCAI criteria for shock; as such, the results we observed may not apply equally to more highly selected cohorts of patients with CS. Our post-discharge mortality analysis should be considered exploratory, as the use of electronic health records rather than the more definitive National Social Security Death Index to determine patient death may underestimate post-discharge mortality by potentially failing to capture patients dying in other health systems. Perhaps the most important limitation of this analysis is the lack of available data regarding comprehensive frailty assessment, do-not-resuscitate orders, or cause of death, preventing us from providing specific insights about the manner in which age-related factors could have affected mortality.

Conclusions

Age and SCAI shock stage synergistically predict higher in-hospital and 1 year mortality in a CICU patient population. By highlighting the very high mortality hazard faced by older patients with severe shock, this study emphasizes the need to better understand the optimal approach to shock management in this vulnerable subgroup. Our data can help to inform prognostic assessment for CS patients by providing real-world data about expected mortality risk out to 1 year

as a function of age and SCAI shock stage, recognizing that decision-making regarding triage must rely on additional patient-specific factors and care preferences. Although older patients had higher measures of non-cardiovascular organ dysfunction and frailty, neither these factors nor shock severity was adequate to explain the association between age and higher mortality. The relationship between age and mortality varied as a function of admission diagnosis, emphasizing the nuances in prognostic assessment for patients with different forms of underlying cardiac disease. Further study will be required to elucidate the underlying pathophysiological mechanisms linking older age to worse outcomes in shock patients, to allow a tailored approach to therapy in this high-risk population.

Conflict of interest

The authors report no relevant conflicts of interest related to this research. D.A.B. has consulted for Getinge, Livanova, M3, Abiomed, Abbott, and Procyrion and has been a speaker for Novartis and Pfizer.

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Author contributions

All authors participated in the creation and production of this manuscript.

Supporting information

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

Table S1. Study definitions of hypotension, tachycardia, hypoperfusion, deterioration and refractory shock. Data from Jentzer, et al. J Am Coll Cardiol 2019.
Table S2. Definition of cardiogenic shock (CS) stages used in this study, based on the Society for Cardiovascular Angiography and Intervention (SCAI) consensus statement classification. Data from Jentzer, et al. J Am Coll Cardiol 2019.
Figure S1. Distribution of SCAI shock stage (A) and use of PAC and MCS in each age group (B).
Figure S2. Hospital mortality as a function of SCAI shock stage and age group in patients with an admission diagnosis of ACS (A) or HF (B).

Figure S3. Forest plot demonstrating adjusted odds ratio (OR) values for hospital mortality using multivariable logistic regression (A) and adjusted hazard ratio (HR) values for one-year mortality using Cox proportional-hazards analysis (B) for each age group compared with each other.

Figure S4. Heat map demonstrating one-year survival by the Kaplan–Meier method as a function of age group (Y axis) and SCAI shock stage (X axis) among the subgroup of patients with an admission diagnosis of HF. Darker colours represent lower survival.

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