Cardiogenic shock during heart failure hospitalizations: Age-, sex-, and race-stratified trends in incidence and outcomes

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Background The objectives were to study the overall and age-, sex-, and race-stratified incidence of cardiogenic shock (CS) during heart failure hospitalizations (HFHs) not complicated by acute coronary syndromes (ACS), utilization of short-term mechanical circulatory support (MCS) and in-hospital mortality with non–ACS-related CS, and respective temporal trends. Data are lacking regarding the epidemiology of non–ACS-related CS during HFHs.

Methods Retrospective observational analysis of the National Inpatient Sample 2005-2014 to identify all HFHs in adult patients without concomitant ACS.

Results Of 8,333,752 HFHs, incidence rate of non–ACS-related CS was 8.7 per thousand HFHs (N = 72,668), a 4-fold increase from 4.1 to 15.6 per thousand HFHs between 2005 and 2014 (P_{trend} < .001). Among those with non–ACS-related CS, utilization rates of intra-aortic balloon pump, extracorporeal membrane oxygenation, and temporary ventricular assist devices were 12.8%, 1.4%, and 2.5%, respectively. Respective 2005 to 2014 trends were 14.2% to 10.7%, 0.6% to 1.8%, and 0.8% to 2.7% (P_{trend} for all, <.001). In-hospital mortality rate was 27.1%, with a substantial decrease from 42.4% in 2005 to 23.3% in 2014 (P_{trend} < .001). These temporal trends were largely consistent across age, sex, and race subgroups.

Conclusion During HFHs in the United States, non–ACS-related CS occurred infrequently but was associated with substantial mortality. Non–ACS-related CS incidence and certain MCS utilization rates increased, and in-hospital mortality rate decreased between 2005 and 2014. These trends were generally homogenous across the age, sex, and race groups. The observed trends in incidence and mortality may be a reflection of increased identification of CS during HFHs, although further study is needed to assess whether temporal changes in care may have influenced outcomes. (Am Heart J 2019;213:18-29.)

Cardiogenic shock (CS) is a low-output circulatory state resulting in hypoxia and life-threatening end-organ hypoperfusion.[1] Acute coronary syndromes (ACSs) with left ventricular dysfunction or mechanical complications are the most frequent cause (5%-12% incidence), and these have been the focus of most research in CS.[1,2] Worsening or advanced/end-stage heart failure (HF) presenting in the acute state accounts for around 10%-30% of CS cases, resulting from either underlying disease progression or poor adherence to guideline-based medical therapies.[1,3] CS is an infrequent presentation of acute HF, resulting from underlying ACS.[4-6] In the Acute Decompensated Heart Failure National Registry of 100,000 HF hospitalizations (HFHs), 3% had a systolic blood pressure <90 mm Hg at admission, although they were not labeled as having CS.[7] Irrespective of the etiology, CS is associated with high mortality ranging from 27% to 51% or higher.[1]

Earlier diagnosis and prompt revascularization have resulted in improved outcomes in ACS complicated by CS, although the utility of mechanical circulatory support (MCS) with intra-aortic balloon pump (IABP) was questionable.[8-13] Although there were no recent pharmacologic developments for the management of CS in HF, short-term MCS with IABP, ventricular assist devices (VADs), or extracorporeal membrane oxygenation (ECMO) are being used to improve hemodynamic instability in these patients.[1] Such an approach

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demonstrated therapeutic potential in numerous small studies.[14-19] Also, the implementation of "shock teams" and higher hospital experience of CS cases were associated with improved mortality.[1,20] Epidemiological data regarding the true incidence and outcomes of CS during HFHs without concomitant ACS are lacking. We sought to determine the overall and age-, sex-, and race-stratified incidence of CS during an HFH without ACS, utilization of short-term MCS and in-hospital mortality with CS, and the respective temporal trends.

Methods

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Data source

Data were obtained from the United States Healthcare Cost and Utilization Project National Inpatient Sample (NIS) years 2005 through 2014.[21] The NIS contains ~8 million unweighted discharge records per year and is a 20% stratified sample of all-payer inpatient admissions from acute care hospitals. Stratified sampling is done based on geographic region, location, teaching status, ownership, and bed size. Discharge weights were provided for each record which was used to obtain national estimates.

Study population and outcomes

HFHs were recognized in patients ≥18 years of age by identifying the following *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes in the primary discharge diagnosis position: 398.91, 402.x1, 404.x1, 404.x3, and 428 (N = 10,325,767). Cases with a coexisting discharge diagnosis of ACS (*ICD-9-CM* codes 410, 411.1; 4.8%) and with missing values for age (<0.1%), sex (<0.1%), mortality (<0.1%), and race (15%) were excluded. Non–ACS-related CS was identified using *ICD-9-CM* code 785.51 in any discharge diagnosis position in this cohort. Similar strategies for identification of HF and CS were used previously.[11,22] Patient characteristics (age, sex, race, primary insurance, median income quartile), admission characteristics (elective, weekend), hospital characteristics (region, bed number, teaching status), and Elixhauser comorbidities were extracted from the NIS. Patients were categorized into 4 age groups: 18-44 (young), 45-64 (middle aged), 65-79 (old), and ≥80 (very old). Race was categorized as white, black, Hispanic, and others.

Clinical comorbidities (smoking status, atrial fibrillation, chronic kidney disease [CKD], end-stage renal disease [ESRD], ischemic heart disease [IHD], dementia), in-hospital complications (acute kidney injury [AKI], sepsis), and in-hospital procedures were identified using relevant *ICD-9-CM* and Healthcare Cost and Utilization Project Clinical Classification Software diagnosis and procedure codes listed in Supplementary Table I. IHD was identified by the presence of ischemic cardiomyopathy, prior myocardial infarction, prior revascularization, coronary artery disease, or angina. Sepsis was identified by recognizing diagnosis codes for septicemia, sepsis, severe sepsis, and septic shock. AKI requiring hemodialysis was recognized by identifying *ICD-9* codes for both AKI and dialysis in the diagnosis and procedural fields (Supplementary Table I).

Study outcomes

Overall and age-, sex-, and race-stratified incidence of non–ACS-related CS, utilization rates of short-term MCS devices (IABP, temporary VADs, ECMO) and in-hospital mortality rate with CS, and their respective trends were our main outcomes. Overall trends in in-hospital procedures, average length of stay (LOS), and hospitalization costs were examined as secondary outcomes.

Statistical analysis

Differences in patient characteristics with and without non–ACS-related CS were compared using the survey-specific Rao-Scott χ^2 test for categorical variables and Student *t* test for continuous variables. Trends in rates of CS incidence, short-term MCS use, and mortality were analyzed using the Mantel-Haenzsel test for trend.[23] Age-, sex-, and race-stratified overall trends were examined using similar methodology. Survey-design–based logistic regression models accounting for the complex sample design of the NIS were used to analyze unadjusted and adjusted temporal variability (relative to 2005) in CS incidence and mortality.[21] Calendar year was entered as a categorical variable in the regression models. For CS incidence, regression model adjusted for age, sex, and race. Because sepsis-related shock can be coded as CS during an HFH, a sensitivity analysis for incidence was performed excluding cases with sepsis. Adjusted age, sex, race, and IHD-stratified temporal variability in CS incidence was studied using similar regression models.

For CS mortality, the risk-adjusted multivariable logistic regression model included all patient and hospital characteristics, relevant comorbidities, in-hospital complications, and procedures. Because heart transplantation and durable left ventricular assist device (LVAD) placement are associated with improved survival to discharge, a sensitivity analysis for mortality was performed excluding cases with these procedures. Sensitivity analysis excluding cases with sepsis diagnosis was also performed. Risk-adjusted age-, sex-, and race-stratified temporal variability in CS mortality was studied using similar regression models. LOS and inflation-adjusted hospitalization costs were log-transformed because they had a positively skewed distribution, and temporal trends were examined using survey-specific general linear model. Costs were inflation adjusted with January 2014 as reference.[24] To account for possible competing risk of death on LOS and cost outcomes, we also analyzed LOS and cost data in a sensitivity analysis excluding patients who died during the HFHs.

Categorical variables are expressed as percentages and continuous variables as mean (standard error [SE]). Results of logistic regression are reported as odds ratio (OR) and 95% CIs. All reported *P* values are 2-sided. *P* values for trend analysis of LOS and cost are for comparison of geometric means. Statistical analysis was performed using IBM SPSS Statistics 25.0 (IBM Corp, Armonk, NY).

Results

Baseline characteristics

Between 2005 and 2014, 8,333,752 cases of HFHs without ACS were included in our study. Baseline characteristics are presented in Table I. The overall incidence of non–ACS-related CS was 8.7 per thousand HFHs (N = 72,668). Mean patient age with non–ACS-related CS during an HFH (64.6 [0.3] years) was significantly lower compared to cases without CS (72.6 [0.9] years; $P < .001$), and the proportion of males was higher with CS than without (66.4% vs 49.6%; $P < .001$). CS was more frequently diagnosed in larger, teaching hospitals. Higher prevalence of CKD, atrial fibrillation, pulmonary circulation disorders, and in-hospital complications like sepsis and AKI was observed with CS. IHD and cardiovascular risk factors like diabetes mellitus, hypertension, smoking, obesity, and vascular disease were less prevalent with CS during an HFH.

Trends in baseline characteristics with non–ACS-related CS during a HFH are presented in Supplementary Table II. The mean patient age decreased from 66.8 (1.1) years in 2005 to 64.6 (0.5) years in 2014 ($P_{trend} < .001$). Males constituted two-thirds of the sample, and their proportion increased from 63.4% in 2005 to 67.9% in 2014 ($P_{trend} < .001$). Patients of white race were of the highest proportion (63.3%). IHD (50.7%), hypertension (47.2%), CKD/ESRD (45.3%), atrial fibrillation (43.4%), and diabetes mellitus (34.7%) were the most frequent comorbidities; Table I. AKI (60.6%) complicated most cases of CS with an increasing incidence between 2005 and 2014, whereas sepsis complicated around 15% cases with declining rates during this period. Overall and temporal trends in procedural utilization are presented in Supplementary Table III and Supplementary Figure 2.

Trends in incidence of non–ACS-related CS

Overall, the incidence of non–ACS-related CS quadrupled from 4.1 to 15.6 per thousand HFHs between 2005 and 2014 ($P_{trend} < .001$) (unadjusted OR for 2014 compared to 2005: 3.82, 95% CI 3.21-4.54); Figure 1, *A*. After adjusting for patient demographics, a similar increase in the incidence of non–ACS-related CS was observed (OR for 2014 relative to 2005 is 3.70, 95% CI 3.13-4.38); Table III. Similar results were observed in cases with and without IHD and in a sensitivity analysis excluding cases with sepsis; Table II.

There was a higher non–ACS-related CS incidence when HFHs were in males compared to those in females (11.6 vs 5.8 per thousand HFHs, respectively; $P < .001$), and this difference persisted throughout the study period. Overall, the 18- to 44-year group had a higher incidence rate of non–ACS-related CS (21.5 per thousand HFHs) compared to the 45- to 64-year (13.7 per thousand HFHs), 65- to 79-year (8.8 per thousand HFHs), and ≥80-year groups (4.3 per thousand HFHs) ($P < .001$). Overall incidence rate of non–ACS-related CS was 8.2 per thousand HFHs in whites and 9.6 per thousand HFHs in blacks and Hispanics. From 2005 to 2014, the incidence of non–ACS-related CS during HFHs increased significantly in all subgroups studied ($P_{trend} < .001$); Figure 1, *B-D*. Similar increasing trends in non–ACS-related CS incidence were observed in patient demographic adjusted subgroup specific analyses; Table II.

Trends in short-term mechanical circulatory support utilization in CS

Overall, short-term MCS was used in 15% cases, mostly IABP (12.8%) followed by temporary VADs (2.5%) and ECMO (1.4%). Between 2005 and 2014, utilization of any form of short-term MCS and IABP decreased, and utilization rates of ECMO and temporary VADs increased significantly; Figures 2, *A* and 3; Table III. Significant declines in the utilization rates of any form of short term MCS were seen in most subgroups studied; Figure 2, *B-D*. Numerical increase from was noted in the 18- to 44-year group, and rates were relatively stable in blacks and Hispanics; Figure 2, *B-D*.

Non–ACS-related CS in the 18- to 44-year-old patient group had higher IABP, ECMO, and temporary VAD utilization rates compared to the 45- to 64-, 65- to 79-, and ≥80-year groups (IABP: 20.3% vs 16.4% vs 11.5% vs 4.2%, respectively; ECMO 3.7% vs 2.0% vs 0.8% vs 0%, respectively; temporary VAD: 6.6% vs 3.3% vs 1.3% vs 0.2%, respectively; $P < .001$). Between 2005 and 2014, IABP utilization rate remained stable in 18- to 44-year group but decreased significantly in the other age groups; Supplementary Figure 1, *A*. ECMO and temporary VAD utilization rates increased significantly in the 18- to 44-year and 45- to 64-year groups; Supplementary Figure 1, *D* and *G*. ECMO and temporary VAD utilization rates were too low to present meaningful trends in the older patient groups.

Utilization rate of any form of MCS was higher in males compared to females (IABP: 14.2% vs 10.3%, respectively, $P < .001$; ECMO: 1.6% vs 1.0%, respectively, $P < .001$; temporary VAD: 2.9% vs 1.6%, respectively, $P < .001$). Between 2005 and 2014, IABP utilization rates declined in

Table I. Baseline characteristics of the overall study population

	Overall cohort	Cardiogenic shock	
	(N = 8,333,752)	No (n = 8,261,084)	Yes (n = 72,668)
Mean age (SE) (y)	72.5 (1.0)	72.6 (0.9)	64.6 (0.3)
Age groups (y)			
18-44	4.3%	4.3%	10.6%
45-64	23.3%	23.2%	36.5%
65-79	33.8%	33.8%	34.0%
≥80	38.5%	38.7%	18.9%
Male sex	49.8%	49.6%	66.4%
Race			
White	67.7%	67.7%	63.3%
Black	19.9%	19.9%	21.9%
Hispanic	7.8%	7.8%	8.5%
Others	4.6%	4.6%	6.4%
Insurance status			
Medicare/Medicaid	82.9%	83.0%	74.1%
Private	11.7%	11.7%	20.0%
Uninsured/self-pay	3.6%	3.6%	3.6%
Others	1.7%	1.7%	2.3%
Median household income			
1st quartile	34.6%	34.6%	33.4%
2nd quartile	25.1%	25.1%	24.0%
3rd quartile	21.7%	21.7%	22.2%
4th quartile	18.5%	18.5%	20.5%
Elective admission	8.0%	8.0%	10.4%
Weekend admission	22.4%	22.4%	20.3%
Comorbidities			
IHD	53.2%	53.3%	50.7%
Smoking	22.2%	22.2%	20.9%
Anemia	29.0%	29.0%	26.6%
CKD	29.9%	29.8%	39.1%
ESRD	6.2%	6.2%	6.2%
Chronic pulmonary disease	36.8%	36.9%	27.5%
Obesity	15.3%	15.4%	13.0%
Atrial fibrillation	37.5%	37.5%	43.4%
Hypertension	65.9%	66.0%	47.2%
Diabetes mellitus	43.6%	43.7%	34.7%
Fluid and electrolyte disorder	27.2%	27.0%	60.1%
Peripheral vascular disease	11.3%	11.3%	10.5%
Pulmonary circulation disorders	0.3%	0.3%	1.1%
In-hospital complications/procedures			
AKI	17.6%	17.3%	60.6%
Sepsis	1.5%	1.4%	14.5%
PRBC transfusion	6.1%	6.0%	14.6%
ICD	1.3%	1.3%	2.6%
CRT	1.7%	1.7%	2.7%
Swan-Ganz catheter	0.8%	0.7%	17.2%
IABP	0.2%	0.1%	12.8%
ECMO	0.2%	0.003%	1.4%
Temp VAD*	0.03%	0.01%	2.5%
Mechanical revascularization†	0.9%	0.8%	4.3%
LVAD	0.1%	0.1%	8.4%
Heart transplantation	0.1%	0.1%	3.4%
Hospital characteristics			
Hospital region			
Northeast	23.3%	23.3%	21.5%
Midwest	17.8%	17.9%	17.2%
South	42.4%	42.4%	39.4%
West	16.5%	16.4%	22.0%
Teaching hospital	43.5%	43.3%	69.7%
Bed size of hospital			

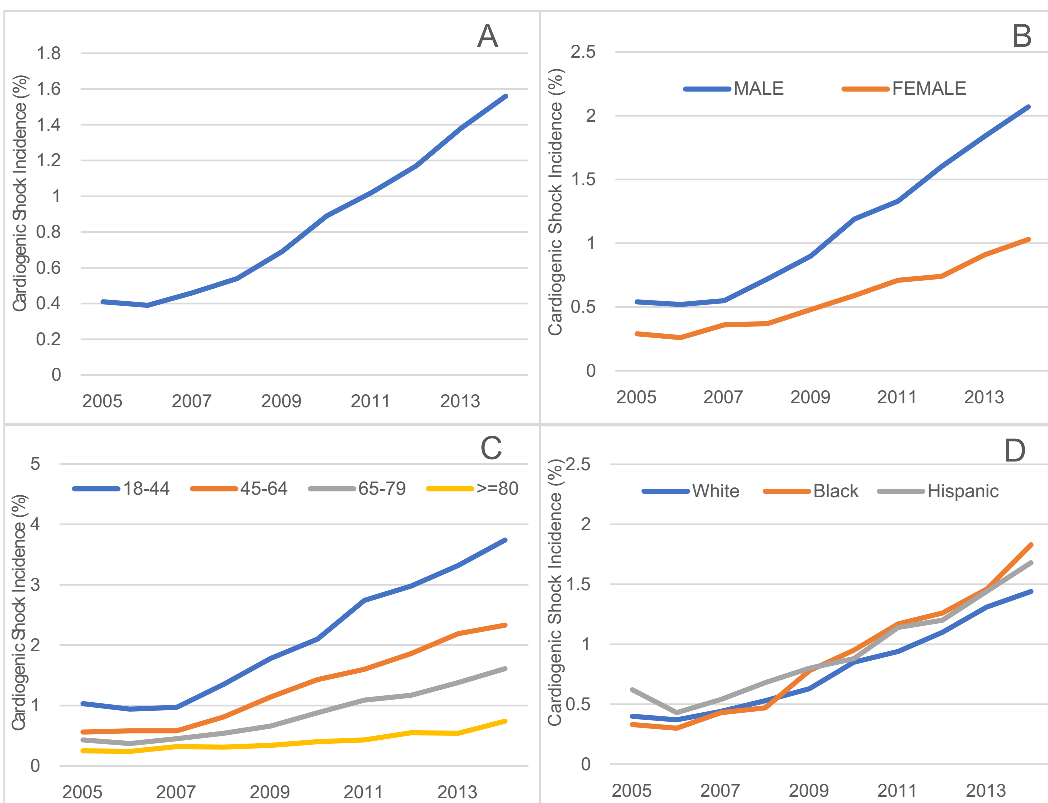
(continued on next page)

Table I (*continued*)

	Overall cohort	Cardiogenic shock	
		No	Yes
	(N = 8,333,752)	(n = 8,261,084)	(n = 72,668)
Small	14.7%	14.7%	7.4%
Medium	26.3%	26.4%	19.5%
Large	59.0%	58.9%	73.1%

P value < .001 for all comparisons except for ESRD (*P* = .875) and peripheral vascular disease (*P* = .008).
PRBC, packed red blood cell; *ICD*, implantable cardioverter-defibrillator; *CRT*, cardiac resynchronization therapy.
* Temporary VADs included percutaneous VAD, ventricular assist systems, and extracorporeal circulatory assist devices.
† Mechanical revascularization included percutaneous coronary intervention and coronary artery bypass grafting.

Figure 1



Trends in the overall (**A**), sex- (**B**), age- (**C**), and race-specific (**D**) incidence rates of cardiogenic shock during a heart failure hospitalization between 2005 and 2014. Significant increases were noted across all categories (male: 5.4-20.6 per thousand HFHs; female: 2.9-10.3 per thousand HFHs; 18-44 years old: 10.3-37.4 per thousand HFHs; 45-64 years old: 5.6-23.3 per thousand HFHs; 65-79 years old: 4.3-16.1 per thousand HFHs; ≥80 years old: 2.5-7.4 per thousand HFHs; white: 4-14.4 per thousand HFHs; black: 3.3-18.3 per thousand HFHs; Hispanic: 6.2-16.3 per thousand HFHs; P_{trend} < .001 for all).

both sex groups, whereas ECMO and temporary VAD use rates increased (P_{trend} < .001 for all); Supplementary Figure 1 *B*, *E*, and *H*. IABP use rates showed a declining trend in whites and Hispanics (P_{trend} < .001) but were stable in blacks (P_{trend} = .163); Supplementary Figure 1, *C*. ECMO and temporary VAD utilization rates significantly increased across all ethnicities (P_{trend} < .001); Supplementary Figure 1, *F* and *I*.

In-hospital mortality with CS

Inpatient mortality with non–ACS-related CS during an HFH was 27.1% during the study period, with a

Table II. Overall and age-, sex-, and race-specific trends in incidence of cardiogenic shock during a heart failure hospitalization

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Overall	Ref	0.94 (0.78-1.12)	1.09 (0.89-1.32)	1.31 (1.11-1.54)	1.66 (1.37-2.01)	2.12 (1.63-2.76)	2.47 (1.98-3.08)	2.80 (2.37-3.31)	3.28 (2.77-3.89)	3.70 (3.13-4.38)
Sepsis excluded	Ref	0.97 (0.82-1.15)	1.16 (0.97-1.38)	1.38 (1.17-1.63)	1.72 (1.41-2.08)	2.22 (1.73-2.87)	2.60 (2.11-3.20)	2.97 (2.54-3.46)	3.46 (2.96-4.03)	3.95 (3.37-4.62)
Cases with IHD	Ref	0.90 (0.74-1.10)	1.13 (0.91-1.34)	1.51 (1.25-1.81)	1.93 (1.57-2.36)	2.45 (1.85-3.24)	2.91 (2.33-3.64)	3.28 (2.75-3.92)	3.83 (3.21-4.57)	4.55 (3.82-5.43)
Cases without IHD	Ref	0.96 (0.77-1.20)	1.05 (0.83-1.35)	1.16 (0.94-1.44)	1.46 (1.15-1.85)	1.88 (1.40-2.51)	2.14 (1.64-2.79)	2.45 (1.99-3.01)	2.89 (2.35-3.55)	3.06 (2.47-3.75)
Age-specific (y)										
18-44	Ref	0.96 (0.63-1.46)	0.99 (0.63-1.55)	1.34 (0.92-1.94)	1.80 (1.22-2.66)	2.11 (1.27-3.49)	2.80 (1.78-4.39)	3.05 (2.02-4.6)	3.35 (2.22-5.07)	3.87 (2.55-5.87)
45-64	Ref	1.05 (0.75-1.46)	1.06 (0.77-1.47)	1.46 (1.10-1.95)	2.07 (1.50-2.86)	2.66 (1.78-3.98)	2.96 (2.11-4.15)	3.40 (2.54-4.56)	4.03 (3.00-5.40)	4.29 (3.19-5.75)
65-79	Ref	0.85 (0.69-1.06)	1.05 (0.83-1.33)	1.25 (1.03-1.51)	1.51 (1.23-1.86)	2.05 (1.58-2.66)	2.53 (2.02-3.16)	2.73 (2.31-3.22)	3.22 (2.71-3.83)	3.74 (3.17-4.41)
≥80	Ref	0.93 (0.73-1.17)	1.26 (1.00-1.58)	1.21 (0.96-1.52)	1.33 (1.06-1.66)	1.57 (1.26-1.95)	1.66 (1.32-2.08)	2.13 (1.73-2.61)	2.47 (2.02-3.02)	2.88 (2.35-3.51)
Sex-specific										
Male	Ref	0.97 (0.78-1.19)	1.01 (0.82-1.26)	1.34 (1.10-1.62)	1.67 (1.36-2.07)	2.21 (1.62-3.0)	2.51 (1.96-3.22)	2.99 (2.47-3.6)	3.44 (2.84-4.15)	3.86 (3.19-4.68)
Female	Ref	0.88 (0.71-1.09)	1.21 (0.95-1.55)	1.26 (1.04-1.53)	1.63 (1.29-2.05)	1.97 (1.57-2.48)	2.40 (1.92-3.00)	2.48 (2.05-3.01)	3.03 (2.48-3.69)	3.41 (2.81-4.14)
Race-specific										
White	Ref	0.94 (0.78-1.13)	1.11 (0.90-1.36)	1.34 (1.12-1.61)	1.58 (1.31-1.90)	2.12 (1.62-2.76)	2.38 (1.89-3.00)	2.75 (2.32-3.25)	3.22 (2.72-3.82)	3.53 (2.99-4.18)
Black	Ref	1.19 (0.84-1.67)	1.28 (0.85-1.94)	1.42 (1.03-1.97)	2.33 (1.52-3.59)	2.84 (1.85-4.37)	3.57 (2.46-5.16)	3.83 (2.78-5.27)	4.46 (3.22-6.18)	5.58 (4.00-7.77)
Hispanic	Ref	0.72 (0.49-1.06)	0.84 (0.58-1.23)	1.13 (0.77-1.64)	1.34 (0.92-1.97)	1.42 (1.00-2.02)	1.91 (1.32-2.76)	1.98 (1.40-2.8)	2.37 (1.69-3.31)	2.73 (1.98-3.78)

Trends are expressed as adjusted ORs (95% CIs) for each year with 2005 as reference. Regression model adjusted for patient demographics (age, sex, and race). *Ref*, referent.

substantial decrease from 42.4% in 2005 to 23.3% in 2014; unadjusted OR for mortality in 2014 versus 2005: 0.41, 95% CI 0.34-0.50; Table IV; Figure 4, *A*. After risk adjustment, around 63% reduction in mortality was observed in 2014 compared to 2005 (OR 0.37, 95% CI 0.30-0.45); Table IV. Similar results were seen in sensitivity analyses excluding cases with sepsis and those receiving LVAD or heart transplant; Table IV.

Mortality rate was higher in females (30.6%) compared to males (25.4%; $P < .001$). Mortality rate was highest in patients ≥80 years (41.4%) compared to those 65-79 years (29.2%), 45-64 years (20.6%), and 18-44 years (17.7%) old ($P < .001$). Mortality rate was highest in whites (28.8%) followed by Hispanics (25.8%) and blacks (22.3%) ($P < .001$). Significant reductions in mortality rates were noted in all sex, age, and race groups during the study period; Figure 4, *B-D*. After risk adjustment, similar reductions in mortality were noted across age, gender, and race groups, although these were less pronounced in Hispanics; Table IV.

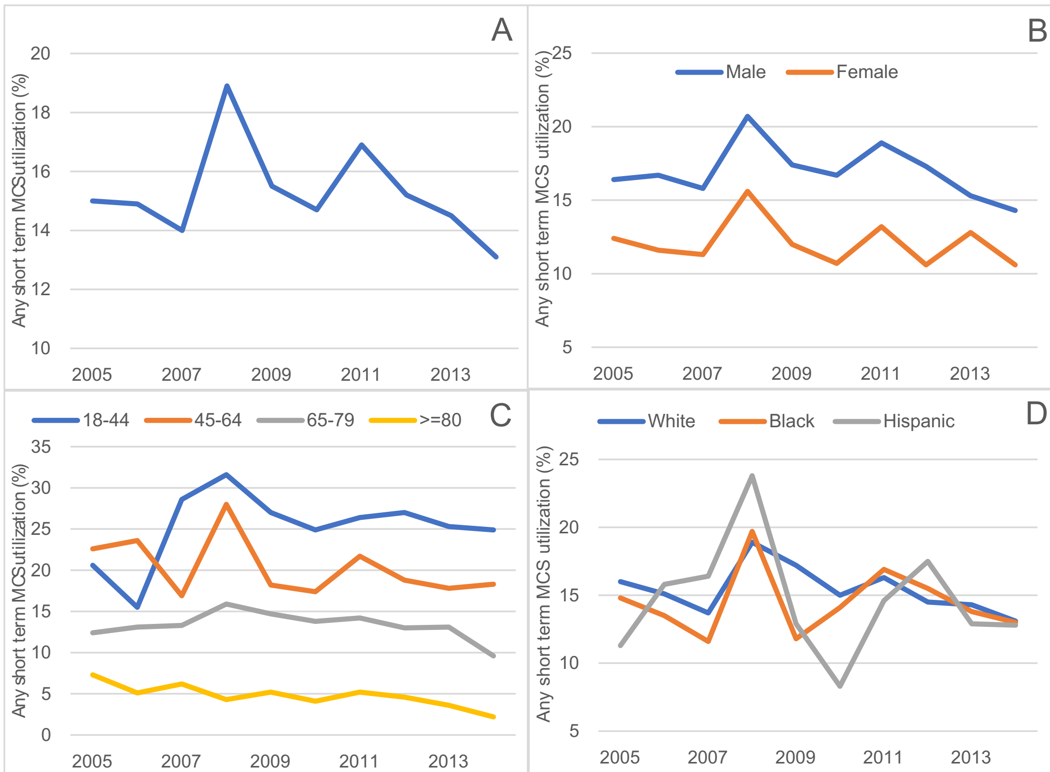
LOS and costs with CS

Average LOS during the study period was 15.7 (0.4) days. LOS remained relatively stable during the study period; Table III; Supplementary Figure 3, *A*. Inflation-adjusted average cost of care per hospitalization was US$ 66,918 (2,805). Average costs remained relatively stable between 2005 and 2014; Table III; Supplementary Figure 3, *B*. In a sensitivity analysis excluding patients who died during the HFH, average LOS numerically decreased from 19.1 (2.8) days to 16.1 (0.7 days) (P = .574) between 2005 and 2014, and average costs significantly decreased from US$ 72,158 (4,612) in 2005 to US$ 60,421 (3,307) in 2014 (P_{trend} = .026); Supplementary Figure 4. Significant subgroup differences were observed in the average LOS and costs in the age, sex, and race groups, and these persisted in the sensitivity analysis excluding patients who died during the HFHs (Supplementary Table IV).

Discussion

Our study presents novel data on the epidemiology of non–ACS-related CS during HFHs in the United States. During HFHs in the United States, CS occurred infrequently but was associated with substantial mortality. Rates of CS incidence and short-term MCS with ECMO and temporary VADs increased, and in-hospital mortality rate decreased between 2005 and 2014. Although these

Figure 2



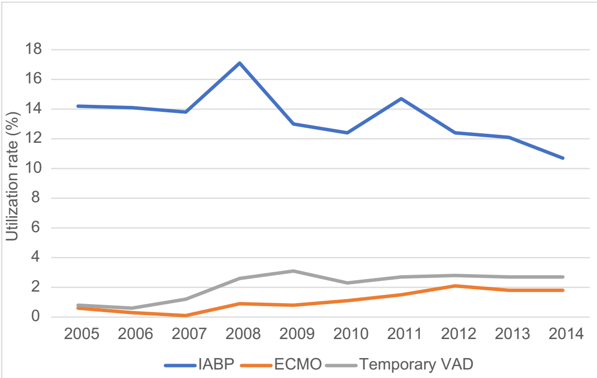
Overall (**A**) and sex- (**B**), age- (**C**), and race- (**D**) stratified trends in the utilization rates of any short-term MCS between 2005 and 2014 with cardiogenic shock during a heart failure hospitalization. There was an overall decline (15% to 13.1%; $P_{trend} < .001$), which was consistent in both sex groups (male: 16.4% to 14.3%; $P_{trend} < .001$; female: 12.4% to 10.6%; $P_{trend} = .043$), certain age groups (45-64 years old: 22.6% to 18.3%; 65-79 years old: 12.4% to 9.6%; ≥80 years old: 7.3% to 2.2%; $P_{trend} < .001$), and in whites (16% to 13.1%; $P_{trend} < .001$). Numerical increase was noted in the 18- to 44-year group (20.6% to 24.9%; $P_{trend} = .282$), and rates were relatively stable in blacks (14.8% to 13%; $P_{trend} = .375$) and Hispanics (11.3% to 12.8%; $P_{trend} = .179$).

trends were generally homogenous across age, sex, and race groups, intergroup disparities were noted.

Non–ACS-related CS is an infrequent complication during an HFH with more recent incidence rates of around 15 CS cases per 1000 HFHs and with a 4-fold increase in the incidence during the study period. Increasing incidence possibly reflects increased recognition of this complication, development of shock teams, and upcoding to improve hospital case-mix indices and to justify the use of MCS devices, supported by the findings that more CS cases were diagnosed in larger teaching hospitals in our study.[25] Most available studies evaluated the occurrence of CS in ACS.[1,2,11-13] Although data from some European registries enrolling 3,000-6,000 patients with acute HF showed that CS is an infrequent presentation of acute HF (2%-14% incidence),[5,26,27] no studies evaluated the incidence of CS during an HFH in nationally representative data from the United States. The higher incidence of CS observed in the European registry data compared to our study can be explained by the high percentage of patients with ACS (30%-40%) in these registry studies.[5,26,27]

In our study, incidence rate and relative temporal increase in non–ACS-related CS during an HFH decreased with increasing age. These findings could be explained by the possibility that older patients are more frequently hospitalized for HF exacerbations (72% of total HF admissions in this study), which could be a result of having a lower threshold for admission given the patients' age or because of other age-related issues such as polypharmacy and noncompliance. Younger patients are more likely to be hospitalized for significant worsening of the HF disease process which could be complicated by CS. Variations in etiology of HF between age groups could also have a contributory pathophysiological role in the development of CS. We also observed a decrease in the mean patient age when non–ACS-related CS complicated an HF across the study period. Increased prevalence of comorbidities and in-hospital complication rates of AKI suggest that patients developing non–ACS-related CS during an HFH are more

Figure 3



Trends in short-term mechanical circulatory support utilization rates between 2005 and 2014 with cardiogenic shock during a heart failure hospitalization. Rates of IABP use decreased (14.2% to 10.7%) and ECMO and VAD use increased significantly (ECMO: 0.6% to 1.8%; VAD: 0.8% to 2.7%; P_{trend} < .001 for all).

complicated in the recent times. Supporting out findings, in a large study of 316,905 intensive care unit admissions between 1997 and 2012 in Paris of which 6.1% developed CS, the mean patient age reduced by almost 3 years and prevalence rates of comorbidities and in-hospital complications increased across the study period.[28] These findings reflect an overall increase in the complexity of patients with non–ACS-related CS and stress the necessity to investigate therapies which can improve outcomes in these younger and sicker patients.

With regard to utilization of short-term MCS devices observed in this study, focus shifted from a higher use of IABP to increasing utilization of temporary VADs and ECMO more recently. IABP utilization rate remained almost stable between 2005 and 2011 and then declined in 2014. Findings from the Intraaortic Balloon Pump in Cardiogenic Shock-2 (IABP-SHOCK 2) trial that IABP did not improve outcomes in postinfarction CS published in 2012 could have influenced the IABP utilization trend[9], whereas growing experience with VADs and ECMO in refractory CS might have driven their increased utilization.[16-19] It is important to note that the clinical phenotype of CS in the IABP-SHOCK 2 trial is different from CS in HF, and extrapolation of the IABP-SHOCK 2 data when treating non–ACS-related CS in HF patients is not recommended.

More recent observational data demonstrate that IABP support stabilized patients with CS and end-stage HF, providing additional time to aid appropriate decision making and as a bridge to durable VAD placement or transplant, findings which might increase IABP utilization in severe CS in HF.[14,15] Available data also suggest that percutaneous temporary VADs are more effective at reversing hemodynamic compromise in severe refractory CS compared to IABP, findings which may drive increased utilization.[29] Decreased utilization of any form of MCS with increasing age as noted in our study could be explained by the possibility that more aggressive care maybe offered to younger patients. Poor outcomes were observed in older patients who receive MCS support, especially if MCS cannot be a bridge to transplant or durable VAD.[17]

Similar to declining mortality trends observed in CS complicating ACS[11-13,30], in-hospital mortality substantially declined with non–ACS-related CS during HFHs in our study. Although these findings are encouraging and signify probable overall improvements in patient management with regard to early diagnosis and use of short-term MCS and durable VADs,[1] the substantial mortality reduction in the absence of proven therapies to treat non–ACS-related CS maybe also be a reflection of increased identification of this complication in lower-risk patients over time. The concept of the “shock team” to initiate early and appropriate management strategies in patients with CS has been gaining prominence, and recent retrospective observations have demonstrated improved outcomes in CS with the involvement of such teams.[31-33] Appropriately designed prospective studies should evaluate how such teams can improve outcomes in the HF-related CS population. In our study, overall survival was highest in the younger age groups, and they had a higher relative survival improvement between 2005 and 2014 in this study. Increasing age was shown to be an independent predictor of mortality in severe HF and CS,[1,3,6,17,28,30] and the highest age groups were also less likely to receive aggressive care and device support as seen in our study.

An inverse relation was noted between increasing age and average LOS/hospitalization costs; Supplementary Table III. These findings possibly resulted from age-related decline in resource utilization and increased in-hospital mortality in older patients. Interestingly, in a sensitivity analysis excluding patients who died during the HFHs, average LOS remained stable, whereas average costs decreased during the study period. Decreased utilization of certain forms of MCS and heart transplantation, and increased identification of lower risk patients during the study period could have resulted in the reduced costs when patients survived CS. There were more than 2-fold higher mean LOS and more than 3-fold higher mean hospital costs in the 18- to 44-year patient group compared to the ≥80-year group. The same pattern of resource utilization might explain the observed differences among sex subgroups. Overall, our study findings demonstrate that the groups with the lowest mortality rates had highest average LOS and costs.

The most important strength of our study is the large sample size of a nationally representative cohort of HFHs which was collected using validated methods to reduce selection bias.[21] This allowed us to present accurate

Table III. Trends in mechanical circulatory support utilization and outcomes with cardiogenic shock during a heart failure hospitalization

Variable (n)	Overall (72,688)	2005 (3196)	2006 (3083)	2007 (3394)	2008 (4336)	2009 (5926)	2010 (7585)	2011 (8878)	2012 (10,145)	2013 (12,050)	2014 (14,095)	*P* value
Procedures, n (%)												
IABP	9339 (12.8%)	453 (14.2%)	436 (14.1%)	467 13.8%)	742 (17.1%)	771 (13.0%)	942 (12.4%)	1303 (14.7%)	1260 (12.4%)	1455 (12.1%)	1510 (10.7%)	<.001
ECMO	1017 (1.4%)	20 (0.6%)	9 (0.3%)	5 (0.1%)	37 (0.9%)	50 (0.8%)	81 (1.1%)	131 (1.5%)	210 (2.1%)	215 (1.8%)	260 (1.8%)	<.001
Temporary VAD	1785 (2.5%)	25 (0.8%)	19 (0.6%)	42 (1.2%)	112 (2.6%)	184 (3.1%)	175 (2.3%)	238 (2.7%)	285 (2.8%	325 (2.7%)	380 (2.7%)	<.001
Any short-term MCS	10,901 (15.0%)	478 (15.0%)	460 (14.9%)	474 (14.0%)	821 (18.9%)	918 (15.5%)	1116 (14.7%)	1499 (16.9%)	1540 (15.2%)	1745 (14.5%)	1850 (13.1%)	<.001
Outcomes												
Mortality, n (%)	19,722 (27.1%)	1354 (42.4%)	1237 (40.1%)	1272 (37.5%)	1190 (27.4%)	1612 (27.2%)	1825 (24.1%)	2353 (26.5%)	2685 (26.5%)	2905 (24.1%)	3290 (23.3%)	<.001
Mean LOS (SE), d	15.7 (0.4)	15.5 (2.0)	14.6 (1.0)	15 (1.5)	16.7 (1.3)	16.5 (1.6)	15.2 (1.0)	16 (1.3)	15.7 (0.6)	16.1 (0.8)	15.2 (0.5)	.883
Mean cost of care (SE), US$	66,198 (2805)	59,344 (8216)	53,134 (4301)	63,175 (7175)	75,579 (8966)	71,116 (10,228)	71,286 (11,371)	78,896 (9567)	67,533 (4089)	65,645 (3546)	59,556 (3187)	.437

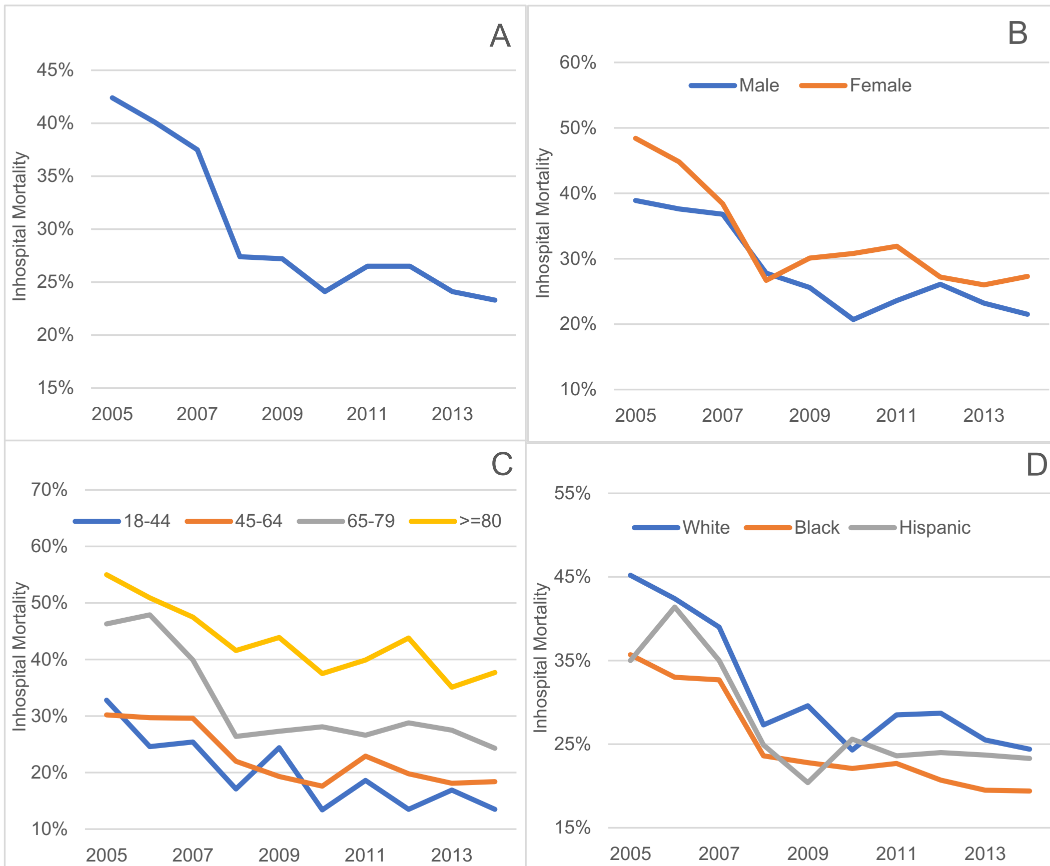
Table IV. Risk-adjusted overall and age-, sex-, and race-specific trends in in-hospital mortality with cardiogenic shock during a heart failure hospitalization

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Overall	Ref	0.93 (0.74-1.17)	0.75 (0.60-0.94)	0.48 (0.38-0.60)	0.49 (0.39-0.61)	0.41 (0.33-0.52)	0.48 (0.39-0.60)	0.45 (0.37-0.55)	0.40 (0.32-0.48)	0.37 (0.30-0.45)
Excluding LVAD/OHT cases	Ref	0.88 (0.70-1.10)	0.72 (0.57-0.91)	0.49 (0.39-0.62)	0.49 (0.39-0.61)	0.41 (0.32-0.51)	0.48 (0.39-0.59)	0.45 (0.37-0.55)	0.40 (0.33-0.49)	0.37 (0.30-0.45)
Excluding sepsis cases	Ref	0.90 (0.70-1.17)	0.74 (0.58-0.95)	0.50 (0.39-0.64)	0.52 (0.41-0.66)	0.41 (0.32-0.52)	0.49 (0.39-0.62)	0.45 (0.36-0.56)	0.41 (0.33-0.51)	0.36 (0.29-0.45)
Age-specific (y)										
18-44	Ref	0.81 (0.34-1.93)	0.79 (0.34-1.82)	0.40 (0.15-1.09)	0.54 (0.26-1.13)	0.26 (0.12-0.59)	0.38 (0.18-0.81)	0.25 (0.12-0.53)	0.33 (0.16-0.72)	0.22 (0.11-0.46)
45-64	Ref	0.98 (0.58-1.67)	0.83 (0.51-1.36)	0.57 (0.35-0.92)	0.48 (0.31-0.75)	0.42 (0.26-0.66)	0.59 (0.37-0.92)	0.46 (0.30-0.71)	0.42 (0.27-0.65)	0.40 (0.26-0.62)
65-79	Ref	1.08 (0.74-1.58)	0.72 (0.50-1.05)	0.39 (0.26-0.57)	0.42 (0.30-0.59)	0.42 (0.30-0.59)	0.41 (0.30-0.55)	0.40 (0.30-0.55)	0.39 (0.29-0.52)	0.32 (0.24-0.44)
≥80	Ref	0.95 (0.61-1.47)	0.79 (0.51-1.24)	0.64 (0.42-0.97)	0.73 (0.47-1.14)	0.52 (0.34-0.79)	0.61 (0.41-0.93)	0.69 (0.46-1.03)	0.47 (0.32-0.70)	0.53 (0.35-0.78)
Sex-specific										
Male	Ref	0.93 (0.68-1.26)	0.84 (0.61-1.15)	0.55 (0.41-0.75)	0.48 (0.36-0.64)	0.37 (0.27-0.50)	0.45 (0.34-0.59)	0.47 (0.36-0.62)	0.41 (0.31-0.54)	0.35 (0.27-0.46)
Female	Ref	0.93 (0.63-1.36)	0.63 (0.44-0.89)	0.37 (0.25-0.54)	0.49 (0.35-0.69)	0.48 (0.35-0.68)	0.53 (0.38-0.73)	0.40 (0.29-0.55)	0.36 (0.26-0.50)	0.38 (0.28-0.52)
Race-specific										
White	Ref	0.94 (0.72-1.24)	0.71 (0.55-0.93)	0.43 (0.33-0.56)	0.49 (0.39-0.63)	0.38 (0.29-0.50)	0.49 (0.38-0.63)	0.45 (0.36-0.57)	0.38 (0.31-0.48)	0.34 (0.27-0.43)
Black	Ref	0.81 (0.43-1.52)	0.76 (0.39-1.47)	0.51 (0.26-0.98)	0.51 (0.28-0.91)	0.47 (0.26-0.83)	0.50 (0.29-0.86)	0.46 (0.26-0.82)	0.43 (0.24-0.75)	0.42 (0.24-0.72)
Hispanic	Ref	1.28 (0.58-2.80)	0.99 (0.49-2.01)	0.61 (0.29-1.29)	0.37 (0.17-0.80)	0.57 (0.29-1.17)	0.44 (0.22-0.88)	0.40 (0.20-0.80)	0.39 (0.20-0.80)	0.41 (0.21-0.80)

Trends are expressed as adjusted ORs (95% CIs) for each year with 2005 as reference. Regression model adjusted for patient demographics, hospital characteristics, comorbidities, in-hospital procedures, and complications. Dementia was not included in age group specific analysis for age < 65 years; extracorporeal membrane oxygenation and OHT were not included when age was ≥80 years. *OHT*, orthotropic heart transplant.

trends in incidence and outcomes. To the best of our knowledge, this is the largest and the first study to report such findings. Our study does have important limitations. Importantly, the sampling unit in the NIS is individual hospitalizations and not individual patients. Such a sampling strategy could result in double counting of

Figure 4



Overall (**A**) and sex- (**B**), age- (**C**), and race- (**D**) stratified trends in inhospital mortality with cardiogenic shock during a heart failure hospitalization between 2005 and 2014. Significant decline was noted across all categories between 2005 and 2014 (male: 38.9% to 21.5%; female: 48.4% to 27.3%; 18-44 years old: 32.8% to 13.5%; 45-64 years old: 30.2% to 18.4%; 65-79 years old: 46.3% to 24.3%; ≥80 years old: 55% to 37.7%; white: 45.2% to 24.4%; black: 35.7% to 19.4%; Hispanic: 35% to 23.3%; $P_{trend} < .001$ except in Hispanic group in which $P_{trend} = .005$).

patients who have multiple admissions. For this reason, we did not discuss the observed demographic differences in greater detail, as such differences could have been affected by the sampling design. Similarly, lack of appropriate data on interhospital transfers should be considered when interpreting our study findings because such a limitation can also result in double counting of cases, resulting in underestimation of outcomes. Like any retrospective observational study, there is a possibility of residual confounding that cannot be entirely disregarded. Being an administrative database, NIS does not provide information on important clinical variables like ejection fraction, hemodynamics, laboratory data, and medications such as inotrope use which will better classify the severity of CS. The possibility that cases of HF-related troponin elevation being misdiagnosed as ACS exists, and we might have excluded such cases from our study which could have resulted in some underrepresentation of non–ACS-related CS incidence. The database does not allow to distinguish between CS present on admission versus CS that developed during the hospitalization. Miscoding of diagnostic and procedure codes resulting in misclassification bias, coding inconsistencies across hospitals, and upcoding across time might have also contributed to the observed trends in incidence and outcomes. Cost data were missing for around 15% of the sample mostly in the earlier years. Hence, cost data trends should be interpreted with caution.

Conclusion

During HFHs in the United States, non–ACS-related CS occurred infrequently but was associated with substantial mortality. Non–ACS-related CS incidence and use of temporary VAD and ECMO increased, and in-hospital mortality rate decreased between 2005 and 2014. Although these trends were generally homogenous across age, sex, and race groups, intergroup disparities were noted. The observed trends in incidence and mortality may be a reflection of increased identification of non–ACS-related CS during HFHs, although further study is needed to assess whether temporal changes in care may have influenced overall outcomes. Our study findings highlight the need for further research on best practices and the role of MCS devices in the management of non–ACS-related CS complicating HFHs. Clinical factors responsible for observed disparities in resource utilization and outcomes should be clarified in future studies to improve overall outcomes.

Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.03.015.

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