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Sex Differences in Management, Time to Intervention, and In-Hospital Mortality of Acute Myocardial Infarction and Non-Myocardial Infarction Related Cardiogenic Shock

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Abstract: Background/Objectives: Cardiogenic shock (CS) is associated with high mortality, particularly in women. With early intervention being a cornerstone of CS management, this study aims to explore whether sex differences exist in the utilization of critical interventions, timing of treatment, and in-hospital mortality for patients with acute myocardial infarction (AMI) and non-AMI-CS. **Methods:** For this retrospective cohort study, we queried the National Inpatient Sample (years 2016–2021) for CS-related hospitalizations. We assessed sex differences in utilization, timing, and outcomes of CS interventions, adjusting for demographics, comorbidities, and prior cardiac interventions via multivariate logistic regressions. **Results:** Of 1,052,360 weighted CS hospitalizations, 60% were for non-AMI-CS and 40% were for AMI-CS. Women with CS had lower rates of all interventions. For AMI-CS, women had higher likelihoods of in-hospital mortality after revascularization (adjusted odds ratio 1.15 [95% confidence interval 1.09–1.22]), mechanical circulatory support (MCS) (1.15 [1.08–1.22]), and right heart catheterization (RHC) (1.10 [1.02–1.19]) (all $p < 0.001$). Similar trends were seen in the non-AMI-CS group. Women with AMI-CS were less likely to receive early (within 24 h of admission) revascularization (0.93 [0.89–0.96]), MCS (0.76 [0.73–0.80]), or RHC (0.89 [0.84–0.95]); women with non-AMI-CS were less likely to receive early revascularization (0.78 [0.73–0.84]) or RHC (0.83 [0.79–0.88]) (all $p < 0.001$). Regardless of CS type, in-hospital mortality was not significantly different between men and women receiving early MCS or revascularization. **Conclusions:** Sex disparities in the frequency of treatment of CS persist on a national scale, with women being more likely to die following treatment and less likely to receive early treatment. However, in-hospital mortality does not differ significantly when men and women are treated equally within 24 h of admission, suggesting that early intervention should be made a priority to mitigate sex-based differences in CS outcomes.

Keywords: cardiogenic shock; sex disparities; outcomes; mechanical circulatory support; percutaneous coronary intervention

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1. Introduction

Cardiogenic shock (CS) is defined as a state of decreased circulation causing hypoxia and end-organ hypoperfusion. It is frequently precipitated by acute myocardial infarction (AMI) [1]. Despite advancements in medical interventions over the past 20 years, CS remains associated with high mortality ranging between 30 and 50% [2–5]. There exist marked sex disparities in mortality associated with CS in the United States [6–8]. The current literature suggests insufficient recognition of symptoms in women, faltering guideline-directed medical therapy or interventions during the first 24 h, and inadequate utilization of mechanical circulatory support (MCS) devices as underlying reasons for the observed mortality difference [9–11].

Recently, the DanGer Shock trial has driven the point of early aggressive treatment of AMI-CS, finding that prompt, routine use of percutaneous left ventricular assist devices (pLVAD) decreases the risk of all-cause mortality [12]. This is especially pertinent when considering a recent cohort study that found women to be less likely to receive pLVAD when hospitalized for CS [13]. Given that earlier intervention can result in improved clinical outcomes, we aimed to investigate whether differences in timely intervention were associated with higher mortality among women compared to men.

2. Methods

2.1. Study Data

Data were obtained from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) database, which is sponsored by the Agency of Healthcare Research and Quality. The NIS is the largest publicly available all-payer administrative database in the United States. It contains hospitalization data from a stratified 20% sample of over 1000 hospitals across the nation participating in the HCUP, and, when weighted, can be used to estimate nationwide trends and incidence.

2.2. Study Population and Outcomes

The database was queried for adult patients (≥18 years) admitted with CS from 2016 to 2021 using the International Classification of Disease 10th Revision Clinical Modification Codes (ICD-10-CM) of R57.0. Previous studies comparing ICD-10 coding of CS to physician adjudication of CS in random samples of inpatients within hospital systems have validated that CS is reliably coded, with a positive predictive value of 93.5% [14]. We categorized these hospitalizations based on the presence of AMI on admission into two cohorts: non-AMI-CS and AMI-CS. Hospitalizations missing mortality or sex data were excluded. The study flowchart is included in Figure S1.

Baseline demographics, comorbidities, and prior interventions were identified with ICD-10-CM codes. These characteristics included census-defined age group, race/ethnicity, quartile of median household income, insurance, hospital type, hospital teaching status, obesity, dyslipidemia, diabetes mellitus, hypertension, tobacco use, peripheral vascular disease, chronic heart failure, chronic kidney disease, chronic liver disease, valvular heart disease, coronary artery disease, stroke, prior percutaneous intervention (PCI), and prior coronary artery bypass graft (CABG).

The procedural outcomes analyzed were revascularization (percutaneous coronary intervention [PCI] and coronary artery bypass graft [CABG]), MCS (intra-aortic balloon pump [IABP], percutaneous left ventricular assist device [pLVAD], extracorporeal membrane oxygenation [ECMO]), RHC, and advanced heart failure therapies (LVAD and heart transplant). The clinical outcomes studied included in-hospital mortality, use of invasive mechanical ventilation, major bleeding, acute kidney injury, and stroke. Table S1 includes a complete list of all ICD-10 diagnosis and procedure codes used.

2.3. Statistical Analysis

All data and subsequent analyses represent weighted national estimates, which were performed using HOSP_NIS as a clustering variable and NIS_STRATUM to account for different strata, as recommended by the AHRQ methods [15]. Differences in baseline data, procedural outcomes, and clinical outcomes between the type of CS and sex were compared using Pearson's χ^2 test for categorical variables and the Mann–Whitney test for continuous variables.

Multivariable logistic regressions that accounted for survey weighting were used to assess sex differences in use of intervention at any point during hospitalization, early treatment (within 24 h of admission), and adverse clinical outcomes for both AMI and non-AMI-CS, adjusting for all baseline demographics, comorbidities, and prior interventions. Further subgroup analyses were performed to assess sex differences in in-hospital mortality associated with receiving early versus late intervention.

Statistical significance was defined with a type I error of <0.05. All analyses were performed using STATA Statistical Software version 18.0.

3. Results

3.1. Baseline Characteristics

Our study included 1,052,360 weighted hospitalizations with CS between 2016 and 2021. As seen in Table 1, both non-AMI-CS and AMI-CS had a higher incidence in men compared to women (non-AMI-CS 61.8% vs. 38.1%; AMI-CS 63.6% vs. 36.3%; $p < 0.001$). Women were more likely to be older with CS. Women with CS, compared to men, had higher frequencies of obesity, valvular heart disease, and stroke, and lower frequencies of coronary artery disease and prior PCI or CABG ($p < 0.001$).

Table 1. Baseline characteristics of patients stratified by CS type and sex (weighted).

	Non-AMI-CS 631,655 (60.0)			**AMI-CS 420,705 (40.0)**		
	Male 390,505 (61.8)	**Female 241,150 (38.2)**	***p*-Value <0.001**	**Male 267,810 (63.7)**	**Female 152,895 (36.3)**	***p*-Value <0.001**
Demographics						
Age Group						
18–44	39,125 (10.0)	24,930 (10.3)	<0.001	11,845 (4.4)	5795 (3.8)	<0.001
45–64	141,780 (36.3)	72,050 (29.9)		96,105 (35.9)	41,370 (27.0)	
65–84	182,565 (46.8)	116,715 (47.4)		137,165 (51.2)	82,500 (53.9)	
85+	27,035 (6.9)	27,455 (11.4)		22,695 (8.5)	23,230 (15.2)	
Age (Mean, Standard Deviation)	64.4 (0.08)	66.3 (0.09)	<0.001	67.1 (0.06)	70.3 (0.08)	<0.001
Race/Ethnicity						
White	246,835 (65.6)	147,395 (63.4)	<0.001	183,020 (71.4)	103,525 (70.4)	<0.001
Black	69,525 (18.5)	50,275 (21.6)		25,015 (9.7)	19,365 (13.2)	
Hispanic	34,005 (9.0)	19,785 (8.5)		25,700 (10.0)	13,000 (8.8)	
Asian	11,365 (3.0)	7065 (3.0)		10,675 (4.2)	5080 (3.5)	
Native American	2570 (0.7)	1505 (0.6)		1715 (0.7)	1170 (0.8)	
Other	11,785 (3.1)	6585 (2.8)		10,215 (4.0)	4875 (3.3)	

Table 1. *Cont.*

	Non-AMI-CS 631,655 (60.0)			AMI-CS 420,705 (40.0)		
	Male 390,505 (61.8)	**Female 241,150 (38.2)**	***p*-Value <0.001**	**Male 267,810 (63.7)**	**Female 152,895 (36.3)**	***p*-Value <0.001**
Quartile of Median Household Income by Zipcode (Percentile)						
<25th	116,585 (30.5)	76,505 (32.3)	<0.001	76,210 (29.0)	47,690 (31.7)	<0.001
26–50th	99,445 (26.0)	61,950 (26.1)		70,715 (27.0)	40,985 (27.3)	
51–75th	90,070 (23.6)	54,665 (23.0)		63,025 (24.0)	34,420 (22.9)	
76–100th	76,250 (19.9)	44,125 (18.6)		52,075 (19.9)	27,325 (18.2)	
Insurance						
Medicare	223,675 (57.4)	155,185 (64.4)	<0.001	154,770 (57.9)	106,735 (69.9)	<0.001
Medicaid	55,630 (14.3)	31,890 (13.2)		28,365 (10.6)	14,545 (9.5)	
Private	82,505 (21.2)	43,480 (18.0)		60,715 (22.7)	24,240 (15.9)	
Self-Pay	13,670 (3.5)	5905 (2.5)		12,610 (4.7)	4630 (3.0)	
No Charge	695 (0.2)	365 (0.2)		810 (0.3)	305 (0.2)	
Other	13,805 (3.5)	4040 (1.7)		10,105 (3.8)	2275 (1.5)	
Hospital Type						
Government	47,950 (12.3)	28,495 (11.8)	0.013	26,165 (9.8)	14,035 (9.2)	<0.001
Private, Non-Profit	301,035 (77.0)	185,990 (77.1)		200,540 (74.9)	116,325 (76.0)	
Private, For-Profit	41,520 (10.6)	26,665 (11.0)		41,105 (15.4)	22,535 (14.7)	
Hospital Teaching Status						
Rural	13,175 (3.4)	9290 (3.9)	<0.001	12,140 (4.5)	8195 (5.4)	<0.001
Urban, Non-Teaching	52,265 (13.4)	34,915 (14.5)		46,230 (17.3)	26,635 (17.4)	
Urban, Teaching	325,065 (83.2)	196,945 (81.7)		209,440 (78.2)	118,065 (77.2)	
Comorbidities and Prior Interventions						
Obesity	68,960 (17.7)	49,945 (20.7)	<0.001	42,130 (15.7)	27,410 (17.9)	<0.001
Dyslipidemia	162,685 (41.7)	91,920 (38.1)	<0.001	136,680 (51.0)	75,520 (49.4)	<0.001
Diabetes Mellitus	149,720 (38.3)	88,565 (36.7)	<0.001	112,160 (41.9)	67,555 (44.2)	<0.001
Chronic Hypertension	296,000 (75.8)	175,060 (72.6)	<0.001	199,995 (74.7)	117,175 (76.6)	<0.001

Table 1. *Cont.*

	Non-AMI-CS 631,655 (60.0)			AMI-CS 420,705 (40.0)		
	Male 390,505 (61.8)	**Female 241,150 (38.2)**	***p*-Value <0.001**	**Male 267,810 (63.7)**	**Female 152,895 (36.3)**	***p*-Value <0.001**
Tobacco Use	48,555 (12.4)	22,225 (9.2)	<0.001	46,430 (17.3)	21,345 (14.0)	<0.001
Peripheral Vascular Disease	21,535 (5.5)	11,165 (4.6)	<0.001	19,510 (7.3)	11,575 (7.6)	0.137
Chronic Heart Failure	156,605 (40.1)	96,585 (40.0)	0.859	95,455 (35.6)	57,405 (37.6)	<0.001
Chronic Kidney Disease	175,165 (44.9)	90,745 (37.6)	<0.001	89,720 (33.5)	49,225 (32.2)	<0.001
Chronic Liver Disease	101,045 (25.9)	56,175 (23.3)	<0.001	61,715 (23.0)	31,420 (20.6)	<0.001
Valvular Heart Disease	100,290 (25.7)	69,700 (28.9)	<0.001	46,935 (17.5)	32,640 (21.4)	<0.001
Coronary Artery Disease	195,860 (50.2)	86,305 (35.8)	<0.001	202,640 (75.7)	103,145 (67.5)	<0.001
Stroke	13,035 (3.3)	8715 (3.6)	0.007	11,500 (4.3)	7470 (4.9)	<0.001
Prior PCI	38,505 (9.9)	14,760 (6.1)	<0.001	34,094 (12.7)	15,360 (10.0)	<0.001
Prior CABG	39,770 (10.2)	12,175 (5.0)	<0.001	24,925 (9.3)	9785 (6.4)	<0.001

Results presented as n (%).Comparisons made using Pearson's χ^2 test for categorical variables and Mann–Whitney test for continuous variables. All analyses are survey weight adjusted. Abbreviations: AMI-CS, acute myocardial infarction cardiogenic shock; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

3.2. Procedural and Clinical Outcomes

For both types of CS, women had significantly lower frequencies of almost every type of intervention compared to men ($p < 0.001$), the only exception being heart transplant for AMI-CS (Table 2). Women had higher frequencies of in-hospital mortality, use of mechanical ventilation, and stroke during hospitalization, and lower frequencies of major bleeding events and acute kidney injury compared to men. Hospital length of stay and total charges were significantly lower for women than men. These trends were observed after adjusting for baseline characteristics and comorbidities, as well (Tables S2 and S3).

Table 2. Frequency of procedural and clinical outcomes stratified by sex and CS type.

	Non-AMI-CS 631,655 (60.02)			AMI-CS 420,705 (39.98)		
	Male 390,505 (61.8)	**Female 241,150 (38.2)**	***p*-Value <0.001**	**Male 267,810 (63.7)**	**Female 152,895 (36.3)**	***p*-Value <0.001**
Procedural Outcomes						
Revascularization	39,770 (10.2)	15,395 (6.4)	<0.001	140,215 (52.4)	67,770 (44.3)	<0.001
PCI	9385 (2.4)	4555 (1.9)	<0.001	104,185 (38.9)	53,160 (34.8)	<0.001

Table 2. *Cont.*

	Non-AMI-CS 631,655 (60.02)			AMI-CS 420,705 (39.98)		
	Male 390,505 (61.8)	**Female 241,150 (38.2)**	***p*-Value <0.001**	**Male 267,810 (63.7)**	**Female 152,895 (36.3)**	***p*-Value <0.001**
CABG	32,110 (8.2)	11,570 (4.8)	<0.001	47,465 (17.7)	18,735 (12.3)	<0.001
MCS	49,290 (12.6)	21,795 (9.0)	<0.001	96,320 (36.0)	41,710 (27.3)	<0.001
IABP	27,615 (7.1)	11,745 (4.9)	<0.001	65,870 (24.6)	29,565 (19.3)	<0.001
pLVAD	18,655 (4.8)	6875 (2.5)	<0.001	32,750 (12.2)	13,050 (8.5)	<0.001
ECMO	11,300 (2.9)	6445 (2.7)	0.026	7885 (2.9)	2635 (1.7)	<0.001
RHC	82,485 (21.1)	40,015 (16.6)	<0.001	51,600 (19.3)	25,800 (16.9)	<0.001
Advanced Heart Failure Therapy	17,100 (4.4)	5590 (2.3)	<0.001	1580 (0.6)	510 (0.3)	<0.001
LVAD	10,630 (2.7)	3100 (1.3)	<0.001	1300 (0.5)	380 (0.3)	<0.001
Heart Transplant	6595 (1.7)	2530 (1.0)	<0.001	310 (0.1)	130 (0.1)	0.151
Clinical Outcomes						
In-Hospital Mortality	118,205 (30.3)	85,360 (35.4)	<0.001	90,940 (34.0)	58,355 (38.2)	<0.001
Invasive Mechanical Ventilation	106,950 (27.4)	74,690 (31.0)	<0.001	89,655 (33.5)	52,860 (34.6)	0.001
Major Bleeding	81,895 (21.0)	48,495 (20.1)	<0.001	53,865 (20.1)	29,420 (19.2)	0.003
Acute Kidney Injury	265,625 (68.0)	149,005 (61.8)	<0.001	163,645 (61.1)	85,090 (55.7)	<0.001
Acute Kidney Injury Requiring Dialysis	31,800 (8.1)	17,715 (7.4)	<0.001	18,270 (6.8)	8.755 (5.7)	<0.001
Stroke	985 (0.3)	1025 (0.4)	<0.001	645 (0.2)	605 (0.4)	<0.001
Total Hospitalization Cost in USD (Mean, Standard Error)	268,220.4 (4607.4)	233,424.5 (3528.7)	<0.001	254,776.1 (2762.1)	216,624.1 (2376.2)	<0.001
Length of Stay in days (Mean, Standard error)	12.65 (0.10)	11.82 (0.10)	<0.001	9.99 (0.06)	9.32 (0.07)	<0.001

Results presented as (%), unless otherwise noted. Comparisons made using Pearson's χ^2 test for categorical variables. All analyses are survey weight adjusted. Abbreviations: AMI-CS, acute myocardial infarction cardiogenic shock; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MCS, mechanical support device; IABP, intra-aortic balloon pump; pLVAD, percutaneous left ventricular support device; ECMO, extracorporeal membrane oxygenation; RHC, right heart catheterization; LVAD, left ventricular assist device.

3.3. Outcomes After Intervention for AMI-CS

Women with AMI-CS undergoing revascularization had higher mortality (aOR: 1.15; 95% CI: 1.09–1.22; $p < 0.001$) and were more likely to require mechanical ventilation (aOR: 1.07; 95% CI: 1.02–1.12; $p = 0.003$) and have a stroke (aOR: 1.62; 95% CI: 1.12–2.35; $p < 0.001$) during their hospitalization compared to men (Table 3). When MCS was utilized, women were more likely to have higher mortality (adjusted odds ratio (aOR): 1.15; 95% CI: 1.08–1.22;

$p < 0.001$), be placed on mechanical ventilation (aOR: 1.12; 95% CI: 1.06–1.19; $p < 0.001$), or have a major bleeding event (aOR: 1.08; 95% CI: 1.01–1.15; $p = 0.01$) during their hospitalization than men. After RHC, women were more likely to die (aOR: 1.10; 95% CI: 1.02–1.19; $p < 0.001$) or be placed on mechanical ventilation (aOR: 1.12; 95% CI: 1.04–1.21; $p = 0.002$) during their hospitalization than men. No significant differences in adverse clinical outcomes between men and women receiving advanced heart failure therapy were noted. Subgroup analyses for women with AMI-CS by race are included in Supplemental Table S4.

Table 3. Odds ratios of clinical outcomes in women versus men with AMI-CS based on first intervention type received.

Outcomes in Women Compared to Men	Unadjusted Odds Ratio	*p*-Value	Model 1 (Only Demographics) Odds Ratio	*p*-Value	Model 2 (All Baseline Characteristics) Odds Ratio	*p*-Value
Revascularization						
In-Hospital Mortality	1.23 (1.18–1.29)	<0.001	1.13 (1.08–1.19)	<0.001	1.15 (1.09–1.22)	<0.001
IMV	1.06 (1.01–1.10)	0.011	1.06 (1.01–1.10)	0.013	1.07 (1.02–1.12)	0.003
Major Bleeding	1.02 (0.97–1.07)	0.322	1.02 (0.98–1.08)	0.245	0.98 (0.94–1.04)	0.689
AKI	0.79 (0.76–0.83)	<0.001	0.73 (0.70–0.76)	<0.001	0.71 (0.67–0.74)	<0.001
AKI Requiring Dialysis	0.89 (0.81–0.98)	0.021	0.87 (0.79–0.97)	0.013	0.86 (0.77–0.96)	0.007
Stroke	1.78 (1.25–3.52)	0.001	1.67 (1.16–2.40)	0.006	1.62 (1.12–2.35)	0.010
MCS						
In-Hospital Mortality	1.19 (1.13–1.26)	<0.001	1.12 (1.06–1.19)	<0.001	1.15 (1.08–1.22)	<0.001
IMV	1.11 (1.05–1.17)	<0.001	1.10 (1.04–1.17)	0.001	1.12 (1.06–1.19)	<0.001
Major Bleeding	1.10 (1.04–1.17)	0.001	1.11 (1.04–1.18)	0.001	1.08 (1.01–1.15)	0.015
AKI	0.78 (0.74–0.82)	<0.001	0.74 (0.70–0.78)	<0.001	0.72 (0.68–0.76)	<0.001
AKI Requiring Dialysis	0.85 (0.77–0.94)	0.003	0.84 (0.76–0.94)	0.002	0.83 (0.74–0.93)	0.002
Stroke	1.52 (0.92–2.50)	0.104	1.46 (0.87–2.45)	0.153	1.33 (0.77–2.29)	0.309
RHC						
In-Hospital Mortality	1.12 (1.04–1.20)	0.001	1.06 (0.99–1.15)	0.085	1.10 (1.02–1.19)	0.008
IMV	1.09 (1.02–1.18)	0.008	1.11 (1.04–1.20)	0.003	1.12 (1.04–1.21)	0.002
Major Bleeding	1.03 (0.96–1.11)	0.357	1.05 (0.98–1.14)	0.158	1.03 (0.95–1.12)	0.378
AKI	0.71 (0.66–0.76)	<0.001	0.68 (0.63–0.73)	<0.001	0.69 (0.64–0.75)	<0.001

Table 3. *Cont.*

Outcomes in Women Compared to Men	Unadjusted Odds Ratio	*p*-Value	Model 1 (Only Demographics) Odds Ratio	*p*-Value	Model 2 (All Baseline Characteristics) Odds Ratio	*p*-Value
AKI Requiring Dialysis	0.76 (0.67–0.86)	<0.001	0.73 (0.64–0.83)	<0.001	0.76 (0.66–0.87)	<0.001
Stroke	1.12 (0.63–1.99)	0.687	1.06 (0.59–1.90)	0.837	0.96 (0.52–1.77)	0.901
Advanced Heart Failure Therapy						
In-Hospital Mortality	1.13 (0.58–2.20)	0.705	1.12 (0.48–2.59)	0.790	1.37 (0.54–3.50)	0.503
IMV	1.17 (0.63–2.15)	0.618	1.11 (0.55–2.25)	0.751	1.16 (0.58–2.34)	0.667
Major Bleeding	1.26 (0.77–2.08)	0.352	1.64 (0.91–2.96)	0.096	1.59 (0.87–2.89)	0.126
AKI	0.77 (0.44–1.35)	0.363	0.85 (0.48–1.51)	0.579	0.81 (0.41–1.58)	0.525
AKI Requiring Dialysis	1.21 (0.57–2.58)	0.616	1.53 (0.61–3.87)	0.360	1.76 (0.58–5.33)	0.317
Stroke	1.55 (0.14–17.6)	0.721	9.66 (0.52–179)	0.124	N/A	N/A

All analyses involve multivariate logistic regression and are survey weight adjusted. Model 1 includes adjustment with year of NIS data, age group, race, household income quartile, insurance status, hospital type, and teaching status. Model 2 includes adjustment with all model 1 covariates as well as past medical history of diabetes mellitus, hypertension, dyslipidemia, tobacco use, obesity, chronic kidney disease, liver disease, peripheral vascular disease, coronary artery disease, chronic heart failure, valvular heart disease, stroke, prior PCI, and prior CABG. Abbreviations: AMI-CS, acute myocardial infarction cardiogenic shock; MCS, mechanical support device; RHC, right heart catheterization; IMV, invasive mechanical ventilation; AKI, acute kidney injury.

3.4. Outcomes After Intervention for Non-AMI-CS

Following revascularization, women with non-AMI-CS were more likely to die (aOR: 1.38; 95% CI: 1.23–1.56; $p < 0.001$) and be placed on mechanical ventilation (aOR: 1.11; 95% CI: 1.00–1.24; $p = 0.050$) during their hospitalization than men (Table 4). Women receiving MCS were more likely to die (aOR: 1.31; 95% CI: 1.21–1.43; $p < 0.001$), be placed on mechanical ventilation (aOR: 1.28; 95% CI: 1.18–1.40; $p < 0.001$), or have a major bleeding event (aOR: 1.10; 95% CI: 1.02–1.18; $p = 0.012$) during their hospitalization than men. The same was true after RHC for in-hospital mortality (aOR: 1.32; 95% CI: 1.22–1.43; $p < 0.001$) and mechanical ventilation usage (aOR: 1.27; 95% CI: 1.17–1.36; $p < 0.001$). No significant differences in adverse clinical outcomes between men and women receiving advanced heart failure therapy were noted. Subgroup analyses for women with non-AMI-CS by race are included in Supplemental Table S4.

Table 4. Odds ratios of clinical outcomes in women versus men with non-AMI-CS based on first intervention type received.

Outcomes in Women Compared to Men	Unadjusted Odds Ratio	*p*-Value	Model 1 (Only Demographics) Odds Ratio	*p*-Value	Model 2 (All Baseline Characteristics) Odds Ratio	*p*-Value
Revascularization						
In-Hospital Mortality	1.43 (1.28–1.59)	<0.001	1.37 (1.22–1.54)	<0.001	1.38 (1.23–1.56)	<0.001
IMV	1.11 (1.00–1.23)	0.033	1.10 (0.99–1.23)	0.060	1.11 (1.00–1.24)	0.050
Major Bleeding	1.11 (1.02–1.21)	0.011	1.16 (1.06–1.27)	0.001	1.09 (0.99–1.19)	0.068
AKI	0.86 (0.79–0.94)	0.001	0.86 (0.78–0.94)	0.001	0.82 (0.74–0.90)	<0.001

Table 4. *Cont.*

Outcomes in Women Compared to Men	Unadjusted Odds Ratio	*p*-Value	Model 1 (Only Demographics) Odds Ratio	*p*-Value	Model 2 (All Baseline Characteristics) Odds Ratio	*p*-Value
AKI Requiring Dialysis	1.01 (0.85–1.21)	0.856	0.99 (0.82–1.19)	0.924	0.95 (0.78–1.16)	0.638
Stroke	1.29 (0.67–2.48)	0.439	1.42 (0.71–2.86)	0.318	1.32 (0.66–2.65)	0.423
MCS						
In-Hospital Mortality	1.30 (1.20–1.40)	<0.001	1.30 (1.20–1.42)	<0.001	1.31 (1.21–1.43)	<0.001
IMV	1.27 (1.17–1.37)	<0.001	1.27 (1.17–1.39)	<0.001	1.28 (1.18–1.40)	<0.001
Major Bleeding	1.12 (1.05–1.20)	0.001	1.14 (1.06–1.23)	<0.001	1.10 (1.02–1.18)	0.012
AKI	0.68 (0.63–0.73)	<0.001	0.67 (0.62–0.73)	<0.001	0.66 (0.60–0.73)	<0.001
AKI Requiring Dialysis	0.91 (0.82–1.02)	0.114	0.91 (0.81–1.02)	0.126	0.94 (0.82–1.06)	0.324
Stroke	1.64 (0.96–2.83)	0.070	1.69 (0.96–2.98)	0.068	1.64 (0.93–2.89)	0.089
RHC						
In-Hospital Mortality	1.30 (1.21–1.39)	<0.001	1.31 (1.22–1.41)	<0.001	1.32 (1.22–1.43)	<0.001
IMV	1.30 (1.21–1.39)	<0.001	1.31 (1.22–1.41)	<0.001	1.27 (1.17–1.36)	<0.001
Major Bleeding	1.01 (0.95–1.08)	0.609	1.02 (0.96–1.09)	0.427	0.98 (0.91–1.04)	0.507
AKI	0.69 (0.65–0.73)	<0.001	0.68 (0.64–0.72)	<0.001	0.73 (0.68–0.77)	<0.001
AKI Requiring Dialysis	0.95 (0.86–1.04)	0.285	0.95 (0.85–1.04)	0.273	1.00 (0.90–1.11)	0.970
Stroke	1.45 (0.89–2.37)	0.127	1.54 (0.93–2.56)	0.090	1.55 (0.91–2.63)	0.104
Advanced Heart Failure Therapy						
In-Hospital Mortality	1.05 (0.81–1.36)	0.671	1.13 (0.86–1.50)	0.361	1.20 (0.88–1.63)	0.242
IMV	1.00 (0.81–1.23)	0.952	0.99 (0.79–1.24)	0.969	1.05 (0.84–1.31)	0.635
Major Bleeding	1.03 (0.88–1.20)	0.665	0.99 (0.84–1.16)	0.906	1.02 (0.87–1.20)	0.768
AKI	0.62 (0.52–0.72)	<0.001	0.61 (0.52–0.71)	<0.001	0.68 (0.57–0.81)	<0.001
AKI Requiring Dialysis	0.79 (0.59–1.05)	0.115	0.76 (0.57–1.03)	0.081	0.79 (0.57–1.09)	0.157
Stroke	1.45 (0.65–3.20)	0.354	1.39 (0.60–3.22)	0.432	1.44 (0.62–3.35)	0.393

All analyses involve multivariate logistic regression and are survey weight adjusted. Model 1 includes adjustment with year of NIS data, age group, race, household income quartile, insurance status, hospital type, and teaching status. Model 2 includes adjustment with all model 1 covariates as well as past medical history of diabetes mellitus, hypertension, dyslipidemia, tobacco use, obesity, chronic kidney disease, liver disease, peripheral vascular disease, coronary artery disease, chronic heart failure, valvular heart disease, stroke, prior PCI, and prior CABG. Abbreviations: AMI-CS, acute myocardial infarction cardiogenic shock; MCS, mechanical support device; RHC, right heart catheterization; IMV, invasive mechanical ventilation; AKI, acute kidney injury.

3.5. Incidence and Mortality Following Early Intervention

For both types of shock, women had a lower frequency of receiving CABG, IABP, pLVAD, and RHC within 24 h of admission compared to men (Figure 1). Women with AMI-CS additionally had lower frequencies of undergoing placement on ECMO and PCI within 24 h. This was similarly reflected after adjusting for covariates, with women with AMI-CS being less likely to receive any type of revascularization, MCS, or RHC than men and women with non-AMI-CS being less likely to receive any type of revascularization, IABP, pLVAD, RHC, or LVAD than men (Figure 2). In-hospital mortality did not change significantly between men and women with AMI-CS undergoing early revascularization, pLVAD, ECMO, or RHC (Figure 3). For those with non-AMI-CS, in-hospital mortality did not change significantly when treated early with PCI, pLVAD, ECMO, or RHC (Figure 3). For AMI-CS, women receiving early interventions of any revascularization or within 24 h were far less likely to die during their hospitalization than women who received intervention after 24 h or not at all; meanwhile, for non-AMI-CS, this was the case for women receiving early CABG, IABP, or RHC (Table 5).

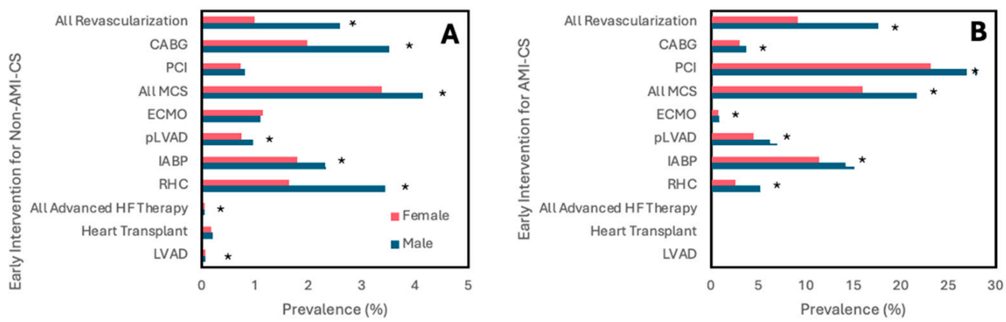

Figure 1. Frequency of early intervention within 24 h stratified by sex and CS type. Unadjusted results. (**A**,**B**) shows results for non-AMI-CS and AMI-CS, respectively. Abbreviations: AMI-CS, acute myocardial infarction cardiogenic shock; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MCS, mechanical support device; IABP, intra-aortic balloon pump; pLVAD, percutaneous left ventricular support device; ECMO, extracorporeal membrane oxygenation; RHC, right heart catheterization; LVAD, left ventricular assist device. * $p < 0.001$.

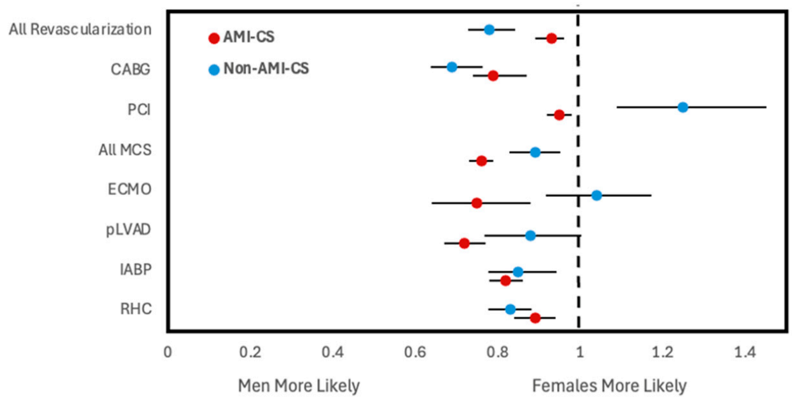

Figure 2. Adjusted odds ratios of receiving early intervention within 24 h of admission stratified by CS type. All analyses involve multivariate logistic regression and are survey weight adjusted. Odds ratios reported are adjusted for year of NIS data, age group, race, household income quartile, insurance status, hospital type and teaching status as well as past medical history of diabetes mellitus, hypertension, dyslipidemia, tobacco use, obesity, chronic kidney disease, liver disease, peripheral vascular disease, coronary artery disease, chronic heart failure, valvular heart disease, stroke, prior PCI, and prior CABG. Note: advanced heart failure therapies data not reported due to low counts preventing proper construction of logistic regression. Abbreviations: AMI-CS, acute myocardial infarction cardiogenic shock; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MCS, mechanical support device; IABP, intra-aortic balloon pump; pLVAD, percutaneous left ventricular support device; ECMO, extracorporeal membrane oxygenation; RHC, right heart catheterization.

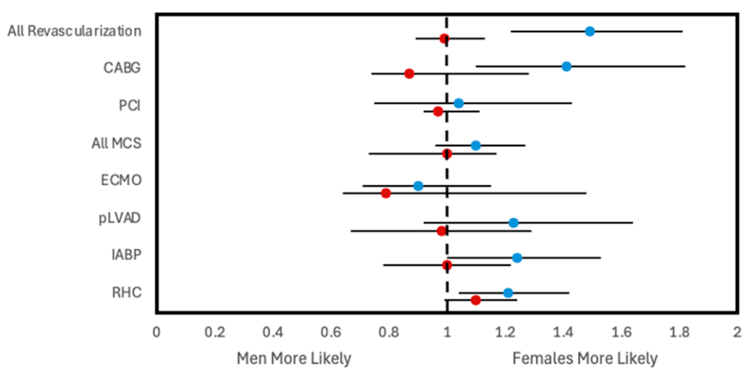

Figure 3. Adjusted odds ratios of in-hospital mortality following early intervention within 24 h of admission stratified by CS type. All analyses involve multivariate logistic regression and are survey

weight adjusted. Each regression is performed on a dataset filtered to only include CS patients who received a particular intervention within 24 h. Odds ratios reported are adjusted for year of NIS data, age group, race, household income quartile, insurance status, hospital type and teaching status as well as past medical history of diabetes mellitus, hypertension, dyslipidemia, tobacco use, obesity, chronic kidney disease, liver disease, peripheral vascular disease, coronary artery disease, chronic heart failure, valvular heart disease, stroke, prior PCI, and prior CABG. Regression. Note: advanced heart failure therapies data not reported due to low counts preventing proper construction of logistic. Abbreviations: AMI-CS, acute myocardial infarction cardiogenic shock; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MCS, mechanical support device; IABP, intra-aortic balloon pump; pLVAD, percutaneous left ventricular support device; ECMO, extracorporeal membrane oxygenation; RHC, right heart catheterization.

Table 5. Odds ratios of in-hospital mortality in women receiving early (within 24 h) versus late or no intervention by CS type.

In-Hospital Mortality in Women Receiving Early Intervention Compared to Women Not Receiving Early Intervention	Unadjusted Odds Ratio	*p*-Value	Model 1 (Only Demographics) Odds Ratio	*p*-Value	Model 2 (All Baseline Characteristics) Odds Ratio	*p*-Value
AMI-CS						
Revascularization	0.65 (0.61–0.69)	<0.001	0.66 (0.62–0.70)	<0.001	0.77 (0.72–0.82)	<0.001
PCI	0.66 (0.63–0.71)	<0.001	0.68 (0.64–0.72)	<0.001	0.79 (0.74–0.85)	<0.001
CABG	0.63 (0.55–0.73)	<0.001	0.63 (0.55–0.74)	<0.001	0.69 (0.59–0.82)	<0.001
MCS	0.87 (0.82–0.93)	<0.001	0.94 (0.88–1.00)	0.068	1.06 (0.99–1.14)	0.073
IABP	0.69 (0.64–0.75)	<0.001	0.72 (0.67–0.78)	<0.001	0.83 (0.77–0.91)	<0.001
pLVAD	1.50 (1.35–1.68)	<0.001	1.67 (1.49–1.88)	<0.001	1.78 (1.58–2.01)	<0.001
ECMO	1.71 (1.32–2.2)	<0.001	2.38 (1.83–3.10)	<0.001	2.15 (1.62–2.85)	<0.001
RHC	0.87 (0.79–0.96)	0.005	0.90 (0.819–0.99)	0.048	0.979 (0.88–1.08)	0.688
Non-AMI-CS						
Revascularization	0.42 (0.37–0.49)	<0.001	0.42 (0.36–0.49)	<0.001	0.57 (0.49–0.67)	<0.001
PCI	0.76 (0.60–0.95)	0.017	0.70 (0.55–0.88)	0.003	0.87 (0.68–1.12)	0.296
CABG	0.32 (0.27–0.39)	<0.001	0.33 (0.28–0.40)	<0.001	0.46 (0.38–0.56)	<0.001
MCS	0.92 (0.82–1.01)	0.109	0.97 (0.87–1.09)	0.663	1.05 (0.94–1.18)	0.360
IABP	0.64 (0.54–0.74)	<0.001	0.65 (0.55–0.77)	<0.001	0.78 (0.67–0.93)	0.005

Table 5. *Cont.*

In-Hospital Mortality in Women Receiving Early Intervention Compared to Women Not Receiving Early Intervention	Unadjusted Odds Ratio	*p*-Value	Model 1 (Only Demographics) Odds Ratio	*p*-Value	Model 2 (All Baseline Characteristics) Odds Ratio	*p*-Value
pLVAD	1.41 (1.14–1.74)	0.001	1.48 (1.19–1.84)	<0.001	1.56 (1.24–1.96)	<0.001
ECMO	1.31 (1.10–1.57)	0.002	1.52 (1.26–1.82)	<0.001	1.40 (1.15–1.69)	0.001
RHC	0.42 (0.37–0.46)	<0.001	0.45 (0.39–0.50)	<0.001	0.50 (0.44–0.57)	<0.001

All analyses involve multivariate logistic regression and are survey weight adjusted. Model 1 includes adjustment with year of NIS data, age group, race, household income quartile, insurance status, hospital type, and teaching status. Model 2 includes adjustment with all model 1 covariates as well as past medical history of diabetes mellitus, hypertension, dyslipidemia, tobacco use, obesity, chronic kidney disease, liver disease, peripheral vascular disease, coronary artery disease, chronic heart failure, valvular heart disease, stroke, prior PCI, and prior CABG. Abbreviations: AMI-CS, acute myocardial infarction cardiogenic shock; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MCS, mechanical support device; IABP, intra-aortic balloon pump; pLVAD, percutaneous left ventricular support device; ECMO, extracorporeal membrane oxygenation; RHC, right heart catheterization; LVAD, left ventricular assist device.

4. Discussion

To our knowledge, this study is the first to examine sex differences in management and outcomes of patients with AMI-CS and non-AMI-CS utilizing time to intervention. We found that (1) women with either type of CS are less likely to undergo interventions during hospitalization than men; (2) even after receiving intervention, in-hospital mortality, mechanical ventilation, and major bleeding are more likely to occur in women with CS than men; (3) among patients undergoing intervention, women are less likely to have an intervention performed within 24 h of admission; and (4) with early intervention, there was no difference in mortality among women and men.

Previous studies have demonstrated that women are less likely to receive MCS therapies in CS and experience a 10% higher mortality risk [11]. Not only did we confirm these findings, but we also found that women had significantly lower frequencies of nearly all types of interventions compared to men and were less likely to receive these interventions early. This was associated with higher frequencies of in-hospital mortality, invasive mechanical ventilation, and stroke during hospitalization. Prior analyses of NIS data from 2006 to 2015 found that for AMI-CS, women were more likely to die during their hospitalization than men (aOR 1.11, 95% CI: 1.06–1.16 $p < 0.001$) [16]. Despite significant recognition of sex disparities in management and mortality rates of many conditions, our analysis shows that the situation has yet to improve significantly in the subsequent decade for CS.

The results of this study suggest that ongoing sex disparities in mortality and outcomes of CS may be related to time to intervention. When women and men are similarly treated with early intervention for CS, outcomes are comparable. Additionally, women with CS undergoing any revascularization, IABP, or RHC within 24 h of admission were far less likely to die during their hospitalization than women who received intervention after 24 h or not at all. Both findings point to late intervention as a plausible explanation for the observed outcome differences and demonstrate the tangible impact of timely intervention in narrowing the sex gap in clinical outcomes for CS. However, this does not negate systemic factors contributing to these disparities. These require further investigation of sex disparities related to cost and provider communication, as well as provider and institutional bias or understanding of individualized patient needs.

Research has explored the elevated mortality in women with CS, especially within the context of AMI [8]. One hypothesis posits that women in low-output states are less likely to be recognized by providers as experiencing CS. Even for those in CS, implicit biases by providers may also lead to underestimation of the shock severity stage, leading to less prioritization of intervention [17]. Also, providers may unconsciously favor men for more aggressive interventions based on historical trends or assumptions about procedural benefit [16]. This is supported by studies on sex-based differences in time to treatment for AMI, showing delays at every stage of care (from symptom onset to EMS call, EMS to hospital admission, and hospital admission to reperfusion therapy) [18]. Early intervention has been shown to be crucial in the treatment of CS, leading to better post-procedure outcomes and lower rates of in- and out-of-hospital mortality [18–20]. Reasons for this include improved perfusion, resulting in the prevention of irreversible ischemic damage and pathologic cardiac remodeling.

Clinically, improving recognition of low-output states in women can lead to decreased time to treatment for CS. When looking at the temporal trends of women undergoing AMI, female sex has been associated with a greater time to reperfusion even when adjusting for all baseline characteristics and types of reperfusion therapy used [21,22]. It is equally important to note that when performing a clinical assessment of suspected AMI, symptom presentation varies not only by sex but also by race; for example, Black women are more likely to present with GI distress, while White women are more likely to present with typical chest pain [23,24]. Noting these differences in symptom presentation is significant, as an atypical presentation with acute-onset GI distress can modify the differential to include a diagnosis of GERD or peptic ulcer disease, which would subsequently contribute to poorer outcomes, especially in Black women. This might also explain the lower odds of procedural utilization for CS seen in Black women compared to White women.

Lastly, structural inequities, including access to resources and socioeconomic barriers, must be considered in understanding these sex disparities. As seen in our study, women with CS had higher frequencies of being on Medicare versus private insurance and of being hospitalized at a rural or non-teaching urban hospital versus a teaching urban hospital, were more racially diverse, and were in lower household income brackets compared to men with CS. The delays in care could also be explained differences in insurance status across sexes, which could limit their access to guideline-directed care. Prior studies have demonstrated that women with CS are less likely to be treated or be transferred to CS "hub" hospitals that have the infrastructure to perform more advanced interventions [5]. These systemic factors likely contribute to the observed sex disparities, highlighting the need for policy-level changes and targeted efforts to improve equity in care delivery for women with CS.

Limitations

There were a few limitations that were present in this study. The retrospective design of the study inherently limits the ability to draw causal conclusions. Results reflect associations and trends in data that strongly imply but cannot confirm our findings. The diagnosis of CS was based on ICD-CM codes used for billing purposes, which are susceptible to erroneous coding. Also, the NIS database recorded the time in units of days as opposed to hours, so more exact timing information was not available. The lack of granular temporal data limits the ability to causally link intervention timing to outcomes, as we cannot determine whether shorter delays within a 24 h window translate to better prognosis. This limitation could also contribute to misclassification of patients who received treatment just before or after the threshold, which could dilute the observed impact of early intervention. In addition, NIS does not provide detailed inpatient data, such as medication use and any disparities between sexes that may also affect outcomes. Data included information on hospitalizations as opposed to patient-level data, which opens the possibility of repeat patients in the sample. These repeat hospitalizations may also differ by sex, which could bias the observed disparities. Additionally, specific data, such as vital signs, laboratory data, and echocardiogram data, were not available. Finally, there was a lack of information on post-discharge outcomes, which could have provided further insight into post-intervention results in the management of CS.

5. Conclusions

Our study found that despite stark differences in access to early intervention for CS between men and women, in-hospital mortality did not differ significantly between sexes when treated equally within 24 h of admission. Early intervention plays a role in mitigating sex-based differences in CS outcomes and should be prioritized in the management of CS. Future research should focus on recognizing the atypical presentations of CS in women, identifying signs and symptoms earlier in the disease course, and validating our findings in other cohorts.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jcm14010180/s1, Figure S1: Study population selection flowchart. Table S1. ICD-10 diagnosis and procedure codes used during analysis. Table S2. Odds ratios of procedural and clinical outcomes in patients with AMI-CS. Table S3. Odds ratios of procedural and clinical outcomes in patients with non-AMI-CS. Table S4. Adjusted odds ratios of procedural utilization during AMI-CS and Non-AMI-CS hospitalizations in female patients by race.

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Institutional Review Board Statement: This study utilizes data from the National Inpatient Sample (NIS), a publicly available, de-identified database provided by the Healthcare Cost and Utilization Project. The NIS dataset contains no direct patient identifiers, and all data are anonymized in accordance with the Health Insurance Portability and Accountability Act. As such, this study does not involve human subject research as defined by federal regulations, and it is exempt from IRB review.

Informed Consent Statement: Patient consent was waived due to publicly available and de-identified nature of the data.

Data Availability Statement: Researchers can access the NIS by purchasing it through the HCUP Central Distributor. Details on how to obtain the data, including pricing and data use agreements, are available on the HCUP website (www.hcup-us.ahrq.gov). Due to data use agreements, the raw data cannot be shared directly by the authors. However, all methods and codes used for data analysis will be made available upon request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

CS	Cardiogenic shock
AKI	Acute kidney injury
AMI	Acute myocardial infarction
MCS	Mechanical circulatory support
RHC	Right heart catheterization
HCUP	Healthcare Cost and Utilization Project

NIS	National Inpatient Sample
PCI	Percutaneous intervention
CABG	Coronary artery bypass graft
IABP	Intra-aortic balloon pump
pLVAD	Percutaneous left ventricular assist device
LVAD	Left ventricular assist device
ECMO	Extracorporeal membrane oxygenation
aOR	Adjusted odds ratio

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