ORIGINAL RESEARCH

Survival Following Edge-to-Edge Transcatheter Mitral Valve Repair in Patients With Cardiogenic Shock: A Nationwide Analysis

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BACKGROUND: Edge-to-edge transcatheter mitral valve repair as salvage therapy in high surgical risk patients with severe mitral regurgitation presenting with cardiogenic shock (CS) has been described in small case series, but large clinical results have not been reported. This study aimed to evaluate outcomes of transcatheter mitral valve repair with MitraClip in patients with mitral regurgitation and CS using a large national database.

METHODS AND RESULTS: From January 2014 to March 2019, we identified hospitalizations for CS in patients with mitral valve disease using data from Centers for Medicare and Medicaid Services. Those with a prior surgical or percutaneous mitral valve intervention were excluded. We compared survival between patients who underwent MitraClip during the index hospitalization and those who did not using propensity-matched analysis. The analysis included 38 166 patients (mean age, 71±11 years, 41.6% women) of whom 622 (1.6%) underwent MitraClip. MitraClip was increasingly used during CS hospitalizations over the study period ($P<0.001$). After matching, patients receiving MitraClip had significantly lower in-hospital mortality (odds ratio, 0.6; 95% CI, 0.47–0.77; $P<0.001$) and 1-year mortality (hazard ratio, 0.76; 95% CI, 0.65–0.88; $P<0.001$) compared with those without MitraClip. The survival benefit associated with MitraClip was consistent across subgroups of interest, with the exception of patients requiring acute mechanical circulatory support or hemodialysis at index.

CONCLUSIONS: In patients with mitral regurgitation presenting with CS, use of MitraClip is increasing and associated with greater in-hospital and 1-year survival. Further studies are warranted to optimize patient selection and procedure timing for those receiving MitraClip as a treatment option in CS.

Key Words: all-cause mortality ■ cardiogenic shock ■ MitraClip ■ mitral regurgitation ■ transcatheter mitral valve repair

anagement of severe mitral regurgitation (MR) in patients presenting with cardiogenic shock (CS) remains challenging because of complications including respiratory failure from acute pulmonary edema and multiorgan dysfunction.[1,2] Inotropic and mechanical circulatory support may be lifesaving, but MR and shock may persist without definitive treatment. Surgical mitral valve repair or replacement in these critically ill patients carries significant mortality and morbidities.[3] The typical pathology of severe MR in CS consists of either a flail leaflet segment secondary to ruptured chordae or papillary muscle because of acute myocardial infarction, or progressive decompensation with chronic MR from leaflet restriction because of ischemic or non-ischemic cardiomyopathy. Given the high surgical risk in this patient population,

CLINICAL PERSPECTIVE

What Is New?
- This study reports clinical outcomes for a large nationwide cohort of patients who underwent transcatheter mitral valve repair with MitraClip in the setting of cardiogenic shock.
- Over the study period from 2014 through early 2019, the use of transcatheter mitral valve repair during cardiogenic shock hospitalizations increased significantly.
- In a matched-cohort analysis of 1192 patients, MitraClip therapy was associated with higher in-hospital and 1-year survival in patients with mitral regurgitation and cardiogenic shock.

What Are the Clinical Implications?
- MitraClip may be considered as a therapeutic option for some critically ill patients.
- Clinical studies on the patient and procedural characteristics associated with MitraClip in the setting of cardiogenic shock could further improve outcomes by optimizing procedural timing and patient selection.

Nonstandard Abbreviations and Acronyms

CCS	Clinical Classification Software
CS	cardiogenic shock
MCS	mechanical circulatory support
MR	mitral regurgitation
TMVr	transcatheter mitral valve repair

edge-to-edge transcatheter mitral valve repair (TMVr) has been attempted as salvage therapy in isolated case reports or small case series.[4–18] Currently, the only US Food and Drug Administration-approved edge-to-edge TMVr device is the MitraClip system (Abbott, Santa Clara, CA). Large clinical series on the safety and efficacy of MitraClip in critically ill patients with CS have not been reported. Our study aims to evaluate the short- and mid-term outcomes associated with MitraClip therapy in patients with CS derived from a large national database.

METHODS

Data Source

This retrospective study used data from the Centers for Medicare and Medicaid Services, consisting of Part A and Part B institutional claims for US Fee-for-Service Medicare beneficiaries, as well as deidentified patient demographics (age, sex, geographic location, race, or ethnicity), date of death if applicable, and Medicare insurance enrollment information. Our study used a deidentified database and thus was exempt from institutional review board approval. Deidentified health information can be used as specified in the Health Insurance Portability and Accountability Act Privacy Rule, and informed consent was therefore exempt. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

Patients were eligible for study inclusion if they had a primary or secondary diagnosis of CS (*International Classification of Diseases, Ninth Edition, [ICD-9]* 785.51, *International Classification of Diseases, Tenth Revision [ICD-10]* R57.0) during an inpatient encounter occurring January 1, 2014 through March 31, 2019. To account for hospital transfers within a single episode of care, the index event included all inpatient encounters following the initial CS diagnosis if a subsequent hospital admission occurred within 24 hours of hospital discharge ("consecutive claims"). Only index events that occurred at, or were transferred to, hospitals where MitraClip was performed were included in the analysis. Patients with a diagnosis of mitral valve disease occurring during or before the index event were included, while those with a prior surgical or percutaneous mitral valve intervention were excluded. The study cohort was further limited to patients with continuous, Fee-for-Service (non-health maintenance organization) Medicare enrollment for at least 1 year before hospital admission and at least 30 days after hospital discharge, retaining those who died at any time following the index event. To evaluate the impact of MitraClip on clinical outcomes in the setting of CS, the final study cohort was dichotomized into patients who underwent a MitraClip procedure (*ICD-9* 35.97, *ICD-10* 02UG3JZ) during the index event (MitraClip group) versus those who did not (non-MitraClip group).

As a proxy for CS etiology, Clinical Classification Software (CCS) developed through the Healthcare Cost and Utilization Project was used to classify each CS index event (Table S1). The CCS is a tool for clustering patient diagnoses and procedures into clinically meaningful categories and has been used previously to study CS.[19,20] Baseline comorbidities were identified using primary and secondary diagnosis codes captured during inpatient and outpatient encounters occurring before the index event (Table S2).[21,22] Propensity scores for undergoing MitraClip were computed for every patient in the study cohort on the basis of a multivariable

logistic regression model. Patient characteristics incorporated into the propensity score were quintiles for age, sex, race, and pre-selected baseline comorbidities including hypertension, chronic heart failure, pulmonary disease, renal disease, peripheral vascular disease, atrial fibrillation, cerebrovascular disease, prior ventricular tachycardia or fibrillation, prior myocardial infarction, concomitant tricuspid regurgitation, and aortic stenosis. Hospitalization characteristics included in the propensity score were year of index admission, the presence of consecutive claims during the index event (ie, hospital transfers), and the use of acute mechanical circulatory support (intra-aortic balloon pump, extracorporeal membrane oxygenation, or Impella), mechanical ventilation, hemodialysis, and coronary interventions (percutaneous coronary intervention or coronary artery bypass grafting) during the index event. Propensity score matching was performed using a nearest neighbor approach with a caliper of 0.2, followed by exact matching on CCS categories for the index event.

Index Event and Long-Term Outcomes

For patients undergoing MitraClip during the index event, the timing of the MitraClip procedure relative to other pre-selected hospital procedures (eg, percutaneous coronary intervention, intra-aortic balloon pump, mechanical ventilation) was reported based on procedure dates available in the Medicare inpatient claims data. The median number of days from admission or discharge relative to the MitraClip procedure was computed based on admission date and discharge date, respectively. Total length-of-stay, number of days spent in an intensive or coronary care unit, and discharge status are reported for each matched group. In-hospital mortality is defined based on date of death relative to admission and discharge dates for the index event.

To assess long-term outcomes, follow-up through June 30, 2019 was available in the Medicare claims data. All-cause mortality through 1-year post index hospitalization included deaths that occurred during the index hospitalization. A landmark analysis evaluated all-cause mortality from the time of live discharge, excluding those patients who died during the index event. For the main analysis, patients were censored at the time of heart transplant, implant of a left ventricular assist device (LVAD), surgical or transcatheter mitral valve intervention occurring after the index event, or at the end of Medicare enrollment. A sensitivity analysis was performed using a composite end point of death, heart transplant, or LVAD implant.

Given the acute critical nature of CS and that patients in the MitraClip group had to survive the index hospitalization until the time of the MitraClip procedure, a second sensitivity analysis was performed to mitigate potential immortal time bias. An additional person-time variable of "treatment time" was incorporated into the propensity score matching algorithm: for the MitraClip arm, treatment time was the number of days from hospital admission to MitraClip procedure; for the control group, a random time between the admission date and the date of discharge or death was assigned to each patient in order to calculate the treatment time, as described previously.[23] For the second sensitivity analysis, patients were matched with treatment time incorporated into the propensity score matching algorithm and the outcomes of in-hospital and 1-year all-cause mortality were re-assessed.

Predictors of Mortality After MitraClip

To identify independent predictors of in-hospital and 1-year mortality, a multivariable analysis was performed. The predictors of interest were age, sex, race and patient comorbidities including concomitant aortic or tricuspid valve disease, hypertension, chronic heart failure, pulmonary disease, renal failure, peripheral vascular disorder, prior ventricular tachycardia or fibrillation, atrial fibrillation or flutter, prior acute myocardial infarction, and cerebral vascular disease. For in-hospital mortality, logistic regression was used to perform a multivariable analysis on the adjusted effect of each predictor by including all covariates in the model. Similarly, Cox regression was used to assess 1-year mortality.

Statistical Analysis

Continuous variables were compared using Student t-test or Mann-Whitney test if the distribution was not normal and categorical variables were compared using a Chi-square (χ^2) test. The standardized mean differences were computed for all variables used for matching, and standardized mean differences values >0.1 were considered meaningful. Event-free survival was estimated by the Kaplan-Meier method from the index hospitalization until 1 year post discharge, and differences between matched cohorts were compared using a univariate Cox proportional hazards model. The proportional hazards assumption was tested using Schoenfeld residuals and was met. Results in relevant subgroups defined by age, sex, race, and characteristics of the index hospitalization are reported on the basis of crude mortality rates using the log-rank test. All analyses were performed on R version 3.6.0 and matching was performed using the MatchIt package.

RESULTS

Study Population

Of 320 204 US Medicare beneficiaries with a diagnosis of CS during an inpatient encounter occurring from

January 2014 through March 2019, there were 38 166 patients who met study inclusion and exclusion criteria. Within the final study cohort, there were 622 patients with a MitraClip procedure during the index inpatient event and 37 544 patients without. After 1:1 propensity and exact matching, each arm included 596 patients, resulting in a total 1192 patients for analysis (Figure 1).

Patient characteristics for the 2 groups before and after matching are reported in Table 1. Before matching, patients receiving MitraClip during a CS hospitalization were younger, more likely to be White, and more likely to have consecutive hospitalizations (ie, inter-hospital transfers) during the index event compared with those without MitraClip. The CCS categories and interventions performed during the index hospitalization were significantly different before matching, as was the year of admission, with MitraClip hospitalizations falling later during the study period. The proportion of male patients and the prevalence of most comorbidities was similar between groups with the exception of hypertension and atrial fibrillation, both of which were higher for the non-MitraClip group before matching. After matching, the 2 groups were well balanced with no significant difference across all variables of interest (Table 1). The standardized mean differences estimates were <0.1 for all matched parameters. Propensity score density plots and love plots for matched covariates demonstrated close matching between the 2 groups (Figure S1).

MitraClip Use in CS Over Time

Figure 2 illustrates a steady increase in the use of MitraClip during CS hospitalizations from 2014 through 2019. While the total proportion of CS hospitalizations that include a MitraClip procedure remains exceedingly low at <1%, there has been a >3-fold increase in use over the 5 years of the study period, from 0.1% in 2014 to >0.3% in 2018 and the first quarter of 2019 (P<0.001).

Index Hospitalization of Patients With CS

Among those patients who underwent MitraClip during the index CS hospitalization, the timing of the MitraClip procedure relative to hospital admission, discharge or death, and other cardiovascular interventions are illustrated in Figure 3. The MitraClip procedure occurred a median 6.0 days (interquartile range [IQR], 2.0–130) after hospital admission and 7 days (IQR, 4.0–14) before discharge or death. Coronary interventions including percutaneous coronary intervention or coronary artery bypass grafting were performed in 94 patients (15.8%) and
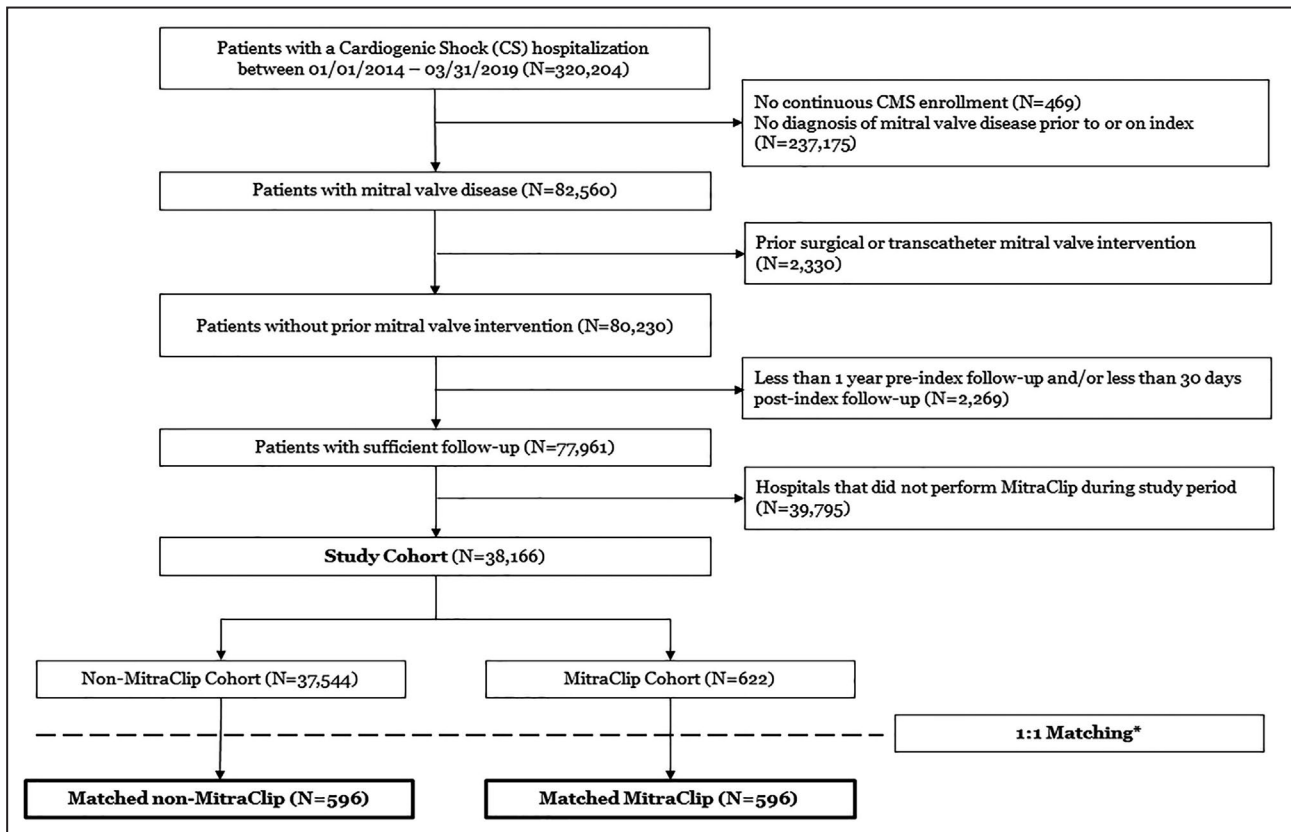
Figure 1. Cohort diagram for MitraClip in cardiogenic shock.
CS indicates cardiogenic shock. *Exact matching on Clinical Classification Software categories for index cardiogenic shock hospitalization; propensity score matching on age, sex, race, presence of consecutive claims, index year, selected comorbidities, and selected interventions during index cardiogenic shock hospitalization. CMS indicates Centers for Medicare and Medicaid Services.

Table 1. Baseline Characteristics for Study Cohort Before and After Matching

All Variables Expressed as N (%)	Before Matching			After Matching		
	Non-MitraClip (N=37 544)	MitraClip (N=622)	P Value	Non-MitraClip (N=596)	MitraClip (N=596)	P Value
Patient demographics						
Age, y			<0.001			0.322
≤63	7180 (19.1)	44 (7.1)		55 (9.2)	44 (7.4)	
64–69	7456 (19.9)	93 (15.0)		78 (13.1)	92 (15.4)	
70–74	7402 (19.7)	112 (18.0)		109 (18.3)	110 (18.5)	
75–81	8516 (22.7)	170 (27.3)		185 (31.0)	163 (27.3)	
≥82	6990 (18.6)	203 (32.6)		169 (28.4)	187 (31.4)	
Female	15 624 (41.6)	269 (43.2)	0.437	247 (41.4)	257 (43.1)	0.598
Race†, White	29 028 (77.3)	515 (82.8)	0.001	481 (80.7)	492 (82.6)	0.455
Index hospitalization						
Consecutive hospitalizations‡	4641 (12.4)	131 (21.1)	<0.001	108 (18.1)	114 (19.1)	0.710
Index year			<0.001			0.894
2014–2015	12 817 (34.1)	118 (19.0)		112 (18.8)	114 (19.1)	
2016–2017	14 712 (39.2)	250 (40.2)		249 (41.8)	241 (40.4)	
2018–2019 Q1	10 015 (26.7)	254 (40.8)		235 (39.4)	241 (40.4)	
Pericarditis, endocarditis, and myocarditis; cardiomyopathy	13 536 (36.1)	217 (34.9)	0.576	205 (34.4)	205 (34.4)	>0.999
Acute myocardial infarction	10 559 (28.1)	116 (18.6)	<0.001	108 (18.1)	108 (18.1)	>0.999
Coronary atherosclerosis and other heart disease	26 307 (70.1)	421 (67.7)	0.214	406 (68.1)	406 (68.1)	>0.999
Pulmonary heart disease	12 830 (34.2)	292 (46.9)	<0.001	278 (46.6)	278 (46.6)	>0.999
Cardiac dysrhythmias	28 338 (75.5)	513 (82.5)	<0.001	497 (83.4)	497 (83.4)	>0.999
Cardiac arrest and ventricular fibrillation	12 867 (34.3)	127 (20.4)	<0.001	121 (20.3)	121 (20.3)	>0.999
Congestive heart failure; non-hypertensive	25 323 (67.4)	507 (81.5)	<0.001	489 (82.0)	489 (82.0)	>0.999
Index circulatory support (IABP/Impella/ECMO)	8847 (23.6)	216 (34.7)	<0.001	178 (29.9)	195 (32.7)	0.318
Index mechanical ventilation	16 344 (43.5)	292 (46.9)	0.097	250 (41.9)	271 (45.5)	0.243
Index coronary interventions (PCI/CABG)	8287 (22.1)	95 (15.3)	<0.001	75 (12.6)	94 (15.8)	0.135
Index hemodialysis	6782 (18.1)	110 (17.7)	0.848	112 (18.8)	101 (16.9)	0.450
Patient comorbidities						
Hypertension	33 760 (89.9)	542 (87.1)	0.027	530 (88.9)	520 (87.2)	0.421
Chronic heart failure	29 423 (78.4)	494 (79.4)	0.560	496 (83.2)	475 (79.7)	0.136
Atrial fibrillation/flutter	29 207 (77.8)	396 (63.7)	<0.001	407 (68.3)	389 (65.3)	0.296
Renal failure	20 336 (54.2)	340 (54.7)	0.837	354 (59.4)	330 (55.4)	0.178
Pulmonary disease	21 120 (56.3)	331 (53.2)	0.140	338 (56.7)	318 (53.4)	0.269
Prior myocardial infarction	18 560 (49.4)	288 (46.3)	0.131	269 (45.1)	277 (46.5)	0.684
Peripheral vascular disorder	14 442 (38.5)	235 (37.8)	0.759	198 (33.2)	225 (37.8)	0.116
Concomitant valvular disease (tricuspid and/or aortic)	12 581 (33.5)	209 (33.6)	0.996	215 (36.1)	204 (34.2)	0.544
Cerebral vascular disease	10 591 (28.2)	175 (28.1)	>0.999	178 (29.9)	168 (28.2)	0.566
Prior ventricular tachycardia/fibrillation	10 164 (27.1)	152 (24.4)	0.155	150 (25.2)	149 (25.0)	>0.999

†The reference group for race is "Non-White", which combined all the other Centers for Medicare and Medicaid Services race categories including Black, Asian, Hispanic, North American native, and others because of the cell size suppression policy.

‡Consecutive hospitalization defined as a subsequent inpatient admission that occurred within 24 hours of prior inpatient discharge.

occurred a median of 5.5 days (IQR, 0.0–14) before the MitraClip procedure. Acute mechanical circulatory support including intra-aortic balloon pump, Impella, or extracorporeal membrane oxygenation was required in 195 patients (32.7%) and was initiated at a median of 1 day (IQR, 0.0–6.0) before MitraClip. Mechanical ventilation was used in 271 patients (45.5%) and hemodialysis in 101 patients (16.9%), both commonly occurring on the same day as MitraClip. Mechanical ventilation was initiated at a median of 0.0 days (IQR, 0.0–7.0) before MitraClip. Hemodialysis was used at a median of 0.0 days relative to MitraClip (IQR, 7.0 before 5.0 post-MitraClip).
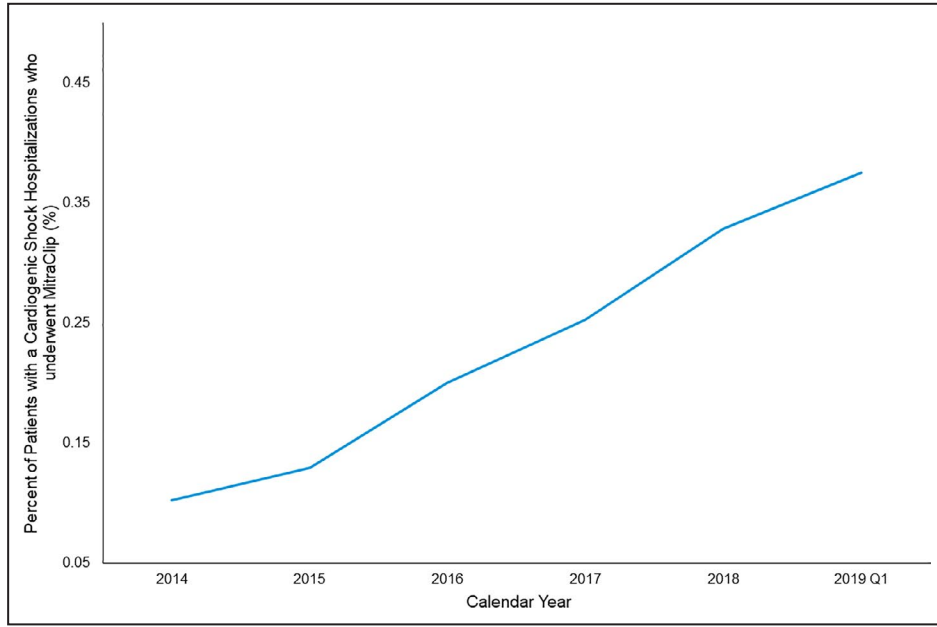
Figure 2. MitraClip usage in cardiogenic shock hospitalizations over time.

Among the matched cohort, patients who received MitraClip spent more days in an intensive or coronary care unit than the non-MitraClip group (9.0 days [IQR, 3.0–17] versus 7.0 days [IQR, 2.0–14]; P=0.017) during the index hospitalization. When considering only those patients who survived the index hospitalization, combined intensive care unit or coronary care unit stay was similar between groups (MitraClip, 9.0 days [IQR, 3.0–16]; non-MitraClip, 8.0 days [IQR, 3.0–16]; P=0.725). Total length-of-stay was longer in the MitraClip group for the overall cohort (MitraClip, 16 days [IQR, 10–25]; non-MitraClip, 12 days [IQR, 7.8–20]; P<0.001), as well as within those who survived the index hospitalization (MitraClip, 17 days [IQR,

11–26]; non-MitraClip, 14 days [IQR, 9–22]; P=0.002). The discharge status, including in-hospital mortality, was significantly different for the 2 groups within the matched cohort (Table 2). In particular, patients who received MitraClip had significantly lower in-hospital mortality compared with matched patients who did not undergo MitraClip during the index hospitalization (24.8% versus 35.4%, odds ratio [OR], 0.6 [95% CI, 0.47–0.77]; P<0.001).

Mid-Term Outcomes

Patients who underwent MitraClip had significantly higher 1-year survival following the CS episode
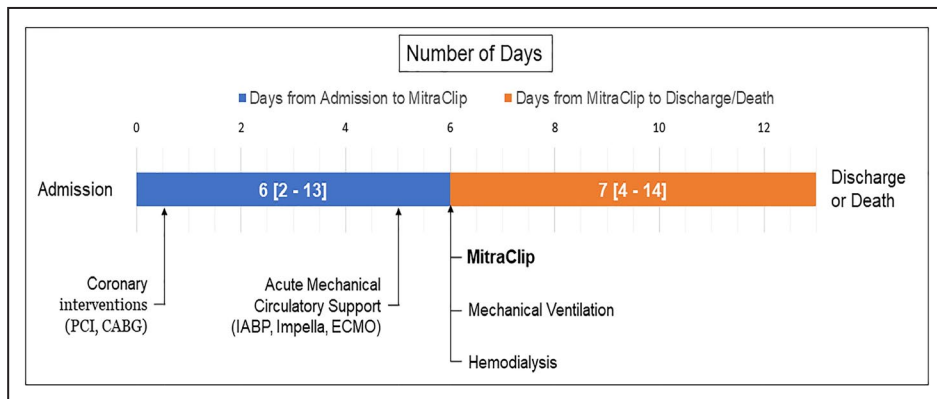

Figure 3. Within the MitraClip arm (n=596), timing of the MitraClip procedure relative to other events during index hospitalization.
CABG indicates coronary artery bypass grafting; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; and PCI, percutaneous coronary intervention. Days reported as median (interquartile range).

Table 2.   Discharge Status for Matched Population

Discharge Status for Index Event, n (%)	Non-MitraClip (n=596)	MitraClip (n=596)	P Value
In-hospital mortality	211 (35.4)	148 (24.8)	<0.001
Discharged to home/self-care/HHA	179 (30.0)	208 (34.9)	
Transferred to short-term hospital/SNF/IPT/LTC/Others	174 (29.2)	220 (36.9)	
Hospice—medical facility/home	32 (5.4)	20 (3.4)	

HHA indicates home health agency; IPT, integrated physical therapy; LTC, long-term care; and SNF, skilled nurse facility.

compared with matched patients without MitraClip, driven largely by mortality events in the non-MitraClip cohort during the index hospitalization (hazard ratio [HR], 0.76 [95% CI, 0.65–0.88], $P<0.001$) (Figure 4). When considering the composite end point of death, LVAD implant, or heart transplant, MitraClip was also associated with a survival benefit (HR, 0.66 [95% CI, 0.57–0.77], $P<0.001$) (Figure S2). In a landmark analysis, after excluding patients who died during the index hospitalization, patients who received MitraClip and were discharged alive had similar mid-term survival compared with those without MitraClip (HR, 0.85 [95% CI, 0.68–1.1], $P=0.131$) (Figure S3).

In a sensitivity analysis to control for potential immortal time bias, the treatment time was well balanced between matched cohorts (MitraClip: 9.1±10.3 days, non-MitraClip: 8.4±9.6 days, $P=0.230$, standardized mean differences=0.049). After controlling for the period of time leading up to the MitraClip procedure

during which death cannot occur, the results were consistent wherein MitraClip was associated with lower in-hospital mortality (24.8% versus 31.8%; OR, 0.71 [95% CI, 0.55–0.91], $P=0.0069$) and higher 1-year survival (HR, 0.78 [95% CI, 0.67–0.90]; $P=0.001$).

The improved 1-year survival associated with MitraClip was consistent across various subgroups of interest, including age ≥75 years, sex, race, and diagnoses during index hospitalization including acute MI, coronary atherosclerosis, pulmonary heart disease, and cardiac dysrhythmias (Figure 5). For the subgroups of acute mechanical circulatory support (MCS) and hemodialysis, however, the survival benefit associated with MitraClip was observed only among patients who did not require these advanced interventions, and not for those who did (acute MCS, $P_{interaction}=0.004$; hemodialysis, $P_{interaction}=0.011$). A CCS classification of pericarditis, endocarditis, myocarditis, or cardiomyopathy during the index hospitalization also significantly impacted the survival benefit associated with MitraClip ($P_{interaction}=0.031$). It is noted that the subgroups with fewer patients may lack of power to detect a significant effect. Furthermore, since the subgroups were not balanced on the patient characteristics, these results should be interpreted with caution.

Predictors of In-Hospital and 1-Year Mortality After MitraClip

Independent predictors of in-hospital and 1-year mortality after MitraClip are listed in Table 3. Peripheral vascular disease was an independent predictor of in-hospital
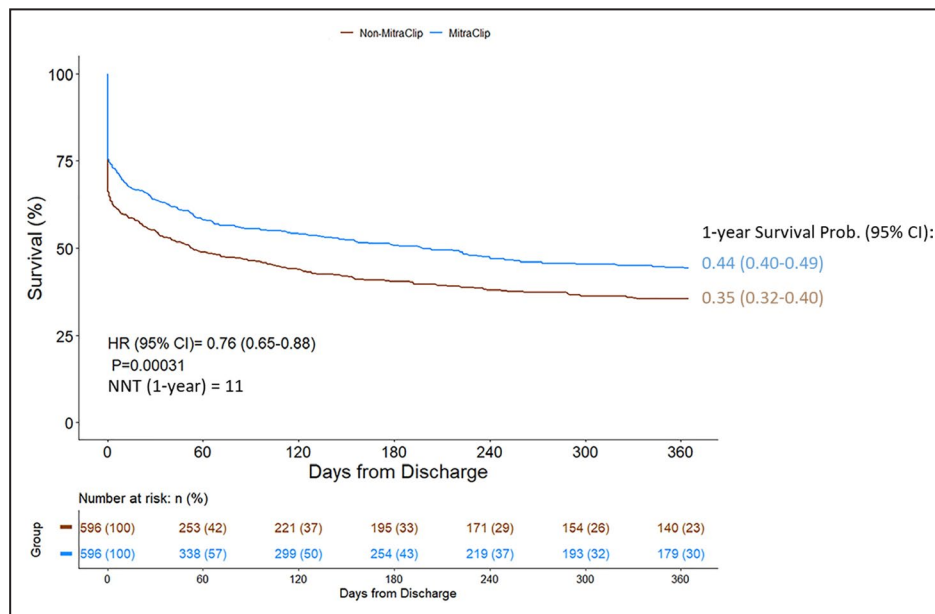

Figure 4.   Kaplan-Meier survival curve in hospitalized patients with mitral regurgitation and cardiogenic shock.
NNT indicates numbers needed to treat.

Hazard Ratio

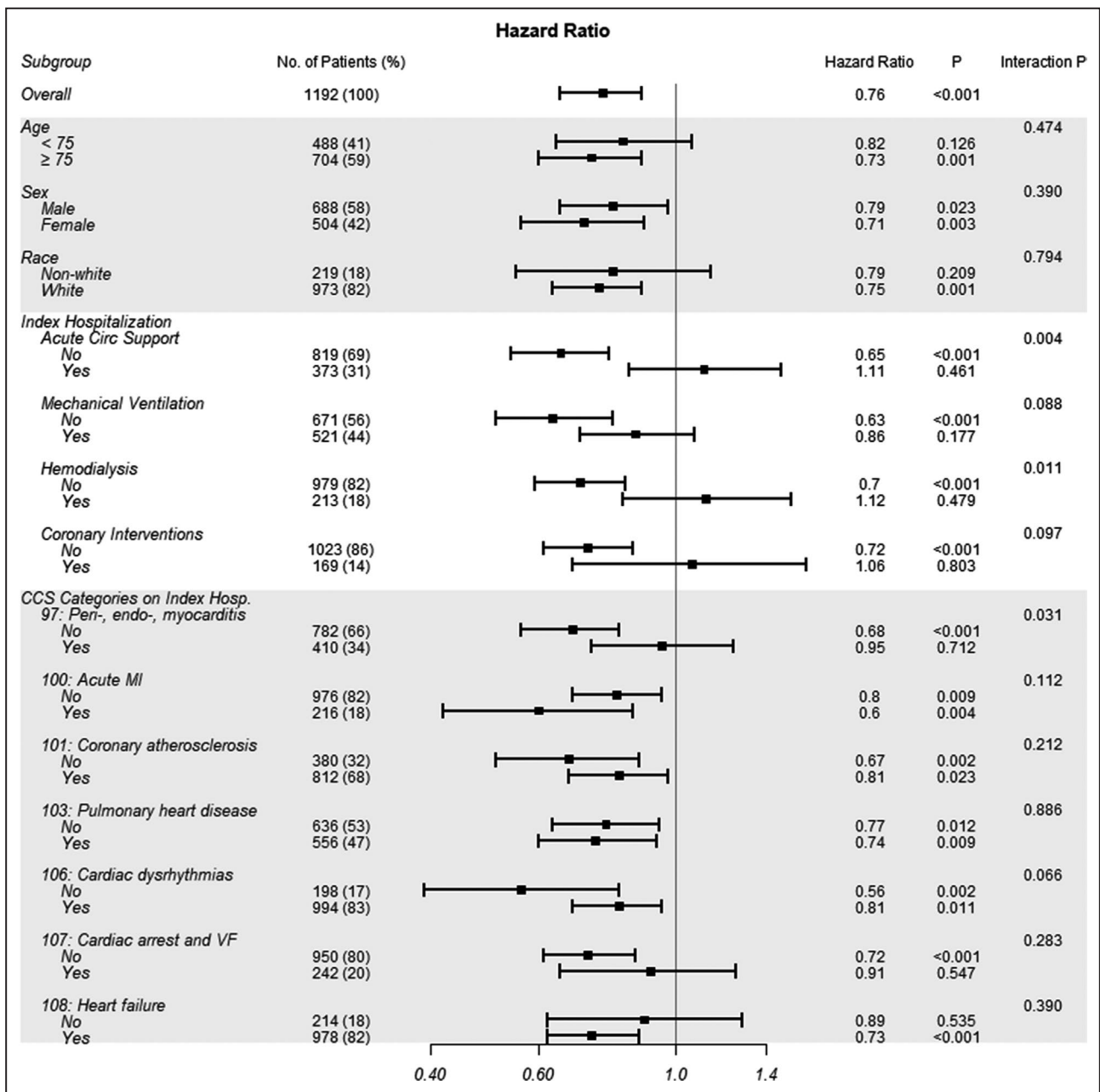| Subgroup	No. of Patients (%)		Hazard Ratio	P	Interaction P
Overall	1192 (100)		0.76	<0.001	
Age					0.474
< 75	488 (41)		0.82	0.126	
≥ 75	704 (59)		0.73	0.001	
Sex					0.390
Male	688 (58)		0.79	0.023	
Female	504 (42)		0.71	0.003	
Race					0.794
Non-white	219 (18)		0.79	0.209	
White	973 (82)		0.75	0.001	
Index Hospitalization					
Acute Circ Support					0.004
No	819 (69)		0.65	<0.001	
Yes	373 (31)		1.11	0.461	
Mechanical Ventilation					0.088
No	671 (56)		0.63	<0.001	
Yes	521 (44)		0.86	0.177	
Hemodialysis					0.011
No	979 (82)		0.7	<0.001	
Yes	213 (18)		1.12	0.479	
Coronary Interventions					0.097
No	1023 (86)		0.72	<0.001	
Yes	169 (14)		1.06	0.803	
CCS Categories on Index Hosp.					
97: Peri-, endo-, myocarditis					0.031
No	782 (66)		0.68	<0.001	
Yes	410 (34)		0.95	0.712	
100: Acute MI					0.112
No	976 (82)		0.8	0.009	
Yes	216 (18)		0.6	0.004	
101: Coronary atherosclerosis					0.212
No	380 (32)		0.67	0.002	
Yes	812 (68)		0.81	0.023	
103: Pulmonary heart disease					0.886
No	636 (53)		0.77	0.012	
Yes	556 (47)		0.74	0.009	
106: Cardiac dysrhythmias					0.066
No	198 (17)		0.56	0.002	
Yes	994 (83)		0.81	0.011	
107: Cardiac arrest and VF					0.283
No	950 (80)		0.72	<0.001	
Yes	242 (20)		0.91	0.547	
108: Heart failure					0.390
No	214 (18)		0.89	0.535	
Yes	978 (82)		0.73	<0.001	

Scale: 0.40   0.60   1.0   1.4

Figure 5.   Subgroup analysis for unadjusted 1-year mortality with MitraClip therapy according to subgroups of interest.
CCS indicates Clinical Classification Software; MI, myocardial infarction; and VF, ventricular fibrillation.

mortality, while consecutive hospitalization during index event, more recent hospitalization, and prior history of ventricular arrhythmias were protective. Independent predictors of 1-year mortality were pulmonary disease, renal failure, and peripheral vascular disease, while hypertension and chronic heart failure were protective.

DISCUSSION

Our matched cohort analysis, reporting the largest MitraClip series in hospitalized patients with a diagnosis of CS, supports the following key findings: (1) MitraClip, though used rarely in patients with CS, is increasingly being considered as a potential therapeutic option. (2) Among patients with a CS hospitalization during our study period, those receiving MitraClip were more likely to be older, White, have consecutive hospitalizations (ie, inter-hospital transfers), and require MCS during index hospitalization. (3) After propensity score matching, percutaneous edge-to-edge repair with MitraClip in patients with MR and CS was associated with reduced in-hospital mortality and greater 1-year survival, compared with

Table 3. Multivariate Predictors of In-Hospital and 1-Year Mortality following MitraClip in Cardiogenic Shock (n=596)

Covariate	In-Hospital All-Cause Mortality		1-y All-Cause Mortality	
	OR (95% CI)	P Value	HR (95% CI)	P Value
Age at index, y				
≤63	1 (ref)		1 (ref)	
64–69	1.48 (0.56–4.25)	0.442	1.14 (0.67–1.93)	0.629
70–74	2.36 (0.94–6.59)	0.081	1.23 (0.73–2.07)	0.431
75–81	2.14 (0.87–5.9)	0.116	1.32 (0.8–2.17)	0.276
≥82	1.7 (0.69–4.71)	0.272	1.39 (0.85–2.29)	0.187
Sex (female)	1.17 (0.78–1.77)	0.450	1.06 (0.84–1.35)	0.612
Race (White)	0.78 (0.45–1.37)	0.375	1.08 (0.78–1.5)	0.624
Consecutive hospitalization during index event	0.54 (0.3–0.93)	0.030	0.87 (0.65–1.16)	0.336
Index, y				
2014–2015	1 (ref)		1 (ref)	
2016–2017	0.53 (0.32–0.89)	0.017	0.76 (0.56–1.02)	0.071
2018–2019 Q1	0.45 (0.26–0.77)	0.003	0.76 (0.56–1.03)	0.079
Concomitant valvular disease (tricuspid and/or aortic)	1.33 (0.86–2.05)	0.195	1.03 (0.8–1.31)	0.833
Hypertension	0.75 (0.37–1.55)	0.426	0.66 (0.44–0.99)	0.046
Chronic heart failure	0.63 (0.32–1.23)	0.172	0.68 (0.46–0.99)	0.042
Pulmonary disease	1.45 (0.92–2.28)	0.108	1.45 (1.13–1.87)	0.004
Renal failure	1.47 (0.93–2.35)	0.105	1.77 (1.35–2.32)	<0.001
Peripheral vascular disorder	2.11 (1.36–3.29)	<0.001	1.44 (1.12–1.84)	0.004
Prior ventricular tachycardia/fibrillation	0.52 (0.3–0.87)	0.015	0.9 (0.68–1.19)	0.445
Atrial fibrillation/flutter	0.99 (0.61–1.63)	0.964	1.14 (0.86–1.51)	0.357
Prior myocardial infarction	1 (0.65–1.56)	0.991	0.89 (0.69–1.15)	0.360
Prior cerebral vascular disease	0.86 (0.54–1.37)	0.541	1 (0.77–1.3)	0.996

HR indicates hazard ratio; and OR, odds ratio.

* In-hospital mortality is multivariable logistic regression; 1-year mortality is multivariable Cox regression.

patients who did not receive MitraClip, that was largely driven by survival during the index hospitalization. (4) On subgroup analysis, the survival benefit associated with MitraClip was consistent across most subgroups of interest with the exception of those requiring acute MCS and hemodialysis during the index hospitalization.

CS remains a potentially fatal condition and is commonly attributable to acute myocardial infarction or decompensated heart failure.[1,2] Severe MR may result from mechanical complications of acute myocardial infarction leading to papillary muscle dysfunction or rupture, acute chordal rupture in patients with chronic primary MR, or progressive decompensation of cardiomyopathy with chronic MR. The goal of care in CS is to hemodynamically stabilize patients and to reverse multiorgan dysfunction, followed by bridge to recovery or more definitive therapies. Although inotropic and mechanical circulatory support are the first-line therapy in these patients, in the presence of severe MR, they do not address the underlying etiology and many patients may require mitral valve intervention. Although mitral valve surgery may provide a definitive treatment, given the acuity of their conditions and presence of

multiorgan dysfunction, a majority of these patients are not suitable surgical candidates. TMVr may be an emerging therapeutic option to address MR and stabilize patients with CS sufficiently to enable recovery or bridge to more advanced therapies. The mechanism of clinical improvement after TMVr may be because of the rapid decrease in left ventricle, left atrium, and pulmonary artery pressures, and the corresponding increase of cardiac output observed after a successful correction of the MR.[24] As shown in our study, MitraClip use in this critically ill patient population has increased over time. Therefore, evaluating the clinical impact of this therapy in patients with MR and CS is timely.

Our study represents the largest known description of patients with a diagnosis of CS who underwent MitraClip procedure. The association of MitraClip with improved in-hospital and 1-year survival aligns with results reported in prior single-center and small multicenter studies (Table 4).[4–18] Together, these findings suggest the use of MitraClip as a potential therapy in critically ill patients with MR. After controlling for patient demographics and comorbidities, as well as the treating hospital and the presence of inter-hospital transfers, MitraClip was associated with a 10.6% absolute reduction of in-hospital mortality

Table 4.   Prior Case Reports and Case Series Reporting MitraClip Use in Cardiogenic Shock

Study	No.	Age (y)	Women	STS PROM (%)	Prior MI	On MCS	Primary MR	DOA to MitraClip (d)	LOS (d)	In-Hospital Mortality	Follow-Up (mo)	Follow-Up Mortality
Zuern CS et al (2011)[4]	1	51	0	...	1	1	0	10	17	0	3	0
Pleger ST et al (2013)[5]	6	68.7 [7.6]	1 (17%)	27.3 [21.4]	5 (83%)	0	2 (33%) Mixed	41.2 [41.6] {10–113}	53.7 [41.1] {13–119}	0	...	...
Couture P et al (2014)[6]	1	78	0	83	1	1	0	60	81	0	12	0
Wolff R et al (2014)[7]	1	68	0	64	1	1	1	1	14	0	6	0
Bahlmann E et al (2015)[8]	1	77	0	78*	1	1	1	...	16	0	...	...
Tang GHL et al (2018)[9]	1	77	1	...	0	1	1	...	15	0	9	0
Buckert D et al (2017)[10]	1	78	0	18.4	1	1	1	...	14	0	4	0
Hernandez M et al (2018)[11]	1	70	0	7.1	1	1	1 Mixed	3	33	0	6	0
Haberman D et al (2019)[12]	20	68.1 [9.9]	14 (70%)	...	20 (100%)	7	0	32 [25] {7–90}	...	1 (5%)	Median, 15 {3–88}	2
Rizik DG et al (2019)[13]	3	72, 92, 81	0	...	1 (33%)	2	2 (67%)	...	7, 3, 4 Post-op	0	1	0
Chan V et al (2019)[14]	27	71 [13]	10 (37%)	18.5	5 (19%)	5	2	Median, 23 (9–37)	Median, 40 {22–70} Post-op	8 (30%)	6.7 [8.9]	17 (63%)
Cheng R et al (2019)[15]	29	65.5 [17.0]	5 (17%)	...	10 (35%)	8 (28%)	...	...	...	5 (17%)	14.8 [15.7]	7 (24%)
Flint K et al (2019)[16]	12	71.7 [12.8]	3 (25%)	23.9 [18.2]	4 (33%)	5 (42%)	10 (83%) 6 Mixed	...	...	1 (8%)	Median, 6.6 {1.4–12.6}	5 (42%)
Garcia S et al (2020)[17]	11	74.5 [13.3]	5 (45%)	15.5 [IQR, 6.9–39.1]	5 (45%)	5 (45%)	7 (64%)	...	...	3/11 (27%)	12	6/9 (66%)
Estevez-Loureiro R et al (2020)[18]	44	70.0 [10.8]	16 (36%)	15.1 {6.2–23.2}	44 (100%)	16 (36%)	44 (10%)	Median, 18 {13–36.8}	Median, 16 {8–27} Post-op	4 (9%)	6	8 (18%)

All variables expressed as n (%), mean (SD), (range) , and interquartile range. DOA indicates date of admission; IQR, interquartile range; LOS, length of stay; MCS, mechanical circulatory support; MI, myocardial infarction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; and STS PROM, Society of Thoracic Surgeons predicted risk of operative mortality.
*EuroScore listed, as STS PROM score was not available.

in our US nationwide study of all-comer patients with CS. When considering only patients who survived the index hospitalization in a landmark analysis, patients with and without MitraClip had similar 1-year survival, suggesting that the effect was driven by in-hospital survival. One potential explanation would be by reducing the MR and improving forward flow, MitraClip in the presence of CS may allow sufficient stabilization of the patient to enable successful hospital discharge. Notably, only 32.5% of patients in the analytic cohort were discharged home from the CS hospitalization, either to self-care or with the support of a home health agency. This finding suggests that despite hospital discharge, patients who underwent MitraClip in the context of CS still need significant time and resources to recover.

Two sensitivity analyses were performed as part of the current study. In the first, a composite end point of death, heart transplant, or LVAD implant reinforced the robustness of the survival benefit associated with MitraClip by treating heart transplant and LVAD as equivalent end points to mortality rather than censoring for these clinically relevant events. The second sensitivity analysis controlled for potential survivor bias given that patients receiving MitraClip had to survive the index hospitalization long enough to undergo the procedure while those in the control group had no such requirement. While this marginally impacted in-hospital survival in the control group, the significant in-hospital survival effect associated with MitraClip was maintained, suggesting that immortal time bias does not drive the results observed in this observational study.

Within the MitraClip group, pulmonary disease, renal failure, and peripheral vascular disorder were independent predictors of reduced 1-year survival following CS. This speaks to the high burden of preexisting comorbidities in patients with CS that may increase their mortality risk. Interestingly, chronic heart failure was protective, which might be because of the potential ability of a compromised left ventricle over a normal one to withstand severe MR. Further analysis would be necessary to confirm this hypothesis.

Subgroup analyses showed that the survival benefit associated with MitraClip was consistent irrespective of age, sex, race, and other cardiac risk factors. However, this effect was significantly impacted by certain high-risk features in this CS cohort. For example, MitraClip therapy was not associated with improved survival among patients requiring MCS or hemodialysis during the index hospitalization. In our study, patients who received MitraClip often needed mechanical ventilation or hemodialysis on the same day as the procedure. In the unmatched study cohort, there was a higher prevalence of MCS use in patients receiving MitraClip. These temporally associated events and need for MCS may be surrogate markers of the critically ill nature of

patients with CS who received MitraClip, and suggests that patient selection is important to ensure improved outcomes with MitraClip in the setting of CS. The use of hemodialysis is particularly relevant given that renal failure was associated with greater 1-year mortality for patients who received MitraClip.

Irrespective of MitraClip therapy, 1-year mortality among patients who were successfully discharged in our study remained high at ≈40%. This is reflective of the extremely high-risk nature of CS. However, we note this is comparable with the 31.2% 1-year mortality of patients with functional MR who underwent MitraClip in the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy) Registry,[25] highlighting the complexity of treating MR in patients with advanced cardiovascular disease. Importantly, when considering the composite end point of all-cause mortality, heart transplant, or LVAD, the benefit associated with MitraClip in our study was maintained, reinforcing the potential impact on key clinical end points.

Study Limitations

Our study has several limitations. First, our data are derived from an administrative claims database, which lacks granular clinical details such as MR etiology and severity of CS, as well as MitraClip procedural characteristics such as amount of residual MR. However, given the challenges of informed consent and randomization in critically ill patients, administrative claims data provide a viable approach to study the real-world use of MitraClip in a large nationwide cohort of patients with CS. Second, outcomes were not centrally adjudicated in this retrospective observational cohort study. However, the primary end point of all-cause mortality has been widely validated in Centers for Medicare and Medicaid Services claims data and has been shown to demonstrate close concordance with trial-adjudicated mortality. Third, although we attempted to control for all available variables in the propensity matching, as the study is observational residual confounding may be present. Importantly, the clinical decision to perform a MitraClip procedure on a patient in CS cannot be elucidated in a retrospective observational cohort. While our second sensitivity analysis aimed to account for potential immortal time bias in the matched cohort, it is plausible that patients selected to receive MitraClip were those more likely to survive long-term. Finally, the reported P-values are at a nominal alpha level without controlling for the potential inflation of the Type I error rate.

CONCLUSIONS

In patients with MR presenting with CS, use of TMVr with MitraClip is increasing and is associated with

greater in-hospital and 1-year survival. MitraClip may be a treatment option for critically ill patients with CS, and further study is warranted to optimize procedural timing and patient selection associated with the improved outcomes, particularly in those patients requiring acute MCS and hemodialysis.

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SUPPLEMENTAL MATERIAL

Table S1. Clinical Classification Software (CCS) categories for cardiogenic shock developed through the Healthcare Cost and Utilization Project (HCUP).[19, 20]

CCS Categories	Description	ICD-9-CM	ICD-10-CM
97	Pericarditis, endocarditis, and myocarditis; cardiomyopathy (no TB or STDs)	032.82, 036.40, 036.41, 036.42, 036.43, 074.20, 074.21, 074.22, 074.23, 112.81, 115.03, 115.04, 115.13, 115.14, 115.93, 115.94, 130.3, 391.0, 391.1, 391.2, 391.8, 391.9, 392.0, 393, 398.0, 398.90, 398.99, 420.0, 420.90, 420.91, 420.99, 421.0, 421.1, 421.9, 422.0, 422.90, 422.91, 422.92, 422.93, 422.99, 423.0, 423.1, 423.2, 423.3, 423.8, 423.9, 425.0, 425.1, 425.11, 425.18, 425.2, 425.3, 425.4, 425.7, 425.8, 425.9, 429.0	A36.81, A38.1, A39.50, A39.51, A39.52, A39.53, B26.82, B33.20, B33.21, B33.22, B33.23, B33.24, B37.6, B58.81, I01.0, I01.1, I01.2, I01.8, I01.9, I02.0, I09.0, I09.2, I09.9, I23.0, I30.0, I30.1, I30.8, I30.9, I31.0, I31.1, I31.2, I31.3, I31.4, I31.8, I31.9, I32, I33.0, I33.9, I38, I39, I40.0, I40.1, I40.8, I40.9, I41, I42.0, I42.1, I42.2, I42.3, I42.4, I42.5, I42.7, I42.8, I42.9, I43, I51.4
100	Acute myocardial infarction	410.0, 410.00, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.2, 410.20, 410.21, 410.22, 410.3, 410.30, 410.31, 410.32, 410.4, 410.40, 410.41, 410.42, 410.5, 410.50, 410.51, 410.52, 410.6, 410.60, 410.61, 410.62, 410.7, 410.70, 410.71, 410.72, 410.8, 410.80, 410.81, 410.82, 410.9, 410.90, 410.91, 410.92	I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I22.0, I22.1, I22.2, I22.8, I22.9, I21.9, I21.A1, I21.A9
101	Coronary atherosclerosis and other heart disease	411.0, 411.1, 411.8, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.0, 414.00, 414.01, 414.06, 414.2, 414.3, 414.4, 414.8, 414.9, V45.81, V45.82	I20.0, I20.1, I20.8, I20.9, I23.7, I24.0, I24.1, I24.8, I24.9, I25.10, I25.110, I25.111, I25.118, I25.119, I25.2, I25.5,

			I25.6, I25.750, I25.751, I25.758, I25.759, I25.811, I25.82, I25.83, I25.84, I25.89, I25.9, Z95.1, Z95.5, Z98.61
103	Pulmonary heart disease	415.0, 415.1, 415.12, 415.13, 415.19, 416.0, 416.1, 416.2, 416.8, 416.9, 417.0, 417.1, 417.8, 417.9, V12.55	I26.01, I26.02, I26.09, I26.90, I26.92, I26.99, I27.0, I27.1, I27.2, I27.81, I27.82, I27.89, I27.9, I28.0, I28.1, I28.8, I28.9, Z86.711, I27.20, I27.21, I27.22, I27.23, I27.24, I27.29, I27.83
106	Cardiac dysrhythmias	427.0, 427.1, 427.2, 427.31, 427.32, 427.60, 427.61, 427.69, 427.81, 427.89, 427.9, 785.0, 785.1	I47.0, I47.1, I47.2, I47.9, I48.0, I48.1, I48.2, I48.3, I48.4, I48.91, I48.92, I49.1, I49.2, I49.3, I49.40, I49.49, I49.5, I49.8, I49.9, R00.0, R00.1, R00.2
107	Cardiac arrest and ventricular fibrillation	427.41, 427.42, 427.5	I46.2, I46.8, I46.9, I49.01, I49.02
108	Congestive heart failure; non-hypertensive	398.91, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9	I09.81, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.9, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89

Table S2. Diagnosis and Procedure Codes used to define index event, baseline characteristics and interventions.

Diagnosis Codes		
Conditions	**ICD-9-CM**	**ICD-10-CM**
Cardiogenic shock	785.51	R57.0
Heart failure (Primary diagnosis)	402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, 428, 428.9, 428.1, 428.2, 428.21, 428.22, 428.23, 428.3, 428.31, 428.32, 428.33, 428.4, 428.41, 428.42, 428.43	I11.0, I13.0, I13.2, I50.9, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43
Mitral Valve Disease	424.0	I34.0, I34.1, I34.2, I34.8, I34.9
Hypertension	401.x, 402.x–405.x	I10.x, I11.x–I13.x, I15.x, O10.x, O11.x, O16.x
Chronic Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
Atrial Fibrillation/Flutter	427.31, 427.32	I48.0, I48.1, I48.2, I48.3, I48.4, I48.91, I48.92
Renal Failure	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x	N18.x, N19.x, Z49.0x, Z49.3x, Z91.15, Z94.0, Z99.2
Pulmonary Disease	490 -496, 500-505, 506.4	J40.x–J47.x, J60.x–J67.x, J68.4
Myocardial Infarction	410.xx, 411.1, 412	I20.0, I21.x, I22.x, I25.110, I25.2, I25.7x

Peripheral Vascular Disorder	093.0, 437.3, 440.x, 441.x, 443.1–443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I72.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.1, I79.8, K55.1, K55.8, K55.9, Z95.8
Concomitant Valvular Disease (Tricuspid and/or Aortic)	424.1, 424.2	I35.0, I35.1, I35.2, I35.8, I35.9, I36.0, I36.1, I36.2, I36.8, I36.9
Cerebral Vascular Disease	362.34, 430.x - 438.x	G45.x, G46.x, H34.0, I60.x - I69.x
Ventricular Tachycardia/Fibrillation	427.0, 427.1, 427.2, 427.41, 427.42	I47.0, I47.2, I47.9, I49.01, I49.02, I49.2
Procedure Codes		
Procedure	**ICD-9-PCS**	**ICD-10-PCS**
MitraClip	35.97	02UG3JZ
Heart Transplant	37.51	02YA0Z[0/1/2]
LVAD	37.66	02HA0QZ
Mitral Valve Interventions	35.02, 35.12, 35.23, 35.24, 35.97	02QGxxx, 02UGxxx, 02RGxxx, 027Gxxx, 02NGxxx, 02CGxxx, 02VGxxx
Circulatory Support (IABP/Impella/ECMO)	37.61, 37.68, 39.65	5A02[1/2]10, 5A1522[3/F/G/H], 5A021[1/2][6/D]
Mechanical Ventilation	96.70, 96.71, 96.72	5A19[3/4/5]5Z
Coronary Interventions (PCI/CABG)	36.07, 36.06, 00.66, 36.1x	027[0-3]x[4-7]x, 027[0-3]x[D-G]x, 027[0-3]xZx, 021[0-3][0/4]xx
Hemodialysis	39.95	5A1D[0/6/7-9]0Z

CABG=coronary artery bypass graft; ECMO=extracorporeal membrane oxygen; IABP=intraortic balloon pump; ICD=International Classification of Diseases; *LVAD=Left Ventricular Assist Device;* PCI=percutaneous coronary intervention

Figure S1(A). Propensity score density plots for MitraClip and non-MitraClip groups before (left) and after (right) matching.
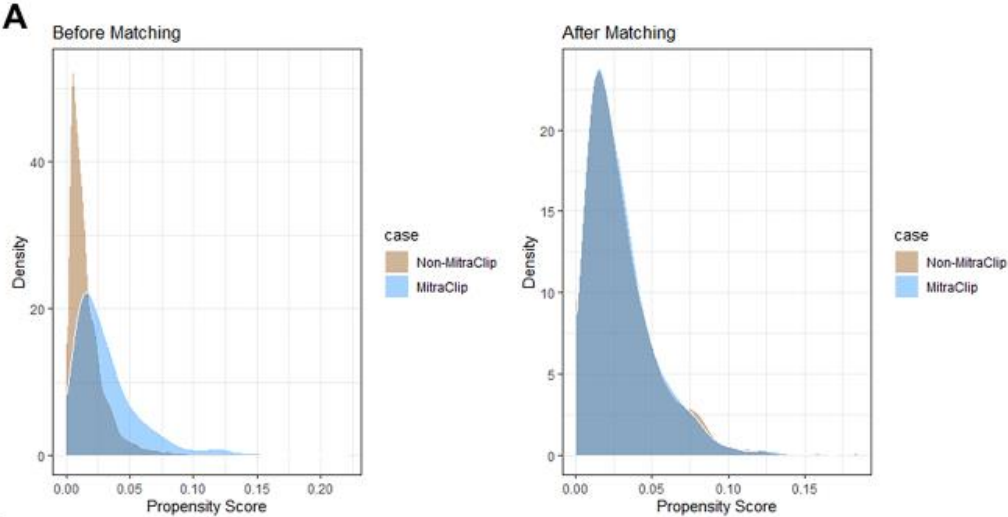
Figure S1(B). Love plots showing covariate balance before (brown) and after (blue) matching.
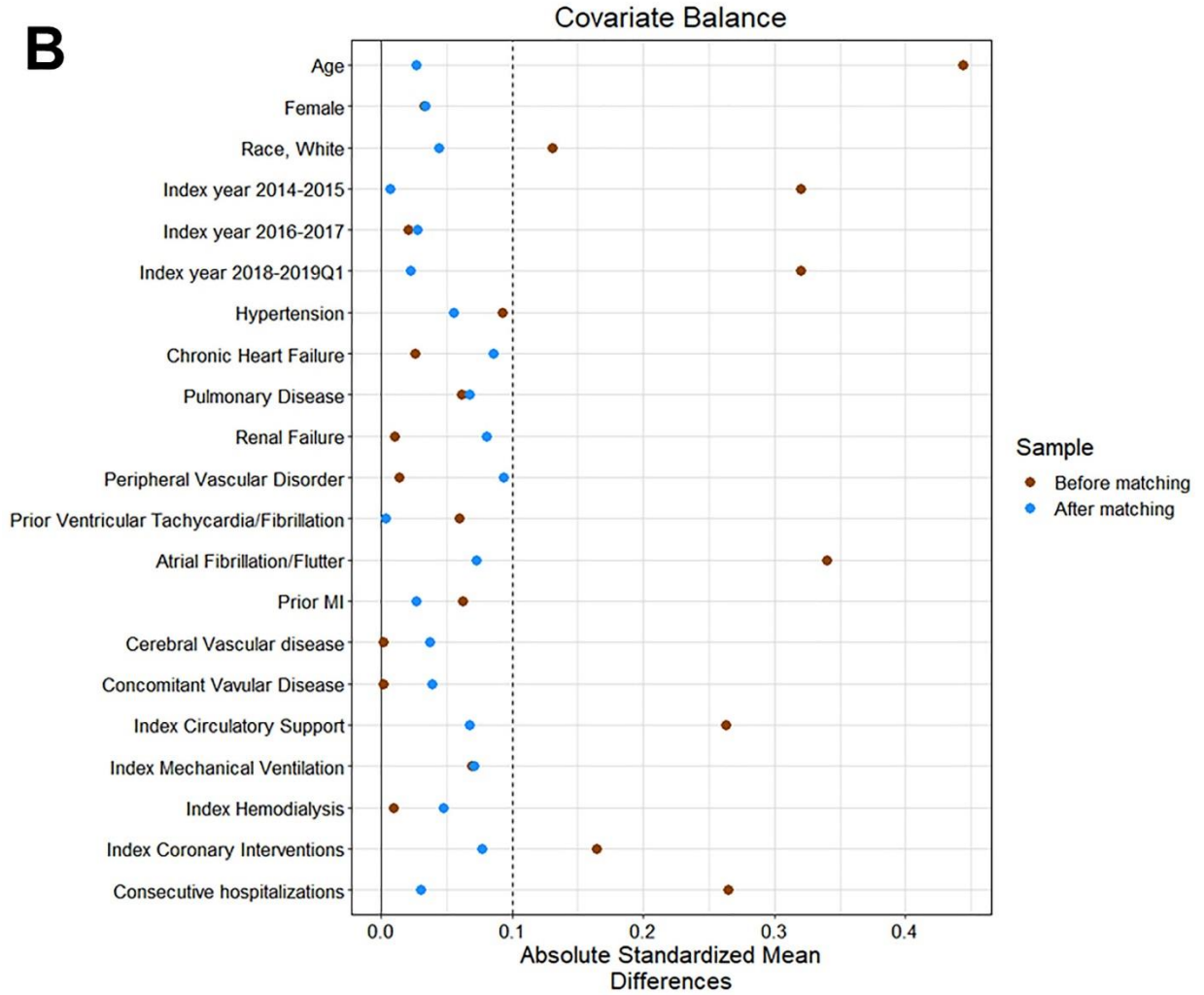
Figure S2. Kaplan Meier Curve for composite endpoint of freedom from all-cause mortality, left ventricular assist device (LVAD) implant, or heart transplant.
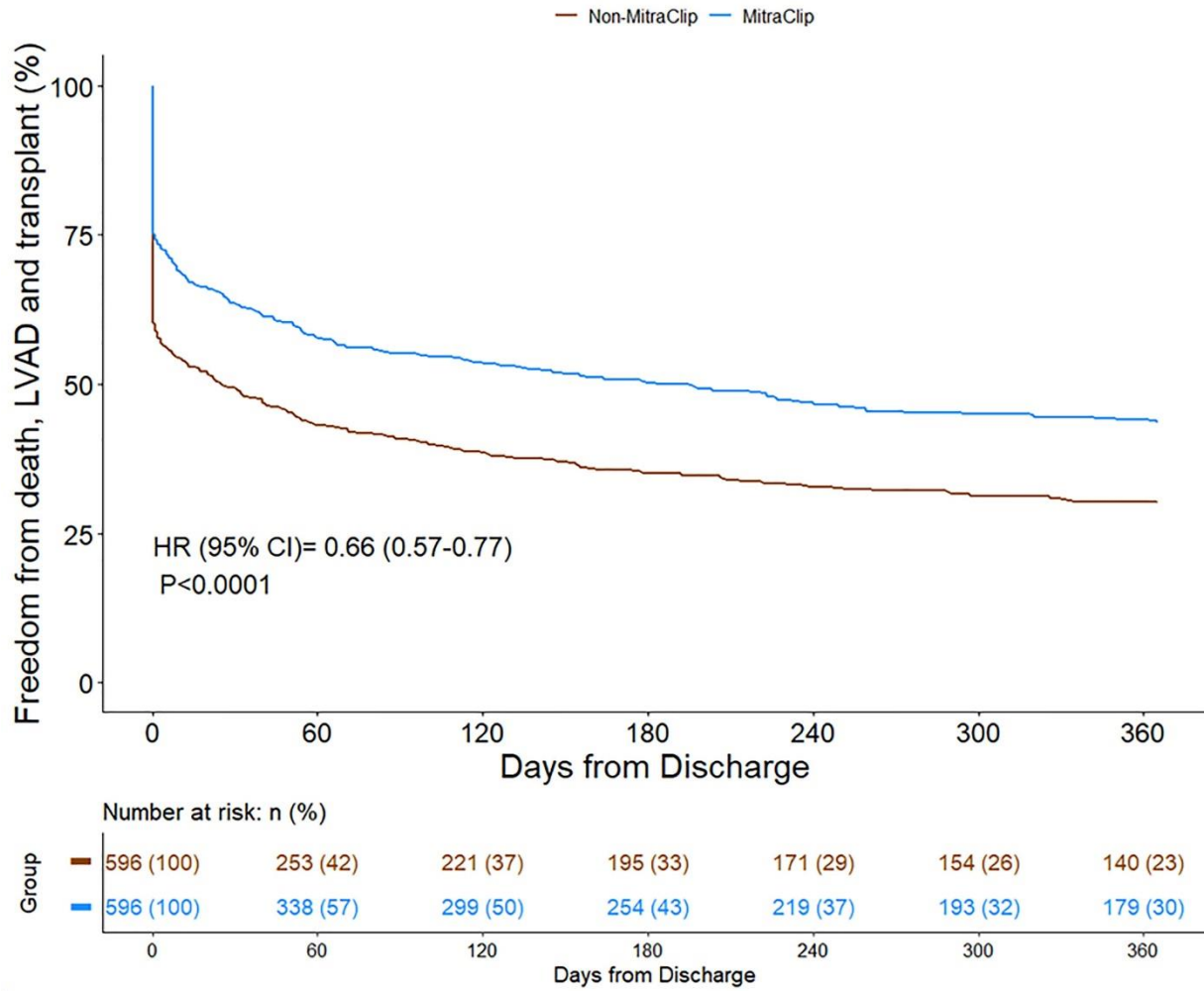
Figure S3. Landmark analysis showing Kaplan Meier survival curve in patients with mitral regurgitation and cardiogenic shock who were discharged live from index hospitalization.