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Research Letter

Acute myocardial infarction in heart transplant recipients: An 18-year national study

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ABSTRACT

Among 11,622,528 acute myocardial infarction (AMI) hospitalizations, 892 had a history of heart transplantation (HT). In comparison to AMI admissions without HT, those with prior HT were more frequently complicated with cardiac arrest (8.3 % vs 5.0 %, $p < 0.001$), acute non-cardiac organ failure (17.4 % vs 9.4 %) (p < 0.001), lower rates of coronary angiography (55.4 % vs 63.6 %, $p < 0.001$), comparable rates of percutaneous coronary intervention (38.8 % vs 41.5 %, $p = 0.10$), higher rates of pulmonary artery catheterization (2.7 % vs 1.1 %, p < 0.001), invasive mechanical ventilation and acute hemodialysis compared to AMI admissions without HT. Compared to AMI admissions without HT, prior HT recipients had higher in-hospital mortality (11.8 % vs 6.2 %, adjusted odds ratio 2.87 [95 % CI 2.23–3.70]; $p < 0.001$).

1. Introduction

Cardiac transplantation has emerged as a life-sustaining therapy in patients with end-stage heart failure, with a median survival of about 11 years [1]. Recent trends show an increase in the number of cardiac transplants worldwide together with a significant improvement in post-transplant outcomes [1]. The number of cardiac transplants increased significantly in 2021, where 3817 transplants were performed in the United States [2]. Patients with heart transplantation (HT) are at an increased risk of non-cardiac organ complications such as infections, stroke, renal dysfunction, and therefore have higher long-term mortality [1,3,4]. Notwithstanding advancements in immunosuppressive therapies, coronary artery disease (CAD) has emerged as a long-term complication and continues to limit survival in patients with HT. [5] Notably, the emergence of CAD in HT patients is multifactorial, with immune-mediated processes playing a dominant role, most prominently, coronary allograft vasculopathy (CAV) [6]. Clinically, AMI patients with a history of HT present atypically in comparison to non-transplant AMI patients [7]. They often lack the classic symptoms of angina due to the absence of afferent fibers, regardless of partial innervation, resulting in delay to diagnosis and management [6]. Despite increasing incidence, there is paucity of data on the prognosis and management of AMI in patients with history of HT. In light of this background, we sought to evaluate the management and outcomes of HT patients with AMI using a national database.

2. Methods

We used the National (Nationwide) Inpatient Sample (NIS), the largest all-payer database of hospital inpatient stays in the United States and a part of the Healthcare Quality and Utilization Project (HCUP) for this analysis [8]. Adult admissions (>18 years) with AMI in the primary diagnosis field were identified from the HCUP-NIS database (2000–2017), using International Classification of Diseases 9.0 Clinical Modification [ICD-9CM] 410.x and ICD-10CM I21.x-22.x codes [9,10]. Admissions with a history of HT were identified using ICD-9CM V42.1 and ICD-10CM Z94.1 in any of the secondary diagnosis fields similar to published literature [11,12]. The comorbidity burden was estimated using the Charlson Comorbidity Index (Deyo's modification) [12,13]. Characteristics including demographics, hospital size and region, acute organ failure, utilization of mechanical circulatory support, cardiac procedures including coronary angiography, percutaneous coronary intervention(PCI), coronary artery bypass grafting (CABG) and non-cardiac organ support use were identified for all admissions using methods similar to previous publications (Supplementary Table 1) [9,10]. Recommendations from the HCUP-NIS, such as use of survey procedures, discharge weights to generate national estimates and use of trend weights for samples from 2000 to 2011 to adjust for the 2012 HCUP-NIS re-design were adhered to during analysis [14]. Chi-square or Fischer Exact test were used to compare categorical variables as appropriate, and *t*-tests or Kruskal-Wallis H test were used to continuous variables. All analyses were performed using SPSS v27.0 (IBM Corp, Armonk NY).

3. Results

Between January 1, 2000 and December 31, 2017, there were a total of 11,622,528 hospitalizations with a primary diagnosis of AMI. Among these, 892 had a history of HT. The mean age of AMI admission in those with HT was 60.5 ± 13.0 years and 68.1 % ($n = 607$) were male. HT

Abbreviations: AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; HCUP, Healthcare Cost and Utilization Project; HT, heart transplantation; ICD-9CM, International Classification of Diseases-9 Clinical Modification; ICD-10CM, International Classification of Diseases-10 Clinical Modification; NIS, National/Nationwide Inpatient Sample; NSTEMI, non-ST-segment elevation myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarctio.

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recipients with AMI were younger (60.5 ± 13.0 vs 67.6 ± 14.2, $p < 0.001$), more frequently admitted to urban teaching hospitals (60.2 % vs 49.3 %), large-sized hospitals (74.3 % vs 63.3 %), and to hospitals in the West (27.2 % vs 17.4 %) compared to AMI admissions without HT (Table 1). Temporal trends revealed a significant increase in NSTEMI presentation with a concomitant decline in STEMI presentation among AMI admissions with HT (Fig. 1).

Compared to AMI admissions without HT, those with prior HT were more frequently complicated with cardiac arrest (8.3 % vs 5.0 %) and and higher rates of acute non-cardiac organ failure (17.4 % vs 9.4 %) (both $p < 0.001$). Rates of cardiogenic shock were comparable in both groups (Table 1). Lower use of coronary angiography (55.4 % vs 63.6 %, $p < 0.001$) but similar rates of PCI (38.8 % vs 41.5 %, $p = 0.10$) were seen AMI admissions with HT compared to those without. Among HT recipients, use of coronary angiography (69.5 % vs 48.0 %) and PCI (51.9 % vs 31.7 %) were significantly higher in STEMI admissions compared to NSTEMI admissions (both $p < 0.001$). In comparisons of other in-hospital procedures, HT recipients had lower use of coronary artery bypass grafting (1.2 % vs 9.2 %, $p < 0.001$), higher rates of pulmonary artery catheterization (2.7 % vs 1.1 %, $p < 0.001$), invasive mechanical ventilation and acute hemodialysis compared to AMI admissions without HT (Table 1). Use of mechanical circulatory support was comparable in both groups (6.1 % vs 4.8 %, $p = 0.08$) (Table 1).

Among AMI admissions with HT, 105 (11.8 %) died during hospitalization. In this group, a higher proportion of deaths were seen in those with STEMI (19.5 % vs 7.7 %, $p < 0.001$) as compared to those with NSTEMI. In comparison to AMI admissions without HT, recipients of HT had significantly higher in-hospital mortality (11.8 % vs 6.2 %, adjusted odds ratio 2.87 [95 % CI 2.23–3.70]; $p < 0.001$, Supplementary Table 2). The median length of stay (median [interquartile range] 3 [2–6] vs 3 [2–6]; $p = 0.28$) and hospitalization charges (median [interquartile range] $39,164 [18,603-69,849] vs $39,332 [19,128-72,254]; $p = 0.37$) were comparable for AMI admissions with and without HT. Among those that survived hospital stay, AMI admissions with HT were more often transferred to another hospital (26.7 % vs 12.6 %), had lower rates of dismissal to skilled nursing facilities (6.5 % vs 13.4 %). and were less likely to be discharged home with or without home health care (66.8 % vs 73.1 %) compared to those without HT.

4. Discussion

Over this 18-year study period, we identified 892 AMI admissions with prior HT. Despite higher clinical acuity as noted by higher rates of cardiac arrest and non-cardiac acute organ failure, admissions with HT had lower use of coronary angiography and coronary artery bypass grafting. Prior HT was associated with higher in-hospital mortality and lower rates of discharges to home despite comparable lengths of stay.

An important finding was the higher incidence of cardiac arrest (CA) complicating AMI in those with HT compared to those without. Several studies have demonstrated underlying CAV as a potential cause of arrhythmias in addition to factors such as higher donor age and reduced left ventricular function [15]. Denervation in transplanted heart and repetitive surgical intervention promoting new re-entry pathways may also contribute to faster heart rates, precipitating arrhythmias [16,17]. These underlying or newly precipitated arrhythmias may lead to higher rates of CA post HT. Although the 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines have a class II b recommendation for using implantable cardioverter defibrillator (ICD) in patients with CAV and left ventricular dysfunction after HT [18], benefits associated with placement of an ICD or permanent pacemaker to prevent CA and subsequent sudden cardiac death remain uncertain [19].

Our study identified lower use of coronary angiography and CABG in HT patients. The higher rates of multiorgan failure and acute kidney injury in admissions with prior HT may explain lower use of invasive therapies as providers may delay these interventions until clinical

Table 1
Baseline and clinical characteristics of AMI admissions with heart transplantation.

Characteristics		Prior heart transplant $N = 892$	No heart transplant $N =$ 11,621,637	P
Age (years)		60.5 ± 13.0	67.6 ± 14.2	<0.001
Female sex		284 (31.9)	4,617,704 (39.7)	<0.001
Race	White	554 (62.2)	7,392,860 (63.6)	<0.001
	Black	136 (15.2)	922,011 (7.9)	
	Others[a]	202 (22.6)	3,306,766 (28.5)	
Primary payer	Medicare	589 (66.0)	6,695,393 (57.6)	<0.001
	Medicaid	59 (6.7)	714,745 (6.2)	
	Private	200 (22.4)	3,240,140 (27.9)	
	Others[b]	44 (4.9)	971,359 (8.4)	
Quartile of median household income for zip code	0-25th	258 (29.4)	2,769,356 (24.4)	<0.001
	26th–50th	188 (21.4)	3,086,586 (27.2)	
	51st–75th	195 (22.3)	2,784,461 (24.5)	
	75th–100th	236 (26.9)	2,714,662 (23.9)	
Charlson Comorbidity Index	0–3	381 (42.8)	4,363,909 (37.5)	0.002
	4–6	347 (39.0)	5,173,028 (44.5)	
	≥7	163 (18.3)	2,084,700 (17.9)	
Hospital teaching status and location	Rural	67 (7.5)	1,298,782 (11.2)	<0.001
	Urban non-teaching	287 (32.2)	4,594,996 (39.5)	
	Urban teaching	537 (60.2)	5,727,859 (49.3)	
Hospital bed-size	Small	64 (7.2)	1,301,610 (11.2)	<0.001
	Medium	165 (18.5)	2,961,983 (25.5)	
	Large	662 (74.3)	7,358,045 (63.3)	
Hospital region	Northeast	123 (13.8)	2,282,696 (19.6)	<0.001
	Midwest	174 (19.5)	2,656,898 (22.9)	
	South	352 (39.5)	4,663,547 (40.1)	
	West	242 (27.2)	2,018,496 (17.4)	
AMI type	STEMI	308 (34.6)	4,319,789 (37.2)	0.11
	NSTEMI	583 (65.4)	7,301,848 (62.8)	
Cardiac arrest		74 (8.3)	584,189 (5.0)	<0.001
Cardiogenic shock		40 (4.5)	557,934 (4.8)	0.75
Multiorgan failure		155 (17.4)	1,094,593 (9.4)	<0.001
Coronary angiography		494 (55.4)	7,389,558 (63.6)	<0.001
Percutaneous coronary intervention		346 (38.8)	4,824,511 (41.5)	0.10
Coronary artery bypass grafting		10 (1.2)	1,071,145 (9.2)	<0.001
Mechanical circulatory support	Total	54 (6.1)	554,904 (4.8)	0.08
	IABP	49 (5.5)		0.17

(continued on next page)

Table 1 (*continued*)

Characteristics	Prior heart transplant $N = 892$	No heart transplant $N =$ 11,621,637	*P*
		528,949 (4.6)	
pLVAD	5 (0.6)	26,124 (0.2)	0.05
ECMO	0 (0.0)	5901 (0.1)	1.0
Pulmonary artery catheterization	24 (2.7)	126,619 (1.1)	<0.001
Invasive mechanical ventilation	74 (8.3)	697,350 (6.0)	0.005
Acute hemodialysis	14 (1.5)	66,672 (0.6)	0.001

Represented as percentage or mean ± standard deviation.
Abbreviations: AMI: acute myocardial infarction; ECMO: extracorporeal membranous oxygenation; IABP: intra-aortic balloon pump; NSTEMI: non-ST-segment-elevation myocardial infarction; pLVAD: percutaneous left ventricular assist devices; STEMI: ST-segment-elevation myocardial infarction.
[a] Hispanic, Asian or Pacific Islander, Native American, Others.
[b] Private, Self-Pay, No Charge, Others.

stabilization. While these findings of lower utilization of invasive management are consistent with previous studies [12], more recently an aggressive approach including revascularization has been shown to improve in-hospital outcomes of HT recipients [11]. Additionally given the evidence that long-term survival of HT recipients is improved with PCI when CAV is at less advanced stages [20], greater attention to management strategies of these patients is required to improve associated outcomes.

Higher cardiac mortality in HT recipients, as depicted by our study (11.8 % vs 6.2 %) is often attributed to CAV [2,5,9]. Intravascular ultrasound has demonstrated continuing increase in intimal hyperplasia, especially within the first year after heart transplantation, as the underlying pathophysiological culprit for CAV progression and severity [15]. Distinctively, these patients develop coronary lesions in distal vessels leading to obliterative disease devoid of collateral vessel development, even in wholly occluded vessels [8]. This is expected to contribute to higher mortality risk after AMI, especially in those presenting with STEMI. In agreement, HT recipients presenting with STEMI had higher in-hospital mortality compared to NSTEMI admissions.

4.1. Limitations

The present report has several limitations despite using internal and external quality control measures by the HCUP-NIS. Echocardiographic data, angiographic variables, and hemodynamic parameters were unavailable in this database, limiting physiological disease severity assessments. Due to the limitations of an administrative database, this study is unable to assess rejection, immunosuppressive interventions, use of implantable cardiac devices and re-transplantation, which are associated with significant differences in outcomes in this population. Despite these limitations, this study addresses a significant knowledge gap highlighting the management and outcomes associated with AMI in HT recipients.

5. Conclusions

Among hospitalizations with AMI, those with prior HT were associated with a hospital course complicated by higher rates of cardiac arrest and multiorgan failure. These together with the lower use of guideline-directed therapies may have contributed to the greater in-hospital mortality in AMI admissions with prior HT. The present analysis highlights the need for further dedicated research to understand the impact of timely interventions in relation to severity of coronary disease in this vulnerable population.

CRediT authorship contribution statement

Study design, literature review, statistical analysis: SS, SHP, PRS, GG.
Data management, data analysis, drafting manuscript: SS, SHP, SV.
Access to data: SS, SHP, PRS, GG, WC, SV.
Manuscript revision, intellectual revisions, mentorship: WC, SV.
Final approval: SS, SHP, PRS, GG, WC, SV.

Role of funding source

None.

Disclosures

All authors have no relevant disclosures to report.

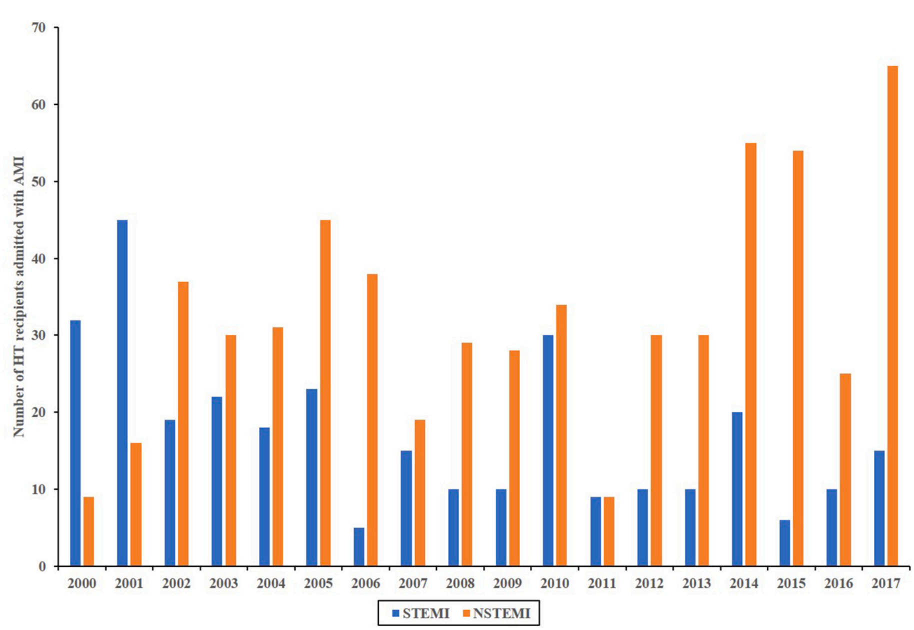

Fig. 1. Temporal trends of HT recipients hospitalized with AMI
Legend: Number of HT recipients hospitalized with AMI stratified by type of AMI presentation.
Abbreviations: AMI: acute myocardial infarction; HT: heart transplant; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100167.

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