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## The impact of peripheral arterial disease on patients with mechanical circulatory support.

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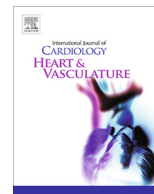
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## The impact of peripheral arterial disease on patients with mechanical circulatory support

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### ABSTRACT

**Background:** Left ventricular assist devices (LVAD) are indicated as bridging or destination therapy for patients with advanced (Stage D) heart failure and reduced ejection fraction (HFrEF). Due to the clustering of the mutual risk factors, HFrEF patients have a high prevalence of peripheral arterial disease (PAD). This, along with the fact that continuous flow LVAD influence shear stress on the vasculature, can further deteriorate the PAD.

**Methods:** We queried the National Inpatient Sample (NIS) database (2002–2014) to identify the burden of pre-existing PAD cases, its association with LVAD, in-hospital mortality, and other complications of LVAD. The adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated using the Cochran–Mantel–Haenszel test.

**Results:** A total of 20,817 LVAD patients, comprising of 1,625 (7.8%) PAD and 19,192 (91.2%) non-PAD patients were included in the study. The odds of in-hospital mortality in PAD patients were significantly higher compared to non-PAD group (OR 1.29, CI, 1.07–1.55,  $P = 0.007$ ). The PAD group had significantly higher adjusted odds as compared to non-PAD group for acute myocardial infarction (aOR 1.29; 95% CI, 1.07–1.55,  $P = 0.007$ ), major bleeding requiring transfusion (aOR, 1.286; 95% CI, 1.136–1.456,  $P < 0.001$ ), vascular complications (aOR, 2.360; 95% CI, 1.781–3.126,  $P < 0.001$ ), surgical wound infections (aOR, 1.50; 95% CI, 1.17–1.94,  $P = 0.002$ ), thromboembolic complications (aOR, 1.69; 95% CI, 1.36–2.10,  $P < 0.001$ ), implant-related complications (aOR, 1.47; 95% CI, 1.19–1.80,  $P < 0.001$ ), and acute renal failure (aOR, 1.26; 95% CI, 1.12–1.43,  $P < 0.001$ ).

**Conclusion:** PAD patients can have high LVAD associated mortality as compared to non-PAD.

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**Abbreviations:** BiVAD, biventricular assist device; CAD, coronary artery disease; CABG, coronary artery bypass surgery; CKD, chronic kidney disease; LOS, length of stay; LVAD, left ventricular assist device; OMT, optimal medical therapy; MCS, mechanical circulatory support; NIS, National Inpatient Sample; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

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### 1 Introduction

Left ventricular assist devices (LVAD) are a continuous flow ventricular support device used in addition to the optimal medical therapy (OMT) in the management of advanced heart failure (stage-D; advanced heart failure requiring intervention) [1]. It has two major indications in HFrEF patients, a bridge to transplant (BTT) or destination therapy (DT). LVAD has proven benefits in patients with circulatory failure but has also been implicated in a variety of device-related and heart failure-related complications. HFrEF patients receiving LVAD devices have underlying atherosclerotic shares most of its risk factors and co-morbidities, including

old age, smoking, hypertension, diabetes mellitus, atrial fibrillation, coronary artery disease (CAD), and chronic kidney disease. It is not uncommon for PAD to coexist with HFrEF owing to a high prevalence of similar atherosclerotic risk factors (smoking, hyperlipidemia, diabetes, and hypertension) [2,3]. HFrEF patients on second generation LVAD can have a further decline in the function of peripheral vasculature due to a reduction in the pulsatile flow and continuous flow-induced endothelial dysfunction. The presence of pre-existing PAD in LVAD patients can worsen peripheral vascular complications and is a relative contraindication for LVAD therapy [2,4]. The 2013 International Society for Heart and Lung Transplantation Guidelines for Mechanical Circulatory Support guidelines, therefore, recommend that patients with atherosclerotic vascular disease or significant risk factors for developing PAD should be screened prior to the use of mechanical circulatory support (Class IIa; Level of evidence C). Despite these recommendations, the subsequent outcomes of LVAD placement in a pre-existing PAD have not yet been explored. Looking at the paucity of data on LVAD and PAD, we sought to determine LVAD-related complications and mortality in PAD patients.

## 2 Methods

The national inpatient sample (NIS) database is a publicly available database of ~8 million yearly discharges from non-federal hospitals [5]. Due to the unidentified nature of data, our study was exempt from institutional review board (IRB). We queried NIS (2002–2014) using the International Classification of Disease, Ninth Edition, Clinical Modification (ICD-9-CM) codes for PAD (440.0–440.4, 440.8, 440.9, 443.1, 443.8, 443.81, 443.82, 443.89, 443.9, 447.1, V43.4) and procedure LVAD due to HFrEF stage D with ICD-9CM code for LVAD Heart Assist System (37.66). (supplementary table-1) The exclusion criteria included ICD-9-CM codes for orthotopic heart transplantation (ICD codes 37.5, 37.51, and 33.6), biventricular assist device (BiVAD) implantation (ICD code 37.52) and percutaneous or non-percutaneous short-term mechanical circulatory support (MCS) placement using codes (37.68, 37.60, 37.62, 37.65).

The PAD and non-PAD groups were matched based on the prior history of percutaneous coronary intervention (PCI), alcohol use disorder, collagen vascular disease, liver disease, hypothyroidism, lymphoma, tumors, and valvular disease. The primary outcome of the study was in-hospital mortality. Secondary outcomes included device-related infection including implant site wound infection, wound dehiscence, device-related mechanical complication, conduction defects like complete heart block, respiratory complications (pneumothorax, other iatrogenic respiratory complications, postoperative aspiration pneumonia), renal complications (acute renal failure, acute renal failure requiring dialysis), thromboembolic complications causing stroke, deep intra-organ hemorrhage in CNS, pulmonary, gastrointestinal, genitourinary and major bleed requiring transfusion. (Supplementary table-2).

Continuous variables were reported as weighted mean values and standard deviation (SD). Categorical variables were compared using the Chi-square test, whereas continuous variables were compared using independent t-tests. Univariate and multiple logistic regression analyses were performed to analyze the association between the LVAD and the primary and secondary outcomes in PAD patients. The regression model was adjusted for patient demographics (age, race, and gender), urgency of procedure (elective versus emergent), Elixhauser co-morbidities, other relevant co-morbidities which includes; CAD, carotid artery disease, prior coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI), previous TIA/stroke and smoking, patients'

insurance, socioeconomic status (SES), and hospital characteristics. (Supplementary table-3) Linear regression models were used to assess the length of stay (LOS). The logarithmic transformation of LOS was performed to adjust for positively skewed data. Adjusted odds ratio (aOR) were calculated, and p-values of less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS v21 (IBM Corp, Armonk, NY, USA).

## 3 Results

### 3.1 Search results and demographics

A total of 20,817 patients (nationally weighted patient sample) with stage D HFrEF who underwent LVAD placement comprising of 1,625 (7.8%) PAD and 19,192 (92.2%) non-PAD patients. In a weighted sample data, the patient demographic difference of PAD vs. non-PAD group showed a mean age of 59.83 vs. 55.11 ( $P < 0.001$ ), respectively. Patients in PAD group were predominantly men (80.6% vs 75.6%,  $P < 0.001$ ), and Caucasians (72% vs 65.5%,  $P < 0.001$ ). Of all 1,625 patients with PAD who underwent LVAD, only 2.4% underwent a heart transplant. The group differences in PAD vs. non-PAD in terms of patient characteristics and comorbidities are shown in [Table 1](#).

### 3.2 Pooled analysis

The adjusted odds of in-hospital mortality were significantly higher for PAD group (24.1% vs 17.3%, aOR 1.641; 95% CI, 1.41–1.90,  $P < 0.001$ ) compared to non-PAD. There was no significant difference in the LOS between the two groups S (median LOS days 29, range 0–53 days Vs. median 28 days, range 3–53 days,  $P = 0.19$ ) on the risk-adjusted linear regression model. (supplemental table 4) Multiple logistic regression model used to analyze group complication differences in PAD vs non-PAD. The PAD group had significantly higher odds as compared to non-PAD group for acute myocardial infarction (16.7% vs 12.8% a OR, 1.291; 95% CI, 1.071–1.555,  $P = 0.007$ ), major bleeding requiring transfusion (32.9% vs 28.1% a OR, 1.286; 95% CI, 1.136–1.456,  $P < 0.001$ ), vascular complications (5.4% vs 2.6% a OR, 2.360; 95% CI, 1.781–3.126,  $P < 0.001$ ), surgical wound infections (5.1% vs 4.4% a OR, 1.505; 95% CI, 1.169–1.937,  $P = 0.002$ ), thromboembolic complications (11.1% vs 7.2% aOR, 1.695; 95% CI, 1.366–2.104,  $P < 0.001$ ), implant-related complications (8.4% vs 6.7% a OR, 1.468; 95% CI, 1.194–1.804,  $P < 0.001$ ), and acute renal failure (55.9% vs 50.5% a OR, 1.265; 95% CI, 1.117–1.433,  $P < 0.001$ ). The rate of wound dehiscence and mechanical complications were higher in the PAD group as compared to non-PAD group, but the difference was not statistically significant (1.2% vs 0.9%,  $P = 0.97$ ) and (3% vs 2.8%,  $P = 0.23$ ), respectively ([Fig. 1](#)). The temporal trends in LVAD utilization in PAD have been noticed to be increasing over the study period ([Fig. 2](#)).

An adjusted odds ratio (aOR) was calculated to control for the impact of differences in the comorbidities and demographics on the overall mortality. The aOR of mortality appears to be significantly higher in patients with PAD undergoing device implantation when adjusted for congestive heart failure (aOR 1.5, 95% CI 1.0–2.3,  $p < 0.0001$ ), coagulopathy (aOR 1.5, 95% CI 1.3–1.6,  $p < 0.0001$ ), hypertension (aOR 1.03, 95% CI 1.03–1.25,  $p = 0.008$ ), liver disease (aOR 1.6, 95% CI 1.3–1.9,  $p < 0.0001$ ), paralysis (aOR 2.2, 95% CI 1.7–2.9,  $p < 0.0001$ ) and rheumatoid arthritis (aOR 1.3, 95% CI 1.9–2.7,  $p < 0.0001$ ). The detailed determinants of mortality and regression coefficients are given in the Supplementary table 5.

**Table 1**

Left ventricular assist device patients' characteristics stratified by peripheral arterial disease and non-peripheral arterial disease status.

Variable	PAD	No PAD	P-Value
<b>Age</b>	59.8 ± 12.4	55.1 ± 14.6	<0.001
<b>Female</b>	19.4%	24.4%	<0.001
<b>Carotid artery disease</b>	2.3%	0.5%	<0.001
<b>Coronary artery disease</b>	33.3%	46.2%	<0.001
<b>Prior Percutaneous coronary intervention.</b>	3.6%	4.0%	0.547
<b>Prior Coronary artery bypass surgery</b>	7.3%	3.8%	<0.001
<b>Smoking</b>	4.1%	2.9%	0.010
<b>HIV</b>	0.3%	0.1%	0.041
<b>Alcohol Abuse</b>	2.9%	2.2%	0.062
<b>Deficiency Anemia</b>	21.2%	18.7%	0.014
<b>Rheumatoid arthritis/Collagen vascular disease</b>	1.2%	1.0%	0.369
<b>Chronic Blood Loss Anemia</b>	1.5%	1.8%	0.378
<b>Chronic Lung Disease</b>	26.0%	16.5%	<0.001
<b>Coagulopathy</b>	46.1%	33.2%	<0.001
<b>Depression</b>	11.0%	9.0%	0.007
<b>Diabetes mellitus, Uncomplicated</b>	27.0%	22.2%	<0.001
<b>Diabetes mellitus, Complicated</b>	8.7%	6.3%	<0.001
<b>Drug Abuse</b>	0.6%	2.0%	<0.001
<b>Hypertension</b>	48.0%	39.1%	<0.001
<b>Hypothyroidism</b>	11.0%	9.6%	0.073
<b>Liver Disease</b>	2.4%	3.2%	0.080
<b>Metastatic Cancer</b>	0.3%	0.2%	0.185
<b>Fluid and Electrolyte disorders</b>	61.5%	57.7%	0.003
<b>Obesity</b>	9.0%	13.5%	<0.001
<b>Renal Failure</b>	41.8%	32.4%	<0.001
<b>Solid Tumor Without Metastasis</b>	1.2%	0.8%	0.087
<b>Pulmonary Circulation Disorders</b>	0.6%	0.3%	0.122
<b>Psychosis</b>	2.4%	2.6%	0.679
<b>Peptic Ulcer Disease</b>	0.0%	0.0%	1.000
<b>Valvular Disease</b>	0.3%	0.4%	0.833
<b>Race</b>			<0.001
White	72.0%	65.5%	
Black	16.1%	22.2%	
Hispanic	6.5%	6.2%	
Asian or Pacific Islander	1.1%	1.9%	
Native American	0.0%	0.3%	
Other	4.3%	4.3%	
<b>Elective hospitalization</b>	34.5%	32.7%	0.152
<b>Primary expected payer</b>			<0.001
Medicare	54.4%	43.5%	
Medicaid	9.0%	11.8%	
Private Insurance	32.4%	39.9%	
Self-Pay	0.6%	1.6%	
No Charge	0.3%	0.1%	
Other	3.3%	3.1%	
<b>Median Household Income</b>			0.181
0 to 25 percentiles	25.4%	25.8%	
26 to 50 percentiles	25.9%	24.7%	
51 to 75 percentiles	26.8%	25.4%	
76 to 100 percentiles	22.0%	24.1%	
<b>Bed Size</b>			0.039
Small	1.1%	1.6%	
Medium	8.1%	9.6%	
Large	90.8%	88.8%	
<b>Location/Teaching Status</b>			0.064
Rural	0.3%	0.4%	
Urban Non-teaching	5.3%	4.1%	
Urban Teaching	94.4%	95.5%	
<b>Hospital Region</b>			<0.001
Northeast	14.7%	19.9%	
Midwest	31.4%	29.1%	
South	38.6%	34.0%	
West	15.3%	17.0%	

**Abbreviations:** PAD: Peripheral arterial disease.

## 4 Discussion

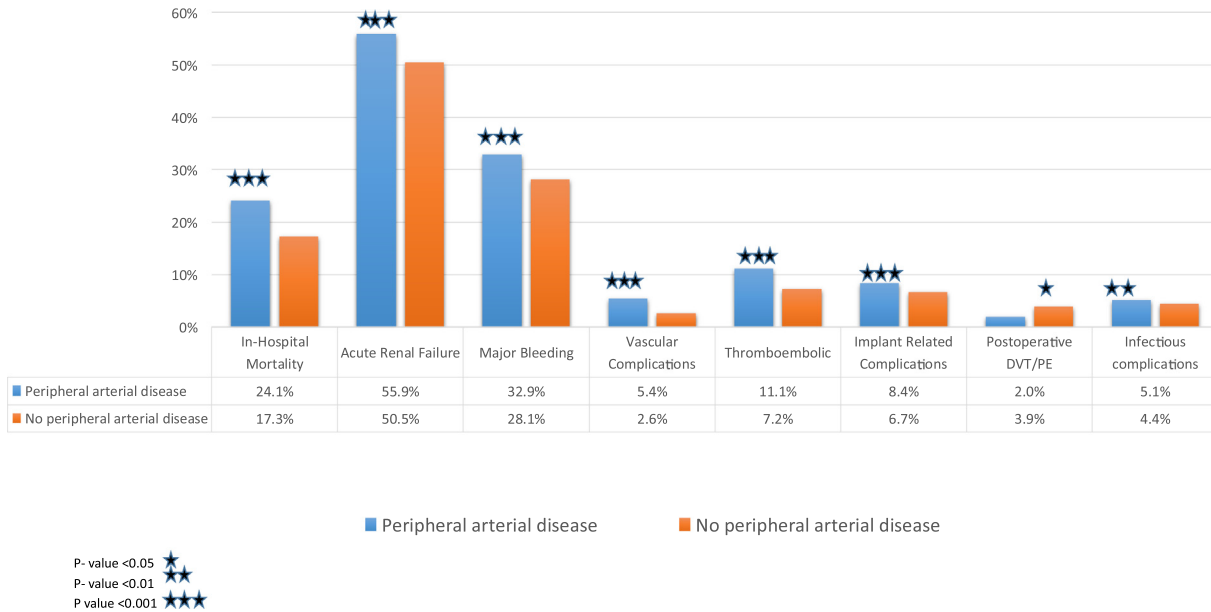
This is the first known largest comparison of outcomes of LVAD in patients with and without PAD by using the NIS database (2002–2014). In this large contemporary analysis, we observed: (1) PAD

patients who underwent LVAD have higher co-morbidities compared with patients without PAD. (2) Patients with PAD who received LVAD were at increased risk for in-hospital mortality and complications compared to those without PAD. (3) In the matched analysis, PAD patients have a higher likelihood of developing cardiac, vascular, renal, and surgical complications as compared to non-PAD. (4) The national utilization of LVAD has been significantly increased in recent years.

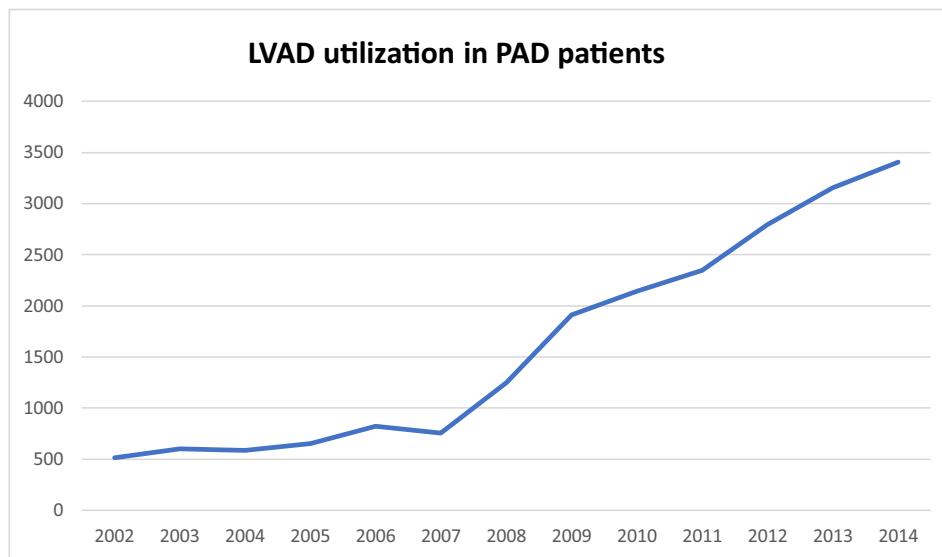
LVAD improves the quality of life (QoL), functional capacity, and mortality in HFrEF patients. 1 Over the last decade, the survival of HF has significantly improved secondary to LVAD implantation with a rapidly evolving technology, enhanced procedural and patient selection guidelines, multidisciplinary approach, and improved perioperative care [2,4]. However, further identification of manageable co-morbidities that impact outcomes following LVAD implantation is needed. The presence of PAD is known to be associated with adverse cardiovascular outcomes of LVAD patients [6–8]. PAD represents a complex co-morbidity in patients with refractory heart failure who undergo LVAD implantation. These patients are known to have higher rates of in-hospital mortality such as; myocardial infarction, major bleeding, vascular complications, thromboembolic complications, and acute kidney injury compared to those without PAD [6,9]. PAD, therefore, is considered a relative contraindication for heart transplantation, especially when it limits the rehabilitation process, and revascularization is not an option [10]. This explains why only 2.9% of the total 22,318 heart transplant recipients and 11.05% of the total LVAD patients had a diagnosis of PAD, in the international heart and lung transplant registry (2006 and 2012) and Medicare database study (total of 2,152 recipients between 2004 and 2011) [11,12]. Our study further revealed the declining trend of these population, only 7.8% out of 20,817 LVAD patients had a diagnosis of PAD. (Fig. 3) These results indicate that despite a high prevalence of PAD in HFrEF patients, there is a hesitancy for these patients to have LVAD implantation.

Patients with PAD undergoing LVAD implantation are at a higher risk of in-hospital and out-hospital mortality. The eighth annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) reported 22,866 patients with LVAD implantation between June 23, 2006, and December 31, 2016. Follow up data of this population show that the presence of PAD increased both early and late mortality [13]. Similarly, orthotopic heart transplant recipients with symptomatic PAD also have lower survival rates compared with those without PAD [14]. Our findings are consistent with these studies, and significantly higher mortality in the PAD group raises concerns about the safety of LVAD in these patients. It also highlights the importance of timely identification and management of PAD, especially if patients have HFrEF and would be requiring an LVAD.

Our study also shows a significant burden of associated co-morbidities in patients having PAD and LVAD. These patients are at an increased risk for major bleeding events. Previous studies also have reported higher HAS-BLED scores in the PAD group as compared to non-PAD [15]. Both PAD and CAD have similar risk factors. Therefore, it is common to have concomitant PAD in advanced heart failure patients with LVAD device [16,17]. Patients with LVAD need to anticoagulated to prevent the risk of device thrombosis. These patients, if started an antiplatelet for associated CAD, can potentially worsen the risk of bleeding in these patients [18]. In addition to anticoagulation, critical limb ischemia is an independent factor associated with major bleeding in patients with PAD [19]. Ironically, PAD in LVAD patients also increases the risk of thrombosis. Further factors than increase the prevalence of vascular complications include multiple secondary co-morbidities and atherosclerotic risk factors. These observations explain the significantly higher odds of major bleeding, thrombosis, and vascular



**Fig. 1.** Outcomes of left ventricular assist device surgery in patients with and without peripheral arterial disease.



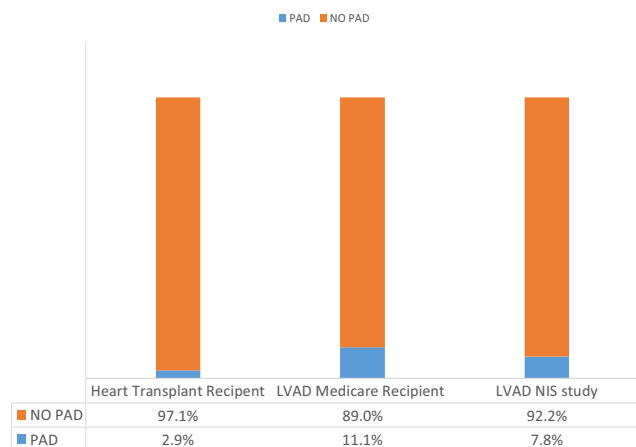
**Fig. 2.** Utilization of LVAD over the study period.

complications in the PAD-LVAD group seen in our study. Our study also indicates a substantial increase in the odds of MI in PAD patients with LVAD. As expected, PAD is a coronary artery equivalent, which underscores the importance of aggressive treatment of PAD patients [20]. Interestingly, the prevalence of stable CAD was reduced in PAD patients due to a high number of coronary artery bypass graft (CABG) procedures during the LVAD implantation.

Our study closes the gaps between the clinical practice and the said recommendations. We have identified the burden and complications of PAD in LVAD patients. We suggest that due to increased morbidity and mortality associated with PAD, the screening process of these patients prior to LVAD implantation should be re-emphasized. Screening for PAD using Doppler ultrasound following LVAD implantation is difficult due to changes in the waveforms

driven by the continuous arterial flow pattern generated by the LVAD [21]. Recently computational flow analysis has been used to study PAD in patients with continuous-flow LVAD, which has shown promising results as compared to Doppler ultrasound [21]. It is unclear if endovascular or surgical revascularization will improve outcomes in this population.

Our study has several limitations. This is a retrospective analysis of cross-sectional data of NIS, so it is difficult to draw a causal relationship between PAD and LVAD complications. Unmeasured confounders would have occurred in assessing the severity and etiology of HF. A subgroup analysis on follow up duration could not be done as the data represents a snapshot of the in-hospital course. Due to the retrospective cross-sectional nature of the study and limited applicability of the ICD coding the INTERMACS classification for advanced heart failure could not be performed.



**Fig. 3.** Peripheral arterial disease prevalence in heart transplant and left ventricular assist device recipients based on registries and national inpatient sample study.

## 5 Conclusion

Patients with PAD and LVAD had higher odds of in-hospital mortality and morbidity compared to those without PAD.

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None.

## Disclosures

All the authors have substantially contributed in the design of the work. Yasser Al-khadra performed the analysis. YS, WU, TM and MCA drafted the work, and did critical revision. All the authors agreed for final approval and in agreement to be accountable for all aspects of the work in question related to the accuracy of the content.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2020.100509>.

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