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Cost and inpatient burden of peripheral artery disease: Findings from the National Inpatient Sample

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HIGHLIGHTS

- It is estimated that as many as 8.5 million Americans suffer from peripheral artery disease (PAD).
- The rate of hospitalizations for PAD was 89.5/100,000, with 45% of these having Fontaine class III-IV disease.
- The proportion of hospitalizations resulting in MALE was 45.8%.
- Median hospital length-of-stay (LOS) was 5 (3, 9) days and costs were $15,755 ($8,972, $27,800).

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ABSTRACT

Background and aims: We aimed to examine the prevalence, demographics, clinical outcomes and economic burden of hospitalizations for patients with PAD.
Methods: Using the National Inpatient Sample, we retrospectively evaluated patients hospitalized with PAD in 2014. Hospitalizations in patients with PAD were identified by the presence of an International Classification of Diseases-9th Revision (ICD-9) diagnosis code of 440.20–440.24. We calculated hospitalization rates/100,000 patients, the proportion of hospitalizations with a major adverse limb event (MALE), as well as minor amputation, mortality, median (interquartile range) length-of-stay (LOS) and treatment costs (in 2017 US$). A separate analysis of hospitalizations of patients with clinical limb ischemia defined as Fontaine class III or IV PAD (440.22, resting pain; 440.23–440.24, ulcers or gangrene) was also performed.
Results: We identified 286,160 hospitalizations for patients with PAD. The rate of hospitalizations for PAD was 89.5/100,000, with 137,050 (or 45%) of these having Fontaine class III-IV disease. The proportion of hospitalizations resulting in MALE, major or minor lower extremity amputation or in-hospital death was 45.8%, 8.9%, 8.2% and 3.1%, respectively. Median hospital LOS was 5 (3, 9) days and costs were $15,755 ($8972, $27,800), resulting in an annual cost burden for hospitalization of patients with PAD of ~$6.31 billion. In hospitalizations of Fontaine class III-IV PAD, MALE, major and minor amputation and death occurred in 60.9%, 16.8%, 15.8% and 3.3% of cases, respectively. Median LOS and costs were 7 (4, 11) days and $18,984 ($10,913, $31,816).
Conclusions: Hospitalizations of patients with PAD represent a substantial medical and financial burden for patients and the US healthcare system.

1. Introduction

It is estimated that as many as 8.5 million Americans suffer from peripheral artery disease (PAD) [1,2]. Patients diagnosed with PAD may be asymptomatic or have non-specific, subtle symptoms, such as paresthesia, cold extremities, reduced peripheral pulse or murmurs in the peripheral arteries (Fontaine stage I) [3,4]. PAD patients may also present with symptoms ranging from mild claudication (pain, aching or fatigue in muscles of the lower extremities that occur with exertion and relieved with rest) (Fontaine stage II), pain at rest, mostly in the feet

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(Fontaine stage III) up to necrosis and/or gangrene of the toes or lower extremities (Fontaine stage IV). The presence of critical limb ischemia (CLI) (often associated with Fontaine stages III or IV disease) typically necessitates intervention including percutaneous or surgical revascularization or amputation, and continues to be a major cause of vascular-related morbidity and mortality [5].

The aim of the current study was to provide data on hospitalization rates, associated in-hospital mortality and treatment costs, as well as the need for revascularization or amputation among patients with PAD.

2. Patients and methods

We utilized the 2014 Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) for this study [6]. The NIS is among the largest publicly available inpatient databases in the US and approximates a 20% sample of discharges from hospitals across the country. It contains data on hospital inpatient stays and covers all patients, including those with Medicare, Medicaid, private insurance and the uninsured. The 2014 inpatient core file contains data on 7,071,762 hospitalizations occurring between January 1, 2014 and December 31, 2014, drawn from 4411 hospitals across 44 states.

Hospitalizations of adult patients (a patient may have had ≥1 hospitalization) with PAD were identified in the NIS database using the International Classification of Diseases-9th Revision (ICD-9) diagnosis codes of 440.20 through 440.24. To assure the identification of all patients with PAD, we included admissions with a relevant ICD-9 code in the primary or non-primary coding positions [7]. The 2014 NIS contains a maximum of 30 ICD-9 diagnosis codes and 15 procedural codes for each encounter. Hospitalizations in patients with PAD were further categorized according to disease severity using the Fontaine staging system [3,4]. ICD-9 codes of 440.20 and 440.21 were used to classify those with Fontaine stage I (asymptomatic) and II (intermittent claudication) PAD, respectively. Hospitalizations in patients with stage III (pain at rest) PAD were identified by the presence of an ICD-9 code of 440.22 and stage IV (necrosis and/or gangrene of the limb) by ICD-9 codes 440.23 or 440.24 [4].

Descriptive statistics were reported for all demographics, comorbidities (including the AHRQ Elixhauser comorbidity index) [8] and study endpoints. For categorical variables, reporting included the proportion per study cohort. For continuous variables, results were presented as medians with 25%, 75% (or interquartile (IQR)) ranges. Study endpoints included hospitalization rates for PAD per 100,000 patients, the proportion of hospitalizations in patients with PAD resulting in a major adverse limb event (MALE), minor amputation or in-hospital mortality; as well as, hospital length-of-stay (LOS) and treatment costs, excluding professional fees (in 2017 US$) and discharge disposition. MALE was defined as undergoing surgical or percutaneous revascularization or having a major amputation of a lower extremity. Costs were inflated to 2017 values using the Consumer Price Index for Medical Care [9].

Analysis of the abovementioned endpoints were further stratified based upon Fontaine staging, with separate analyses restricted to patients with Fontaine stage I or II disease and those with critical limb ischemia (CLI) defined as Fontaine stage III or IV being performed. Further a sensitivity analysis was performed wherein only patients admitted with a primary ICD-9 diagnosis code for PAD were included.

All data management and statistical analyses were performed IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, New York, US). As this analysis was only performed on data which was de-identified and in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996 to preserve participant anonymity and confidentiality, it was deemed exempt from institutional review board oversight.

The preparation of this report was in accordance with the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) statement [10].

3. Results

Of the 7,071,762 hospitalizations in the 2014 NIS, 286,160 were in patients with a discharge diagnosis code for PAD, 149,119 (or 52%) had Fontaine stage I or II disease and 137,050 (or 48%) had Fontaine stage III or IV disease. The median age of these patients was 70 (61, 79) years and 40% of hospitalizations were in women (Table 1). The median number of Elixhauser comorbidities per person was 9 (6, 11) in the overall PAD population. Comorbid coronary disease was present in 53% of patients admitted for PAD, 50% also were diagnosed with diabetes and ~20% had a history of prior stroke or carotid artery stenosis.

The 2014 rate of hospitalizations for patients with PAD was 89.5 per 100,000 patients, with rate of 42.8 per 100,000 for patients with Fontaine stage III or stage IV disease (Table 2). The proportion of hospitalizations resulting in MALE was 45.8%. Major or minor lower extremity amputation occurred in 8.9% and 8.2% of hospitalizations respectively, and in-hospital death in 3.1%. Median hospital LOS was 5 (3, 9) days and costs were $15,755 ($8972, $27,800), resulting in a total annual cost burden for hospitalization in patients with PAD of ~$6.31 billion. One-half (50.6%) of all hospitalizations resulted in discharge to an intermediate or skilled nursing facility or required additional home healthcare.

Among hospitalizations of Fontaine stage I or II PAD patients, MALE, major and minor amputation and death occurred in 45.8%, 1.7%, 1.2% and 2.8%, respectively. In these patients with less severe disease, the median LOS was 4 (2, 7) days and median total hospital costs were $13,311 ($7692, $23,560). In hospitalizations of Fontaine stage III or IV PAD, MALE, major and minor amputation and death occurred in 60.9%, 16.8%, 15.8% and 3.3%, respectively. In these patients with more severe disease, the median LOS was 7 (4, 11) days and median total hospital costs were $18,984 ($10,913, $31,816), corresponding to an annual cost burden of ~$3.5 billion. Nearly two-thirds

Table 1
Baseline demographics and comorbidities of hospitalizations of people with peripheral artery disease in 2014.

	All PAD[a] N = 286,160 n (%)	Fontaine Stage I or II N = 149,110 n (%)	Fontaine Stage III or IV N = 137,050 n (%)
Age, years, median (IQR)	70 (61, 79)	70 (62, 78)	69 (61, 79)
Female	115,322 (40.3)	60,700 (40.7)	54,480 (39.8)
Race			
White	193,948 (67.8)	106,510 (74.8)	87,438 (63.8)
Black	47,154 (16.5)	18,785 (13.2)	28,369 (20.7)
Hispanic	24,656 (8.6)	10,540 (7.4)	14,116 (10.3)
Asian	4218 (1.5)	2025 (1.4)	2193 (1.6)
Native American	1502 (0.5)	620 (0.4)	882 (0.6)
Other	7829 (2.7)	3855 (2.7)	3974 (2.9)
Income quartile			
1 ($1–39,999)	93,128 (32.8)	46,120 (31.5)	47,008 (34.3)
2 ($40,000–50,999)	81,000 (28.3)	42,900 (29.3)	38,100 (27.8)
3 ($51,000–65,999)	62,319 (21.7)	33,080 (22.6)	29,239 (21.4)
4 ($66,000+)	46,928 (16.4)	24,315 (16.6)	22,613 (16.5)
Chronic conditions, median (IQR)	9 (6, 11)	8 (6, 11)	9 (7, 11)
Coronary artery disease	152,940 (53.4)	86,540 (58.0)	66,400 (48.4)
Myocardial infarction	51,795 (18.1)	30,689 (20.6)	21,106 (15.4)
PCI	37,487 (13.1)	23,371 (15.7	14,116 (10.3)
CABG	47,216 (16.5)	28,440 (19.1)	18,776 (13.7)
Diabetes	142,180 (49.7)	66,795 (44.8)	75,385 (55.0)
Heart failure	44,390 (15.5)	20,505 (13.8)	23,885 (17.4)
Hypertension	226,530 (79.2)	116,975 (78.4)	109,555 (79.9)
Hyperlipidemia	159,385 (55.7)	90,675 (60.8)	68,710 (50.1)
Chronic kidney disease	101,565 (35.5)	46,885 (31.4)	54,680 (39.9)
Stroke	38,059 (13.3)	23,395 (15.7)	14,664 (10.7)
Carotid stenosis	19,459 (6.8)	13,977 (9.4)	5482 (4.0)
Obesity	36,250 (12.7)	19,430 (13.0)	16,820 (12.3)
Prior amputation	34,625 (12.1)	55,713 (37.4)	21,106 (15.4)

[a] ICD-9 codes in the primary or non-primary position.

Table 2
Outcomes of hospitalizations of people with peripheral artery disease in 2014.

	All PAD[a] N = 286,160 n (%)	Fontaine Stage I or II N = 149,110 n (%)	Fontaine Stage III or IV N = 137,050 n (%)
MALE or in-hospital death	136,795 (47.8)	50,995 (34.2)	85,800 (62.6)
MALE	130,955 (45.8)	47,515 (31.9)	83,440 (60.9)
Percutaneous revascularization	63,880 (22.2)	23,865 (16.0)	40,015 (29.2)
Surgical revascularization	60,850 (21.3)	28,090 (18.8)	32,760 (23.9)
Sequential revascularization	13,890 (4.9)	6295 (4.2)	7595 (5.5)
Major amputation	25,475 (8.9)	2470 (1.7)	23,005 (16.8)
Discharge disposition			
In-hospital death	8725 (3.1)	4155 (2.8)	4570 (3.3)
Discharge to intermediate or skilled nursing facility	85,585 (29.9)	30,600 (20.5)	54,965 (40.1)
Home healthcare	59,145 (20.7)	28,385 (19.0)	30,760 (22.5)
Hospital transfer	6705 (2.3)	3290 (2.2)	3415 (2.5)
Routine discharge or against medical advice	125,805 (43.9)	82,570 (55.4)	43,235 (31.6)
Minor amputation	23,365 (8, 2)	1740 (1, 2)	21,625 (15, 8)
Length-of-stay, days, median (IQR)	5 (3, 9)	4 (2, 7)	7 (4, 11)
Total hospital costs, 2017 US$, median (IQR)	15,755 (8972, 27,800)	13,311 (7692, 23,560)	18,984 (10,913, 31,816)
Total annual cost burden, 2017US$	6,306,307,158	2,813,176,993	3,493,130,165

[a] ICD-9 codes in the primary or non-primary position.

(62.5%) of hospitalizations for patients with of Fontaine stage III or IV PAD resulted in discharge to an intermediate or skilled nursing facility or required additional home healthcare.

Upon sensitivity analysis of PAD hospitalizations identified using ICD-9 codes in the primary position only, 96,245 admissions for PAD were included, of which 66.4% were classified as Fontaine stage III or IV (Table 3). The rate of hospitalizations for patients with PAD was 30.2 per 100,000 patients. The proportion of hospitalizations resulting in MALE, major or minor lower extremity amputation were 81.5%, 12.6%, 9.1% respectively; in-hospital death occurred in 1.7% of hospitalizations (Table 4). Median hospital LOS was 4 (2, 8) days and costs were $16,857 ($10,607, $27,437), resulting in a total annual cost burden for hospitalization of patients with PAD of ~$2.1 billion. Approximately 47% of all PAD hospitalizations resulted in discharge to an intermediate or skilled nursing facility or required additional home healthcare. Among hospitalizations limited to Fontaine stage III or IV PAD, MALE, major and minor amputation and death occurred in 78.9%, 18.1%, 13.5% and 2.3%, respectively. Median LOS and costs were 6 (3, 9) days and $18,487 ($11,193, $30,075). About 59% of hospitalizations for patients with of Fontaine stage III or IV PAD resulted in discharge to an intermediate or skilled nursing facility or required additional home healthcare.

Table 3
Sensitivity analysis: baseline demographics and comorbidities of hospitalizations of people with peripheral artery disease in 2014.

	All PAD[a] N = 96,245 n (%)	Fontaine Stage III or IV N = 63,910 n (%)
Age, years, median (IQR)	69 (61, 78)	70 (62, 80)
Female	38,690 (40.2)	26,523 (41.5)
Race		
White	66,987 (69.6)	42,245 (66.1)
Black	17,613 (18.3)	13,293 (20.8)
Hispanic	7315 (7.6)	5368 (8.4)
Asian	1155 (1.2)	767 (1.2)
Native American	481 (0.5)	383 (0.6)
Other	2791 (2.9)	1853 (2.9)
Income quartile		
1 ($1–39,999)	32,242 (33.5)	22,049 (34.5)
2 ($40,000–50,999)	27,526 (28.6)	18,023 (28.2)
3 ($51,000–65,999)	20,693 (21.5)	13,485 (21.1)
4 ($66,000 +)	15,784 (16.4)	10,353 (16.2)
Chronic conditions, median (IQR)	7 (5, 10)	8 (6, 11)
Coronary artery disease	46,198 (48.0)	30,549 (47.8)
Myocardial infarction	1396 (14.5)	8883 (13.9)
PCI	11,646 (12.1)	7094 (11.1)
CABG	13,571 (14.1)	8883 (13.9)
Diabetes	44,658 (46.4)	32,211 (50.4)
Heart failure	7507 (7.8)	6711 (10.5)
Hypertension	77,188 (80.2)	51,676 (81.0)
Lipid disorders	52,839 (54.9)	33,297 (52.1)
Chronic kidney disease	26,371 (27.4)	20,962 (32.8)
Stroke	9528 (9.9)	6711 (10.5)
Carotid stenosis	4812 (5.0)	2876 (4.5)
Obesity	9240 (9.6)	6071 (9.5)
Prior amputation	9432 (9.8)	8308 (13.0)

[a] ICD-9-codes in the primary position only.

4. Discussion

The current study used a large nationally-representative administrative claims database to evaluate hospitalizations of patients experiencing PAD in the US. Our study demonstrated that MALE or in-hospital death occurred in nearly half of all hospitalizations for PAD. When evaluating only those hospitalizations for the most severe disease (Fontaine stage III-IV), the incidence of MALE or death rose to over

Table 4
Sensitivity analysis: outcomes of hospitalizations of people with peripheral artery disease in 2014.

	All PAD[a] N = 96,245 n (%)	Fontaine Stage III or IV N = 63,910 n (%)
MALE or in-hospital death	78,825 (81.9)	50,808 (79.5)
MALE	78,440 (81.5)	50,425 (78.9)
Percutaneous revascularization	35,322 (36.7)	22,816 (35.7)
Surgical revascularization	43,118 (44.8)	23,838 (37.3)
Sequential revascularization	9528 (9.9)	5432 (8.5)
Major amputation	12,127 (12.6)	11,568 (18.1)
Discharge disposition		
In-hospital death	1636 (1.7)	1470 (2.3)
Discharge to intermediate or skilled nursing facility	27,622 (28.7)	24,222 (37.9)
Home healthcare	17,805 (18.5)	13,165 (20.6)
Hospital transfer	1540 (1.6)	1278 (2.0)
Routine discharge or against medical advice	23,582 (49.5)	23,838 (37.3)
Minor amputation	8758 (9.1)	8628 (13.5)
Length-of-stay, days, median (IQR)	4 (2, 8)	6 (3, 9)
Total hospital costs, 2017US$, median (IQR)	16,857 (10,607, 27,437)	18,487 (11,193, 30,075)
Total annual cost burden, 2017US $	2,105,325,047	1,519,181,202

[a]ICD-9-codes in the primary position only.

62%. These high incidence rates of MALE are concerning since following an index MALE, patients have a significantly increased risk of experiencing subsequent hospitalizations (hazard ratio [HR] = 7.2; $p < 0.0001$), amputations (HR = 197.5; $p < 0.0001$) and death (HR = 3.23; $p < 0.001$) [11]. Upon limiting our analysis to admissions coded for PAD in the primary position only (a more specific schema for identifying a PAD-related hospitalization), fewer PAD admissions were identified, but the incidence of MALE or death during these hospitalizations was substantially higher, approaching 82%. Finally, this study shows that hospitalizations due to PAD results in a substantial economic burden to the US healthcare system, with median costs per admission exceeding $15,000 and a total cost for PAD hospitalization surpassing $6 billion per year.

Our study's findings are consistent with prior burden-of-illness studies focusing on hospitalizations for PAD [7]. Malyar and colleagues used data from a German nationwide database covering the years 2005, 2007 and 2009 that included a total of 1.3 million PAD-related hospitalizations. They found that about one-third of hospitalizations were in patients with CLI, that hospitalizations for PAD were frequently associated with major amputation (up to 4.6% of hospitalizations) and in-hospital mortality (up to 5.8% of hospitalizations). Similar to our study, Malyar et al. also found the proportion of PAD patients undergoing a major amputation (absolute difference of 6.5% and 9.9%) and in-hospital mortality (absolute differences of 3.2% and 4.3%) was higher in patients with Fontaine stage III or IV disease, respectively, compared to PAD patients of all stages.

PAD is regularly associated with the presence of modifiable risk factors including smoking, type 2 diabetes, hyperlipidemia and hypertension. Its treatment includes addressing known risk factors, with goals to preserve limb viability, improve functional capacity and decrease major adverse cardiovascular events (MACE) [12]. In addition to exercise and lifestyle modification, the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend antiplatelet therapy (with aspirin, clopidogrel or both, depending on symptom severity), statins and cilostazol in patients with claudication [13]. Finally, these guidelines recommend patients with comorbid hypertension and/or diabetes be treated with appropriate medications to obtain goal blood pressure and glycemic control.

The high rate of hospitalization for PAD observed in our study raises the question of whether more should be done to promote early detection and treatment of PAD upon diagnosis. According to a recent review by US Preventive Services Task Force [14], there are a paucity of studies evaluating screening, primary prevention and early treatment of PAD. They found few studies addressing the benefits of treating screen-detected PAD, while two studies showed no benefit of using the ABI to manage daily aspirin therapy in unselected populations and two studies showing no benefit from exercise therapy. Consequently, the task force concluded that currently available evidence is insufficient to assess the balance of benefits and harms of screening for PAD risk with the ankle-brachial index (ABI) in asymptomatic adults. While the Society for Vascular Surgery [15] recommends against screening with the ABI in adults in the absence of risk factors, history and signs or symptoms of PAD, they do state it is reasonable to screen adults at higher risk. This recommendation has been echoed by AHA/ACC guidelines, which recommend screening using the ABI in patients at an increased risk of PAD. These risk factors include patients $\geq$65 years-of-age, $\geq$50 years-of-age with risk factors for atherosclerosis or a family history of PAD, and patients < 50 years-of-age with diabetes and $\geq$1 other risk factor for atherosclerosis [13].

There are some limitations of our analysis that merit discussion. First, the 2014 NIS dataset is a 20% sample of all US hospital discharges rather than patients [6]. As a result, it is possible a patient was counted more than once in our analysis (if they had > 1 hospitalization for PAD during the year). Second, as with all claims databases, the NIS may contain inaccuracies or omissions in coding of diagnoses (e.g., percentage of patients with hyperlipidemia or carotid stenosis appear lower might have been anticipated) or procedures, leading to the potential for misclassification bias [16]. To partially address this concern with respect to PAD, our initial analysis looked for PAD codes in any position (to maximize sensitivity). We also performed a sensitivity analysis restricting inclusion to hospitalizations with a code in the primary position only. The latter strategy should have the effect of increasing the specificity of a PAD diagnosis. We also used validated coding schema, whenever possible, to identify comorbidities in our study [8]. Next, the NIS database does not contain data on ABI values, lower extremity symptom severity or medication use [6]. As a result, we were dependent on ICD-9 coding to assess the presence and severity of PAD (which we translated to Fontaine staging) [7] and were unable to determine to what extent patients were receiving guideline-directed pharmacologic treatments (e.g. statins). Finally, as our study utilized data from US hospitalized patients, our results are most generalizable to a US population [16]. This being said, many of our study's conclusions were consistent with prior hospitalization database studies using similar methods [7].

4.1. Conclusion

This nationwide population-based analysis of hospitalizations of patients with PAD suggests a substantial burden of PAD on the US healthcare system exists. Hospitalizations for MALE is frequent in PAD patients, despite guideline recommendations for the use of antiplatelet agents, statins and blood pressure and glycemic control. Further interventions in the form of more aggressive screening and treatment modalities are needed to improve outcomes in patients with PAD.

Conflicts of interest

CIC reports grants from Bayer AG during the conduct of the study, grants from Janssen Scientific Affairs LLC, grants from Bayer Pharma AG, grants from Pfizer, and grants from outside the submitted work. WFP reports grant funding and consultancy fees from Abbott, Alere, Banyan, Cardiorentis, Janssen Pharmaceuticals, Portola, Roche, The Medicines Company, Prevencio, and Singulex. MJA reports consultancy fees and honoraria from and is on the speakers bureau of Genentech, Janssen Pharmaceuticals, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, and Medscape; consultancy fees and honoraria from Nestle, Daiichi Sankyo, and Portola; honoraria from and is on the speakers bureau of Chiesi USA, Inc; and patents/royalties from Duke University. The other authors report no conflicts.

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Author contributions

CGK and CIC contributed to the design and implementation of the research, all authors contributed to the analysis of the results and to the writing of the manuscript.

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