Comorbid Pad And Mvd: A Retrospective Nrd Analysis Of Trends, Outcomes, And Readmissions

Miguel Algara

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Comorbid PAD and MVD:
A Retrospective NRD Analysis of Trends, Outcomes, and Readmissions

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Miguel A. Algara, 2022
ABSTRACT

Background: Previous studies on select populations have shown worsened limb outcomes among patients with comorbid Peripheral artery disease (PAD) and Microvascular disease (MVD), however this connection has not been studied in larger populations. Using a national database, we aimed to analyze the frequency of Major Adverse Limb Events (MALE), as well as Major Adverse Cardiac Events (MACE), Mortality, and other comorbidities for patients with comorbid PAD/MVD, as compared to patients with PAD or MVD alone.

Methods: Using 2011 to 2018 National Readmission Database (NRD) data, we identified the frequency of PAD and MVD-related admissions based on ICD-9/10 codes. The primary outcomes of interest were MALE, MACE, and mortality, while secondary outcomes were length of stay and hospitalization cost. Patient socio-demographic characteristics, including age, gender, insurance and household income; and comorbidities were compared by disease group using standardized differences, with values of $d \geq 0.20$ equivalent to a small effect size or larger highlighted. Outcomes were stratified by disease status (PAD-only, MVD-only, and comorbid PAD+MVD), with MVD-only patients serving as the reference group.

Results: There were 21,270,666 MVD-only, 9,133,256 PAD-only, and 3,568,847 comorbid PAD/MVD-related hospitalizations from 2011 to 2018. There were no significant differences in age or sex between all three groups ($d<0.20$). Patients with MVD-only had rates of 7.71%, 67.44%, 55.70%, 2.22% for CLI, Diabetes, Renal failure, and prior amputation respectively. Compared to them, PAD-only patients’ rates were 15.35%, 38.59%, 25.08%, and 7.62% ($d=0.43, -0.66, -0.73, 0.71$ respectively). Comorbid patients’ rates were 29.81%, 80.38%, 62.72%, and 16.17% ($d=0.90, 0.38, 0.16, 1.18$ for MVD-only vs PAD+MVD, while for PAD-only vs PAD+MVD $d=0.47, 1.03, 0.89, 0.47$). From 2011 to 2018 there was a 20% increase in...
MVD-only admissions from 2,478,490 to 2,968,604. Similarly, PAD-only rose by 29% from 1,028,521 to 1,353,793, while the PAD+MVD group increased by 28% from 397,326 to 507,404 (Ptrend <.0001).

**Conclusion:** Patients with comorbid PAD/MVD have higher rates of comorbidities such as diabetes, renal disease, and CLI. They also have significantly worse rates of limb amputation, and slightly worse rates of MACE. We have shown that the diagnosis of MVD significantly increases the chances of minor and major amputation for PAD patients. Moreover, MVD also results in small but significant increase in the risk of MACE, and in an increased likelihood of hospital readmission. Identifying this subgroup of patients could be critical in improving limb outcomes. Future efforts in screening PAD patients for microvascular disease could help decrease amputation rates and potentially have a modest improvement in major adverse cardiovascular events as well.
ACKNOWLEDGEMENTS

I am incredibly grateful for all of the support and advice of Dr. Carlos Mena-Hurtado, Dr. Kim Smolderen, and Dr. Kristie Harris. I also want to thank my fellow VAMOS group member Waleed Siddiqui for his invaluable help with readmission modeling. Without their assistance and guidance this research would not have been possible.
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INTRODUCTION

Lower extremity Peripheral Artery disease (PAD) remains one of the largest burdens on the global healthcare system. Globally PAD affects over 230 million patients.\textsuperscript{(12)(33)} In the US alone the burden of PAD exceeds $4.4 billion per year.\textsuperscript{(17)} Current pathophysiological knowledge of PAD dictates that it is a disorder that can affect all vascular beds.\textsuperscript{(29)} All cases are caused by buildup of atherosclerotic plaques that impede blood flow.\textsuperscript{(36)} This reduced blood flow can result in ischemia with activity, and in more severe forms at rest. Progression of disease can lead to intermittent claudication, in which patients experience temporary pain with exertion.\textsuperscript{(11)} The feared complication of PAD is critical limb ischemia, which is considered the most advanced form of the disease, and has the worst outcomes.\textsuperscript{(28)} Although early management of PAD has good prognosis, many patients are not diagnosed until late in the disease.\textsuperscript{(13)} At that point revascularization, or in the worst cases, amputation, is necessary. Currently, in the US, revascularization approaches include open surgical and endovascular procedures. While research is still ongoing to determine which approach results in better outcomes, the number of endovascular procedures has grown in recent years.\textsuperscript{(5)} Despite the increase in these limb-saving procedures, there is still a significant number of PAD patients that undergo both major and minor amputations every year.\textsuperscript{(11)} Furthermore, while the mortality of PAD and CLI appears to have decreased or stabilized in recent years, the number of hospitalizations has increased.\textsuperscript{(5)(28)}

Microvascular disease (MVD), is typically defined as a dysfunction of vessels measuring $\sim$100 um.\textsuperscript{(15)} Unlike PAD, the literature regarding pathophysiology of MVD is sparser. MVD is most commonly thought of as a complication of diabetes mellitus (DM).\textsuperscript{(32)(34)} Landmark clinical trials such as the UK Prospective Diabetes Study further strengthen the evidence of a link between MVD and DM.\textsuperscript{(1)} The feared complications of microvascular disease include kidney failure, and
chronic pain due to neuropathic pain. In fact, research suggests that the triad of retinopathy, nephropathy, and neuropathy is unique to patients with diabetes and microvascular disease.\(^{(14)}\) Unlike PAD, MVD has not been independently linked to worsened limb outcomes such as amputation. Early management of MVD revolves around controlling blood glucose levels. In fact, strong glycemic control has been shown to decrease rates of retinopathy.\(^{(1)}\) More recent trials have shown blood pressure management also plays a key role, with ACE inhibitors becoming a staple of management of microvascular disease.\(^{(34)}\) Another distinction between PAD and MVD is a lack of robust epidemiological data for MVD. Because of this it is unclear how MVD is trending compared to other vascular disorders.

Although both macrovascular (PAD) and microvascular (MVD) can affect peripheral vessels, their resulting pathologies are different. For example, PAD is generally seen as a large peripheral vessels disease that is a result of atherosclerosis, which commonly results in limb-threatening ischemia. Microvascular disease, on the other hand, is seen as small vessel disease that is result of diabetes, and can result in retinopathy, neuropathy, or nephropathy to name a few. Despite the pervasive link of MVD and DM, recent research has shown that the combination of PAD and MVD, regardless of DM, synergistically increases the risk of amputation.\(^{(6)}\) According to research done by Beckman et. al amputation risk is increased in patients with MVD independent of traditional risk factors.\(^{(6)}\) Furthermore, their key finding was that the risk of amputation increases synergistically if the patients have comorbid PAD. Also of note, Beckman et. al described a modest risk increase in MI, coronary revascularization, and death among those with comorbid PAD/MVD.\(^{(6)}\) However, there remain many unanswered questions in the existing literature including the role of sex, the relationship between microvascular and macrovascular disease and the prognostic value of microvascular disease in patients with established
macrovascular disease. We hope to take research of the connection between PAD and MVD a step further by using a larger, more diverse patient database and broadening our search to include other outcomes besides of major limb amputations such as surgical and endovascular revascularizations, STEMI, NSTEMI, and ischemic strokes. Consequently, by increasing both the scope of the research, plus the size and diversity of the patient population we hope to increase our understanding of the burden of disease in patients with comorbid PAD and MVD, and how such comorbidity affects different disease groups. Additionally, we are also analyzing the trends in hospitalization among PAD, MVD, and comorbid patients and examining their comorbidities in order to find predictors of our outcomes of interest.

The connection between PAD and MVD remains understudied, to our knowledge there are no large-scale studies quantifying MALE, MACE, and mortality in this specific patient population. Thus, we examined such outcomes in comorbid PAD+MVD, in addition to patient trends and risk profiles. By increasing our understanding of the relationship between micro and macrovascular disease we hope to establish the prognostic value of microvascular disease in those patients with established macrovascular disease. Our hope is this thesis will contribute to the body of knowledge that provides healthcare providers with better ways to assess risk and manage patients who suffer from both diseases. Our proposed hypothesis is that patients with comorbid PAD and MVD will have higher rates of major adverse limb events such as major amputations or revascularization procedures (defined as MALE), and MI, or ischemic stroke (defined as MACE) and a higher readmission rate compared to those with either just PAD or MVD alone.
METHODS

Student Contribution

Original NIS coding was provided by Drs. Harris and Luna, and was modified by the thesis author to enable usage with the NRD. The student was also responsible for assembling and cleaning the entire NRD 2011-2018 database, and for gathering and adding all the necessary ICD codes. The student independently verified all ICD codes, and Dr. Luna served as secondary verifier. The student was also responsible for the data analysis, with guidance provided by Drs. Mena, Smolderen, and Harris. Readmission coding provided by HCUP was applied with guidance from Waleed Tariq Siddiqui. Finally, readmission modeling required assistance from Yale’s StatLab consultant Gigi Zheng.

Ethics Statement

This study was exempt from the Institutional Review Board approval as this a publicly available deidentified national database.

Data Source

The NRD database is part of the Healthcare Cost and Utilization Project and is sponsored by the Agency for Healthcare Research and Quality (AHRQ). The hospital readmission data were obtained from the NRD database from 2011 through 2018. The NRD contains nearly 50% of in-hospital admissions/readmissions with de-identified patient data from across the USA. (35) Access to the database was obtained through a license by the VAMOS research Lab at the Yale School of Medicine.

Hospital teaching status, size, and location, are some of the criteria used for stratified sampling of hospitals. All hospitalizations are deidentified and included in the NRD as a unique observation with one primary discharge diagnosis and 29 secondary diagnoses (up to 39 with the
transition to ICD10 in q4 2015 and onwards) during the hospitalization. Each hospital admission includes patients’ comorbidities, primary and secondary procedures, insurance status, hospital cost, in-hospital outcomes as well as some demographics.\textsuperscript{(5)} Unfortunately, unlike the NIS, the NRD does not include racial demographic information. Unique to the NRD, a patient linker is also included, which allows for the tracking of patients across multiple hospitalizations. This patient linkage is what allows assessment of rehospitalizations, unlike similar databases such as the National inpatient survey (NIS).

**Study Population**

Our initial population was defined as all patients with a primary or secondary diagnosis of PAD or MVD, identified using the *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) codes for years 2011 to 2015 (q1 through q3) and *International Classification of Diseases, Tenth Edition, Clinical Modification* (ICD-10-CM) codes for 2015 q4 through 2018 with the codes described in supplementary Table 1. It should be noted that some of these codes do not specifically code for PAD or MVD. Instead, some codes act as a proxy. For example, peripheral neuropathy or diabetic retinopathy codes were used as a proxy for MVD. The proxy codes used for MVD are the same that were validated by the research of Beckman et al.\textsuperscript{(6)} The PAD and revascularization procedure codes were validated in previous VAMOS research by Anantha-Narayanan et al.\textsuperscript{(5)}

From this combined group of PAD and MVD admissions we extracted hospitalization data for patients with ICD codes for PAD but no MVD (PAD-only group), MVD but no PAD (MVD-only group), and comorbid PAD and MVD (PAD+MVD group). We then used codes for specific outcomes for our analysis such as major and minor amputations, endovascular and surgical revascularizations, ST and non-ST elevation myocardial infarctions, ischemic strokes,
in-hospital mortality, cost, and LOS. These ICD codes are also included in the supplementary Table 1. The NRD includes up to 30 diagnoses and 15 procedure codes for the years 2011 to 2015 (q1-q3) and up to 40 diagnoses and 25 procedure codes after the third quarter of 2015. Patients under 18 years were excluded, as well as patients with non-atherosclerotic causes of PAD, lower extremity trauma, and patients that received non-PAD related amputations. These strategies and codes are in line with previously published work.({a}{b}{c}{d}{e}{f})

Figure 1. Flow chart of patient selection with inclusion and exclusion criteria


Because the US transitioned to the ICD-10-CM/Procedure Coding System (PCS) coding scheme on October 1, 2015, there were 9 months of ICD-9-CM and 3 months of ICD-10-CM/PCS codes for 2015. To include the years 2015 q4 through 2018 we used ICD code conversion software to convert ICD-9-CM codes to ICD-10-CM codes. This process has been validated in previous literature.({g}{h})
As suggested in previous literature, all ICD-10 diagnosis and procedure codes were independently reviewed by the thesis author and contributor Dr. Paulina Luna for validation.\(^{(7)}\)

We have also adapted a study design checklist proposed by Khera et al, originally made for the NIS, to improve study design as well as validity and generalizability of results.\(^{(19)}\)(\(^{(20)}\))

**Table 1. Methodological checklist for studies published using the NRD survey data.\(^{(19)}\)(\(^{(20)}\))**

<table>
<thead>
<tr>
<th>Section A. Research Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the study consider that it can only detect diseases conditions, procedures, and diagnostic tests in hospital settings?</td>
</tr>
<tr>
<td>Yes.</td>
</tr>
<tr>
<td>2. Does the study acknowledge that it includes encounters, not individual patients?</td>
</tr>
<tr>
<td>Yes. Instead of referring to “patients” we have used “hospitalization.”</td>
</tr>
<tr>
<td>Section B. Data Interpretation</td>
</tr>
<tr>
<td>3. Does the study attempt to identify disease conditions or procedures of interest using administrative codes or their combinations that have been previously validated?</td>
</tr>
<tr>
<td>Yes. Diseases and/or procedures have been identified using the previously validated and/or published administrative codes.(^{(2)})((^{(5)}))</td>
</tr>
<tr>
<td>4. Does the study limit its assessment to only in-hospital outcomes, rather than those occurring after discharge?</td>
</tr>
<tr>
<td>Yes.</td>
</tr>
<tr>
<td>5. Does the study distinguish complications from comorbidities or clearly not where it cannot?</td>
</tr>
<tr>
<td>Yes.</td>
</tr>
<tr>
<td>Section C: Data Analysis</td>
</tr>
<tr>
<td>6. Does the study clearly account for the survey design of the NRD and its components— clustering, stratification, and weighting?</td>
</tr>
<tr>
<td>Yes. As instructed by HCUP, all analyses used the “survey” functions (SURVEYMEANS, SURVEYLOGISTIC, and SURVEYFREQ), clustering (HOSP_NRD), weighting (DISCWT), and stratification (NRD_STRATUM) of the NRD.</td>
</tr>
<tr>
<td>7. Does the study adequately address changes in data structure over time (for trend analyses)?</td>
</tr>
<tr>
<td>Yes, this was addressed in the methods section.</td>
</tr>
</tbody>
</table>
Study Definitions and Outcomes

Hospitalization-related sociodemographic factors included age, sex, insurance status, and median household income based on the hospitalization’s zip code. Hospital-related factors included hospital bed size, location, and teaching status. The following Elixhauser comorbidities were used to assist in evaluating risk profiles: Hypertension, Valvular Disease, Diabetes, Coronary artery disease, congestive heart Failure, Chronic lung disease, Renal Failure, Anemia, Hypothyroidism, Obesity, Smoking, Dyslipidemia, Prior Amputation.\(^{(10)}\) In addition to the Elixhauser comorbidities, a primary or secondary diagnosis of chronic limb ischemia (CLI) was included as a proxy of disease severity.\(^{(23)}\) Schizophrenia, bipolar disease, and other stress-related disorders were included given research suggesting a connection between mental health disorders and cardiovascular disease.\(^{(8)}\)(30)

Annual weighted PAD-only, MVD-only, and PAD+MVD admissions were calculated using the SURVEYFREQ function. The type of admission (ED vs Elective admissions) was used as a proxy of access to care. Primary outcomes of interest included MALE which encompassed minor and major amputations, and inpatient endovascular and surgical revascularization. In addition, MACE was included which comprises ST- and Non-ST-segment elevation myocardial infarctions, and ischemic strokes. Finally, in-hospital mortality was also a primary outcome. Revascularization and amputation procedures were defined similarly as previous studies.\(^{(5)}\) Endovascular revascularizations consisted of iliac, femoral, popliteal, and infra-popliteal balloon angioplasty plus or minus lower extremity stenting procedures. Surgical revascularizations included endarterectomy as well as lower extremity bypass procedures. Major amputations were comprised of disarticulation at the ankle or knee plus amputations below or above the knee. Minor amputations were those occurring throughout the foot, plus or minus toe removal. The ICD-9-CM
and ICD-10-CM codes used for these outcomes are described in Supplementary Table 1. Secondary outcomes were median Length of stay (LOS) and hospitalization costs (in US dollars), which were also compared according to disease group.

**Statistical Analysis**

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and in accordance with the recommended methodological standards mentioned previously. All hospital admissions are linked to a discharge weight that can be used to analyze projected national estimates for in-hospital outcomes after accounting for the hierarchical structure of the data set, as described by HCUP. Weighted data were combined across years 2011 to 2018 to compare patient risk profiles (demographics, comorbidities) and hospital-level factors between disease groups (PAD-only vs MVD-only vs PAD+MVD). Categorical variables were summarized as frequencies and percentages and continuous variables as medians and interquartile ranges, with data stratified by disease group. Due to the large sample size, differences between the two groups were evaluated with Cohen’s d, using standardized difference for continuous variables and standardized differences for proportions for categorical and dichotomous variables. Differences equivalent to a small effect size or large (i.e., absolute values ≥0.20) were highlighted. Emergency department vs elective admissions, in addition to other comorbidities such as cardiovascular disease (CAD, HTN), renal disease, psychiatric disease, and others were compared by disease group and were also evaluated with Cohen’s d. Median LOS and costs accrued in PAD-only vs MVD-only vs PAD+MVD were compared using non-parametric Wilcoxon rank sum test.

Annual rates for hospitalizations, major and minor amputations, in-patient endovascular and surgical revascularizations, STEMI, NSTEMI, ischemic stroke, and in-hospital mortality were
calculated for each disease group, adjusting for changes in NRD structure over time. The Cochran-Mantel-Haenszel test was used to evaluate the temporal trends for these rates by disease group.\(^{(16)(38)}\)

Hierarchical multivariable logistic regression modeling was used to evaluate the association between disease group and MALE, MACE, and in-hospital mortality. The models were adjusted for patient risk profiles including demographics and comorbidities. These analyses accounted for the complex NRD survey design in which discharges are weighted based on the stratification of hospitals by ownership (Private vs Nonprofit), location, and bed size, and for the clustering of discharges within hospitals.\(^{(16)(19)(31)}\)

**RESULTS**

**Patient Demographics**

A total of 33,972,772 PAD or MVD-related admissions occurred between 2011 and 2018. Median age of the PAD-only cohort was 72.88 years, while MVD-only patients had a median age of 67.47 years, and the median age of the comorbid group was 69.79 years. Males represented 55%, 51%, and 59% of the PAD-only, MVD-only, and PAD+MVD groups respectively. A total of 78% of PAD-only patients were on Medicare, compared to 67% in the MVD-only group, and 77% in the comorbid group. A detailed breakdown of patient demographics is available in table 2.

**Table 2. Patient Demographics by Disease Group**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PAD-ONLY</th>
<th>MVD-ONLY</th>
<th>PAD+MVD</th>
<th>P-VALUE</th>
<th>STANDARDIZED MEAN DIFFERENCE (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=33,972,772</td>
<td>9,133,256</td>
<td>21,270,666</td>
<td>3,568,847</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years, median (Q1,Q3)</td>
<td>72.88 (63.94, 81.39)</td>
<td>67.47 (55.98, 78.37)</td>
<td>69.79 (60.38, 78.77)</td>
<td>&lt;.0001</td>
<td>-0.0353</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAD-ONLY VS MVD-ONLY</td>
</tr>
<tr>
<td>Sex, n(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PAD-ONLY VS PAD+MVD</td>
</tr>
<tr>
<td>Female</td>
<td>4,119,612(45.11%)</td>
<td>10,514,557(49.43%)</td>
<td>1,454,239(40.75%)</td>
<td>&lt;.0001</td>
<td>-0.0958</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MVD-ONLY VS PAD+MVD</td>
</tr>
</tbody>
</table>

A detailed breakdown of patient demographics is available in table 2.
| Male | 5,013,645 (54.89%) | 10,756,110 (50.57%) | 2,114,609 (59.25%) |
| Insurance Status, n(%) | <.0001 | 0.1887 | 0.0035 | -0.1826 |
| Medicare | 7,160,947 (78.41%) | 14,288,520 (67.17%) | 2,749,860 (77.05%) |
| Medicaid | 593,648 (6.50%) | 2,521,958 (11.86%) | 302,835 (8.49%) |
| Private Insurance | 1,041,816 (11.41%) | 3,246,396 (15.26%) | 392,073 (10.99%) |
| Self-pay | 127,271 (1.39%) | 576,199 (2.71%) | 47,007 (1.32%) |
| No Charge | 18,314 (0.20%) | 85,082 (0.40%) | 7,077 (0.20%) |
| Other | 178,089 (1.95%) | 518,043 (2.44%) | 65,650 (1.84%) |
| Missing | 13,171 (0.14%) | 34,468 (0.16%) | 4,345 (0.12%) |
| Median Household Income, n(%) | <.0001 | -0.0607 | -0.0251 | 0.0355 |
| Quartile 1 (lowest) | 2,819,192 (30.87%) | 7,053,533 (33.16%) | 1,139,507 (31.93%) |
| Quartile 2 | 2,387,633 (26.14%) | 5,586,040 (26.26%) | 929,205 (26.04%) |
| Quartile 3 | 2,112,701 (23.13%) | 4,761,195 (22.38%) | 817,109 (22.90%) |
| Quartile 4 (highest) | 1,689,388 (18.50%) | 3,559,284 (16.73%) | 634,755 (17.79%) |
| Missing | 124,342 (1.36%) | 310,614 (1.46%) | 48,271 (1.35%) |

**Risk Profiles**

Hypertension represented one of the most common comorbidities amongst all groups. In the PAD-only cohort 68% had a diagnosis of hypertension, whereas MVD-only and PAD+MVD has 67%, and 69%. Diabetes was also quite prevalent, with 39% 67%, and 80% among PAD-only, MVD-only, and PAD+MVD respectively. Renal failure was present in 25% of PAD-only patients, 56% of MVD-only patients, and 63% of patients in the comorbid group. There was also a significant difference in smoking; 46% of PAD-only hospitalizations, 31% of MVD hospitalizations, 38% of PAD+MVD hospitalizations were smokers with the difference between PAD-only and MVD-only being significant (d=0.35). Prior amputation accounted for 8% of PAD-only patients, 2% of MVD-only, and 16% of PAD+MVD patients. The rest of patient comorbid characteristics are included in table 3.

Table 3. Patient Comorbidities by Disease Group

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PAD-ONLY</th>
<th>MVD-ONLY</th>
<th>PAD+MVD</th>
<th>P-VALUE</th>
<th>STANDARDIZED MEAN DIFFERENCE (d)</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th>Condition</th>
<th>Control</th>
<th>PAD ONLY (21,270,666)</th>
<th>MVD ONLY (3,568,847)</th>
<th>PAD vs MVD</th>
<th>PAD ONLY vs PAD+MVD</th>
<th>MVD ONLY vs PAD+MVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension, n(%)</strong></td>
<td>6,192,147 (67.80%)</td>
<td>14,152,606 (66.54%)</td>
<td>2,462,770 (69.01%)</td>
<td>&lt;.0001</td>
<td>-0.0316</td>
<td>0.0309</td>
</tr>
<tr>
<td><strong>Valvular Disease, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Diabetes, n(%)</strong></td>
<td>3,524,172 (38.59%)</td>
<td>2,462,770 (69.01%)</td>
<td>2,462,770 (69.01%)</td>
<td>&lt;.0001</td>
<td>0.6776</td>
<td>1.0337</td>
</tr>
<tr>
<td><strong>Coronary artery disease, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Heart Failure, n(%)</strong></td>
<td>4,952,811 (54.23%)</td>
<td>8,075,151 (37.96%)</td>
<td>2,099,861 (58.84%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Renal Failure, n(%)</strong></td>
<td>4,952,811 (54.23%)</td>
<td>8,075,151 (37.96%)</td>
<td>2,099,861 (58.84%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Anemia, n(%)</strong></td>
<td>6,192,147 (67.80%)</td>
<td>14,152,606 (66.54%)</td>
<td>2,462,770 (69.01%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Hypothyroidism, n(%)</strong></td>
<td>3,524,172 (38.59%)</td>
<td>2,462,770 (69.01%)</td>
<td>2,462,770 (69.01%)</td>
<td>&lt;.0001</td>
<td>0.6776</td>
<td>1.0337</td>
</tr>
<tr>
<td><strong>Obesity, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Smoking, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Dyslipidemia, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Prior Amputation, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>CLI, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Depression, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Schizophrenia, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Bipolar, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Anxiety, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
<tr>
<td><strong>Other Stress-related disorders, n(%)</strong></td>
<td>1,016,443 (11.13%)</td>
<td>1,617,455 (7.60%)</td>
<td>359,229 (10.07%)</td>
<td>&lt;.0001</td>
<td>-0.2314</td>
<td>-0.0619</td>
</tr>
</tbody>
</table>

**Primary and Secondary Outcomes**

Looking at the number of MALEs as a whole, there was a significant difference between the PAD-only and the MVD-only (13% vs 0.5%, d=1.9), however there was no significant difference between PAD-only and the comorbid subgroup (d<0.20). In terms of major adverse cardiovascular events, the comorbid subgroup had the highest percentage, however the difference was not significant (d<0.20) when compared to the PAD-only subgroup. However, compared the
MVD-only subgroup, the increase in MACE is significant (d=0.22). Finally, there was no statistically significant difference in mortality amongst all three subgroups (d<0.20 for all).

However, when analyzing the subcategories of MALE there are statistically significant differences. There was a large significant difference in the number of minor and major amputations among the three subgroups (d>0.20). Of note, the comorbid group had a higher percentage of both minor and major amputations than the PAD group (d=0.64 and 0.32 for minor and major amputations respectively). On the other hand, the PAD-only subgroup had a significantly higher percentage of both endovascular and surgical revascularization procedures (d>0.20). The comorbid group also had worse secondary outcomes, which were length of stay (LOS) and total charges, however these differences were not statistically significant (d<0.20 for all comparisons).

Table 4. Primary and Secondary Outcomes by Disease Group

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>PAD-ONLY</th>
<th>MVD-ONLY</th>
<th>PAD+MVD</th>
<th>P-VALUE</th>
<th>STANDARDIZED MEAN DIFFERENCE (d)</th>
<th>PAD-ONLY VS MVD-ONLY</th>
<th>PAD-ONLY VS PAD+MVD</th>
<th>MVD-ONLY VS PAD+MVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=33,972,772</td>
<td>9,133,256</td>
<td>21,270,666</td>
<td>3,568,847</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor Amputation, n(%)</td>
<td>223,241 (2.44%)</td>
<td>135,477 (0.64%)</td>
<td>262,930 (7.37%)</td>
<td>&lt;.0001</td>
<td>-0.7516 0.6368 1.3884</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Amputation, n(%)</td>
<td>351,183 (2.58%)</td>
<td>38,235 (0.18%)</td>
<td>162,009 (4.54%)</td>
<td>&lt;.0001</td>
<td>-1.481 0.3238 1.8049</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Amputation, n(%)</td>
<td>443,994 (4.86%)</td>
<td>171,075 (0.80%)</td>
<td>407,237 (11.41%)</td>
<td>&lt;.0001</td>
<td>-1.0149 0.5098 1.5247</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular Revascularization, n(%)</td>
<td>668,121 (7.21%)</td>
<td>52,961 (0.25%)</td>
<td>235,075 (6.59%)</td>
<td>&lt;.0001</td>
<td>-1.8952 -0.0532 1.842</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical Revascularization, n(%)</td>
<td>500,990 (5.49%)</td>
<td>7,545 (0.04%)</td>
<td>113,631 (3.18%)</td>
<td>&lt;.0001</td>
<td>-2.8102 -0.3132 2.4971</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any Revascularization, n(%)</td>
<td>1,020,386 (11.17%)</td>
<td>59,157 (0.28%)</td>
<td>315,356 (8.84%)</td>
<td>&lt;.0001</td>
<td>-2.0999 -0.1436 1.9563</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Adverse Limb Events (MALE)</td>
<td>1,217,247 (13.33%)</td>
<td>96,889 (0.46%)</td>
<td>455,406 (12.76%)</td>
<td>&lt;.0001</td>
<td>-1.9377 -0.0276 1.9102</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>368,267 (4.03%)</td>
<td>613,832 (2.89%)</td>
<td>149,809 (4.20%)</td>
<td>&lt;.0001</td>
<td>-0.191 0.0231 0.2141</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>640,087 (7.01%)</td>
<td>1,085,322 (5.10%)</td>
<td>294,116 (8.24%)</td>
<td>&lt;.0001</td>
<td>-0.1862 0.0967 0.2829</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>175,518 (1.92%)</td>
<td>345,737 (1.63%)</td>
<td>60,412 (1.69%)</td>
<td>&lt;.0001</td>
<td>-0.094 -0.0712 0.0228</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Adverse Cardiovascular Events (MACE)</td>
<td>902,192 (9.88%)</td>
<td>1,584,635 (7.45%)</td>
<td>379,912 (10.65%)</td>
<td>&lt;.0001</td>
<td>-0.1702 0.0459 0.2161</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died During Admission, n(%)</td>
<td>368,142 (4.03%)</td>
<td>694,932 (3.27%)</td>
<td>130,858 (3.67%)</td>
<td>&lt;.0001</td>
<td>-0.1202 -0.0543 0.0659</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of Stay, days, median (Q1,Q3)</td>
<td>3.48 (1.72, 6.68)</td>
<td>3.50 (1.85, 6.51)</td>
<td>4.40 (2.24, 8.26)</td>
<td>&lt;.0001</td>
<td>-0.0006 0.023 0.0202</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Charges, dollars, median (Q1, Q3)</td>
<td>41,496 (21684, 82186)</td>
<td>34,433 (18457, 67591)</td>
<td>46,333 (23795, 93405)</td>
<td>&lt;.0001</td>
<td>-0.0054 0.0059 0.0093</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Trends in Hospitalization for PAD, MVD Patients**

Trends in hospitalization are shown in figure 2. Between 2011 and 2018 there was a 24% overall increase in hospitalization among all PAD and MVD patients. The largest increase among the disease subgroups was within the PAD-only group, with a 32% increase during the study period. The MVD-only and PAD+MVD subgroups had an increase in hospitalizations of 20% and 28% respectively.

![Figure 2. Yearly Trends in Discharges by Disease Group](image)

The trends in MALE can be seen in figure 3. Although there has been a stable decrease MALE in general, including a 10% decrease in MALE among PAD-only patients from 2011 to 2018, there was a 20% increase in MALE within the PAD+MVD subgroup. Due to this increase, after 2015 the comorbid group has the largest percentage of MALE among all subgroups.
In-hospital mortality trends are included in figure 4. Mortality slowly increased among all 3 subgroups. However, there were no significant changes in mortality relative to each other, with PAD-only having the highest % of mortality at 4.0%, while MVD-only and PAD+MVD had 3.1% and 3.7% respectively. There was a small decrease in mortality among the MVD-only subgroup, going from 3.5% in 2011 to 3.1% in 2018.
Multivariable Models for Comorbid PAD+MVD-related Admission Outcomes

Initial results from the unadjusted multivariable models show a very large significant odds ratio in both endovascular and surgical revascularization for the PAD-only subgroup (OR=31 and 164 respectively) as compared to the MVD-only subgroup. On the other hand, the PAD+MVD subgroup had significantly larger ORs in both minor and major amputations (OR=12 and 26) as compared to the MVD-only subgroup. These results are maintained after model adjustment, as can be in table 5.

Table 5. Multivariable Models for Major Adverse Limb Outcomes broken down by category

<table>
<thead>
<tr>
<th>Variable</th>
<th>Endovascular Revascularization</th>
<th>Surgical Revascularization</th>
<th>Minor Amputation</th>
<th>Major Amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Diagnosis Group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted Model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVD-only</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>PAD-only vs MVD-only</td>
<td>31.104</td>
<td>30.094</td>
<td>32.148</td>
<td>163.566</td>
</tr>
<tr>
<td>PAD+MVD vs MVD-only</td>
<td>28.244</td>
<td>27.371</td>
<td>29.145</td>
<td>92.685</td>
</tr>
<tr>
<td><strong>Adjusted Model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVD-only</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>PAD-only vs MVD-only</td>
<td>31.006</td>
<td>30.098</td>
<td>31.941</td>
<td>116.151</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.085</td>
<td>1.075</td>
<td>1.095</td>
<td>0.919</td>
</tr>
<tr>
<td>Age</td>
<td>0.986</td>
<td>0.986</td>
<td>0.987</td>
<td>0.981</td>
</tr>
<tr>
<td>ED Visit</td>
<td>0.447</td>
<td>0.437</td>
<td>0.458</td>
<td>0.353</td>
</tr>
<tr>
<td>Elective Admission</td>
<td>1.701</td>
<td>1.654</td>
<td>1.75</td>
<td>3.42</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.038</td>
<td>1.026</td>
<td>1.051</td>
<td>1.144</td>
</tr>
<tr>
<td>Valvular Disease</td>
<td>0.684</td>
<td>0.671</td>
<td>0.698</td>
<td>0.383</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.142</td>
<td>1.129</td>
<td>1.154</td>
<td>0.848</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>0.943</td>
<td>0.931</td>
<td>0.955</td>
<td>0.91</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>0.778</td>
<td>0.77</td>
<td>0.786</td>
<td>0.965</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>1.149</td>
<td>1.134</td>
<td>1.163</td>
<td>0.759</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.01</td>
<td>0.997</td>
<td>1.023</td>
<td>0.893</td>
</tr>
<tr>
<td>Diagnosis Group</td>
<td>MALE</td>
<td>MACE</td>
<td>In-Hospital Mortality</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>------</td>
<td>----------------------</td>
<td></td>
</tr>
<tr>
<td>Variable</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Diagnosis Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted Model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVD-only</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>PAD-only vs MVD-only</td>
<td>33.598</td>
<td>32.851</td>
<td>34.362</td>
<td>1.362</td>
</tr>
<tr>
<td>PAD+MVD vs MVD-only</td>
<td>31.959</td>
<td>31.298</td>
<td>32.634</td>
<td>1.48</td>
</tr>
<tr>
<td>Adjusted Model</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVD-only</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>PAD-only vs MVD-only</td>
<td>36.655</td>
<td>35.942</td>
<td>37.383</td>
<td>1.06</td>
</tr>
<tr>
<td>PAD+MVD vs MVD-only</td>
<td>37.076</td>
<td>36.319</td>
<td>37.849</td>
<td>1.024</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.937</td>
<td>0.93</td>
<td>0.944</td>
<td>1.04</td>
</tr>
<tr>
<td>Age</td>
<td>0.98</td>
<td>0.979</td>
<td>0.98</td>
<td>0.995</td>
</tr>
<tr>
<td>ED Visit</td>
<td>0.407</td>
<td>0.399</td>
<td>0.415</td>
<td>0.987</td>
</tr>
<tr>
<td>Elective Admission</td>
<td>2.299</td>
<td>2.249</td>
<td>2.351</td>
<td>0.387</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.112</td>
<td>1.101</td>
<td>1.124</td>
<td>1.314</td>
</tr>
</tbody>
</table>

Alternatively, the unadjusted model for the composite category of MALE has the PAD-only group with a slightly larger OR than the comorbid group (OR 34 vs 32). In the MACE models the difference between subgroups is smaller. However, the comorbid group does have a slightly larger OR than the PAD-only group (OR 1.5 vs 1.4). The in-hospital mortality model shows the PAD-only subgroup has minor increase in mortality as compared to the PAD+MVD subgroup (OR=1.2 vs 1.1 respectively). The adjusted models have very similar outcomes; however, the main difference is the adjusted model has a higher odds ratio for MALE in the comorbid subgroup than the PAD-only, but the difference is small (OR=37.1 vs 36.7 for comorbid and PAD-only respectively). The rest of the results for the adjusted models can be seen in table 6.

Table 6. Multivariable Models for all primary outcomes
Rehospitalization Rates

30-day readmission rates were similar among all three subgroups. There were minor decreases in hospitalization rates in both MVD-only and PAD+MVD subgroups (11.9% to 11.3% and 12.2% to 12.0% for MVD-only and PAD+MVD), but the PAD-only subgroup had a small increase, from 12.1% to 12.2% between 2011 and 2018.

Table 7. 30-day Readmission Rates

<table>
<thead>
<tr>
<th>YEAR</th>
<th>TOTAL DISCHARGES</th>
<th>READMISSIONS</th>
<th>PERCENT READMISSIONS</th>
<th>TOTAL DISCHARGES</th>
<th>READMISSIONS</th>
<th>PERCENT READMISSIONS</th>
<th>TOTAL DISCHARGES</th>
<th>READMISSIONS</th>
<th>PERCENT READMISSIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>1,028,521</td>
<td>124,003</td>
<td>12.06%</td>
<td>2,478,490</td>
<td>295,080</td>
<td>11.91%</td>
<td>397,326</td>
<td>48,520</td>
<td>12.21%</td>
</tr>
<tr>
<td>2012</td>
<td>1,029,947</td>
<td>124,075</td>
<td>12.05%</td>
<td>2,474,433</td>
<td>283,832</td>
<td>11.47%</td>
<td>402,553</td>
<td>47,608</td>
<td>11.83%</td>
</tr>
<tr>
<td>2013</td>
<td>1,052,857</td>
<td>125,703</td>
<td>11.94%</td>
<td>2,452,430</td>
<td>278,840</td>
<td>11.37%</td>
<td>421,794</td>
<td>49,513</td>
<td>11.74%</td>
</tr>
<tr>
<td>2014</td>
<td>1,051,264</td>
<td>134,596</td>
<td>12.80%</td>
<td>2,501,292</td>
<td>300,812</td>
<td>12.03%</td>
<td>447,248</td>
<td>55,358</td>
<td>12.38%</td>
</tr>
<tr>
<td>2015</td>
<td>1,119,966</td>
<td>144,179</td>
<td>12.87%</td>
<td>2,635,456</td>
<td>310,398</td>
<td>11.78%</td>
<td>461,758</td>
<td>52,907</td>
<td>11.46%</td>
</tr>
<tr>
<td>2016</td>
<td>1,212,542</td>
<td>152,684</td>
<td>12.59%</td>
<td>2,828,523</td>
<td>338,193</td>
<td>11.96%</td>
<td>456,443</td>
<td>56,776</td>
<td>12.44%</td>
</tr>
<tr>
<td>2017</td>
<td>1,284,366</td>
<td>158,999</td>
<td>12.38%</td>
<td>2,931,438</td>
<td>341,126</td>
<td>11.64%</td>
<td>474,321</td>
<td>58,492</td>
<td>12.33%</td>
</tr>
<tr>
<td>2018</td>
<td>1,353,793</td>
<td>165,719</td>
<td>12.24%</td>
<td>2,968,604</td>
<td>334,705</td>
<td>11.27%</td>
<td>507,404</td>
<td>60,972</td>
<td>12.02%</td>
</tr>
</tbody>
</table>

Cox Rehospitalization Models

Results from the unadjusted cox rehospitalization model shows a 4% increase in hospitalization within 180 days for the comorbid group compared to the PAD-only group. The difference in the adjusted model is slightly smaller (3%) but still significant (p<0.0001). Heart
failure and valvular disease also had minor yet significant impacts in the adjusted cox models (p<0.0001). Interestingly, diabetes was not a significant factor in the adjusted cox model (p=0.0236).

Table 8. 180-day Cox Rehospitalization Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Unadjusted Model</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MVD-only</td>
<td>1 [Reference]</td>
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<td></td>
</tr>
<tr>
<td>PAD-only vs MVD-only</td>
<td>1.046</td>
<td>1.044</td>
<td>1.048</td>
</tr>
<tr>
<td>PAD+MVD vs MVD-only</td>
<td>1.083</td>
<td>1.080</td>
<td>1.086</td>
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<td><strong>Adjusted Model</strong></td>
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<td>MVD-only</td>
<td>1 [Reference]</td>
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<tr>
<td>PAD-only vs MVD-only</td>
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<td>1.041</td>
<td>1.047</td>
</tr>
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<td>PAD+MVD vs MVD-only</td>
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<td>1.074</td>
<td>1.080</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.988</td>
<td>0.986</td>
<td>0.990</td>
</tr>
<tr>
<td>Female</td>
<td>0.999</td>
<td>0.999</td>
<td>0.999</td>
</tr>
<tr>
<td>Age</td>
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<td>1.001</td>
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<td>0.994</td>
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<tr>
<td>Hypertension</td>
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<td>1.012</td>
<td>1.020</td>
</tr>
<tr>
<td>Valvular Disease</td>
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<td>0.995</td>
<td>0.999</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.006</td>
<td>1.004</td>
<td>1.008</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
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<td>1.018</td>
<td>1.024</td>
</tr>
<tr>
<td>Heart Failure</td>
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<td>0.997</td>
<td>1.001</td>
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<tr>
<td>Chronic Lung Disease</td>
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<td>Hypothyroidism</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>Dyslipidemia</td>
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<td>0.994</td>
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<tr>
<td>Depression</td>
<td>1.006</td>
<td>0.995</td>
<td>1.017</td>
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<td>Schizophrenia</td>
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<td>Bipolar</td>
<td>1.013</td>
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<tr>
<td>Anxiety</td>
<td>0.995</td>
<td>0.982</td>
<td>1.008</td>
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</table>

Results of the 365-day cox rehospitalization model were similar to the 180-day model. In the unadjusted model the HR for the PAD+MVD group was 1.121, whereas the PAD-only group was 1.071, which means there is a 5% increase in rehospitalization in the comorbid group compared to the PAD-only subgroup (p<0.0001). Such difference is maintained in the
adjusted models. Similar to the 180-day model, heart failure and valvular disease are among the most important factors for rehospitalization. The rest of the adjusted model is included in table 10.

Table 9. 365-day Cox Rehospitalization Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
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<td>Diagnosis Group</td>
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<tr>
<td>Unadjusted Model</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MVD-only</td>
<td>1 [Reference]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD-only vs MVD-only</td>
<td>1.071</td>
<td>1.070</td>
<td>1.072</td>
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<tr>
<td>PAD+MVD vs MVD-only</td>
<td>1.121</td>
<td>1.119</td>
<td>1.123</td>
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<td>Adjusted Model</td>
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<td></td>
</tr>
<tr>
<td>MVD-only</td>
<td>1 [Reference]</td>
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<td></td>
</tr>
<tr>
<td>PAD-only vs MVD-only</td>
<td>1.067</td>
<td>1.065</td>
<td>1.069</td>
</tr>
<tr>
<td>PAD+MVD vs MVD-only</td>
<td>1.118</td>
<td>1.116</td>
<td>1.120</td>
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<tr>
<td>Sex</td>
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<td></td>
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</tr>
<tr>
<td>Male</td>
<td>0.991</td>
<td>0.990</td>
<td>0.992</td>
</tr>
<tr>
<td>Female</td>
<td>0.998</td>
<td>0.998</td>
<td>0.998</td>
</tr>
<tr>
<td>Age</td>
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<td>1.004</td>
<td>1.008</td>
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<tr>
<td>Selective Admission</td>
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<td>Hypertension</td>
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<tr>
<td>Valvular Disease</td>
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<tr>
<td>Diabetes</td>
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<td>1.007</td>
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<tr>
<td>Coronary Artery Disease</td>
<td>1.01</td>
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<td>1.011</td>
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<tr>
<td>Heart Failure</td>
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<td>1.052</td>
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<td>Chronic Lung Disease</td>
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<td>Hypothyroidism</td>
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<td>Dyslipidemia</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>Bipolar</td>
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<td>1.009</td>
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<tr>
<td>Anxiety</td>
<td>1.016</td>
<td>1.014</td>
<td>1.018</td>
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<tr>
<td>Other Stress-related disorders</td>
<td>0.992</td>
<td>0.985</td>
<td>0.999</td>
</tr>
</tbody>
</table>
DISCUSSION

Our main findings are that between 2011 and 2018 there has been an increase in the hospitalization rate of PAD-only patients that is higher than other subgroups, that patients with comorbid PAD+MVD have higher acuity risk profiles, and that patients with comorbid PAD+MVD have higher rates of major and minor amputation, and MACE compared to patients with PAD or MVD alone.

Patient risk profiles are generally consistent with results from similar national databases such as the NIS, and previous studies of PAD+MVD, with some key differences.\(^{(5)}\)(\(^{(6)}\)) Firstly, in the NIS study there is a single subgroup for PAD and thus it is not possible to differentiate between PAD-only and PAD+MVD comorbid patients. On the other hand, while Beckman et. al.’s study also at the same subgroups, because it is based on a very particular subset of patients (VA) its results are harder to generalize. For example, when comparing to PAD studies done on the NIS, the percentage of hypertension and renal failure are within 5% for the date range between 2011 and 2018.\(^{(5)}\) However, two major differences stand out. First, the percentage of PAD-only patients with diabetes. The NIS study found that ~60% of all PAD patients had diabetes, whereas the VA cohort study that PAD-only patients had a much lower rate of DM at 32%.\(^{(5)}\)(\(^{(6)}\)) Our study found that about 39% of PAD-only patients have diabetes. The most likely reason for the increased rate of diabetes between our study and the VA cohort is that, as the NIS study showed, the rate of DM among PAD patients has been steadily rising from 2011 to 2017. On the other hand, when combining the PAD-only and PAD+MVD subgroups and comparing their rate of DM to that found in all PAD patients of the NIS study we can see they are relatively close at 55% vs 60% for our study vs the NIS study.\(^{(5)}\)
The other important discrepancy in patient risk profiles is the percentage of patients with prior amputations. Similarly to the decreased rate of DM compared to the NIS study which found a rate of previous amputation of around 16%, our study found a lower rate of previous amputation for PAD-only patients, of 8%.\(^{(5)}\) However, as with diabetes, it is likely that because of the patients in the PAD+MVD subgroup that would have otherwise been considered in the PAD subgroup the number of patients with previous amputation is lower than expected. Combining the PAD-only and PAD+MVD prior amputation rates increases to 11% thus decreasing the difference between the NIS study and our own. Unfortunately, prior amputations were not studied in the VA cohort so it is not possible to compare to that study. CLI was not reported either, but there are striking differences in the rates of CLI. Patients in the comorbid group were twice as likely to have CLI than those in the PAD-only group, which was statistically significant (d=0.47). This large difference is further evidence of worsened disease burden among those with comorbid PAD and MVD, and is one to have a strong impact on patient’s quality of life.\(^{(40)}\)

Between 2011 and 2018 we found an overall increase in the hospitalization rates of patients from all combined subgroups of 24%. In comparison, there was an overall 5% decrease in MALEs during the same timeframe. This decrease in MALEs is reflected in both the PAD and MVD only subgroups, but interestingly not in the comorbid subgroup, which instead saw an increase in MALEs of 17%. A possible theory for this is that the PAD/MVD subgroup saw an increase either in diabetes or worsening rates of CLI within this time frame, thus leading to increased risk of amputations among the comorbid subgroup.\(^{(6)}\) Trends in mortality were consistently around 3.5-4.0% across all 3 subgroups with minor variation throughout the time period.
We also provide more evidence that the presence of MVD is a separate risk factor for amputation and other cardiovascular events, independent of the risk associated with PAD. There was a significant difference in the number of both minor and major amputations (d=1.4 and 1.8 respectively) when comparing the MVD only to the MVD/PAD subgroup. This is reflected in our multivariate modeling, which shows the increase in amputation remains even after accounting for other cardiovascular and comorbid factors. In contrast, unlike the risk of amputation, the risk of endovascular or surgical revascularization is higher for those with PAD-only and does not increase in the presence of MVD. The risk of major cardiac events is also increased among patients with comorbid PAD+MVD. Initial unadjusted modeling showed a slightly worsened OR for PAD-only compared to the comorbid subgroup. However, after accounting for cardiovascular and other risk factors and comorbidities the PAD+MVD group had a worse risk of MACE than the PAD-only group, suggesting the addition of microvascular disease leads to higher rates of major adverse cardiac events. This small increase in risk of MACE is similar to what was seen in the Beckman et al. paper. One exception to this is that increase is not reflected in the number of strokes, which is similar among all three subgroups. Unlike MALE and MACE, we did not find a significant difference in mortality, LOS, or cost per hospitalization (d<0.20).

**Implications for Diagnosis and Management**

Our research shows that, as previously hypothesized, there is a strong association between MALEs and MVD, and that association is synergistic with PAD. Given these findings, it is possible that diagnosing MVD could become an important factor in determining which patients are at highest risk for limb amputation. At the very least, physicians that diagnose MVD in patients with PAD should increase foot surveillance to identify signs and symptoms of CLI early. Furthermore, we hope that this research shows the need for updated guidelines within for
PAD and CLI. Although readmission numbers were similar across all groups, our cox model showed that the comorbid group had a 5.1% (42% relative difference) increase in rehospitalization. In addition to the rehospitalization risk, the increased number of CLI, prior amputations, and worsened risk of major amputation all highlight the fact that the comorbid group has a higher acuity and more costly than the PAD-only group. Such knowledge could be key in decreasing poor outcomes in this subset of patients.

**Future Directions**

Our results highlight the need for increased research into the connection of macro and microvascular disease. Bench research to elucidate the molecular mechanism responsible for worsened outcomes could result in new therapies directed specifically for patients with comorbid PAD and MVD. On the other hand, clinical research could focus on earlier diagnosis through screening, which could minimize or decrease disease progression for comorbid patients.

**Limitations**

There are many known limitations of using large public databases such as the NRD. First, the NRD by its nature only captures in-patient data. Hence it is very likely that the true burden on disease in the general population is higher than what our data shows. Second, the NRD was specifically designed to capture discharges rather than individual patients. Although it is possible to link different hospitalizations in order to track patient readmissions, such a process only allows tracking within the same calendar year. Third, there is little consensus among the cardiovascular research community regarding ICD9/10 coding schemes. For example, although the ICD definition of PAD is better validated, the coding for MVD has less evidence for it. This means that there still remains a potential for misclassification. Finally, as a retrospective study, the potential for
confounding and selection bias should be considered, and causality cannot be derived from our results.

**COVID-19 Impact**

None to report.

**CONCLUSION**

We have shown that between 2011 and 2018 there was a significant increase in the number of hospitalizations among patients with PAD and MVD, whereas the rates of rehospitalization have remained stable in the same time period. In addition, we conclude that the diagnosis of MVD significantly increases the chances of minor and major amputation for PAD patients. Moreover, MVD also results in small but significant increase in the risk of MACE, and in an increased likelihood of hospital readmission. Therefore, we suggest increased observation of patients with PAD that are found to have MVD, as that could lead to decreased amputation in this particular subset of patients. Future research could focus on the benefits of screening for MVD in PAD patients.
REFERENCES


