Justification and Methods for the Critical Limb Ischemia & Chronic Kidney Disease—Amputations and Mortality (CLICK-A&M) Study Using the Premier Healthcare Database

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Abstract

Introduction. Approximately 238 million people were diagnosed with peripheral artery disease (PAD) in 2015, making it a growing global problem. Untreated PAD can progress to critical limb ischemia (CLI), the most severe form of the disease. There is growing evidence that microvascular diseases increase the risk of amputations. In particular, chronic kidney disease (CKD) is known to cause medial arterial calcification, a known risk factor for complications in patients with CLI. The current study describes the underlying rationale, objectives, and methods to explore PAD, CLI, and CKD associations. **Methods.** The Premier Healthcare Database was used to conduct this retrospective observational study of patients with PAD or CLI. Adult patients, who were discharged between 2016 and 2021, were included in the study. **Results.** There were 874,788 patients diagnosed with PAD at baseline, of which 7,823 patients (0.9%) had CLI. CKD was reported among 105,474 (12%) patients with PAD and 1,482 (19%) patients with CLI. About 44.3% of patients were female, and 55.6% were males. Approximately 78.3% were White, 12% were Black, and 4.4% were Hispanic. About 46.4% and 7.3% of patients had Medicare and Medicaid, respectively. **Conclusion.** With a high volume of patient information on outcomes such as amputations and mortality, the Critical Limb Ischemia & Chronic Kidney Disease—Amputations & Mortality (CLICK-A&M) study will provide real-world insight into CKD prevalence among patients with PAD or CLI. Using advanced statistical methods, we aim to identify areas for improvement in diagnosing, treating, and managing patients with PAD, CLI, and CKD.

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Peripheral artery disease (PAD) is a circulatory condition affecting noncardiac, non-intracranial arteries.[1,2,3] The most common cause of PAD is atherosclerosis, whereas its association with inflammatory disorders of the arterial walls or noninflammatory arteriopathies is less common.[3] PAD of the lower extremities involves decreased perfusion rates due to the narrowing of the supplying blood vessels.[1,2] In the United States alone, about 6.5 million patients who are 40 years or older were diagnosed with PAD. This number continues to increase nationwide as the elderly population continues to grow.[4] Risk factors such as age, smoking, hypertension, diabetes mellitus, and chronic kidney disease (CKD), aggravate the risk for PAD.[4,5] A PAD condition left untreated can lead to critical limb ischemia (CLI), a severe form of the disease characterized by rest pain, ulceration, and gangrene. Studies have reported that up to 11% of patients diagnosed with PAD progress to CLI.[6,7] Medial arterial calcification (MAC), an alteration of the arterial wall characterized by non-obstructive calcium deposition in the tunica media, is associated with higher rates of complications due to CLI.[8] The prevalence of CLI in the United States is approximately

2 million, projected to increase due to a growing population with known risk factors.[9,10] Though non-traumatic amputation rates, in general, have declined since the late 1990s, the rate of amputations amongst CLI patients has remained strikingly high. Some studies have reported rates as high as 15% after 1 year of diagnosing CLI.[9,11]

The prevalence of CLI patients with diabetes mellitus has substantially increased since 2009.[12] There is growing evidence that microvascular diseases, such as MAC, increase the risk of amputations independent of preexisting PAD or diabetes.[4,13,14] Thus, assessing the relationship between CLI and diseases predisposing patients to MAC is integral. One of the major predisposing factors for MAC is chronic kidney disease (CKD).[8] CKD is a progressive medical condition characterized by impaired kidney functioning resulting from decreased glomerular filtration rate (GFR) for more than 3 months.[15] The global prevalence of CKD is estimated to be about 13.4%, and 47 million patients have been affected in the United States alone.[16,17] The global prevalence of CKD among type-2 diabetes patients is approximately 50%.[18]

The study will also explore whether the risk and prevalence of PAD or CLI, and associated complications, differ with CKD stages, race, ethnicity, insurance status, and various comorbid conditions such as diabetes mellitus, hypertension, and hyperlipidemia. Multivariable multivariate analysis will be performed in this study using clinical and sociodemographic covariates to test multiple hypotheses. Where applicable, we will utilize propensity score matching and other sampling techniques to account for variability in data. This study describes the underlying rationale, objectives, methods, and population description. The methods used in this project will serve as a background for future screening and intervention studies and the early management of patients with PAD or CLI and CKD.

Methods

Study design and data source. The Premier Healthcare Database (PHCD)[29] was used to conduct this retrospective observational study of patients with PAD and CLI. The PHCD is an extensive hospital-based, service-level, all-payer database containing clinical and healthcare utilization information from more than 4,400 hospitals, health systems, and over 225,000 other providers and organizations in the U.S. The PHCD emerged as a collaboration initiative between American Health Care Systems, Sun Health, and Premier, Inc in 1997.[19] This curated database has been extensively used for academic research and clinical and financial outcomes of health care policies and initiatives.[20] A wide range of therapeutic areas is covered in the PHCD, facilitating insight into patient characteristics, patterns of patient care, outcomes, and the burden of illness over time. These insights are helpful for various developments and initiatives in the medical field.[20] It represents approximately 25% of all U.S. admissions from the geographically diverse non-governmental community, teaching hospitals, and rural and urban health systems. The PHCD contains data from standard hospital discharge files, including patient demographics and disease states; health insurance type; admission and discharge diagnoses; admission source and type; discharge status and disposition; and hospital pharmacy medication use.

Using unique masked identifiers allows tracking patients across inpatient and outpatient settings within the same hospital. All data in the PHCD are statistically de-identified and compliant with the Health Insurance Portability and Accountability Act;[29] this study was exempt from the Institutional Review Board review. The Miami Cardiac & Vascular Institute Foundation funded access to the PHCD. External funding sources were not utilized to support this study.

Study objectives. The primary objectives of this study are (1) To assess and characterize the presence and severity of CKD burden among individuals with PAD or CLI; and (2) To determine the relationships of clinical risk factors, insurance status, race, and ethnicity with the presence of CKD among individuals with PAD or CLI.

The secondary study objectives are: (1) to examine the association of clinical risk factors, CKD, amputation, and death; (2) to determine the relationships of clinical risk factors, CKD, and amputations with race, ethnicity, and insurance status; and (3) to develop population-based assessments that may inform future protocols to optimize outcomes in patients with PAD or CLI.

Study population. The study used hospitalization and healthcare utilization data between 2016 and 2021. We included all adult PAD or CLI patients discharged between 2016 and 2021 in the analysis. All International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes within the I70 section, including the terms "rest pain," "ulceration," or "gangrene," were used to identify patients with CLI. Appropriate I70 ICD-10-CM codes, excluding the terms "rest pain," "ulceration," or "gangrene," were used to identify patients with PAD. The Current Procedural Terminology (CPT) codes were used to identify patients who underwent lower extremity revascularization or amputation.

Study timeline. After beginning the study, we intend to complete the analysis and disseminate the results by October 2023.

Patient characteristics, clinical characteristics, and outcomes. The baseline data included (1) demographic characteristics such as age, sex, race, marital status, and insurance information; (2) clinical event information such as admission date, discharge date, ICD-10-CM codes, CPT codes, Healthcare Common Procedure Coding System (HCPCS) codes, date of procedure, length of stay (LOS), hospital type, and discharge disposition (home, SNF, expired, etc.); (3) All Patients Refined Diagnosis Related Groups

(APR-DRG) classification for inpatient hospital encounters; (4) detail of drug/supply/service charges for each hospital encounter; (5) general lab results such as microbiology, microbiology sensitivity, glucose, complete blood count, lipid panel, etc., for select hospital encounters; and (6) vitals data such as height, weight, blood pressure, respiratory rate, heart rate, partial pressure of oxygen (PO_2), etc, for select hospital encounters. We grouped patients' hospital length of stay into 5 categories: Up to 1 week; >1 week to <1 month; 1 to <2 months; 2 to <3 months; and 3 or more months. Conditions such as PAD, CLI, CKD stages 1-5, lower extremity revascularization, amputation, diabetes, renal failure, carotid artery disease, coronary artery disease, dyslipidemia, hypertension, prior coronary artery bypass graft surgery (CABG), and other comorbidities were identified using ICD-10-CM and CPT codes (**Supplemental Table S1**).

Data handling and statistical analysis. Descriptive and summary statistics were calculated for all variables of interest in this study. All data were imported and analyzed using SAS software, version 9.4. In future studies, continuous variables will be summarized by using the number of subjects (N), the number of subjects in a subgroup (n), mean ± standard deviation (SD) or 95% confidence interval (CI), median, interquartile range, minimum, and maximum. Frequencies and percentages will summarize categorical variables. The Chi-square test will be utilized to find differences in proportions. Where applicable, an independent *t* test or Mann-Whitney test will be used to find differences in means between the 2 groups. Analysis of variance (ANOVA) or the Kruskal-Wallis test will be utilized to find differences in means among more than 2 groups. Multiple multivariate regression methods such as Linear, Logistic, and Poisson regression and other machine learning methods will be used to find associations between dependent (amputations, death, LOS, cost, etc) and independent variables of interest. Additional statistical techniques will be used to create patient groups with similar clinical and demographic characteristics, including propensity score matching and clustering. A *P*-value of .05 or less will be considered statistically significant.

Results

The data consisted of 12,514,966 hospital visits over 6 years from 878,788 unique patients. The data included 874,788 patients with an established diagnosis of PAD at baseline (ICD-10-CM: I70.XX), of which 7823 patients (0.9%) had CLI. In the data, 388,027 (44.3%) patients were female, while 486,647 (55.6%) were males. The mean age of the entire sample was 70 (95% CI, 62-78) years. The majority of patients were White (78.3%), about 12% were Black, and 4.4% were of Hispanic ethnicity. Approximately 45.3% of patients were married, and 46.5% were single. The mean hospital length of stay was 2.3 ± 10.1 days. Medicare insurance was reported by 46.4%, and Medicaid was reported by 7.2% of the patients. About 1.5% of the total patient population reported receiving dialysis (n = 13,373).

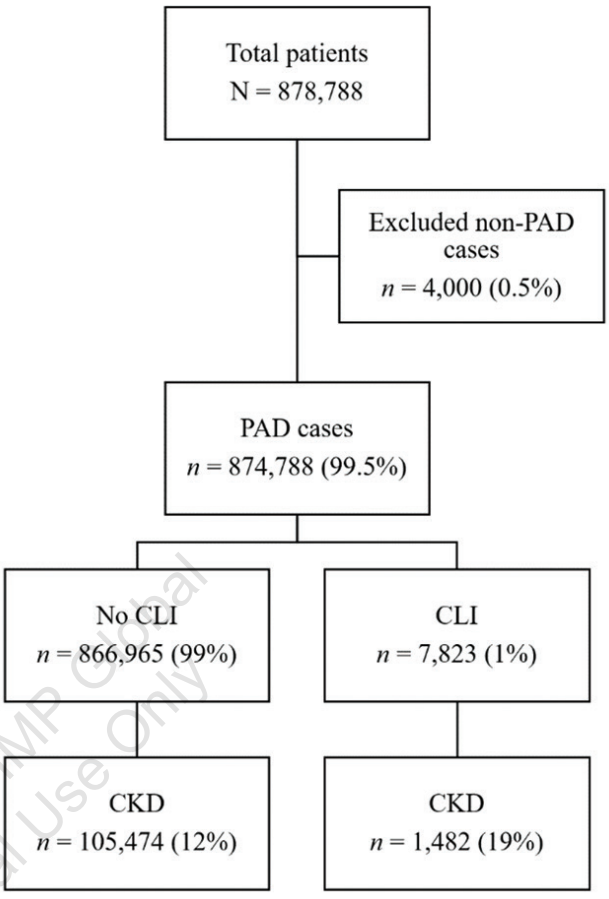

FIGURE 1. Flow chart for inclusion of PAD or CLI cases in the United States, Premiere Healthcare Database (2016-2021). PAD = peripheral arterial disease; CLI = critical limb ischemia; CKD = chronic kidney disease.

Among patients with PAD, 12% had CKD (n = 105,474), and 88% reported no CKD. Among patients with CLI, 19% had CKD (n = 1482) and 81% reported no CKD (**Figure 1**). Further analysis will include the subdivision of CKD patients into 3 groups: CKD Stage 1 or 2, CKD Stage 3 or 4, and CKD Stage 5.

Any minor or major amputations were reported among 86,252 (9.9%) patients, and revascularization was performed among 143,411 (16.4%) patients. Atrial fibrillation was diagnosed among 92,869 (10.6%) patients. Around 1.3% of patients had 'expired' as their discharge disposition. Diabetes and hypertension were reported among 263,600 (30.1%) and 440,850 (50.4%) patients. Past nicotine use was reported by 19.3% of patients. Prevalence of ischemic (1.5%) or hemorrhagic (0.2%) stroke was less among this sample. Major adverse cardiovascular events were reported among 51,081 (5.8%) patients. The prevalence of coronary artery disease and carotid artery disease was 261,844 (29.9%) and 59,980 (6.9%), respectively. The baseline sociodemographic and clinical characteristics of the study population are summarized in **Table 1**.

TABLE 1. Characteristics of the study population with peripheral arterial disease (PAD), Premiere Healthcare Database (2016-2021).

Characteristics	PAD Patients (N = 874,788)
Critical limb ischemia	7823 (0.9%)
Age (years)	
<20	386 (0.0%)
20-29	1699 (0.2%)
30-39	7058 (0.8%)
40-49	31,215 (3.6%)
50-59	125,239 (14.3%)
60-69	256,291 (29.3%)
70-79	270,340 (30.9%)
≥80	182,560 (20.9%)
Mean age (years)	69.5 ± 11.5
Sex	
Female	388,027 (44.3%)
Male	486,647 (55.6%)
Unknown	114 (0.1%)
Race	
White	647,596 (74.0%)
White Hispanic	37,776 (4.3%)
Black	108,422 (12.4%)
Black Hispanic	1200 (0.1%)
Other	66,144 (7.6%)
Unknown	13,650 (1.6%)
Insurance categories	
Medicare	406,127 (46.4%)
Medicare managed	249,325 (28.5%)
Medicaid	63,412 (7.2%)
Private	84,336 (9.6%)
Self pay	44,086 (5.0%)
Uninsured or other	27,502 (3.1%)
Length of stay	
1 week or less	782,369 (89.4%)
>1 week to 2 weeks	59,421 (6.8%)
>2 weeks to 1 month	27,230 (3.1%)
>1 month to 2 months	4851 (0.6%)
>2 months	917 (0.1%)
Mean length of stay (days)	2.3 ± 10.1
Current smoker	14,802 (1.7%)
Past nicotine use	168,398 (19.3%)
Receiving dialysis	13,373 (1.5%)
Revascularization	143,411 (16.4%)
Amputation	86,252 (9.9%)
Expired	11,233 (1.3%)

Discussion

Using a large-scale database such as Premier Healthcare Database from Premier, Inc, we intend to explore the relationships between PAD, CLI, various stages of CKD, race, demographics, diabetes mellitus, and other common comorbid conditions. Likewise, we will also explore whether these factors influence the risk and prevalence of generalized adverse outcomes such as amputation, prolonged hospital length of stay, and mortality. Additional factors such as pro-inflammatory cytokines, metabolic toxins, dietary and lifestyle factors, pre-existing comorbidities, and adverse effects of medications on mediating or moderating the adverse outcomes of PAD or CLI will also be explored as secondary objectives of this study.

The current challenge in treating and managing patients with CKD and concomitant PAD or CLI lies within the interrelationship between these disorders. Patients with CKD are at an estimated 6.5 times greater risk of developing PAD than healthy patients, and this risk increases with the severity of renal dysfunction.[21] Recent research suggests that this phenomenon is influenced by a combination of factors, including metabolic disturbances, inflammation, and extracellular matrix (ECM) composition changes.[21] CKD decreases renal clearance of uremic toxins, which is responsible for endothelial damage and precipitation of PAD and CLI.[22] Furthermore, vascular dysfunction seems to occur among CKD patients due to increased circulating levels of pro-inflammatory markers, such as interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α.[21,23,24] Dysregulation of matrix metalloproteinases (MMPs) in CKD can also contribute to peripheral artery disease because of corresponding ECM irregularity, promoting atherosclerotic change in the vasculature.[21] Not only does CKD predispose to PAD and CLI, but it also complicates its subsequent treatment. Due to dramatic impairments in phosphate and calcium hemostasis, CKD predisposes arterial stiffening secondary to MAC.[8,24,25] Hence, CKD is an independent risk factor for complications after CLI interventions such as surgical bypass and endovascular revascularization.[26-28] Patients

TABLE 1. Characteristics of the study population with peripheral arterial disease (PAD), Premiere Healthcare Database (2016-2021).

Characteristics	PAD Patients (N = 874,788)
Comorbidities	
Atrial fibrillation	92,869 (10.6%)
Alcohol-related disorders	15,864 (1.8%)
Anemia (blood loss)	33,907 (3.9%)
Anemia	23,190 (2.7%)
Carotid artery disease	59,980 (6.9%)
Coronary artery disease	261,844 (29.9%)
Dementia	29,327 (3.4%)
Depression	47,867 (5.5%)
Dilated cardiomyopathy	4312 (0.5%)
Diabetes	263,600 (30.1%)
Dyslipidemia	283,639 (32.4%)
Hemorrhage	1278 (0.1%)
Hypertension	440,850 (50.4%)
Hyperlipidemia	317,760 (36.3%)
Hypothyroidism	57,347 (6.6%)
Myocardial infarction	26,152 (3.0%)
Past myocardial infarction	68,295 (7.8%)
Obesity	71,296 (8.2%)
Other peripheral circulatory diseases	28,029 (3.2%)
Pericarditis	319 (0.0%)
Postoperative deep vein thrombosis	7796 (0.9%)
Postoperative infarction	249 (0.0%)
Postoperative respiratory failure	1882 (0.2%)
Prior coronary artery bypass graft surgery	71,793 (8.2%)
Prior cerebrovascular accidents	280 (0.0%)
Prior percutaneous transluminal coronary angioplasty	6450 (0.7%)
Rheumatoid arthritis	10,938 (1.3%)
Weight loss	5495 (0.6%)
Renal failure	67,214 (7.7%)
Major adverse cardiovascular events	51,081 (5.8%)
Stroke	
Ischemic	12,699 (1.5%)
Hemorrhagic	2031 (0.2%)
Angina	4613 (0.5%)
Cardiac arrest	4341 (0.5%)

Data presented as count (percentage) or mean ± standard deviation.

with CKD undergoing endovascular revascularization are more likely to suffer perioperative complications, post-procedural amputations, reinterventions, and death.[8] This risk is magnified in CKD patients with diabetes, as this population has a higher risk of developing complications than patients affected by either disease alone. Given these associations, our project proposes to explore the differences in adverse outcomes such as amputation and death among patients with PAD, CLI, and progressively worsening stages of CKD. Both prospective longitudinal and retrospective studies are planned to understand these assertions.

PAD, CLI, and CKD are undoubtedly public health issues; however, troubling trends in the prevalence and management of these conditions amongst minorities, particularly the Black race, raise concerns about racial disparities. People who are Black and older than 40 years are more than twice as likely as other races to suffer from PAD at every age above this limit.[29] People of Hispanic ethnicity report lower rates of PAD than patients who are Black and White.[30] A community-based cohort study found that the 80-year risk of developing PAD was 19% for the White race, 22% for Hispanic ethnicity, and 30% for the Black race.[4] The differences in risk for developing PAD could be attributed to the differences in the prevalence of known risk factors such as smoking, diabetes, hypertension, and hyperlipidemia among these races and ethnicities.[29] However, the shockingly high PAD rates amongst the Black race can also be potentially associated with social determinants of health—such as discrepancies in healthcare access, income, and education.[29] Patients belonging to racial minority groups are likely to present during the late stages of PAD or CLI and are less likely to receive adequate care and treatment. Despite proven therapeutic strategies to treat PAD and CLI, the REACH (Reduction of Atherothrombosis for Continued Health) registry revealed that patients of the Black race and Hispanic ethnicity with PAD were prescribed statins and aspirin less often than patients of the White race.[31] Risk factor control among PAD and CLI patients of the Black race is poor, and this discrepancy is associated with major adverse vascular outcomes.[32] Due to these factors, limb salvage is less common among Black and other racial minority populations with CLI prior to urgent amputations.[33] Even when patients of a minority group with CLI receive limb salvage treatment via endovascular or open surgery, their odds of amputation within 2 years are greater than patients from the White population.[34]

These disparities amongst racial minorities are not limited to PAD and CLI but also CKD.

The 2021 United States Renal Data System (USRDS) annual report indicates that the prevalence of CKD was highest among the Black population, with an all-cause hospitalization rate of 15% or higher compared to the White population with CKD.[35] Renal transplants have been proven to improve survival among CKD patients; however, patients who are Black or Hispanic are less likely than patients who are White to be preemptively listed for transplantation.[36] There also appears to be a higher prevalence of PAD among CKD patients who are Black compared to the White race.[35] Unfortunately, patients of the Black race, comorbid with CLI and CKD, suffer worse outcomes after lower extremity revascularization, as the Black race was found to be an independent risk factor for graft failure in a recent study.[27] Patients of the Black race who undergo hemodialysis were also more likely to experience amputation after an infra-inguinal bypass surgery.[37] These trends merit further analysis of the relationship between race, PAD, CLI, and CKD to promote health equity and address current disparities in the field. In the current project, we intend to explore these racial and ethnic disparities in greater detail using a large database. Such racial and ethnic disparities are great barriers to providing social justice and equitable health care.

The disease burden of PAD or CLI among patients with Medicare is also an area of concern. According to current data, the 4-year mortality risk after endovascular treatment among the Medicare population is 54%.[10] While this could reflect poor outcomes associated with PAD or CLI; recent research indicates that a patient's healthcare plan can influence the quality of care and outcomes. In a retrospective cohort study of 1,687,724 PAD and CLI patients, the evidence showed differences in the delivery of care and outcomes based on insurance status.[38] Medicare and Medicaid patients were more likely to present with advanced stages of PAD or CLI, and a higher prevalence of endovascular treatment, in-hospital complications, amputation, and mortality after limb removal.[38]

Patients with private insurance have reported lower odds of amputation[39] compared to other insurance statuses. These findings raise concerns related to socioeconomic disparities in the treatment of PAD and CLI. Further investigations are warranted to explore these discrepancies and analyze these associations among patients comorbid with PAD or CLI and CKD. These factors are concerning because according to United States Census Bureau Reports in 2020, more than 18.4% and 17.8% of the United States population depend on Medicare and Medicaid, respectively, whereas 8.6% were uninsured.[40] Most PAD or CLI patients in this population are expected to experience disparities in healthcare delivery and limited access to resources.

While CKD has been found to influence the pathogenesis and outcomes related to PAD or CLI, its treatment, mainly hemodialysis, can also affect these associations. Hemodialysis is a therapeutic intervention designed to filter the blood among patients with CKD who can no longer maintain adequate renal clearance of metabolic end products due to worsening GFR.[41] Patients with PAD or CLI, CKD, and on hemodialysis have been associated with adverse outcomes following open lower-extremity bypass surgery, including increased rates of readmission, postoperative myocardial infarction, amputation, and mortality compared to patients not on hemodialysis.[27,42] This trend was also reported among individuals receiving hemodialysis who were undergoing isolated tibial endovascular intervention for CLI. These patients reported higher cardiac and major limb events[43] as compared to patients not receiving hemodialysis. The risk factors for mortality after endovascular treatment include age over 80, non-ambulatory status, and heart failure.[44] Furthermore, cerebrovascular disease, lack of cilostazol use, and poor below-the-knee run-off are possible risk factors for major limb events.[44] Tissue loss is associated with both mortality and limb events in this population.[44] We intend to explore whether these factors had any bearing on influencing the progression as well as the management of PAD and CLI.

In a study, the prevalence of PAD in any CKD patient was 26% and increased with more advanced CKD, with 33% of Stage 5 patients presenting with PAD.[45] This trend is also reflected in the prevalence of PAD or CLI amongst CKD patients.[46] This population is significantly more likely to suffer worse post-procedural outcomes because of perioperative complications and the need for reintervention.[46] Given the prevalence of PAD or CLI in CKD populations and the effect of renal insufficiency on PAD or CLI progression and management, it is imperative to further assess the relationship between CKD stages and outcomes after lower extremity vascular interventions. Moreover, a better understanding of how racial disparities, healthcare coverage, and hemodialysis affects PAD or CLI outcomes among CKD patients could guide healthcare providers in delivering personalized and evidence-based treatment plans for improving survival rates and quality of life among these patients.

Strength and limitations. The current study uses a large-scale and systematically collected nationally representative database. Therefore, the findings in this study have greater internal and external validity. The PHCD also has a large population base spread across several states and regions within the U.S. Therefore, the findings in the proposed projects are generalizable to the entire hospitalized population within the U.S.

Nevertheless, the specific objectives of the PHCD are not the same as this project, because of which some surrogate information bias may be present in the analysis. We assume that the stringent process of accounting for covariates and propensity score matching may minimize the effects of these types of biases. In addition, since the data have already been collected, some confounding errors may not be accounted for in the analysis. The PHCD only records hospital episodes and does not capture all longitudinal data before and after hospitalizations. Therefore, the

PHCD does not have all the data on pre- and post-hospitalization. Additionally, laboratory test results may not be available after the patient leaves the hospital. Information on all prescribed medications and their duration of post-discharge use could be limited. Incorporating such data could have significantly improved the findings of this project.

Conclusion

With a high volume of patient information on outcomes such as amputations and mortality, the Critical Limb Ischemia & Chronic Kidney Disease - Amputations & Mortality (CLICK-A&M) study will provide real-world insight into CKD prevalence among patients with PAD or CLI. In addition, this database also contains information on demographics, insurance coverages, and comorbidities. Using advanced statistical methods, we aim to identify areas for improvement in diagnosing, treating, and managing patients with co-existing PAD, CLI, or CKD. We aim to highlight this significant clinical problem that needs further investigation and evidence-based recommendations. The information gained from this study will add to the growing pool of evidence on PAD, CLI, and CKD outcomes with unique information on racial and health insurance disparities and other significant outcomes in patients across the United States.

References

1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res*. 2015;116(9):1509-1526. doi:10.1161/CIRCRESAHA.116.303849
2. Criqui MH, Matsushita K, Aboyans V, et al. Lower extremity peripheral artery disease: contemporary epidemiology, management gaps, and future directions: a Scientific Statement from the American Heart Association. *Circulation*. 2021;144(9):e171-e191. Epub 2021 Jul 28. doi:10.1161/CIR.0000000000001005
3. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. *BMJ*. 2018;360. doi:10.1136/bmj.j5842
4. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation*. 2021;143(8):e254-e743. Epub 2021 Jan 27. doi:10.1161/CIR.0000000000000950
5. Firnhaber JM, Powell CS. Lower extremity peripheral artery disease: diagnosis and treatment. *Am Fam Physician*. 2019;99(6):362-369.
6. Uccioli L, Meloni M, Izzo V, Giurato L, Merolla S, Gandini R. Critical limb ischemia: current challenges and future prospects. *Vasc Health Risk Manag*. 2018;14:63-74. eCollection 2018. doi:10.2147/VHRM.S125065
7. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FGR. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg* 2007;45 Suppl S:S5-67. doi:10.1016/j.jvs.2006.12.037
8. Lanzer P, Hannan FM, Lanzer JD, et al. Medial arterial calcification: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2021;78(11):1145-1165. doi:10.1016/j.jacc.2021.06.049
9. Duff S, Mafilios MS, Bhounsule P, Hasegawa JT. The burden of critical limb ischemia: a review of recent literature. *Vasc Health Risk Manag*. 2019;15:187-208. eCollection 2019. doi:10.2147/VHRM.S209241
10. Mustapha JA, Katzen BT, Neville RF, et al. Disease burden and clinical outcomes following initial diagnosis of critical limb ischemia in the Medicare population. *JACC Cardiovasc Interv*. 2018;11(10):1011-1012. doi:10.1016/j.jcin.2017.12.012
11. Aday AW, Matsushita K. Epidemiology of peripheral artery disease and polyvascular disease. *Circ Res*. 2021;128(12):1818-1832. Epub 2021 Jun 10. doi:10.1161/CIRCRESAHA.121.318535
12. Geiss LS, Li Y, Hora I, Albright A, Rolka D, Gregg EW. Resurgence of diabetes-related nontraumatic lower-extremity amputation in the young and middle-aged adult U.S. population. *Diabetes Care*. 2019;42(1):50-54. Epub 2018 Nov 8. doi:10.2337/dc18-1380
13. Behroozian A, Beckman JA. Microvascular disease increases amputation in patients with peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2020;40(3):534-540. Epub 2020 Feb 20. doi:10.1161/ATVBAHA.119.312859
14. Beckman JA, Duncan MS, Damrauer SM, et al. Microvascular disease, peripheral artery disease, and amputation. *Circulation*. 2019;140(6):449-458. Epub 2019 Jul 8. doi:10.1161/CIRCULATIONAHA.119.040672
15. Charles C, Ferris AH. Chronic kidney disease. *Prim Care*. 2020;47(4):585-595. doi:10.1016/j.pop.2020.08.001
16. Lv JC, Zhang LX. Prevalence and disease burden of chronic kidney disease. *Adv Exp Med Biol*. 2019;1165:3-15. *Adv Exp Med Biol*. doi:10.1007/978-981-13-8871-2_1
17. Gaitonde DY, Cook DL, Rivera IM. Chronic kidney disease: detection and evaluation. *Am Fam Physician*. 2017;96(12):776-783.
18. Thomas MC, Cooper ME, Zimmet P. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. *Nat Rev Nephrol*. 2016;12(2):73-81. Epub 2015 Nov 10. doi:10.1038/nrneph.2015.173
19. Scott L. SunHealth, AmHS/Premier to merge. *Mod Healthc*. 1995;25(48):2-3.
20. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects—advantages and disadvantages. *Nat Clin Pract Rheumatol*. 2007;3(12):725-32. doi:10.1038/ncprheum0652
21. Serra R, Bracale UM, Ielapi N, et al. the impact of chronic kidney disease on peripheral artery disease and peripheral revascularization. *Int J Gen Med*. 2021;14:3749-3759. eCollection 2021. doi:10.2147/IJGM.S322417
22. Gondouin B, Cerini C, Dou L, et al. Indolic uremic solutes increase tissue factor production in endothelial cells by the aryl hydrocarbon receptor pathway. *Kidney Int*. 2013;84(4):733-744. Epub 2013 May 1. doi:10.1038/ki.2013.133
23. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. *Blood Purif*. 2015;39(1-3):84-92. Epub 2015 Jan 20. doi:10.1159/000368940
24. Provenzano M, Rivoli L, Garofalo C, et al. Renal resistive index in chronic kidney disease patients: Possible determinants and risk profile. *PLoS One*. 2020;15(4):e0230020. eCollection 2020. doi:10.1371/journal.pone.0230020
25. Perticone M, Maio R, Sciacqua A, et al. Serum phosphorus levels are associated with endothelial dysfunction in hypertensive patients. *Nutr Metab Cardiovasc Dis*. 2016;26(8):683-688. Epub 2016 Feb 22. doi:10.1016/j.numecd.2016.02.003
26. Gkremoutis A, Bisdas T, Torsello G, et al. Early outcomes of patients with chronic kidney disease after revascularization for critical limb ischemia. *J Cardiovasc Surg (Torino)*. 2021;62(2):104-110. Epub 2020 Dec 14. doi:10.23736/S0021-9509.20.11661-6
27. Ambur V, Park P, Gaughan JP, et al. The impact of chronic kidney disease on lower extremity bypass outcomes in patients with critical limb ischemia. *J Vasc Surg*. 2019;69(2):491-496. Epub 2018 Aug 25. doi:10.1016/j.jvs.2018.05.229
28. Narcisse DI, Weissler EH, Rymer JA, et al. The impact of chronic kidney disease on outcomes following peripheral vascular intervention. *Clin Cardiol*. 2020;43(11):1308-1316. Epub 2020 Aug 11. doi:10.1002/clc.23444
29. Hackler EL, 3rd, Hamburg NM, White Solaru KT. Racial and ethnic disparities in peripheral artery disease. *Circ Res*. 2021;128(12):1913-1926. Epub 2021 Jun 10. doi:10.1161/CIRCRESAHA.121.318243
30. Forbang NI, Hughes-Austin JM, Allison MA, Criqui MH. Peripheral artery disease and non-coronary atherosclerosis in Hispanics: another paradox? *Prog Cardiovasc Dis*. 2014;57(3):237-243. Epub 2014 Aug 2. doi:10.1016/j.pcad.2014.07.008

31. Meadows TA, Bhatt DL, Hirsch AT, et al. Ethnic differences in the prevalence and treatment of cardiovascular risk factors in US outpatients with peripheral arterial disease: insights from the reduction of atherothrombosis for continued health (REACH) registry. *Am Heart J.* 2009;158(6):1038-1045. doi:10.1016/j.ahj.2009.09.014

32. Pohlman FW, Ford CB, Weissler EH, et al. Impact of risk factor control on peripheral artery disease outcomes and health disparities. *Vasc Med.* 2022;27(4):323-332. 2022;27(4):323-332. Epub 2022 Apr 7. doi:10.1177/1358863X221084360

33. Holman KH, Henke PK, Dimick JB, Birkmeyer JD. Racial disparities in the use of revascularization before leg amputation in Medicare patients. *J Vasc Surg* 2011;54(2):420-426. e421. Epub 2011 May 14. doi:10.1016/j.jvs.2011.02.035

34. Mathlouthi A, Zarrintan S, Khan MA, Malas M, Barleben A. Contemporary outcomes of limb-salvage procedures using Vascular Quality Initiative-Medicare-linked data: Racial and ethnic disparities persist. *J Vasc Surg.* 2022;75(6):2013-2018. Epub 2022 Feb 8. doi:10.1016/j.jvs.2022.01.120

35. System USRD. 2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2021.

36. Nissaisorakarn P, Xiao H, Doshi MD, Singh N, Lentine KL, Rosas SE. Eliminating racial disparities in kidney transplantation. *Clin Transplant.* 2021;35(8):e14397. Epub 2021 Jul 12. doi:10.1111/ctr.14397

37. Arhuidese I, Wang S, Locham S, Faateh M, Nejim B, Malas M. Racial disparities after infrainguinal bypass surgery in hemodialysis patients. *J Vasc Surg.* 2017;66(4):1163-1174. Epub 2017 Jun 21. doi:10.1016/j.jvs.2017.04.044

38. Kim LK, Swaminathan RV, Minutello RM, et al. Trends in hospital treatments for peripheral arterial disease in the United States and association between payer status and quality of care/outcomes, 2007-2011. *Catheter Cardiovasc Interv.* 2015;86(5):864-872. Epub 2015 Oct 8. doi:10.1002/ccd.26065

39. Henry AJ, Hevelone ND, Belkin M, Nguyen LL. Socioeconomic and hospital-related predictors of amputation for critical limb ischemia. *J Vasc Surg.* 2011;53(2):330-339. e331. Epub 2010 Dec 15. doi:10.1016/j.jvs.2010.08.077

40. United States Census Bureau. Health Insurance Coverage in the United States: 2020. United States Census Bureau. Published 2022. Accessed December 16, 2022. https://www.census.gov/library/publications/2021/demo/p60-274.html#:~:text=Of%20the%20subtypes%20of%20health,2.8%20percent)%2C%20and%20Department%20of

41. Elliott DA. Hemodialysis. *Clin Tech Small Anim Pract.* 2000;15(3):136-148. doi:10.1053/svms.2000.18297

42. Kumada Y, Nogaki H, Ishii H, et al. Clinical outcome after infrapopliteal bypass surgery in chronic hemodialysis patients with critical limb ischemia. *J Vasc Surg.* 2015;61(2):400-404.

43. Davies MG, El-Sayed HF. Outcomes of isolated tibial endovascular interventions for tissue loss in cli patients on hemodialysis. *J Endovasc Ther.* 2015;22(5):681-689. Epub 2015 Aug 18. doi:10.1177/1526602815602074

44. Higashino N, Iida O, Soga Y, et al. 10-year clinical outcomes of hemodialysis patients with peripheral arterial disease due to infrainguinal disease undergoing endovascular therapy. *Heart Vessels.* 2022;37(8):1453-1461. Epub 2022 Feb 10. doi:10.1007/s00380-022-02032-z

45. System USRD. 2020 USRDS Annual data report: epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2020.

46. Arinze NV, Gregory A, Francis JM, Farber A, Chitalia VC. Unique aspects of peripheral artery disease in patients with chronic kidney disease. *Vasc Med.* 2019;24(3):251-260. Epub 2019 Mar 1. doi:10.1177/1358863X18824654

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Supplemental Materials

SUPPLEMENTAL TABLE S1. Disease conditions or procedures with their respective ICD-10-CM (normalized) and CPT codes.

Disease Condition or Procedure	Codes
Peripheral arterial disease	I70XX
Critical limb ischemia	I7022, I7023, I7024, I7025, I7026, I7032, I7033, I7034, I7035, I7036, I7042, I7043, I7044, I7045, I7046, I7052, I7053, I7054, I7055, I7056, I7062, I7063, I7064, I7065, I7066, I7072, I7073, I7074, I7075, I7076
Chronic kidney disease	
Stage 1	N181
Stage 2	N182
Stage 3	N183, N1830, N1831, N1832
Stage 4	N184
Stage 5	N185
Renal failure	N170, N171, N172, N178, N179, N19, N990
End-stage renal disease	N186, Z992, Z9115
Any cardiac complications (arrest, insufficiency, cardiorespiratory failure, congestive heart failure)	I9771, I97710, I97711, I9779, I97790, I97791
Shock	T811, T8110 (unspecified), T8111 (cardiogenic), T8112 (septic), T8119 (hypovolemic)
Hemorrhage or hematoma	I9761, I97610, I97611, I97618
Vascular complications	S7510, S75101, S75102, S75109, S7511, S75111, S75112, S75119, S7512, S75121, S75122, S75129, S7519, S75191, S75192, S75199, S35514, S35515, S35516, S3510, S3511, S3512, S3519, S2540, S25401, S25402, S25409, S2541, S25411, S25412, S25419, S2542, S25421, S25422, S25429, S2549, S25491, S25492, S25499
Postoperative infarction or hemorrhage	I97811, I97821
Pericardial complications	I312 (hemopericardium) and I314 (cardiac tamponade), I10_PR codes 0W9D00Z, 0W9D0ZZ, 0W9D30Z, 0W9D3ZZ, 0W9D40Z, 0W9D4ZZ (pericardiocentesis)

SUPPLEMENTAL TABLE S1. Disease conditions or procedures with their respective ICD-10-CM (normalized) and CPT codes.

Disease Condition or Procedure	Codes
Dyslipidemia	E780, E781, E782, E783, E784, E785, E786, E7870, E7871, E7872, E7879, E7881, E7889, E789
Carotid artery disease	I6521, I6522, I6523, I6529
Current smoker	F17210, F17211, F17213, F17218, F17219
Atrial fibrillation/flutter	I480, I481, I482, I483, I484, I489, I4891, I4892
Prior myocardial infarction	I252
Hypertension	I10, I11, I12, I13, I15
Obesity	E66
Weight loss	R634
Anemia	D50-D53
Alcohol-related disorders	F10
Diabetes mellitus	E10-E14
Angina pectoris	I20
Myocardial infarction	I21-I24
Cardiac arrest	I46
Cerebral infarction	I63
Nontraumatic subarachnoid hemorrhage, Nontraumatic intracerebral hemorrhage, Other and unspecified nontraumatic intracranial hemorrhage	I60-I62
Coronary artery disease	I20, I21, I22, I23, I24, I25
Prior CABG	Z951
Amputation (CPT codes)	27290, 27295, 27580, 27590, 27591, 27592, 27594, 27594, 27596, 27598, 27599, 27871, 27880, 27881, 27882, 27884, 27886, 27888, 27889, 28800, 28805, 28810, 28820, 28825, 0Y62, 0Y63, 0Y64, 0Y67, 0Y68, 0Y6C, 0Y6D, 0Y6F, 0Y6G, 0Y6H, 0Y6J, 0Y6M, 0Y6N, 0Y6P, 0Y6Q, 0Y6R, 0Y6S, 0Y6T, 0Y6U, 0Y6V, 0Y6W, 0Y6X, 0Y6Y
Revascularization (CPT codes)	0238T, 3722, 3723
Dialysis (CPT codes)	90935, 90937, 90940, 9095, 90960, 90989, 90993, 90997, 90999, S9335