**Trends in Rates of Lower Extremity Amputation and Contributing Factors Among Veterans in the United States, 2008-2018**

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**Abstract**

To be done after the draft is ready.

**Introduction**

Motivation and knowledge gap not filled yet. In this study, we characterized the trend of lower-extremity amputation (LEA) and three major risk factors (i.e. diabetes, chronic kidney disease (CKD), and smoking) among over 9 million veterans in the United States (US) from 2008 to 2018. Then, we examined the magnitude of risk factors associated with LEA among a longitudinal cohort of 6,617,635 US veterans. Based on the longitudinal cohort estimates, we further decomposed the incidence trend of LEA to three categories of risk factors: demographics, diabetes, CKD, and other clinical factors.

**Methods**

*Study Population*

We used the Corporate Data Warehouse at Department of Veterans Affairs (VA) databases in this study.1-9 The Department of Veterans Affairs has the largest integrated healthcare system in the US (the Veterans Health Administration, VHA), with 170 Medical Centers and 1,074 outpatient sites covering over 9 million veterans.10 We used the VA Managerial Cost Accounting System Laboratory Results to obtain selected inpatient and outpatient laboratory results, including low-density lipoprotein (LDL) and high-density lipoprotein (HDL).11 The United States Renal Data System (USRDS) was used to identify incidence of kidney transplantation and dialysis.12 The study was approved by the Institutional Review Board of the VA Saint Louis Healthcare System.

*LEA and the denominator*

LEA was identified using Current Procedural Terminology, 4th Edition (CPT-4), the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), or International Classification of Diseases, 10th Revision, Procedure Coding System (ICD-10-PCS) codes (Supplementary Table 1). It was further stratified into below ankle, below knee, and above knee LEA.

The number of US Veterans who had at least one inpatient or outpatient visit with the VA healthcare system between October 1, 2008 and September 30, 2018 were considered as the denominator to calculate the rate of LEA and clinical factors in each fiscal year. One patient can have at most one amputation per year, and if one patient had multiple types of LEA in a year, the highest level of LEA was considered (above knee > below knee > below ankle).

*Clinical factors*

The clinical factors associated with LEA were selected based on previous studies.13 CKD stages were determined using the average level (ml/min per 1.73 ) of Estimated Glomerular Filtration Rate (eGFR) in that year: eGFR >= 60 was defined as no CKD, eGFR between 45 and 59 was defined as CKD 3A, eGFR between 30 and 44 was defined as CKD 3B, eGFR between 15 and 29 was defined as CKD 4, and eGFR < 15 was defined as CKD 5 or end-stage renal disease (ESRD). ESRD was further categorized into ESRD, kidney transplantation, or dialysis using USRDS. Type 2 diabetes, cancer, cerebrovascular disease, cardiovascular disease, dementia, hypertension, chronic lung disease, and peripheral artery disease were defined using ICD codes (Supplementary Table 2).14 The VA transitioned from ICD-9 to ICD-10 coding system on October 1, 2015, so ICD-9 and ICD-10 codes were used before and after the transition date. Hyperlipidemia was defined as mean LDL level in that year greater than 190 mg/dl or mean HDL level in that year less than 40 mg/dl.

*Cohort Construction*

Figure 1 demonstrates the cohort construction process. The inclusion criteria were: 1) the veteran had at least one inpatient/outpatient visit or VA enrollment between October 1 2003 and September 30, 2008 (), 2) the veteran was not dead and had no LEA before T0, 3) The veteran had been in the VA healthcare system for at least one year to ensure their clinical diagnosis or laboratory checks are accurate stable. These inclusion criteria resulted in a longitudinal cohort of 6,617,635 veterans. The baseline clinical characteristics except for CKD and hyperlipidemia were identified using ICD-9-CM codes. Baseline CKD category was determined using the average eGFR level one year before using criteria defined above. Similarly, baseline hyperlipidemia was identified using average LDL and HDL level one year before .

*Statistical analysis*

We calculated crude rates, as well as age-, gender-, and race-adjusted LEA rates using direct standardization with the population structure in 2018 as the reference.15 The 95% confidence intervals (CIs) of the rates were calculated using normal approximation of binomial CI. To demonstrate the trend of LEA, we plotted the rates of LEA and by LEA types, as well as their 95% CIs by year. To show major risk factors of LEA, we stratified the rates of LEA by type 2 diabetes, CKD category, and smoking. Since the frequency of kidney transplantation and dialysis was very low and the rates were not stable, we combined them with ESRD as CKD 5 in the plots.

We used Cox proportional hazard models to measure the magnitude of baseline risk factors associated with LEA in the longitudinal cohort. Apart from the clinical factors, we also included baseline age, gender, race as covariates, and the age was included as a spline. In Cox regression models, hazard ratios (HRs) and 95% CI were reported. If 95% CI of the HR did not include one, the variable was considered statistically significant. All data cleaning and statistical modeling were performed using SAS Enterprise Guide Version 7.1. The data visualization was performed using R 3.5.1.16

**Results**

*Trend of LEA and major risk factors*

Table 1 presents the detailed information about VA healthcare system users, the number of amputations, and crude rates, as well as their 95% CIs from 2008 to 2018. There were around 4 million users each year and the number remained stable, while the number of amputations had a gentle increasing trend. Figure 2A show the trend of LEA rates, as well as their 95% CIs between fiscal year 2008 and 2018. There was a very moderate increasing or non-decreasing trend of LEA, which was primarily influenced by below ankle amputation (Figure 2B).

Figure 3 presents the rates of LEAs stratified by type 2 diabetes, CKD categories, and smoking status. The adjusted LEA rate was significantly higher among veterans with type 2 diabetes than those without type 2 diabetes (Figure 3A). There was a slight increase in adjusted LEA rate among type 2 diabetes group, while there was a moderate decrease among non-diabetes group (Figure 3B). Figure 3C shows that higher CKD levels had higher LEA rates, and there was a moderate increasing trend of LEA rates among different CKD groups (Figure 3D). Similarly, Figure 3E demonstrates current and former smoker had significant higher LEA rates than non-smokers, while the former smokers had LEA rates closer to never smokers. The LEA rate among different smoking groups had been consistently increasing from 2008 to 2018, and current and former smokers had a faster increasing trend than non-smokers.

Figure 4 demonstrates the maps of adjusted LEA rates by Federal Information Processing Standards (FIPS) code. The geographical distribution of LEA rates generally agreed with population density: higher LEA rates in Western coast and the East, but lower rates in the Midwest. We did not see significant changes in geographical distribution across 2008, 2013, and 2018.

*Risk profiling of LEA*

There were 6,617,635 participants (78.4% white; 93.4% male; median [interquartile range, IQR] age, 60.5 years [48.5-70.2]) in the overall cohort, who had 10,946 LEAs in a median follow-up time of 10.5 (IQR: 6.5-10.8) years. The demographic characteristics and clinical risk factors of the overall cohort and by amputation are shown in Table 2. Male other race veterans were more likely to have LEA than their counterparts. We can observe significantly higher rates of selected clinical factors among veterans who had one LEA than those who never had. It is to be noted that there were only slightly higher rates of former smokers among participants who had LEA than those who never had.

Table 3 presents the results of Cox regression models for any amputation, below ankle, below knee, and above knee amputation. The results were consistent across the four models. There was considerable disparity among different gender and race groups. The primary risk factors were type 2 diabetes, CKD, peripheral artery disease, and other race.

*Driving factors of LEA rate*

**Discussion**

Transition from ICD-9 to ICD-10.

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