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RESEARCH ARTICLE

Temporal Trends and Mortality Patterns in Peripheral Arterial Disease: A Comprehensive Analysis of Hospitalized Patients in Kazakhstan between 2014 and 2021

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Abstract

Background Peripheral artery disease (PAD) is a global health concern associated with arterial narrowing or blockage, leading to significant morbidity and mortality. The aim of this study is to assess the disease burden and trends in mortality utilizing nationwide administrative health data.

Methods This retrospective study utilized data from the Unified National Electronic Healthcare System (UNEHS) from 2014 to 2021. Patients meeting PAD criteria were included, with demographic and clinical data analyzed. Cox regression and Competing Risk Analysis assessed mortality risks.

Results Between 2014 and 2021, 19,507 individuals were hospitalized due to PAD, with 8,332 (43%) being women and 11,175 (57%) men. The incidence of PAD increased markedly over the observation period, rising from 79 individuals per million population (PMP) in 2014 to 309 PMP in 2021. Concurrent heart failure (HF), acute myocardial infarction (AMI), diabetes, and essential hypertension were prevalent in 50%, 27%, 27%, and 26% of the PAD patients, respectively. Competing Risk Analysis showed a subdistribution hazard ratio (SHR) of 6.53 [95% CI: 4.65–9.19] for individuals over 80 years. Heart failure was associated with lower all-cause HR [0.80, 95% CI: 0.76–0.86, $p < 0.001$] but higher SHR [1.30, 95% CI: 1.18–1.44, $p < 0.001$]. Comorbidities such as heart failure, stroke, and acute myocardial infarction significantly increased mortality risks, while essential hypertension was associated with lower risk of death.

Conclusion The significant rise in the incidence rate of PAD underscores the growing burden of the disease, highlighting the urgent need for targeted preventive and management strategies in Kazakhstan.

Keywords Peripheral Artery Disease (PAD) · Vascular Disease · Nationwide Administrative data · Competing risk Analysis · Charlson Comorbidity Index

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1 Introduction

Peripheral artery disease (PAD) arises from the narrowing or blockage of arteries responsible for delivering blood to the lower extremities, abdomen, arms and head, excluding coronary artery and aorta, with the primary cause being atherosclerosis. It is discerned from the term PAD, which is commonly used for lower extremity artery disease (LEAD) consistent with ESVS guidelines on PAD [1]. It presents significant challenges to healthcare systems globally, associated with functional deterioration, diminished mobility [2], and cardiovascular events such as acute coronary syndromes [3], strokes [4], limb amputations, and high mortality [5]. Approximately 60% of individuals diagnosed with peripheral artery disease also present with ischemic heart disease, while around 30% exhibit cerebrovascular disease [6]. Furthermore, between 40 and 60% of PAD patients die as a result of coronary artery disease, while 10–20% of deaths are attributed to cerebrovascular diseases, and another 10% result from other vascular events [7].

The Global Peripheral Artery Disease Study revealed that approximately 202 million individuals worldwide were affected by PAD in 2010, with nearly 70% of cases concentrated in low- and middle-income countries (LMIC) [8]. A more recent systematic review incorporating data from 118 studies across 33 countries estimated that approximately 237 million individuals aged ≥ 25 years were afflicted with PAD globally in 2015, with 73% of cases occurring in LMICs, with a higher proportion of affected women [9]. This translates into a 17% increase in prevalance over a five-year period. Moreover, the Global Burden of Disease Study indicated that there were 11 million incident cases of PAD in 2016 [10]. While the prevalence and mortality rates of cardiovascular diseases (CVDs), including PAD, are on the rise, there remains a scarcity of recent global epidemiological data on this particular disease. The incidence of cardiovascular diseases in Kazakhstan increased from 1845.5 to 2597.5 per 100,000 person between 2004 and 2017 [11]. In addition, all-cause death among stroke and acute myocardial infarction patients increased significantly from 2014 to 2019 [12, 13]. There is a paucity of data regarding the epidemiology of PAD in Kazakhstan. While stroke and ischemic heart diseases are acknowledged as serious conditions with significant burden to the healthcare system, the burden of PAD which could be as disabling does not receive a deserved attention. Therefore, the aim of this study is to assess the disease burden and trends in mortality utilizing nationwide administrative health data.

2 Methods

2.1 Study Design and Population

The data of this retrospective study were extracted from the Unified National Electronic Healthcare System (UNEHS) for the years 2014–2021. Details about UNEHS and its databases are provided elsewhere [14]. Patients meeting the criteria for PAD, as indicated by International Classification of Diseases (ICD) codes, were included in the analysis. A list of the relevant ICD-10 codes for PAD is provided in Supplementary Table 1. Following data cleaning and management procedures, the sample size consisted of 19,507 individuals with unique population registry numbers (RPN IDs). Population figures were obtained from the Statistics Committee of the Ministry of National Economy of the Republic of Kazakhstan [15].

2.2 Exposures and Covariates

The analysis incorporated data, including individuals' date of birth, sex, ethnicity, place of residence (urban or rural), date of PAD diagnosis, and, if applicable, date of death and cause of death. Age categories were defined according to stratification of the Centers for Disease Control and Prevention [16] as follows: (1) below 50 years, (2) 50–59 years, (3) 60–69 years, (4) 70–79 years., and (5) above 80 years. The study encompassed over 50 nationalities, with Kazakhs and Russians constituting the majority; hence, ethnicity was classified into Kazakhs, Russians, and others.

Comorbid conditions, including acute myocardial infarction (AMI), cerebrovascular diseases (CVD), heart failure (HF), chronic obstructive pulmonary disease (COPD), diabetes mellitus (DM), essential hypertension, atherosclerotic heart disease (ASHD), chronic kidney disease CKD), and obesity, were included in the analysis. In addition, the Charlson Comorbidity Index (CCI) was included as a continuous variable [17]. The CCI was utilized for standardized and objective assessment of comorbidity burden, aiding in risk adjustment, outcome prediction, and clinical decision-making. The identification of these diseases relied on ICD-10 codes, which are provided in Supplementary Tables 2, and data linkage was performed using unique RPN IDs.

2.3 Outcome Assessment

The subpopulation was assessed for the incidence of PAD, as well as all-cause mortality, and cause-specific mortality rates. The ICD-10 codes utilized to define cause-specific mortality are detailed in Supplementary Table 3. Any death that transpired during the observation period was recorded as all-cause mortality. The rates were computed by dividing the absolute numbers by the total population size at the end of each year.

In the survival analysis, the entry time was defined as the date of the initial admission, and the follow-up continued until the date of death or December 31, 2021, whichever occurred first. Censoring occurred for patients who were still alive at the end of the study period. For the Competing Risk Analysis, death from specific causes (related to PAD or cardiovascular disease) was considered the primary event of interest, while death from any other cause was treated as a competing event. The subdistribution hazard ratio (SHR) from the Fine-Gray model was used to quantify the association between covariates and the cumulative incidence of the primary event. The SHR represents the relative risk of the primary event happening in the presence of competing events, compared to a baseline reference.

2.4 Statistical Analysis

All characteristics were presented as categorical variables, with incidence, all-cause mortality, and cause-specific mortality rates evaluated as absolute numbers and rates per 1,000,000 population for each year of the observation period. After confirming the corresponding assumptions, Cox regression analyses were conducted to demonstrate crude and adjusted hazard ratios for all-cause and cause-specific mortality separately. Competing Risk Analysis (CRA), which extends the Cox proportional hazards model to competing-risks data by considering the subdistribution hazard [18], was employed, limiting the analysis to death related to PAD and death from other causes. The strength of association between each predictor variable and the outcome was assessed using the subdistribution hazard ratio (SHR) with its 95% confidence interval (CI), representing the ratio of hazards associated with the cumulative incidence function (CIF) in the presence and absence of a prognostic factor.

Three sets of multivariable analysis models were constructed to test the adjusted effect of variables on mortality for both analysis types. Models were incrementally adjusted for potential confounders depending on theoretical background and availability in the database. In the first model, only socio-demographic predictors (age, gender, ethnicity, and place of residency) were included. In the second model, comorbid conditions and CCI were added to Model 1. Model fit for Cox regression was evaluated using likelihood ratio (LR) test, and global goodness-of-fit test. In Competing Risk Analysis, comparison of cumulative incidence of the event of interest between groups was conducted using the Fine and Gray model [19]. The significance level was set at 0.05. All statistical analyses were performed using STATA 16.1.

This study used secondary data derived from the UNEHS, with no direct involvement of patients. Consequently, the requirement for informed consent from study participants was waived by the Nazarbayev University Institutional Review Ethics Committee (NU-IREC 490/18112021).

3 Results

3.1 Socio-demographic Characteristics

Table 1 outlines the baseline characteristics of the patients. Between 2014 and 2021, a total of 19,507 individuals were hospitalized due to peripheral artery diseases, with 8,332 (43%) being women and 11,175 (57%) men. Among the patients, only 1,214 (6%) were under the age of 50. The majority was Kazakhs (47%), residing in urban areas (76%). Comorbidities of heart failure (HF), cardiovascular disease (CVD), acute myocardial infarction (AMI), diabetes, and essential hypertension were present in 50%, 41%, 27%, 27%, and 26% of the subpopulation, respectively (Table 1).

The mortality rate per 100,000 patient-years among Russians was 49.4 [95% CI: 47.6–51.4], as opposed to Kazakhs: 25.9 [95% CI: 24.8–26.9], $p < 0.001$ (Table 1). Mortality rates categorized by Charlson Comorbidity Index (CCI) indicated that patients with 1–2 comorbidities had a rate of 27.9 [95% CI: 26.5–29.3], while those with a CCI of 7 or higher had a mortality rate of 61.8 [95% CI: 57.5–66.3] per 100,000 patient-years.

3.2 Incidence, all-cause and cause-specific Mortality

The age- and sex-specific incidence rate (IR) among PAD patients over the observation period is presented in Fig. 1. The IR among men rose dramatically till 70–75 years old, while for women, the growth is more gradual, peaking at 80–85 years of age. The IR based on hospital admission and discharge status increased significantly over the observation period: 79 people per million population (PMP) in 2014 and 309 PMP in 2021 (Fig. 2). The cause-specific mortality increased approximately tenfold during 2014–2021: from 4 PMP to 43 PMP. Approximately the same tendency was observed for all-cause mortality during the study period: from 11 PMP in 2014 to 88 PMP in 2021.

3.3 Hazard Ratios and Subdistribution Hazard Ratios by Predictors

According to the adjusted Cox regression analysis in Table 2, patients older than 80 years of age had all-cause HR of 7.92 [95% CI: 6.46–9.72], cause-specific HR of 8.54

Table 1 Baseline characteristics of all PAD patients between 2014 and 2021 in Kazakhstan

	Total ($n = 19,507$)	Women ($n = 8,332$; 43%)	Men ($n = 11,175$; 57%)	p-value	Mortality rate per 100,000 person-years [95% CI]
Demographics					
Age, n (%)				< 0.001	
<= 49 y.o.	1,214 (6)	452 (5)	762 (7)		8.88 [7.32–10.8]
50–59 y.o.	3,498 (18)	1,119 (13)	2,379 (21)		18.9 [17.7–20.4]
60–69 y.o.	7,077 (36)	2,635 (32)	4,442 (40)		31.4 [30.1–32.8]
70–79 y.o.	5,451 (28)	2,716 (33)	2,735 (24)		46.3 [44.4–48.3]
>= 80 y.o.	2,267 (12)	1,410 (17)	857 (8)		85.4 [80.8–90.3]
Ethnicity, n (%)				< 0.001	
Kazakh	9,075 (47)	3,593 (43)	5,482 (49)		25.9 [24.8–26.9]
Russian	6,899 (35)	3,132 (38)	3,767 (34)		49.4 [47.6–51.4]
Other	3,533 (18)	1,607 (19)	1,926 (17)		40.8 [38.6–43.1]
Residence, n (%)				< 0.001	
Urban	14,894 (76)	6,591 (79)	8,303 (74)		36.9 [35.9–38.0]
Rural	4,613 (24)	1,741 (21)	2,872 (26)		31.6 [29.9–33.3]
Comorbid conditions					
AMI	5,270 (27)	1,847 (22)	3,423 (31)	< 0.001	40.7 [39.1–42.4]
CVD	8,029 (41)	3,841 (46)	4,188 (37)	< 0.001	33.9 [32.7–35.2]
Stroke	2,256 (12)	886 (11)	1,370 (12)	< 0.001	63.6 [60.1–67.3]
HF	9,675 (50)	4,029 (48)	5,646 (51)	0.003	36.2 [35.1–37.4]
COPD	2,323 (12)	824 (10)	1,499 (13)	< 0.001	46.4 [43.7–49.3]
DM	5,343 (27)	2,762 (33)	2,581 (23)	< 0.001	41.8 [40.0–43.7]
Hypertension	5,135 (26)	2,444 (29)	2,691 (24)	< 0.001	28.4 [27.0–29.9]
ASHD	3,509 (18)	1,260 (15)	2,249 (20)	< 0.001	31.5 [29.7–33.3]
CKD	2,982 (15)	1,402 (17)	1,580 (14)	< 0.001	42.9 [40.7–45.4]
Obesity	1,918 (10)	1,041 (12)	877 (8)	< 0.001	31.5 [29.2–33.9]
Charlson Index				< 0.001	
1–2	7,850 (40)	3,170 (38)	4,680 (42)		27.9 [26.5–29.3]
3–4	6,995 (36)	2,985 (36)	4,010 (36)		33.0 [31.7–34.3]
5–6	3,293 (17)	1,520 (18)	1,773 (16)		45.7 [43.4–48.1]
>= 7	1,369 (7)	657 (8)	712 (6)		61.8 [57.5–66.3]

AMI– acute myocardial infarction; CVD - cerebrovascular diseases; HF– heart failure; COPD - Chronic obstructive pulmonary disease; DM - diabetes mellitus; ASHD - Atherosclerotic heart disease; CKD - chronic kidney disease

[95% CI: 6.08–12.0] with $p < 0.001$ for both. The unadjusted model and Model 1 for all-cause and cause-specific mortality analysis are presented in Supplementary Tables 4 and 5, respectively. On the other hand, the adjusted Competing Risk Analysis showed a SHR of 6.53 [95% CI: 4.65–9.19], $p < 0.001$, for the same group of people. The unadjusted model and Model 1 for Competing Risk Analysis are presented in Supplementary Table 6. All-cause HR for people of urban residency compared to rural ones was 1.09 [95% CI: 1.03–1.16] ($p = 0.006$), while SHR was 1.17 [95% CI: 1.05–1.29] ($p = 0.004$).

The change from lower to higher risk of death in different analysis types was shown for HF (Table 2). The HR for all cause mortality was 0.80 [95% CI: 0.76–0.86] with $p < 0.001$, while for cause specific mortality it was 1.17 [95% CI: 1.06–1.30] with $p = 0.002$. The adjusted Fine and Grey model showed that a history of stroke was associated with a 189% [SHR = 2.89, 95% CI: 2.61–3.22], MI with 57% [SHR = 1.57, 95% CI: 1.43–1.72], and HF with 30% [HR = 1.30, 95%CI: 1.18–1.44] higher risk of cause-specific death of PAD patients with other causes of death censored. On the other hand, results show that essential hypertension was associated with 11% [SHR = 0.89, 95% CI: 0.81–0.98, $p = 0.017$] lower risk of death in the subpopulation.

4 Discussion

This study represents the first comprehensive evaluation of the escalating burden of peripheral artery disease, encompassing assessments of both all-cause and cause-specific mortality in Kazakhstan, the largest Central Asian country. Over the period from 2014 to 2021, the incidence rate surged fourfold, accompanied by an eightfold increase in all-cause

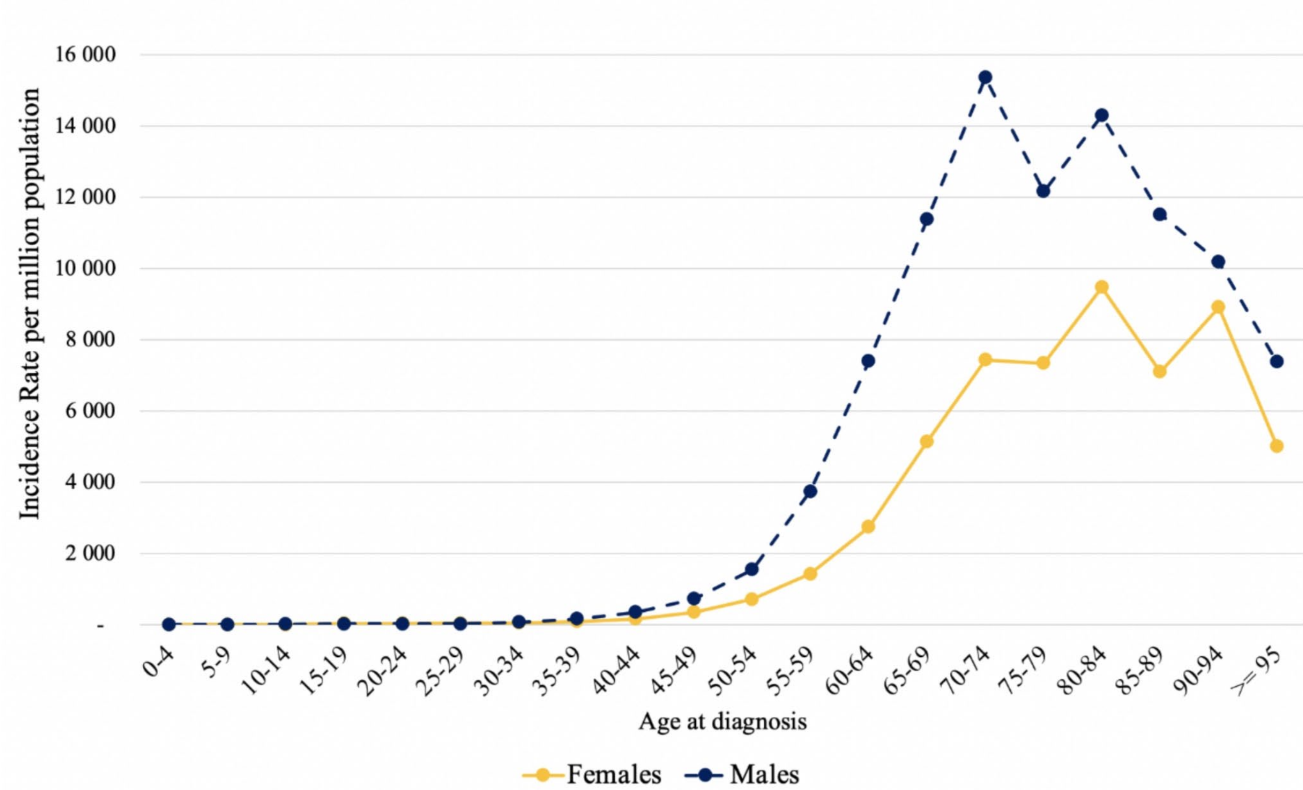

Fig. 1 Average age- and sex-specific incidence of PAD in Kazakhstan between 2014–2021

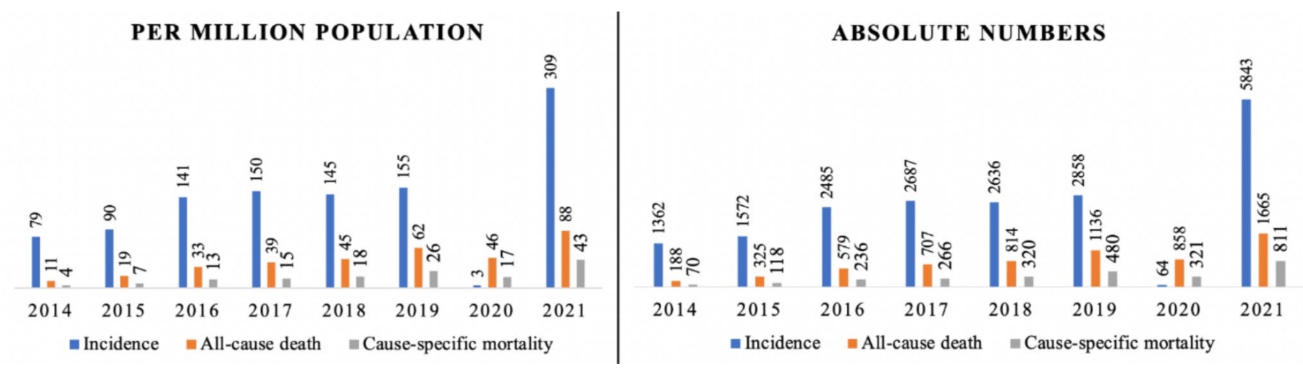

Fig. 2 Incidence, all-cause mortality and cause-specific mortality of PAD patients in Kazakhstan by years: (**a**) rate per million population; (**b**) absolute numbers

mortality and a tenfold rise in cause-specific mortality. This underscores the urgent need for heightened awareness, early detection, and effective management strategies to address the burgeoning burden of PAD in the region.

4.1 Incidence of Hospital Admissions of PAD

Our study findings reveal a notable increase in the incidence of hospital admissions of PAD beyond the age of 50, with a remarkable escalation observed with each successive decade, aligning with similar trends documented in international studies [20, 21]. Moreover, it is worthy of mention that the prevalence of PAD may be substantially underestimated, given that nearly 90% of cases remain asymptomatic and undetected [22, 23]. We suspect that the increase in the number of cases of the disease from 2014 to 2021 is likely in part results from improved diagnosis, given the chronic nature of PAD attributed to the accumulation of atherosclerotic plaques over the years, and commonly asymptomatic presentation. Concurrently, the decrease in 2020 can be linked to underdiagnosis due to lockdowns during the COVID-19 pandemic, when priority was given to infection prevention and management of critical conditions only [24]. The significant escalation of incidence in 2021 may indicate

Table 2 Association between socio-demographic factors, comorbidities, surgical interventions and mortality of PAD patients between 2014–2021

Variable	All-cause mortality		Cause-specific mortality		Cardiac mortality (other causes censored)	
	HR [95% CI]	p-value	HR [95% CI]	p-value	SHR [95% CI]	p-value
Demographic features						
Age (<=49 years (ref))						
50–59 years	2.03 [1.65–2.50]	< 0.001	2.06 [1.45–2.92]	< 0.001	1.99 [1.41–2.83]	< 0.001
60–69 years	3.09 [2.53–3.77]	< 0.001	3.02 [2.16–4.22]	< 0.001	2.75 [1.96–3.84]	< 0.001
70–79 years	4.61 [3.77–5.63]	< 0.001	5.01 [3.58–7.00]	< 0.001	4.33 [3.09–6.05]	< 0.001
>= 80 y.o.	7.92 [6.46–9.72]	< 0.001	8.54 [6.08–12.0]	< 0.001	6.53 [4.65–9.19]	< 0.001
Sex (Women (ref))						
Men	1.15 [1.09–1.21]	< 0.001	1.14 [1.05–1.24]	0.001	1.13 [1.04–1.22]	0.004
Ethnicity (Kazakh (ref)						
Russian	1.51 [1.43–1.60]	< 0.001	1.75 [1.60–1.92]	< 0.001	1.66 [1.51–1.81]	< 0.001
Other	1.28 [1.19–1.37]	< 0.001	1.47 [1.32–1.64]	< 0.001	1.44 [1.29–1.61]	< 0.001
Residence (Rural (ref))						
Urban	1.09 [1.03–1.16]	0.006	1.12 [1.01–1.24]	0.034	1.17 [1.05–1.29]	0.004
Comorbid conditions						
AMI	1.03 [0.97–1.10]	0.271	1.49 [1.36–1.64]	< 0.001	1.57 [1.43–1.72]	< 0.001
CVD	0.61 [0.58–0.65]	< 0.001	0.88 [0.80–0.98]	0.016	0.99 [0.90–1.10]	0.979
Stroke	2.21 [2.05–2.38]	< 0.001	3.13 [2.82–3.47]	< 0.001	2.89 [2.61–3.22]	< 0.001
HF	0.80 [0.76–0.86]	< 0.001	1.17 [1.06–1.30]	0.002	1.30 [1.18–1.44]	< 0.001
COPD	0.97 [0.89–1.04]	0.338	1.01 [0.89–1.13]	0.924	1.02 [0.91–1.15]	0.736
DM	0.73 [0.68–0.79]	< 0.001	0.98 [0.86 – 1.10]	0.708	1.03 [0.92–1.16]	0.597
Hypertension	0.77 [0.72–0.82]	< 0.001	0.84 [0.77–0.92]	< 0.001	0.89 [0.81–0.98]	0.017
ASHD	0.81 [0.76–0.87]	< 0.001	0.88 [0.79–0.97]	0.01	0.93 [0.84–1.03]	0.172
CKD	1.02 [0.95–1.09]	0.562	1.09 [0.98–1.21]	0.127	1.10 [0.99–1.23]	0.073
Obesity	0.91 [0.84–0.99]	0.034	0.91 [0.79–1.03]	0.138	0.92 [0.81–1.05]	0.221
CCI	1.25 [1.22–1.28]	< 0.001	1.05 [1.00–1.09]	0.017	0.99 [0.96–1.03]	0.798

AMI– acute myocardial infarction; CVD - cerebrovascular diseases; HF– heart failure; COPD - Chronic obstructive pulmonary disease; DM - diabetes mellitus; ASHD - Atherosclerotic heart disease; CKD - chronic kidney disease; CCI - Charlson Comorbidity Index

changes in the accessibility and quality of medical care [25], and the overall mortality has also increased, confirming this.

4.2 Sex, age and PAD

The results of this study highlight a delayed peak incidence of PAD in women compared to men, potentially attributable to the hormonal protective effects against endothelial dysfunction, a crucial initial step in atherosclerosis and PAD development [26, 27]. The differences in smoking habits between men and women, with a higher prevalence among men, may contribute to the observed sex disparities in PAD incidence as well [28]. Furthermore, prior studies conducted in Kazakhstan indicate that men, compared to women, exhibit a higher prevalence of established vascular disease risk factors, such as type 1 diabetes, as well as a history of acute myocardial infarction and stroke, which share underlying vascular pathophysiology with PAD [12, 13, 29].

4.3 Ethnicity and PAD

The results of the current study show that people of Russian ethnicity have approximately 2-fold higher mortality rates compared to Kazakhs. Similar results were found for other cardiovascular diseases in Kazakhstan [12, 13, 30]. In a population-based study by Sharygin and Gulliot, Russians had higher rates of adult mortality in contrast to Central Asians, with the observed discrepancy attributed to increased risk of death associated with alcohol consumption [31]. The body mass index (BMI), which varies among different ethnic groups, may also be responsible. A study conducted by Yelshibayeva et al. highlighted variations in coronary atherosclerosis characteristics among different ethnic groups in Kazakhstan, potentially indicating metabolic abnormalities influencing PAD [32]. Metabolic differences associated with BMI may modify the risk of PAD, underscoring the importance of considering ethnic characteristics in the development of prevention and treatment strategies.

4.4 Mortality of PAD Patients

According to global literature, the mortality rates among individuals with PAD rise significantly with advancing age, a trend consistent with the findings of our study. Over the observation period, there was a notable increase in both all-cause mortality, which rose 9-fold, and cause-specific mortality, which increased 12-fold. These trends align with similar observations reported worldwide [33]. The escalating mortality rates in PAD patients over time can be accounted for by various factors. First, there may be an upsurge in the prevalence of PAD-associated risk factors, including diabetes, essential hypertension, cardiovascular diseases, and smoking, consequently leading to a higher incidence of the disease and subsequent mortality. Predictive models from previous studies suggest a further increase in mortality rates by 2030 [34]. Second, demographic shifts, such as aging populations, and disparities in access to healthcare services may also play a role in the increasing mortality trends observed in PAD.

4.5 Cardiovascular Disease and PAD

The association between cardiovascular diseases (CVD) and mortality among patients with peripheral arterial disease (PAD) is widely recognized. Typically, the presence of one or more comorbid CVD increases the risk of death by over 40% [5]. However, in this study, acute myocardial infarction (AMI) and heart failure (HF) showed similar tendencies for cause-specific mortality, while hypertension and atherosclerotic heart disease (ASHD) displayed a declining trend. One possible explanation is that individuals with hypertension may demonstrate better treatment compliance and receive more attentive care, resulting in a higher percentage of treatment control within this population. For example, research indicates that adherence to pharmacotherapy for hypertension one year after initiation of treatment is typically reported in less than 50% of patients [35, 36]. Patients with AMI and HF may have advanced PAD as a manifestation of long-term severe atherosclerosis, as opposed to people with hypertension and early atherosclerosis, with asymptomatic or mild PAD [37, 38]. A cross-sectional study among the Kazakhstani population revealed that a majority of hypertensive individuals were taking antihypertensive medications, suggesting a more likely blood pressure control [39]. In this study, only essential hypertension was considered as a comorbid condition. Studies suggest that patients newly diagnosed with hypertension who exhibit good or intermediate adherence to therapy have lower mortality rates compared to those with poor adherence [40, 41]. It is essential to note that factors not considered in this study may have had confounding effects and could potentially explain the lower mortality rates among individuals with essential hypertension. Additionally, the inclusion of information on other diseases closely linked to hypertension and ASHD may have reflected their true effects on PAD patients.

4.6 Cerebrovascular Disease and PAD

Peripheral artery disease serves as a sensitive indicator of other manifestations of atherosclerosis, including cerebrovascular diseases [42]. The association between stroke and higher risk of death among PAD patients, as indicated by our study results, underscores the significant impact of cerebrovascular complications on the prognosis of individuals with PAD. This finding is consistent with existing literature that highlights the adverse outcomes associated with stroke in this patient population [43, 44]. One possible explanation for the increased risk of death among PAD patients with stroke is the compounded burden of atherosclerotic disease affecting multiple vascular beds. Stroke represents a critical event in the natural history of atherosclerosis, often resulting in substantial neurological deficits and functional impairments [45, 46]. These disabilities can significantly impact the overall health status and quality of life of PAD patients, making them more vulnerable to adverse cardiovascular events and mortality.

4.7 COPD, CKD and PAD

Both PAD and COPD share common risk factors, such as smoking, advanced age, and systemic inflammation, which can contribute to the development and progression of both diseases [47]. These shared risk factors may lead to a higher prevalence of COPD among PAD patients, as observed in accordance with the results of the current study. COPD is associated with systemic inflammation, oxidative stress, and endothelial dysfunction, which can promote the progression of atherosclerosis and exacerbate vascular damage in PAD [48]. Additionally, COPD-related hypoxemia and impaired pulmonary function can intensify cardiovascular strain, resulting in increased cardiac workload and a higher risk of adverse cardiovascular events, including myocardial infarction and heart failure, which are major contributors to mortality in PAD patients [47]. As for the CKD, only Competing Risk Analysis showed significant increase of mortality risk among PAD patients. CKD and PAD often coexist due to shared risk factors, which can mutually exacerbate each other, leading to a vicious cycle of worsening clinical outcomes. CKD is associated with systemic inflammation, endothelial dysfunction, and accelerated atherosclerosis, all of which contribute to the pathogenesis and progression of PAD as well [49].

4.8 Diabetes, Obesity and PAD

The relationship between diabetes, obesity and PAD is straightforward. Comorbid diabetes and obesity can significantly impact the mortality in PAD patients [50, 51]. Individuals with diabetes often experience accelerated atherosclerosis due to chronic hyperglycemia, insulin resistance, dyslipidemia, and endothelial dysfunction [52]. Consequently, diabetic PAD patients are at higher risk of critical limb ischemia, non-healing wounds, and lower limb amputations, all of which increase the likelihood of mortality. While diabetes and obesity are independently associated with PAD, the findings of this study did not reveal a significant impact thereof on mortality risks. This lack of significance may be ascribed to the presence of other comorbid conditions in the analysis.

Despite the expected association of obesity with chronic low-grade inflammation, insulin resistance, dyslipidemia, and endothelial dysfunction, all of which can exacerbate the progression of atherosclerosis and peripheral arterial damage, certain studies suggest a protective effect of obesity on disease development and progression, a phenomenon referred to as the "obesity paradox" [53]. It can be explained by possible genetic factors evaluated through mendelian randomization studies, dysfunction of adipose tissue, and body fat distribution rather than mere adiposity [54].

4.9 Strengths and Limitations

The epidemiological evaluation conducted in this study offers several notable insights. Firstly, it presents a thorough depiction of PAD in Kazakhstan. The absence of large studies examining PAD incidence and mortality using nationwide databases in Central Asian nations further underscores the significance of these findings. Our results have the potential to inform the development of enhanced protocols and strategies for PAD management within healthcare systems, taking socio-demographic variables and cultural nuances into account.

However, despite these strengths, several limitations are worthy of mention. First, relying solely on hospitalization records captures only a portion of PAD cases, overlooking asymptomatic patients and outpatients hence potentially underestimating PAD incidence and mortality rates. Second, the dataset used lacks some key information such as smoking habits, ankle-brachial index, lipid profiles, body mass index (BMI), physical activity, and specific medications, which are critical both in risk and outcomes. Without these data, it is difficult to fully comprehend which factors causally, if any, affect the outcomes. Additionally, the regression effect estimates for mortality may be influenced by the lack of control for unmeasured confounders. Given the absence of abovementioned key information, the effect estimates could be biased, potentially affecting the interpretation of associations between covariates and mortality outcomes. As a result, caution is advised when interpreting these findings, as unmeasured confounders could alter the observed relationships.

5 Conclusion

This study represents the first investigation on the prevalence and impact of peripheral artery disease in Kazakhstan, marking a significant contribution to our understanding of this condition within the largest Central Asian nation. Through a retrospective analysis of nationwide health system records spanning from 2014 to 2021, our findings reveal a notable rise in the incidence of PAD, which, in turn, contributes to the overall disease burden. This increase highlights the pressing need for improved strategies in both the management of PAD and the implementation of preventive measures. These results provide a crucial resource for health policymakers as they develop more effective interventions aimed at reducing the growing burden of PAD in Kazakhstan.

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Author Contributions All authors approved the final version of manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GZ analyzed and interpreted data and drafted the article. AA involved in interpretation of data and drafting the article. SY involved in acquisition of data and revision of the manuscript. TA involved in interpretation of data and drafting the article. YeS involved in analysis of data and article drafting. DV and IF involved in acquisition of data and revision of the manuscript. AS and YaS involved in interpretation of data and drafting the article. ZM and ZY involved in conception and design of study and revised the article. AG involved in interpretation of data and revision of the manuscript. All authors read and approved the final version of the manuscript.

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Data Availability The data that support the findings of this study are available from the Republican Center for Electronic Health of the Ministry of Health of the Republic of Kazakhstan but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author, Gaipov A., upon reasonable request and with permission of the Ministry of Health of the Republic of Kazakhstan.

Declarations

Ethics Approval and Consent to Participate The study was approved by the Institutional Review Ethics Committee of Nazarbayev University (NU-IREC 490/18112021), with exemption from informed consent.

Consent for Publication Not applicable.

Competing Interests The authors declare no competing interests.

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