

Macrovascular Complications in Patients with Diabetes Mellitus: Incidence and Impact on Survival in Kazakhstan

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Abstract

Background and aim: Diabetic patients are at an increased risk for the development of macrovascular complications such as acute myocardial infarction (AMI), stroke and lower-limb amputations (LLA). This study aimed to explore a. the incidence of hospital admission for macrovascular complications (AMI, stroke, and LLA); b. to assess the impact of hospital admission on survival in a large population with diabetes mellitus living in Kazakhstan.

Materials and methods: Retrospective observational study using a nationwide anonymized electronic database of 98.469 hospitalized diabetic patients from Kazakhstan between November 2013 and December 2019. The incidence of hospital admissions for AMI, stroke and LLA were obtained to calculate their all-time cumulative incidence, and survival rate at follow-up.

Results: The all-time cumulative incidence of hospital admissions was 1.30% for AMI, 1.94% for stroke and 2.94% for LLA. The incidence of macrovascular complications was statistically significantly higher in males compared to females (p -value<0.05). 29.03% of diabetic patients with AMI, 25.16% with stroke and 29.80% with LLA died during the follow-up period. Individuals with AMI had 3.58 (95% CI 3.20; 4.01) times, with stroke 3.86 (95% CI 3.52; 4.24) times and with LLA 3.63 (95% CI 3.38; 3.88) times higher hazard of 6-year death compared to diabetic patients free of these complications. The stratified survival analysis by sex indicated the lower survival in women than in men, and the lower survival in older age groups.

Conclusion: The results from this study shows that cumulative incidence of AMI and stroke among diabetic patients admitted in the hospitals in Kazakhstan between 2013-2019 years was similar to the estimates from other countries, but the incidence of LLA was significantly higher in Kazakhstan. Patients with diabetes mellitus (DM) in Kazakhstan are at high risk of excess mortality if they suffer from macrovascular complications. More research is required to explore the reasons for the high incidence of those complications, in order to propose systematic solutions for lowering the incidence and improve survival.

Introduction

The prevalence of DM is increasing from year to year. Thus, if in 2017 DM cases reached staggering 451 million worldwide (among 18–99 years old), by 2045, it is projected to hit 693 million cases [1]. The mortality rate of DM was around 5 million (among 20–99 years old) in 2017 that is almost 10% of all deaths worldwide [1]. According to the International Diabetes Federation, the prevalence of DM in Kazakhstan was 6.2% (1.15 mln individuals) in 2019 [2]. The study NOMAD estimated a period prevalence between 2014–2016 of 8.2% [3]. High prevalence and mortality rates have a dramatic impact on healthcare expenditures. In 2017, the global expenditure on DM patients, aged 18–99 years, reached 850 billion USD, and it is expected to rocket up to 958 billion USD by 2045 [1].

Patients with diabetes mellitus are at high risk of cardiovascular complications with approximately a two-fold increased risk compared to non-diabetic subjects. These complications are also associated with an

increased risk of death [4]. In particular, diabetic patients with acute cardiovascular diseases (CVD) such as acute myocardial infarction (AMI), stroke and lower limb amputation (LLA) have a 4-fold increase in mortality rate compared to diabetic patients without such complications [5, 6].

According to the Global Burden of Diseases, from 1990 through 2019, the disability adjusted life years (DALYs) for diabetic patients increased to 24.4%, ranking the disease at the 6th place among causes of the burden of disease [7]. In order to slow down the increasing public health impact of DM, it is crucial to explore complications of DM patients and address targeted measures against them [8].

Obviously, there are huge gaps in the valid knowledge about the incidence of DM-related complications, including acute cardiovascular and cardio-cerebral events, as well as lower limb amputations. Most research evidence comes from high-income countries that represent about 10% of the global population, while there are scanty data on the situation in Central Asia, particularly in Kazakhstan.

With these concepts in mind, we aimed to a. Determine the incidence of hospital admission for macrovascular complications (AMI, stroke, and LLA); b. Assess the impact of hospital admission on survival in a large population with DM living in Kazakhstan.

Methods

Data source and study population

This retrospective observational study used a nationwide anonymized database of hospitalized diabetic patients from Kazakhstan obtained from the Republican Center of Electronic Healthcare. Inclusion criteria was a) age > 18 years, and b) hospital admission with a diagnostic code of DM (all types) between 3 November 2013 and 31 December 2019. The database consisted of 652,048 observations. One single hospitalization may have multiple observations, as these represent claims submitted for specific medical procedures that may occur during the same hospitalization. Patients were identified by RpnID - a unique individual population registry number, which is used across all electronic health systems. 91,108 diabetic patients with unique RpnID numbers were identified. Apart from that, 48,559 (7.4%) observations did not include RpnID. A probabilistic approach for imputation of missing data was applied by finding duplicates among existing RpnID numbers based on the following five variables: birth date, sex, ethnicity, home address and region of residence. Following this, 17,342 observations that did not include RpnID were replaced by existing RpnID numbers. The remaining 31,217 observations were assigned with new 7,361 unique RpnID, which had the identical information for birth date, sex, ethnicity and region. Overall, firstly, after deleting 4,336 duplicates of RpnID by all variables, and then, 549,243 duplicates of RpnID separately for observations with and without complications of interest the database consisted of 98,469 diabetic patients with corresponding RpnID numbers, including an array of demographic and social covariates. The flow-chart of the data cleaning process is illustrated in Fig. 1.

Variables

We identified incident cases of the three DM-related complications of interest applying International Classification of Diseases codes, Tenth Revision (ICD-10) and International Classification of Diseases codes, Ninth Revision (ICD-9): AMI, both haemorrhagic and ischaemic strokes, LLA (including toe, foot, amputation below knee or other unspecified LLA). The specific codes utilized were: for AMI ICD-10 codes of I21, I22, I23, I24, for stroke ICD-10 codes of I61, I63, I62, I64 codes, for LLA ICD-9 codes of 84.10, 84.11, 84.12. For descriptive statistics, categorical age (< 54, 54–65, > 65 years), sex (male, female), ethnicity (kazakh, russian, other), region of residence (north, south, east, west and central) and residency (urban, rural) variables were used. The primary outcomes were incidence of hospital admissions for the above mentioned DM-related complications and following death.

Data analysis

Statistical calculations were performed using STATA 16 statistical software (StataCorp) [9]. The descriptive statistics of study population and all-time cumulative incidence of DM-related complications was calculated and presented as percentages. Additionally, case fatality rates for each complication were estimated and compared at their 1st, 7th and 28th days. Following this, crude and stratified by age categories and sex, non-parametric Kaplan-Meier survival curves were assessed for AMI, stroke and LLA among hospitalized diabetic patients. Patients were followed up from the day of hospital admission (day 1). The last day of follow-up was the death date or the last day of observation period (December 2019). The log-rank test was used to compare survival between groups. Statistical significance was considered at p-value < 0.05. Cox proportional hazards regression was used to estimate unadjusted effect size estimates.

Ethics

The study was approved by the Institutional Research Ethics Committee (NU IREC #203/29112019).

Results

Baseline characteristics

The population analyzed in this work consists of 98,469 patients with a mean follow-up period of 3.42 ± 1.78 years (range 0 to 6.17 years). 37.28% were younger than 54 years, and 29.15% were older than 65 years. 59.82% were females. Ethnicity information was divided into three groups: Kazakhs (60.14%), Russians (19.29%) and Others (20.57%). In addition, 59.14% of the patients were from urban settings. Database also contained information about the regions of Kazakhstan, where the hospitalization took place. The 17 regions registered in the database were divided into five categories: North (24.30%), South (23.55%), East (29.01%), West (14.03%) and Central (9.11%) (**Table 1**).

Incidence of macrovascular complications

The all-time cumulative incidence of AMI, stroke and LLA was 1.30%, 1.94% and 2.94%, respectively. (**Table 1**).

Sex-stratified incidence of three complications was calculated. The incidence of AMI and stroke was higher in males compared to females (1.45% vs 1.19%, $p<0.001$, and 3.67% vs 2.45%, $p<0.001$, respectively, while the incidence of stroke was similar (1.95% in males vs 1.93% in females, p -value 0.06). **(Figure 2a)**.

In addition, age-stratified incidence of AMI, stroke and LLA variables were calculated. The incidence of AMI was 0.57% in the younger than 54 years group, and it was 2.5 fold lower than in the 54-65 years group (1.43%), 3.6 times lower than in the older than 65 years group (2.08%), (p -value <0.001). The incidence of stroke showed the same trend and it was 0.93%, 2.26% and 2.85%, respectively. Almost the same situation in the LLA variable. Incidence of 1.26% of the younger than 54 years group was the lowest, and it was lower for 2.5 times than in the 54-65 years group (3.16%) and 3.8 times lower than in the older than 65 years group (4.85%), (p -value <0.001) **(Figure 2b)**.

Survival analysis

Overall, 29.03% of patients with AMI, 25.16% of patients with stroke and 29.80% with LLA died during the follow-up period. Mortality after the first event of AMI and stroke at 1st, 7th and 28th days was: 8.76%; 16.0%; 19.72% for AMI and 2.52%; 9.33%; 14.36% for stroke.

According to the Kaplan-Meier survival curves **(Figures 3a-3d)**, diabetic patients with any of these macrovascular complications had lower survival in comparison with individuals without these complications (p -value <0.001 for all graphs). Individuals with AMI had 3.58 (95% CI 3.20; 4.01) times, with stroke 3.86 (95% CI 3.52; 4.24) times and with LLA 3.63 (95% CI 3.38; 3.88) times higher hazard of 6-year death compared to diabetic patients free of complications.

Even though, the incidence of DM-related complications was higher in men than in women, the sex-stratified survival analysis showed that men had better survival than women, while age-stratified analysis demonstrated the patients older than 54 years showed lower survival than the same individuals younger than 54 years **(Figures 4a-4c, Figures 5a-5c)**.

The stratified analysis by sex showed that survival after AMI was lower among women than in men (HRs of mortality 4.30 (95% CI 2.75; 4.94) vs. 2.78 (95% CI 2.30; 3.37)) **(Figures 6a-6b)**. While stratified analysis of survival following AMI by age categories demonstrated that diabetics at younger age groups had higher survival after AMI than older groups. HRs of mortality among diabetics after AMI aged younger than 54 years were higher than HRs among individuals aged 54-65 and 65 years, 4.78 (95% CI 3.32; 6.93) vs. 2.85 (95% CI 2.30; 3.54) and 2.68 (95% CI 2.33; 3.08) respectively **(Figures 6c-6e)**.

Additionally, the survival during this period after first hospitalization due to stroke was lower among women than in men with HRs 4.26 (95% CI 3.80; 4.77) vs. 3.25 (95% CI 2.76; 3.83) **(Figures 6a-6b)**. Trend was similar with regard to age - 54-65 and older than 65-year old patients had lower survival after the first stroke event than individuals younger 54 years. HRs were 4.40 (95% CI 3.24; 5.98) among patients

younger than 54 years, 3.48 (95% CI 2.92; 4.14) among those aged 54-65 years and 2.91 (95% CI 2.59; 3.28) among diabetics older than 65 years (**Figures 6c-6e**).

Sex-stratified cumulative survival analysis after first hospitalization due to LLA indicated that women had higher risk of mortality than men with HR 4.07 (95% CI 3.71; 4.46) vs. 3.26 (95% CI 2.93; 3.63) (**Figures 6a-6b**). In age-stratified analysis, 54-65 years old and older than 65 years diabetic individuals after LLA showed lower survival in comparison with the patients at age younger than 54. Stratified HRs were 3.75 (95% CI 2.92; 4.82) among patients younger than 54 years, 3.42 (95% CI 2.99; 3.89) among those aged 54-65 years and 2.46 (95% CI 2.25; 2.68) among diabetics older than 65 years (**Figures 6c-6e**).

Discussion

This is the first and largest observational retrospective study with electronic health data from all over Kazakhstan, shedding a light on the incidence of macrovascular complications and their impact on survival among diabetic patients and corroborating that the global unmet need associated with macrovascular complications also affects the Kazakhstani diabetic patients.

According to the results, cumulative incidence of AMI, stroke, and LLA was 1.30%, 1.94%, and 2.94%, respectively. Those complications have a significant impact on survival of diabetic patients.

Ischemic heart disease and cerebrovascular disease represents the main causes of life lost to premature death in Kazakhstan [10]. Cardio-metabolic factors related with DM and their vascular complications, as dietary risks, high systolic blood pressure and high body mass index were the highest ranked risk factors for disease burden in Kazakhstan. Despite of progress due to reform over the past few years resulting in improvements in prevention and management of non-communicable disorders in the country [11], those health problems still have a significant public health impact and call for continuing strengthening of the health system to respond to their significant burden, including the evaluation of those interventions [12]. Along with increasing incidence and prevalence of DM in Kazakhstan, about 80% of diabetic patients are overweight or obese and uncontrolled elevated blood pressure is also highly prevalent, factors that contribute to the development of DM-related micro- and macrovascular complications [13–15].

The incidence of AMI found in this work is lower than has been reported in Africa, Americas, Europe and Eastern Mediterranean, but higher than in South-East Asia and Western Pacific; stroke was higher in Europe and Western Pacific, and lower in Africa, Americas, South-East Asia and Eastern Mediterranean. Studies from Spain and Israel with hospitalized diabetic patients reported a similar 2.0–3.0% incidence of AMI [16, 17].

LLA were significantly higher in Kazakhstan than in any of those regions [18]. LLA has shown incidence ranging from 0.02–2.48% [19–21]. The higher observed incidence of LLA in our study could be associated with high prevalence of risk factors among diabetic patients in Kazakhstan [19], resembling the trends in low- and middle-income countries (LMICs), where the incidence is increasing, possibly due to poor control of vascular risk factors among diabetic patients.

We observed a higher incidence of AMI, stroke and LLA in men [19–26], while mortality was higher in women compared to men [26–28]. Although there is still a gap in explanation of this observation, previously it was found that diabetic women had a higher overall CVD risk at baseline [29], including higher body fat percentage and higher abdominal fat, a factor that is associated with insulin-resistance, but also were less likely to reach recommended levels of low-density lipoprotein (LDL) and cholesterol [30, 31]: men may be treated more intensively [32]. But, there could be other socio-economic factors associated with sex-differences in mortality after macrovascular complications in diabetic patients [33]. Regarding LLA, men could seek less foot care and have a greater risk for development of foot ulcers, which is associated with higher incidence of LLA [20].

The incidence of all macrovascular complications in our study increased with age: factors like a higher presence of comorbidities, obesity, low level of physical activity, hyperglycemia and a longer duration of the disease are risk factors positively associated with CVDs and LLA [34]. Older age has been consistently associated with higher incidence of stroke and AMI [35]. However, fewer studies reported the incidence stratified by age categories for AMI, stroke and LLA [17, 20, 28].

Mortality rates for these complications were almost similar: 29.03% for AMI, 25.16% for stroke and 29.80% for LLA during the follow-up. The 5-year mortality rate due to AMI and stroke in other studies varied between 13.9%-50% [36–40] having been reported to be 62% for LLA [41].

Mortality reflects an increased risk of post-hospitalization mortality [37, 38, 42–44]. Overall, diabetic patients suffering from AMI, stroke or LLA have a significantly higher risk of death during 6 year of follow up [4, 45]. Some differences observed in the estimates from other studies could be partially explained by the diversity of data sources and methodologies applied in each study, by the heterogeneity in the characteristics of study populations, but may also be associated with the variations in care for diabetic patients in different countries.

Strengths and limitations.

Overall, this observational retrospective study has certain strengths. First, we have investigated the incidence of macro-vascular complications using a large database that covered all hospitalization cases with DM from all regions of Kazakhstan. We assume that the findings reflected the real situation of incidence and mortality after those events. To our knowledge, this is the first study in Kazakhstan and Central Asia to utilize such a large database, therefore representing an important contribution to understand the epidemiology of DM-related macrovascular complications in Kazakhstan.

Inevitably, this research has several limitations. Even though this study utilized a representative sample of diabetic patients, some major variables were not available for the analysis, including the type of DM, duration of DM, treatments, laboratory measures or comorbidities, including obesity, or health behaviors such as smoking or alcohol consumption, or lifestyle factors, such as level of physical activity and eating behavior. It is possible that the hospitalized population might be at a more progressed stage of the disease and have been prescribed different medications, which might affect consequent complications.

Secondly, we used a probabilistic approach for imputations of missing RpnID, thus, our estimates of incidence could be underestimated. Third, there could be potential misclassification bias as diagnosis of DM and DM-related complications were defined by ICD-9 and ICD-10 codes. Fourth, the mortality rates for AMI and stroke could be underestimated as some cases could be coded with codes for main hospitalization reasons which might not be related to them.

Conclusion

This data demonstrates that patients with DM in Kazakhstan are at high risk of excess mortality if they suffer from macro-vascular complications, AMI, stroke and LLA. More research is required to characterize sub-populations of diabetic patients at higher risk for the incidence of those complications, but it is also important that Kazakhstan continues to improve the quality of care of its healthcare system to provide the integrated care required for managing a complex condition as DM.

Abbreviations

AMI: acute myocardial infarction; LLA: lower limb amputations; DM: diabetes mellitus; CVD: cardiovascular diseases; ICD-10: International Classification of diseases, Tenth Revision; ICD-9: International Classification of Diseases, Ninth Revision; LMICs: low- and middle-income countries; LDL: low-density lipoprotein.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Research Ethics Committee (NU IREC #203/29112019).

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from 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 the contract-agreement for the current study, and so are not publicly available. Data is however available from the authors upon reasonable request and with permission of Ministry of Health of the Republic of Kazakhstan.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ASS contributed to conception, study design, data acquisition, analysis, interpretation of the data, literature search, wrote and drafted the first manuscript and provided final approval for the submission. BO, TM contributed to data analysis, interpretation of the data, literature search, wrote and drafted the first manuscript and provided final approval for the submission. AS, NG, AG: Analyzed and interpreted the data; Reviewed the manuscript. All authors read and approved the final manuscript.

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References

1. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*. 2018 Apr;138.
2. International Diabetes Federation. Ninth edition. 2019. <https://diabetesatlas.org/en/resources/> Accessed 19 Apr 2021.
3. Toktarova Naila BRDA. The prevalence of type 2 diabetes mellitus among the adult population of Kazakhstan (results of the NOMAD registry national study). [in Russian]. *Medicine (Almaty)*. 2017;6(180):43–51.
4. Tancredi M, Rosengren A, Svensson A-M, Kosiborod M, Pivodic A, Gudbjörnsdottir S, et al. Excess Mortality among Persons with Type 2 Diabetes. *New England Journal of Medicine*. 2015 Oct 29;373(18).
5. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson A-M, Miftaraj M, et al. Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes. *New England Journal of Medicine*. 2017 Apr 13;376(15).

6. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018 Nov;392(10159).
7. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 2020 Oct;396(10258).
8. Harding JL, Pavkov ME, Magliano DJ, Shaw JE, Gregg EW. Global trends in diabetes complications: a review of current evidence. *Diabetologia*. 2019 Jan 31;62(1).
9. StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.
10. Institute for Health Metrics and Evaluation (2015). Country profile: Kazakhstan. Seattle, WA.
11. World Health Organization. Better noncommunicable disease outcomes: challenges and opportunities for health systems. 2014.
12. Knai C, Nolte E, Brunn M, Elissen A, Conklin A, Pedersen JP, et al. Reported barriers to evaluation in chronic care: Experiences in six European countries. *Health Policy*. 2013 May;110(2–3).
13. World Health Organization. Kazakhstan. Nutrition, Physical Activity and Obesity. 2013. https://www.euro.who.int/__data/assets/pdf_file/0019/243307/Kazakhstan-WHO-Country-Profile.pdf?ua=1 Accessed 29 Mar 2021
14. Helble M, Francisco K. The imminent obesity crisis in Asia and the Pacific: first cost estimates. Asian Development Bank Institute Working Paper Series. 2017;
15. Supiyev A, Kossumov A, Kassenova A, Nurgozhin T, Zhumadilov Z, Peasey A, et al. Diabetes prevalence, awareness and treatment and their correlates in older persons in urban and rural population in the Astana region, Kazakhstan. *Diabetes Research and Clinical Practice*. 2016 Feb;112.
16. Issa M, Alqahtani F, Ziada KM, Stanazai Q, Aljohani S, Berzingi C, et al. Incidence and Outcomes of Non-ST Elevation Myocardial Infarction in Patients Hospitalized with Decompensated Diabetes. *The American Journal of Cardiology*. 2018 Oct;122(8).
17. Reges O, Leibowitz M, Hoshen M, Leventer-Roberts M, Greenland P, Balicer R. Diabetes control: Incidence of acute myocardial infarction and all-cause mortality among patients with 3–6 years' disease duration. *European Journal of Preventive Cardiology*. 2017 Jul 7;24(10).
18. Kosiborod M, Gomes MB, Nicolucci A, Pocock S, Rathmann W, Shestakova M v., et al. Vascular complications in patients with type 2 diabetes: prevalence and associated factors in 38 countries (the DISCOVER study program). *Cardiovascular Diabetology*. 2018 Dec 28;17(1).
19. Sarfo-Kantanka O, Sarfo FS, Kyei I, Agyemang C, Mbanya JC. Incidence and determinants of diabetes-related lower limb amputations in Ghana, 2010–2015- a retrospective cohort study. *BMC Endocrine Disorders*. 2019 Dec 1;19(1).
20. Gandhi SK, Waschbusch M, Michael M, Zhang M, Li X, Juhaeri J, et al. Age- and sex-specific incidence of non-traumatic lower limb amputation in patients with type 2 diabetes mellitus in a U.S. claims database. *Diabetes Research and Clinical Practice*. 2020 Nov;169.

21. Fosse S, Hartemann-Heurtier A, Jacqueminet S, Ha Van G, Grimaldi A, Fagot-Campagna A. Incidence and characteristics of lower limb amputations in people with diabetes. *Diabetic Medicine*. 2009 Apr;26(4).
22. Lopez-de-Andres A, Jimenez-Garcia R, Hernandez-Barrera V, Jimenez-Trujillo I, Gallardo-Pino C, de Miguel AG, et al. National Trends over One Decade in Hospitalization for Acute Myocardial Infarction among Spanish Adults with Type 2 Diabetes: Cumulative Incidence, Outcomes and Use of Percutaneous Coronary Intervention. *PLoS ONE*. 2014 Jan 15;9(1).
23. Dumitra Bălan PAB. Incidence and type of stroke in patients with diabetes. Comparison between diabetics and nondiabetics. *ROMANIAN JOURNAL OF INTERNAL MEDICINE*. 2009;47(3):249–55.
24. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. *The Lancet*. 2014 Jun;383(9933).
25. Li T-C, Wang H-C, Li C-I, Liu C-S, Lin W-Y, Lin C-H, et al. Establishment and validation of a prediction model for ischemic stroke risks in patients with type 2 diabetes. *Diabetes Research and Clinical Practice*. 2018 Apr;138.
26. Glovaci D, Fan W, Wong ND. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. *Current Cardiology Reports*. 2019 Apr 4;21(4).
27. Roche MM, Wang PP. Sex Differences in All-Cause and Cardiovascular Mortality, Hospitalization for Individuals With and Without Diabetes, and Patients With Diabetes Diagnosed Early and Late. *Diabetes Care*. 2013 Sep;36(9).
28. Alonso-Morán E, Orueta JF, Esteban JIF, Axpe JMA, González MLM, Polanco NT, et al. The prevalence of diabetes-related complications and multimorbidity in the population with type 2 diabetes mellitus in the Basque Country. *BMC Public Health*. 2014 Dec 10;14(1).
29. Juutilainen A, Kortelainen S, Lehto S, Ronnema T, Pyörala K, Laakso M. Gender Difference in the Impact of Type 2 Diabetes on Coronary Heart Disease Risk. *Diabetes Care*. 2004 Dec 1;27(12).
30. Homko CJ, Zamora L, Santamore WP, Kashem A, McConnell T, Bove AA. Gender Differences in Cardiovascular Risk Factors and Risk Perception Among Individuals With Diabetes. *The Diabetes Educator*. 2010 May;36(3).
31. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues – the biology of pear shape. *Biology of Sex Differences*. 2012;3(1).
32. Gan SC, Beaver SK, Houck PM, MacLehose RF, Lawson HW, Chan L. Treatment of Acute Myocardial Infarction and 30-Day Mortality among Women and Men. *New England Journal of Medicine*. 2000 Jul 6;343(1).
33. Capewell S, MacIntyre K, Stewart S, Chalmers JW, Boyd J, Finlayson A, et al. Age, sex, and social trends in out-of-hospital cardiac deaths in Scotland 1986–95: a retrospective cohort study. *The Lancet*. 2001 Oct;358(9289).
34. Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in Older Adults. *Diabetes Care*. 2012 Dec 1;35(12).

35. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovascular Diabetology*. 2018 Dec 8;17(1).
36. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson A-M, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *New England Journal of Medicine*. 2018;
37. Icks A, Claessen H, Morbach S, Glaeske G, Hoffmann F. Time-Dependent Impact of Diabetes on Mortality in Patients With Stroke: Survival up to 5 years in a health insurance population cohort in Germany. *Diabetes Care*. 2012 Sep 1;35(9).
38. Eriksson M, Carlberg B, Eliasson M. The Disparity in Long-Term Survival after a First Stroke in Patients with and without Diabetes Persists: The Northern Sweden MONICA Study. *Cerebrovascular Diseases*. 2012;34(2).
39. Nauta ST, Deckers JW, Akkerhuis KM, van Domburg RT. Short- and Long-Term Mortality After Myocardial Infarction in Patients With and Without Diabetes: Changes from 1985 to 2008. *Diabetes Care*. 2012 Oct 1;35(10).
40. Afanasiev SA, Garganeeva AA, Kuzheleva EA, Andriyanova A v., Kondratieva DS, Popov S v. The Impact of Type 2 Diabetes Mellitus on Long-Term Prognosis in Patients of Different Ages with Myocardial Infarction. *Journal of Diabetes Research*. 2018 Jul 10;2018.
41. Stern JR, Wong CK, Yerovinkina M, Spindler SJ, See AS, Panjaki S, et al. A Meta-analysis of Long-term Mortality and Associated Risk Factors following Lower Extremity Amputation. *Annals of Vascular Surgery*. 2017 Jul;42.
42. Miettinen H, Lehto S, Salomaa V, Mahonen M, Niemela M, Haffner SM, et al. Impact of Diabetes on Mortality After the First Myocardial Infarction. *Diabetes Care*. 1998 Jan 1;21(1).
43. Chun BY, Dobson AJ, Heller RF. The Impact of Diabetes on Survival Among Patients With First Myocardial Infarction. *Diabetes Care*. 1997 May 1;20(5).
44. Tachkov K, Mitov K, Koleva Y, Mitkova Z, Kamusheva M, Dimitrova M, et al. Life expectancy and survival analysis of patients with diabetes compared to the non diabetic population in Bulgaria. *PLOS ONE*. 2020 May 11;15(5).
45. Schofield CJ, Libby G, Brennan GM, MacAlpine RR, Morris AD, Leese GP. Mortality and Hospitalization in Patients After Amputation: A comparison between patients with and without diabetes. *Diabetes Care*. 2006 Oct 1;29(10).

Tables

Table 1. Demographic characteristics of the study population.

Characteristics	Diabetic patients with AMI N=1,278 (1.30%)	Diabetic patients with stroke N=1,908 (1.94%)	Diabetic patients with LLA N=2,896 (2.94%)	Diabetic patients without complications N=92,553 (93.99%)	Total N=98,469 (100.0%)
Age, (years)					
<54	208 (16.28%)	342 (17.93%)	461 (15.92%)	35,718 (38.59%)	36,711 (37.28%)
54-65	474 (37.09%)	748 (39.20%)	1,044 (36.05%)	30,848 (33.33%)	33,055 (33.57%)
>65	596 (46.64%)	818 (42.87%)	1,391 (48.03%)	25,987 (28.08%)	28,703 (29.15%)
Sex					
Male	575 (44.99%)	772 (40.46%)	1,451 (50.10%)	36,849 (39.81%)	39,567 (40.18%)
Female	703 (55.01%)	1,136 (59.54%)	1,445 (49.90%)	55,704 (60.19%)	58,902 (59.82%)
Region of Kazakhstan					
North	353 (27.62%)	595 (31.20%)	831 (28.71%)	22,189 (23.98%)	23,921 (24.30%)
South	304 (23.79%)	467 (24.49%)	729 (25.19%)	21,745 (23.50%)	23,198 (23.55%)
East	273 (21.36%)	360 (18.88%)	778 (26.88%)	27,180 (29.37%)	28,559 (29.01%)
West	240 (18.78%)	247 (12.95%)	389 (13.45%)	12,955 (14.00%)	13,809 (14.03%)
Central	108 (8.45%)	238 (12.48%)	167 (5.77%)	8,472 (9.15%)	8,968 (9.11%)
Ethnicity					
Kazakh	637 (49.84%)	1,073 (56.24%)	1,274 (43.99%)	56,304 (60.83%)	59,222 (60.14%)
Russian	328 (25.67%)	402 (21.07%)	828 (28.59%)	17,488 (18.90%)	18,995 (19.29%)
Other	313 (24.49%)	433 (22.69%)	794 (27.42%)	18,761 (20.27%)	20,252 (20.57%)
Residency					

Urban	877 (68.62%)	1,242 (65.09%)	1,912 (66.02%)	54,309 (58.68%)	58,236 (59.14%)
Rural	401 (31.38%)	666 (34.91%)	984 (33.98%)	38,244 (41.32%)	40,233 (40.86%)
Death rate	371 (29.03%)	480 (25.16%)	863 (29.80%)	13,680 (14.78%)	15,335 (15.57%)

Figures

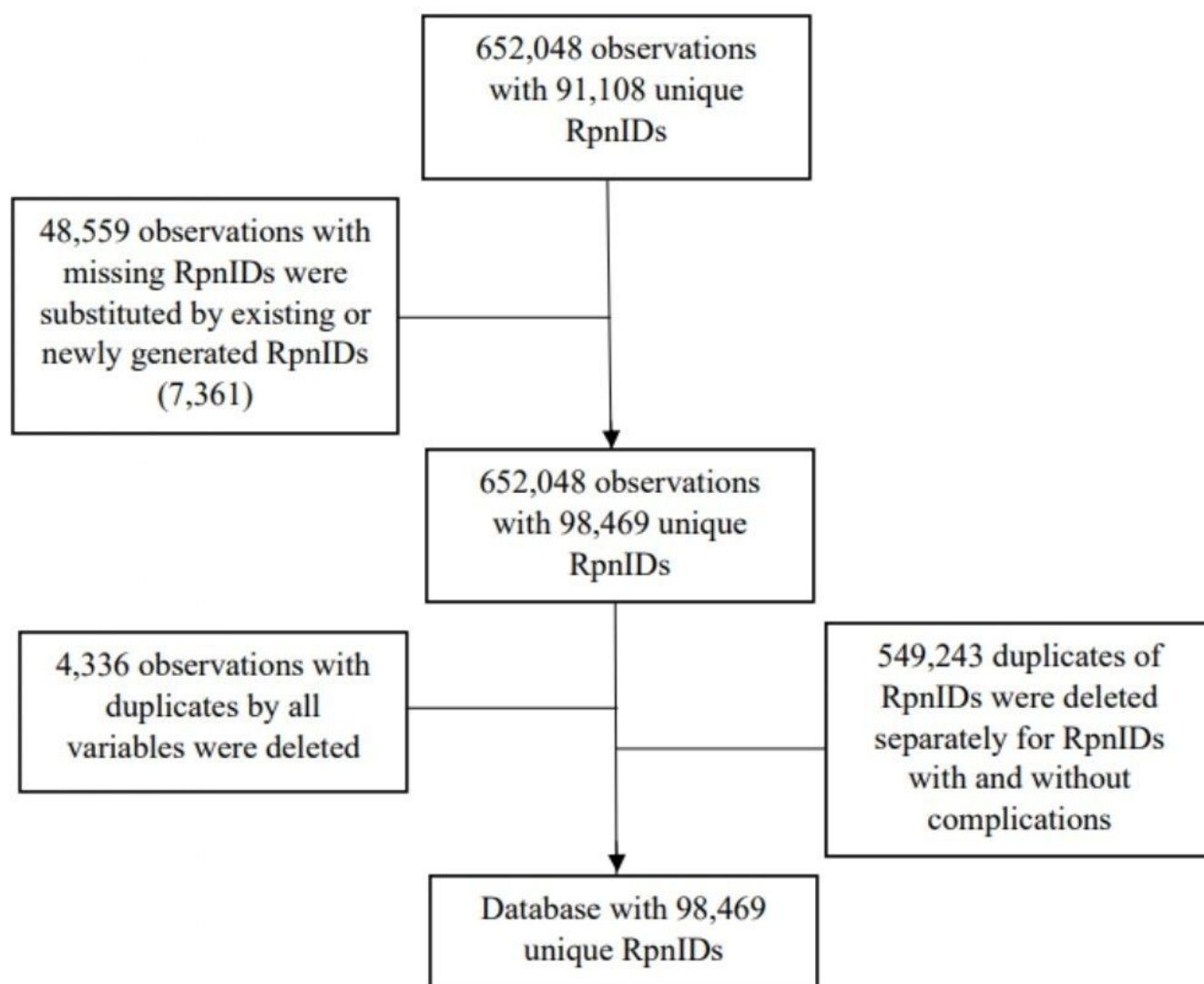


Figure 1

Flow chart of data cleaning process.

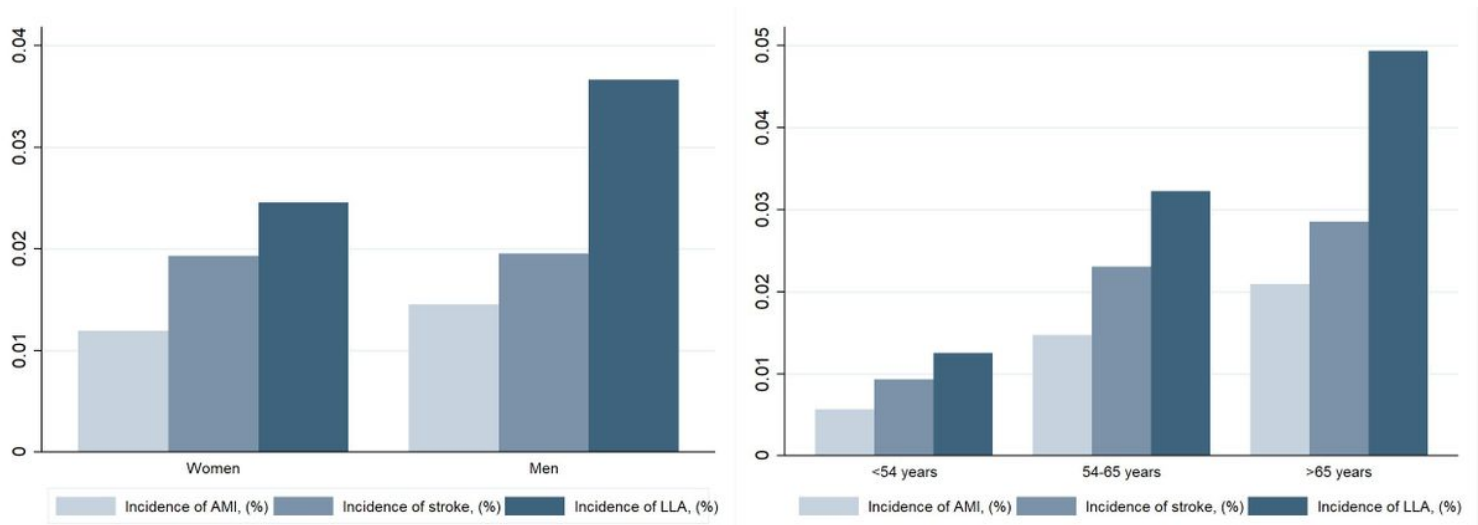


Figure 2

Incidence of macrovascular complications (AMI, stroke and LLA) stratified by sex (Figure 2a) and age groups (Figure 2b)

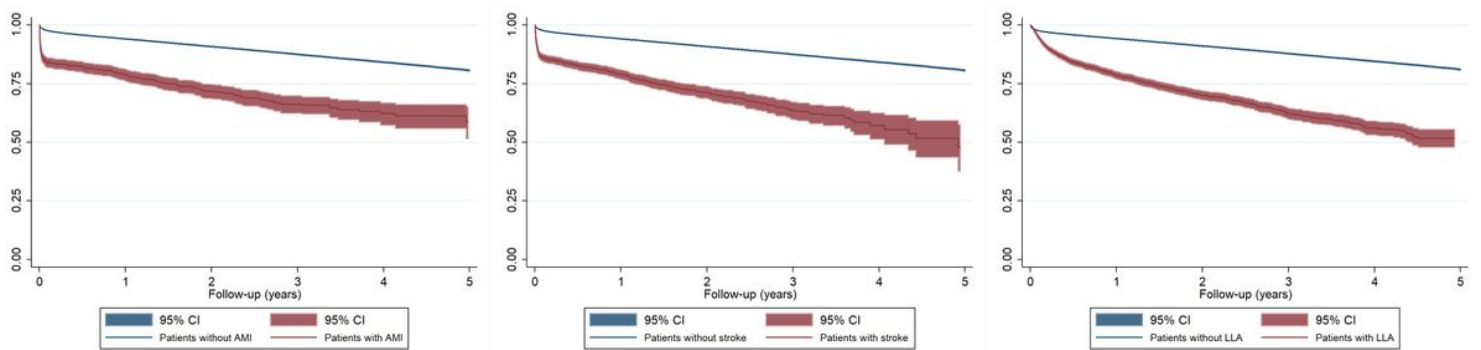


Figure 3

KM curves for diabetic patients with and without macrovascular complications. Figure 3a - KM survival curve for diabetic patients with and without AMI; Figure 3b - KM survival curve for diabetic patients with and without stroke; Figure 3c - KM survival curve for diabetic patients with and without LLA.

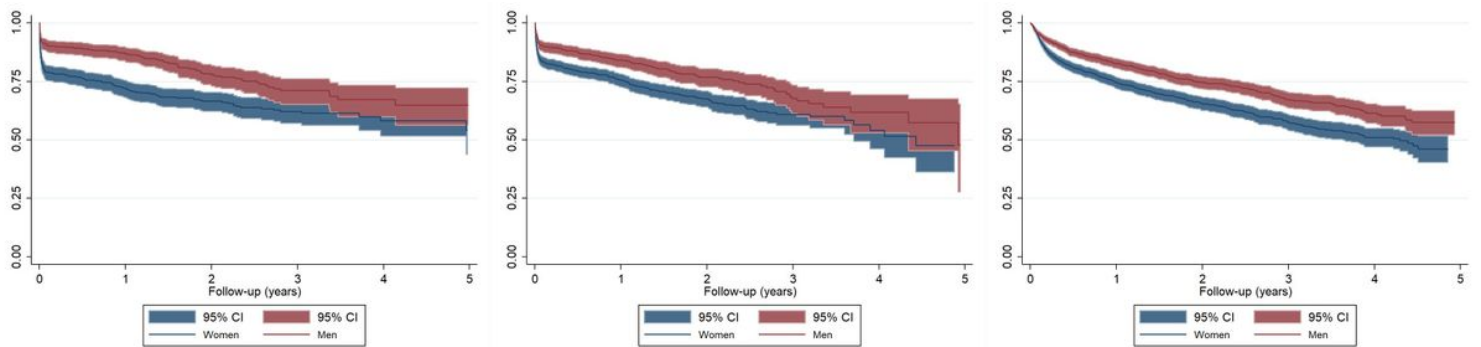


Figure 4

KM curves for diabetic patients with macrovascular complications stratified by Sex. Figure 4a - KM survival curve after AMI stratified by Sex; Figure 4b - KM survival curve after stroke stratified by Sex; Figure 4c - KM survival curve after lower limb amputations stratified by Sex

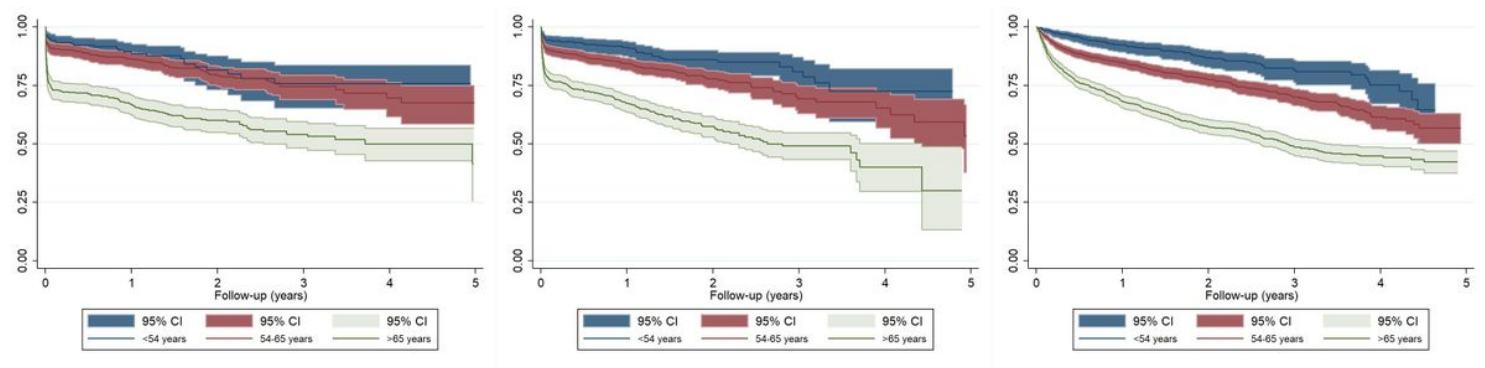


Figure 5

KM curves for diabetic patients with macrovascular complications stratified by Age categories. Figure 5a - KM survival curve after AMI stratified by Age categories; Figure 5b - KM survival curve after stroke stratified by Age categories; Figure 5c - KM survival curve after lower limb amputations stratified by Age categories

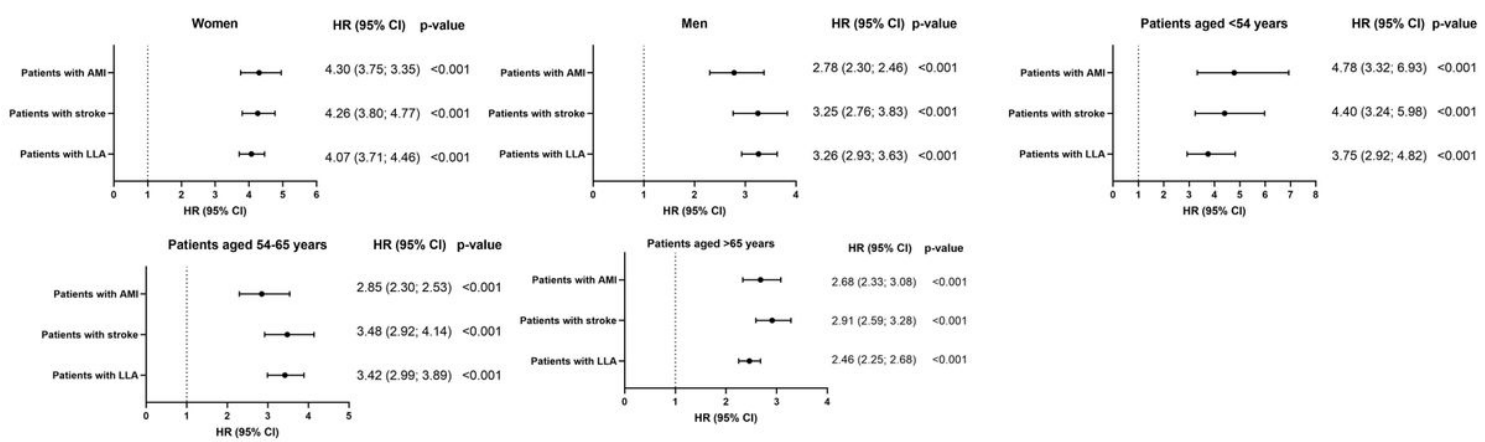


Figure 6

Forest plots of hazard ratios of mortality with corresponding 95% CI among diabetic patients stratified by age and sex groups (controls are diabetic patients without complications of interest). Figure 6a-6b - Forest plots of hazard ratios of mortality with corresponding 95% CI among diabetic patients stratified by sex; Figures 6c-6e - Forest plots of hazard ratios of mortality with corresponding 95% CI among diabetic patients stratified by age groups