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Association between NPS and all-cause and cardiovascular mortality in US adults with diabetes *mellitus*

Asociación entre la puntuación pronóstica napolitana y la mortalidad por todas las causas y de origen cardiovascular en adultos de EUA con diabetes mellitus

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ABSTRACT

Objective: this study aimed to assess the association between the Naples Prognostic Score (NPS) and all-cause as well as cardiovascular mortality in US adults with type 2 diabetes *mellitus* (T2DM).

Methods: data were obtained from the National Health and Nutrition Examination Survey (NHANES) spanning 2001-2018. Multivariable-adjusted Cox proportional hazards models, Kaplan-Meier survival analysis, and restricted cubic spline (RCS) analyses were used to evaluate the relationship between NPS and mortality outcomes. Subgroup analyses were conducted based on age, sex, education, body mass index (BMI), smoking status, alcohol consumption, and histories of hypertension and hyperlipidemia.

Results: a total of 3,663 adults with T2DM were included. Higher NPS was significantly associated with increased all-cause and cardiovascular mortality after adjustment for potential confounders (all *p*-values < 0.001). Compared to Group 0 (NPS = 0), Group 2 (NPS = 3-4) had a hazard ratio (HR) of 2.22 (95 % CI: 1.46-3.38; $p < 0.001$) for all-cause mortality and an HR of 2.23 (95 % CI: 1.01-4.93; $p =$

0.047) for cardiovascular mortality. RCS analysis demonstrated a J-shaped non-linear association between NPS and all-cause and cardiovascular mortality (p for nonlinearity < 0.0001 and 0.0192, respectively).

Conclusion: the results of this study suggest that NPS is independently associated with increased risks of all-cause and cardiovascular mortality in US adults with T2DM. These findings indicate that NPS may be a useful prognostic marker in this population and help inform clinical management strategies.

Keywords: Diabetes. The Naples Prognostic Score. All-cause mortality. CVD mortality.

RESUMEN

Objetivo: este estudio tiene como objetivo evaluar la relación entre el NPS y la mortalidad por todas las causas y la mortalidad cardiovascular en pacientes con diabetes de tipo 2.

Método: este estudio utilizó el conjunto de datos de la encuesta nacional de salud y nutrición (NHANES) (2001-2018). Se utilizó el modelo Cox corregido por múltiples variables, el análisis de supervivencia Kaplan-Meier y el análisis de triple empalme restrictivo (RCS) para explorar la asociación entre el NPS en pacientes con diabetes de tipo 2 y la mortalidad por todas las causas y enfermedades cardiovasculares (CVD). Se realizaron análisis de subgrupos basados en la edad, el sexo, el nivel de educación, el IMC, el tabaquismo, el consumo de alcohol, los antecedentes de hipertensión y los antecedentes de hiperlipidemia para explorar más a fondo estas asociaciones.

Resultados: este estudio incluyó 3.663 pacientes con diabetes de tipo 2. Después de ajustar muchos factores relacionados (todos los

valores *p* son inferiores a 0,001), el NPS se asoció significativamente con la mortalidad por todas las causas y la mortalidad cardiovascular en pacientes con diabetes de tipo 2. En comparación con el grupo 0 (NPS = 0), la relación de riesgo de mortalidad por todas las causas en el Grupo 2 (NPS = 3-4) fue (HR: 2,22, IC 95 %: 1,46-3,38, $p < 0,001$) y la relación de riesgo de mortalidad cardiovascular también fue (HR = 2,23, IC 95 % = 1,01-4,93, $p = 0,047$). El RCS mostró que el NPS en pacientes con diabetes de tipo 2 estaba relacionado con la mortalidad por todas las causas y la muerte cardiovascular en forma de J no lineal (no lineal $p < 0,0001$, no lineal $p = 0,0192$).

Conclusiones: los resultados de este estudio sugieren que el NPS puede ser un indicador pronóstico potencial de resultados adversos en pacientes con diabetes de tipo 2 y es valioso para predecir los resultados clínicos de la diabetes de tipo 2 y guiar las estrategias de tratamiento de seguimiento.

Palabras clave: Diabetes. Puntuación pronóstica napolitana. Mortalidad por todas las causas. Mortalidad por enfermedades cardiovasculares.

INTRODUCTION

Type 2 diabetes *mellitus* (T2DM) is a chronic progressive disease characterized by the presence of years of insulin resistance and hyperinsulinaemia before the onset of hyperglycaemia (1). Its prevalence has continued to rise in recent years, and the International Diabetes Federation predicts that by 2045, 783.2 million adults worldwide will have diabetes *mellitus* (DM) (2). Diabetes increases the risk of multiple complications, including cardiovascular disease, nephropathy, retinopathy, and neuropathy, and it carries a significantly increased risk of all-cause mortality and cardiovascular

death (3,4). Diabetes has become a serious global public health problem. Therefore, timely identification of additional risk factors is important to prevent, delay, or reduce the progression of diabetes and diabetes-related deaths.

An ideal prognostic scoring system should provide independent prognostic parameters that reflect the patient's overall condition, are easily recognizable during the diagnostic process, and are less costly in clinical practice. Recently, a composite prognostic score, the Naples prognostic score (NPS), calculated from serum albumin and total cholesterol concentrations, neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR), was first NPS has been reported as a strong prognostic indicator for colorectal cancer (CRC) (5). NPS, as a novel complementary indicator reflecting the nutritional immune status and inflammation level of the patient's body, is closely associated with disease severity and prognosis in many malignant and benign diseases (6-10). Previous studies have shown that T2DM is essentially a chronic low-grade inflammatory disease with elevated serum levels of the inflammatory biomarkers c-reactive protein (CRP), the pro-inflammatory cytokines interleukin (IL)-1β, IL-6, tumour necrosis factor-alpha (TNF-α), and plasminogen activator inhibitor (PAI-1) (11,12). At the same time, chronic inflammation can lead to adipocyte accumulation and insulin resistance through inflammatory factors such as TNF-α and CRP, resulting in changes in body weight and albumin levels (13,14). Prospective studies have shown that higher plasma levels of CRP, fibrinogen, IL-6, and PAI can be used to predict the risk of developing T2DM, and that many of these inflammatory markers are strongly associated with the prognosis of diabetes (15-20). In addition, albumin levels have been associated with the development and prognosis of diabetes and its complications (21,22).

Thus, inflammation may play a crucial role in the development of diabetes, ultimately reducing the survival of diabetic patients. Currently, most studies on inflammatory markers to assess the prognosis of diabetes have focused on a single factor. However, reliance on a single inflammatory marker may not provide sufficient accuracy to estimate the prognosis of diabetic patients. Therefore, we conducted this study to investigate the association between NPS and the risk of all-cause and cardiovascular mortality in a large nationally representative sample of diabetic patients.

MATERIALS AND METHODS

Data sources

The National Health and Nutrition Examination Survey (NHANES) is a nationwide cross-sectional program conducted annually in the United States to assess the health and nutritional status of non-institutionalized civilians. Moreover, it combines interviews, physical examinations, and laboratory tests, with data collected at participants' homes and mobile examination centers. The NHANES protocols are approved by the National Center for Health Statistics (NCHS) Ethics Review Board, and all participants provided written informed consent.

This study included data from nine NHANES cycles conducted between 2001 and 2018, encompassing 94,514 individuals. Type 2 diabetes *mellitus* was defined based on any of the following criteria:

- Self-reported physician diagnosis;
- Fasting blood glucose ≥ 126 mg/dL;
- 2-hour plasma glucose ≥ 200 mg/dL on an oral glucose tolerance test;
- Glycated hemoglobin (HbA1c) ≥ 6.5 %;
- Self-reported use of insulin or other glucose-lowering medications.

We excluded individuals who:

- Were under 20 years of age;
- Had missing diabetes-related data;
- Lacked key laboratory variables (e.g., total cholesterol, albumin, neutrophil and lymphocyte counts);
- Had a missing covariate or survival data.

After applying exclusion criteria, 3,663 adult participants with T2DM were included in the final analysis. A detailed flowchart of the selection process is provided in figure 1.

Definitions of NPS

The definition of NPS is based on the following four parameters: serum albumin, TC, LMR, and NLR. Gennaro Galizia et al previously reported that the cut-off values were serum albumin of 40 g/L, TC of 180 mg/dL, NLR of 2.96, and LMR of 4.44. Patients with serum albumin, TC, or LMR lower than 4 mg /dL, respectively, scored 1; otherwise, they scored zero, 180 mg /dL, and 4.44, respectively; otherwise, they scored zero. Patients with an NLR higher than 2.96 scored one point, and those lower than 2.96 scored zero. The sum of the scores of each parameter was the NPS. Patients were classified into three groups according to the NPS: patients with an NPS of 0 were in group 0, patients with an NPS of 1 or 2 were in group 1, and patients with an NPS of 3 or 4 were in group 2.

Mortality outcomes

Participants' survival status as of 31 December 2019 was determined by linking study data to the National Death Index (NDI). This document provides the most recent linkage between selected National Centre for Health Statistics (NCHS) surveys and the NDI (data available at https://www.cdc.gov/nchs/data-linkage/mortality.htm).

Deaths from any cause are considered all-cause deaths. Cause-specific deaths were identified using International Classification of Diseases, Tenth Edition (ICD-10) codes, and cardiovascular mortality was defined by ICD-10 codes I00-I09, I11, I13, I20-I51 (23). The baseline time for calculating survival time was defined as the time of NHANES data collection.

Covariate definitions

Age (in years), sex (male or female), race (non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, or other race), educational attainment (less than high school, high school, or more than high school), poverty-to-income ratios (household income divided by the poverty line based on household size using the US Health and Department of Human Services guidelines), smoking and drinking habits, comorbid disease status, and substance use. Body mass index (BMI < 25.0, 25.0-30, or ≥ 30 kg/m^2) was measured, and blood samples were collected at mobile centres. Those who responded affirmatively were categorized as participants with a history of smoking and drinking based on their responses to whether they had smoked at least 100 cigarettes in their lifetime and had had at least 12 drinks in 1 year.

Blood pressure was measured by a trained physician using a mercury sphygmomanometer with an appropriately sized cuff. Three blood pressure measurements were taken, and the mean of the three measurements was defined as systolic blood pressure (SBP) and diastolic blood pressure (DBP). Hypertension was defined as a self-reported history of hypertension or use of antihypertensive medications or a systolic BP ≥ 130 mmHg or DPB ≥ 80 mmHg.

Participants who met at least one of the following criteria were considered to have hyperlipidaemia: 1) total cholesterol level equal to or greater than 200 mg/dL; 2) triglyceride level equal to or greater than 150 mg/dL; 3) HDL cholesterol level less than 40 mg/dL for men and less than 50 mg/dL for women; 4) LDL cholesterol level equal to or greater than 130 mg/dL; and 5) self-reported use of cholesterol-lowering medications.

Statistical analysis

Data were analyzed in this study using RStudio 4.4.1. *p*-Values less than 0.05 were considered statistically significant. All analytical procedures strictly followed the NHANES guidelines for analysis and reporting. Continuous variables that conformed to normal distribution were expressed as mean ± standard deviation, continuous variables that did not conform to normal distribution were expressed as median (25th percentile, 75th percentile), and categorical variables were expressed as numerical and weighted percentages. The Wilcoxon rank sum test was used for continuous variables and the Chi-square test for categorical variables. Kaplan-Meier analyses were used to investigate the association between NPS and all-cause and cardiovascular disease mortality in patients with T2DM. After adjusting for multiple covariates, multivariate Cox regression analyses were applied to examine further the effect of NPS on all-cause and cardiovascular disease mortality in patients with T2DM, and the results were expressed as hazard ratios (HR) and 95 % confidence intervals (CI). A total of the following three models were used in this study: Model 1 was unadjusted, Model 2 was adjusted for age, gender, race, education level, marital status, and poverty-to-income ratio, and Model 3 further incorporated history of smoking, alcohol consumption,

BMI, history of hypertension, history of hyperlipidemia, use of glucose-lowering medications, and duration of diabetes *mellitus* based on Model 2.

The above analyses were performed using data weighted with the NHANES recommended weights. We combined restricted cubic spline (RCS) analyses with multivariate corrected COX regression models to assess the non-linear associations between NPS and patients with T2DM regarding all-cause and cardiovascular mortality, and further explored threshold effects. Finally, we constructed subgroup analyses combined with interaction analyses to jointly assess potential differences in the association with all-cause and cardiovascular mortality among stroke patients with T2DM across subgroups. These subgroups were defined according to age (< 60 vs ≥ 60 years), sex (female vs male), education (below high school level vs high school level vs above high school level), BMI (< 25 vs 25-30 vs ≥ 30 kg/m^2), smoking (yes vs no), alcohol consumption (yes vs no), and the presence of a specific medical history (e.g., hypertension, hyperlipidaemia).

RESULTS

Baseline characteristics of study participants

A total of 3,663 patients with T2DM were included in the analysis. The median age was 61 years (interquartile range: 51-70), with 1,941 (52.22 %) males and 1,722 (47.78 %) females. The cohort was predominantly non-Hispanic white (64.02 %). Based on the Naples Prognostic Score (NPS), participants were categorized into Group 0 (NPS = 0; *n* = 479), Group 1 (NPS = 1-2; *n* = 2,338), and Group 2 (NPS = 3-4; *n* = 846).

Compared to Group 0, participants in Group 2 were generally older

and more likely to be non-Hispanic white women with a history of alcohol consumption. They exhibited a higher prevalence of hypertension and hyperlipidemia. They were also more likely to be on glucose-lowering medications, have a longer diabetes duration, and show higher neutrophil and monocyte counts, along with elevated NLR values. In contrast, they had lower diastolic blood pressure, lymphocyte counts, LMR values, serum albumin, total cholesterol, and triglycerides. No significant differences were observed among the groups regarding education level, marital status, poverty-to-income ratio, smoking status, or BMI. Detailed characteristics are presented in table I.

Kaplan-Meier analysis

During a median follow-up period of 5.9 years, 768 participants (20.97 %) died from all causes, including 320 (6.2 %) deaths attributed to cardiovascular disease. Kaplan-Meier survival curves (Fig. 2) revealed that higher NPS scores were significantly associated with increased risks of both all-cause and cardiovascular mortality among T2DM patients (log-rank test, $p < 0.001$ for both outcomes).

Multivariate Cox analysis

In the fully adjusted model (Model 3), which accounted for age, sex, race, education, poverty-to-income ratio, smoking and alcohol use, BMI, history of hypertension and hyperlipidemia, use of hypoglycemic agents, and duration of diabetes, NPS remained a significant predictor of both all-cause and cardiovascular mortality ($p < 0.001$).

Compared with Group 0, individuals in Group 2 had a hazard ratio (HR) of 2.22 (95 % CI: 1.46-3.38; p for trend < 0.001) for all-cause mortality and 2.23 (95 % CI: 1.01-4.93; p for trend < 0.001) for

cardiovascular mortality (Table II).

Non-linear relationships

As shown in figure 3, the restricted cubic spline analysis revealed a non-linear association between NPS and all-cause and cardiovascular mortality. The hazard ratios remained relatively stable when NPS was below 2, followed by a marked and progressive increase in risk at higher NPS values. This pattern reflects a J-shaped relationship, where the increased mortality risk becomes significant at NPS ≥ 2, indicating a potential threshold effect. Specifically, among T2DM patients with NPS scores of 0 to 2, increasing NPS was not associated with a marked rise in mortality risk. However, when NPS was ≥ 2, the risk of all-cause and cardiovascular death increased significantly ($p < 0.0001$ and p_non-linear = 0.0192, respectively).

Subgroup analysis

Subgroup analyses stratified by age, sex, education, BMI, smoking, alcohol use, and history of hypertension and hyperlipidemia were performed to examine effect modification (Fig. 4A-B). The association between NPS and all-cause mortality was consistent across most subgroups, except in individuals under 60 years of age, where the association was not statistically significant (HR: 1.20; 95 % CI: 0.89-1.62; $p = 0.20$). In contrast, NPS was significantly associated with cardiovascular mortality in participants aged ≥ 60 years (HR: 1.54; 95 % CI: 1.29-1.83; $p < 0.001$), those with a history of alcohol use (HR: 1.68; 95 % CI: 1.35-2.11; $p < 0.001$), and those with hypertension (HR: 1.52; 95 % CI: 1.25-1.83; $p < 0.001$). These associations held regardless of sex, BMI, education level, or hyperlipidemia status. No significant interactions were detected

across most stratification variables (p_interaction > 0.05), except for educational level, which showed a significant interaction effect on all-cause mortality (p_interaction = 0.013).

DISCUSSION

In this cohort study of patients with T2DM, we found that higher NPS were significantly associated with increased all-cause and cardiovascular mortality. These associations exhibited a J-shaped nonlinear pattern, with a marked increase in risk observed when NPS was ≥ 2. Importantly, these relationships persisted independently of traditional risk factors, including lifestyle factors, BMI, diabetes duration, medication use, and comorbid conditions. The associations remained robust across most stratified analyses by age, sex, education, BMI, smoking status, alcohol use, and history of hypertension or hyperlipidaemia. To our knowledge, this is the first study to evaluate the prognostic value of NPS concerning all-cause and cardiovascular mortality in individuals with T2DM. Given its simplicity, affordability, and ability to reflect nutritional and inflammatory status, NPS may be a practical tool for early risk stratification in clinical practice for patients with T2DM.

Chronic, low-grade inflammation is a central mechanism in the pathogenesis of T2DM. It disrupts pancreatic and adipose tissue homeostasis, impairs lipid metabolism, and reduces glucose uptake, thereby contributing to insulin resistance (24). Pro-inflammatory cytokines (TNFα, IL-1β and IL-6) initiate inhibitory phosphorylation and activate serine kinases in adipocytes, such as IκB kinase β (IKKβ), c-Jun N-terminal kinase (JNK), ribosomal protein S6 kinase (S6K), and mammalian target of rapamycin 32 (mTOR32), which mediate the insulin receptor substrate 1 (IRS1) inhibitory phosphorylation, causing

insulin resistance (25-28). These pathways are also activated by toll-like receptors (TLRs), perpetuating cytokine production and fueling a vicious cycle of inflammation, insulin resistance, and vascular damage (29,30). Anti-inflammatory interventions, including targeted biologics or small molecule inhibitors, have improved glycaemic control and enhanced insulin secretion (31,32).

Meanwhile, chronic low-grade inflammation in diabetic patients can lead to atherosclerosis, which increases the risk of cardiovascular death (33,34). In addition, inflammation can lead to malnutrition, causing people with diabetes to have reduced albumin, which has strong anti-inflammatory activity (35,36). Several prior studies support the prognostic role of inflammatory and nutritional markers in T2DM. For example, Tang et al. reported that higher systemic immune-inflammation index (SII) levels were independently associated with increased risks of all-cause and cardiovascular mortality in T2DM (37). Similarly, Zhang et al. found that inflammatory biomarkers such as NLR, MLR, SII, AISI, SIRI, dNLR, and all-cause mortality and cardiovascular mortality in patients with type 2 diabetes were significantly associated (38). Moreover, indicators of malnutrition such as the geriatric nutritional risk index (GNRI), prognostic nutritional index (PNI), and controlling nutritional status (CONUT) score have also been linked to mortality in T2DM patients, particularly those with complications like diabetic foot ulcers (39).

However, most previous studies have focused on individual inflammatory or nutritional markers, which may not adequately capture the multifaceted risk profile of patients with T2DM. In contrast, NPS integrates key inflammatory (NLR and LMR) and nutritional (serum albumin and total cholesterol) components, offering a more holistic assessment of patient status. While NPS has primarily

been investigated in oncological settings, its role in chronic metabolic diseases like T2DM has remained underexplored. Our findings suggest that NPS could be a valuable tool for early prognostic evaluation in T2DM. Notably, the J-shaped association implies that modest elevations in NPS may not confer immediate risk, but a threshold effect appears once NPS reaches 2 or higher. Early identification of such patients may facilitate timely nutritional interventions and targeted therapies to modulate inflammation and improve long-term outcomes.

NPS includes not only serum albumin and total cholesterol levels, which reflect the nutritional status of the organism, but also immune-inflammatory markers such as NLR and LMR, which allow for a more comprehensive and effective assessment of a patient's physical condition on admission, and it has been associated with a wide range of disease outcomes (6-10). Although research on NPS has focused on tumour-related diseases, its role in non-tumour diseases is unclear. This study first analyzed the relationship between NPS and all-cause mortality and cardiovascular mortality in T2DM patients. The results showed that higher levels of NPS were significantly associated with higher all-cause mortality and cardiovascular mortality. Both showed a J-type non-linear relationship, suggesting that NPS scoring is performed in the early stages of disease in T2DM patients. The J-shaped pattern in the spline curves indicates that the prognostic value of NPS is not linear across its entire range. Rather, the mortality risk is minimal or slightly reduced at lower NPS levels, but increases substantially once NPS reaches 2 or higher. This non-linear, threshold-like escalation in risk is consistent with a J-shaped association. Moreover, it may reflect the compounding effects of malnutrition and systemic inflammation on long-term outcomes in patients with T2DM.

For patients with NPS equal to or greater than 2, in their treatment process, Timely nutritional support and appropriate improvement of their inflammatory and immune status may improve the long-term prognosis of patients.

In the subgroup analyses of this study we found that NPS was significantly associated with all-cause mortality and cardiovascular mortality in the type 2 diabetes *mellitus* population with age greater than or equal to 60 years. This may be since age is already a risk factor for type 2 diabetes *mellitus*, and older adults are at a higher risk of developing type 2 diabetes *mellitus* due to the combined effects of increased insulin resistance and islet dysfunction (40). With an increasingly aging population, and given our findings, it is all the more important to assess the overall status of patients early in the course of the disease in this group, and to individualize treatment according to life expectancy and solid age of the patient, with established targets for glycaemic control, to reduce the risk of mortality in the elderly population with type 2 diabetes *mellitus*.

This study has several strengths. It included a relatively large sample size and adjusted for a broad range of potential confounders. Moreover, it was based on a nationally representative cohort, which enhances the generalizability of the findings. Importantly, NPS incorporates both inflammatory and nutritional dimensions, offering improved prognostic accuracy compared to single-parameter indices.

Strengths and limitations

However, several limitations must be acknowledged. First, the observational design precludes any causal inference. Second, NPS was calculated based on a single time-point measurement, which may not reflect dynamic inflammatory or nutritional status changes over

time. Third, although baseline covariates were carefully adjusted for, residual or unmeasured confounding cannot be ruled out. Fourth, we lacked detailed clinical data to assess the severity of diabetes or the presence of complications, which could influence mortality risk.

CONCLUSION

This study demonstrates that the NPS is significantly associated with both all-cause mortality and cardiovascular death in patients with type 2 diabetes *mellitus*. These findings suggest that NPS can serve as a reliable indicator of systemic inflammation and nutritional status in diabetic patients. Modulating NPS within a certain range may hold potential for improving the long-term prognosis of these individuals, highlighting the value of NPS as a prognostic tool in clinical practice.

REFERENCES

1. Demir S, Nawroth PP, Herzig S, Ekim Üstünel B. Emerging Targets in Type 2 Diabetes and Diabetic Complications. Adv Sci 2021;8(18):2100275. DOI: 10.1002/advs.202100275
2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional, and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract 2022;183:109119. DOI: 10.1016/j.diabres.2021.109119
3. Zhang X, Zhao S, Huang Y, Ma M, Li B, Li C, et al. Diabetes-Related Macrovascular Complications Are Associated With an Increased Risk of Diabetic Microvascular Complications: A Prospective Study of 1518 Patients With Type 1 Diabetes and 20,802 Patients With Type 2 Diabetes in the UK Biobank. J Am

Heart Assoc 2024;13(11):e032626. DOI: 10.1161/JAHA.123.032626

4. Wang L, Li X, Wang Z, Bancks MP, Carnethon MR, Greenland P, et al. Trends in Prevalence of Diabetes and Control of Risk Factors in Diabetes Among US Adults, 1999-2018. JAMA 2021;326(8):704. DOI: 10.1001/jama.2021.9883
5. Galizia G, Lieto E, Auricchio A, Cardella F, Mabilia A, Podzemny V, C et al. Naples Prognostic Score, Based on Nutritional and Inflammatory Status, is an Independent Predictor of Long-term Outcome in Patients Undergoing Surgery for Colorectal Cancer. Dis Colon Rectum 2017;60(12):1273. DOI: 10.1097/DCR.0000000000000961
6. Qiu Y, Chen Y, Shen H, Yan S, Li J, Wu W. Naples Prognostic Score: A Novel Predictor of Survival in Patients with Triple-Negative Breast Cancer. J Inflamm Res 2024;17:5253-69. DOI: 10.2147/JIR.S472917
7. Artac I, Karakayali M, Omar T, Ilis D, Arslan A, Hakan Sahin M, et al. Predictive Value of the Naples Prognostic Score on Long-Term Outcomes in Patients with Peripheral Artery Disease Revascularized via Percutaneous Intervention. Ann Vasc Surg 2024;102:121-32. DOI: 10.1016/j.avsg.2023.11.028
8. Li J, Yang W, Yuan Y, Zuo M, Li T, Wang Z, et al. Preoperative Naples prognostic score is a reliable prognostic indicator for newly diagnosed glioblastoma patients. Front Oncol 2022;12:775430. DOI: 10.3389/fonc.2022.775430
9. Yang ZW, Wei XB, Fu BQ, Chen JY, Yu DQ. Prevalence and Prognostic Significance of Malnutrition in Hypertensive Patients in a Community Setting. Front Nutr 2022;9:822376. DOI: 10.3389/fnut.2022.822376

10. Liu R, Chen C, Zhao Y, Tang Y, Shen W, Xie Z. The Osaka prognostic score and Naples prognostic score: novel biomarkers for predicting short-term outcomes after spontaneous intracerebral hemorrhage. BMC Neurol 2023;23(1):272. DOI: 10.1186/s12883-023-03287-3
11. Sorski L, Gidron Y. The Vagal Nerve, Inflammation, and Diabetes—A Holy Triangle. Cells 2023;12(12):1632. DOI: 10.3390/cells12121632
12. Dehghan M, Ghorbani F, Najafi S, Ravaei N, Karimian M, Kalhor K, et al. Progress toward molecular therapy for diabetes mellitus: A focus on targeting inflammatory factors. Diabetes Res Clin Pract 2022;189:109945. DOI: 10.1016/j.diabres.2022.109945
13. Saukkonen T, Mutt SJ, Jokelainen J, Saukkonen AM, Raza GS, Karhu T, et al. Adipokines and inflammatory markers in elderly subjects with high risk of type 2 diabetes and cardiovascular disease. Sci Rep 2018;8(1):12816. DOI: 10.1038/s41598-018-31144-8
14. Prattichizzo F, De Nigris V, Spiga R, Mancuso E, La Sala L, Antonicelli R, et al. Inflammageing and metaflammation: The yin and yang of type 2 diabetes. Ageing Res Rev 2018;41:1-17. DOI: 10.1016/j.arr.2017.10.003
15. Jin Z, Zhang Q, Liu K, Wang S, Yan Y, Zhang B, et al. The association between interleukin family and diabetes mellitus and its complications: An overview of systematic reviews and meta-analyses. Diabetes Res Clin Pract 2024;210:111615. DOI: 10.1016/j.diabres.2024.111615
16. Yan Y, Lu H, Zheng Y, Lin S. Association Between Systemic Immune Inflammation Index and Diabetes Mellitus in the

NHANES 2003-2018 Population. J Endocr Soc 2024;8(8):bvae124. DOI: 10.1210/jendso/bvae124

17. Cox AJ, Agarwal S, M Herrington D, Carr JJ, Freedman BI, Bowden DW. C-reactive protein concentration predicts mortality in type 2 diabetes: the Diabetes Heart Study. Diabet Med 2012;29(6):767-70. DOI: 10.1111/j.1464-5491.2011.03560.x
18. Chen G, Che L, Lai M, Wei T, Chen C, Zhu P, et al. Association of neutrophil-lymphocyte ratio with all-cause and cardiovascular mortality in US adults with diabetes and prediabetes: a prospective cohort study. BMC Endocr Disord 2024;24(1):64. DOI: 10.1186/s12902-024-01592-7
19. Dong G, Gan M, Xu S, Xie Y, Zhou M, Wu L. The neutrophil–lymphocyte ratio as a risk factor for all-cause and cardiovascular mortality among individuals with diabetes: evidence from the NHANES 2003–2016. Cardiovasc Diabetol 2023;22(1):267. DOI: 10.1186/s12933-023-01998-y
20. Meng C, Liu K. Non-linear association of the systemic immune-inflammatory index with mortality in diabetic patients. Front Endocrinol 2024;15:1334811. DOI: 10.3389/fendo.2024.1334811
21. Liu S, Qiu C, Li W, Li X, Liu F, Hu G. Blood urea nitrogen to serum albumin ratio as a new prognostic indicator in type 2 diabetes mellitus patients with chronic kidney disease. Sci Rep 2024;14(1):8002. DOI: 10.1038/s41598-024-58678-4
22. Zhang J, Deng Y, Wan Y, He S, Cai W, Xu J. Association Between Serum Albumin Level and Microvascular Complications of Type 2 Diabetes Mellitus. Diabetes Metab Syndr Obes Targets Ther 2022;15:2173-82. DOI: 10.2147/DMSO.S373160
23. Hong C, Zhu H, Zhou X, Zhai X, Li S, Ma W, et al. Association of

Blood Urea Nitrogen with Cardiovascular Diseases and All-Cause Mortality in USA Adults: Results from NHANES 1999–2006. Nutrients 2023;15(2):461. DOI: 10.3390/nu15020461

24. Lontchi-Yimagou E, Sobngwi E, Matsha TE, Kengne AP. Diabetes Mellitus and Inflammation. Curr Diab Rep 2013;13(3):435-44. DOI: 10.1007/s11892-013-0375-y
25. Hattori S. Anti-inflammatory effects of empagliflozin in patients with type 2 diabetes and insulin resistance. Diabetol Metab Syndr 2018;10(1):93. DOI: 10.1186/s13098-018-0395-5
26. Caratti G, Stifel U, Caratti B, Jamil AJM, Chung KJ, Kiehntopf M, et al. Glucocorticoid activation of anti-inflammatory macrophages protects against insulin resistance. Nat Commun 2023;14(1):2271. DOI: 10.1038/s41467-023-37831-z
27. Anusree SS, Sindhu G, Preetha Rani MR, Raghu KG. Insulin resistance in 3T3-L1 adipocytes by TNF-α is improved by punicic acid through upregulation of insulin signalling pathway and endocrine function, and downregulation of pro-inflammatory cytokines. Biochimie 2018;146:79-86. DOI: 10.1016/j.biochi.2017.11.014
28. Henstridge DC, Bruce CR, Pang CP, Lancaster GI, Allen TL, Estevez E, et al. Skeletal muscle-specific overproduction of constitutively activated c-Jun N-terminal kinase (JNK) induces insulin resistance in mice. Diabetologia. 2012;55(10):2769-2778. doi:10.1007/s00125-012-2652-8
29. Bayan N, Yazdanpanah N, Rezaei N. Role of toll-like receptor 4 in diabetic retinopathy. Pharmacol Res 2022;175:105960. DOI: 10.1016/j.phrs.2021.105960
30. Jin M, Fang J, Wang JJ, Shao X, Xu SW, Liu PQ, et al. Regulation of toll-like receptor (TLR) signaling pathways in atherosclerosis:

from mechanisms to targeted therapeutics. Acta Pharmacol Sin 2023;44(12):2358-75. DOI: 10.1038/s41401-023-01123-5

31. Reynolds L, Luo Z, Singh K. Diabetic complications and prospective immunotherapy. Front Immunol 2023;14:1219598. DOI: 10.3389/fimmu.2023.1219598
32. Luo J, Ning T, Li X, Jiang T, Tan S, Ma D. Targeting IL-12 family cytokines: A potential strategy for type 1 and type 2 diabetes mellitus. Biomed Pharmacother 2024;170:115958. DOI: 10.1016/j.biopha.2023.115958
33. Kanter JE, Bornfeldt KE. Inflammation and diabetes-accelerated atherosclerosis: myeloid cell mediators. Trends Endocrinol Metab 2013;24(3):137-44. DOI: 10.1016/j.tem.2012.10.002
34. Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, et al. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox Biol 2019;20:247-60. DOI: 10.1016/j.redox.2018.09.025
35. Sheinenzon A, Shehadeh M, Michelis R, Shaoul E, Ronen O. Serum albumin levels and inflammation. Int J Biol Macromol 2021;184:857-62. DOI: 10.1016/j.ijbiomac.2021.06.140
36. Arques S. Human serum albumin in cardiovascular diseases. Eur J Intern Med 2018;52:8-12. DOI: 10.1016/j.ejim.2018.04.014
37. ang Y, Feng X, Liu N, Zhou Y, Wang Y, Chen Z, et al. Relationship between systemic immune inflammation index and mortality among US adults with different diabetic status: Evidence from NHANES 1999-2018. Exp Gerontol 2024;185:112350. DOI: 10.1016/j.exger.2023.112350
38. Zhang J, Fan X, Xu Y, Wang K, Xu T, Han T, et al. Association between inflammatory biomarkers and mortality in individuals with type 2 diabetes: NHANES 2005–2018. Diabetes Res Clin

Pract 2024;209:111575. DOI: 10.1016/j.diabres.2024.111575

39. Hong J, Huang QQ, Liu WY, Hu X, Jiang FF, Xu ZR, et al. Three Nutritional Indices Are Effective Predictors of Mortality in Patients With Type 2 Diabetes and Foot Ulcers. Front Nutr 2022;9:851274. DOI: 10.3389/fnut.2022.851274
40. Cigolle CT, Blaum CS, Lyu C, Ha J, Kabeto M, Zhong J. Associations of Age at Diagnosis and Duration of Diabetes With Morbidity and Mortality Among Older Adults. JAMA Netw Open 2022;5(9):e2232766. DOI: 10.1001/jamanetworkopen.2022.32766

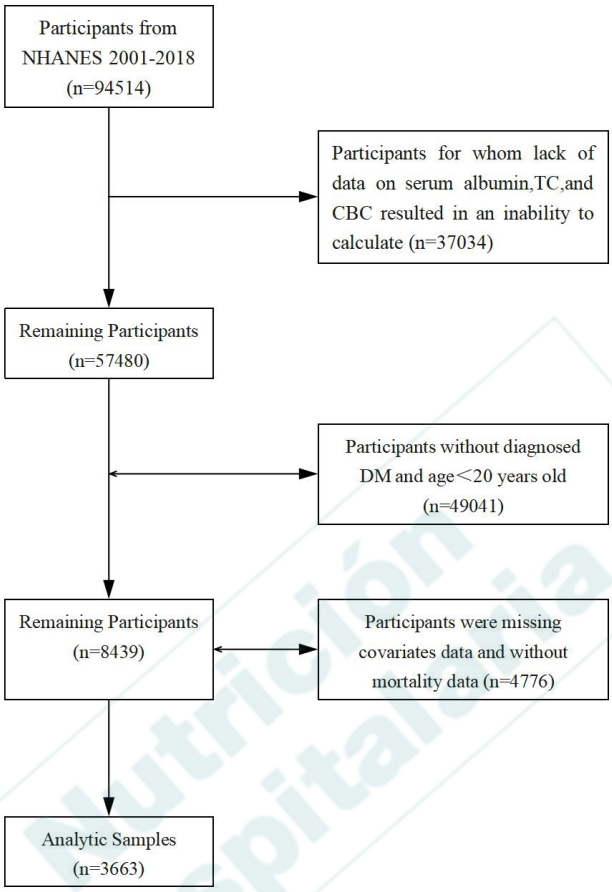

Figure 1. The flow chart of individual inclusion and exclusion in this study.

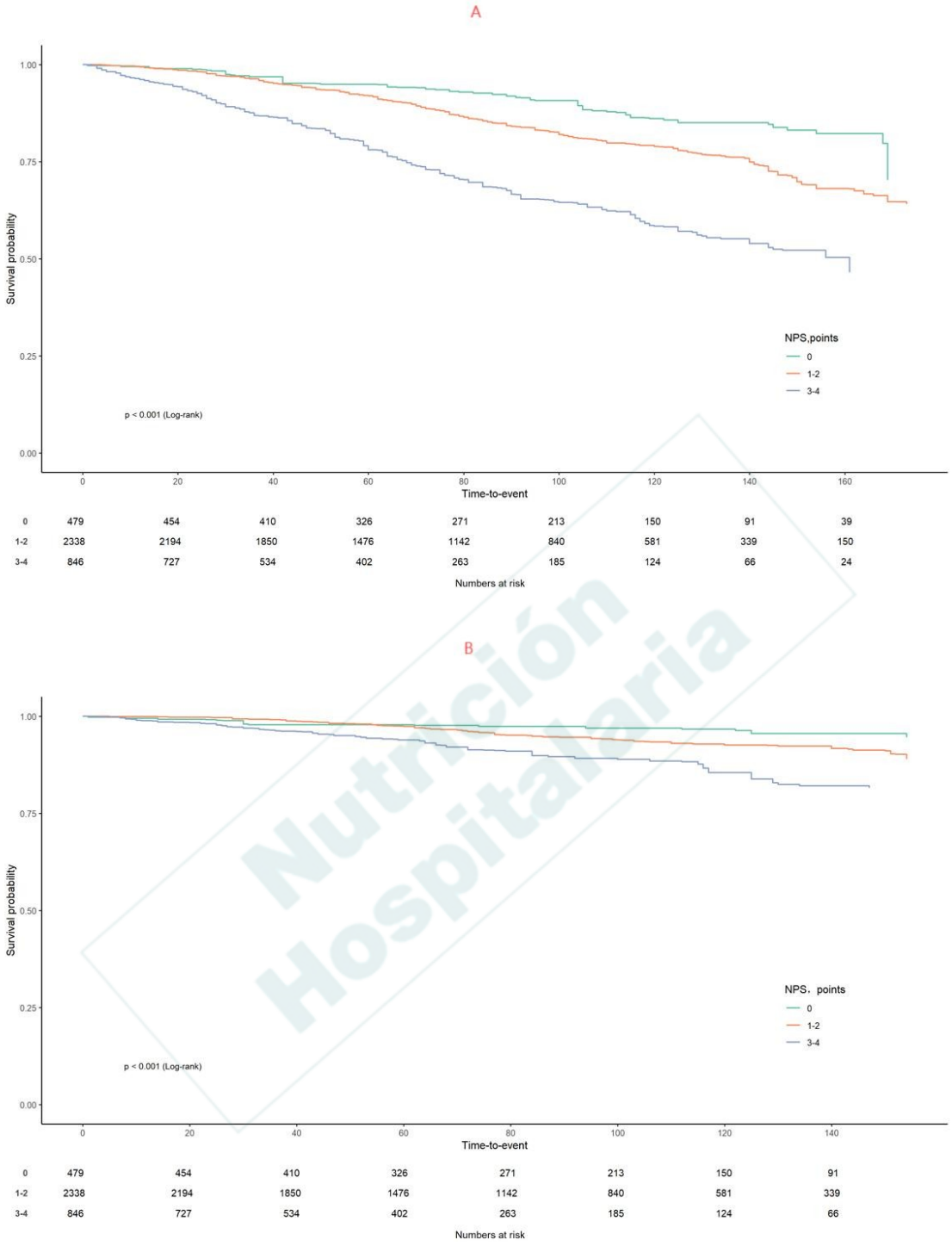

Figure 2. Kaplan-Meier survival curve of mortality: A. For all-cause mortality. B. For cardiovascular mortality (NPS: the Naples Prognostic Score).

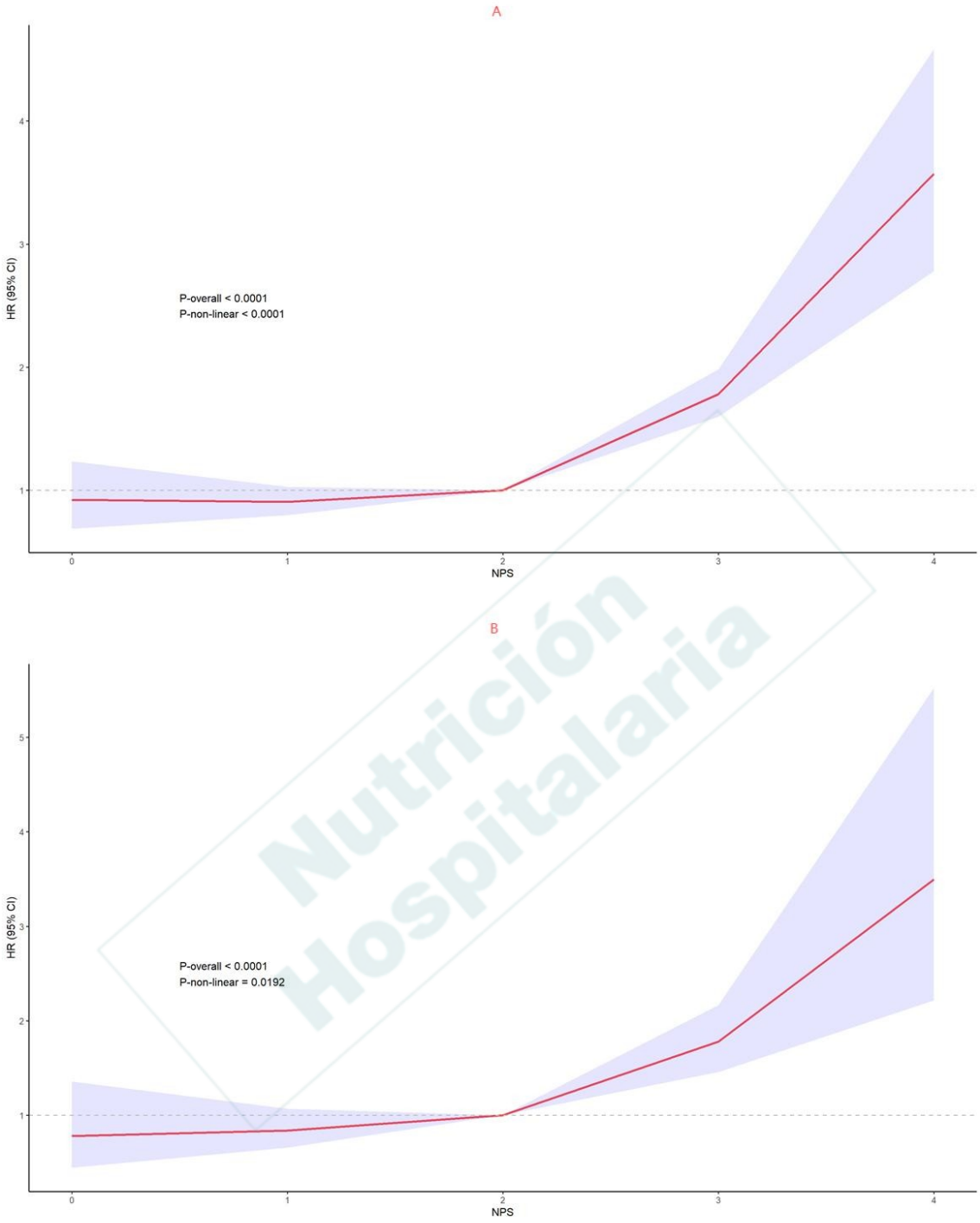

Figure 3. Restricted cubic spline curves illustrate the association between the NPS and mortality risk in patients with type 2 diabetes, adjusted for covariates included in Model 3. A. All-cause mortality. B. Cardiovascular mortality. Red lines, HRs, and shaded areas indicate 95 % confidence intervals. The risk remains stable at lower NPS values and increases sharply at NPS ≥ 2, indicating a J-shaped

relationship. Both associations are statistically significant and non-linear.

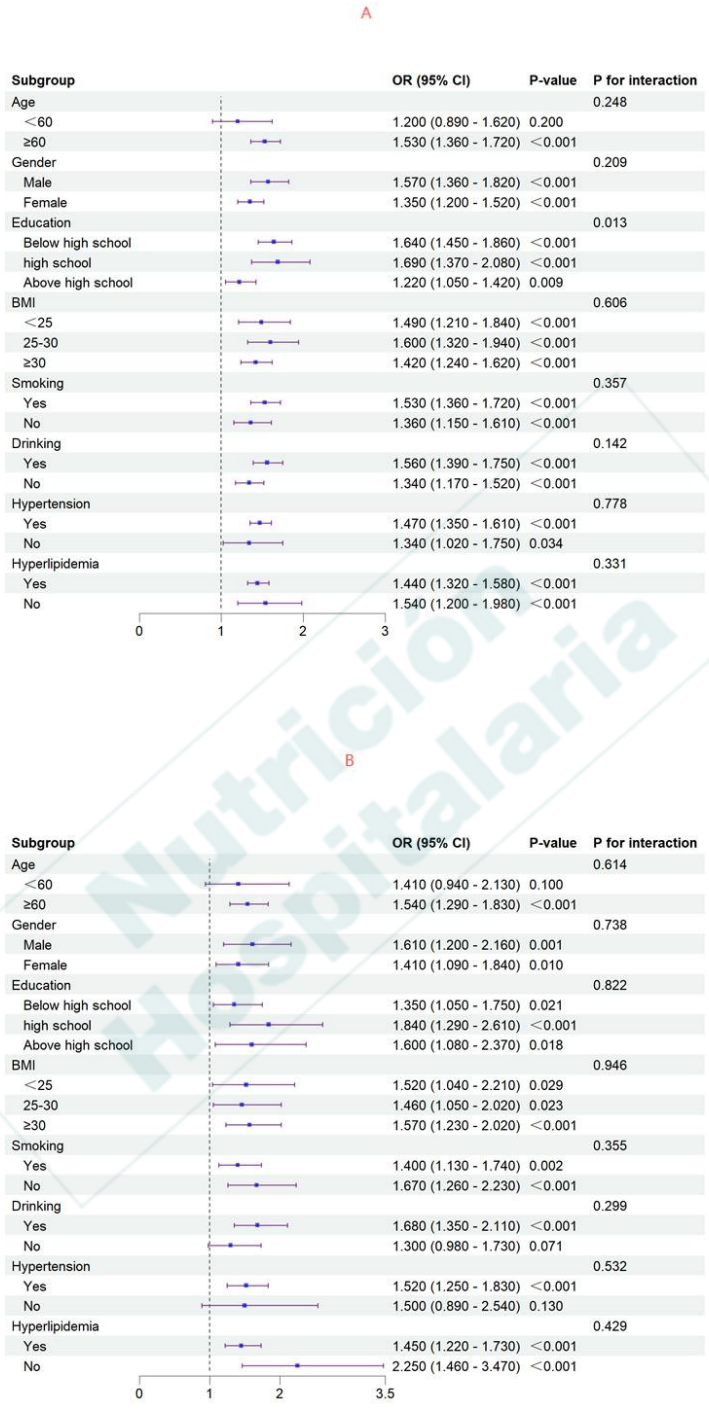

Figure 4. Association between NPS and all-cause and cardiovascular mortality in different subgroups of diabetic patients: A. For all-cause mortality. B. For cardiovascular mortality.

Table I. Baseline characteristics of subjects

Characteristic	**Total (*n* = 3663)**	***NPS points***			***p-value***
		0 (*n* = 479)	**1-2 (*n* = 2338)**	**3-4 (*n* = 846)**	
Age (years)	61.00 (51.00, 70.00)	55.00 (48.00, 63.00)	60.00 (50.00, 69.00)	65.00 (55.00, 74.00)	< 0.001
Gender (n, %)					< 0.001
Male	1941 (52.22 %)	310 (67.46 %)	1076 (46.61 %)	336 (41.20 %)	
Female	1722 (47.78 %)	169 (32.54 %)	1262 (53.39 %)	510 (58.80 %)	
Race (n, %)					< 0.001
Mexican American	656 (8.95 %)	123 (15.96 %)	428 (8.79 %)	105 (5.91 %)	
Non-Hispanic black	950 (14.19 %)	142 (19.64 %)	209 (14.37 %)	60 (9.24 %)	
Non-Hispanic white	1362 (64.02 %)	119 (50.21 %)	835 (63.12 %)	408 (73.78 %)	
Other Hispanic	365 (5.39 %)	48 (6.02 %)	236 (5.63 %)	81 (4.43 %)	
Other race	330 (7.45 %)	47 (8.16 %)	217 (8.07 %)	66 (5.40 %)	
Education (n, %)					> 0.9
Below high school	1234 (22.71 %)	168 (24.67 %)	790 (22.41 %)	276 (22.55 %)	
High school	854 (25.10 %)	114 (25.09 %)	537 (25.03 %)	203 (25.28 %)	
Above high school	1575 (52.19 %)	197 (50.23 %)	1011 (52.56 %)	367 (52.18 %)	
Marital status (n, %)					0.054

Married	2195 (64.46 %)	294 (65.55 %)	1379 (63.28 %)	522 (67.13 %)	
Unmarried	312 (8.45 %)	47 (9.94 %)	207 (9.32 %)	58 (5.33 %)	
Other	1156 (27.09 %)	138 (24.51 %)	752 (27.40 %)	266 (27.53 %)	
Family PIR (%)	2.55 (1.33, 4.55)	2.27 (1.16, 3.96)	2.57 (1.33, 4.61)	2.50 (1.46, 4.63)	0.1
Drinking (*n*, %)	2136 (61.14 %)	265 (58.15 %)	1421 (64.41 %)	450 (53.67 %)	< 0.001
Smoking (*n*, %)	1882 (51.62 %)	215 (46.65 %)	1187 (51.51 %)	480 (54.39 %)	0.2
BMI (kg/m^2)					0.5
< 25	468 (10.87 %)	66 (9.88 %)	292 (11.01 %)	110 (11.00 %)	
25-30	1048 (25.83 %)	145 (30.21 %)	692 (25.71 %)	211 (24.00 %)	
≥ 30	2147 (63.29 %)	268 (59.91 %)	1354 (63.28 %)	525 (65.01 %)	
DBP (mm Hg)	69.00 (61.00, 77.00)	73.00 (64.00, 80.00)	70.00 (61.00, 77.00)	66.00 (58.00, 75.00)	< 0.001
SBP (mm Hg)	126.00 (116.00, 139.00)	125.00 (116.00, 139.00)	126.00 (116.00, 139.00)	128.00 (115.00, 141.00)	0.7
Laboratory results					
Neutrophil count (× 10^9/L)	4.50 (3.60, 5.60)	4.00 (3.50, 5.00)	4.30 (3.50, 5.40)	5.40 (4.40, 6.60)	< 0.001
Lymphocytes (× 10^9/L)	2.00 (1.60, 2.60)	2.70 (2.10, 3.30)	2.10 (1.70, 2.60)	1.60 (1.30, 2.10)	< 0.001
Monocytes (×10^9/L)	0.60 (0.50, 0.70)	0.50 (0.40, 060)	0.60 (0.50, 0.70)	0.60 (0.50, 0.70) <0.001	< 0.001
NLR	2.20 (1.65, 2.94)	1.58 (1.26, 2.00)	2.08 (1.59, 2.59)	3.33 (2.75, 4.09)	< 0.001
LMR	3.60 (2.80, 4.75)	5.50 (4.88, 6.33)	3.67 (3.00, 4.63)	2.367 (2.17, 3.38)	< 0.001
Serum albumin (g/L)	41.00 (39.00, 43.00)	42.00 (41.00, 44.00)	42.00 (40.00, 44.00)	39.00 (37.00, 41.00)	< 0.001

TC (mg/dL)	174.00(149.00,206.00)	216.00(198.00,241.00)	177.00(151.00,206.00)	153.00(134.00, 169.00)	< 0.001
TG (mg/dL)	160.00(105.00,238.00)	209.00(142.00,296.00)	163.00(106.00,245.00)	138.00(94.00, 195.00)	< 0.001
HDL-C (mg/dL)	45.00 (38.00, 54.00)	45.00 (39.00, 55.00)	45.00 (38.00, 55.00)	44.00 (37.00, 53.00)	0.12
FPG (mg/dL)	130.00 (103.00, 181.00)	129.00 (102.00, 200.00)	129.00 (103.00, 179.00)	134 (105.00, 180.00)	0.5
HbA1c (%)	6.80 (6.10, 8.00)	7.00 (6.20, 8.70)	6.80 (6.10, 7.90)	6.90 (6.20,7.70)	0.2
Diseases, n (%)					
Hypertension	2989 (80.74 %)	367 (76.14 %)	1913 (80.60 %)	709 (83.45 %)	< 0.001
Hyperlipidemia	2995 (83.28 %)	451 (94.94 %)	1934 (85.10 %)	610 (72.48 %)	< 0.001
Antihypertensive drug *n* (%)	3094 (83.84 %)	374 (75.87,%)	1978 (83.41 %)	742 (88.97 %)	< 0.001
Diabetes duration (years)	9.00 (3.00,15.00)	5.00 (2.00, 10.00)	8.00 (3.00, 15.00)	11.00 (5.00, 20.00)	< 0.001

Normally distributed continuous variables are described as means and SEs, and continuo
anormal distribution are presented as medians (interquartile ranges). Categorical v
numbers (percentages). N reflects the study sample while percentages reflect the survey-weighted figures.
Naples Prognostic Score; PIR: povertyincome ratio; BMI: body mass index; SBP: systolic
diastolic blood pressure; NLR: neutrophil-to-lymphocyte ratio; LMR: lymph
cholesterol; TG: total triglyceride; HDL-C: high-density lipoproteincholesterol; FPG: fasting glucose; HbA1c: glycated
hemoglobin.

Table II. Association of the NPS with all-cause and cardiova

diabetes mellitus

Participants	**Model 1**		**Model 2**		**Model 3**	
	HR (95 % CI)	***p*-value**	**HR (95 % CI)**	***p*-value**	**HR (95 % CI)**	***p*-value**
NPS						
All-cause mortality						
Continuous	1.62 (1.49, 1.77)	< 0.001	1.50 (1.38, 1.65)	< 0.001	1.46 (1.33, 1.59)	< 0.001
NPS, points						
0	Ref		Ref		Ref	
1-2	1.62 (1.10, 2.39)	0.0140	1.18 (0.79, 1.75)	0.400	1.08 (0.71, 1.62)	0.700
3-4	3.78 (2.55, 5.59)	< 0.001	2.55 (1.68, 3.88)	< 0.001	2.22 (1.46, 3.38)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001
CVD mortality						
Continuous	1.66 (1.44, 1.90)	< 0.001	1.52 (1.30, 1.79)	< 0.001	1.51 (1.28, 1.78)	< 0.001
NPS, points						
0	Ref		Ref		Ref	
1-2	1.69 (0.83, 3.42)	0.150	1.18 (0.55, 2.54)	0.700	1.13 (0.52, 2.44)	0.800
3-4	3.63 (1.85, 7.13)	< 0.001	2.35 (1.08, 5.12)	0.032	2.23 (1.01, 4.93)	0.047

CI: confidence interval; HR: hazard rate. Model 1: unadjusted. Model 2

education,marriage,family income-poverty ratio (PIR). Model 3: further adjusted for body mass index (BMI), drink, smoke, history of hypertension, history of hyperlipidemia, use of glucose-lowering medications, duration of diabetes mellitus.