Diabetology & Metabolic Syndrome

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Association between magnesium depletion score and all-cause and cause-specific mortality in patients with diabetic kidney disease

Lingzhi Xing[1,4†], Yubowen Gong[2,4†], GuoJia Liao[1,4], Liying Wang[3*] and Ling Chen[4*]

Abstract

Background The prognostic value of Magnesium Depletion Score (MDS) in Diabetic Kidney Disease (DKD) patients is still unclear. This study aimed to determine the associations between MDS and long-term mortality in DKD population.

Methods Data were obtained from the National Health and Nutrition Examination Survey (NHANES III). MDS is calculated from four specific scoring items: estimated glomerular filtration rate (eGFR), heavy drinking, use of proton pump inhibitors (PPI), and use of diuretics. Multivariate Cox proportional hazards regression models was employed to explore the association between MDS and all-cause and cause specific mortality, with emphasis on age-specific analysis.Mediation analysis explored if metabolic indices mediate the relation between MDS and mortality. Sensitive analyses were performed to check the robustness of the main findings.

Results 3,179 patients with DKD were included in this study, with 1,698 females and 1,481 males. The multivariate Cox regression analyses showed higher MDS were significantly associated with the all-cause mortality of DKD population [MDS ≥ 3: adjusted hazard ratio (HR):1.932, 95% confidence interval (CI): 1.339–2.787,$p < 0.001$]. Meanwhile, the trend was also significant in cardiovascular mortality of the DKD population (MDS ≥ 3: HR = 3.688, 95%CI: 1.702–8.577,$p < 0.001$). Heavy drinking was the most influential factor among the four MDS scoring items that affects mortality outcomes. Mediation analysis showed increased MDS could slightly improve metabolic levels, but the improvement was insufficient to reverse the mortality outcome in DKD patients. Subgroup analysis manifested that the result was more applicable for patients over 60. The result of the sensitive analysis confirmed the robustness of the main conclusion.

Conclusions Our study highlights the clinical prognostic value of MDS in predicting the survival of the DKD population, especially among patients over 60. The findings imply that reducing alcohol consumption and

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performing routine cardiovascular health assessments for DKD patients with MDS > 2 are important for prolonging DKD patients' survival time.

Keywords Magnesium depletion score, Diabetic kidney disease, Mortality, Cardiovascular mortality, Heavy drinking, Prognosis

Introduction

Diabetic kidney disease (DKD), the most significant microvascular complication of diabetes, has become a critical issue in diabetic patients as the prevalence of DKD among diabetic patients is as high as 25% globally [1]. In many high and middle-income countries, an increasing number of DKD patients require dialysis or even kidney transplantation, which has put a heavy burden on medical resources and human well-being. The progression of DKD not only increases the incidence of end-stage kidney disease (ESKD) and cardiovascular events but also raises mortality rates [2]. Therefore, identifying and regularly monitoring biomarkers that can predict adverse outcomes in DKD is crucial.

Magnesium Depletion Score (MDS), an innovative anthropometric index introduced by Fan et al. in 2021, is used to identify magnesium level. Compared to markers like magnesium tolerance test (MTT) and serum magnesium, MDS is more convenient and scientifically validated [3]. MTT, though regarded as the gold standard for assessing systemic magnesium status, has limited clinical utility due to its complex procedure [4,5]. Besides, detecting serum magnesium level is a primary method in clinical practice [6], but it represents only about 1% of total body magnesium as most magnesium is stored in bones, muscles, and soft tissues [7]. Therefore, relying solely on serum magnesium levels may overlook cases of magnesium deficiency [8,9]. MDS is a composite score combining factors like alcohol consumption, diuretic use, PPI use, and kidney diseases [10,11] that indicates kidney magnesium resorption status [12]. Given its practicality and precision, the association of MDS with various health conditions such as congestive heart failure, hypertension, systemic inflammation, osteoporosis, kidney stones, and metabolic syndrome has drawn increasing attention. However, research on magnesium in DKD patients is scarce and the prognostic role of MDS in such patients has not been investigated.

Magnesium deficiency could obstruct protein and polynucleotide synthesis [7], impair blood pressure regulation, and interfere with insulin metabolism [13,14], all of which contributes to kidney function decline. However, the kidneys are critical in maintaining magnesium homeostasis as they reabsorb over 80% of serum magnesium [15]. Therefore, impaired kidney function often results in diminished magnesium resorption [16,17]. This situation creates a vicious cycle, further accelerating the progression of DKD and increasing the mortality risk. Based on the current knowledge of magnesium, we hypothesize that magnesium levels may be associated with all-cause and cause-specific mortality, with the MDS potentially acting as a predictive marker for the development of DKD. Investigating the relationship between MDS levels and DKD outcomes is crucial for improving survival time and reducing mortality rate in DKD patients.

In the current study, our aim was to validate (1) the longitudinal association between MDS and all-cause and cause-specific mortality in DKD patients, (2) the risks of all-cause and cause-specific mortality outcomes based on different combinations of MDS scoring items (3) whether metabolic indices serve as a mediator between MDS and mortality. This study may assist physicians in identifying high-risk DKD patients for closer monitoring and providing timely treatment.

Methods

Data source

The National Health and Nutrition Examination Survey (NHANES), an ongoing study program in the US, offers population estimates regarding nutrition and health of adults and children. The survey employed a stratified, multistage probability design to get a representative sample. Data are collected through home interviews, health exams at mobile centers, and laboratory specimen analyses [18]. All data are publicly accessible on the NHANES website (https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

Population selection

First, 135,310 NHANES (1988–2018) participants were reviewed. After excluding those without diabetes diagnosis ($n = 122,295$), under 18 ($n = 158$), or pregnant ($n = 34$), 12,823 respondents were chosen. To be a diabetic patient, one must meet criteria like: (1) fasting blood glucose (FBG) ≥ 126 mg/dL (7.0 mmol/L); (2) 2-hour plasma glucose (OGTT) ≥ 200 mg/dL (11.1 mmol/L); (3) glycated hemoglobin (HbA1c) ≥ 6.5% (48 mmol/mol); and (4) those answering affirmatively to having diabetes or with antidiabetic medication history. Then, participants lacking follow-up data ($n = 6$), medication and serum creatinine records ($n = 3,420$), and without DKD diagnosis ($n = 6,218$) were further excluded. Considering clinical evidence, DKD is defined as diabetics with chronic kidney disease (CKD). CKD inclusion criteria: albumin-to-creatinine ratio (ACR) ≥ 30 mg/g and/or eGFR < 60 mL/

min/1.73 m^2 [19]. Finally, 3,179 participants diagnosed with DKD were included in the study (Fig. 1).

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Definition of MDS

MDS was calculated by summing four specific scores: (1) current use of diuretics was assigned 1 point; (2) current use of PPIs also received 1 point [20]. The specific drugs included in the study were shown in Supplemental Table1(TableS1); (3) An eGFR between 60 mL/min/1.73 m^2 and 90 mL/min/1.73 m^2 was scored 1 point, while an eGFR below 60 mL/min/1.73 m^2 was assigned 2 points; (4) heavy drinking, defined as more than one drink per day for women and more than two drinks per day for men, was scored 1 point. eGFR was calculated using the CKD-EPI Creatinine Eq. (2021) algorithm (https://www.kidney.org/ckd-e.

pi-creatinine-equation-2021-0#) [21]. According to the Food Patterns Equivalents Database (FPED), alcoholic drinks encompass all types of beer, wine, distilled spirits (including brandy, gin, rum, vodka, and whiskey), cordials, and liqueurs. One drink is defined as containing 0.6 fluid ounces or 14 g of ethanol. The MDS was subsequently categorized into four groups: MDS = 0, MDS = 1, MDS = 2, and MDS ≥ 3 or into three levels: LOW MDS (MDS = 0), MOD MDS (MDS = 1), HI MDS (MDS ≥ 2) [22].

Assessment of covariates

Covariates in this study comprised age, sex, race, blood glucose control (classified as good: HbA1c < 7% or 53 mmol/mol; poor: HbA1c ≥ 7% [23]), BMI (calculated as body weight divided by height squared), heavy drinking (males: alcohol intake > 2 times/day; females: >1 time/day), heavy smoking (individuals who affirmed that they had smoked 100 + cigarettes), hypertension (mean SBP ≥ 140mmHg or DBP ≥ 90mmHg or using antihypertensive medications), cardiovascular disease (CVD) (congestive heart failure, coronary heart disease, angina, heart attack, or stroke), triglyceride and glucose index (TyG) index (ln(fasting TGs × fasting glucose/2)), atherogenic index of plasma (AIP) (calculated by serum TC/HDL-C ratio [24]), cardiometabolic index (CMI) (CMI = triglyceride (TG, mmol/L) / high-density lipoprotein cholesterol (HDL-C, mmol/L), waist circumference (WC, cm)/height (cm) [25]), and estimated glucose disposal rate (eGDR) (calculated using formula: eGDR = 21.158 – (0.09 × WC) – (3.407 × hypertension)–(0.551×HbA1c) with relevant parameters). Magnesium intake in NHANES was collected through a 24-hour dietary recall interview, using the USDA's Food and Nutrient Database for Dietary Studies (FNDDS 3.0) coding. The National Cancer Institute's (NCI) statistical model was applied to adjust for day-to-day variations and estimate the long-term usual intake. Other covariates such as eGFR, HbA1c, TC, TG, BUN, UA, HDL-C, LDL, FBG, serum phosphorus, serum total calcium, statins use, insulin use, metformin use, diuretic use, and PPI use were also included.

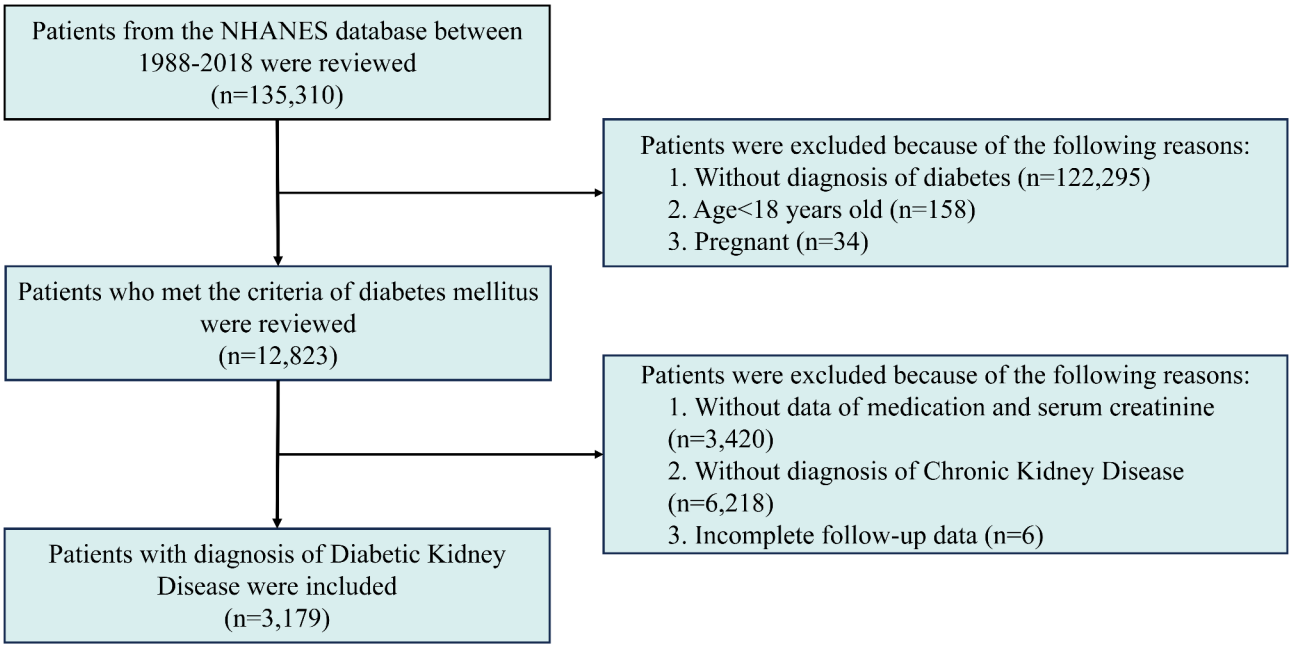

Fig. 1 The participants' selection process in the present study. A total of 135,310 participants from twelve cycles of NHANES between 1988 and 2018 years were reviewed and 3,179 participants with DKD were ultimately included. NHANES: National Health and Nutrition Examination Survey; DKD: diabetic kidney disease; FBG: fasting blood glucose; TG: triglyceride

Outcome measurements

The outcome of the current study was the all-cause and cause-specific mortality of the DKD population. The mortality data for the follow-up population were obtained from the NHANES public-use linked mortality file as of December 31, 2019, which was correlated with NCHS with the National Death Index (NDI) through a probability matching algorithm. The ICD-10 (International Statistical Classification of Diseases, 10th revision) was used to check the specific causes of mortality. The period of follow-up for each participant was determined by the time between the date of NHANES baseline examination and the date of death or 31 December 2019, whichever came first.

Statistical analysis

All data management and analysis were performed using SPSS 26.0 (2019), R Studio Software (version 3.5.2) or GraphPad Prism (version 9.5.1). Two-tailed P value < 0.05 was considered statistically significant. Continuous variables were presented as median(interquartile range) and categorical variables were expressed as counts(percentages), Mann-Whitney test for continuous variables and the Rao-Scott chi-square test for categorical variables were used in this analysis. Multiple imputation was performed for all variables with missing values no more than 30%.

Kaplan-Meier (KM) curves show the overall and cause-specific mortality probabilities of the DKD population with different levels of MDS, with differences compared using the log-rank test. Univariate Cox analysis were conducted and the three multivariate Cox proportional hazards models were fitted to estimate hazard ratios (HRs) between different MDS levels, along with the corresponding 95% confidence intervals (CIs). The proportional hazards assumption of each included variates in the models was checked with the schoenfeld residual test, and no violations were observed. Model 1 was unadjusted; Model 2 was adjusted for age and sex; Model 3 was further adjusted for age, sex, race, blood glucose control, BMI, magnesium intake, heavy drinking, HbA1c, TC, TG, HDL-C, FBG, serum phosphorus, serum total calcium, statins use, insulin use, metformin use, diuretic use, PPI use, eGFR, hypertension and CVD. The inclusion of the components of MDS not only helps control potential confounding effects of independent predictors and ensures the independent association between MDS and prognosis, while preventing the direct influence of individual components from confounding the overall score. Spearman correlation analysis was used to investigate the correlation coefficient score between four MDS scoring items and mortality rate. Subsequently, the mean survival time of individuals from three MDS levels (LOW, MOD and HI MDS) were shown in the bar chart. Structural equation modelling (SEM) was utilized to estimate if the associations between MDS and all-cause/cardiovascular mortality were mediated by AIP, CMI, eGDR, or TyG. The proportion of mediation/suppression effect was calculated by dividing the mediation effect ($\beta A \times \beta B$) by the total effect (βC), and results were shown via directed acyclic graphs. Subgroup analyses were carried out to assess MDS's effects on the incidence of both all-cause and cardiovascular mortality in subgroups like age (< / ≥ 60 years) [26], sex (male/female), CVD (yes/no), hypertension (yes/no), and blood glucose control (good/poor). Sensitivity analyses were conducted to evaluate the robustness of main findings. Participants with CVD developed during or before the survey were excluded to minimize reverse causation bias, and those who died within 2 years after the investigation were also excluded. The main results remained robust after these sensitivity analyses.

Results

Demographic characteristics of the DKD population

3,179 eligible DKD individuals from NHANES III (1988–2018) were identified and split into Survivors (n = 1,127) and Non-survivors (n = 2,052) groups based on survival status. The mean age was 71(14) years. Comparing the two groups, no significant sex difference (64.5% vs. 64.6%), but 73.3% of Non-Hispanic whites died in the Non-survivors group. The Non-survivors' average body mass index (BMI) was lower than the Survivors' (29.13 vs. 31.37). Over half of the DKD population had hypertension (2,429 cases), and CVD prevalence was higher in the Non-survivors group (829 cases vs. 360 cases). The Non-survivors were more likely to have higher lab indices (eGDR, TyG, TC, TG, BUN, LDL, FBG, CMI, AIP), lower eGFR, and worse blood glucose control (all P < 0.05). No significant differences in sex, magnesium intake, UA, and serum calcium between the groups (Table 1).

Survival patterns of DKD population in different levels of MDS

Among the 3,179 individuals with DKD, various causes of death were identified. The top six prevalent causes of death were all-cause mortality, cardiovascular mortality, malignant neoplasms mortality, diabetes mellitus mortality, cerebrovascular mortality, and lower respiratory mortality (TableS2). After implementing KM analysis, significant statistical differences were only observed in the all-cause and cardiovascular mortality of the DKD population with varied levels of MDS (P < 0.0001 and P = 0.0022, respectively) (Fig. 2A-F). Therefore, subsequent analyses focused exclusively on all-cause and cardiovascular mortality.

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Table 1 Baseline characteristics of participants in NHANES 1988–2018, stratified by survivors or Non-survivors

Variables	Total patients (*n* = 3,179)	Survivors (*n* = 1,127)	Non-survivors (*n* = 2,052)	*P* value
Demographic data				
Age (years)	71(14)	67(15)	73(14)	< 0.001
Sex,*n*(%)				0.505
Male	1,481(46.60)	526(35.50)	955(64.50)	
Female	1,698(53.40)	601(35.40)	1,097(64.60)	
Race,*n*(%)				< 0.001
Mexican American	445(14.00)	148(33.30)	307(66.70)	
Non-Hispanic White	1,453(45.70)	388(26.70)	1,065(73.30)	
Non-Hispanic Black	988(31.12)	399(40.43)	589(59.61)	
Other Race	273(9.21)	171(62.82)	102(37.23)	
BMI (kg/m2)	30.01(8.17)	31.37(8.99)	29.13(7.65)	< 0.001
Heavy drinking,*n*(%)	223(70.00)	129(11.40)	94(4.60)	< 0.001
Heavy smoking,*n*(%)	573(18.00)	38(3.37)	535(26.07)	0.005
Hypertension,*n*(%)	2,429(76.40)	927(82.30)	1,052(73.20)	< 0.001
CVD,*n*(%)				< 0.001
Yes	1,189(37.40)	360(30.20)	829(69.80)	
No	1,990(62.60)	767(38.50)	1,284(61.50)	
Laboratory data				
Magnesium intake (mg)	224(133)	224(134)	224(133)	0.583
eGFR (mL/min/1.73m2)	49.8188(17.03)	52.4436(16.04)	48.1831(17.54)	< 0.001
eGDR (mg/kg/min)	4.4692(2.24)	4.1123(2.34)	4.5683(2.12)	< 0.001
TyG	6.8218(0.88)	6.8555(0.77)	7.0189(0.91)	< 0.001
HbA1c (%,mmol/mol)	6.5(48)	6.6(49)	6.4(46)	< 0.001
Blood glucose control,*n*(%)				0.021
Good	1,869(58.80)	633(56.20)	810(39.50)	
Poor	1,310(41.20)	494(43.80)	1,242(60.50)	
TC (mmol/L)	4.7580(1.78)	4.4740(1.49)	5.0757(1.87)	< 0.001
TG (mmol/L)	1.4790(0.99)	1.4450(0.97)	1.4925(1.03)	< 0.001
BUN (mmol/L)	7.32(3.93)	7.140(3.92)	7.500(4.29)	< 0.001
UA (umol/L)	386.65(136.80)	392.6(124.90)	386.6(143.45)	0.879
HDL-C (mmol/L)	1.22(0.50)	1.24(0.52)	1.22(0.49)	0.405
LDL (mmol/L)	2.7410(1.50)	2.483(1.24)	3.00(1.60)	< 0.001
FBG (mg/dL)	136.4(51.86)	133(49.75)	138(55.10)	0.04
Serum phosphorus (mmol/L)	1.113(0.26)	1.13(0.20)	1.13(0.26)	< 0.001
Serum total calcium (mg/dL)	9.30(0.50)	9.30(0.50)	9.30(0.50)	0.993
CMI	0.92(1.17)	0.89(1.05)	0.97(1.22)	< 0.001
AIP	4.08(1.68)	3.76(1.50)	4.34(1.74)	< 0.001
Medications				
Statins use,*n*(%)	213(6.70)	117(10.40)	96(4.60)	< 0.001
Insulin use,*n*(%)	92(2.90)	32(2.80)	60(2.90)	0.913
Metformin use,*n*(%)	28(0.90)	20(1.80)	8(0.40)	< 0.001
Diuretic use,*n*(%)	16(0.50)	10(0.90)	6(0.30)	0.071
PPI use,*n*(%)	207(6.50)	52(4.60)	155(7.60)	< 0.001
MDS,*n*(%)				< 0.001
0	89(2.80)	54(4.80)	35(1.70)	
1	212(6.70)	94(8.50)	116(5.70)	
2	2,509(78.90)	834(74.00)	1,675(81.60)	
≥ 3	369(12.20)	143(12.70)	226(11.60)	

Note: Data are displayed as the median (interquartile range) or unweighted frequency counts (weighted percentage) as appropriate. The Mann-Whitney test for continuous variables and the Rao-Scott chi-square test for categorical variables were used in this analysis. TC, total cholesterol; TG, triglyceride; BUN, blood urea nitrogen; UA, uric acid; HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; FBG, fasting blood glucose. For categorical variables,*P* value was calculated by Chi-square test. For continuous variables, Independent Samples t-test was used to calculate*P* value

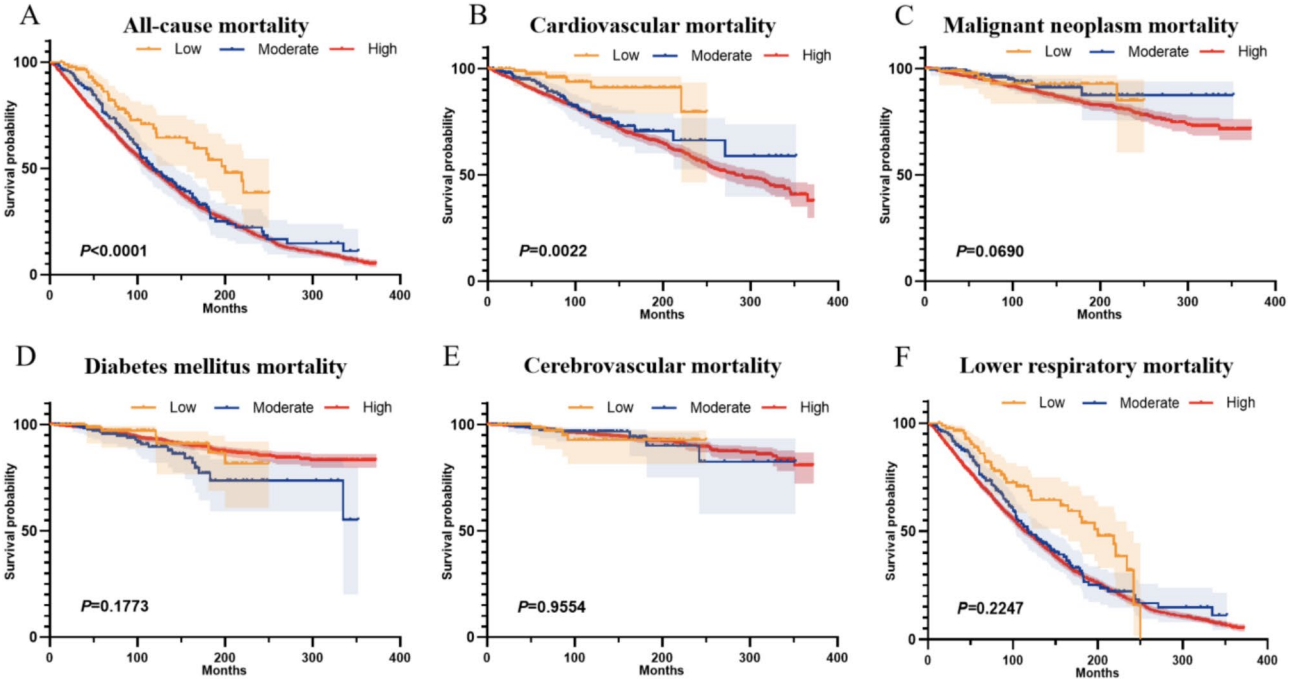

Fig. 2 Kaplan-Meier curves show the all-cause and cause-specific mortality probabilities of the DKD population in different levels of MDS. (**A**) all-cause mortality with different levels of MDS; (**B**) cardiovascular-specific mortality; (**C**) malignant neoplasm-specific mortality; (**D**) diabetes mellitus-specific mortality; (**E**) cerebrovascular-specific mortality; (**F**) lower respiratory-specific mortality

In all-cause and cardiovascular mortality, the KM curves showed that LOW MDS level showed significantly higher all-cause as well as cardiovascular survival probabilities when compared with those in MOD and HI MDS levels. Interestingly, around 100 months, the survival rates of MOD and HI MDS levels in both all-cause and cardiovascular mortality slightly converged. After 100 months, the survival rate of the MOD MDS level surpassed the HI MDS level again (Fig. 2A, B).

Association between MDS and all-cause mortality and cardiovascular mortality of DKD population

Cox proportional hazards models were employed to examine the relationship between MDS levels and all-cause/cardiovascular mortality. In univariate cox analysis, higher MDS was associated with higher risks of both all-cause and cardiovascular mortality. The risks of all-cause and cardiovascular deaths was 1.730 (95%CI: 1.212–2.470) and 3.191 (95%CI: 1.387–7.341) times higher in participants with MDS ≥ 3 than those with MDS = 0 without adjustment ($P < 0.01$). Also, age, sex, race, BMI, eGFR, HbA1c, TG, BUN, UA, serum phosphorus, CVD and CMI were related to clinical outcomes (TableS3). After adjusting for age and sex via multivariable Cox regression model, higher MDS levels were significantly associated with increased all-cause and cardiovascular mortality risks (Table 2Model 2). MDS remained an independent predictor of both all-cause and cardiovascular mortality even after adjusting for multiple factors in a multivariable Cox regression model (Table 2Model 3). The risk of all-cause and cardiovascular mortality was 1.932 (95%CI: 1.339–2.787) and 3.688 (95%CI: 1.586–8.577) times higher in participants with MDS ≥ 3 than those with MDS = 0 (P for trend < 0.001).

Spearman correlation coefficient score of four MDS scoring items and mortality rate

Spearman correlation analyses were also conducted to investigate the relativity between four MDS scoring items (eGFR, heavy drinking, PPI use, diuretic use) and mortality risk in DKD population. The results showed that eGFR and heavy drinking have higher correlation coefficient score (0.15 and 0.129 respectively, all$P < 0.001$, Fig. 3A). The bar charts showed the different combination of MDS scoring items in different populations: MDS = 1 (eGFR < 90 or Heavy drinking or Diuretic use or PPI use), MDS = 2 (eGFR < 60 or eGFR < 90 + Heavy drinking or eGFR < 90 + Diuretic use or eGFR < 90 + PPI use or Heavy drinking + PPI use or Heavy drinking + Diuretic use) and MDS ≥ 3 (eGFR < 60 + Heavy drinking or eGFR < 60 + Diuretic use or eGFR < 60 + PPI use or eGFR < 90 + Heavy drinking + Diuretic use or eGFR < 90 + Heavy drinking + PPI use). In MDS = 1 group, individuals who got 1 point from PPI use had the longest mean survival time while those who scored in Heavy drinking had the lowest mean survival time (119.15 months and 95.68 months respectively, Fig. 3B). In MDS = 2 group, individuals who got 2

Table 2 Multivariate Cox analysis of endpoint events in patients with diabetic kidney disease

	Events/Total	Model 1		Model 2		Model 3	
		HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
All-cause mortality	2052/3179						
MDS = 0	35/89	Reference	0.003	Reference	0.002	Reference	0.004
MDS = 1	116/212	1.581(1.083,2.307)	0.018	1.531(1.049,2.235)	0.027	1.724(1.178,2.523)	0.005
MDS = 2	1675/2509	1.809(1.294,2.529)	< 0.001	1.825(1.305,2.551)	< 0.001	1.864(1.321,2.631)	< 0.001
MDS ≥ 3	226/369	1.730(1.212,2.407)	0.003	1.767(1.237,2.523)	0.002	1.932(1.339,2.787)	< 0.001
Cardiovascular mortality	690/3179						
MDS = 0	6/89	Reference	0.008	Reference	0.006	Reference	0.015
MDS = 1	37/212	2.908(1.227,6.892)	0.015	2.798(1.180,6.631)	0.019	3.391(1.428,8.054)	0.006
MDS = 2	575/2509	3.613(1.616,8.078)	0.002	3.648(1.631,8.156)	0.002	3.839(1.700,8.672)	0.002
MDS ≥ 3	72/369	3.191(1.387,7.341)	0.006	3.669(1.421,7.521)	0.005	3.688(1.586,8.577)	< 0.001

Note: HR, hazard ratio; CI, confidence interval;

Model 1: unadjusted model

Model 2: adjusted for age and sex

Model 3: adjusted for age, sex, race, Blood glucose control, BMI, Magnesium intake, Heavy drinking, HbA1c, TC, TG, HDL-C, FBG, Serum phosphorus, Statins use, Insulin use, Metformin use, Diuretic use, PPI use, eGFR, Hypertension and CVD

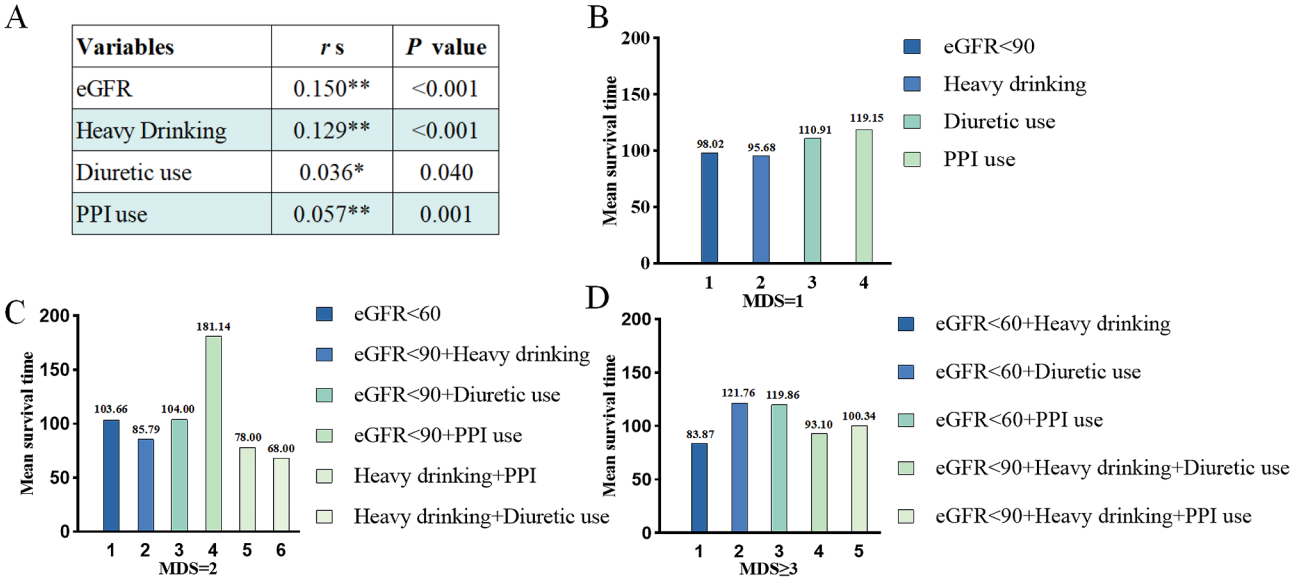

Fig. 3 (**A**) Spearman correlation coefficient score between four MDS scoring items and mortality rate in DKD patients. (**B-D**) The bar charts show the different mean survival time of DKD population with different MDS points. eGFR: estimated glomerular filtration rate; PPI: proton pump inhibitors

points from eGFR < 90 + PPI use had the longest mean survival time while those who scored in Heavy drinking + Diuretic use had the lowest mean survival time (181.14 months and 68.00 months respectively, Fig. 3C). And in MDS ≥ 3 group, individuals who got 3 points from eGFR < 60 + Diuretic use had the longest mean survival time while those who scored in eGFR < 60 + Heavy drinking had the lowest mean survival time (121.76 months and 83.87 months respectively, Fig. 3D). Due to the limitations of the NHANES medication database, there were no individuals using both diuretics and PPIs. As a result, the score composition for the MDS = 4 group was restricted to 1 point for diuretic or PPI use, 2 points for eGFR < 90, and 1 point for heavy drinking, making further stratification unfeasible. To ensure data completeness, the mean survival time for individuals with MDS = 4 was calculated, with a specific mean survival time of 58.85 months. In populations with different MDS scores, all combination groups with the lowest average survival time contained Heavy drinking.

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Mediation analyses

Mediation analysis indicated that metabolic indices including AIP, TyG, eGDR and CMI suppressed 18.1%, 26.4%, 25.9% and 10.9% of the association between MDS and all-cause mortality, respectively (Fig. 4A-D, Supplemental Table4). However, due to the masking effect in the

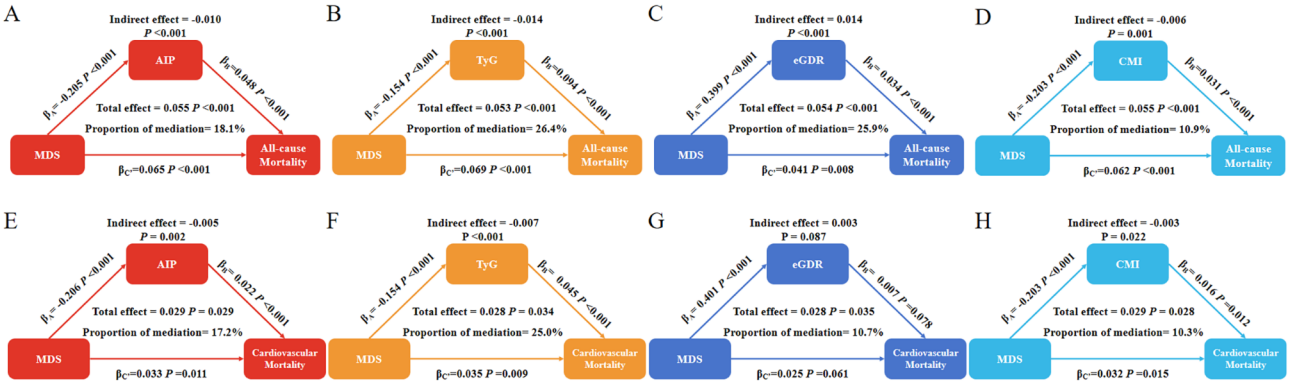

Fig. 4 Analysis of the mediation by metabolic indices of the associations of CMI and all-cause mortality and cardiovascular mortality. Association between MDS, mediation variables and all-cause mortality. (**A-D**) association between MDS, mediation variables and cardiovascular mortality. (**E-H**) Fully adjusted logistic regression models controlled for age, sex, race, blood glucose control, BMI, magnesium intake, heavy drinking, HbA1c, TC, TG, HDL-C, FBG, serum phosphorus, serum total calcium, statins use, insulin use, metformin use, diuretic use, PPI use, eGFR, hypertension and CVD. βA represents the effects of MDS on mediators; βB represents the effects of the mediators on outcomes; βC represents the effects of MDS on outcomes with mediators. Proportion of mediation was calculated via dividing indirect effect by direct effect. MDS: magnesium depletion score; AIP: atherogenic index of plasma; TyG: triglyceride and glucose index; eGDR: estimated glucose disposal rate; CMI, cardiometabolic index

mediation analysis of MDS and all-cause mortality, the results may underestimate the actual clinical mediation effects.

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Subgroup analyses

Subgroup analyses were performed to examine the robustness of the association between MDS and all-cause and cardiovascular mortality in different population settings (Fig. 5). The predictive performance of MDS on all-cause mortality was only modified by age (P for interaction < 0.001), patients over 60 years old with DKD in MDS ≥ 3 had a significant hazard ratio (HR = 1.145, MDS = 0 as reference) for all-cause mortality ($P = 0.009$). The relationship in other subgroups maintained consistent with the main results (P for interaction > 0.05 for sex, race, CVD, hypertension and blood glucose control).

[Cut]

Sensitivity analyses

To further investigate the robustness of the main findings, several sensitive analyses were performed. First, after excluding the participants with a history of CVD events (including congestive heart failure, coronary heart disease, angina, heart attack and stroke) at baseline, the MDS still remained significantly associated with all-cause and cardiovascular mortality (TableS5). After excluding the participants who died within 2 years after the survey, we confirmed the consistent associations between MDS and all-cause as well as cardiovascular mortality in the modified DKD population (TableS6).

Discussion

In this large prospective study on US adults, we found a positive correlation between MDS and all-cause and cardiovascular mortality in DKD patients. The association was more significant for all-cause mortality among individuals over 60 and remained robust for cardiovascular mortality across all ages. In addition, heavy drinking turned out to be the most hazardous factor among four MDS scoring items. Our findings emphasized the importance of maintaining low MDS scores, especially preventing heavy drinking, to prolong the mean survival time of DKD patients. Additionally, increased MDS could slightly improve metabolic levels, but the improvement was insufficient to reverse the mortality outcome in DKD patients.

Current evidence suggests that among patients with CKD, patients with insufficient magnesium intake showed higher risk of mortality [27]. Additionally, Ye et al. observed that in patients with cardiovascular diseases, the risk of both all-cause and cardiovascular mortality was more than twofold higher in participants with MDS ≥ 3 compared with those with MDS = 0 [28]. Although different studies have highlighted the promising predictive role of the MDS in different diseases, none have explored the prognosis role of the MDS in DKD population.

In the current study, we found that MDS is positively correlated with the risk of all-cause mortality and cardiovascular mortality in DKD patients. Previous studies had proved that magnesium plays a crucial role in various metabolic reactions [29,30]. However, deficiency of magnesium can result in decrease in protein synthesis, impediment to polynucleotide synthesis [31], abnormalities in blood pressure control, and disruptions in insulin metabolism [13,14]. Meanwhile, kidneys are responsible

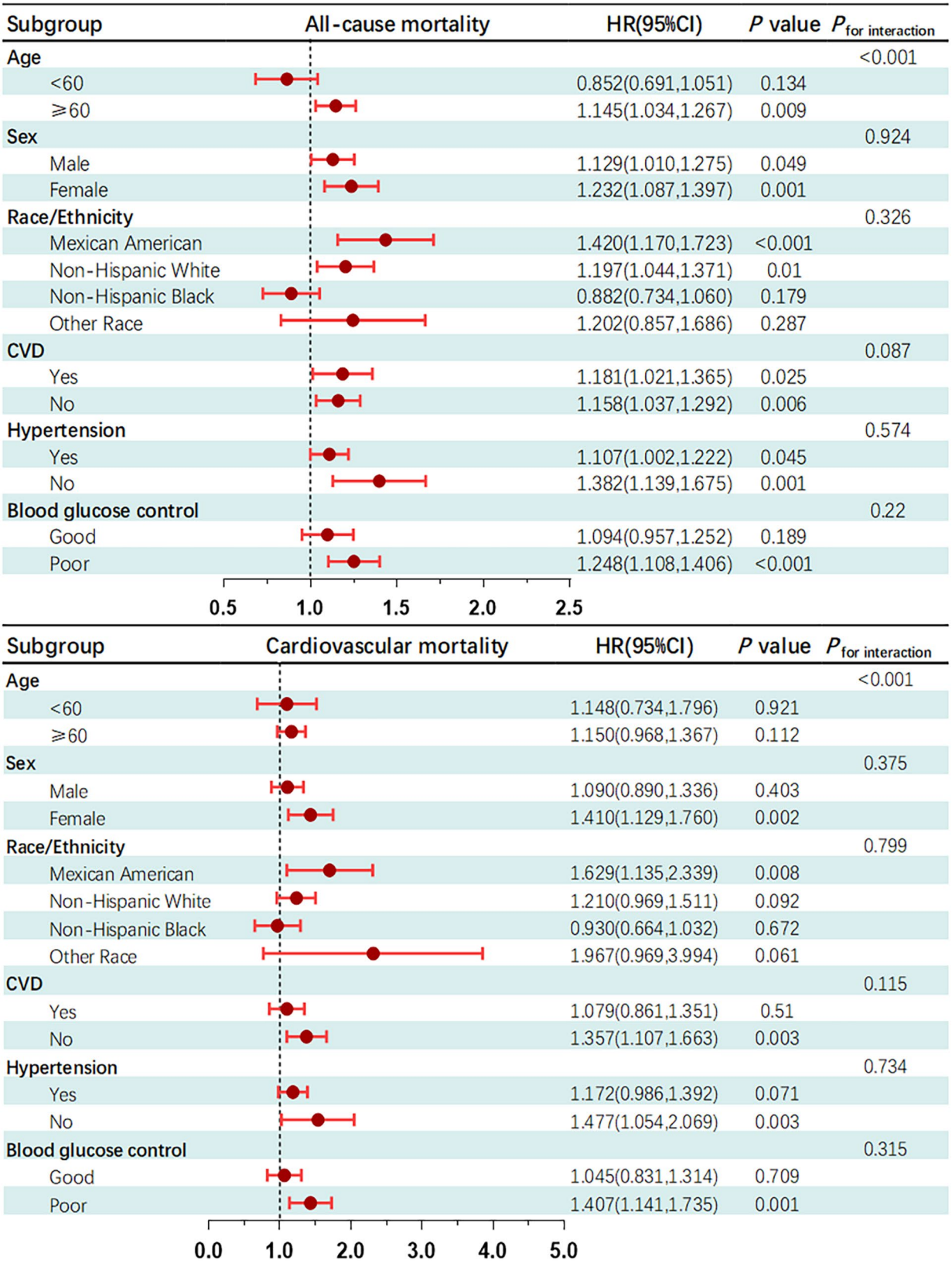

Fig. 5 (See legend on next page.)

(See figure on previous page.)

Fig. 5 Subgroup analyses show the associations between MDS and all-cause as well as cardiovascular mortality of the DKD population. The red box means HR value, and the bars on both sides of box mean 95% CI of HR. The subgroup analysis adjusted for age, sex, race, Blood glucose control, BMI, Magnesium intake, Heavy drinking, HbA1c, TC, TG, HDL-C, FBG, Serum phosphorus, Statins use, Insulin use, Metformin use, Diuretic use, PPI use, eGFR, Hypertension and CVD. (**A**) the association between MDS and all-cause mortality; (**B**) the association between MDS and cardiovascular mortality. CVD: Cardiovascular Disease

for maintaining magnesium homeostasis by reabsorbing the majority of magnesium from the bloodstream [15]. As kidney function declines in DKD patients, the ability to reabsorb magnesium is diminished, resulting in increased urinary magnesium loss. This depletion creates a vicious cycle, which may possibly contribute to the progression and poorer prognosis of patients with diabetic kidney disease.

MDS reflects patients' magnesium status, and its four indicators are closely tied to the kidneys. eGFR has been shown to be associated with electrolyte loss [32]. The U-shaped relation between alcohol consumption and kidney function shows that kidney damage from alcohol rises with consumption severity [33]. Loop-blocking diuretics cause magnesium loss via effects on the renin-angiotensin-aldosterone system and calcium and parathyroid hormone levels [34]. PPIs reduce kidney magnesium resorption by down-regulating the activity of TRPM6 [11,35]. In summary, magnesium and kidneys are closely linked, and MDS is a potent predictive tool as it encompasses the multifaceted role of magnesium depletion in metabolic dysfunction, vascular health, and renal impairment, crucial for DKD prognosis.

In our investigation of the mean survival time of DKD patients with different MDS scores, we found that heavy drinking had the most significant impact on survival time among four MDS scoring items. This result may be due to several reasons: First, heavy drinking causes a surge in the urinary excretion of magnesium, making its impact more pronounced compared to the other three indicators [36]. Second, heavy alcohol consumption is also related to arteriosclerosis and elevated blood pressure, which can lead to cardiovascular events. Third, heavy drinking is associated with a higher risk of heart disease, liver disease, stroke, seizures, and mortality including all-cause, cancer, and accidents, all of which contribute to a shorter survival time for patients.

In the indicators affected by magnesium, most reflect metabolic levels in the body, such as white blood cells, neutrophils, HbA1c, TG, HDL-C, and FBG, which provides new insights for our research. We assume that the MDS not only reflects the magnesium status in patients but also indicates their metabolic condition through glomerular filtration, lifestyles, and medications. Therefore, we hypothesize that MDS may influence all-cause and cardiovascular mortality by affecting metabolic indicators. To verify this hypothesis, we conducted mediation analysis using four common metabolic indices AIP, TyG, eGDR and CMI. However, the results showed that AIP, TyG and CMI had a suppression effect on the relationship between MDS and mortality, while eGDR had a mediating effect. Previous studies have indicated that AIP, TyG and CMI are positively correlated with mortality, whereas eGDR is negatively correlated with mortality in metabolic syndrome, systemic inflammation and hypertension [24,37–39]. We speculate several reasons for the findings: (1) MDS includes PPI and diuretic use. Higher MDS scores suggest higher medication use likelihood, which improves metabolic levels [40–43]. But the suppression effect is insufficient to reverse the outcomes. (2) DKD patients may have renal function decline symptoms and take other metabolism-related medications, thus affecting metabolic indices. MDS is an effective mortality predictor in DKD patients, but whether MDS affects metabolism and mortality needs further study.

We also identified age as a potential factor influencing the relationship between MDS and outcomes. Previous studies indicated that because of the structural characteristics of kidneys, renal parenchymal volume decreases by 10% every decade starting from age 30 to 40, with the most rapid decline occurring around age 60. Additionally, the prevalence of CKD increases substantially in the elderly due to to a significant increase in the incidence of eGFR decline beginning at age 60 [26]. Therefore, age 60 was selected as cut-off value and the results were more referential significant for individuals over 60. These findings underscore the importance of close clinical monitoring and regular kidney function assessments in patients aged 60 and above.

Interestingly, for the convergence of LOW MDS and HI MDS level around 100 months, we hypothesize HI MDS patients may have more obvious symptoms, follow medical advice better, and adhere to treatment, thus relieving symptoms. In contrast, MOD MDS patients may have less obvious symptoms and lower compliance. Lack of severe symptoms may lead to complacency or false sense of security, resulting in disease progression that may not manifest clinically until later stages. No studies have explained this, but clinicians should closely monitor MOD MDS patients to prevent a sharp drop in survival rates.

This study had several strengths including its large and nationally representative data resource from NHANES, high follow-up rate, detailed socioeconomical data and laboratory data. Notably, this study is the first of its kind to compare mortality outcomes in participants with DKD

using the updated linked mortality data through December 2018. Combining multiple NHANES cycles with a longer follow-up period significantly strengthens the statistical robustness compared with previous studies. Moreover, we adjusted for various potential confounders, including socioeconomic status and lifestyle factors. In clinical practice, our results highlighted the promising application prospect of MDS in DKD patients. And the prospective, population-based study design helps us to determine the robust evidence between MDS and mortality of the DKD population. Finally, the sensitive analysis shows consistent associations as we determine in the main findings.

Our study has several limitations. First, as an observational study, we are unable to establish definite causality and reverse causality may exist. However, it seems minimal as results were stable after excluding those with endpoints in the first two years. Second, as the baseline average age was 71(14), raising concerns about elder patients' ability to identify medications and adhere to instructions, potentially causing bias. Third, although our model adjusts for many covariates, residual confounding remains. Other baseline-reported variables like comorbidities may have changed during follow-up, which should be considered when interpreting findings. Fourth, due to the limitations of the NHANES medication database, there are no recorded cases of individuals simultaneously using both diuretics and proton pump inhibitors (PPIs). Fifth, due to the limitations of the NHANES database we couldn't evaluate if MDS is a more optimal magnesium deficiency indicator compared to serum magnesium. Moreover, Some outcomes had wide CIs, indicating low statistical power due to few reported events. Over half of the population had an MDS of 2, which may affect MDS group distribution differences and results, so these outcome estimates should be interpreted cautiously.

Conclusions

Our research found a significant positive correlation between MDS and both all-cause and cardiovascular mortality in DKD patients, particularly among those over the age of 60, and highlighted the predictive value of MDS for mortality in DKD patients, suggesting that MDS is a valuable index for assessing prognosis and guiding clinical treatment. Among four MDS scoring items, alcohol consumption has the strongest impact on mortality. This underscores that for DKD patients over 60, reducing the frequency and the amount of alcohol consumption, and simultaneously conducting regular MDS monitoring and cardiovascular examinations are crucial for prolonging their survival time and avoid poor prognosis. Furthermore, we revealed that although elevated MDS slightly improved metabolic levels, but the changes were insufficient to reverse the mortality outcomes in DKD patients. Further investigation is needed to elucidate the mechanisms by which MDS impacts prognosis in DKD and to assess the potential clinical benefits of magnesium repletion strategies in this population.

Supplementary Information

The online version contains supplementary material available athttps://doi.org/10.1186/s13098-025-01688-7.

Supplementary Material 1

Author contributions

Lingzhi Xing: Conceptualization, Formal analysis, Project administration. Yubowen Gong: Conceptualization, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Project administration. GuoJia Liao: Formal analysis. Liying Wang: Conceptualization, Writing - Review & Editing, Funding acquisition, Project administration. Ling Chen: Resources, Writing - Review & Editing, Supervision, Funding acquisition, Project administration.

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Data availability

The data that support the findings of this study are available fromhttps://www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate Informal consent was obtained from all adult participants of the NHANES, and the protocol was approved by the NCHS Research Ethics Review Board.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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