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Original Communication

Prognostic Value of the Magnesium Depletion Score for Mortality Outcomes Among NAFLD Patients

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Abstract

Background: The magnesium depletion score (MDS), a novel clinical score, incorporates alcohol consumption, kidney disease, use of diuretics and proton pump inhibitors (PPIs) to assess magnesium levels. However, the prognostic significance of the MDS individuals with nonalcoholic fatty liver disease (NAFLD) remains uncertain. This research aimed to explore the relationship between the MDS and mortality outcomes in NAFLD patients, including all-cause mortality, cancer mortality, and cardiovascular disease (CVD) mortality. **Method**: Data acquired on 16,394 NAFLD patients from the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2018 were analyzed in this cohort study. Mortality outcomes were assessed using the linked National Death Index, which included all-cause mortality, cancer mortality, and CVD mortality. Cox proportional hazards models were used to determine the hazard ratios (HRs) for mortality outcomes related to the MDS. Subgroup analyses were also performed to explore the potential modifying influences of different demographic and clinical characteristics. **Result**: An elevated MDS was associated with significantly higher risks of all-cause mortality (HR 1.22; 95% CI, 1.15–1.30), cancer mortality (HR 1.15; 95% CI, 1.03–1.28), and CVD mortality (HR 1.33; 95% CI, 1.18–1.51). While these associations remained consistent in many subgroups, factors such as gender, education level, and alcohol consumption influenced the link between the MDS and mortality. **Conclusion**: The MDS is as an innovative and feasible prognostic indicator for mortality among NAFLD patients. Incorporating the MDS into clinical practice could improve risk stratification and inform targeted interventions aimed at diminishing the risk of mortality linked to magnesium deficiency within this group.

Keywords: magnesium; NAFLD; NHANES

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is becoming more common among the population worldwide. This ailment includes a range of conditions, from simple buildup of fat in the liver, referred to as steatosis, to nonalcoholic steatohepatitis (NASH), marked by inflammation and harm to liver cells. NASH can progress to fibrosis (scarring) and even cirrhosis, independent of excessive alcohol consumption. Although steatosis does not correlate with increase in liver-associated morbidity or mortality, NASH can develop into severe conditions, such as cirrhosis and hepatocellular carcinoma (HCC), eventually leading to liver failure and requiring transplantation [1]. In 2020, some experts proposed renaming NAFLD as "metabolic dysfunction-associated fatty liver disease" (MAFLD) to emphasize the reciprocal relationship between fatty liver disease and metabolic change [2]. The increased rates in obesity and diabetes in the US and Europe have led to a growing prevalence of NAFLD, which has become one of the leading contributors to chronic liver conditions. As a result, the rates of hepatic decompensation, HCC, and deaths associated with NASH-related cirrhosis are anticipated to rise by 2–3-fold by 2030 [3]. The economic impact associated with NAFLD is significant [4,5]. In the USA, roughly 80 to 100 million people are impacted by NAFLD, making it a serious public health issue. The financial costs are notable, with expenses surpassing $103 billion each year [5]. In contrast to individuals with advanced fibrosis, a considerable percentage of those with early-stage NAFLD go undiagnosed. Consequently, the majority of economic and health burden associated with NAFLD arise during the later stages of this condition. Simple, reliable, and non-invasive markers are therefore desperately needed to identify people who are at high risk for NAFLD. Future healthcare expenses may be reduced if this illness is identified and treated early [6].

Magnesium ranks as the fourth most prevalent mineral within the human body [7]. Approximately 53% is found in the bones, 46% in muscles and soft tissues, and only 1% in the bloodstream [8]. Magnesium ions are crucial for almost all significant metabolic and biochemical functions at the cellular level. They are vital for bone development, the functioning of neuromuscular systems, and various signaling pathways. Magnesium is also crucial for the storage

and transfer of energy, in addition to its functions in the metabolism of glucose, lipids, and proteins. Moreover, it enhances the stability of DNA and RNA and participates in the process of cell proliferation [9]. Approximately 20% of individuals in developed nations are believed to experience magnesium deficiency [10], probably as a result of inadequate intake of this essential mineral. Furthermore, more than half of the American population fails to achieve the recommended dietary intake for magnesium, leading to an estimated prevalence of magnesium deficiency of around 15% [11]. Earlier research found a link between the levels of magnesium in the serum and diet, and conditions such as hypertension and diabetes mellitus (DM) [12–14]. Research has also established a potential connection between magnesium intake and NAFLD. One study indicated that higher magnesium intake may correlate with reduced risks of developing fatty liver disease and prediabetes [15]. Another investigation reported an inverse relationship between cumulative magnesium intake during early adulthood and the risk of NAFLD in midlife [16]. Furthermore, lower serum magnesium levels have been independently linked to biopsy-confirmed hepatic steatosis and steatohepatitis [17]. Generally, however, the serum magnesium is not an accurate indicator of the magnesium content within different body compartments and may not truly represent the overall magnesium status of the body. This inconsistency is largely due to the kidneys' function in reabsorbing over 80% of plasma magnesium, an essential mechanism for maintaining magnesium balance. Therefore, a serum magnesium level that falls within the normal range does not eliminate the possibility of magnesium deficiency [18]. Currently, no available method is deemed adequate for assessing the magnesium status of patients.

Magnesium depletion score (MDS) is an extensive scoring method that aims to assess the use of magnesium by clinical measures and medication history. Several factors that are prevalent in the US population can diminish the magnesium reabsorption capacity of the kidney, including alcohol consumption, kidney disease, and the use of diuretic and proton pump inhibitors (PPIs) [19]. MDS tallying points based on these risk factors and related pathophysiological mechanisms that influence renal magnesium reabsorption. This makes it superior to the use of serum levels for evaluating chronic magnesium status. MDS could improve the identification of individuals with low magnesium utilization as well as providing a more accurate assessment of total body magnesium status [19]. Research has indicated a link between MDS and certain diseases. For example, Zhao *et al*. [20] reported a relationship between MDS and the likelihood of congestive heart failure within the US civilian population. Furthermore, a positive relationship was observed between MDS and the occurrence of chronic obstructive pulmonary disease (COPD) [21].

To our knowledge, the association between MDS and the prognosis of NAFLD has not yet been investigated. In the present study we therefore analyzed the National Health and Nutrition Examination Survey (NHANES) database to investigate the relationship between MDS and mortality outcomes from NAFLD in American adults.

2. Materials and Methods

2.1 Study Population

This survey gathered extensive information regarding the health and nutrition of the American population by utilizing a mix of interviews and physical assessments. The information collected includes demographic, dietary, socioeconomic, and health-related details, in addition to medical, physiological, and laboratory examination results. The NHANES database undergoes regular updates, with new datasets generally made available every two years or so. This study included data from approximately 10 cycles of the NHANES conducted between 1999 and 2018. The initial sample comprised around 101,316 individuals. The Hepatic Steatosis Index (HSI) algorithm was applied to determine NAFLD [22]. HSI is a non-invasive scoring system validated across diverse populations for NAFLD screening. It incorporates aspartate aminotransferase (AST), alanine aminotransferase (ALT), body mass index (BMI), sex, and diabetes status, and is calculated as: HIS = 8 $\times$ (ALT/AST ratio) + BMI (with an additional 2 points for diabetes and 2 points for females). A threshold of HSI $\geq$36 demonstrates high specificity (92%) and sensitivity (93%) for detecting hepatic steatosis compared to imaging-based diagnoses [22]. Therefore, the HSI $\geq$36 was selected as the diagnostic criterion for NAFLD in this analysis.

Excluded from the study were individuals aged 18 years, and those with incomplete MDS information and mortality outcome data, ambiguous medical histories, or lacking sufficient information to allow calculation of the HSI. The final cohort for statistical analysis was comprised of 16,394 patients diagnosed with NAFLD (Fig. 1).

2.2 Assessment of MDS

MDS was assessed using method described previously for evaluating the systemic magnesium status [19]. This approach involves tallying points based on four criteria: (1) individuals who are currently on diuretics score 1 point; (2) the use of PPIs scores 1 point; (3) a glomerular filtration rate (eGFR) estimated between 60 and 90 mL/min/1.73 m^2 scores 1 point, while an eGFR $\leq$60 mL/min/1.73 m^2 scores 2 points; (4) heavy alcohol consumption—drinking (>1 drink per day for women and >2 drink per day for men)—scores 1 point. Participants with an MDS scores between 0 and 1 are categorized into the low MDS group, those with a score of 2 fall into the medium MDS category, while those scoring between 3 and 5 are placed in the high MDS group.

2.3 Primary Outcomes

The main focus of this research was all-cause mortality, cancer mortality and cardiovascular disease (CVD)

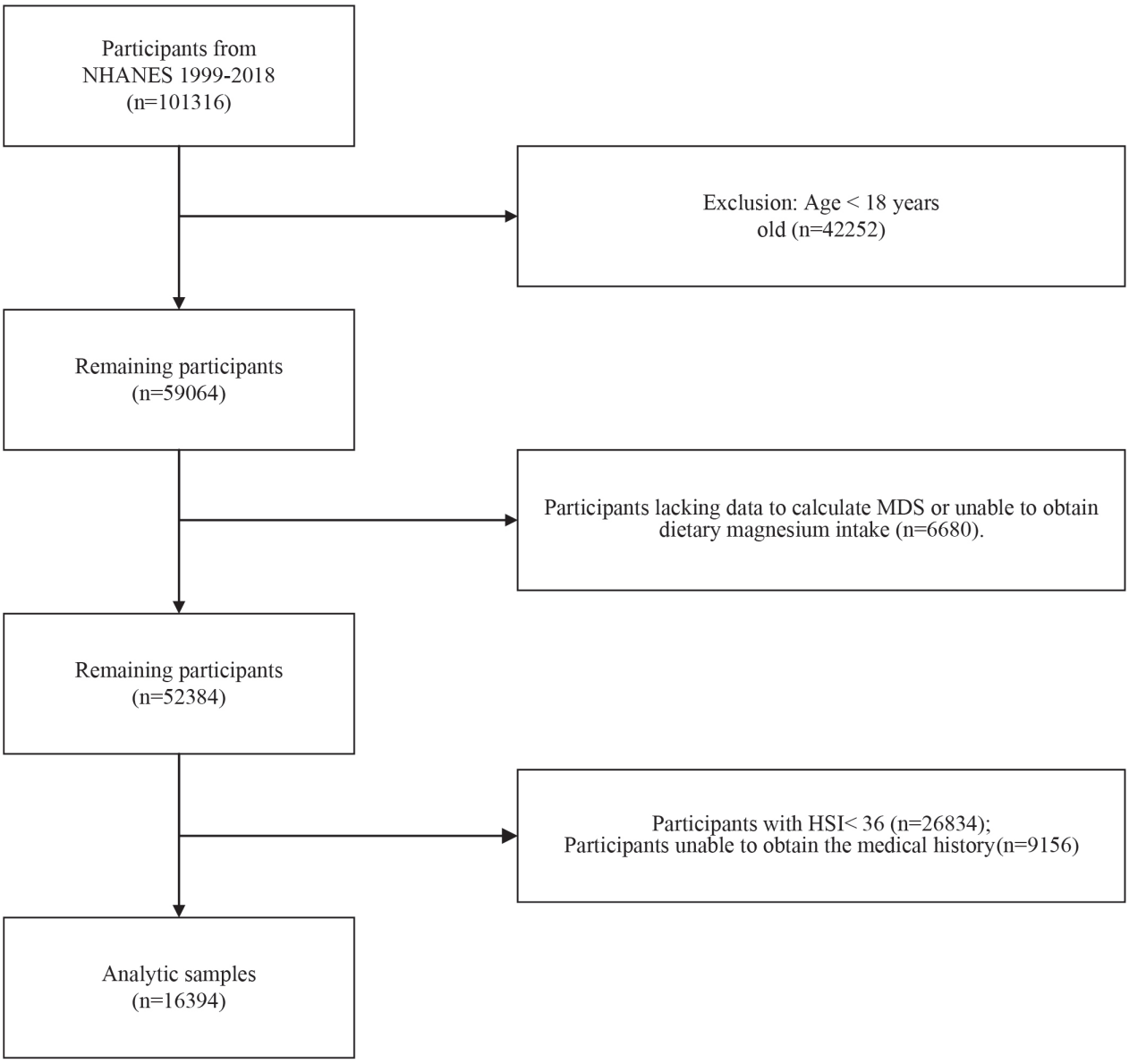

Fig. 1. Flow chart for enrollment of study participants. Abbreviations: MDS, magnesium depletion score; HSI, hepatic steatosis index; NHANES, National Health and Nutrition Examination Survey.

mortality. Data on mortality for the group under investigation were accessible up to December 31, 2019. A rigorous technique was used to match study participants to the National Death Index database of the Center for Disease Control and Prevention. All-cause mortality, cancer mortality (codes C00-C97), and CVD mortality (codes I00-I09, I11, I13, I20-I51) were categorized using the International Classification of Diseases, Tenth Revision (ICD-10).

2.4 Covariates

The covariates for study participants encompassed sociodemographic, behavioral, health characteristics, and biochemical information. These were gathered using surveys and laboratory assessments. The demographic details comprised age, gender, race, educational attainment, marital status, family poverty-to-income ratio (Family PIR), BMI, dietary magnesium intake, as well as smoking and alcohol use. Biochemical data included the levels of triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), eGFR, serum creatinine (Cr), serum albumin and glycated hemoglobin A1c (HbA1c) levels.

Dietary magnesium intake data from the NHANES were collected through two 24-h dietary recalls. These were conducted at the Mobile Examination Center (MEC) and via telephone 3 to 10 days later, using a United States Department of Agriculture (USDA)-developed tool by trained interviewers. To reduce bias, the average intake over two days was calculated and categorized it into quartiles.

Health information included hypertension, hyperlipidemia, DM, prediabetes, COPD and CVD. Prediabetes was defined as HbA1c measurements ranging from 5.7% to 6.5%, a fasting plasma glucose (FPG) value of 5.6 to 7.0 mmol/L, or a 2-hour FPG reading during an oral glucose tolerance test (OGTT) falling between 7.8 and 11.1 mmol/L. In contrast, diabetes was identified by a physician's self-reported diagnosis of the condition or by having HbA1c levels of 6.5% or higher, FPG levels of 7 mmol/L or higher, or 2-h plasma glucose readings of 11.1 mmol/L or higher during the OGTT [23]. The diagnosis of hypertension in participants included a number of criteria: either receiving a diagnosis from a physician, recording systolic blood pressure (SBP) $\geq$140 mmHg, or diastolic blood pressure (DBP) $\geq$90 mmHg, or self-reporting the use of antihypertensive drugs.

2.5 Statistical Analysis

This study adhered to the statistical analysis procedures recommended by the Centers for Disease Control and Prevention (CDC). NHANES has a complex probability clustering design that assigns distinct sample weights to each respondent. Consequently, all statistical analyses conducted in the present study accounted for these weights and utilized the appropriate survey weights (MEC2yr) for weighting. Continuous variables were reported using means and standardized differences, while categorical variables were represented by frequencies and percentages. Weighted *t*-tests were utilized to assess statistical differences among continuous variables, while weighted χ^2 tests were employed to evaluate differences among categorical variables. The outcome variable in our study was time-to-event data with right-censoring. To examine the relationship between MDS and both all-cause and cause-specific mortality, we employed univariate and multivariate weighted Cox proportional hazards models, reporting the hazard ratio (HR) and 95% confidence intervals (CI). The proportional hazard assumption of the model was verified with Schoenfeld residuals (**Supplementary Fig. 1**).

The log-rank test and Kaplan-Meier analysis were used to evaluate cumulative survival rates among the various MDS groups. To reduce the impact of confounding variables, sensitivity analyses were conducted through the gradual adjustments of covariates in three separate models (Models 1–3). Furthermore, restricted cubic spline (RCS) regression was employed to illustrate the possible dose-response connection between MDS and mortality rates in individuals with NAFLD. Stratified analyses were also used to investigate the association between MDS and mortality, taking into account interactions across different demographic groups. R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria) and EmpowerStats software (version 2.0, X&Y Solutions, Inc. Boston, MA, USA) were used to perform all of the analyses in this study. Statistical significance was defined as a p-value ≤ 0.05.

3. Result

3.1 Baseline Characteristics of the Study Population

The characteristics of participants at baseline across the three MDS groups are shown in Table 1. Notably, the average age in the high MDS group was significantly older (68.08 $\pm$ 0.29 years) compared to the low (43.18 $\pm$ 0.19 years) and medium (59.38 $\pm$ 0.26 years) MDS groups. Participants in the low MDS group had lower BMI, HbA1c, CR, HDL-c, TG, and SBP compared to those in the high MDS group, but high values of TC, albumin, LDL-c, and eGFR. The low MDS group were generally better educated, had higher income levels, higher total magnesium intake, and were less frequently divorced, separated, or widowed. They were also more likely to consume alcoholic beverages compared to their high MDS group. Furthermore, participants in the low MDS group had lower rates of DM, hypertension, CVD, hyperlipidemia, and COPD.

3.2 Associations Between MDS and All-Cause Mortality in NALFD Patients

A total of 2783 deaths were reported in the study cohort over the median follow-up period of 14 years. To assess the relationship between MDS and the risk of all-cause mortality in individuals with NAFLD, we conducted weighted Cox regression analyses. In the unadjusted model, a one-point increase in MDS was associated with a 136% increase in the risk of all-cause mortality (Table 2). This association remained statistically significant after adjusting for potential confounders. In the fully adjusted model (Model 3), each one-point increase in MDS was associated with a 22% higher risk of all-cause mortality (Table 2). Furthermore, individuals in the medium MDS group had a 20% higher risk of all-cause mortality compared to the low MDS group, while those in the high MDS group exhibited a 64% increased risk (Table 2). In sensitivity analysis, the association between MDS and mortality risk remained robust even after excluding individuals who died within the first two years of follow-up (**Supplementary Table 1**).

Kaplan-Meier survival curves were used to examine the prognostic significance of MDS in NAFLD patients (**Supplementary Fig. 2**). The high MDS group demonstrated the highest mortality risk compared to the low and medium MDS groups. Additionally, RCS analysis and fully adjusted and weighted multivariate Cox regression analysis were employed to further explore the relationship between MDS and all-cause mortality. RCS analysis found no evidence of a nonlinear association between MDS and mortality risk (**Supplementary Fig. 3**).

3.3 Associations Between MDS and the Risk of Cancer Mortality in NALFD Patients

Of the 2783 deaths recorded in the study cohort, 638 were attributed to cancer. The relationship between MDS and cancer mortality in these patients was evaluated using weighted Cox regression analysis. In the unadjusted

Table 1. Baseline characteristics of the population under investigation.

Characteristics	Overall	MDS			*p*-values
		Low (0–1)	Medium (2)	High (3–5)	
Age (years)	47.06 (0.20)	43.18 (0.19)	59.38 (0.26)	68.08 (0.29)	<0.0001
Sex (%)					<0.0001
Female	18,375 (50.57)	14,086 (49.70)	2812 (51.52)	1477 (59.92)	
Male	18,669 (49.43)	14,474 (50.30)	2968 (48.48)	1227 (40.08)	
Race/ethnicity, n (%)					<0.0001
White	17,554 (71.27)	12,359 (68.40)	3469 (81.79)	1726 (83.23)	
Black	7296 (9.95)	5614 (10.26)	1128 (8.43)	554 (9.61)	
Mexican	6340 (7.66)	5572 (8.95)	573 (2.99)	195 (2.11)	
Other	5854 (11.12)	5015 (12.39)	610 (6.79)	229 (5.05)	
Family PIR, n (%)					<0.0001
<1.3	10,931 (20.11)	8664 (20.95)	1498 (15.73)	769 (19.80)	
1.3–3.5	14,165 (35.83)	10,779 (35.62)	2228 (34.90)	1158 (41.00)	
>3.5	11,948 (44.06)	9117 (43.43)	2054 (49.37)	777 (39.20)	
Marital status, n (%)					<0.0001
Divorced/Separated/Widowed	8180 (18.29)	5216 (15.36)	1867 (27.07)	1097 (35.62)	
Married/Living with a partner	22,556 (64.63)	17,614 (64.89)	3438 (64.52)	1504 (61.46)	
Never married	6308 (17.08)	5730 (19.75)	475 (8.41)	103 (2.92)	
Education, n (%)					<0.0001
College graduate or above	17,898 (39.73)	13,499 (39.10)	2911 (40.21)	1488 (47.11)	
Some college	10,822 (31.53)	8492 (31.94)	1593 (30.12)	737 (29.61)	
High school or less	8324 (28.74)	6569 (28.97)	1276 (29.67)	479 (23.28)	
Total magnesium intake (mg/day)	312 (2.09)	316 (2.18)	306 (4.11)	255 (4.51)	<0.0001
Smoking, n (%)					<0.0001
Former or Now	17,303 (46.59)	12,713 (45.12)	3111 (522.01)	1479 (52.66)	
Never	19,741 (53.41)	15,847 (54.88)	2669 (47.99)	1225 (47.34)	
Alcohol consumption, n (%)					<0.0001
Never	5031 (10.77)	3821 (10.73)	774 (9.80)	436 (13.79)	
Former	6471 (14.30)	4456 (13.10)	1260 (16.86)	755 (23.95)	
Mild	12,474 (36.29)	9427 (35.60)	2071 (39.17)	976 (38.25)	
Moderate	5635 (17.36)	4522 (17.52)	804 (17.22)	309 (15.48)	
Heavy	7433 (21.29)	6334 (23.05)	871 (16.95)	228 (8.54)	
HbA1c (%)	5.57 (0.01)	5.51 (0.01)	5.72 (0.02)	5.96 (0.03)	<0.0001
BMI (kg/cm^2)	28.82 (0.07)	28.57 (0.07)	29.39 (0.12)	30.67 (0.18)	<0.0001
Systolic Blood Pressure (mmHg)	122 (0.17)	120 (0.17)	128 (0.34)	132 (0.47)	<0.0001
HDL-c (mg/dL)	53.05 (0.17)	52.47 (0.18)	55.55 (0.36)	54.47 (0.48)	<0.0001
LDL-c (mg/dL)	116 (0.40)	117 (0.45)	117 (0.91)	107 (1.33)	<0.0001
Cr (μmol/L)	0.89 (0.00)	0.83 (0.00)	1.04 (0.01)	1.25 (0.02)	<0.0001
eGFR (mL/min/1.73 m^2)	93.77 (0.27)	100.14 (0.23)	74.12 (0.31)	57.69 (0.47)	<0.0001
CVD, n (%)					<0.0001
No	32,937 (91.46)	26,740 (94.94)	4528 (82.99)	1669 (66.14)	
Yes	4104 (8.53)	1818 (5.06)	1251 (17.01)	1035 (33.86)	
Hypertension, n (%)					<0.0001
No	21,296 (62.85)	19,218 (71.19)	1750 (37.63)	328 (14.30)	
Yes	15,748 (37.15)	9342 (28.81)	4030 (62.37)	2376 (85.70)	
DM, n (%)					<0.0001
No	19,146 (58.63)	16,214 (62.91)	2211 (46.34)	721 (32.13)	
preDM	11,534 (28.75)	8531 (27.23)	2064 (34.06)	939 (35.75)	
DM	6364 (12.62)	3815 (9.86)	1505 (19.61)	1044 (32.11)	
COPD					<0.0001
No	35,455 (96.00)	27,682 (97.04)	5363 (93.19)	2410 (89.15)	
Yes	1589 (4.00)	878 (2.96)	417 (6.81)	294 (10.85)	

Table 1. Continued.

Characteristics	Overall	MDS			*p*-values
		Low (0–1)	Medium (2)	High (3–5)	
Hyperlipidemia					<0.0001
No	10,180 (28.59)	8766 (31.83)	1072 (18.24)	342 (11.17)	
Yes	26,864 (71.41)	19,794 (68.17)	4708 (81.76)	2362 (88.83)	
TC (mg/dL)	197 (0.40)	196 (0.45)	201 (0.72)	194 (1.39)	<0.0001
Serum albumin (g/dL)	4.29 (0.00)	4.31 (0.00)	4.25 (0.01)	4.17 (0.01)	<0.0001
TG (mg/dL)	133 (1.28)	130 (1.47)	143 (2.58)	148 (3.56)	<0.0001

Abbreviations: MDS, Magnesium Depletion Score; Family PIR, family poverty income ratio; BMI, body mass index; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; TC, total cholesterol; Cr, creatinine; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus.

Table 2. Results of Cox regression analysis of the correlation between MDS and all-cause mortality in the NAFLD population.

MDS	Crude model	Model 1	Model 2	Model 3
Low	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium (HR 95% CI)	3.69 (3.29, 4.13) ***	1.31 (1.17, 1.46) ***	1.37 (1.22, 1.55) ***	1.20 (1.07, 1.36) **
High (HR 95% CI)	9.43 (8.22, 10.83) ***	2.09 (1.81, 2.41) ***	2.14 (1.83, 2.49) ***	1.64 (1.40, 1.91) ***
Per point increase in MDS	2.36 (2.25, 2.48) ***	1.32 (1.26, 1.39) ***	1.36 (1.28, 1.44) ***	1.22 (1.15, 1.30) ***

Note: Crude model: without adjustment.

Model 1: Adjusted for age (continuous variable), sex, race/ethnicity.

Model 2: Model 1 plus smoke, alcohol consumption, Family PIR, education, HbA1c, BMI, marital status.

Model 3: Model 2 plus dietary magnesium intake, Cr (continuous variable), TC (continuous variable), HDL-c (continuous variable), CVD, preDM.

Abbreviations: NAFLD, nonalcoholic fatty liver disease. $^{**}p < 0.01$, $^{***}p < 0.001$.

model, a one-point increase in MDS correlated with a 115% increased risk of cancer mortality (**Supplementary Table 2**). This relationship reminded significant after controlling for confounding variables. In the adjusted model (Model 3), each additional one point increase in MDS was associated with a 15% increase in the risk of cancer mortality (**Supplementary Table 2**). Furthermore, in comparison to the low MDS group, the adjusted model revealed a 7% higher risk of cancer mortality for the medium MDS group and a 65% increased risk for the high MDS group (**Supplementary Table 2**).

Kaplan-Meier curves revealed the rate of cancer mortality throughout the entire follow-up period was considerably lower in the low and moderate MDS group compared to the high MDS category (**Supplementary Fig. 4**). Furthermore, RCS analysis found no indication of a nonlinear association between MDS levels and the risk of cancer mortality in the study cohort (**Supplementary Fig. 5**).

3.4 Associations Between MDS and the Risk of CVD Mortality in NALFD Patients

A total of 1509 deaths in the study population were linked to CVD. In the unadjusted model, one point increase in MDS was associated with a 196% greater risk of mortality from CVD (**Supplementary Table 3**). Once all factors were considered, each additional point in MDS resulted in a 33% increase in the likelihood of CVD mortality (**Supplementary Table 3**). Moreover, in comparison to the low MDS group, the adjusted model revealed a 37% increased risk of CVD mortality in the medium MDS group and 138% increased risk in the high MDS group (**Supplementary Table 3**).

Kaplan-Meier curves revealed a significantly elevated risk of CVD mortality in individuals with high MDS compared to those with low or medium MDS scores (**Supplementary Fig. 6**). Furthermore, RCS analysis found no evidence of a nonlinear relationship between MDS and the risk of CVD death (all nonlinear $p > 0.05$) (**Supplementary Fig. 7**).

3.5 Stratification Analysis of the Relationship Between MDS and Risk of Mortality in NAFLD Patients

We next conducted a stratified analysis. The association between MDS and all-cause mortality in NAFLD patients across several subgroups was shown in Fig. 2, with the results indicating consistent relationships in most subgroup. Importantly, evaluations based on age, race, family PIR, and BMI did not show any significant interactions, suggesting these variables did not alter the predictive influence of MDS on all-cause mortality in NAFLD patients. Conversely, sex, smoking, alcohol consumption, and educational achievement all had a significant impact on the

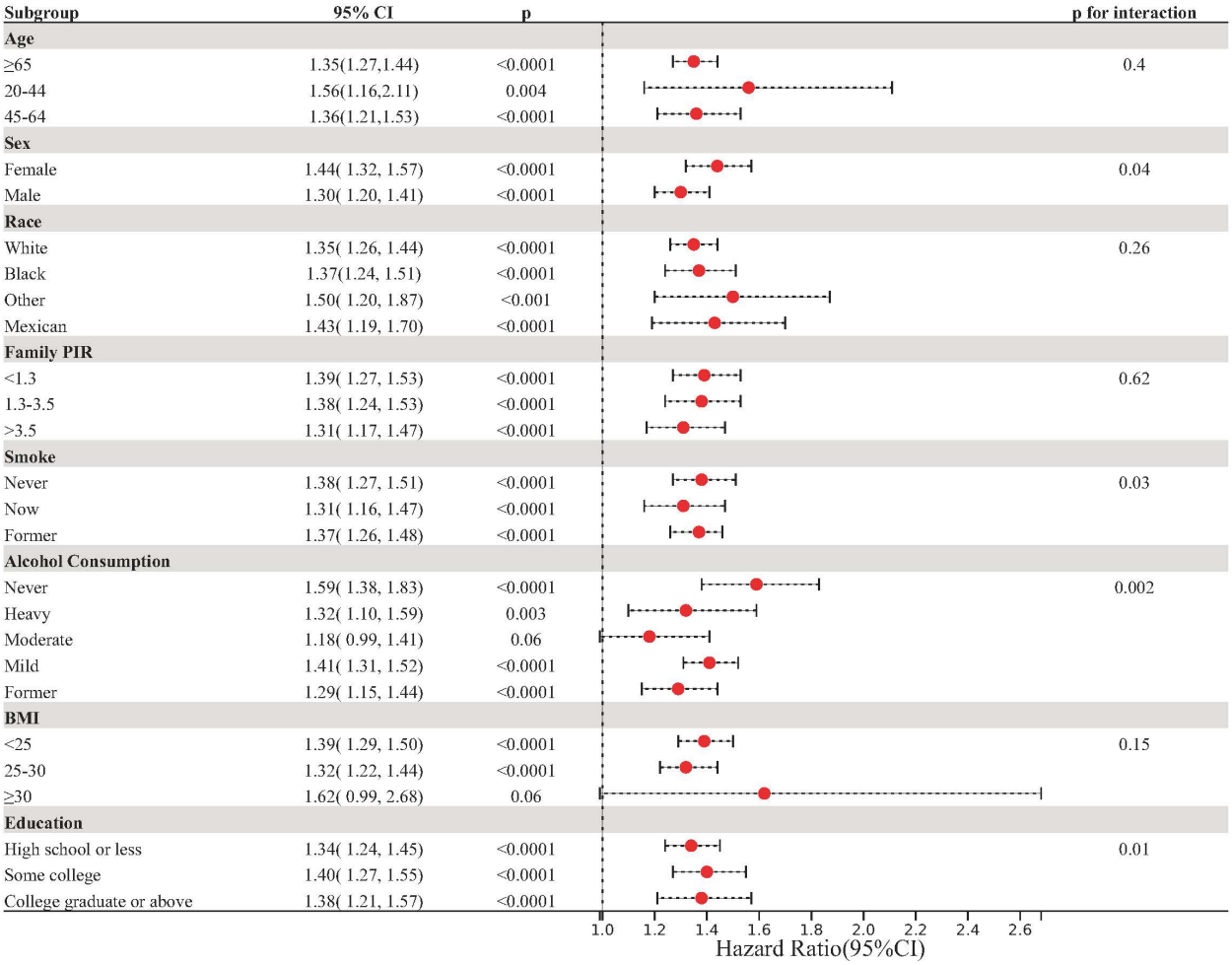

Fig. 2. Subgroup analysis of the association between MDS and all-cause mortality risk in patients with NAFLD. Subgroup analysis of the association between MDS and all-cause mortality risk (Hazard ratio, 95% CI) across different demographic data in patients with NAFLD. The adjustment of HRs involves the following covariates (excluding the stratified variables): age, sex, race/ethnicity, smoke, alcohol consumption, dietary magnesium intake, Family PIR, education, HbA1c, BMI, marital status, Cr, TC, HDL-c, CVD, preDM. CI, confidence intervals; HR, hazard ratio.

association between MDS and all-cause mortality. The risk was notably higher in participants who were female, non-smokers, non-drinkers, and had a college degree or above. These observations are essential for evaluating and controlling the mortality risk in NAFLD patients.

The correlation between MDS and the risk of cancer mortality in individuals with NAFLD did not differ significantly across subgroups categorized by age, sex, family PIR, smoking and education. This suggests that stratification with these variables did not modify the predictive ability of MDS in relation to cancer mortality. Importantly, the impact of MDS on the risk of cancer mortality showed significant variation according to alcohol consumption, particularly among heavy drinkers (HR, 2.31; 95% CI, 1.58–3.38) and mild drinkers (HR, 2.45; 95% CI, 2.13–2.82) ($p = 0.01$ for interaction) (**Supplementary Fig. 8**).

The association between MDS and CVD mortality in NAFLD patients remained consistent across subgroups stratified by age, sex, smoking status, family PIR, and education indicating these variables did not modify the predictive impact of MDS on CVD mortality (**Supplementary Fig. 9**).

4. Discussion

This extensive population-based study examined the relationships between MDS and the risk of mortality (all-cause, cancer, and CVD) among patients with NALFD. Our results demonstrated a clear and graduated link between higher MDS levels and increased risks of mortality, even after accounting for possible confounding factors. In particular, patients categorized as high MDS showed a significantly increased risk of mortality compared to those in the low MDS group. Stratified analyses revealed these associations were largely consistent across various demographic and clinical subgroups, although certain factors such as sex, education, and alcohol use appeared to modify the impact

of MDS on mortality. These results emphasize the significance of MDS as a prognostic factor in patients with NAFLD, highlighting the need for focused interventions to reduce these risks.

Serum magnesium is a well-studied biomarker, with low levels frequently associated with liver disease. Magnesium deficiency can adversely affect the progression of liver disease, probably because of its detrimental impact on mitochondrial bioenergetics. This deficiency negatively affects the synthesis of ATP in liver cells, increases oxidative stress within the liver, and ultimately worsens liver injury [24]. Insulin resistance is crucial for the development of NAFLD [25]. Magnesium is essential for the regulation of insulin secretion and its subsequent effects on liver, muscle, and adipose tissues through binding to the insulin receptor. Higher magnesium levels could therefore be a defense against steatosis and the development of NAFLD [26]. Cross-sectional studies have shown that individuals with NAFLD generally exhibit reduced magnesium consumption or lower serum magnesium levels compared to those without NAFLD [15,17].

A recent meta-analysis, encompassing over 1 million individuals and more than 52,000 deaths, found that higher dietary magnesium intake was associated with a reduced risk of all-cause and cancer-related mortality. However, no significant association was observed for CVD [27]. These findings highlight the potential protective role of magnesium in certain health outcomes, although its effects may vary across different disease categories. Building on these observations, another study used data from NHANES III to further explored the relationship between total magnesium intake and mortality due to liver diseases. A total of 13,504 participants underwent liver ultrasound examinations to assess hepatic steatosis. Interestingly, a borderline significant association was found between higher magnesium intake and a reduced risk of mortality of liver disease (p = 0.05) [28]. Moreover, in fully adjusted models, each 100 mg increase in daily magnesium intake was linked to a striking 49% reduction in the risk of death from liver diseases. Although the exact mechanisms remain unclear, these results may be attributed to the well-documented role of magnesium in mitigating inflammation and improving insulin resistance—two critical factors implicated in the progression of liver diseases. Several randomized controlled trials have shown that magnesium supplementation can significantly improve markers of inflammation and insulin resistance, particularly in individuals at high risk of magnesium deficiency or those with existing metabolic disturbances [29–31]. Taken together, these findings suggest that the beneficial effects of magnesium on the outcomes of liver disease could be mediated through its ability to modulate inflammation and insulin resistance pathways. This provides a plausible explanation for the observed inverse relationship between magnesium intake and liver disease mortality in the NHANES III cohort, underscoring the importance of magnesium in maintaining liver health. Furthermore, magnesium supplementation may offer long-term survival benefits for patients with NAFLD, highlighting its potential as a therapeutic target in this population.

Current research indicates that moderate magnesium deficiency is widespread in the United States [32]. To overcome the challenges in assessing magnesium deficiency, the MDS system was developed as a straightforward and user-friendly tool. MDS has been validated using the Magnesium Tolerance Test (MTT), thus proving its effectiveness in identifying magnesium deficiency. Additionally, MDS has been associated with a range of diseases and conditions [19,33,34]. In patients with chronic kidney disease, an independent association was found between MDS >2 and increased long-term mortality, both all-cause mortality and CVD mortality [34]. In a study of 42,711 NHANES participants, including 5015 with CVD, higher MDS was significantly associated with increased risks of all-cause and CVD mortality. Among CVD patients, 2285 all-cause and 927 CVD deaths were recorded. MDS ≥ 2 was associated with increased risk of CVD mortality, with each one point increase in the score being strongly predictive of total and specific CVD mortality, consistent across subgroups [33]. Luo *et al*. [35] reported an interesting correlation between MDS and sleep apnea, suggesting that MDS could be linked to longer sleep duration in older individuals. Another study suggested that MDS could be a standalone linear risk indicator for metabolic syndrome in US adults, irrespective of sociodemographic and behavioral variables [36].

To the best of our knowledge, this is the first study to evaluate the association between MDS and mortality in patients with NAFLD. Our findings demonstrate that MDS is as a strong and independent predictor of mortality risk in this population, including all-cause, cancer, and CVD mortality. In particular, subgroup analyses revealed that the association between MDS and all-cause mortality was significantly influenced by alcohol consumption, with this risk being more pronounced among non-drinkers (HR, 1.59; 95% CI, 1.38–1.83; p = 0.002 for interaction). This disparity may be attributed to the acute diuretic effect of alcohol on magnesium, which increases urinary excretion. Furthermore, manifestations of alcoholism are often linked to magnesium deficiency, and therapeutic benefits have been observed in alcoholic patients treated with magnesium supplementation [35]. Our results also indicate that the association between MDS and all-cause mortality in NAFLD patients was significantly stronger in those with higher education levels (p = 0.01 for interaction). This may be partly explained by behavioral differences across education levels. Highly educated individuals are often busy professionals who may adopt dietary patterns that inadvertently lead to insufficient magnesium intake, such as consumption of processed foods that are low in magnesium-rich whole grains, nuts, and leafy greens [11]. Despite engaging in healthier lifestyle choices such as regular exercise and not smoking,

the inadequate intake of magnesium could exacerbate mortality risk when combined with NAFLD. Additionally, the association between MDS and all-cause mortality was significantly modified by genders ($p < 0.05$ for interaction), with a stronger link observed for females. This increased risk in women may be due to biological and hormonal differences, as estrogen plays a protective role in metabolic regulation. This protection diminishes post-menopause, potentially amplifying the impact of magnesium deficiency [37]. Women may also exhibit greater sensitivity to nutritional magnesium deficiency due to lower baseline stores compared to men [38]. These findings highlight the importance of considering sex-specific factors when evaluating and managing mortality risk in NAFLD patients.

This research has several important advantages. It is the first extensive national investigation of the relationship between MDS and NAFLD, making use of the carefully constructed NHANES database. To ensure the representativeness of our findings for the entire US population, NHANES sampling weights were applied to all analyses. Additionally, we improved the validity of our findings by carefully adjusting for relevant confounders and performing sensitivity and subgroup analyses. The results demonstrated both biological plausibility and internal consistency. Furthermore, both recall and interviewer bias were reduced, since neither the participants nor the interviewers had knowledge of the study hypothesis while gathering data. The clinical utility of MDS lies in risk stratification and targeted interventions. High-risk patients (MDS $\geq$3) may benefit from: regular hepatic/cardiovascular monitoring; magnesium supplementation (300–400 mg/day) for those with dietary insufficiency; medication optimization (e.g., magnesium-sparing diuretics, PPI deprescribing); and dietary modifications that emphasizes leafy greens/nuts. These strategies align with evidence from trials showing the anti-inflammatory/insulin-sensitizing effects of magnesium [19,29–31,39]. Future trials should aim to validate these interventions in high-MDS cohorts in order to establish causality.

Although our research revealed a correlation between overall, cancer, and CVD mortality in people with NAFLD, certain inherent limitations exist. First, our ability to evaluate how MDS affects liver-related diseases mortality in NAFLD patients is limited by the lack of cause-specific mortality data for liver-related ailments. Second, the lack of serum magnesium data in NHANES prevented us from comparing the effectiveness of MDS with the serum magnesium levels as an indicator of magnesium deficiency. Future studies should directly compare MDS and serum magnesium to determine their complementary roles in risk stratification. This could help clarify whether MDS provides additional prognostic information beyond traditional serum magnesium assessment. Third, although we adjusted for several covariates in our analysis, we were unable to adjust separately for other medications that may affect magnesium metabolism (e.g., β-adrenergic agonists, bisphosphonates, and additional insulin formulations) due to limitations in the NHANES data. Therefore, residual confounding cannot be completely ruled out, and further studies that incorporate detailed medication history and more comprehensive dietary assessments are needed to validate the results. Fourth, although MDS takes into account the use of PPIs and diuretics, it fails to include other drugs that influence magnesium levels, including tetracyclines, bisphosphonates, β-adrenergic agonists, and insulin [40]. Fifth, the NHANES dataset, while nationally representative through its multistage sampling design, lacks sufficient granularity to analyze geographic variations such as state-level differences or urban versus rural disparities. Sixth, since this study is based on NHANES data, which primarily reflects the situation in the United States, the external generalizability of the results is somewhat limited. Future research should conduct external validation in cohorts from other regions with different population characteristics and healthcare systems to further confirm the prognostic value of MDS in various contexts. Seventh, while our study rigorously analyzed mortality endpoints, the NHANES-linked National Death Index lacks granular ICD-10 coding for NAFLD-specific mortality. This limitation precludes differentiation between liver-related versus other causes of death in advanced NAFLD. To validate the prognostic specificity of MDS, future studies should prioritize multinational collaborations with registries that capture liver-specific mortality and integrate histological endpoints. Concurrently, interventional trials are necessary to assess whether magnesium repletion directly reduces hepatic decompensation events in biopsy-proven NASH patients with elevated MDS. Eighth, we relied on the noninvasive Hepatic Steatosis Index (HSI) rather than imaging or histological gold standards to diagnose NAFLD, which may lead to misclassification of some individuals. Future studies should incorporate imaging or pathological data to externally validate the diagnostic performance of HSI in various subgroups, thereby ensuring its reliability in large-scale epidemiological studies. Finally, intervention studies are needed to determine whether magnesium supplementation can reduce liver-related complications in biopsy-proven NASH patients with high MDS scores. To further clarify the biological role of magnesium in NAFLD progression, we plan to conduct animal and cell-based studies to examine its effects on inflammation and insulin resistance, as well as clinical trials to evaluate whether magnesium supplementation improves metabolic health and patient outcomes.

5. Conclusion

This study found that MDS may serve as an innovative and feasible prognostic indicator of in NAFLD patients, while highlighting the need for targeted interventions to reduce the associated risks for this condition.

Availability of Data and Materials

The detailed data supporting the conclusions of this article are available at https://www.cdc.gov/nchs/nhanes.

Author Contributions

YD, WW and BS designed the study. YD and WW drafted the manuscript. YD, WX and YF acquired, analyzed, and interpreted the data. YD and WW revised the manuscript for important intellectual content. All authors drafted the work or reviewed it critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the NCHS Research Ethics Review Board (ERB) (https://www.cdc.gov/nchs/nhanes/irba98.htm). All patients or their families/legal guardians provided written informed consent prior to their involvement. This study strictly adhered to the ethical principles of the Declaration of Helsinki and approved by Shanghai Tongji hospital Ethics Committee (Ethical Approval Number: K-W-2024-006).

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR33514.

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