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Original Communication

Prevalence and Prognostic Significance of Malnutrition in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD)

Jing Xu[1,†], Jing Li[1,†], Hanhan Chen[1], Qing Li[1], Yingyi Wu[1], Xujiao Chen[1], Xiangjun Kong[1,*]

[1]Department of Ultrasound, Ningbo Medical Center Lihuili Hospital, 315000 Ningbo, Zhejiang, China
*Correspondence: nwl_890704@163.com (Xiangjun Kong)
[†]These authors contributed equally.
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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) has become the primary cause of chronic liver disease. Although malnutrition is a common late-stage clinical consequence during the course of organ dysfunction and death in critical patients, it has not received sufficient attention in the context of NAFLD. The aim of this study was to explore the prevalence and prognostic significance of malnutrition in patients with NAFLD using three simple tools for nutrition assessment. **Methods**: Participants (n = 3908) in the National Health and Nutrition Examination Survey (NHANES) database were divided into NAFLD (n = 1737) and non-NAFLD (n = 2171) groups. The controlling nutritional status (CONUT) score, prognostic nutrition index (PNI), and nutrition risk index (NRI) were applied to investigate the association between malnutrition and mortality among NAFLD patients. **Results**: The median age of participants was 54.0 years, with females accounting for 52.2% of the study cohort. A majority of elderly male participants had NAFLD, and up to 18% of NAFLD patients suffered from malnutrition. During the average period of follow-up (24.4 $\pm$ 7.2 months), 36 all-cause deaths occurred in the NAFLD group. Multivariate analysis revealed that malnutrition was associated with significantly higher mortality compared with normal nutrition. The adjusted hazard ratio (HR) for PNI was 4.44 (95% CI: 2.07–9.53, $p < 0.001$), and for NRI it was 6.98 (95% CI: 1.47–33.11, $p = 0.014$). The CONUT score also showed a trend for association with higher mortality. **Conclusion**: Malnutrition is a common comorbidity in NAFLD patients and is closely associated with poor prognosis and higher mortality. The three nutrition assessment tools employed in this study could be used to improve the predictive ability of nutritional status for mortality among NAFLD patients.

Keywords: all-cause mortality; body mass index; malnutrition; nutrition assessment; NAFLD

1. Introduction

The incidence of non-alcoholic fatty liver disease (NAFLD) has increased in recent years, with a global prevalence of 25%. The capacity of the liver to process primary metabolic energy substrates diminishes following the development of NAFLD. This results in the accumulation of toxic lipids and the induction of liver cell stress, which gradually leads to inflammation, tissue damage, and even death. Although NAFLD is the leading cause of chronic liver disease, most patients are diagnosed with mild or mild-to-moderate fatty liver disease, without further progression to fibrosis or advanced cirrhosis. However, similar to diabetes, hypertension, and metabolic syndrome, the high prevalence of NAFLD and the possibility of disease progression still pose a potential risk to patient health [1,2].

The majority of NAFLD patients suffer obesity, and generally present with a heavier body weight and higher body mass index (BMI). In contrast, malnutrition is generally associated with lower BMI. Nevertheless, recent studies have emphasized that BMI is not a good indicator of nutritional status, and some obesity may actually be due to poor nutritional quality [3,4]. Malnutrition and changes in the intestinal microbiota can also affect the progression of NAFLD [1,5]. Obesity, usually defined as having too much body fat, is damaging to human health. At present, the incidence of obesity is still on the rise worldwide [6]. In recent years, people have gained a lot of knowledge related to the biology of obesity, but the information is still limited in controlling the prevalence of obesity. More and more scholars believe that BMI alone cannot be relied on to assess obesity, and that insulin resistance and genetics seem to play a more important role in determining the risk of obesity comorbidities. There is also much unknown about the effects of interactions between individual behavior and life circumstances. Sarcopenic obesity has become an important research area to verify the poor prognosis of malnutrition-related diseases in the future [7]. However, BMI is still used as easy tool to quickly and directly classify patients for risk and monitor changes in obesity [8].

Malnutrition is a common late-stage clinical consequence during the course of organ dysfunction and death in critically ill patients. It is often caused by inadequate nutrient intake, malabsorption, or disproportionality. However, early nutritional status is a significant predictor of disease progression and long-term prognosis in such patients. Severe malnutrition is strongly linked to prognosis and complications, but such relationships are still unclear in NAFLD patients, especially the early nutritional status.

Recently, several malnutrition scales have attracted increasing attention and are now widely used in the clinical setting. These include the controlling nutritional status (CONUT) score, prognostic nutrition index (PNI), and nutrition risk index (NRI), all of which provide an accurate evaluation of the nutritional status and malnutrition. These three objective scales provide a better reflection of the patients' nutritional status than BMI. Specifically, the malnutrition status determined by the scales has been correlated with an elevated risk of adverse long-term consequences, including death and severe disability [9]. Malnutrition also contributes to a higher incidence of dysfunction and mortality in patients with diabetes, chronic kidney disease (CKD) and cardiovascular disease. The aim of this study was therefore to explore the prevalence of malnutrition among NAFLD patients in the United States, as well its association with adverse clinical events. In addition, we explored the predictive significance of malnutrition for the prognosis of NAFLD patients, as evaluated by CONUT, PNI and NRI.

2. Methods

2.1 Study Population

All study participants were recruited from the National Health and Nutrition Examination Survey (NHANES) database. NHANES is a major program of the National Center for Health Statistics (NCHS) first implemented by the Centers for Disease Control and Prevention (CDC) in the early 1960s, and which then became a continuous program in 1990. An independent data subset was formed every two years. This can be analyzed individually or combined with other subsets according to the corresponding sampling strata and weighting parameters. NHANES is a cross-sectional database with continuous, national, stratified, and multi-stage sampling survey data from the general population of the United States. It includes self-reporting parameters (demographics, health condition, health-related behaviors, history of use of medical service), physical examination, and laboratory tests. All participants in NHANES have a unique serial number which can be matched to the National Death Index (NDI) to obtain his/her death information. Detailed information is publicly accessible via a website (https://www.cdc.gov/nchs/nhanes/index.htm). The NCHS institutional review board approved the NHANES protocol and informed consent was obtained from all participants.

2.2 Inclusion and Exclusion Criteria

This study initially recruited 9254 participants in the NHANES database from 2017 to 2018. Exclusion criteria were: (1) $<$18 years of age; (2) history of hepatitis (e.g., viral hepatitis, autoimmune hepatitis); (3) heavy alcohol consumption, defined as $>$3 drinks per day for males, and $>$2 drinks per day for females; (4) HIV infection; (5) pregnancy; (6) controlled attenuation parameter (CAP) data was unavailable; (7) CONUT, NRI or PNI could not be used for analysis. Following application of the exclusion criteria, 3908 participants were included in the final analysis (Fig. 1).

2.3 Data Collection

Information was collected from the NHANES database in relation to demographics, lifestyle and chronic diseases. Demographics and lifestyle data included gender, age, race/ethnicity, education level and marital status. Race/ethnicity was classified as Mexican American, non-Hispanic white, non-Hispanic black, and other races. Education level was classified as below high school, high school, and college degree and above. Marital status was classified as married/live with partner, divorced/widowed/separated, and never married. Chronic diseases included liver diseases, hypertension, diabetes, hypercholesterolemia, and CKD. The presence of liver diseases in our study was defined as self-reported confirmed diagnosis from doctors. Hypertension was defined as self-reported confirmed diagnosis from doctors, use of anti-hypertensive drugs, systolic blood pressure (SBP) of 140 mmHg and higher, or diastolic blood pressure (DBP) of 90 mmHg and higher. Diabetes was defined as self-reported confirmed diagnosis from doctors, use of anti-diabetes drugs or insulin injection, glycated hemoglobin (HbA1c) $\geq$6.5%, or fasting blood glucose (FBG) $\geq$7.0 mmol/L. Hypercholesterolemia was defined as self-reported confirmed diagnosis from doctors, use of lipid-lowering drugs, or total cholesterol (TC) $\geq$6.21 mmol/L. CKD was defined as an estimated glomerular filtration rate (eGFR) of $<$90 mL/min/1.73 m^2 [10].

Physical examination and collection of biological samples were performed at mobile examination centers (MECs). Physical evaluation included height, waist circumference, DBP, and SBP. BMI was calculated as weight (kg)/height $(m)^2$. Elevated waist circumference was defined as $\geq$102 cm for males and $\geq$88 cm for females. SBP and DBP were recorded as the average value from three consecutive measurements. Biological samples were collected in accordance with standard procedures, followed by the evaluation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, white blood cell count, lymphocyte count, TC, high-density lipoprotein-cholesterol (HDL-C), triglyceride (TG), FBG, HbA1c, and C-Reactive protein (CRP). The CKD epidemiology collaboration (CKD-EPI) equation was utilized to calculate eGFR.

2.4 Determination of NAFLD and Evaluation of Nutritional Status

Hepatic steatosis was quantified by measuring ultrasound attenuation of echoes [11,12], and NAFLD was defined by CAP. Vibration controlled transient elastography (VCTE) was used at MECs to control attenuation and ob-

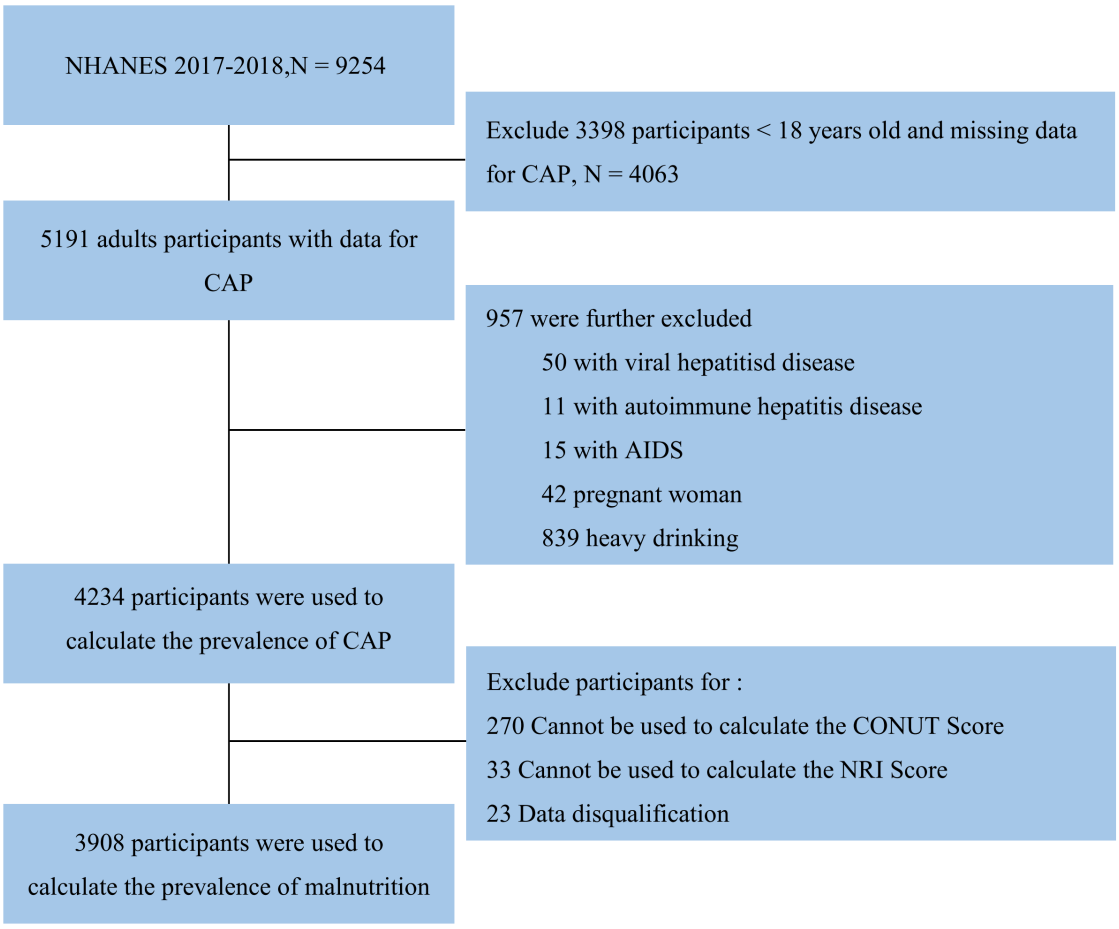

Fig. 1. Flow Chart. Abbreviations: NHANES, National Health and Nutrition Examination Survey; CAP, controllable attenuation parameter; CONUT, controlling nutritional status score; NRI, nutritional risk index.

tain CAP data. Participants with CAP ≥274 dB/m were confirmed as having NAFLD [13,14].

Nutritional status was evaluated by CONUT, PNI and NRI using the scoring criteria described below [15].

CONUT was developed by Ulibarri *et al.* [16] in 2005 for the screening and identification of malnutrition among hospital patients. The score refers to the patient's serum albumin level, TC and lymphocyte count. A score of 0–1 points indicates no malnutrition, while scores of 2–4, 5–8, and 9–12 points indicate mild, moderate and severe malnutrition, respectively.

PNI is calculated as 10 × serum albumin (g/dL) + 0.005 × lymphocyte count (per mm^3). A PNI score >38 points indicates no malnutrition, while 35–38 and <35 points indicate moderate and severe malnutrition, respectively.

NRI is calculated as 1.489 × serum albumin (g/L) + 41.7 × [present body weight (kg)/ideal body weight (kg)]. The Lorentz formula is used to calculate the ideal body weight (w). For men: w = (height (cm) – 100) – [(height – 150)/4], while for women: w = (height (cm) – 100) – [(height – 150)/2.5]. When the present body weight is higher than the ideal body weight, the body weight is set as: present body weight/ideal body weight = 1. According to the baseline NRI reported in a previous study, participants are then divided into four nutritional status categories: (a) no malnutrition (NRI ≥100), mild malnutrition (97.50 ≤ NRI ≤ 99.99), moderate malnutrition (83.50 ≤ NRI ≤ 97.49), and severe malnutrition (NRI <83.50).

2.5 Study Outcomes

The primary outcome was all-cause death. This information was obtained by association matching with the NDI. Death events were collected up until December 31, 2019.

2.6 Statistical Analysis

Continuous variables were presented as the mean and standard deviation when normally distributed, or as the median and interquartile range (IQR) when non-normally distributed. Categorical variables were expressed as counts and percentages. All included participants were divided into two groups according to their NAFLD status. The *t*-test or Wilcoxon rank-sum test were employed to compare differences in continuous variables between the NAFLD and non-NAFLD groups, while the chi-square test or Fisher's exact test were used for categorical variables.

Table 1. Baseline characteristics of the study cohort.

Characteristic	Overall (n = 3908)	NAFLD (n = 1737)	No NAFLD (n = 2171)	*p* value
Female, n (%)	2041 (52.2)	809 (46.6)	1232 (56.7)	<0.001
Age, years	54.0 (36.0, 66.0)	57.0 (43.0, 67.0)	50.0 (32.0, 65.0)	<0.001
Race, n (%)				<0.001
Mexican	497 (12.7)	281 (16.2)	216 (9.9)	
Others	1176 (30.1)	510 (29.4)	666 (30.7)	
non-Hispanic White population	1335 (34.2)	610 (35.1)	725 (33.4)	
non-Hispanic Black population	900 (23.0)	336 (19.3)	564 (26.0)	
Marital Status, n (%)				<0.001
Married or Cohabiting	2252 (60.4)	1099 (64.8)	1153 (56.7)	
Widowed, Divorced or Separated	862 (23.1)	376 (22.2)	486 (23.9)	
Unmarried	614 (16.5)	220 (13.0)	394 (19.4)	
Education, n (%)				0.916
< High school	772 (19.8)	346 (20.0)	426 (19.6)	
High school	935 (24.0)	410 (23.7)	525 (24.2)	
> High school	2194 (56.2)	976 (56.4)	1218 (56.2)	
Waist Circumference, cm	100.0 ± 17.0	109.3 ± 15.6	92.5 ± 14.2	<0.001
BMI, kg/m^2	28.3 (24.6, 33.3)	31.8 (27.9, 36.7)	25.9 (22.7, 29.5)	<0.001
<25	1060 (27.1)	151 (8.7)	909 (41.9)	
25–29.9	1264 (32.3)	517 (29.8)	747 (34.4)	
≥30	1584 (40.5)	1069 (61.5)	515 (23.7)	
Cotinine, n (%)				<0.001
>10 ng/mL	767 (19.6)	297 (17.1)	470 (21.6)	
LOD-10 ng/mL	1678 (42.9)	731 (42.1)	947 (43.6)	
< LOD	1463 (37.4)	709 (40.8)	754 (34.7)	
Activity, n (%)				0.860
No	1624 (41.6)	726 (41.8)	898 (41.4)	
Moderate strength	1262 (32.3)	553 (31.8)	709 (32.7)	
High strength	1022 (26.2)	458 (26.4)	564 (26.0)	
CVD, n (%)	432 (11.7)	230 (13.6)	202 (10.0)	<0.001
Liver condition, n (%)	167 (4.5)	106 (6.3)	61 (3.0)	<0.001
Diabetic, n (%)	861 (22.0)	587 (33.8)	274 (12.6)	<0.001
CKD, n (%)	343 (8.8)	170 (9.8)	173 (8.0)	0.046
HBP, n (%)	1797 (46.0)	985 (56.7)	812 (37.4)	<0.001
Hypercholesterolemia, n (%)	1736 (44.5)	934 (53.9)	802 (37.0)	<0.001
DBP, mmHg	72.2 ± 12.6	73.6 ± 12.8	71.1 ± 12.4	<0.001
SBP, mmHg	126.7 ± 19.9	130.1 ± 18.7	124.0 ± 20.4	<0.001
Lymphocyte number (1000 cells/μL)	2.1 (1.7, 2.6)	2.2 (1.8, 2.7)	2.0 (1.6, 2.5)	<0.001
White blood cell count (1000 cells/μL)	6.9 (5.7, 8.4)	7.3 (6.1, 8.7)	6.6 (5.4, 8.1)	<0.001
Potassium, mmol/L	4.1 ± 0.4	4.1 ± 0.4	4.1 ± 0.4	0.006
Sodium, mmol/L	140.0 (139.0, 142.0)	140.0 (139.0, 142.0)	140.0 (139.0, 142.0)	0.408
Creatinine, μmol/L	72.8 (59.8, 87.7)	73.8 (59.8, 88.6)	71.9 (58.9, 86.8)	0.049
Uric acid, μmol/L	316.3 ± 82.4	337.4 ± 83.0	299.4 ± 77.9	<0.001
Bilirubin, μmol/L	6.8 (5.1, 10.3)	6.8 (5.1, 8.6)	6.8 (5.1, 10.3)	0.445
Phosphorus, mmol/L	1.2 ± 0.2	1.1 ± 0.2	1.2 ± 0.2	<0.001
GGT, μ/L	19.3 (13.6, 27.3)	22.5 (16.8, 34.5)	16.0 (12.8, 23.3)	<0.001
Calcium, mmol/L	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	0.859
Blood urea nitrogen, mmol/L	5.9 ± 2.3	6.1 ± 2.5	5.7 ± 2.2	<0.001
Alkaline phosphatase, U/L	72.4 ± 23.4	75.4 ± 23.3	70.0 ± 23.2	<0.001
AST, U/L	23.1 (20.1, 28.2)	24.1 (20.1, 29.2)	22.1 (20.1, 27.2)	<0.001
ALT, U/L	19.9 (15.9, 28.0)	24.0 (17.9, 33.1)	17.9 (14.8, 23.9)	<0.001
Albumin, g/L	42.9 (40.8, 45.0)	42.9 (39.8, 45.0)	42.9 (40.8, 45.0)	<0.001
Vitamin D, nmol/L	69.1 ± 32.0	68.2 ± 31.1	69.9 ± 32.8	0.098

Table 1. Continued.

Characteristic	Overall (n = 3908)	NAFLD (n = 1737)	No NAFLD (n = 2171)	*p* value
eGFR, mL/min/1.73 m^2	94.3 ± 24.4	91.8 ± 23.9	96.3 ± 24.6	<0.001
Bicarbonate, mmol/L	25.7 ± 2.5	25.6 ± 2.5	25.8 ± 2.5	0.084
CRP, mg/dL	1.9 (0.9, 4.4)	2.7 (1.3, 5.7)	1.4 (0.7, 3.2)	<0.001
HDL, mmol/L	1.3 (1.1, 1.6)	1.2 (1.0, 1.4)	1.4 (1.2, 1.7)	<0.001
Total cholesterol, mmol/L	4.8 (4.1, 5.5)	4.8 (4.2, 5.6)	4.7 (4.1, 5.4)	<0.001
LDL, mmol/L	2.9 ± 0.9	2.9 ± 1.0	2.8 ± 0.9	0.092
Triglyceride, mmol/L	1.1 (0.7, 1.5)	1.3 (0.9, 1.829)	0.8 (0.6, 1.3)	<0.001

Abbreviations: NAFLD, non-alcoholic fatty liver disease; No NAFLD, no non-alcoholic fatty liver disease; BMI, body mass index; LOD, limit of detection; CVD, cardiovascular disease; CKD, chronic kidney diseases; HBP, high blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; CPR, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Kaplan-Meier curves were plotted to estimate cumulative mortality, with the *p* value derived from the log-rank test. Both univariate and multivariate Cox proportional hazard models were used to investigate correlations between the three scales (CONUT, PNI and NRI) and all-cause death. Gender, age, race and education were adjusted in Model 1. Model 2 further adjusted for cotinine activity, hypertension, diabetes, hypercholesterolemia, and cardiovascular disease. Model 3 finally adjusted for ALT, AST, gamma-glutamyl transferase (GGT), bilirubin, total alkaline phosphatase, and HDL-C. The threshold for significance was set at $p = 0.05$. All statistical analyses were carried out with Stata Version 17.0 (Stata Corp., College Station, TX, USA).

3. Results

3.1 Baseline Information

A total of 3908 participants in the NHANES database were analyzed, with a median age of 54.0 years and comprising 52.2% females (Table 1). The NAFLD group had 1737 participants and the non-NAFLD group had 2171. NAFLD participants were more often elderly males and had a larger waist circumference, higher BMI, and more frequent comorbid chronic diseases (e.g., hypertension, diabetes, hypercholesterolemia, and CKD) compared to non-NAFLD participants. They also had significantly higher AST, ALT, CRP and TG levels, but lower HDL-C and eGFR levels (all $p < 0.005$).

3.2 Incidence of Malnutrition among NAFLD Patients

Approximately 21% of the overall study cohort showed malnutrition according to the CONUT index (Table 2). The incidence of malnutrition in the NAFLD group was 18%, 11% and 1% according to CONUT, PNI and NRI, respectively. Among obese NAFLD patients (BMI ≥30), the incidence of malnutrition assessed by CONUT and PNI was 19% and 15% (**Supplementary Table 1**), indicating that BMI is not a good indicator of nutritional status.

3.3 Impact of Malnutrition Identified by CONUT on the Survival of NAFLD Patients

A total of 70 all-cause deaths occurred during the 24.4 ± 7.2 months of average follow-up time, of which 36 occurred in the NAFLD group. Kaplan-Meier survival analysis revealed that participants with malnutrition had a significantly increased risk of all-cause death (Fig. 2). This was further demonstrated by unadjusted Cox regression analysis of the overall cohort, as well as after adjustment in multivariate models, as shown in Table 3 (for model 3, hazard ratio (HR): 2.05, 95% CI: 1.23–3.43, $p = 0.006$). Malnutrition in the NAFLD group was also associated with increased all-cause mortality in multivariate adjusted model 3 (HR: 1.77, 95% CI: 0.85–3.70, $p = 0.129$), although this did not reach statistical significance (Table 3).

3.4 Impact of Malnutrition Identified by PNI on the Survival of NAFLD Patients

Unadjusted Cox regression analysis of the overall cohort showed that malnutrition was associated with a 4.66-fold increase in all-cause mortality. This result remained significant in multivariate adjusted model 3 (HR: 2.86, 95% CI: 1.67–4.89, $p < 0.001$). The association between malnutrition and increased mortality was stronger in NAFLD participants, with a 6.5-fold increase in the risk of all-cause death in the unadjusted model, and a similar increase in adjusted model 3 (HR: 4.44, 95% CI: 2.07–9.53, $p < 0.001$). No significant association between malnutrition and survival was found in non-NAFLD participants.

3.5 Impact of Malnutrition Identified by NRI on the Survival of NAFLD Patients

In the overall cohort, malnutrition was associated with a 5.98-fold increase in all-cause mortality (Table 3). This result remained significant in multivariate adjusted model 3 (HR: 5.06, 95% CI: 2.31–11.09, $p < 0.001$). The correlation between malnutrition and survival was even stronger in the NAFLD group, with a 13.58-fold increase in the risk of all-cause death in the unadjusted model, and a strong asso-

Table 2. Incidence of malnutrition as determined by the CONUT, PNI and NRI scales.

Nutritional Scale	Overall (n = 3908)	NAFLD (n = 1737)	No NAFLD (n = 2171)	*p* value
CONUT, n (%)	818 (20.9)	312 (18.0)	506 (23.3)	<0.001
PNI, n (%)	394 (10.1)	196 (11.3)	198 (9.1)	0.026
NRI, n (%)	171 (4.4)	17 (1.0)	154 (7.1)	<0.001

Abbreviations: NAFLD, non-alcoholic fatty liver disease; No NAFLD, no non-alcoholic fatty liver disease; CONUT, controlling nutritional status score; PNI, prognostic nutritional index; NRI, nutritional risk index.

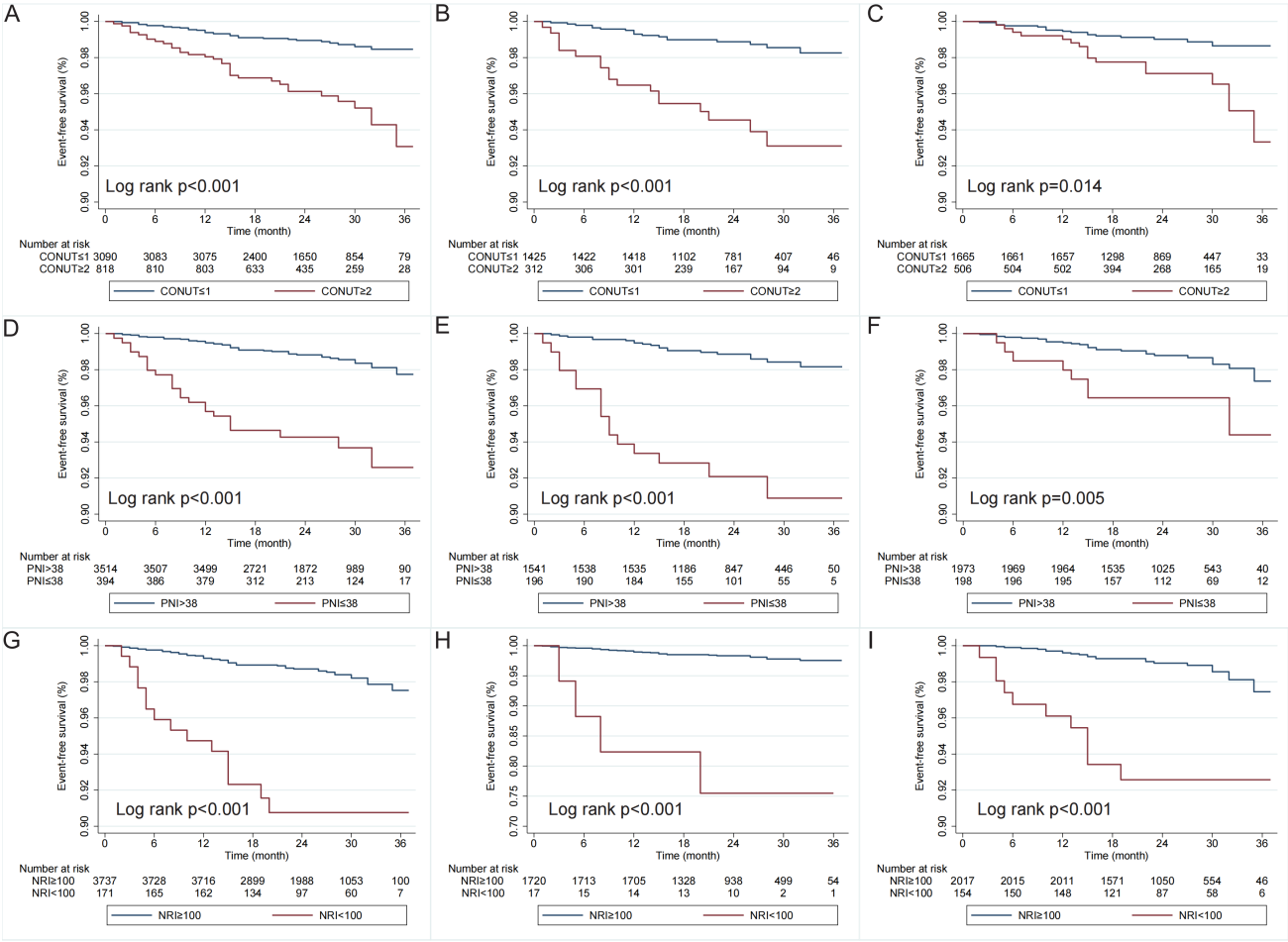

Fig. 2. Survival curves for NAFLD and non-NAFLD patients according to malnutrition status as defined by CONUT, PNI, and NRI scores. (A): CONUT in overall patients, 818 malnourished participants were assessed by the CONUT. (B): CONUT in NAFLD patients, 312 malnourished participants were assessed by the CONUT. (C): CONUT in non-NAFLD patients, 506 malnourished participants were assessed by the CONUT. (D): PNI in overall patients, 394 malnourished participants were assessed by the PNI. (E): PNI in NAFLD patients, 196 malnourished participants were assessed by the PNI. (F): PNI in non-NAFLD patients, 198 malnourished participants were assessed by the PNI. (G): NRI in overall patients, 171 malnourished participants were assessed by the NRI. (H): NRI in NAFLD patients, 17 malnourished participants were assessed by the NRI. (I): NRI in non-NAFLD patients, 154 malnourished participants were assessed by the NRI. Abbreviations: NAFLD, non-alcoholic fatty liver disease; No NAFLD, no non-alcoholic fatty liver disease; CONUT, controlling nutritional status score; PNI, prognostic nutritional index; NRI, nutritional risk index.

ciation in adjusted model 3 (HR: 6.98, 95% CI: 1.47–33.11, $p = 0.014$). The association was weaker in the non-NAFLD group, but remained significant.

4. Discussion

NAFLD is the most common chronic disease in both adults and children globally, with a prevalence of approximately 30% in Western countries. More than one quarter

Table 3. Association of malnutrition, as defined by CONUT, PNI and NRI scores, with all-cause mortality.

	Overall		NAFLD		No NAFLD	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
CONUT						
Unadjusted	3.75 (2.35–5.99)	<0.001	4.65 (2.42–8.93)	<0.001	3.16 (1.61–6.21)	0.001
Model 1	2.47 (1.52–4.02)	<0.001	2.89 (1.47–5.71)	0.002	2.19 (1.09–4.39)	0.027
Model 2	2.36 (1.42–3.91)	0.001	1.93 (0.94–3.96)	0.073	2.69 (1.29–5.59)	0.008
Model 3	2.05 (1.23–3.43)	0.006	1.77 (0.85–3.70)	0.129	2.17 (1.03–4.58)	0.043
PNI						
Unadjusted	4.66 (2.85–7.64)	<0.001	6.49 (3.36–12.53)	<0.001	2.95 (1.33–6.52)	0.008
Model 1	3.84 (2.32–6.36)	<0.001	7.18 (3.64–14.18)	<0.001	1.87 (0.84–4.18)	0.125
Model 2	3.54 (2.12–5.92)	<0.001	5.49 (2.75–10.98)	<0.001	1.89 (0.82–4.35)	0.135
Model 3	2.86 (1.67–4.89)	<0.001	4.44 (2.07–9.53)	<0.001	1.26 (0.53–3.03)	0.600
NRI						
Unadjusted	5.98 (3.38–10.59)	<0.001	13.58 (4.80–38.44)	<0.001	6.17 (3.01–12.66)	<0.001
Model 1	5.07 (2.81–9.13)	<0.001	16.11 (5.48–47.42)	<0.001	5.40 (2.58–11.30)	<0.001
Model 2	5.46 (2.87–10.39)	<0.001	11.83 (3.73–37.51)	<0.001	5.15 (2.28–11.65)	<0.001
Model 3	5.06 (2.31–11.09)	<0.001	6.98 (1.47–33.11)	0.014	3.25 (1.11–9.50)	0.031

Abbreviations: NAFLD, non-alcoholic fatty liver disease; No NAFLD, no non-alcoholic fatty liver disease; HR, hazard ratio; CI, confidence interval; CONUT, controlling nutritional status score; PNI, prognostic nutritional index; NRI, nutritional risk index.

Model 1 adjust Gender, age, race, education.

Model 2 adjust Gender, age, race, education, cotinine, activity, HBP, diabetic, hypercholesterolemia, CVD.

Model 3 adjust Gender, age, race, education, cotinine, activity, HBP, diabetic, hypercholesterolemia, CVD, BMI, AST, ALT, GGT, bilirubin, alkaline phosphatase, HDL.

of the United States population shows a positive diagnosis for NAFLD with ultrasound [17]. This varies from steatosis or simple fat accumulation exceeding the standard ratio, to non-alcoholic steatohepatitis (NASH), and to more severe inflammation and hepatocyte death. These conditions accelerate the progression to liver fibrosis or cirrhosis, making NAFLD the most common cause of liver disease [2,14]. In the present study, VCTE was used as a non-invasive diagnostic tool to obtain a relatively accurate assessment of hepatic steatosis, thereby allowing the prevalence of NAFLD to be determined through CAP. It is well known that ultrasound propagation is significantly attenuated in liver adipose tissue. The VCTE technique exploits this feature to assess the degree of hepatic steatosis by CAP quantitative analysis, thus providing a novel technique for the diagnosis of fatty liver. VCTE can quantitatively assess the liver tissue in a non-invasive way and at multiple angles to provide reliable, accurate and intuitive results. Although it may not be completely sensitive, fatty liver can be detected when hepatic steatosis reaches 20%. Compared with invasive liver biopsy, VCTE is safe and has a wider detection area, thus making it more suitable for large-scale studies and minimizing the interference caused by sampling error [18].

NAFLD is generally described as a hepatic manifestation of metabolic syndrome [19]. In October 2020, the Asia Pacific Society for the Study of the Liver (APASL) issued guidelines for the diagnosis and management of metabolically-associated fatty liver disease (MAFLD). The specific diagnostic criteria are the presence of hepatic steatosis with one of the following three conditions: overweight/obesity, type 2 diabetes, or metabolic dysfunction. Therefore, most participants in the current study met the diagnostic criteria for both MAFLD and NAFLD. However, some NAFLD subjects with normal weight and no diabetes could not be classified as MAFLD [20–22]. A growing number of studies have reported the presence of nutrient deficiencies in NAFLD patients that are likely to be related to prognosis. For example, low serum vitamin D levels correlate with both the severity of liver inflammation and the progression of NAFLD [23–25]. Vitamin D has anti-proliferative, anti-inflammatory, and also anti-fibrotic effects [26]. It is still unclear whether vitamin D deficiency is a contributing factor for NAFLD, or for the impaired metabolic capacity following hepatic steatosis. However, vitamin D deficiency is prevalent in both NAFLD adolescents and adults [23]. A study of Chinese stroke patients reported that a large proportion of those who were obese or overweight, as defined by BMI, also had malnutrition and a higher mortality rate [27]. Hence, the nutritional status of the overweight or obese population should not be overlooked, especially in patients with NAFLD.

In 2018, the Global Leadership Initiative on Malnutrition proposed diagnostic criteria for malnutrition in order to build a global consensus on the concept of adult malnutrition in clinical settings. Multiple assessment tools for nutri-

BMI≥ 25kg/m² in NAFLD patients, n=1,586	
SCORE	Malnutrition
CONUT	n=287(18%)
PNI	n=355(22%)
NRI	n=2(0.1%)

BMI < 25kg/m² in NAFLD patients, n=151	
SCORE	Malnutrition
CONUT	n=25(17%)
PNI	n=13(9%)
NRI	n=15(10%)

Fig. 3. The prevalence of malnutrition in NAFLD patients stratified by BMI. Abbreviations: BMI, body mass index; NAFLD, non-alcoholic fatty liver disease.

tional status were recommended so that researchers could choose the appropriate tools for screening based on nutritional assessment objectives, subject characteristics, and clinical needs. Nutritional risk screening 2002 (NRS-2002) and the malnutrition universal screening tool (MUST) can effectively identify malnutrition in hospitalized patients [28,29]. For cerebral stroke patients, malnutrition evaluated by the geriatric nutritional risk index (GNRI) has been linked to long-term all-cause mortality [27]. For heart failure patients, mini nutritional assessment (MNA) and MNA-short form (MNA-SF) are the optimal nutritional assessment and screening tools used to predict outcome [30]. CONUT is also a predictor of mortality from cardiovascular disease and chronic liver disease [31–34].

Unfortunately, early nutrition issues among NAFLD patients are not yet well recognized in clinical practice, and relevant nutritional therapy interventions have not been fully utilized. The incidence of malnutrition in patients with advanced liver disease is high, but their nutritional grade varies greatly between different studies. The impact of late complications and the choice of screening tools also pose major challenges for clinical nutritional assessment. Early nutritional assessment therefore appears to be increasingly important. CONUT, PNI and NRI were used in the present study to evaluate the nutritional status of NAFLD patients. All three scales use serum albumin to assess body protein storage. Lymphocyte count is also included in CONUT and PNI, while height and weight are included in NRI. Albumin is the most frequently used blood biomarker for the screening of malnutrition. A previous study on the relationship between NAFLD and hemodialysis (HD) reported a negative correlation between the severity of hepatic steatosis and serum albumin levels that may affect the prognosis of HD patients [35]. Another study found that NAFLD patients with low serum albumin levels had significantly higher mortality from COVID-19 infection [36]. In addition to serum albumin, TC and lymphocyte count are two essential biomarkers of malnutrition in the elderly population [37] as well as having prognostic value [38,39]. In summary, the CONUT, PNI and NRI tools used in the present study include serum albumin, TC and lymphocyte count, thereby allowing reliable evaluation of nutritional status.

The incidence of malnutrition determined by CONUT, PNI and NRI in our study population was 18%, 11% and 1%, respectively. The much lower incidence found with NRI might be due to the influence of body weight on nutritional assessment with this scale. The different results suggest that each method is dependent on the characteristics of subjects. Nevertheless, the three scales showed similar prognostic performance in our study, with each finding that all-cause mortality was higher in participants with malnutrition. This association was even stronger in those with NAFLD, highlighting that more attention should be paid to the assessment of early nutritional status and to nutritional grade stratification in such patients. Additional health education, preventive intervention and targeted treatments should be offered to individuals with NAFLD.

A total of 2848 participants in this study were obese or overweight, with 40% having a BMI of $\geq$30. In the NAFLD group (n = 1737), 91% of participants had a BMI $\geq$25, and $>$60% were overweight. A heavier body weight has traditionally been considered to indicate over-nutrition, or good nutritional status. The proportion of obese or overweight NAFLD patients (n = 1586) with malnutrition according to CONUT, PNI and NRI was 18% (n = 287), 22% (n = 335), and 0.1% (n = 2), respectively. Moreover, these patients had increased all-cause mortality (Fig. 3). The concept of high body weight being indicative of good nutritional status should be reviewed, since the BMI value alone does not appear to be a good indicator of nutritional status in humans. More comprehensive nutritional assessment methods need to be incorporated into clinical practice. Although many studies have recommended different methods, a consensus has yet to be reached.

The CONUT, PNI and NRI scales are easy to perform and analyze, and can rapidly detect malnutrition in NAFLD patients. Nevertheless, there are several limitations to this study. First, cholesterol levels are generally higher in NAFLD patients, and the CONUT scoring criteria could underestimate the nutritional status. Similarly, the NRI method might also underestimate the nutrition status in some underweight patients. Second, the number of participants with moderate or severe malnutrition in this study was limited and could not be further examined using a more meticulous nutritional stratification method. Finally, the effect of improving the nutritional status on survival outcome was not examined. Further studies are therefore required to better understand the impact of nutritional intervention on patients with malnutrition, as well as to generalize the current findings to other populations.

5. Conclusion

In summary, malnutrition is frequently observed in NAFLD patients, including those who are overweight or obese. NAFLD patients with malnutrition have significantly higher all-cause mortality compared to those with a normal nutritional status. As NAFLD becomes more common, greater attention should be paid to nutritional status. Clinicians should also provide nutritional guidance and supplementation in a timely manner according to individual circumstances. Finally, the three nutrition assessment tools employed in this study were shown to be feasible and effective for the prediction of mortality among NAFLD cases.

Availability of Data and Materials

Datasets are not available to the public but are available upon reasonable request from the corresponding author.

Author Contributions

XJ, Conceptualization; writing-original draft; data analysis and interpretation. LJ, Conceptualization; writing-review and editing; data acquisition and curation. CHH, Writing-original draft; data analysis; software. LQ, Design; Writing-review and editing; data analysis. WYY, Writing-review and editing; data acquisition and analysis. CXJ, Writing-review and editing; data acquisition and analysis. KXJ, Conceptualization; design; writing-review and editing. All authors contributed to editorial changes in the manuscript. 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 NHANES survey data is publicly available. The survey protocol was approved by the National Center for Health Statistics Ethics Review Board. The studies involving human participants were reviewed and approved by Ethical approval for the use of the NHANES survey data from 2017 to 2018 were obtained from the National Center for Health Statistics (NCHS) Research Ethics Review Board (ERB) through Protocol Number #2018-01. All methods were undertaken in accordance with the relevant guidelines and regulations. NHANES has previously obtained written informed consent from all participants.

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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/IJVNR26099.

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