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Nutritional status assessment and its links with chronic disease prognosis and surgical outcomes

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Nutritional status assessment and its links with chronic disease prognosis and surgical outcomes

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Editorial: Nutritional status assessment and its links with chronic disease prognosis and surgical outcomes

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Editorial on the Research Topic
Nutritional status assessment and its links with chronic disease prognosis and surgical outcomes

Nutritional disorders are closely linked to poor health outcomes including prolonged hospital stays, postoperative complications, cancer treatment toxicity, shorter survival, and reduced quality of life (1). While the use of nutritional assessment tools for both diagnostic and outcome measurement purposes has been widely explored, the interplay among various nutritional disorders remains under-explored in the literature. Special attention should be given to screening markers and those that are easily applicable in clinical practice, such as the Prognostic Nutritional Index (PNI) and the GNRI (Geriatric Nutritional Risk Index), which offer practical, bedside solutions for assessing patient risk (2–4).

This Research Topic aimed to provide a comprehensive update on the scientific evidence regarding nutritional status assessment tools as prognostic indicators for clinical and surgical outcomes.

In this Research Topic, 17 papers cover the aforementioned aspects, exploring these tools in diverse clinical settings. These studies elucidate the potential of nutritional and body composition indices to improve patient outcomes through more personalized and targeted interventions.

Several studies in this Research Topic emphasize the critical role of body composition in predicting clinical outcomes, particularly in cancer patients. Sarcopenia and sarcopenic obesity were found to be significantly associated with poor overall survival and recurrence-free survival in patients with primary liver cancer (Li et al.). Moreover, sarcopenia emerged as a significant prognostic factor for shortened survival following pancreatectomy, highlighting its link to an elevated risk of mortality (Zhong et al.). These findings underscore the need for further research to clarify how sarcopenia influences long-term outcomes after cancer-related surgeries.

The importance of body composition was further reinforced by studies on colorectal cancer and abdominal surgery. The Cancer Cachexia Index and the cachexia index based on hand-grip strength (H-CXI) were identified as superior prognostic tools for predicting postoperative outcomes in colorectal cancer patients with H-CXI showing particular effectiveness for short-term clinical outcomes (Yan et al.). Additionally, muscle atrophy and

high subcutaneous adipose tissue (SAT) radiodensity were associated with poor prognosis in patients with hepatocellular carcinoma, suggesting that targeted interventions such as nutritional therapy and exercise may help improve outcomes in this high-risk group (Ohara et al.).

Of particular note is the research on novel methods for assessing muscle mass, with ultrasound (US) highlighted as a feasible alternative to computed tomography, especially when enhanced by advanced measuring software (Palmas et al.). This approach could have significant implications for clinical practice by making muscle mass assessment more accessible, less invasive, and easier to perform.

The critical role of various nutritional indices as prognostic tools across different clinical settings was highlighted in our Research Topic. The prognostic significance of the pan-immune-inflamation value (PIV) was consistently demonstrated across different geographical regions, tumor stages, and treatment strategies, with sensitivity analyses confirming the stability of these results (Hai-Jing et al.). Similarly, the Geriatric Nutritional Risk Index (GNRI) emerged as a valuable predictor, not only of immunotherapy response in cancer patients (Zhang et al.) but also as an effective tool for stratifying patients undergoing hemodialysis on a global scale (Hung et al.). In parallel, the PNI was found to offer superior predictive value for adverse outcomes, particularly in patients with diabetic kidney disease, where it exhibited a stronger correlation with renal histologic changes compared to other nutritional scores (Xing et al.). Further expanding on the significance of nutritional screening, malnutrition risk was shown to significantly increase the likelihood of heart disease in middle-aged Koreans (Park and Bu). This finding underscores the need for larger studies to further validate the GNRI's efficacy in predicting disease risk in the general adult population. Additionally, a simplified nutritional prognostic score, ALTA, was developed specifically for patients with HBV-related acute-on-chronic liver failure, proving to be superior in predicting short-term mortality compared to existing scores (Song et al.).

Regarding the contributions that explored the role of dietary intake, particularly antioxidant-rich diets, in health outcomes, one study investigated the relationship between the Composite Dietary Antioxidant Index (CDAI) and mortality among adults with hypertension. The findings revealed that a higher CDAI was associated with reduced all-cause, cardiovascular, and cancer mortality, underscoring the potential benefits of an antioxidant-rich diet in improving outcomes for hypertensive individuals (Zhou et al.). Another study focused on the relationship between CDAI and hyperlipidemia, utilizing data from the National Health and Nutrition Examination Survey (NHANES; Qin et al.). The results indicated a linear negative association between CDAI and the risk of developing hyperlipidemia, suggesting that increasing the intake of antioxidant-rich foods could be an effective strategy for preventing hyperlipidemia.

Overall, the findings in this Research Topic highlight the critical need for standardized and comprehensive nutritional assessment tools in clinical practice. By integrating these tools into patient care, healthcare providers can better predict outcomes and tailor interventions to improve long-term health across various diseases and surgical scenarios.

Author contributions

GC: Conceptualization, Writing – original draft, Writing – review & editing. BV: Writing – original draft, Writing – review & editing. GP: Writing – original draft, Writing – review & editing. RE: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prognostic significance of the pretreatment pan-immune-inflammation value in cancer patients: an updated meta-analysis of 30 studies

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Background: The pan-immune-inflammation value (PIV) has been reported as a promising prognostic biomarker in multiple cancers but still remains inconclusive. The objective of this study is to systematically investigate the association of the pretreatment PIV with survival outcomes in cancer patients, based on available literature.

Methods: Online databases including PubMed, Embase and the Web of Science were thoroughly searched for studies evaluating the prognostic role of the pretreatment PIV in cancers from the inception to June 2023. Hazard ratios (HRs) with 95% confidence intervals (CIs) were always assessed using a random-effects model. Statistical analyses were performed using Stata 12.0.

Results: Thirty studies were finally included after comprehensively study searching. In total, 8,799 cancer patients were enrolled in this meta-analysis. The pooled results demonstrated that patients in the high PIV group had a significantly poorer overall survival (HR = 2.07; 95%CI: 1.77–2.41; I^2 = 73.0%) and progression-free survival (HR = 1.83; 95%CI: 1.37–2.45; I^2 = 98.2%) than patients in the low PIV group. The prognostic significance of the PIV score on overall survival and progression-free survival was observed across various geographical regions, tumor stages and treatment strategies. Sensitivity analyses supported the stability of the above combined results.

Conclusion: This meta-analysis demonstrated that the pretreatment PIV could be a non-invasive and efficacious prognostic biomarker for cancer patients.

KEYWORDS

cancer, pan-immune-inflammation value, overall survival, progression-free survival, meta-analysis

1. Introduction

With the global population and the proportion of elderly people growing, cancer has become one of the leading causes of death worldwide (1). Although the development of surgery and medical treatment has made great progress in cancer patients, the prognosis for these patients remains not yet satisfactory (2). Therefore, based on the estimated survival time of cancer patients, it is essential to develop individualized and effective treatment strategies to improve their chances of survival. Currently, anti-tumor therapy relies primarily on a

conventional staging system. Nevertheless, in clinical practice, the staging system alone is not able to support treatment decision-making as well as prognosis assessment well (3, 4). It is therefore urgent to construct novel prognostic markers to guide more precise treatment for cancer patients.

The accumulating evidence suggests that host inflammation and immune status play an important role in the progression, treatment response and survival outcomes of cancer patients (5, 6). Based on this insight, several inflammation/immune-related biomarkers have been developed to predict the clinical outcomes of cancer patients, such as neutrophil to lymphocyte ratio (NLR) (7), platelet to lymphocyte ratio (PLR) (8) and monocyte to lymphocyte ratio (MLR) (9). Recently, a newly developed prognostic biomarker- the pan-immune-inflammation value (PIV), has garnered significant interest of clinicians (10). PIV integrates neutrophils, platelets, monocytes and lymphocyte together, and has been reported to be a better prognostic predictor than these simple biomarkers, including NLR, PLR and MLR (11, 12). To be specific, PIV is calculated using serum neutrophil, platelet, monocyte and lymphocyte (neutrophil x platelet x monocyte/lymphocyte), which was first introduced by Fuca et al. (13) in 2020 as a prognostic index for metastatic colorectal cancer receiving chemotherapy combined with target therapy. After that, the prognostic role of the PIV has been explored in various cancers (14–16). A recent meta-analysis of 15 studies demonstrated that a high PIV was associated with a poor prognosis in cancer patients (17). Nonetheless, it is important to note that some common tumor types, such as pancreatic cancer and hepatic cancer, were not available in this meta-analysis. Besides, abstract without sufficient data was also included for analysis. These factors undoubtedly have a certain impact on the universality and reliability of the results.

As growing body of additional research has been addressed to further explore the prognostic value of PIV in cancer patients. We therefore performed an updated pooled analysis to systematically explore the relationship between the pretreatment PIV and survival outcomes in cancer patients.

2. Methods

2.1. Search strategy

This meta-analysis was conducted as per the PRISMA guidelines (18) (see PRISMA checklist in the Supplementary Information) to identify literature evaluating the association of pretreatment PIV with survival outcomes in cancer patients. Related studies from the Web of Science, PubMed, and Embase were thoroughly examined from the inception to June 30, 2023. The key word "pan-immune-inflammation value" was applied to search potential studies. During the search process, studies published in any language were included. In addition, references to enrolled studies and related reviews were prudently scanned for additional reporting. The search was performed by two investigators (Y-HJ and RS) independently.

2.2. Study selection

The inclusion criteria were as follows: (1) patients were pathologically diagnosed as cancer; (2) patients were divided into two groups according to the pretreatment PIV cut-off value; (3) studies investigated the relationship between the pretreatment PIV and survival outcomes of cancer patients. The exclusion criteria were: (1) letters, case reports, abstracts or reviews; (2) duplicated studies.

2.3. Data extraction and quality assessment

Data extraction and subsequent cross-checks were performed by two independent reviewers (YH-J and RS). Information extracted from included studies was as follows: first author, year of publication, country, study interval, sample size, cancer type, selection method, cut-off value, period of blood collection, information on exclusion of diseases affecting blood parameters, age, sex, tumor stage, treatment strategy, survival data and follow-up time. The quality assessment of included literature was evaluated via the method by Lin et al. (19). After careful evaluation from 9 domains, a study could get a total score ranging from 0 to 9. Quality assessment was not used as exclusion criterion for included studies.

2.4. Outcome assessment

In this study, the primary endpoint was to explore the relationship between the pretreatment PIV and survival outcomes in cancer patients. Long-term survival outcomes included overall survival (OS), progression-free survival (PFS), disease-free survival (DFS) and recurrence-free survival (RFS). Since DFS, RFS and PFS share the similar endpoints, they were analyzed together as one outcome, PFS, as previously suggested (20, 21).

2.5. Statistical analysis

Stata 12.0 statistical software was used to perform all the statistical analyses. Hazard ratios (HRs) with 95% confidence intervals (CIs) reported from multivariate analyses were preferentially used to incorporate survival outcomes. Otherwise, univariate assessments were the sources of effect sizes. In addition, for studies whose survival data were not directly available, corresponding HRs with 95% CIs were extracted from the survival curves through the methods reported by Tierney et al. (22). In the present study, I^2 statistics were utilized to evaluate inter-study heterogeneity, and a random-effects model was always performed, which accounts for variance across included studies (23, 24). Subgroup analyses and meta-regression analyses were applied to explore the sources of heterogeneity. Leave-one-out sensitivity analyses were utilized to assess the reliability of pooled results. Possible publication bias was evaluated using Begg's test. If there was a significant publication bias, a trim and fill analysis was employed to assess the impact of it on the pooled result. p values <0.05 were considered statistically significant.

3. Results

3.1. Study characteristics

The initial search of online databases yielded a total of 162 records. By removing duplicated studies, and reviewing titles, abstracts and

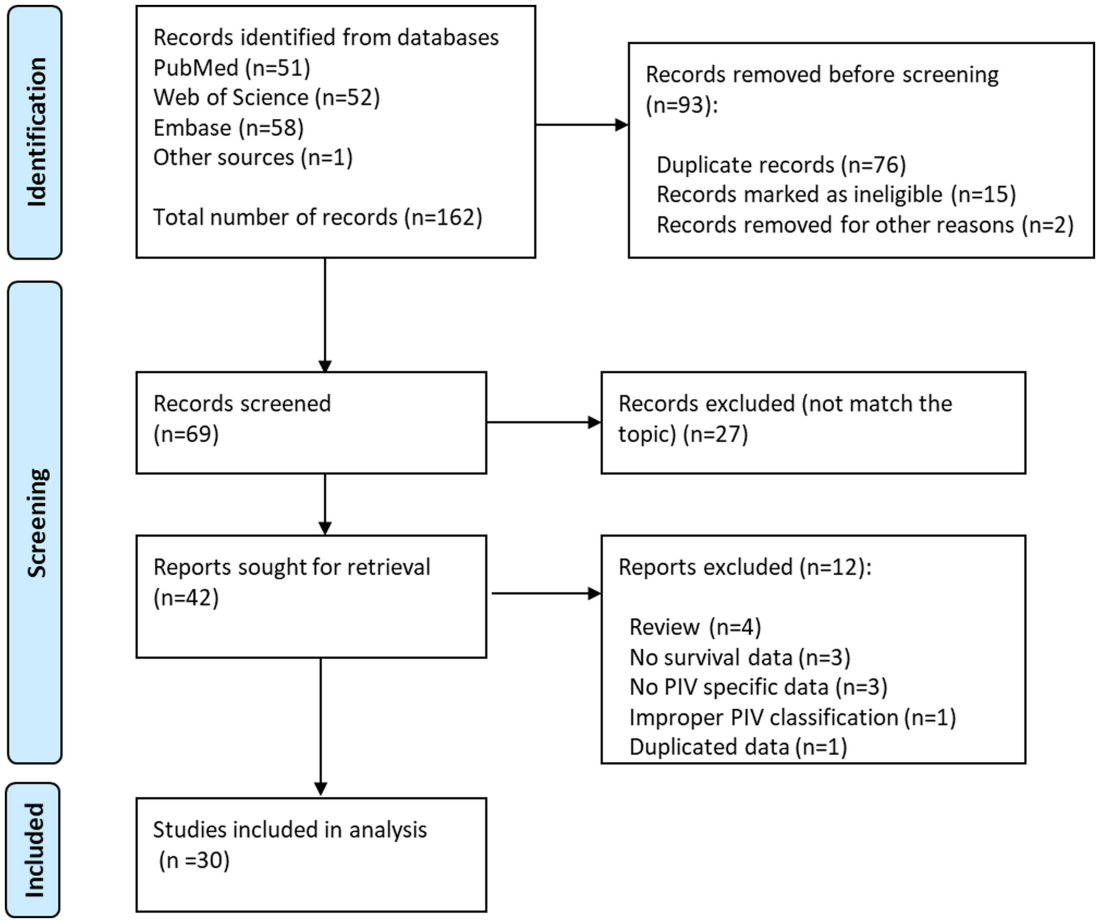

FIGURE 1
The PRISMA flowchart of study selection.

full-text studies, 30 studies (11–16, 25–48) with 32 cohorts were ultimately incorporated in our meta-analysis (Figure 1), The main characteristics of these studies were shown in Tables 1, 2. In total, 8,799 participants from China, Germany, Italy, Japan, Slovenia, Spain and Turkey were enrolled in the present study. These studies were published from 2020 to 2023, with a sample size ranging from 49 to 1,312. The most common cancer type was gastrointestinal cancer, followed by breast cancer and lung cancer. As regards blood parameters, the period of blood collection before treatment ranged from 1 day to 1 month, and most of the included studies did not mention the exclusion of diseases affecting hematological parameters. The cut-off value of PIV ranged from 164.6 to 600.0. In terms of main primary treatments, surgery was performed in 8 cohorts, chemo/radiotherapy was performed in 8 cohorts and immunotherapy contained treatment was performed in 7 cohorts. The median follow-up time ranged from 9.5 to 78.4 months. The literature quality of these studies was good with a median score of 8 (range: 7–9, Supplementary Table S1).

3.2. Relationship between the PIV and OS

A total of 8,462 patients from 27 cohorts were included in the pooled analysis of OS. The pooled result revealed that higher PIV predicted poorer OS (HR = 2.07; 95%CI:1.77–2.41; I^2 = 73.0%; Figure 2). Furthermore, subgroup analyses based on country, study center, sample size, cancer type, selection method, cut-off value, treatment strategy, tumor stage, analysis method and follow-up time were performed. As shown in Table 3 and Supplementary Figure S1, the pooled outcomes from all subgroup analyses consistently revealed that patients in the high PIV group had a significantly worse OS compared to those in the low PIV group. In addition, a meta-regression analysis based on these variables was performed to investigate the source of heterogeneity. As shown in Supplementary Table S2, none of these covariates had a significant effect on the hazard ratios of OS (all p values>0.05).

3.3. Relationship between the PIV and PFS

In total, 25 cohorts involving 5,391 patients reported on PFS. The pooled HR was 1.83 (95%CI: 1.37–2.45; I^2 = 98.2%), suggesting that higher PIV was associated with a significantly worse PFS (Figure 3). Similarly, subgroup analyses based on above variables were performed due to the significant heterogeneity existed. We found that in almost all subgroups analyses, patients in the high PIV group has an inferior PFS, except for the pooled results from melanoma (HR = 1.13; 95% CI: 0.86–1.47) and univariate analysis (HR = 1.53;

TABLE 1 Basic information of included studies.

References	Country	Study design	Study interval	Cancer type	Sample size	Age, years (Median/ Mean)	Sex (Male/ Female)	Selection method	Cut-off value	The period of blood collection	Exclusion of diseases affecting blood parameters
Baba et al. (14) (training)	Japan	S;R	2005–2020	Esophageal cancer	433	66.5 ± 8.5	376/57	ROC	164.6	Within 1 week before treatment	NA
Baba et al. (14) (validation)	Japan	S; R	2005–2020	Esophageal cancer	433	66.3 ± 8.9	384/49	ROC	164.6	Within 1 week before treatment	NA
Chen et al. (15)	China	S; R	2014–2019	Lung cancer	94	48 (Range, 18–76)	55/39	Median	364	Within 3 weeks before treatment	Yes
Corti et al. (16)	Italy	M; R	2014–2020	Colorectal cancer	163	NA	90/73	MSR	492	Within 1 week before treatment	NA
Demir et al. (25)	Turkey	S; R	2006–2020	Breast cancer	243	36 (Range, 21–40)	0/243	Median	301	Before treatment	Yes
Efil et al. (26)	Turkey	S; R	2008–2016	Colorectal cancer	304	62 (Range, 19–91)	182/122	Median	491	Within 2 weeks before treatment	NA
Fucà et al. (13)	Italy	M; R	2008–2018	Colorectal cancer	438	62 (IQR, 53–68)	275/163	MSR	380	Before treatment	NA
Fucà et al. (27)	Italy	S; R	2010–2020	Melanoma	228	NA	142/86	MSR	600	Before treatment	NA
Gambichler et al. (28)	Germany	S; R	NA	Merkel cell carcinoma	49	77 (Range, 51–95)	25/24	ROC	372	Within 1 week at diagnosis	NA
Guven et al. (29)	Turkey	S; R	2016–2020	Multiple cancers	120	61 (IQR, 54–67)	86/34	Median	513.4	Before treatment	NA
Guven et al. (30)	Turkey	S; R	2005–2020	Head and neck cell carcinoma	199	59 (IQR, 53–67)	180/19	ROC	404	Within 1 week before treatment	NA
Karadağ et al. (11)	Turkey	S; R	2013–2021	Hepatocellular carcinoma	120	64 (IQR, 55–72)	101/19	Median	286.15	Before treatment	Yes
Kucuk et al. (31)	Turkey	M; R	2010–2021	Lung cancer	89	61 (Range, 37–79)	75/14	ROC	417	Within 1 week before treatment	Yes
Liang et al. (32)	China	S; R	2013–2016	Colorectal cancer	753	NA	473/280	ROC	231	Within 1 week before treatment	NA
Ligorio et al. (33)	Italy	S; R	2014–2020	Breast cancer	57	53 (Range, 26–78)	0/57	Median	285	Before treatment	Yes
Lin et al. (19)	China	S; R	2010–2012	Breast cancer	1,312	48 (IQR, 41–57)	0/1312	MSR	310.2	Within 1 week before treatment	Yes
Mesti et al. (34)	Slovenia	S; R	2018–2020	Melanoma	129	66.2 (Range, 30.1–84.5)	84/53	Median	390	Before treatment	Yes
Pérez-Martelo et al. (35)	Spain	S; R	2015–2018	Colorectal cancer	130	68.8 (Range, 26–88)	96/34	MSR	380	Within 1 month before treatment	NA
Provenzano et al. (36)	Italy	S; R	2008–2020	Breast cancer	78	NA	0/78	Median	228	Within 1 week before treatment	NA

(Continued)

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TABLE 1 (Continued)

References	Country	Study design	Study interval	Cancer type	Sample size	Age, years (Median/ Mean)	Sex (Male/ Female)	Selection method	Cut-off value	The period of blood collection	Exclusion of diseases affecting blood parameters
Qi et al. (37)	China	S;P	2019–2022	Esophageal Cancer	51	62 (Range, 39–75)	44/7	ROC	232.8	Before treatment	NA
Sahin et al. (38)	Turkey	S; R	2008–2019	Breast cancer	743	48.0 (Range, 22.0–83.5)	0/743	ROC	306.4	Within 2 weeks before treatment	Yes
Sato et al. (39)	Japan	S; R	2013–2020	Colorectal cancer	86	70 (Range, 37–93)	50/36	ROC	209	Before treatment	Yes
Sato et al. (40)	Japan	S; R	2000–2019	Colorectal cancer	758	NA	466/292	ROC	376	Before treatment	Yes
Susok et al. (41)	Germany	S; R	NA	Melanoma	62	67 (Range, 18–85)	40/22	ROC	455	Before treatment	NA
Topkan et al. (42)	Turkey	S; R	2007–2020	Glioblastoma Multiform	204	58 (Range, 21–80)	135/69	ROC	385	The first day of treatment	Yes
Topkan et al. (43)	Turkey	S; R	2007–2020	Pancreatic adenocarcinoma	178	57 (Range, 26–79)	137/41	ROC	464	The first day of treatment	Yes
Wang et al. (44)	China	S; R	2010–2018	Gastric cancer	89	59 (Range, 32–78)	69/20	ROC	218.7	Before treatment	NA
Yazgan et al. (45)	Turkey	S; R	2010–2021	Prostate cancer	114	64 (IQR, 60–70)	114/0	Median	366	Within 1 month before treatment	NA
Yeh et al. (46)	China	S; R	2005–2017	Oral cavity cell carcinoma	853	53.5	780/73	ROC	268	Before treatment	NA
Yekedüz et al. (47)	Turkey	M; R	NA	Renal cell carcinoma	152	60 (IQR, 54–67)	117/35	MSR	372	Within 1 week before treatment	NA
Zeng et al. (48) (training)	China	M; R	2018–2020	Lung cancer	53	NA	34/19	Median	581.95	Before treatment	NA
Zeng et al. (48) (validation)	China	M; R	2015–2021	Lung cancer	84	NA	75/9	Median	581.95	Before treatment	NA

Retro, retrospective study; Pro, prospective study; M, multiple center; S, single center; ROC, receiver operator characteristic curve; MSR, maximally selected rank; IQR, interquartile range; NA, not available.

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TABLE 2 Survival information of included studies.

References	Sample	Treatment strategy	Tumor stage	Survival outcomes	Multivariate analysis	Median follow-up time, months
Baba et al. (14) (training)	433 (225:208)	Surgery	Mixed	OS	No	NA
Baba et al. (14) (validation)	433 (210:223)	Surgery	Mixed	OS	Yes	58.8
Chen et al. (15)	94 (47:47)	First-line ALK inhibitor	Mixed	OS;PFS	Yes; Yes	47.0 (IQR, 38.5–55.5)
Corti et al. (16)	163 (63:100)	Immunotherapy	Metastatic	OS;PFS	Yes; Yes	31
Demir et al. (25)	243 (122:121)	Surgery	Mixed	OS	No	NA
Efil et al. (26)	304 (152:152)	Surgery	Non-metastatic	OS; DFS	Yes; Yes	NA
Fucà et al. (13)	438 (230:208)	Chemotherapy combined with target therapy	Metastatic	OS; PFS	Yes; Yes	38.4 (IQR, 27.4–50.9)
Fucà et al. (27)	228 (51:177)	Immunotherapy combined with target therapy	Metastatic	OS; PFS	Yes; Yes	35.3
Gambichler et al. (28)	49 (31:18)	Mixed therapy	Non-metastatic	RFS	No	NA
Guven et al. (29)	120 (60:60)	Immunotherapy	Metastatic	OS; PFS	Yes; Yes	9.62
Guven et al. (30)	199 (101:98)	Chemoradiotherapy	Non-metastatic	OS;DFS	Yes; Yes	71.59
Karadağ et al. (11)	120 (60:60)	Mixed therapy	Mixed	OS	Yes	9.5 (IQR:3–23)
Kucuk et al. (31)	89 (57:36)	Chemoradiotherapy	Non-metastatic	OS; PFS	Yes; Yes	19.7 (Range, 4.0–88.1)
Liang et al. (32)	753 (347:379)	Surgery	Mixed	OS	Yes	NA
Ligorio et al. (33)	57 (29:28)	Taxane/trastuzumab/pertuzumab	Metastatic	OS; PFS	Yes; Yes	36.6
Lin et al. (19)	1,312 (152:1160)	Surgery	Non-metastatic	OS	Yes	78.4 (IQR, 53.1–88)
Mesti et al. (34)	129 (65:64)	Immunotherapy	Metastatic	OS; PFS	No; Yes	22.5
Pérez-Martelo et al. (35)	130 (70:60)	Chemotherapy	metastatic	OS; PFS	Yes; Yes	NA
Provenzano et al. (36)	78 (39:39)	Chemotherapy	metastatic	OS; PFS	Yes; Yes	47.4
Qi et al. (37)	51 (NA:NA)	Neoadjuvant chemoradiotherapy and pembrolizumab	Mixed	PFS	No	20
Sahin et al. (38)	743 (246:351)	Neoadjuvant chemotherapy	Non-metastatic	OS;DFS	No; No	67.5 (Range, 10.5–194.4)
Sato et al. (39)	86 (63:23)	Surgery	Non-metastatic	RFS	Yes	35 (Range, 1–104)
Sato et al. (40)	758 (190:568)	Surgery	Non-metastatic	OS; RFS	Yes; Yes	63.5
Susok et al. (41)	62 (NA:NA)	Immunotherapy	Mixed	PFS	No	NA
Topkan et al. (42)	204 (129:75)	Radiotherapy and temozolomide	Metastatic	OS; PFS	No; No	17.6 (Range, 2:4–108.3)
Topkan et al. (43)	178 (109:69)	Concurrent chemoradiotherapy	Non-metastatic	OS; PFS	Yes; Yes	17.9 (Range, 3.2–104.0)
Wang et al. (44)	89 (34:55)	Surgery	Non-metastatic	DFS	No	29.1 (Range, 4.1–115.8)
Yazgan et al. (45)	114 (57:57)	Androgen receptor-signaling inhibitors	Mixed	OS	Yes	34.6
Yeh et al. (46)	853 (366:487)	Surgery	Mixed	OS;DFS	Yes; Yes	NA
Yekedüz et al. (47)	152 (75:77)	Immunotherapy	Metastatic	OS; PFS	Yes; Yes	29.1
Zeng et al. (48) (training)	53 (27:26)	Immunotherapy and chemotherapy	Mixed	OS; PFS	Yes; Yes	NA
Zeng et al. (48) (validation)	84 (28:56)	Immunotherapy and chemotherapy	Mixed	OS; PFS	Yes; Yes	14

OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; RFS, recurrence-free survival; IQR, interquartile range; NA, not available.

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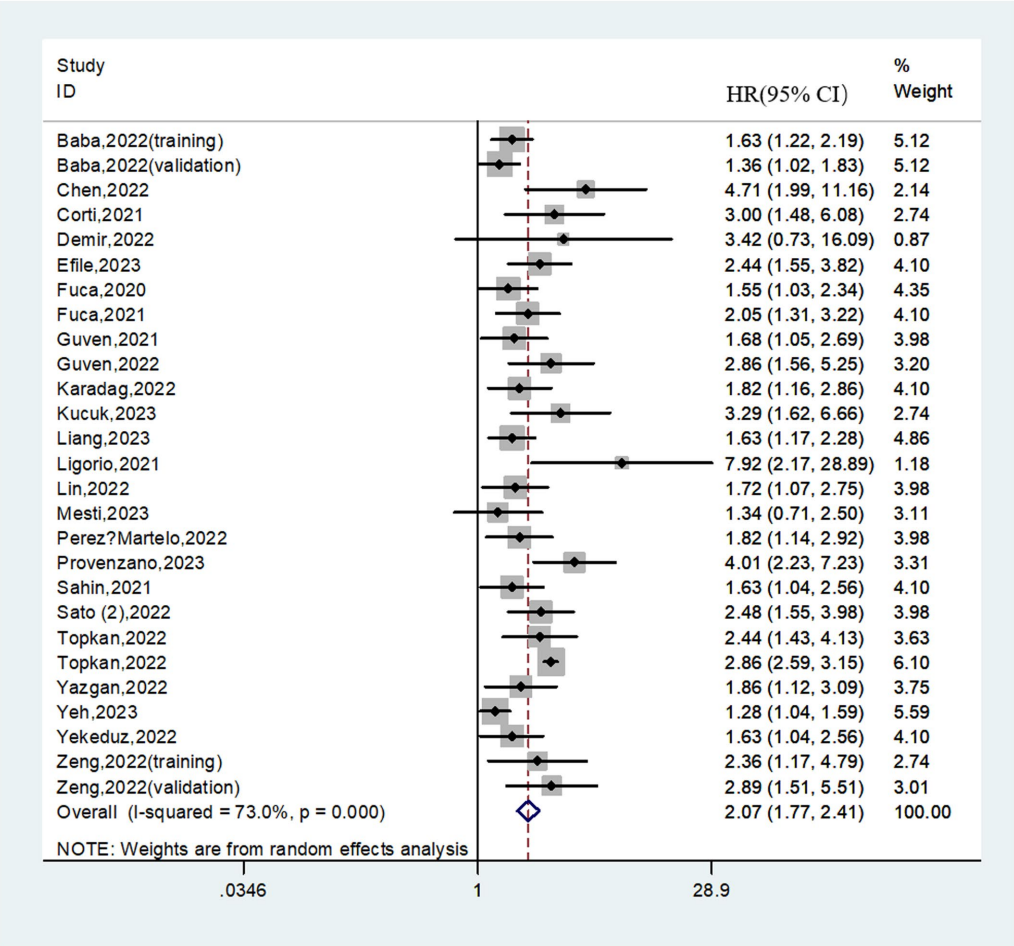

FIGURE 2
Forest plot assessing the relationship between the PIV and OS.

95% CI: 0.99–2.35) (Table 4 and Supplementary Figure S2). Additionally, meta-regression analysis revealed that none of these factors was the source of heterogeneity (all p values>0.05; Supplementary Table S2).

3.4. Sensitivity analyses and publication bias

Sensitivity analyses were conducted to assess the robustness of the pooled OS and PFS. After omitting any individual study, pooled HRs with 95% CIs for both OS and DFS were not significantly altered (Supplementary Figure S3).

The Begg's funnel plots were applied to evaluate the potential publication bias. As shown in Supplementary Figure S4, the funnel plot for PFS was bilaterally symmetric with a Begg's p value of 0.691, indicating that there was no significant publication bias for PFS. While for OS, the Begg's funnel plot was asymmetric with the p value <0.0001, which suggested a high risk of publication bias for this outcome. Trim-and-fill analysis was therefore applied, supplementing a total of 8 unpublished cohorts to balance the funnel plot. Finally, PIV was still associated with inferior OS (HR = 1.82; 95%CI: 1.56–2.13), indicating the robustness of the pooled result.

4. Discussion

Cancer-related inflammation is prevalent in patients with malignant diseases, which has been confirmed to promote cancer progression and advancement (6). Traditionally, host inflammation status can be detected through several blood biomarkers, such as neutrophil count, platelet count, and lymphocyte count. Additionally, evidence from numerous studies has demonstrated that their ratios can be applied to predict patient's short-term and long-term outcomes, especially in cancer patients (7, 8). Importantly, these markers have the natural advantage of being non-invasive, objective, and cost-effective, which provides great potential for their wide clinical applications.

In recent years, a new biomarker, the pan-immune-inflammation value, which consists of serum neutrophil, platelet, monocyte and lymphocyte, has attracted the attention of clinicians due to its promising prognostic significance in several malignancies (12, 30, 39). A recent meta-analysis by Guven et al. (17) has initially demonstrated that high PIV was associated with decreased survival outcomes in

TABLE 3 Subgroup analyses for OS of PIV-high patients vs. PIV-low patients.

Subgroup	Cohorts	Patients	Pooled analysis		I square (%)
			HR	95%CI	
All patients	27	8,462	2.07	1.77–2.41	73.0
Country					
Asian	20	7,239	2.03	1.69–2.43	76.8
Non-Asian	7	1,043	2.23	1.60–3.12	57.5
Study center					
Single center	21	7,483	2.04	1.70–2.44	77.6
Multicenter	6	1,159	2.14	1.63–2.82	26.6
Sample size					
<150	11	1,068	2.34	1.83–3.00	44.8
>150	16	7,574	1.93	1.58–2.36	80.8
Cancer type					
Gastrointestinal	10	3,710	1.96	1.55–2.48	80.3
Breast	5	2,433	2.61	1.56–4.38	63.2
Lung	4	320	3.09	2.15–4.42	0.0
Melanoma	2	357	1.76	1.17–2.63	16.0
Others	6	1,642	1.76	1.37–2.28	51.2
Selection method					
ROC curve	10	4,643	1.97	1.50–2.59	87.5
Median	11	1,396	2.37	1.85–3.03	40.0
MSR	6	2,423	1.81	1.49–2.20	0.0
Cut-off value					
<350	10	5,025	1.75	1.42–2.15	58.6
>350	17	3,437	2.25	1.93–2.62	44.8
Treatment strategy					
Surgery	8	5,089	1.66	1.39–1.98	45.1
Chemo/radiotherapy	8	2059	2.37	1.87–3.01	61.0
Immunotherapy contained	7	929	1.95	1.58–2.39	0.0
Others	4	385	2.71	1.56–4.73	61.7
Tumor stage					
Non-metastatic	7	3,583	2.43	1.99–2.96	41.5
Mixed	10	3,180	1.73	1.43–2.09	47.3
Metastatic	10	1,699	2.06	1.64–2.59	43.9
Analysis method					
Univariate	5	1752	1.72	1.40–2.12	0.0
Multivariate	22	6,710	2.14	1.79–2.55	75.9
Follow-up					
<30 months	8	1,076	2.16	1.69–2.76	61.2
>30 months	12	4,617	2.20	1.74–2.77	57.9
NA	7	2,769	1.69	1.39–2.41	38.4

cancer patients. Nevertheless, this meta-analysis included only 15 studies (including an abstract) and several common cancer types (such as pancreatic cancer, hepatic cancer and prostate cancer) were not available, which made the prognostic value of PIV in cancer patients still inconclusive. To clarify this issue accurately, an updated meta-analysis including 30 studies with 8,799 cancer patients was performed. Through our quantitatively analyses, we convinced that an elevated PIV markedly predicted poorer OS (HR = 2.07; 95%CI: 1.77–2.41) and PFS (HR = 1.83; 95%CI: 1.37–2.45) in cancer patients. Additionally, benefiting from the inclusion of sufficient studies,

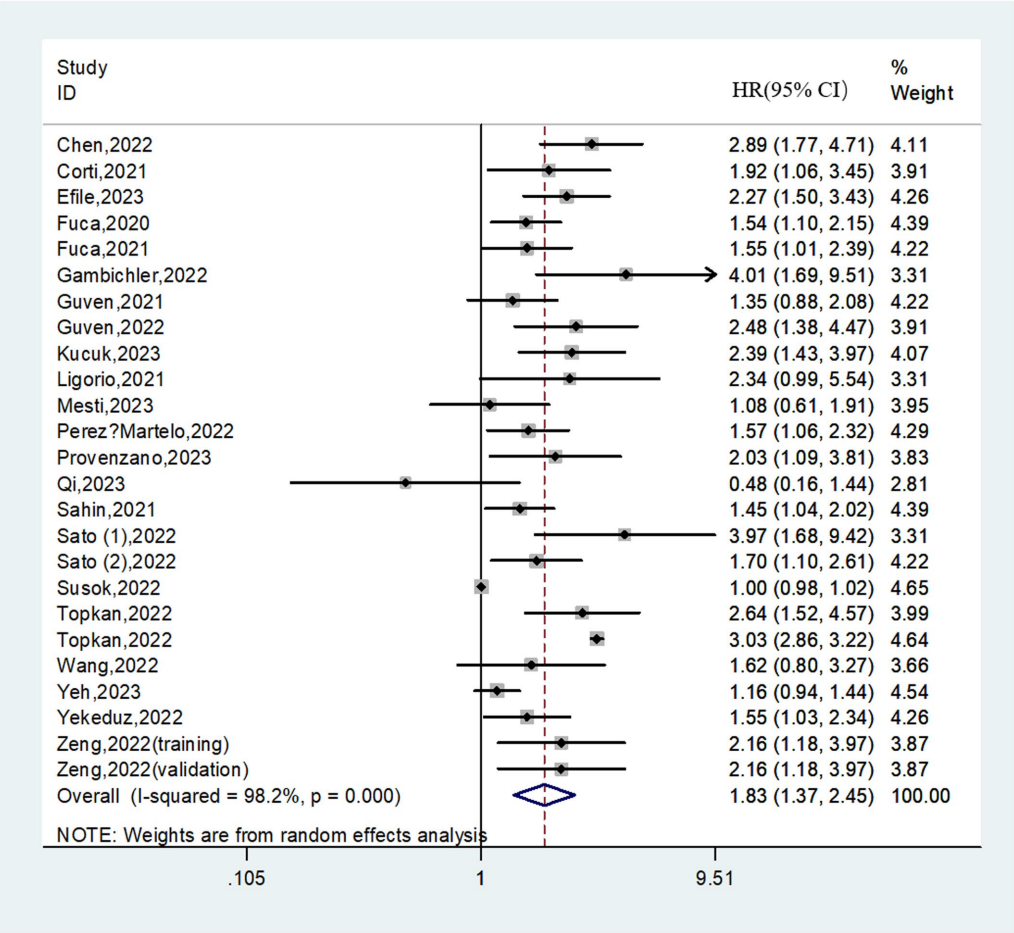

FIGURE 3
Forest plot accessing the relationship between the PIV and PFS.

we were able to perform detailed subgroup analyses, as well as sensitivity and publication bias analyses It can be seen that the PIV achieved reliable performance in predicting prognosis. Therefore, the PIV may be a valuable and effective inflammatory index to evaluate the oncological outcomes of patients with malignancies.

Dysregulation of inflammatory and immune cells in the tumor microenvironment has been identified as being involved in the tumor progression (49–51). Simultaneously, a higher PIV may result from higher neutrophils, monocytes, and platelets and/or lower lymphocytes. Although the detailed mechanisms of the PIV's prognostic value in malignancies are unclear, they can be explained as follows: First, neutrophils, as the most common innate immune cells, have been reported to promote tumor invasion and metastasis by secreting VEGFA, MMPs, and other chemokines such as IL-6 and TGF-β (52, 53). At the same time, elevated neutrophils can also cause T cell activation disorders by largely releasing nitric oxide, arginase, and reactive oxygen species, ultimately inhibiting the body's killing effect on cancer cells (54). Second, monocytes, especially those differentiated into tumor-associated macrophages (TAMs), can induce apoptosis of T cells with antitumor functions (55). In addition, TAM density has been shown to affect tumor tissue angiogenesis by stimulating the production and secretion of pro-angiogenic factors (56, 57). Third, platelets, are reported to induce epithelial–mesenchymal transition and angiogenesis by secreting TGF-β, VEGF and FGF. Moreover, platelets are also able to recruit neutrophils and monocytes, thereby promoting the distant metastasis of tumor cells. Finally, lymphocytes, especially cytotoxic T lymphocytes, play an essential role in cancer immune surveillance and defense (58). It has been reported that high lymphocyte levels in the tumor microenvironment are beneficial for inducing lysis and apoptosis of cancer cells, thereby inhibiting cancer cell proliferation and metastasis (59). On the contrary, lymphopenia has been shown to be associated with a poor prognosis in cancer patients (60).

Notably, the pooled outcomes from subgroup analyses demonstrated that the prognostic value of the PIV for both OS and PFS was consistent in treatment strategies, such as surgery (HR = 1.66 and 1.80), chemo/radiotherapy (HR = 2.37 and 2.06), immunotherapy (HR = 1.95 and 1.40). Given that patients with malignancies would receive one or more anti-tumor treatment strategies, these results showed that PIV could provide prognosis prediction for malignant patients receiving different treatments, especially for those receiving chemo/radiotherapy. In addition, PIV has been shown to have considerable prognostic value across different tumor species, particularly in lung cancer (HR = 3.09 and 2.43). Moreover, the prognostic value of PIV was not affected by the country of publication,

TABLE 4 Subgroup analyses for PFS of PIV-high patients vs. PIV-low patients.

Subgroup	Cohorts	Patients	Pooled analysis		I square (%)
			HR	95% CI	
All patients	**25**	5,391	1.83	1.37–2.45	98.2
Country					
Asian	16	4,057	1.93	1.49–2.50	87.8
Non-Asian	9	1,334	1.59	1.20–2.12	79.2
Study center					
Single center	19	4,412	1.81	1.28–2.55	98.6
Multicenter	6	979	1.80	1.48–2.18	0.0
Sample size					
<150	14	1,171	1.80	1.33–2.43	83.7
>150	11	4,220	1.85	1.36–2.50	91.5
Cancer type					
Gastrointestinal	9	2,197	1.89	1.37–2.60	83.3
Breast	3	878	1.63	1.23–2.15	0.0
Lung	4	320	2.43	1.85–3.19	0.0
Melanoma	5	419	1.13	0.86–1.47	50.8
Others	6	1,577	1.81	1.28–2.55	71.3
Selection method					
ROC curve	12	3,361	1.86	1.19–2.91	99.1
Median	8	919	1.93	1.53–2.44	31.9
MSR	5	1,111	1.58	1.32–1.90	0.0
Cut-off value					
<350	7	1957	1.56	1.12–2.16	59.7
>350	18	3,434	1.92	1.35–2.74	98.7
Treatment strategy					
Surgery	5	2090	1.80	1.22–2.64	72.4
Chemo/radiotherapy	8	2059	2.06	1.53–2.78	84.2
Immunotherapy contained	9	1,042	1.40	1.07–1.82	72.3
Others	3	200	2.96	2.02–4.33	0.0
Tumor stage					
Non-metastatic	**9**	2,495	2.29	1.76–3.00	74.0
Mixed	6	1,197	1.46	1.04–2.04	85.2
Metastatic	10	1,699	1.61	1.39–1.87	0.0
Analysis method					
Univariate	6	1,198	1.53	0.99–2.35	83.4
Multivariate	19	4,193	1.91	1.52–2.39	86.5
Follow-up					
<30 months	9	1,096	1.75	1.24–2.49	83.7
>30 months	10	2,844	1.86	1.56–2.22	21.9
NA	6	1,451	1.59	1.16–2.20	86.8

cut-off value, and tumor stage, further confirming the clinical universality and efficacy of PIV in cancer patients.

This meta-analysis had several limitations must be acknowledged. First, all of the included studies except one by Qi et al. (37) were designed to be retrospective, which may increase the risk of selection bias. Second, the heterogeneities of pooled outcomes for both OS and PFS were remarkable, even though the subgroup analyses and sensitivity analyses showed consistent results, we failed to find the sources of heterogeneity. Third, significant inconsistencies in the measurement of blood parameters in the included studies, including but not limited to factors such as measurement time, may have contributed to the large variability in the cut-off values of PIV, and

may also have had some impact on the confidence of our pooled results. Finally, the cut-off values of PIV varied widely due to various factors such as disease type, population differences, sample size, and detection method, which somewhat limits the clinical use of PIV.

5. Conclusion

In conclusion, the present meta-analysis demonstrates an association between elevated pre-treatment PIV and poor survival outcomes in cancer patients. PIV has the potential to be a noninvasive and effective prognostic biomarker for cancer patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YH-J: Funding acquisition, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. RS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review & editing, Visualization. XJ-Q: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1259929/full#supplementary-material

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Coexistence of muscle atrophy and high subcutaneous adipose tissue radiodensity predicts poor prognosis in hepatocellular carcinoma

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Introduction: We aimed to assess the prognostic implications of muscle atrophy and high subcutaneous adipose tissue (SAT) radiodensity in patients with hepatocellular carcinoma (HCC).

Methods: In this retrospective study, muscle atrophy was assessed using the psoas muscle index (PMI) obtained from computed tomography. SAT radiodensity was evaluated based on radiodensity measurements. Survival and multivariate analyses were performed to identify factors associated with prognosis. The impact of muscle atrophy and high SAT radiodensity on prognosis was determined through survival analysis.

Results: A total of 201 patients (median age: 71 years; 76.6% male) with HCC were included. Liver cirrhosis was observed in 72.6% of patients, and the predominant Child–Pugh grade was A (77.1%). A total of 33.3% of patients exhibited muscle atrophy based on PMI values, whereas 12.9% had high SAT radiodensity. Kaplan–Meier survival analysis demonstrated that patients with muscle atrophy had significantly poorer prognosis than those without muscle atrophy. Patients with high SAT radiodensity had a significantly worse prognosis than those without it. Muscle atrophy, high SAT radiodensity, the Barcelona Clinic Liver Cancer class B, C, or D, and Child–Pugh score $\geq$ 6 were significantly associated with overall survival. Further classification of patients into four groups based on the presence or absence of muscle atrophy and high SAT radiodensity revealed that patients with both muscle atrophy and high SAT radiodensity had the poorest prognosis.

Conclusion: Muscle atrophy and high SAT radiodensity are significantly associated with poor prognosis in patients with HCC. Identifying this high-risk subgroup may facilitate the implementation of targeted interventions, including nutritional therapy and exercise, to potentially improve clinical outcomes.

KEYWORDS

low muscle mass, psoas muscles, skeletal muscle, liver disease, subcutaneous adipose tissue, muscle atrophy

1. Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths, and its incidence has been increasing globally (1). Multiple prognostic factors are critical in the prognosis of HCC. These include the tumor status, as per the Barcelona Clinic Liver Cancer (BCLC) classification, liver function assessment according to the Child–Pugh score and albumin-bilirubin grade, and the patient's general health status evaluated by the Eastern Cooperative Oncology Group performance status (2). While it is challenging to objectively assess a patient's performance status, body composition, particularly muscle mass, offers an objective estimate of a patient's physical, nutritional, and metabolic condition (3). Chronic liver diseases, including HCC, are known to cause secondary sarcopenia (4, 5); in addition, loss of muscle mass in patients with HCC is associated with a poorer prognosis and increased rates of recurrence (6–8). Moreover, in patients with chronic liver diseases, particularly those with liver cirrhosis (LC), the reported prevalence of sarcopenia is notably high and the loss of skeletal muscle mass progresses rapidly (7, 9–11). Therefore, it is crucial to assess muscle mass in patients with HCC to predict prognosis.

Recent studies suggest that aspects of body composition besides muscle mass also correlate with mortality in patients with decompensated cirrhosis and HCC (12). Factors such as subcutaneous adipose tissue (SAT) radiodensity (13, 14), intramuscular fat deposition, and visceral adiposity (15) have been reported as prognostic factors in patients with HCC. In particular, SAT radiodensity can be objectively measured by CT in Hounsfield units (HU), and average SAT radiodensity has been introduced as an indirect surrogate marker of adipose tissue quality (16). Consequently, the evaluation of body composition using CT, such as determining SAT radiodensity or detecting loss of skeletal muscle mass, is increasingly used as a non-invasive clinical tool with prognostic value. Importantly, early and appropriate identification of these abnormalities could enable interventions designed to rectify body composition abnormalities, potentially improving clinical outcomes (3). While a comprehensive analysis using SAT radiodensity and loss of skeletal muscle mass might predict prognosis in patients with HCC with greater accuracy, this approach is not yet fully clarified. In the present study, we aimed to evaluate the impact of muscle atrophy and SAT radiodensity on the prognosis of patients with HCC.

2. Materials and methods

In this retrospective study, we screened HCC patients who underwent proper CT imaging for evaluation of skeletal muscle mass and SAT radiodensity at Hokkaido University Hospital between July 2015 and May 2021. Patients were included if they were diagnosed with HCC according to Guidance by the American Association for the Study of Liver Diseases (17), had adequate clinical information and CT imaging for evaluation of skeletal muscle mass and SAT radiodensity, and were followed up for more than 3 months. We excluded patients with HCC who did not have adequate clinical and CT imaging information or were observed for a period of <3 months.

We collected the following clinical data: sex, age, etiology of chronic liver diseases, body mass index, blood test results, Child–Pugh class, TNM stage, BCLC class, presence of LC, and prognosis. In this study, LC was diagnosed based on liver biopsy, Fibroscan® (Echosens, Paris, France) data, and/or radiologic findings, such as CT or magnetic resonance imaging, and laboratory data, as described in previous studies (18, 19). We investigated the factors associated with prognosis in patients with HCC, including skeletal muscle mass and SAT radiodensity by multivariate analysis. Subsequently, we analyzed the impact of skeletal muscle mass and SAT radiodensity on prognosis of these patients.

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Hokkaido University Hospital. All patients provided written informed consent to participate. This study was registered at the University Hospital Medical Information Network Clinical Trials Registry as UMIN 000030755.

2.1. Skeletal muscle mass calculation by computed tomography imaging

In the present study, to assess muscle atrophy, skeletal muscle mass was evaluated using the psoas muscle index (PMI). PMI was calculated from CT imaging as follows: the sum of the L3 level cross-sectional area of the right and left psoas muscle mass was identified by manual tracing and divided by height squared (cm^2/m^2) (18). Muscle atrophy was also defined according to our previous study as follows: PMI values $<3.74\,cm^2/m^2$ for males, and $<2.29\,cm^2/m^2$ for females (20).

2.2. SAT radiodensity calculation by CT imaging

SAT radiodensity was measured using abdominal plain CT scans taken at the third lumbar vertebra (L3) levels. CT values were measured for regions of interests of four circles on subcutaneous fat away from major vessels. The mean values of these four regions of interests were used as the regions of interest of SAT radiodensity (21). High SAT radiodensity was also defined according to a previous study as follows: High SAT radiodensity > −74 HU for males and > −83 HU for females (14).

2.3. Endpoint

The primary endpoint of this study was to identify the factors associated with overall survival. Overall survival was defined as the duration from the time of inclusion until death. Patients who were still alive or transferred other hospitals were censored on the date of the last follow-up registered in the medical record.

2.4. Statistical analysis

Continuous variables were analyzed using the Mann–Whitney *U* test. Categorical variables were analyzed using the Fisher's exact test.

Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Univariate Cox regression

analysis was conducted for clinical factors and laboratory data; laboratory data that were included in the calculation of the Child–Pugh score and those that violated the proportional hazards assumption were excluded. Multivariate Cox regression analysis was conducted for factors showing significance (defined at $p < 0.1$) in the univariate analysis (22, 23). All p-values were two-tailed, and the level of significance was set at $p < 0.05$. All statistical data were generated using Prism 7.03 (GraphPad Software, Inc., La Jolla, CA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3. Results

3.1. Patient characteristics

Patients with HCC who visited Hokkaido University Hospital between July 2015 and May 2021 were screened for inclusion. Ultimately, 201 patients met the inclusion criteria and were included in this study (Figure 1).

The baseline characteristics of included patients with HCC are shown in Table 1. The median age of patients was 71 years (range: 20–90 years), and 76.6% of them were males. A total of 72.6% had LC. A total of 77.1% had Child–Pugh A. A total of 31.3 and 30.3% had BCLC stage 0 and A. Based on the PMI values, 33.3% patients had muscle atrophy. The definition of high SAT radiodensity in previous reports was adopted (SAT > −74 HU for males and > −83 HU for females) (14), and a total of 12.9% patients had high SAT radiodensity.

3.2. Comparison of prognosis between HCC patients with and without muscle atrophy

As shown in Figure 2, Kaplan–Meier survival analysis revealed that patients with muscle atrophy had a significantly poorer prognosis than those without muscle atrophy (log-rank p-value = 0.004; crude Cox regression hazard ratio [HR]: 1.878, 95% confidence interval [CI]: 1.18–2.99). The comparison between characteristics of patient with or without muscle atrophy are shown in Table 2. Patients with muscle atrophy exhibited significantly higher rates of high SAT radiodensity and lower body mass index compared to those without muscle atrophy.

3.3. Comparison of prognosis in patients with HCC with and without high SAT radiodensity

As shown in Figure 3, Kaplan–Meier survival analysis revealed that patients with high SAT radiodensity had a significantly poorer prognosis than those without it (log-rank p-value <0.001, crude Cox regression HR: 2.66, 95% CI: 1.18–5.96). Table 3 presents a comparison of characteristics between patients with and without high SAT radiodensity. Patients with high SAT radiodensity were significantly more likely to be male, have muscle atrophy and ascites, display lower body mass index, have reduced albumin levels, exhibit lower PMI in males, and have a worse Child–Pugh grade compared to those without it.

3.4. Univariate and multivariate Cox regression analysis regarding clinical factors associated with overall survival

Subsequently, we analyzed the clinical factors associated with overall survival in patients with HCC. Multivariate regression analysis was performed using variables of clinical factors with $p < 0.1$ in the univariate analyses, which were sex and age. Multivariate regression analysis revealed that muscle atrophy (HR, 1.69; 95% CI, 1.09–2.63; $p = 0.019$), high SAT radiodensity (HR, 2.30; 95% CI, 1.23–4.31; $p = 0.01$), and BCLC class B, C, or D (HR, 4.53; 95% CI, 2.76–7.43; $p < 0.001$), and Child–Pugh score ≥ 6 (HR, 1.71; 95% CI, 1.02–2.88; $p = 0.043$) were significantly associated with overall survival in patients with HCC (Table 4).

3.5. Comparison of overall survival among the four classified groups based on muscle atrophy and high SAT radiodensity

Given that high SAT radiodensity and muscle atrophy were found to be significant and independent prognostic factors in patients with HCC, we further classified the patients into four groups based on the presence or absence of muscle atrophy and high SAT radiodensity. As shown in Figure 4, Kaplan–Meier survival analysis revealed that the

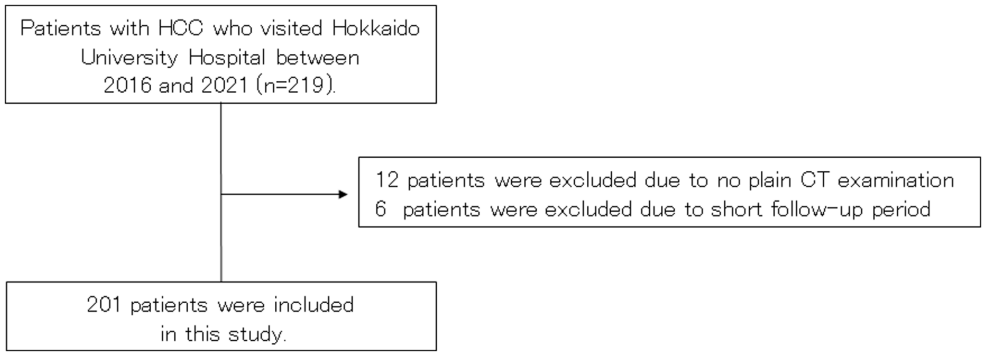

FIGURE 1
Patient flow chart. CT, computed tomography; HCC, hepatocellular carcinoma.

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TABLE 1 Baseline clinical and biochemical characteristics.

Variables	Overall (n = 201)
Age, years	71 (20–90)
Sex, male / female	154 (76.6%) / 47 (23.4%)
Etiology, HBV / HCV / NBNC	59 (29.4%) / 51 (25.4%) / 91 (45.2%)
Liver cirrhosis, + / −	146 (72.6%) / 55 (27.4%)
Stage, I / II / III / IV	67 (33.3%) / 59 (29.4%) / 45 (22.3%) / 30 (15.0%)
BCLC stage, 0 / A / B / C / D	63 (31.3%) / 61 (30.4%) / 43 (21.4%) / 28 (13.9%) / 6 (3.0%)
Child–Pugh grade, A / B / C	155 (77.1%) / 42 (20.9%) / 4 (2.0%)
Child–Pugh score	7 (5–11)
Follow-up period, years	2.84 (0.25–7.01)
PMI, cm^2/m^2	M: 4.15 (0.77–8.65)
	F: 2.81 (0.71–6.62)
Muscle atrophy, + / −	67 (33.3%) / 134 (66.7%)
SAT radiodensity, HU	M: −98.75 (−109.5 – −64.75)
	F: −96.62 (−114.75 – −58.75)
High SAT, + / −	26 (12.9%) / 175 (87.1%)
Body mass index, kg/m^2	24.4 (14.9–36.8)
Ascites, + / −	40 (19.9%) / 161 (80.1%)
Platelet counts, $x10^4/mm^3$	13.6 (3.00–42.4)
Prothrombin time, %	87.2 (19.5–125.4)
Serum albumin, g/dL	3.90 (2.3–4.90)
Aspartate transaminase, IU/L	37 (10–332)
Alanine aminotransferase, IU/L	26 (6–109)
Creatinine, mg/dL	0.79 (0.38–7.43)
Alpha-fetoprotein, ng/mL	6.4 (1.3–413503.0)

Data are presented as number, percentages of patients or median (range) values.
BCLC, the Barcelona Clinic Liver Cancer; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV non-HCV; PMI, psoas muscle mass index; M, male; SAT, subcutaneous adipose tissue.

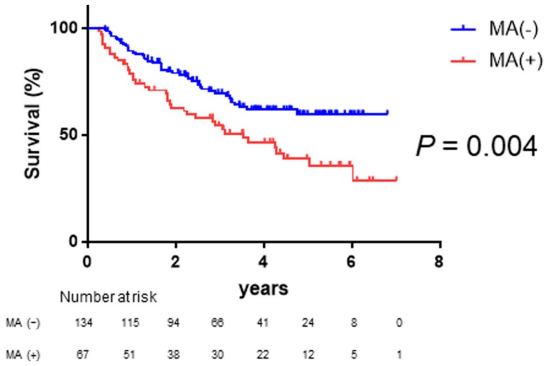

FIGURE 2
Survival rates in patients with and without muscle atrophy Kaplan–Meier estimates of overall survival stratified according to muscle atrophy in patients with HCC. The median overall survival is not reached in patients without muscle atrophy and 3.52 years in patients with muscle atrophy. Patients with muscle atrophy have a poorer prognosis than those without muscle atrophy (log-rank p-value = 0.004; crude Cox regression hazard ratio: 1.88, 95% confidence interval: 1.18–2.99). HCC, hepatocellular carcinoma.

overall survival among four groups was significantly different. In particular, the patients with muscle atrophy and high SAT radiodensity had a poor prognosis (median overall survival in the patients without muscle atrophy and with or without high SAT radiodensity was undefined, 4.29 years in the patients with muscle atrophy and without high SAT radiodensity, and 1.04 years in the patients with muscle atrophy and high SAT radiodensity; $p = 0.002$).

3.6. Stratified analysis

Based on the results presented above (Figure 4), we assessed the prognosis in the entire population, distinguishing between patients with both muscle atrophy and high SAT radiodensity, and those without both before conducting stratified analysis. Patients with both muscle atrophy and high SAT radiodensity had a significantly poorer prognosis than the other patients (log-rank p-value <0.001, Figure 5A; crude Cox regression HR: 4.53, 95% CI: 1.43–14.4). Subsequently, we conducted subgroup analyses based on clinical factors contributing to overall survival of patients with HCC. First, we performed the subgroup analysis stratified with Child–Pugh grade A, B, and C. A total of 77.1% patients had Child–Pugh grade A, and 22.9% had Child–Pugh grade B or C. Among the patients with Child–Pugh grade A, the patients with muscle atrophy tended to have a poor prognosis (log-rank p-value = 0.054, Supplementary Figure 2A; crude Cox regression HR: 1.66, 95% CI: 0.95–2.90), and the patients with high SAT radiodensity had a similar tendency toward a poorer prognosis (log-rank p-value = 0.116, Supplementary Figure 2B; crude Cox regression HR: 1.86, 95% CI: 0.67–5.14). Patients with both muscle atrophy and high SAT radiodensity had a significantly poorer prognosis than the other patients (log-rank p-value = 0.044, Figure 5B; crude Cox regression, HR: 3.48 95% CI: 1.03–11.70). Among the patients with Child–Pugh grade B or C, the patients with muscle atrophy tended to have a poorer prognosis (log-rank p-value = 0.054, Supplementary Figure 2C; crude Cox regression HR: 2.17, 95% CI: 0.95–4.91), and the patients with high SAT radiodensity had a significantly poorer prognosis (log-rank p-value = 0.001, Supplementary Figure 2D; crude Cox regression HR: 3.61, 95% CI: 1.06–12.29). Similar to patients with Child–Pugh grade A, patients with both muscle atrophy and high SAT radiodensity had a significantly poorer prognosis than other patients with Child–Pugh grade B or C (log-rank p-value <0.001, Figure 5C; crude Cox regression, HR: 10.43, 95% CI: 3.76–28.93).

Subsequently, we conducted a subgroup analysis based on BCLC class. A total of 61.7% of patients were BCLC class 0 or A. Among these patients, those with muscle atrophy had a significantly poorer prognosis (log-rank p-value = 0.005, Supplementary Figure 3A; crude Cox regression HR: 2.95, 95% CI: 1.38–6.30), and the patients with high SAT radiodensity had a poorer prognosis (log-rank p-value = 0.02, Supplementary Figure 3B; crude Cox regression HR: 2.98, 95% CI: 1.13–7.84). In addition, the patients with both muscle atrophy and high SAT radiodensity had a significantly poorer prognosis than the other patients (log-rank p-value <0.001, Figure 6A; crude Cox regression HR: 4.51, 95% CI: 1.72–11.85). Afterward, among the patients with BCLC class B, C, or D, the patients with

TABLE 2 Baseline clinical and biochemical characteristics of patients with or without muscle atrophy.

Variables	Without muscle atrophy (*N* = 134)	With muscle atrophy (*N* = 67)	*P*-values
Age, years	70 (20–88)	71 (44–90)	0.057
Sex, male / female	100 (74.6%) / 34 (25.4%)	54 (80.6%) / 13 (19.4%)	0.382
Etiology, HBV / HCV / NBNC	46 (34.3%) / 29 (21.7%) / 59 (44.0%)	13 (19.4%) / 22 (32.8%) / 32 (47.8%)	0.055
Liver cirrhosis, + / −	94 (70.1%) / 40 (29.9%)	52 (77.6%) / 15 (22.4%)	0.315
Stage, I / II / III / IV	49 (36.6%) / 37 (27.6%) / 27 (20.1%) / 21 (15.7%)	18 (26.9%) / 22 (32.8%) / 18 (26.9%) / 9 (13.4%)	0.559
BCLC stage, 0 / A / B / C / D	48 (35.8%) / 36 (26.9%) / 29 (21.7%) / 18 (13.4%) / 3 (2.2%)	15 (22.3%) / 25 (37.4%) / 14 (20.9%) / 10 (14.9%) / 3 (4.5%)	0.258
Child–Pugh grade, A / B / C	108 (80.6%) / 23 (17.2%) / 3 (2.2%)	47 (70.1%) / 19 (28.4%) / 1 (1.5%)	0.162
Child–Pugh score	5 (5–11)	6 (5–11)	0.051
Follow-up period, years	2.92 (0.39–6.81)	2.84 (0.25–7.01)	0.265
PMI, cm^2/m^2	M: 4.70 (3.75–8.65)	M: 2.94 (0.77–3.73)	<0.001
	F: 3.44 (2.30–6.62)	F: 0.71 (1.90–2.15)	<0.001
SAT radiodensity, HU	M: −100.25 (−114.75 – −62.0)	M: −93.25 (−110.75 – −58.75)	0.004
	F: −98.88 (−109.5 – −66.75)	F: −97.50 (−108.25 – −64.75)	0.803
High SAT, + / −	10 (7.5%) / 124 (92.5%)	16 (23.9%) / 51 (76.1%)	0.002
Body mass index, kg/m^2	25.2 (16.3–36.8)	22.5 (14.9–36.1)	<0.001
Ascites, + / −	23 (17.2%) / 111 (82.8%)	17 (25.4%) / 50 (74.6%)	0.191
Platelet counts, $x10^4$ /mm^3	13.9 (4.4–40.0)	13.0 (3.0–42.4)	0.390
Prothrombin time, %	89.6 (19.5–123.30)	84.5 (19.6–125.4)	0.179
Serum albumin, g/dL	3.90 (2.3–4.90)	3.8 (2.3–4.8)	0.318
Aspartate transaminase, IU/L	34.5 (10–332)	38 (116–206)	0.259
Alanine aminotransferase, IU/L	26.5 (6–109)	25 (8–102)	0.860
Creatinine, mg/dL	0.79 (0.38–7.43)	0.80 (0.43–2.11)	0.863
Alpha-fetoprotein, ng/mL	5.9 (1.3–413503.0)	8.2 (1.5–316096.7)	0.176

Data are presented as number, percentages of patients or median (range) values.
BCLC, the Barcelona Clinic Liver Cancer; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV non-HCV; PMI, psoas muscle mass index; M, male; SAT, subcutaneous adipose tissue.

muscle atrophy had a tendency toward a poor prognosis (log-rank *p*-value = 0.13, Supplementary Figure 3C; crude Cox regression HR: 1.53, 95% CI: 0.84–2.75), and the patients with high SAT radiodensity had a poorer prognosis (log-rank *p*-value = 0.006, Supplementary Figure 3D; crude Cox regression HR: 2.59, 95% CI: 1.28–5.21). Patients with both muscle atrophy and high SAT radiodensity had a significantly poorer prognosis than the other patients (log-rank *p*-value <0.001, Figure 6B; crude Cox regression HR: 5.36, 95% CI: 2.34–12.28).

Finally, we conducted a stratified subgroup analysis based on the presence of ascites or pleural effusion. A total of 19.9% of patients had ascites or pleural effusion. Among the 161 patients (80.1%) without ascites, patients with muscle atrophy had a poorer prognosis (log-rank *p*-value = 0.038, Supplementary Figure 4A; crude Cox regression HR: 1.70, 95% CI: 1.02–2.81), and the patients with high SAT radiodensity had a poorer prognosis (log-rank *p*-value = 0.049, Supplementary Figure 4B; crude Cox regression HR: 2.99, 95% CI: 1.01–8.88). Patients with both muscle atrophy and high SAT radiodensity had a tendency toward a poorer prognosis than other patients (log-rank *p*-value = 0.115, Figure 7A; crude Cox regression HR: 2.05, 95% CI: 0.58–7.19). Similarly, among patients with ascites or pleural effusion, patients with muscle atrophy had a poorer prognosis (log-rank *p*-value = 0.041, Supplementary Figure 4C; crude Cox regression HR: 2.40, 95% CI: 1.01–5.7), and patients with high SAT radiodensity had a tendency toward a poor prognosis (log-rank *p*-value = 0.091, Supplementary Figure 4D; crude Cox regression HR: 2.08 95% CI: 0.75–5.77). Patients with both muscle atrophy and high SAT radiodensity had a poorer prognosis than the others (log-rank *p*-value <0.001, Figure 7B; crude Cox regression HR: 6.55, 95% CI: 1.24–34.7).

4. Discussion

In this study, we demonstrated that muscle atrophy and high SAT radiodensity could significantly and independently predict prognosis in patients with HCC. Moreover, we highlighted the importance of evaluating both muscle atrophy and high SAT radiodensity as prognostic factors in patients with HCC because coexistence of muscle atrophy and high SAT radiodensity could predict quite poor prognosis in patients with HCC. Identifying this high-risk subgroup may facilitate the implementation of targeted interventions, including nutritional therapy and exercise, to potentially improve clinical outcomes.

Prognosis in patients with HCC is reported to be associated with functional liver reserve, TNM staging, BCLC class, and performance status. In addition to these factors, loss of skeletal muscle mass is reported to be an important factor associated with prognosis in patients with HCC (8, 24–26). Furthermore, the importance of assessing adipose tissue-related parameters such as intramuscular fat, visceral fat, and SAT radiodensity for predicting prognosis has been recently reported (12–15, 27–29). Among these studies, Ebadi et al. conducted a study on cirrhotic patients, half of which had HCC, and reported that SAT density could stratify prognosis. Moreover, Ebadi et al. suggested that morphological rearrangements of SAT, diagnosed by SAT density, might occur prior to the loss of SAT mass (14). In the present study, we found that HCC patients with high SAT radiodensity had significantly worse prognosis, which was consistent with the results of previous studies.

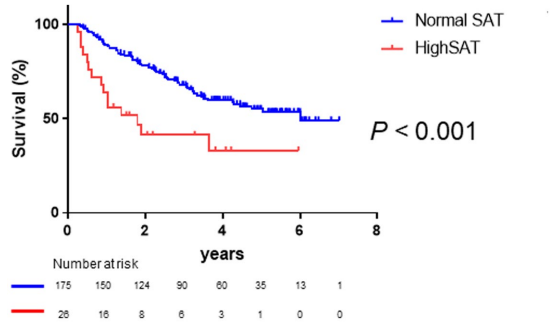

FIGURE 3
Survival rates in patients with normal and high subcutaneous adipose tissue (SAT) radiodensity Kaplan–Meier estimates of overall survival stratified according to SAT radiodensity in patients with HCC. The median overall survival is 6.02 years in patients with normal SAT radiodensity and 1.80 years in patients with high SAT radiodensity. Patients with high SAT radiodensity have a poorer prognosis than those with normal SAT radiodensity (log-rank *p*-value <0.001; crude Cox regression hazard ratio: 2.66, 95% confidence interval: 1.18–5.96). HCC, hepatocellular carcinoma; SAT, subcutaneous adipose tissue.

SAT plays a pivotal role in lipid storage and energy homeostasis and is now recognized for its multifaceted endocrine function, with adipokines playing a role in the regulation of diverse metabolic and inflammatory processes (30). High SAT radiodensity not only indicates a reduced SAT volume but also implies remodeling of adipose tissue, characterized by morphological changes such as atrophy, evidenced by smaller and shrunken adipocytes, expanded interstitial space, and infiltration of mononuclear cells. Therefore, it is suggested that high SAT radiodensity reflects the severe energy depletion associated with cirrhosis, leading to unfavorable clinical outcomes (14).

TABLE 3 Baseline clinical and biochemical characteristics of patients with normal SAT or high SAT.

Variables	Normal SAT (*N* = 175)	High SAT (*N* = 26)	*P*-values
Age, years	70 (20–90)	71 (41–88)	0.330
Sex, male / female	130 (74.3%) / 45 (25.7%)	24 (92.3%) / 2 (7.7%)	0.047
Etiology, HBV / HCV / NBNC	51 (29.1%) / 42 (24.0%) / 82 (46.9%)	8 (30.8%) / 9 (34.6%) / 9 (34.6%)	0.389
Liver cirrhosis, + / −	125 (71.4%) / 50 (28.6%)	21 (80.8%) / 5 (19.2%)	0.479
Stage, I / II / III / IV	60 (34.2%) / 51 (29.2%) / 38 (21.7%) / 26 (14.9%)	7 (26.9%) / 8 (30.8%) / 7 (26.9%) / 4 (15.4%)	0.946
BCLC stage, 0 / A / B / C / D	57 (32.6%) / 54 (30.8%) / 34 (19.4%) / 26 (14.9%) / 4 (2.3%)	6 (23.1%) / 7 (26.9%) / 9 (34.6%) / 2 (7.7%) / 2 (7.7%)	0.177
Child–Pugh grade, A / B / C	141 (80.6%) / 31 (17.7%) / 3 (1.7%)	14 (53.9%) / 11 (42.3%) / 1 (3.8%)	0.012
Child–Pugh score	5 (5–11)	6 (5–11)	0.002
Follow-up period, years	3.08 (0.31–7.01)	1.28 (0.25–5.96)	<0.001
Psoas muscle mass, cm^2/m^2	M: 4.26 (0.77–8.65)	M: 3.31 (1.28–7.59)	0.007
	F: 2.81 (0.71–6.62)	F: 3.48 (1.79–5.17)	0.874
Muscle atrophy, + / −	51 (29.1%) / 124 (70.9%)	16 (61.5%) / 10 (38.5%)	0.002
SAT radiodensity, HU	M: −100.25 (−114.75 – −83.00)	M: −73.38 (−82.25 – −58.75)	<0.001
	F: −99.0 (−109.50 – −80.5)	F: −65.75 (−66.75 – −64.75)	0.002
Body mass index, kg/m^2	24.9 (14.9–36.8)	21.2 (15.1–36.0)	<0.001
Ascites, + / −	27 (15.4%) / 148 (84.6%)	13 (50.0%) / 13 (50.0%)	<0.001
Platelet counts, $x10^4/mm^3$	13.6 (3.00–40.0)	13.95 (5.1–42.4)	0.631
Prothrombin time, %	87.9 (19.5–125.4)	84.0 (42.0–122.2)	0.206
Serum albumin, g/dL	3.90 (2.30–4.90)	3.50 (2.30–4.20)	<0.001
Aspartate transaminase, IU/L	37 (10–332)	39 (16–139)	0.427
Alanine aminotransferase, IU/L	26 (7–109)	24 (6–77)	0.770
Creatinine, mg/dL	0.79 (0.38–7.43)	0.82 (0.48–2.56)	0.291
Alpha-fetoprotein, ng/mL	6.4 (1.3–413503.0)	6.95 (1.5–316096.7)	0.631

Data are presented as number, percentages of patients or median (range) values.
BCLC, the Barcelona Clinic Liver Cancer; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-HBV non-HCV; PMI, psoas muscle mass index; M, male; SAT, subcutaneous adipose tissue.

TABLE 4 Prognostic factors in patients with HCC.

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio	*P*-values	Hazard ratio	*P*-values
Age, >70 years old	1.03 (0.67–1.59)	0.884		
Sex, male	1.01 (0.62–1.66)	0.961		
Liver cirrhosis, +	1.58 (0.92–2.69)	0.095	1.25 (0.69–2.26)	0.460
Child–Pugh score, ≥6	2.84 (1.82–4.43)	<0.001	1.71 (1.02–2.88)	0.043
ALT, >26 IU/L	1.72 (1.11–2.66)	0.016	1.40 (0.88–2.22)	0.160
Creatinine, > 0.79 mg/dL	1.33 (0.87–2.05)	0.193		
Plt, $< 13.6 \times 10^4$ / mm^3	1.14 (0.74–1.75)	0.556		
BCLC stage, B, C, and D	5.31 (3.37–8.37)	<0.001	4.53 (2.76–7.43)	<0.001
Muscle atrophy, +	1.88 (1.22–2.90)	0.004	1.69 (1.09–2.63)	0.019
High SAT, +	2.70 (1.53–4.75)	0.001	2.30 (1.23–4.31)	0.010
Ascites, +	2.23 (1.36–3.67)	0.002	1.03 (0.58–1.83)	0.930

ALT, alanine aminotransferase; BCLC, the Barcelona Clinic Liver Cancer; Plt, platelet counts SAT, subcutaneous adipose tissue.

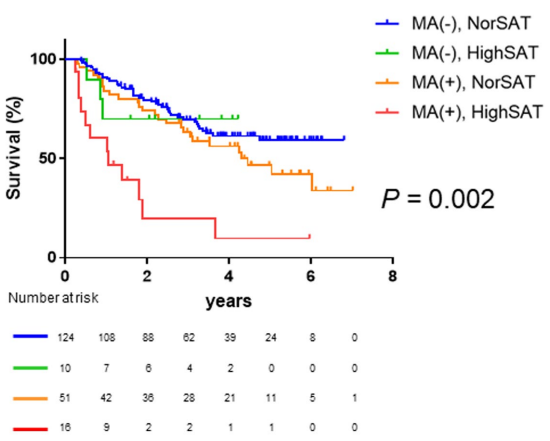

FIGURE 4
Comparison of overall survival among the four classified groups based on muscle atrophy and SAT radiodensity. The median overall survival is not reached in patients without muscle atrophy and normal SAT radiodensity and patients without muscle atrophy and high SAT radiodensity; it is 4.30 years in patients with muscle atrophy and normal SAT radiodensity and 1.04 years in patients with muscle atrophy and high SAT radiodensity. Overall survival is significantly different among the four classified groups based on muscle atrophy and SAT radiodensity ($p = 0.002$). HCC, hepatocellular carcinoma; SAT, subcutaneous adipose tissue.

This study highlighted that multivariate analysis revealed both muscle atrophy and high SAT radiodensity as significant and independent poor prognostic factors. Furthermore, the coexistence of muscle atrophy and high SAT radiodensity was found to be a strong and significant predictor of poor prognosis in patients with HCC. To date, there have been limited studies performing simultaneous analysis of skeletal muscle mass and adipose tissue-related parameters as prognostic factors in HCC. Lim et al. reported that muscle depletion combined with visceral adiposity was a crucial prognostic factor for predicting survival in older patients with HCC who underwent transarterial chemoembolization (27). Additionally, Saeki et al. demonstrated that the absence of muscle depletion combined with a high visceral fat area could serve as a novel biomarker for patients with advanced HCC treated with sorafenib (28). Thus, combining assessment tools for muscle mass- and adipose tissue-related parameters may provide highly accurate stratification of HCC mortality risk. In patients with gastric cancer, subcutaneous but not visceral adipose tissue is a predictive marker of prognosis (31). This study is the first to demonstrate stratification of HCC prognosis based on a combination of muscle atrophy and SAT radiodensity. Furthermore, among Child–Pugh A patients, prognosis could not be stratified by the presence of muscle atrophy or high SAT radiodensity alone; however, the combination of muscle atrophy and SAT radiodensity proved effective in stratifying patients with poor prognosis. Therefore, simultaneous evaluation of muscle atrophy and high SAT radiodensity may hold clinical significance.

In patients with BCLC class B or more, muscle atrophy could not predict prognosis, whereas high SAT radiodensity could stratify prognosis. The reason why muscle atrophy could not predict the prognosis in those patients remains unclear; however, there is a hypothesis. In patients with BCLC class B or more, muscle mass had already decreased due to advanced HCC, and thus, prognosis could be stratified using only SAT radiodensity. In addition, the combination of muscle atrophy and SAT radiodensity more clearly stratified the prognosis. It has been reported that adipose tissue remodeling is observed at the early stages of cachexia (14). Thus, this study's observation might reflect the presence of cancer-related cachexia, which results in poor prognosis.

Skeletal muscle mass is measured using bioelectrical impedance analysis (BIA), CT imaging with specialized software, CT imaging using a simple CT method and PMI calculation, and dual-energy X-ray absorptiometry. Among these, CT is commonly used for diagnostic purposes, recurrence screening, and evaluation of treatment response in patients with HCC (2, 17, 32). Our recent study highlighted that, for an accurate evaluation of relative changes in skeletal muscle mass in patients with chronic liver diseases, including HCC, CT imaging is a suitable method compared to BIA (33). In addition, CT imaging allows for the simultaneous evaluation of SAT radiodensity and muscle area. Therefore, CT imaging is a valuable tool not only for assessing HCC but also for evaluating the nutritional

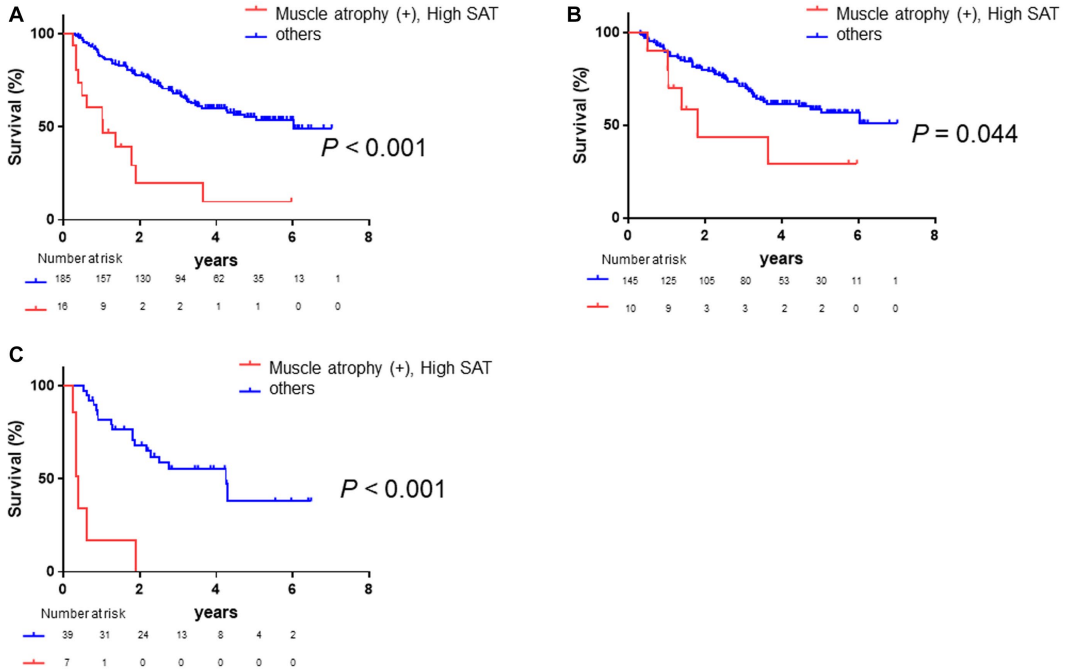

FIGURE 5
Survival rates in all patients and in those stratified by Child–Pugh grade. **(A)** Kaplan–Meier analysis is performed to stratify patients with and without muscle atrophy and high SAT radiodensity. The median overall survival is 1.04 years in patients with both muscle atrophy and high SAT radiodensity and 6.02 years in the other patients. Patients with muscle atrophy and high SAT radiodensity have a poorer prognosis than the other patients (log-rank $p < 0.001$; crude Cox regression HR: 4.53, 95% CI: 1.43–14.4). **(B)** Among patients with Child–Pugh grade A, Kaplan–Meier analysis is performed to stratify patients with and without muscle atrophy and high SAT radiodensity. The median overall survival is 1.79 years in patients with both muscle atrophy and high SAT radiodensity and not reached in the other patients. Patients with both muscle atrophy and high SAT radiodensity have a poorer prognosis than the other patients (log-rank p-value = 0.044; crude Cox regression HR: 3.48, 95% CI: 1.03–11.70). **(C)** Among the patients with Child–Pugh grade B or C, Kaplan–Meier analysis is performed to stratify patients with and without muscle atrophy and high SAT radiodensity. The median overall survival is 0.40 years in patients with both muscle atrophy and high SAT radiodensity and 4.25 years in the other patients. Patients with both muscle atrophy and high SAT radiodensity have a significantly poorer prognosis than the other patients (log-rank p-value <0.001; crude Cox regression HR: 10.43, 95% CI: 3.76–28.93). CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; SAT, subcutaneous adipose tissue.

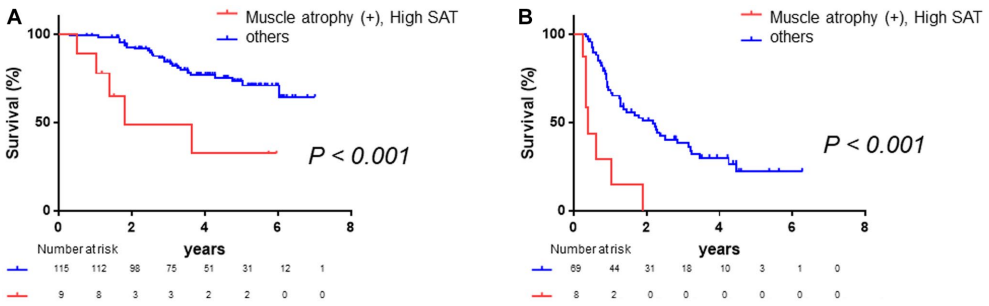

FIGURE 6
Survival rates stratified according to BCLC class. **(A)** Among patients with BCLC class 0 or A, Kaplan–Meier analysis is performed to stratify patients with and without muscle atrophy and high SAT radiodensity. The median overall survival is 1.80 years in patients with both muscle atrophy and high SAT radiodensity and not reached in the other patients. Patients with muscle atrophy and with high SAT radiodensity have a poorer prognosis than the other patients (log-rank p-value <0.001; crude Cox regression HR: 4.51, 95% CI: 1.72–11.85). **(B)** Among patients with BCLC class B, C, or D, Kaplan–Meier analysis was performed to stratify patients with and without muscle atrophy and high SAT radiodensity. The median overall survival is 0.40 years in patients with both muscle atrophy and high SAT radiodensity and 2.18 years in the other patients. Patients with both muscle atrophy and high SAT radiodensity have a poorer prognosis than the other patients (log-rank p-value <0.001; crude Cox regression HR: 5.36, 95% CI: 2.34–12.28). CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; SAT, subcutaneous adipose tissue.

status of patients with HCC. Additionally, even when muscle mass was assessed using the simple method ($n = 145$) (34), which is a simpler CT-based method than PMI, patients with both muscle atrophy and high SAT had a poor prognosis (log-rank p-value <0.001, Supplementary Figure 1; crude Cox regression HR: 4.79, 95% CI: 1.48–15.5).

Our study had several limitations that need to be acknowledged. First, it was a retrospective study conducted at a single center.

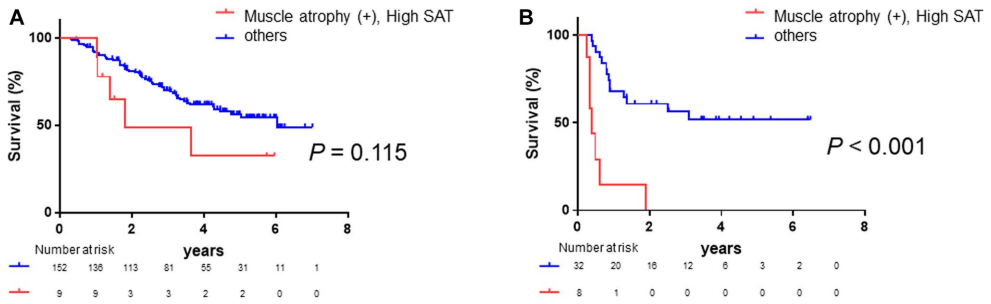

FIGURE 7
Survival rates stratified according to fluid retention **(A)** Among patients without ascites or pleural effusion, Kaplan–Meier analysis is performed to stratify patients with and without muscle atrophy and high SAT radiodensity. The median overall survival is 1.80 years in patients with both muscle atrophy and high SAT radiodensity and 6.03 years in the other patients. Patients with both muscle atrophy and with high SAT radiodensity tend to have a poorer prognosis than the other patients (log-rank *p*-value = 0.115; crude Cox regression HR: 2.05, 95% CI: 0.58–7.19). **(B)** Among patients with ascites or pleural effusion, Kaplan–Meier analysis is performed to stratify patients with and without muscle atrophy and high SAT radiodensity. The median overall survival is 0.40 years in patients with both muscle atrophy and high SAT radiodensity and not reached in the other patients. Patients with both muscle atrophy and with high SAT radiodensity have a poorer prognosis than the other patients (log-rank *p*-value <0.001; crude Cox regression HR: 6.55, 95% CI: 1.24–34.7). CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; SAT, subcutaneous adipose tissue.

In addition, due to the retrospective nature of the study, certain clinical factors were either lacking or incomplete. Therefore, further validation of our results via a prospective multicenter study is required.

In conclusion, muscle atrophy and high SAT radiodensity are significantly associated with poor prognosis in patients with HCC. Our findings highlight the importance of evaluating muscle atrophy and high SAT radiodensity as prognostic factors in patients with HCC. This study is the first to report the significant negative impact of both muscle atrophy and high SAT radiodensity on survival in patients with HCC. In particular, for patients with muscle atrophy and high SAT radiodensity, interventions such as nutritional therapy and exercise may have the potential to improve their clinical outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Hokkaido University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MO: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. GS: Conceptualization, Funding acquisition, Software, Supervision, Visualization, Writing – review & editing. RK: Investigation, Writing – review & editing. TSa: Investigation, Writing – review & editing. TY: Investigation, Writing – review & editing. SY: Investigation, Writing – review & editing. QF: Investigation, Writing – review & editing. ZY: Investigation, Writing – review & editing. SH: Investigation, Writing – review & editing. OM: Investigation, Writing – review & editing. SO: Supervision, Writing – review & editing. YT: Investigation, Methodology, Writing – review & editing. TK: Investigation, Writing – review & editing. NK: Investigation, Writing – review & editing. MaN: Investigation, Methodology, Project administration, Writing – review & editing. TSh: Investigation, Methodology, Writing – review & editing. MiN: Supervision, Writing – review & editing. KO: Methodology, Supervision, Writing – review & editing. NS: Funding acquisition, Supervision, Writing – review & editing.

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Conflict of interest

NS received research grant from Gilead Sciences Inc. and AbbVie Inc. GS received research grants from Gilead Sciences Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1272728/full#supplementary-material

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Impact of sarcopenia and sarcopenic obesity on survival in patients with primary liver cancer: a systematic review and meta-analysis

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Background: Sarcopenia and sarcopenic obesity are associated with an increased possibility of adverse clinical outcomes; however, the effects of sarcopenia and sarcopenic obesity on patients with primary liver cancer remain controversial. Therefore, the present study aimed to determine the impact of sarcopenia and sarcopenic obesity on survival in patients with primary liver cancer.

Methods: We searched studies published in English in PubMed, Embase, Web of Science, and Cochrane Library databases up to 13 November 2022. Cohort studies that reported the association among sarcopenia, sarcopenic obesity, and patient survival were included.

Results: A total of 64 cohort studies with data on 11,970 patients with primary liver cancer were included in the meta-analysis. Sarcopenia was associated with poor overall survival in patients with primary liver cancer [adjusted hazard ratio (HR) 2.11, 95% confidence interval (CI): 1.89–2.36, $P < 0.0001$], with similar findings for sarcopenic obesity (adjusted HR: 2.87, 95% CI: 2.23–3.70, $P < 0.0001$). Sarcopenia was also associated with poor overall survival across the subgroups analyzed by ethnicity, type of liver cancer, treatment modalities, method used to define sarcopenia, and etiology of liver cancer. We also found a negative correlation among sarcopenia, sarcopenic obesity, and recurrence-free/disease-free survival (adjusted HR: 1.73, 95% CI: 1.50–1.99, $P < 0.001$; adjusted HR: 2.28, 95% CI: 1.54–3.35, $P < 0.001$, respectively).

Conclusion: Sarcopenia and sarcopenic obesity were significantly associated with poor overall survival and recurrence-free/disease-free survival in patients with primary liver cancer.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=378433, PROSPERO [42022378433].

KEYWORDS

primary liver cancer, sarcopenia, sarcopenic obesity, muscle depletion, survival

1. Introduction

Primary liver cancer is the sixth most frequently occurring cancer and ranks as the third leading cause of cancer-related mortality worldwide, accounting for 8.3% of total cancer deaths (1), thus resulting in a global medical and economic burden. Hepatocellular carcinoma (HCC) is the predominant type of primary liver cancer, comprising 75%–85% of the cases,

and intrahepatic cholangiocarcinoma (ICC) follows as the subsequent type (1). There are significant gender and racial differences in morbidity and mortality due to primary liver cancer; both morbidity and mortality rates are two-fold to three-fold higher in men than in women in most regions, and the disease is more common among Asians due to a high prevalence of hepatitis B and C (1). It is therefore critical to identify patients with high mortality risk based on the patient's prognosis for determining individualized treatments and improving the survival rate of patients with primary liver cancer. In recent years, researchers have made several efforts to determine the factors that influence the clinical outcomes of patients with liver cancer. Thus far, the Barcelona Clinic Liver Cancer (BCLC), Model for End-Stage Liver Disease (MELD), and the albumin–bilirubin (ALBI) scores have been used clinically to evaluate the prognosis of patients with liver cancer; however, these prognostic tools cannot adequately capture the nutritional and functional status of these patients.

Sarcopenia, as a marker of malnutrition, has been defined by the European Working Group on Sarcopenia in Older People (EWGSOP2) in 2018 as the presence of both low muscle mass and low muscle function (strength or performance) (2). It is difficult to diagnose sarcopenia because of different measuring methods and cutoff values. Sarcopenia is usually evaluated based on grip strength, dual-energy X-ray absorptiometry, computed tomography (CT), and magnetic resonance imaging (MRI) (2). Sarcopenia increases the risk of worse clinical outcomes such as reduced quality of life, development of complications, higher hospitalization cost, and death (3–6). Previous studies have shown that the hospitalization cost of older patients with sarcopenia on admission was five-fold more than those without sarcopenia (7). Sarcopenia is a common condition in patients with oncological and chronic diseases. In a systematic review and meta-analysis that included 38 studies on sarcopenia and solid cancer outcomes, sarcopenia was significantly associated with the poor overall survival of patients (8). Similarly, according to a recent umbrella review of meta-analyses, sarcopenia is associated with adverse clinical outcomes across 12 cancer types: gastric, hepatocellular, urothelial, head and neck, hematologic malignancy, pancreatic, breast, colorectal, lung, esophageal, hematologic malignancies, and ovarian (9). The existence of sarcopenia was found to be associated with a higher risk of death in patients with liver cirrhosis (10), which is likely to progress into liver cancer.

The rate of fat deposition tends to increase in sarcopenic patients, resulting in systemic inflammatory activation and insulin resistance, which subsequently leads to progressive muscle reduction and fat accumulation, especially in conditions such as aging and cachexia (11). This vicious cycle finally results in sarcopenic obesity (SO), which is defined as the co-existence of obesity and sarcopenia (12). More recently, SO has received increasing interest from oncologists because of its adverse outcomes in patients with cancer. SO is an independent prognostic factor affecting the risk of adverse outcomes in oncological patients (13–15).

Several studies, however, reported no association between sarcopenia and prognosis in patients with HCC (16–20). The influence of sarcopenia on survival in patients with liver cancer remains controversial, and a comprehensive analysis based on evidence-based medicine is required. To the best of our knowledge, previous meta-analyses have focused only on HCC patients and did not include data on patients with ICC. Recently, an increasing number of studies have examined the prognostic factors of liver cancer patients. Hence, we analyzed and summarized the relationship among sarcopenia, SO, and survival in patients with primary liver cancer. Our study aimed to determine the impact of sarcopenia and SO on the survival of patients with primary liver cancer.

2. Methods

2.1. Search strategy

We searched studies relevant to the association of sarcopenia, SO, and survival of patients with liver cancer in PubMed, Embase, Web of Science, and Cochrane Library databases up to 13 November 2022. The search keywords included sarcopenia, muscle depletion, muscle weakness, liver cancer, and liver neoplasm. The detailed search strategies are presented in Supplementary Table S1. We restricted the studies to those published in English and conducted on humans. We also retrieved potential studies by reading through the relevant systematic reviews and meta-analyses. The present meta-analysis adhered to the PRISMA guidelines (21), and its protocol was registered on PROSPERO (CRD 42022378433).

2.2. Criteria for selection

Studies that met the following criteria were included: (1) participants: patients with liver cancer confirmed by clinical/imaging or liver biopsy criteria (may include patients evaluated or already listed for liver transplantation), including HCC and ICC; (2) exposures: pretreatment for sarcopenia and/or SO; (3) outcomes: the impact of sarcopenia and/or SO on patient survival; and (4) study design: prospective or retrospective cohort study.

Studies that met the following criteria were excluded: (1) studies lacking the criteria for diagnosing sarcopenia or SO; (2) studies lacking the statistical data on the impact of sarcopenia and/or SO on survival [hazard ratio (HR) and 95% confidence interval (CI)]; and (3) reviews, case reports, editorials, letters, posters, and/or conference abstracts.

The authors XL and XH independently screened the title/abstract of all the identified citations for eligibility by using the abovementioned inclusion/exclusion criteria. Next, they retrieved and rescreened the full texts of relevant articles. For studies with overlapping cohorts, studies having the latest data and/or a larger sample size and/or more data available for subgroup analysis were used. Disagreements were resolved by consensus or discussion.

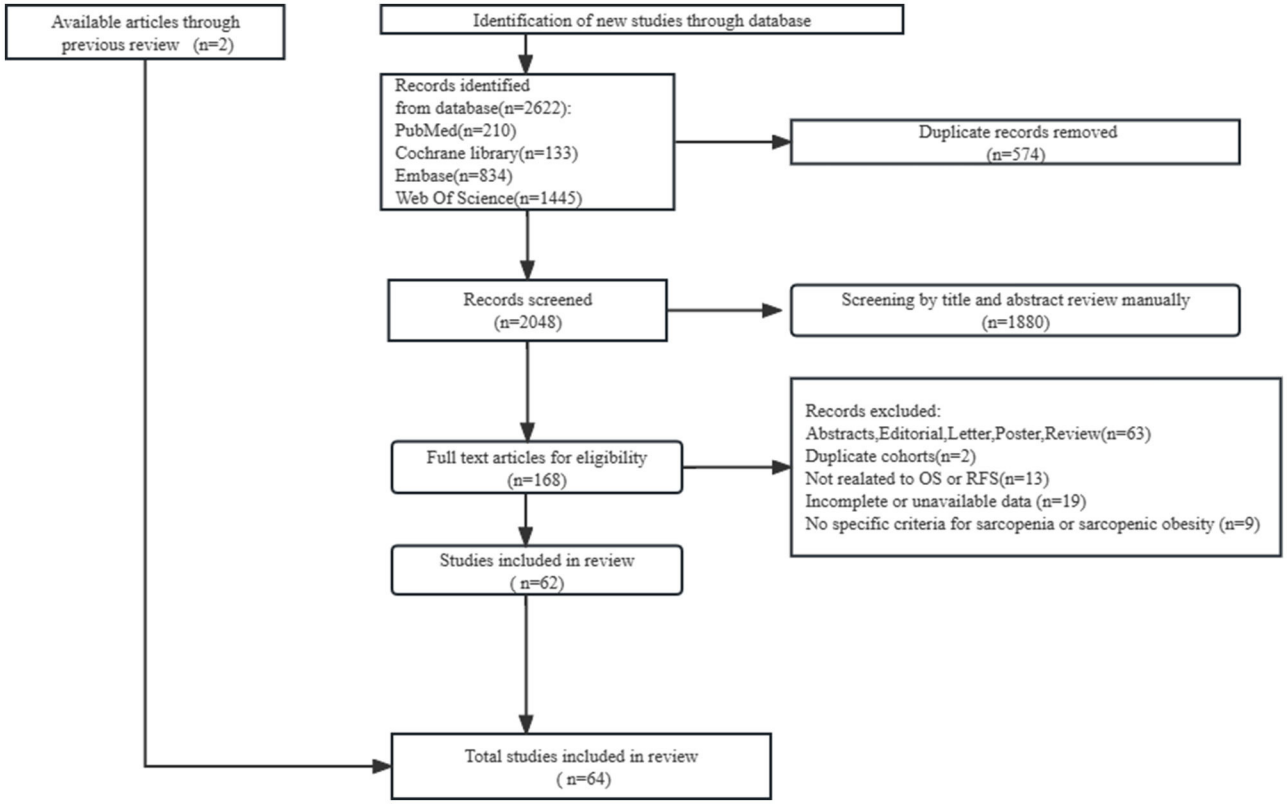

FIGURE 1
PRISMA flow diagram of the search strategy.

2.3. Data acquisition and quality assessment

XL and XH extracted the following data independently from each included study: first author's name, first author's country, published year, ethnicity, study type, type of liver cancer, treatment modalities, etiology of liver cancer, enrolled numbers, patient demographics (including age and sex), duration of follow-up, definitions of sarcopenia and SO, cutoff values of sarcopenia, and number of sarcopenia or SO patients. The quality of the enrolled studies was independently evaluated by the two authors according to the Newcastle–Ottawa Scale (NOS). Discrepancies between both investigators were resolved by consensus and discussion.

2.4. Statistical analysis

The outcomes for the association between sarcopenia and overall survival (OS), recurrence-free survival (RFS), or disease-free survival (DFS) were reported as crude and adjusted HR with corresponding 95% CI values. HR and 95% CI values were directly extracted from univariate and multivariate Cox regression analyses. The impact of sarcopenia and SO on the OS of primary liver cancer patients was assessed by the pooled unadjusted HR or adjusted HR and 95% CI by using a random-effects model (DerSimonian–Laird method) (22). A subgroup analysis for the adjusted HRs was conducted according to ethnicity, type of liver cancer, treatment modalities, method used to define sarcopenia, and etiology of liver cancer. Cochran's Q statistic and I^2 were used to evaluate heterogeneity, with a P-value of <0.1 and $I^2 > 50\%$ considered to show meaningful heterogeneity (23). We assessed publication bias through the utilization of funnel plots in meta-analysis and quantified it using Egger's regression test. We also conducted a meta-analysis of single proportions to determine the prevalence of sarcopenia. All analyses were performed with STATA software v15.0 (StataCorp, College Station, TX, USA), and a P-value of <0.05 was considered to be statistically significant.

3. Results

3.1. Study search and characteristics

The search in PubMed, Embase, Web of Science, and Cochrane Library databases yielded 2,622 relevant citations, of which 574 duplicates and 1,880 unavailable titles/abstracts were excluded. After reviewing the full text of the remaining 168 publications and previous reviews, we included 64 eligible cohort studies with 11,970 patients (Figure 1).

The demographics and characteristics of the included studies are shown in Table 1. In general, 47 of the 64 included studies were conducted in Asia, predominantly in Japan ($n = 31$), and 17 studies were from non-Asian regions. Four studies were prospective, and 60 studies were retrospective.

TABLE 1 Summary characteristics of the included studies.

References	Country	Published year	Ethnicity	Study type	Type of liver cancer	Treatment modalities	Etiology of liver cancer and number	Enrolled number (male/female)	Age in years[a]	Follow-up[a]	Sarcopenia definition	Cut-off value (male/female, cm/m^2)	No. of sarcopenia (male/female)
Meza-Junco et al. (24)	Canada	2013	Caucasian	Prospective	HCC	Liver transplant	Alcohol 13, HBV 16, HCV 53, alcohol + HCV 23, NASH 8, others 3	116 (98/18)	58[b]	12 months	L3-SMI	53 (BMI ≥ 25) or 43 (BMI < 25)/41	35 (30/5)
Itoh et al. (25)	Japan	2014	Asian	Retrospective	HCC	Hepatectomy	NR	190 (146/44)	68 (low visceral area); 69 (high visceral area)[b]	NR	L3-SMI	43.75/41.10	77 (NR)
Fujiwara et al. (26)	Japan	2015	Asian	Retrospective	HCC	Different treatments	HBV 142, HCV 895, HCV + HBV 13, none 207	1,257 (828/429)	68.8[b]	SEVEN	L3-SMI	36.2/29.6	139 (96/43)
Harimoto et al. (27)	Japan	2015	Asian	Retrospective	HCC	Hepatectomy	HBV 8, HCV 51	139 (98/41)	76.5 (sarcopenia); 75.9 (non-sarcopenia)[b]	NR	L3-SMI	43·75/41·10	57 (40/17)
Iritani et al. (28)	Japan	2015	Asian	Retrospective	HCC	Different treatments	HBV 28, HCV 134, HBV + HCV 3, others 52	217 (146/71)	72	637 days	L3-SMI	1.24	24 (NR)
Levolger et al. (29)	Netherlands	2015	Caucasian	Retrospective	HCC	Hepatectomy or RFA	HBV 15, HCV 22	90 (63/27)	62	22.5 months	L3-SMI	52/39.5	52 (39/13)
Valero et al. (16)	USA	2015	Mixed	Retrospective	Primary liver cancer	Hepatectomy or OLT	HBV 10, HCV 28, HBV + HCV 2, none 56	96 (59/37)	61.9[b]	NR	L3-TPA	784.0/642.1 mm^2/m^2	47 (NR)
Voron et al. (30)	France	2015	Caucasian	Retrospective	HCC	Hepatectomy	Alcohol 12, HBV 22, HCV 27, NASH 11, multifactorial 8 l, unknown 29	109 (92/17)	61.66[b]	21.23 months	L3-SMI	52.4/38.9	59 (53/6)
Zhou et al. (31)	China	2015	Asian	Retrospective	ICC	Hepatectomy	NR	67 (22/45)	61	NR	L3-SMI	43.75/41.10	33 (9/24)
Higashi et al. (32)	Japan	2016	Asian	Retrospective	HCC	Hepatectomy	HBV 28, HCV 43, NBNC 101	144 (108/36)	65.1[b]	NR	L3-SMI	43.2/35.3	72 (54/18)

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TABLE 1 (Continued)

References	Country	Published year	Ethnicity	Study type	Type of liver cancer	Treatment modalities	Etiology of liver cancer and number	Enrolled number (male/female)	Age in years[a]	Follow-up[a]	Sarcopenia definition	Cut-off value (male/female, cm/m^2)	No. of sarcopenia (male/female)
Itoh et al. (33)	Japan	2016	Asian	Retrospective	HCC	LDLT	HCV 110	153 (86/67)	57 (low-SVR); 58 (not low-SVR)	5.2 years	None	None	None
Kamachi et al. (34)	Japan	2016	Asian	Retrospective	HCC	Hepatectomy or RFA	HCV 92	92 (65/27)	73 (sarcopenia); 70 (non-sarcopenia)	34.0 months	L3-SMI	52.4/38.5	61 (51/10)
Takagi et al. (35)	Japan	2016	Asian	Retrospective	HCC	Hepatectomy	HBV and/or HCV 171, others 83	254 (207/47)	65.7[b]	NR	L3-SMI	46.4/37.6	118 (93/25)
Yabusaki et al. (36)	Japan	2016	Asian	Retrospective	HCC	Hepatectomy	HBV 50, HCV 88, HBV+HCV 1, others 56	195 (157/38)	66[b]	1,121 days	L3-SMI	43.75/41.10	89 (57/32)
Begini et al. (37)	Italy	2017	Caucasian	Retrospective	HCC	Different treatments	HBV 11, HCV 40, alcohol 22, NASH 19	92 (65/27)	71.60	NR	L3-SMI	53 (BMI $\geq$ 25) or 43 (BMI $<$ 25)/41	37 (20/17)
Hiraoka et al. (38)	Japan	2017	Asian	Retrospective	HCC	Sorafenib	HBV 18, HCV 56, HBV + HCV 2, NBNC 17	93 (81/12)	68.8 (sarcopenia); 68.2 (non-sarcopenia)[b]	NR	L3-PMI	4.24/2.50	20 (19/1)
Nishikawa et al. (39)	Japan	2017	Asian	Retrospective	HCC	Sorafenib	HBV 33, HCV 144, HBV + HCV 4, NBNC 49, unknown 2	232 (181/51)	72	NR	L3-SMI	36.2/29.6	151 (126/25)
Okumura et al. (40)	Japan	2017	Asian	Retrospective	ICC	Hepatectomy	NR	109 (67/42)	68	NR	L3-SMI	52.5/41.2	69 (45/24)
Yuri et al. (41)	Japan	2017	Asian	Retrospective	HCC	RFA	HBV 12, HCV 134, others 36	182 (111/71)	70	4.28 years	L3-PMI	6.31/3.91	90 (63/27)
Antonelli et al. (42)	Italy	2018	Caucasian	Retrospective	HCC	Sorafenib	HBV 13, HCV 46, alcohol 16, NASH 11, others 10	96 (75/21)	69	NR	L3-SMI	53 (BMI $\geq$ 25) or 43 (BMI $<$ 25)/41	47 (28/19)
Ha et al. (43)	Korea	2018	Asian	Retrospective	HCC	NR	HBV 110, HCV 15, Alcohol 27, Unknown 26	178 (141/37)	62.5 (sarcopenia); 58.3 (non-sarcopenia)[b]	NR	L3-SMI	45.8/43	62 (43/19)

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TABLE 1 (Continued)

References	Country	Published year	Ethnicity	Study type	Type of liver cancer	Treatment modalities	Etiology of liver cancer and number	Enrolled number (male/female)	Age in years[a]	Follow-up[a]	Sarcopenia definition	Cut-off value (male/female, cm/m^2)	No. of sarcopenia (male/female)
Kobayashi et al. (44)	Japan	2018	Asian	Retrospective	HCC	TACE and/or TAI	HBV 11, HCV 50, NBNC 41, alcohol 26, NASH 7, PBC 2, cryptogenic 6	102 (70/32)	69	NR	L3-SMI	42/38	31 (14/17)
Saeki et al. (45)	Japan	2018	Asian	Retrospective	HCC	Sorafenib	HBV 20, HCV 54, alcohol 12, others 14	100 (72/28)	70.6[b]	NR	L3-SMI	42/38	46 (NR)
Shiba et al. (46)	Japan	2018	Asian	Retrospective	HCC	Carbon ion radiotherapy	NR	68 (41/27)	77 (sarcopenia); 74 (non-sarcopenia)	33.5 months	L3-SMI	43.75/41.10	22 (11/11)
Shirai et al. (47)	Japan	2018	Asian	Retrospective	HCC	Hepatectomy	HBV and/or HCV 264, others 138	402 (325/77)	67	NR	L3-PMI	6.36/3.92	134 (NR)
Fujita et al. (48)	Japan	2019	Asian	Retrospective	HCC	TACE	HBV 24, HCV 85, alcohol 39, NASH 26, Others 5	179 (130/49)	72	20.3 months	L3-PMI	6.0/3.4	80 (70/10)
Hamaguchi et al. (49)	Japan	2019	Asian	Retrospective	HCC	Hepatectomy	HBV and/or HCV 392, others 214	606 (484/122)	68	NR	L3-SMI	40.31/30.88	84 (NR)
Imai et al. (50)	Japan	2019	Asian	Retrospective	HCC	Sorafenib	HBV 14, HCV 28, others 19	61 (54/7)	67.3[b]	NR	L3-SMI	42/38	25 (22/3)
Kobayashi et al. (14)	Japan	2019	Asian	Retrospective	HCC	Hepatectomy	HBV and/or HCV 302, others 163	465 (367/98)	67.6[b]	NR	L3-SMI	40.31/30.88	31 (24/7)
Kroh et al. (51)	Germany	2019	Caucasian	Retrospective	HCC	Hepatectomy	NR	70 (49/21)	67.74[b]	NR	L3-SMI	53 (BMI $\geq$ 25) or 43 (BMI $<$ 25)/41	33 (21/12)
Labeur et al. (52)	Netherlands	2019	Caucasian	Retrospective	HCC	Sorafenib	HBV 46, HCV 44, alcohol 92, NAFLD-NASH 19, other 17, unknown 71	278 (220/58)	64	54.9 months	L3-SMI	53 (BMI $\geq$ 25) or 43 (BMI $<$ 25)/41	145 (109/36)
Lee et al. (53)	USA	2019	Caucasian	Retrospective	HCC	RT	HBV 113, HCV 14, NBNC 29	156 (128/28)	59	9.3 months	L3-SMI	55/39	99 (81/18)

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TABLE 1 (Continued)

References	Country	Published year	Ethnicity	Study type	Type of liver cancer	Treatment modalities	Etiology of liver cancer and number	Enrolled number (male/female)	Age in years[a]	Follow-up[a]	Sarcopenia definition	Cut-off value (male/female, cm/m^2)	No. of sarcopenia (male/female)
Yugawa et al. (54)	Japan	2019	Asian	Retrospective	ICC	Hepatectomy	HBV 6, HCV 7	61 (42/19)	69 (sarcopenia); 60 (non-sarcopenia)	NR	L3-PMA	34.6/18.1 cm^2	30 (20/10)
Akce et al. (17)	USA	2020	Mixed	Retrospective	HCC	Anti-PD-1 antibody	NR	57 (44/13)	66	NR	L3-SMI	43/39	28 (NR)
Bekki et al. (19)	Japan	2020	Asian	Retrospective	HCC	Hepatectomy	HBV 27, HCV 70	139 (110/29)	NR	2.7 years	L3-SMI	52.4/38.5	86 (80/6)
Choi et al. (55)	Korea	2020	Asian	Prospective	HCC	Different treatments	HBV 177, HCV 22, non-viral 39	238 (193/45)	59	31.8 months	L3-PMI	4.98/1.17	135 (130/5)
Ebadi et al. (56)	Canada	2020	Caucasian	Retrospective	HCC	SIRT	HBV 21, HCV 31, alcohol 14, alcohol and HCV 12, NASH 6, others 17	101 (89/12)	62[b]	14 months	L3-SMI	50/39	57 (NR)
Endo et al. (57)	Japan	2020	Asian	Retrospective	HCC	Lenvatinib	HBV 10, HCV 23, alcohol 17, others 13	63 (53/10)	71	8.3 months	L3-SMI	42/38	22 (16/6)
Faron et al. (58)	Germany	2020	Caucasian	Retrospective	HCC	Yttrium-90 radio embolization	HBV 11, HCV 11, alcohol 9, others 27	58 (45/13)	68[b]	250 days	FFMA (MRI)	3582 mm^2/2301 mm^2	29 (22/7)
Kotoh et al. (59)	Japan	2020	Asian	Retrospective	HCC	Lenvatinib	HBV 7, HCV 20, Others 26	53 (41/12)	72	NR	Handgrip and L3-SMI	26/18 Kg and 42/38	15 (NR)
Lanza et al. (60)	Italy	2020	Caucasian	Retrospective	HCC	TAE	HBV 7, HCV 65, alcohol 33, NASH 21	142 (110/32)	75	27 months[b]	L3-SMI	55/39	121 (97/24)
Santhakumar et al. (61)	New Zealand	2020	Caucasian	Retrospective	HCC	Hepatectomy	HBV 86, HCV 25, alcohol 6, NAFLD 6, others 24	147 (118/29)	59.1[b]	5.9 years	L3-SMI	46.69/31.03	40 (36/4)
Uojima et al. (62)	Japan	2020	Asian	Retrospective	HCC	Lenvatinib	HBV 19, HCV 34, alcohol 24, NASH 16, others 7	100 (75/25)	71.5[b]	NR	L3-SMI	42/38	59 (42/17)

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TABLE 1 (Continued)

References	Country	Published year	Ethnicity	Study type	Type of liver cancer	Treatment modalities	Etiology of liver cancer and number	Enrolled number (male/female)	Age in years[a]	Follow-up[a]	Sarcopenia definition	Cut-off value (male/female, cm/m^2)	No. of sarcopenia (male/female)
Wu et al. (63)	China	2020	Asian	Retrospective	HCC	Sorafenib	HBV 84, HCV 23	137 (120/17)	NR	NR	TSM	39.1 for men	18 (male)
Yeh et al. (20)	China	2020	Asian	Retrospective	HCC	RFA	HBV 43, HCV 61, Alcohol 31	136 (78/58)	63.4[b]	3.84 years	L3-PMI	4.24/2.5	22 (16/6)
Deng et al. (64)	China	2021	Asian	Prospective	ICC	Hepatectomy	HBV 46	121 (52/69)	65	16.1 months	L3-PMI	8.6/6.04	53 (NR)
Guichet et al. (65)	USA	2021	Caucasian	Retrospective	HCC	90Y radio embolization.	HBV 26, HCV 43, alcohol 11, NASH 7, cryptogenic 2, PBC 1, unknown 1	82 (65/17)	65	19.6 months[b]	FFMA(MRI)	31.97/28.95 cm^2	25 (17/8)
Jang et al. (66)	Korea	2021	Asian	Retrospective	HCC	Hepatectomy	HBV 125, HCV 12, non-viral 23	160 (120/40)	55.19[b]	7.9 years	L3-PMI	3.33/2.38	28 (17/11)
Li et al. (67)	China	2021	Asian	Retrospective	ICC	Hepatectomy	HBV 136, HCV 2, hepatolithiasis 83	460 (223/237)	58	NR	L3-SMI	42.6/37.8	281 (137/144)
Liao et al. (68)	China	2021	Asian	Retrospective	HCC	Hepatectomy	HBV 385	452 (386/66)	53.15[b]	NR	L3-SMI	40.86/30.71	NR
Saeki et al. (69)	Japan	2021	Asian	Retrospective	HCC	Sorafenib	HBV 80, HCV 175, HBV + HCV 2, NBNC 99	356 (287/69)	69.5	NR	L3-SMI	45/38	175 (NR)
Salman et al. (70)	Egypt	2021	Caucasian	Prospective	HCC	RFA	HCV 97	97 (72/25)	53.4[b]	NR	L3-SMI	53 (BMI $\geq$ 25) or 43 (BMI < 25)/41	42 (28/14)
Yoshio et al. (71)	Japan	2021	Asian	Retrospective	HCC	Hepatectomy	HBV 61, HCV 86, NBNC 87	234 (183/51)	67.4	NR	L3-SMI	42/38	82 (NR)
Chien et al. (72)	China	2022	Asian	Retrospective	HCC	TACE	HBV 141, HCV 110	260 (192/68)	64[b]	NR	L3-PMI	6.36/3.92	130 (103/27)
Dong et al. (73)	China	2022	Asian	Retrospective	HCC	Lenvatinib	HBV 35, HCV 3, NBNC 2	40 (37/3)	59	9.2 months	L3-SMI	42/38	23 (20/3)
Fujita et al. (74)	Japan	2022	Asian	Retrospective	HCC	Lenvatinib	HBV 28, HCV 35, Alcohol 37, NAFLD 26, Others 4	130 (107/23)	70	NR	L3-PMI	6.0/3.4	63 (58/5)

(Continued)

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TABLE 1 (Continued)

References	Country	Published year	Ethnicity	Study type	Type of liver cancer	Treatment modalities	Etiology of liver cancer and number	Enrolled number (male/female)	Age in years[a]	Follow-up[a]	Sarcopenia definition	Cut-off value (male/female, cm/m^2)	No. of sarcopenia (male/female)
Hayashi et al. (75)	Japan	2022	Asian	Retrospective	HCC	Hepatectomy	HBV 49, HCV 120	303 (221/82)	72 (sarcopenia); 70 (non-sarcopenia)	NR	L3-SMI	52.4/38.9	106 (96/10)
Hou et al. (76)	China	2022	Asian	Retrospective	Combined hepatocellular carcinoma and cholangio carcinoma (cHCC-CC)	Hepatectomy	HBV 119, HCV 3	153 (128/25)	NR	41.3 months	L3-PMI	5.42/4.05	77 (64/13)
Kim et al. (77)	South Korea	2022	Asian	Retrospective	HCC	Hepatectomy	HBV or HCV 120, others 39	159 (133/26)	59.3[b]	45 months	L3-SMI	52.4/38.5	74 (68/6)
Roth et al. (78)	France	2022	Caucasian	Retrospective	HCC	TACE	HBV 21, HCV 64, alcohol 138, NASH 66	225 (200/25)	65	NR	L3-SMI	50/39	130 (120/10)
Tamai et al. (79)	Japan	2022	Asian	Retrospective	HCC	Hepatectomy or RFA	HBV 24, HCV 92, NASH 29, alcohol 29, others 7	181 (129/52)	71.4[b]	39.2 ± 13.7 months	L3-PMI	6.36/3.92	100 (73/27)
Xiao et al. (80)	China	2022	Asian	Retrospective	Primary liver cancer	ICIs	HBV 153, HCV 3, HBV + HCV 2, none 14	172 (149/23)	51.4[b]	9 months	L3-SMI	53 (BMI ≥ 25) or 43 (BMI < 25)/41	68 (52/16)
Yang et al. (81)	China	2022	Asian	Retrospective	HCC	SBRT	HBV 71, HCV 36, HBV + HCV 8, non-virus 22	137 (106/31)	63.8[b]	14.1 months	L3-SMI	49/31	67 (63/4)
Zhang et al. (82)	China	2022	Asian	Retrospective	HCC	TACE	HBV 194, others 34	228 (175/53)	58.9[b]	22.3 months	L3-SMI	45.95/33.96	89 (76/13)

NR, not reported; L3-SMI, skeletal muscle index at the level of third vertebra; L3-PMI, psoas muscle index at the level of third vertebra; L3-PMA, psoas muscle mass area at the level of third vertebra; L3-TPA, total psoas area at the level of third vertebra; FFMA, fat-free muscle area; TSM, total skeletal muscle; SO, sarcopenic obesity; LDLT, living donor liver transplantation; OLT, orthotopic liver transplantation; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; RFA, radiofrequency ablation; TAI, transcatheter arterial infusion; TACE, transcatheter arterial chemoembolization; RT, radiotherapy; SIRT, selective internal radiation therapy; TAE, transarterial embolization; SBRT, stereotactic body radiotherapy; ICIs, immune checkpoint inhibitors; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; NBNC, without HBV or HCV; PBC, primary biliary cholangitis.

[a]Values are median unless indicated otherwise.

[b]Values are mean.

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Of the 11,970 patients, 8,919 were men (74.51%) and 3,051 were women (25.49%), with a median (or mean) age of 51.4–77 years. The median or mean age was not reported in three studies (19, 63, 76). Fifty-six of the 64 studies involved patients with HCC. Seventeen studies enrolled patients with resectable HCC; the remaining treatment regimens included transarterial chemoembolization (TACE), liver transplantation (LT), radiofrequency ablation (RFA), and administration of kinase inhibitors. The curative treatment included liver resection, RFA, and LT, whereas the palliative treatment included intra-arterial chemoembolization, administration of kinase inhibitors, and systemic chemotherapy. Viral hepatitis was the most common etiology of liver cancer, with HCV as the primary cause of viral hepatitis in most included studies ($n = 36$). The other causes of liver cancer include alcohol consumption, non-alcoholic steatohepatitis (NASH), and others. Six studies did not report the etiology of liver cancer. Thirty of the 64 studies reported the duration of follow-up (median or mean), which ranged from 8.3 months to 7.9 years.

3.2. Quality assessment

The quality of the included studies was determined by NOS. Patient selection, comparability, and outcomes were used to evaluate the methodological quality of each study. Supplementary Table S2 shows the evaluation of the quality of the included studies. Based on the NOS score of ≥7, all the included studies were considered to have high quality.

3.3. Definition of sarcopenia and SO

The approaches to identifying sarcopenia and SO in patients were different. In most studies ($n = 61$), the areas of visceral/subcutaneous fat and skeletal muscle were determined by a transverse analysis at the level of the third lumbar vertebra (L3). In 45 studies, sarcopenia was defined by the sex-specific cutoff values of the L3-SMI (skeletal muscle index, cm^2/m^2), which showed a slight variation in those studies (shown in Table 1). Seven studies used different values to define sarcopenia depending on body mass index (BMI) (24, 37, 42, 51, 52, 70, 80). The majority of studies (44 studies) used cutoff values between 40 and 55 cm^2/m^2 in men. Nine studies evaluated sarcopenia based on the L3-PMI (psoas muscle index, cm^2/m^2), and one study used the total skeletal muscle mass (TSM) index. The other two studies defined sarcopenia as low fat-free muscle area (FFMA) based on MRI evaluation. According to these sex-specific cutoff values, 3,957 patients were diagnosed with sarcopenia in 62 studies, yielding a pooled prevalence of 43.2% (95% CI: 37.8%–48.5%). Among the 50 studies reporting the prevalence according to gender, a slight difference in prevalence was observed between female and male patients, with a higher pooled prevalence of 45% among men compared to 42.2% among women.

Four of the 64 studies reported the impact of SO on the survival of liver cancer patients. Regarding the definition of SO, Itoh et al. (33) used low skeletal muscle mass-to-visceral fat area ratio (SVR) to define SO, while Kobayashi et al. (14), Kroh et al. (51), and Liao et al. (68) used the co-existence of sarcopenia and obesity to define SO. However, variations were noted in the definition of obesity. Obesity was defined as the area of visceral adipose tissue at the level of the third lumbar vertebra ≥100 cm^2 in both men and women by Kobayashi et al., while the patients were considered obese if their BMI was ≥25 kg/m^2 in Liao's study; in Kroh's study, obesity was defined by categorizing individuals within the highest two quintiles body fat percentage for men and women.

3.4. OS in sarcopenic patients

Not all the eligible studies reported the HRs of OS. After calculating the data in a univariate analysis of 51 ($n = 9{,}615$) studies, we found that sarcopenia was related to lower OS, with a pooled unadjusted HR of 1.94 (95% CI: 1.76–2.13, $P < 0.0001$; shown in Supplementary Figure S1). A multivariate analysis of 47 studies ($n = 8{,}285$) revealed that the risk of death in sarcopenic patients was 2.11-fold higher than that in non-sarcopenic patients (95% CI: 1.89–2.36, $P < 0.0001$; shown in Figure 2). In most studies, HR was adjusted for age, gender, BMI, alpha-fetoprotein (AFP), tumor stage, and comorbidity. According to sensitivity analysis, no individual study had a significant impact on the pooled unadjusted HR and adjusted HR, thus indicating that the results were robust (Supplementary Figure S2). The test for heterogeneity showed a moderate result for both univariate and multivariate analyses ($I^2 = 44.5\%$ and $P < 0.1$ for the unadjusted HRs; $I^2 = 41.4\%$ and $P < 0.1$ for the adjusted HRs). The funnel plots were asymmetric in both univariate and multivariate analyses (Supplementary Figures S3, S4). Potential publication bias was significant for both unadjusted HRs ($P = 0.000 < 0.05$) and adjusted HRs ($P = 0.000 < 0.05$), according to Egger's test. Therefore, we used the trim-and-fill method by imputing the potential unpublished articles for unadjusted HRs and adjusted HRs to achieve symmetry in the funnel plot (Supplementary Figures S3, S4). The pooled unadjusted and adjusted HRs were 5.42 (95% CI: 4.60–6.50) and 5.251 (95% CI: 4.53–6.87), respectively. We further conducted a subgroup analysis on OS for the adjusted HRs as designed previously. Interestingly, the results showed that sarcopenia was consistently correlated with poor OS across all the analyzed subgroups. Sarcopenia (vs. non-sarcopenia) was associated with low OS in both Asian and non-Asian regions with summary adjusted HR of 2.10 (95% CI: 1.84–2.39) and 2.18 (95% CI: 1.78–2.66), respectively; in patients with HCC and ICC (summary adjusted HR: 2.07, 95% CI: 1.84–2.33; summary adjusted HR: 2.91, 95% CI: 2.15–3.94, respectively); in patients treated with curative and palliative therapies (pooled adjusted HR: 2.45, 95% CI: 2.01–3.00; pooled adjusted HR: 1.93, 95% CI: 171–2.18, respectively); in patients defined by L3-SMI, L3-PMI, and FFMA (MRI; pooled adjusted HR: 2.07, 95% CI: 1.82–2.35; pooled adjusted HR: 2.36, 95% CI: 1.68–3.31; pooled adjusted HR: 2.23, 95% CI: 1.36–3.65, respectively); and in patients with only HCV-related and other causes (pooled adjusted HR: 5.28, 95% CI: 2.14–13.04; pooled adjusted HR: 2.06, 95% CI: 1.85–2.29, respectively; shown in Supplementary Table S3).

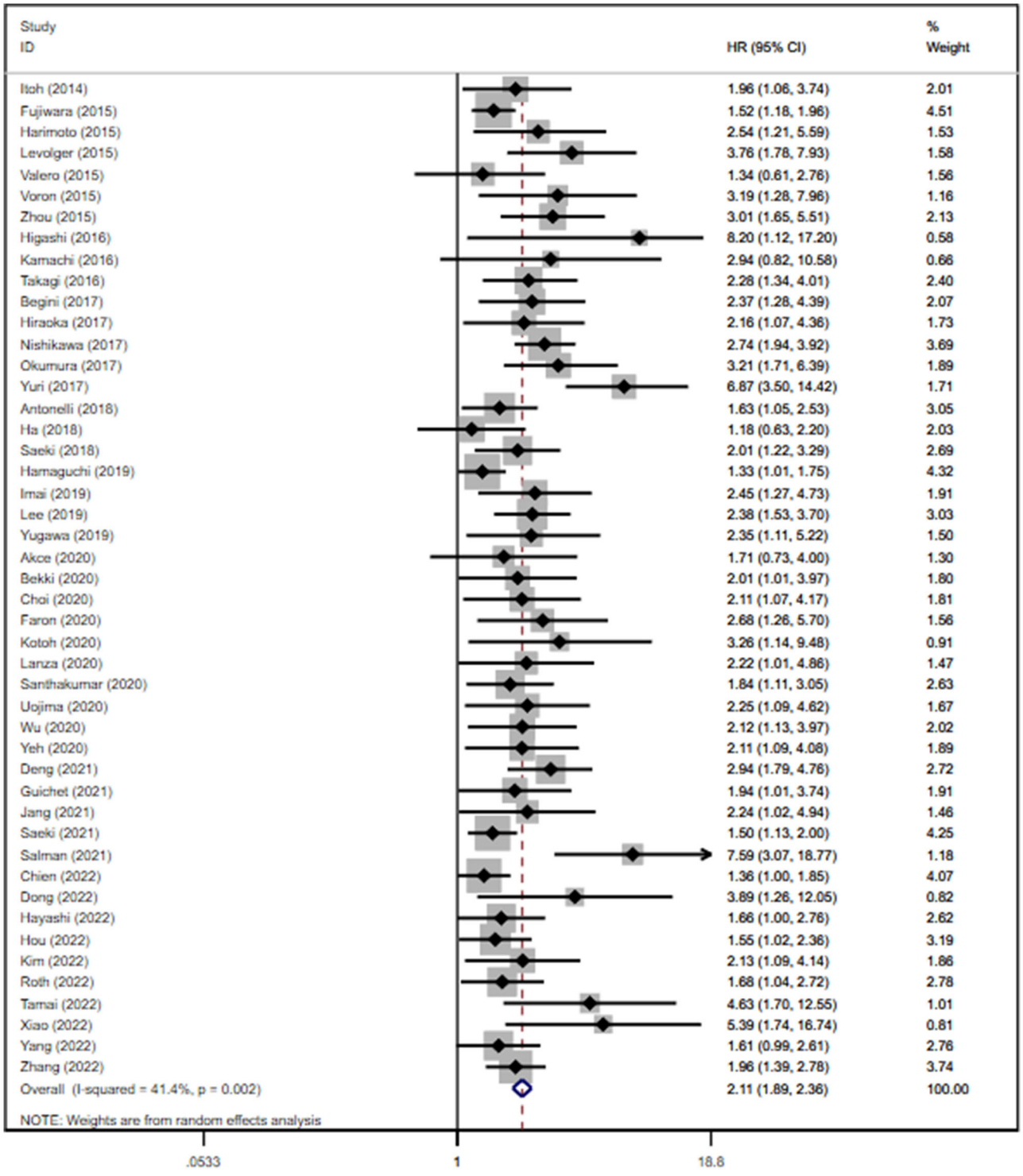

FIGURE 2
Forest plot of the pooled adjusted hazard ratios for the association between sarcopenia and overall survival in patients with primary liver cancer.

3.5. OS in patients with SO

Only four studies reported statistical data regarding the influence of SO on patient survival (14, 33, 51, 68). The prevalence of SO varied greatly among the studies, ranging from 6.67% to 30.00% (characteristics shown in Table 1). We conducted respective analyses of studies reporting unadjusted and adjusted HRs for OS. Patients with SO had a higher risk of death than those without SO (pooled unadjusted HR: 2.08. 95% CI 1.67–2.60, $P < 0.0001$; pooled adjusted HR: 2.87; 95% CI: 2.23–3.70, $P < 0.0001$), as shown in

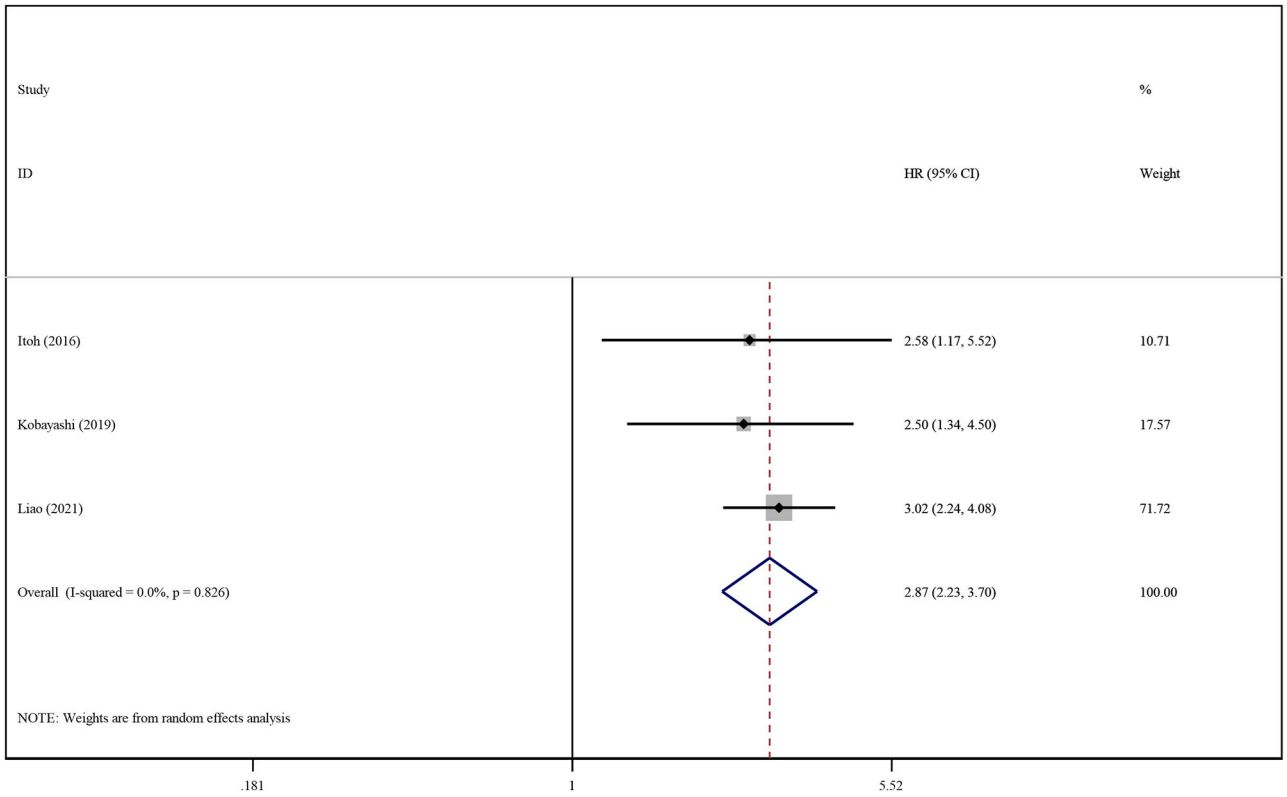

FIGURE 3
Forest plot of the pooled adjusted hazard ratios for the association between sarcopenic obesity and overall survival in patients with primary liver cancer.

Supplementary Figure S5 and Figure 3. The subgroup analysis was not conducted because of the limited number of studies reporting SO data.

3.6. RFS/DFS of the study patients

We conducted separate analyses of studies reporting unadjusted and adjusted HRs for RFS/DFS. A univariate analysis of 16 studies showed poor RFS/DFS in patients with sarcopenia (HR: 1.74, 95% CI: 1.50–2.02, $P < 0.0001$; Supplementary Figure S6), while a multivariate analysis of 11 studies showed a similar result (HR: 1.73, 95% CI: 1.50–1.99, $P < 0.0001$; Figure 4).

Moderate heterogeneity was observed in univariate analysis, while mild heterogeneity was noted in multivariate analysis ($P = 0.027$ and $I^2 = 44.8\%$ for the unadjusted HRs; $P = 0.377$ and $I^2 = 7.0\%$ for the adjusted HRs). Publication bias was not found in the univariate analysis (Egger's test, $P = 0.587$), whereas the multivariate analysis showed the existence of publication bias (Supplementary Figure S7). We further conducted a subgroup analysis on RFS/DFS for the adjusted HRs according to ethnicity, type of liver cancer, and sarcopenia definitions. However, we did not perform a subgroup analysis on RFS/DFS for the adjusted HRs based on treatment modalities because all subjects were treated by hepatectomy. The results are shown in Supplementary Table S4.

The association between SO existence and its influence on RFS/DFS in HCC was analyzed in the same manner. The summary of crude and adjusted HRs were 1.80 (95% CI: 1.33–2.44, $P < 0.001$; Supplementary Figure S8) and 2.28 (95% CI: 1.54–3.35, $P < 0.001$; Figure 5), respectively; this indicated that SO was associated with a lower RFS/DFS.

4. Discussion

In the present meta-analysis, we analyzed 64 studies comprising 11,970 participants diagnosed with primary liver cancer. Sarcopenia is a common disorder in this population, with a pooled prevalence of 43.2%, and it is more prevalent in men. The results revealed a robust association between sarcopenia and/or SO and patient survival. A strong relationship between sarcopenia and adverse clinical outcomes in cancer patients has been reported in prior studies, including depression (83), risk of fall (84), higher risk of complications (85), and cancer recurrence and mortality (9, 13, 15, 86). In 2022, a meta-analysis comprising 280 publications involving 81,814 patients with solid tumors demonstrated that sarcopenia is a prevalent condition in oncological patients with a prevalence of 35.3%; moreover, it is particularly higher in patients with specific cancer types such as esophageal cancer, urothelial cancer, cholangiocarcinoma, prostate cancer, and thyroid cancer (87). A recent study reported that SO affected 20% of cancer patients, demonstrating a significant association with various poor

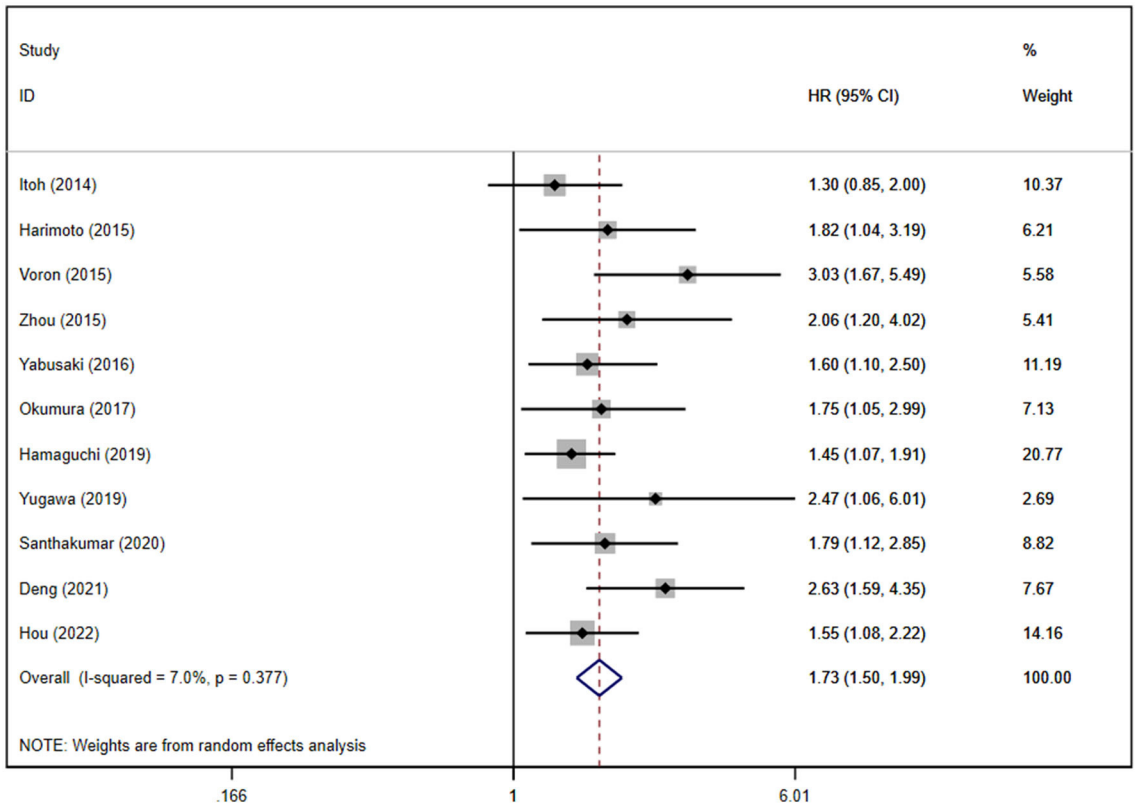

FIGURE 4
Forest plot of the pooled adjusted hazard ratios for the association between sarcopenia and recurrence-free survival or disease-free survival in patients with primary liver cancer.

outcomes in cancer patients, such as low OS, RFS, and longer length of hospital stay, particularly in patients with oropharyngeal cancer and liver cancer (88). A previous systematic review of three articles involving 1,515 liver transplant recipients demonstrated a two-fold increase in mortality rates linked to pre-transplant SO (89).

The underlying mechanisms of sarcopenia and SO are poorly understood. According to prior studies, sarcopenia and SO are multifactorial conditions. The key mechanisms of sarcopenia include aging, inflammation, hormonal changes, inactivity, and low-protein intake. The available evidence indicates that the elderly population, especially individuals aged 65 years and above, is susceptible to anabolic resistance due to decreased availability of post-prandial amino acid, diminished muscle perfusion, and decreased digestive ability caused by the sequestration of amino acids in the splanchnic region (90). Body fat increases with age until 70 years. This accumulation of body fat activates macrophages, mast cells, and T lymphocytes, resulting in the secretion of inflammatory factors such as tumor necrosis factor (TNF), leptin, IL-6, and growth hormone (GH), which induces an array of inflammatory responses (91). Inflammatory factors such as TNF-α and IL-6 facilitate skeletal muscle wasting; the former directly catabolizes skeletal muscle, leading to increased gluconeogenesis, proteolysis, and upregulation of uncoupling proteins (UCPs) 2 and 3 in cachectic skeletal muscle, while the latter suppresses protein synthesis in muscle cells by the Janus kinase signaling pathway (92). Testosterone not only modulates inflammation in skeletal muscle by activating satellite cells to promote muscle regeneration but also increases the utilization of amino acids and androgen receptor expression in skeletal muscle to promote muscle protein synthesis; however, the levels of testosterone decline with age, which is likely to have a negative effect on muscle mass (93). Inactivity can affect muscle metabolism, further exacerbating the catabolic response and decreasing muscle protein synthesis (11). Prior studies have shown that exercise can improve muscle strength and mass, and both resistance training and aerobic exercise are beneficial to sarcopenia (94, 95). A previous review elaborated on the mechanisms of SO, which included lipotoxicity, adipose tissue inflammation, adipose tissue dysfunction, insulin resistance, and systemic chronic sterile low-grade inflammation. The authors proposed intricate interactions between adipose tissue and skeletal muscle, leading to the establishment of a detrimental vicious circle as individual's age, resulting in chronic low-grade local inflammation and systemic inflammation (91). Currently, there is a lack of specific medicines to treat SO. Lifestyle intervention is the most important method to treat SO, including calorie restriction; aerobic exercise; resistance exercise; and supplementation of protein, calcium, and vitamin D (93). Exercise intervention can positively change body composition and improve body weight, BMI, fat mass, body fat percentage, grip strength, and walking speed in the SO population; nutritional intervention can decrease fat mass with no improvement in grip strength (96).

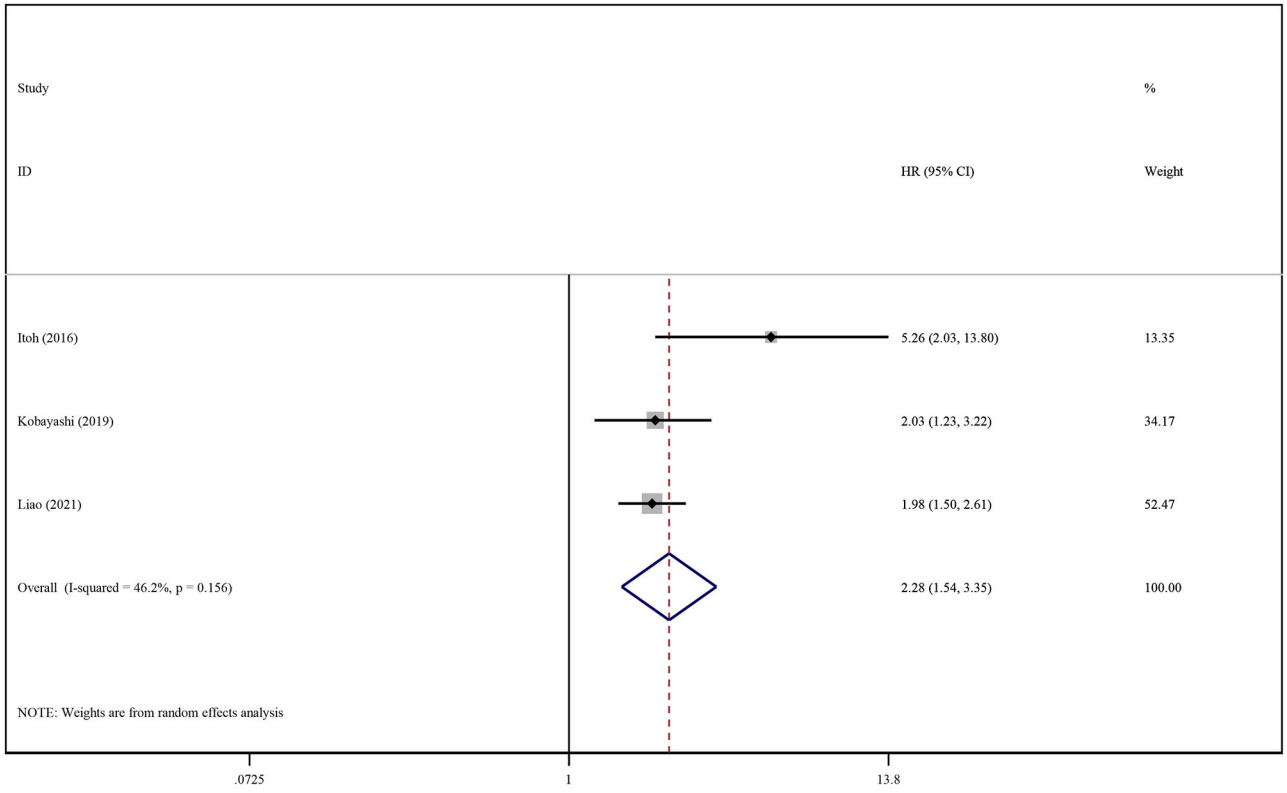

FIGURE 5
Forest plot of the pooled adjusted hazard ratios for the association between sarcopenic obesity and recurrence-free survival or disease-free survival in patients with primary liver cancer.

To the best of our knowledge, this is the first meta-analysis to demonstrate a significant relationship between sarcopenia, SO, and survival in patients with primary liver cancer in a large sample. The study included patients who underwent either curative or palliative treatment. A strength of this meta-analysis is that the study population included patients with HCC and ICC for the first time. Although a prior meta-analysis of studies published before 2017 examined the association between sarcopenia and mortality in HCC patients, one of the studies included not only patients with HCC but also metastatic liver cancer (97). Another meta-analysis included cohorts that overlapped (98), while one study focused only on the prognosis of sarcopenia in HCC patients treated with sorafenib or lenvatinib (99).

Additionally, in the present meta-analysis, a comprehensive search was performed, and studies with overlapping cohorts were excluded. Consequently, our meta-analysis added 40 additional studies that were not analyzed in previous meta-analyses, thus contributing to 64 included studies. We found a correlation between SO and decreased OS. There is, however, a lack of extensive research on the effect of SO on survival in patients diagnosed with liver cancer.

Our study has several limitations. First, this study was constrained by insufficient data from each of the included studies, which is inherent to the nature of meta-analysis. Additionally, not all studies reported an adjusted HR, which could potentially restrict our ability to determine the precise magnitude of the mortality risk between sarcopenic and non-sarcopenic patients. Second, the selection of adjusted variables for the multivariate Cox regression models varied among the studies. Third, the significant results of Egger's tests indicated the presence of publication bias.

Sarcopenia was defined as the presence of both low muscle mass and impaired muscle function, according to EWGSOP2 (2). However, the diagnosis of sarcopenia remains controversial. On the one hand, there is a lack of standardized and feasible methods to measure muscle function or physical performance. Importantly, this limitation applies not only to the current meta-analysis but also to all existing studies that have investigated the impact of sarcopenia and/or SO on patients with malignant carcinomas. On the other hand, only prospective cohort studies are likely to document muscle function. Therefore, all the included studies can only partially define sarcopenia by measuring muscle mass, depending on CT/MRI images at the L3 level, which can be easily obtained from medical records. Hence, the retrospective nature of the included studies is recognized as a limitation of the current study. Given that the majority of the included studies were retrospective cohort studies, it is probable that the results were influenced by selection bias, as only patients who underwent CT scans were included. Furthermore, several methods were used to measure muscle mass, and the studies evaluating SMI and PMI at the L3 level based on CT imaging were included in the present meta-analysis; this may partially result in heterogeneity. We observed slight variations in the actual sex-specific cutoff values

used in different studies. In some studies, the authors predefined the thresholds, whereas other studies derived these thresholds from their own study population to calculate the cutoff values. The thresholds were higher in European and American populations than in Asian populations, which might be explained by the fact that previous western studies were deemed unsuitable for Asian patients. Additionally, different cutoff values might change the magnitude of the association between sarcopenia and survival. Hence, we performed a subgroup analysis to overcome these limitations. The subgroup analysis showed a significant association between sarcopenia and poor OS and RFS/DFS across all the analyzed subgroups. Further prospective studies evaluating both muscle mass and muscle function are necessary to accurately and timely identify sarcopenic patients and to better clarify the relationship between muscle loss and survival.

Unlike previous studies examining the association between sarcopenia and survival in liver cancer patients, there is limited research on the association between SO and survival in liver cancer patients. Of the five studies searched, one study was excluded because it involved patients with other diseases, such as liver cirrhosis and cholestatic diseases (100). Furthermore, the four studies defined SO by using different approaches. Hence, further studies are required to confirm the association between SO and survival.

5. Conclusion

Sarcopenia and SO exhibited a significant association with reduced OS and RFS/DFS in patients with liver cancer. Additionally, the evaluation of sarcopenia and SO needs a consensus regarding their definitions and the utilization of appropriate cutoff values. We suggest that patients with liver cancer should undergo initial evaluation for sarcopenia and SO and receive regular monitoring because of poor prognosis. Further prospective studies are required to integrate sarcopenia and SO into an established prognostic scale specifically tailored for patients with liver cancer.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

XL and ST: study design. XL and XH: methodology and acquisition of data. XL: formal analysis and writing—original draft preparation. XL, XH, LL, and ST: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1233973/full#supplementary-material

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The ability of the geriatric nutritional risk index to predict the risk of heart diseases in Korean adults: a Korean Genome and Epidemiology Study cohort

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Introduction: The predictive ability of nutritional risk index on cardiovascular outcomes in middle-aged and non-hospitalized adults has not yet been reported. This study investigated whether the Geriatric Nutritional Risk Index (GNRI), an index for assessing the risk of developing malnutrition, could predict heart disease in middle-aged Korean adults.

Methods: The cohort used in this study consisted of 3,783 participants selected from 10,030 Korean adults who participated in the Ansan-Ansung cohort study as part of the Korean Genome and Epidemiology Study. The GNRI was determined based on serum albumin level, proportion of current weight, and ideal body weight. Participants were then divided into two groups: GNRI ≤98 and >98, which corresponded to the risk of malnutrition and normal, respectively. The major outcome of this study was coronary artery disease (CAD) or congestive heart failure (CHF) during a 15-year-follow period.

Results: During the follow-up period spanning 2004–2018, 136 events of heart disease occurred. Using a Kaplan–Meier analysis, event-free rates were found to be associated with 90.5% on a GNRI ≤98 and 96.6% on a GNRI >98 ($p < 0.0009$). GNRI ≤98 showed a 3.2-fold (hazard ratio, 3.22; 95% credit interval, 1.49–6.96; $p = 0.0029$) increase in the incidence of heart disease, including CAD or CHF, compared with GNRI >98, after controlling for potential confounders.

Conclusion: Malnutrition risk confers a significantly increased risk for heart disease in middle-aged Koreans. Further studies with larger cohorts are needed to verify the efficacy of the GNRI in predicting disease risk in adults with pre-disease.

KEYWORDS

malnutrition, geriatric, KoGES, heart, aging

1. Introduction

As the older population increases, health problems specific to the aging process and nutritional issues are receiving increasing attention. Nutritional disorders, due to either excess nutrient intake or deficiency, affect the development of diseases in older adults and patients with several diseases (1, 2). In addition, diseases induced by malnutrition tend to have different aspects from those induced by overnutrition, which are usually obesity-related complications such as hypertension, diabetes, and dyslipidemia (2). Malnutrition or the risk factors for malnutrition can lead to the deterioration of body composition, loss of skeletal and cardiac muscles (3, 4), and compromised immune function (5, 6). To date, the health consequences of malnutrition have primarily been investigated in hospitalized patients with several diseases,

because disease status leads to nutritional deficiency. Indeed, a large proportion of patients with end-stage diseases (e.g., cancer or renal disease) are malnourished (3) and exhibit impaired immune function, attenuated wound healing, and disease aggravation (5, 7–9). In particular, malnutrition has been associated with an increased mortality rate in patients with coronary heart disease, heart failure, and older adults (10–12). It has also been associated with the incidence of coronary heart disease in several cross-sectional studies (13, 14). Malnutrition has also been reported at a substantial rate in young and externally healthy individuals with potential health risk factors (15–17). Although obesity has been investigated in various populations, including younger adults, its consequences in several contexts remain to be investigated.

The Geriatric Nutritional Risk Index (GNRI) is an screening tool of nutrition-related risk for estimating the likelihood of morbidity and mortality in older populations and chronically ill patients (14, 18–21). The GNRI comprises two parameters, body weight and serum albumin, which are simple to measure and obtain from routine check-ups in hospitals and community-based health centers (22). Community-based studies have found that a low GNRI indicating the risk of malnutrition is associated with a higher mortality risk due to heart failure (14, 18, 19). This index is usually applied to groups of patients or older adults, mostly those aged 65 years and older. Owing to the aging population in Korea, the number of patients with cardiovascular diseases (CVDs) and heart failure is increasing in Korea. The estimated heart failure rates were 0.77% in 2002 and 2.24% in 2018 (23). The prevalence of heart failure is 0.1–0.7% in young and middle-aged adults aged 50 years or younger, but this number increases to 16.9% in later life (23). In most previous studies, the risk of malnutrition and its outcomes were primarily investigated in older populations, usually those aged 60 years and above (12). These reports, in turn, indicate that malnutrition, which has already been initiated in midlife, affects health outcomes later in life. However, little is known regarding the association between GNRI-assessed the risk of malnutrition and harmful cardiac events in middle-aged adults. Although the main population for assessing the prognostic efficacy of the GNRI is the older population (24), the GNRI has been validated in young adults (25, 26).

Hence, the prognostic efficacy of the GNRI in predicting the occurrence of cardiovascular and heart diseases in conjunction with the aging process should be investigated earlier in an individual's life than previously reported. In addition, few studies have evaluated the link between malnutrition and various cardiovascular complications in a cohort of hospitalized patients (27); however, its consequences in the general population need to be assessed. Thus, the present study aimed to examine whether the GNRI is a valid predictor of heart disease in middle-aged Korean adults.

2. Study population and methods

2.1. Study participants

Participants were enrolled from two community-based cohorts, the Ansung and Ansan cohorts, from the Korean Genome and Epidemiology Study (KoGES) (28). The eligibility criteria for participating in the KoGES were 40–69 years of age and dwelling within the community for 6 months or longer by the time of enrolment. The participants voluntarily enrolled in the study and provided written informed consent. Detailed information on the KoGES design, processes, and participant retention rates has been published previously (28). At the beginning of the study, 10,030 participants were included in KoGES. Baseline measurements were conducted in 2001 and 2002, and biannual follow-up examinations were conducted until 2018. We excluded participants who had not visited for follow-up data collection ($n = 6{,}035$), had a total energy intake value <500 kcal/day, or ≥ 4,500 kcal/day ($n = 147$), had missing data ($n = 6$), or already had coronary artery disease (CAD) and congestive heart failure (CHF) at baseline data collection ($n = 635$). Finally, 3,783 participants were included in the analysis. The procedure for selecting the participants is shown in Figure 1. This study was approved by the institutional review board (IRB) of Daegu University. In addition, the personal identifying information of the study participants was deleted from the dataset prior to acquisition and analysis. The requirement for written informed consent from KoGES study respondents was waived by the IRB of Daegu University.

2.2. Data collection

Demographic information was collected using a standard questionnaire administered during in-person interviews at the KoGES (28). Demographic data included age, sex, and educational level. Body weight, height, BMI (kg/m^2), muscle mass (kg), systolic blood pressure (SBP), diastolic blood pressure (DBP), waist circumference, alcohol intake (currently drinking alcohol), and smoking status (currently smoking cigarettes) were recorded. Body fat and muscle mass were measured using bioelectrical impedance analysis (Biospace, Seoul, Korea) (29). For analysis of GNRI distribution according to BMI criteria, BMI was categorized as either "underweight (BMI < 18.5)," "normal (18.5 ≤ BMI <23)," "overweight (23 ≤ BMI <25)," or "obese (25 ≤ BMI)" according to the BMI classification for Asian and South Asian population suggested by the National Institute of Health (30). Peripheral blood samples were drawn from the study participants (28). Albumin, high-sensitivity C-reactive protein (hs-CRP), triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL), fasting glucose, hemoglobin A1c (HbA1c), blood urea nitrogen (BUN), and creatinine were used as covariates in this study. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, antihypertensive medication use, or a diagnosis made by a medical doctor. Diabetes mellitus (DM) was determined as fasting blood glucose ≥126 mg/dL, HbA1c ≥ 6.5%, antidiabetic treatment use, or a physician's diagnosis. The diagnosis of CAD or CHF, the main outcome of this study, was reported using a questionnaire administered during the KoGES study period. To estimate nutritional intake status, dietary data were collected using a Korea-specific food frequency questionnaire that asked about the frequency and portion size of each food item consumed by each participant during the last year. Daily total nutrient intake was assessed by applying the amount and type of each reported food item to the CAN-Pro 2.0 program developed by the Korean Nutrition Society (31).

2.3. Geriatric nutritional risk index

The GNRI was calculated using the following formula: GNRI = (1.489 × serum albumin [g/L]) + (41.7 × weight [kg]/ideal body

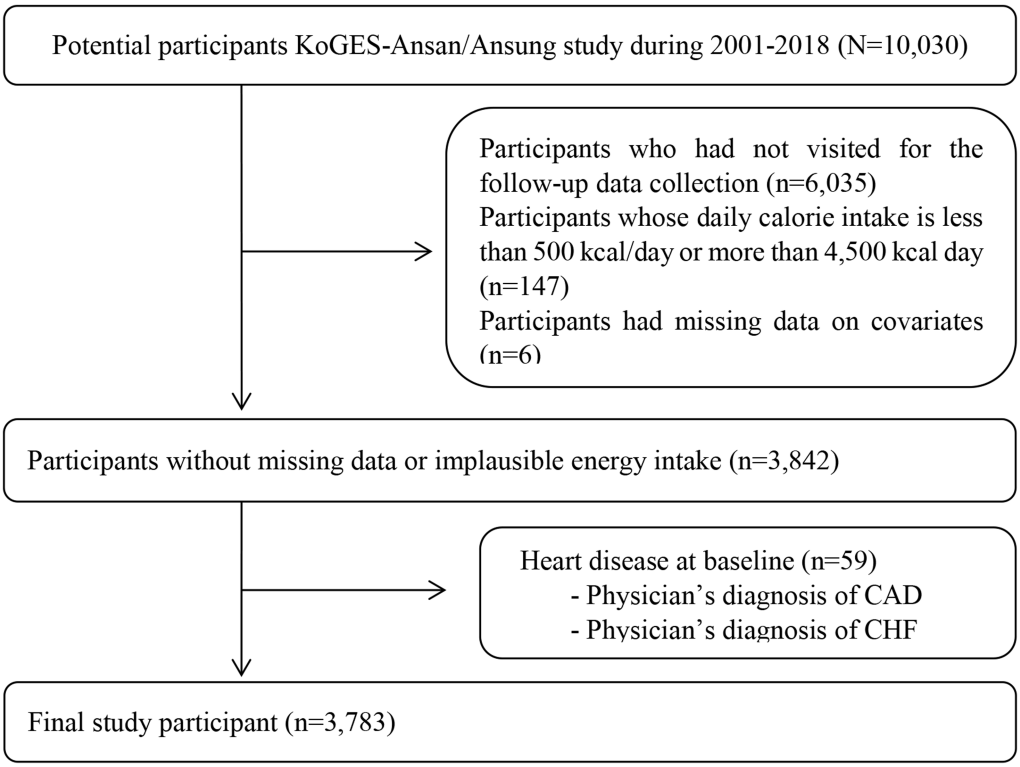


FIGURE 1
Flow diagram for selecting study participants. The requirement of obtaining consents was waived by the Institutional Review Board. KoGES, The Korean Genome and Epidemiology Study; CAD, coronary artery disease; CHF, congestive heart failure.

weight [kg]). Ideal body weight was determined as 22 × the square of height, as previously described (20, 24, 26). The variables used in this formula were assessed during the baseline visit to KoGES. Previously, GNRI values were divided into three categories: < 82, < 92, 92–98, and > 98 for major, moderate, low and no "nutrition-related risk," respectively (21), and into two categories: GNRI <98 and GNRI >98, indicating malnutrition and adequate nutrition, respectively (20). Because the number of participants categorized as 92 < GNRI ≤98, and GNRI <92 was small (less than 5% of total participants) in this study, the presence of malnutrition risk based on GNRI was categorized into two levels: GNRI ≤98; and GNRI >98. Recent studies have shown that the GNRI is applicable to participants regardless of their body fluid status or disease type. Hence, this study did not limit the study participants owing to the presence of disease status.

2.4. Statistical analysis

All data analyses were performed using the SAS software (SAS 9.4; SAS Institute Inc., Cary, NC, United States). Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as numbers and percentages in parentheses. Differences in variables between the groups were evaluated using analysis of variance for continuous variables and the chi-squared test for categorical variables. Fisher's exact test was used when the cell count per event was <5. In this study, multivariate regression analysis was performed to assess the contribution of the measured variables to GNRI values. Kaplan–Meier curves were plotted from the reported date of the diagnosis of heart disease (CAD or CHF) and compared between groups with GNRI ≤98 and GNRI >98. A Cox proportional hazards regression model was used to test the association between the risk of malnutrition based on the GNRI score and the incidence of heart disease. Model 1 was a crude model that only assessed the association between the incidence of heart disease and GNRI, and Model 2 was further adjusted for age, sex, and BMI. Model 3 included the same variables as Model 2 and cigarette smoking status, current alcohol consumption, and educational level. Model 4 added the following variables to Model 3: the presence of hypertension, DM, hyperlipidemia, and any use of medication for these diseases. Statistical significance was confirmed at p-values <0.05.

3. Results

3.1. Baseline characteristics of the study participants between GNRI categories

The baseline characteristics of the study participants are presented in Table 1. The number of participants in GNRI ≤98 and > 98 was 105 and 3,678 patients, respectively. At the initial examination, the ages of the two groups were 55.1 and 50.8 years. The proportion of adults aged 40–50 years among normal participants was the highest among all age groups, while the proportion of adults aged 60–69 years was the highest among participants with GNRI ≤98. Except for the height variable, the values of all anthropometric parameters, body weight, BMI, muscle

TABLE 1 Baseline characteristics of all the subjects between GNRI categories.

	GNRI ≤98 (*n* = 105)	GNRI >98 (*n* = 3,678)	*p* value
Age	55.1 ± 9.1*	50.8 ± 7.9	< 0.0001
40 ≤ year<50	34 (32.4)†	1,931 (52.5)	< 0.0001
50 ≤ year<60	32 (30.5)	1,068 (29.0)	
60 ≤ year<70	39 (37.1)	679 (18.5)	
Sex			
Men	62 (59.1)	1,687 (40.9)	0.0076
Women	43 (45.9)	1,991 (54.1)	
GNRI	95.3 ± 2.4	111.8 ± 7.1	< 0.0001
Body weight (kg)	49.8 ± 5.6	63.9 ± 9.7	< 0.0001
Height (cm)	160.6 ± 8.1	160.2 ± 8.5	0.6172
BMI (kg/m^2)	19.3 ± 1.3	24.8 ± 3.0	< 0.0001
Muscle mass (kg)	38.2 ± 5.6	43.9 ± 8.0	< 0.0001
Waist circumference (cm)	72.2 ± 5.8	82.9 ± 8.5	< 0.0001
SBP (mmHg)	117.4 ± 17.5	120.1 ± 17.4	0.1222
DBP (mmHg)	76.7 ± 10.8	79.9 ± 11.1	0.0033
Albumin (g/L)	3.9 ± 0.2	4.3 ± 0.3	< 0.0001
Triglycerides (mg/dL)	120.6 ± 47.7	161.2 ± 102.0	< 0.0001
Total Cholesterol (mg/dL)	157.7 ± 28.9	191.7 ± 34.0	< 0.0001
HDL-Cholesterol (mg/dL)	47.6 ± 9.9	44.4 ± 9.8	0.0012
Fasting glucose (mg/dL)	80.9 ± 22.3	86.5 ± 19.2	0.0037
HbA1c (%)	5.6 ± 0.9	5.7 ± 0.8	0.2775
hs-CRP (mg/L)	0.27 ± 0.56	0.21 ± 0.57	0.3750
BUN (mg/dL)	13.5 ± 3.4	14.3 ± 3.6	0.0284
Creatinine (mg/dL)	0.8 ± 0.1	0.8 ± 0.2	0.0005
Hypertension (%)	2 (1.9)	521 (14.2)	< 0.0001
Diabetes mellitus (%)	3 (2.9)	189 (5.1)	0.4918
Hyperlipidemia (%)	9 (8.6)	805 (21.9)	0.0011
Medication (%)	1 (1.0)	405 (11.0)	0.0002
Education			
Above high school	73 (69.5)	1,886 (51.3)	0.0002
Below high school	32 (30.5)	1,792 (48.7)	
Current alcohol drinker	55 (52.4)	1,770 (48.1)	0.3894
Current smoker	43 (41.0)	775 (20.5)	< 0.0001

*Mean ± S.E., †number of frequency (%), the *p* values are from ANOVA for continuous variables and Chi square test for categorical variables for assessing the trend of difference between GNRI categories.

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; hs-CRP, high sensitive C-reactive protein; BUN, blood urea nitrogen. Medication: any medication against for diabetes, hypertension and hyperlipidemia.

mass, and waist circumference were lower in participants with GNRI ≤98 than in those with GNRI >98 ($p < 0.0001$ for all). The SBP was not significantly different between the two groups, and the DBP was lower in the malnourished group than in the normal group ($p = 0.0033$). HDL-cholesterol was the only biochemical parameter higher in participants with GNRI ≤98 than in those with GNRI >98. The levels of serum albumin, triglycerides, total cholesterol, fasting glucose, BUN, and serum creatinine were significantly lower in participants with GNRI ≤98 than in those with GNRI >98. No significant differences were found in the HbA1c or hs-CRP levels. Participants with GNRI >98 tended to have higher proportions of hypertension and hyperlipidemia and medication use for treating these diseases. In contrast, participants with GNRI ≤98 tended to have a lower education level and a higher proportion of individuals who currently smoke cigarettes than those with GNRI >98. Table 2 presents the participants' intake statuses. The intake levels of total energy, protein, fat, carbohydrates, calcium, and iron were not significantly different between the two GNRI groups. Participants with GNRI ≤98 ate less sodium but took more energy from alcohol than those with

TABLE 2 Nutrient intake status of study participants.

	GNRI ≤98 (n = 105)	GNRI >98 (n = 3,678)	p
Energy (kcal)	1,961.4 ± 661.3*	1,936.3 ± 588.0	0.6677
Protein (g)	65.2 ± 29.3	65.3 ± 24.3	0.9578
Fat (g)	31.1 ± 20.0	31.9 ± 17.4	0.6600
Carbohydrate (g)	349.9 ± 113.5	342.0 ± 102.8	0.4400
Calcium (mg)	451.8 ± 241.9	472.2 ± 250.4	0.4105
Iron (mg)	10.8 ± 5.1	10.8 ± 4.6	0.9153
Sodium (mg)	3,457.1 ± 1,982.5	3,132.1 ± 1,540.9	0.0348
Energy intake from alcohol	90.6 ± 186.6‡	61.4 ± 140.5	0.0413
Alcohol/energy ratio	4.7 ± 9.6	3.2 ± 7.4	0.0465
Carbohydrate/energy ratio	72.2 ± 7.7	71.1 ± 6.6	0.0970
Protein/energy ratio	13.1 ± 2.8	13.4 ± 2.2	0.1203
Fat/energy ratio	13.6 ± 5.8	14.4 ± 5.2	0.1292
Energy intake status			
<75% KDRI	28 (26.7)†	934 (25.4)	0.5962
75% ≤ KDRI ≤125%	59 (56.2)	2,194 (59.7)	
> 125% KDRI	18 (17.1)	550 (15.0)	

*Mean ± S.E., †Percent intake from total energy intake, ‡Caloric intake from alcohol was calculated by g of alcohol intake/day × 7.0 kcal/g of alcohol.
The p values are from ANOVA or Chi square test for assessing the trend of difference between GNRI categories. KDRI: 2015 Dietary reference intake for Koreans.

TABLE 3 Prevalence of GNRI-assessed malnutrition risk according to BMI of participants (n = 3,783).

	Underweight	Normal	Overweight	Obese	p-value*
Malnourished (GNRI ≤98)	27 (25.7)	78 (74.3)	0 (0.00)	0 (0.00)	< 0.0001
Normal (GNRI >98)	18 (0.5)	990 (26.9)	1,016 (27.6)	1,654 (45.0)	
Total	45	1,068	1,016	1,654	

Data are presented as n (%).
*Fisher's exact test was performed to compare the distribution of BMI between malnourished and normal.
GNRI: geriatric nutritional risk index; Underweight: BMI < 18.5, Normal: 18.5 ≤ BMI <23, Overweight: 23 ≤ BMI <25, Obese: 25 ≤ BMI.

GNRI >98. There were no significant differences in the distribution of participants who consumed total daily energy <75%, > 125%, or 75–125% range of the dietary reference for Koreans.

3.2. Ratio of nutritional risk in participants stratified by BMI

As BMI has been previously used to assess malnutrition status, the study participants were categorized into four weight statuses according to BMI, and the distribution of BMI was compared between the GNRI groups (Table 3). Participants with GNRI ≤98 comprised only underweight and normal individuals without overweight or obese participants. Participants with GNRI >98 had the highest proportion of individuals who were "obese" (45%), and < 30% of participants were "underweight" or "normal" based on BMI criteria.

3.3. Exploring the variables that contribute to the GNRI

The linear association between the GNRI values and several baseline variables was explored to investigate how the GNRI values were affected (Table 4). The GNRI value was significantly associated with age ($\beta = -0.08$, $p < 0.0001$), BMI ($\beta = 1.97$, $p < 0.0001$), sex ($\beta = -1.05$, $p < 0.0001$), hs-CRP ($\beta = -0.33$, $p = 0.0079$), current smoking status ($\beta = -1.12$, $p < 0.0001$), total energy intake ($\beta = -0.06$, $p < 0.0001$), and the level of education ($\beta = 0.83$, $p < 0.0001$). No significant association with the GNRI was found for disease status, including hypertension, diabetes, and hyperlipidemia, or the use of medication against these diseases.

3.4. Accumulated heart disease incidence according to GNRI values during the follow-up period

The event rate of heart disease during the 15-year follow-up period was 3.60% (n = 136 events) in all participants (Table 5). The ratios of diagnosed disease in GNRI ≤98 and GNRI >98 were 9.5% and 3.4% for total heart disease ($p = 0.0009$), 8.6% and 3.3% for CAD ($p = 0.0037$), and 1.0% and 0.2% for CHF ($p = 0.1790$), respectively. In Kaplan–Meier curves, participants in GNRI ≤98 showed a significantly higher incident probability of heart diseases compared with those in GNRI >98 (log-rank test p value = 0.0009) (Figure 2).

TABLE 4 Relationship between GNRI and variables with multivariate regression analyses.

Model fit		
R2	0.6622	< 0.0001*
Intercept	68.48	< 0.0001
Parameter estimates		
	β	
Age	−0.08	< 0.0001
BMI	1.97	< 0.0001
Sex	−1.05	< 0.0001
hs-CRP	−0.33	0.0079
Smoke	−1.12	< 0.0001
Drink	0.17	0.3005
Energy intake	−0.06	< 0.0001
Education	0.83	< 0.0001
Hypertension	0.60	0.0719
Diabetes mellitus	−0.49	0.1383
Hyperlipidemia	0.17	0.6934
Medication	−0.12	0.7408

*The *p*-value was determined with multivariate regression analysis.
BMI, body mass index; hs-CRP, C-reactive protein; GNRI, geriatric nutritional risk index.

TABLE 5 The prevalence of heart disease during 15 year-follow-up period.

Events	*N* (%)		
	GNRI ≤ 98 (*n* = 105)	98 < GNRI (*n* = 3,678)	*p*-value
Total CC events, *n* (%)	10 (9.5)	126 (3.4)	0.0009
Coronary artery disease, *n* (%)	9 (8.6)	122 (3.3)	0.0037
Congestive heart disease, *n* (%)	1 (1.0)	6 (0.2)	0.1790*

The prevalence of cardiac complications was examined between participants with low GNRI and high GNRI, and the difference of prevalence was analyzed by Chi-square analysis.
*Fisher's exact test was performed when the cell counts for each event was less than 5.
GNRI, geriatric nutritional risk index.

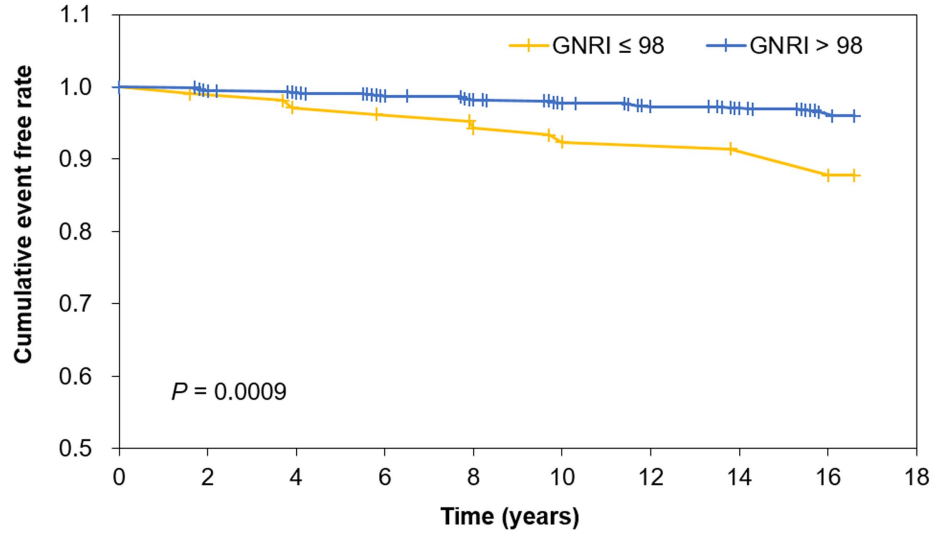
3.5. Association between GNRI and the incidence of heart diseases

Table 6 shows the results of the Cox hazard regression analysis to determine the risk of heart disease based on GNRI score. The participants with GNRI ≤98 showed an increased heart disease risk compared to those with GNRI >98. The crude hazard ratios (95% credit interval, CI) for diagnosis of heart disease without adjustment (Model I) in GNRI ≤98 relative to GNRI >98 was 2.83 (1.49–5.40) (p for trend = 0.0015), respectively. The degree of risk of heart disease in the participants with GNRI ≤98 to the participants with GNRI >98 remained similar after gradual adjustment of age and height (Model II, p for trend = 0.0014), the level of education, smoking and alcohol consumption, total energy intake, sodium intake (Model III, p for trend = 0.0018), and history of diabetes or hyperlipidemia and medication for diabetes and hyperlipidemia (Model IV, p for trend = 0.0029) in various regression models.

4. Discussion

The present study reported an association between the GNRI and the risk of heart disease in middle-aged Korean adults. The results showed that adults with malnutrition risk, as judged by the GNRI, had an increased risk of developing heart diseases, including CVD and CHF, compared to adults with no risk. In this study, various covariates were related to the GNRI, but the significance of the association remained even after adjusting for several covariates. To the best of our knowledge, this is the first study to use the GNRI to predict heart disease in middle-aged Korean adults.

The GNRI has long been used to assess the nutrition-related risk of hospitalized patients and outpatients with various diseases (19, 32). The GNRI mainly comprises serum albumin and body weight, which are regularly assessed in hospitalized patients or the diagnostic procedure of outpatients (22). Serum albumin and BMI are typical indicators of nutritional status and are used to predict mortality and disease-related complications in patients with CAD (33, 34). Heart disease is closely related to malnutrition (4, 10, 12). The relationship between malnutrition and heart disease has been reported in several cross-sectional cohort studies. For instance, malnourished individuals categorized by serum albumin levels showed increased left ventricular mass index and ventricular wall thickness and decreased diastolic function in the general Taiwanese population (35). Another study reported that low muscle mass and strength are associated with heart failure in hospitalized older patients with physical disabilities (36). Under malnutrition status, including weight loss of >5% within the



GNRI	Numbers of people at risk of heart disease								
Malnutrition	105	104	102	101	99	97	97	96	96
Normal	3,678	3,658	3,647	3,631	3,612	3,595	3,578	3,570	3,566
	0	2	4	6	8	10	12	14	16

Time (years)

FIGURE 2
Kaplan–Meier curves for events of heart disease according to GNRI. Disease occurrence was negatively associated with GNRI, with a lower diagnostic-free curve for GNRI ≤98. Log-rank test indicated $p = 0.0009$. GNRI: geriatric nutritional risk index.

TABLE 6 Cox regression analyses for heart disease.

	Hazard ratio (95% CI)		
	GNRI ≤ 98 ($n = 105$)	98 < GNRI ($n = 3,678$)	p-value
Model I	2.83 (1.49–5.40)	1.00 (reference)	0.0015
Model II	3.30 (1.58–6.85)	1.00 (reference)	0.0014
Model III	3.23 (1.54–6.76)	1.00 (reference)	0.0018
Model IV	3.22 (1.49–6.96)	1.00 (reference)	0.0029

Hazard ratio with 95% confidence interval were shown.
Model I: crude model, Model II: adjusted for age, BMI, and sex, Model III: Model II + the degree of education + household income + smoke + drink. Model IV: Model III + diabetes mellitus + hypertension + dyslipidemia + any medication for diabetes, hypertension and hyperlipidemia.

past 6 months, a BMI < 22 and muscle indices were highly correlated with the relative risk of cardiovascular complications, including arrhythmia, myocardial infarction, and CHF in older adult patients (37). In addition, differences in the nutritional status of patients with CVD vary according to sex. In patients with acute myocardial infarction, the risk of malnutrition screened by the "Nutritional Risk Screening 2002 (NRS-2002)" significantly predicted in-hospital mortality in female patients but not in male patients (38) indicating the possibility of malnutrition as a sex-specific factor in predicting disease risk or mortality. Recent studies have indicated that the risk of malnutrition assessed by the GNRI accurately predicts disease risk and cardiovascular mortality (20, 39–41), and these findings appear consistent with those of a previous study assessing a single individual indicator of malnutrition (22, 33, 34). Furthermore, GNRI was associated with all-cause mortality in the general population, including healthy adults, in a national health and nutrition survey conducted in the USA (42). Although participants with GNRI ≤98 all belonged to underweight or normal based on BMI in this study, BMI alone did not predict the risk of heart disease (data are not shown). In addition, the low GNRI group tended to have low fat and muscle mass along with decreased body weight, indicating an overall decline or deterioration in body composition under the conditions of developing malnutrition. In line with a previous report (39), our results indicate that the GNRI is a more dependable index than serum albumin or BMI alone for predicting heart disease in Korean adults.

Most patients with heart disease have multiple comorbidities, are vulnerable to infections or unexpected communicable diseases, and face challenges in clinical management (43–45). Although heart disease does not cause mortality, it is considered life-threatening. According to the Health Insurance Review and Assessment Service in Korea, the number of malnourished patients aged 20 years and diagnosed with malnutrition was 149 and 791, respectively, in 2017 and 335 and 441, respectively, in 2021, which was a 23.9% increase over the last 5 years. Of these, 29.4% were adults in their 60s, with the highest prevalence; however, the prevalence in adults in their 40s and 50s was 20 and 21.9%, respectively (46), indicating that malnutrition begins at an earlier age than the age at which the consequences of malnutrition occur. The age range of the participants was 40–69 years at baseline. Although the GNRI ≤98 group had a higher proportion of older adults aged ≥60 years than the GNRI >98 group, the proportion of participants aged 40–50 years was more than 30% within the group with GNRI ≤98. Studies have also suggested that young and middle-aged adults have nutritional deficiencies and a potential risk of heart failure and malnutrition (47, 48). Although previous studies have focused excessively on malnutrition in the aged

population (20, 24, 39), earlier identification of malnutrition can advance disease treatment and recovery. Hence, our findings indicate the need to identify nutrition-related risk in middle-aged adults to prevent cardiovascular risks later in life.

Regarding the findings of this study, there are possible mechanisms through which risk factors developing malnutrition affects heart disease. Malnutrition hinders the recovery from inflammatory conditions due to disease or infection and continued inflammatory conditions, leading to catabolic reactions that promote protein degradation and muscle wasting (49, 50). In addition, the malnutrition status of the study cohort coincided with high levels of inflammatory mediators such as tumor necrosis factor-alpha (51, 52) and hs-CRP, which are highly correlated with the risk of CVD and heart arrest (18, 50). In line with these findings, hs-CRP was negatively correlated with GNRI score in the regression model adjusted for several covariates in this study. Previously, hs-CRP was associated with atherosclerosis in adults aged 50–64 years (53). Serum albumin, the main component of the GNRI, is closely associated with hs-CRP levels in patients with inflammatory diseases. For instance, patients with higher albumin tend to have higher triceps skinfold measurements reflecting upper arm muscle circumference and lower hs-CRP levels in those with Crohn's disease (54). Moreover, malnutrition is known to weaken immune function owing to the loss of body proteins and energy restriction (55). In addition, sarcopenia is associated with atherosclerosis and impaired endothelial function in older populations (56). Muscle wasting is associated with increased arterial stiffness and risk of CVDs in middle-aged adults (57). Therefore, a positive feedback loop may have existed between inflammation, malnutrition, cardiac muscle weakening, and adverse cardiac events in the study cohort.

In this study, the total calorie and other nutrient intakes at baseline were not significantly different between the GNRI >98 and GNRI ≤98 groups. However, calorie intake from alcohol consumption was significantly higher in participants with GNRI ≤98 and led to a higher ratio of energy from alcohol to total energy intake than in those with GNRI >98. Alcohol intake has been known to be associated with heart failure, cardiomyopathy, and cardiomyopathy-derived mortality and worsens the status of malnutrition (58, 59). Although alcohol consumption in the study participants was approximately 13.0 g per day, a recent study reported that an increase in alcohol consumption was linearly associated with the risk of CAD (60). One study showed that an increase in alcohol consumption increased the risk of CAD by 1.4-fold compared with non-alcohol consumption (60), indicating that habitual alcohol intake increases the risk of heart disease, even in low amounts. Because this study investigated the nutritional intake data of participants only available at baseline, the change in their diet, including nutrient intake, with regard to the incidence of heart disease, needs to be further investigated in a future study. Nevertheless, our data suggest that identifying nutrition-related risk and early nutritional intervention at the earliest possible time could reduce the risk of disease-related complications. According to the American Heart Association and Heart Failure Society guidelines, evaluation of nutritional status is recommended for patients with heart failure (61). In addition, studies have reported that nutritional intervention may improve clinical outcomes in older adults aged ≥60 years (62, 63). A randomized clinical trial and a cross-sectional study of community-dwelling older adults found that supplementing or enhancing their energy status and protein consumption improved their nutritional status (63, 64) and reduced disease prevalence (65). Moreover, sex differences exist in the association of malnutrition with heart disease (38) and cardiovascular outcomes in response to nutritional supplements or dietary patterns of patients (66). However, discrepant results indicate that being underweight and the risk of malnutrition are directly associated with the odds of in-hospital mortality in men but not in women (67). Based on previous studies and reports and the findings of this study, further long-term research is warranted to identify the main modifiable factors that enhance nutritional status assessed by the GNRI, including sex differences, and to confirm whether nutritional interventions intended to enhance the GNRI of malnourished adults provide health benefits later in life.

According to previous studies, the relationship between the GNRI and the HR of all-cause death or disease incidence was not linear. The curve of the plotted GNRI tended to be flat when the GNRI value exceeded 98, which is the cutoff value used in most previous studies (19, 20, 39). This study also did not observe an association when a GNRI cutoff value >98 was used to categorize the participants (data not shown). This suggests that the incidence of cardiac events does not change when the GNRI exceeds a specific threshold. These results may be explicated by the fact that obesity is a risk factor for CAD in relation to the double burden of malnutrition and obesity (5, 15). Hence, malnutrition, not just an absolute deficit in total energy consumption, but in the context of nutrient balance, and its consequences in heart disease need to be further investigated.

This study had several limitations. First, the sample size of the patient cohort was small after applying the exclusion criteria, and unknown confounding factors may have affected the outcomes. Second, only one nutritional risk index (GNRI) was used to screen the nutritional risk of the participants; hence, the data need to be validated using other nutritional assessment tools. Third, the main outcome–the diagnosis of heart disease–was based only on the participants' responses to the questionnaire rather than on an objective assessment. However, the percentage of CAD reported within this study cohort was similar to the statistics reported in the fact sheet provided by the Korean Society of Heart Failure (23) and health checkup questionnaire procedures were conducted by well-trained personnel in this nationwide cohort study (28). Although the sample size and number of outcome events in this study were relatively small, the results suggest the usefulness of GNRI in predicting heart disease risk in middle-aged adults. The GNRI has mostly been studied in clinical settings; however, the results of this study can also be applied to middle-aged populations at the community level. Large-scale surveys are required to confirm the results of this study and elucidate the precise underlying mechanisms.

5. Conclusion

This study demonstrated that the GNRI score in middle-aged Korean adults, predicts adverse cardiovascular events later in life. Adding the GNRI score to the existing risk prediction model significantly increases its ability to predict cardiovascular events. The GNRI could be used as a practical tool to formulate routinely tested parameters for high-throughput screening of the long-term risk of CAD in the area of public health, which might support the prognostic stratification of high-risk community populations.

Data availability statement

The data presented in this study are available on request from the corresponding author upon reasonable request.

Ethics statement

The studies involving humans were approved by Institutional review board of Daegu University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JP: Investigation, Writing – original draft, Writing – review & editing. SB: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Low geriatric nutritional risk index as a poor prognostic biomarker for immune checkpoint inhibitor treatment in solid cancer

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Objective: In this investigation, we focused on the geriatric nutritional risk index (GNRI), a comprehensive metric that takes into account the patient's ideal weight, actual weight, and serum albumin levels to measure malnutrition. Our primary objective was to examine the predictive value of GNRI-defined malnutrition in determining the response to immunotherapy among cancer patients.

Methods: Relevant articles for this study were systematically searched in PubMed, the Cochrane Library, EMBASE, and Google Scholar up to July 2023. Our analysis evaluated overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR) as clinical outcomes.

Results: This analysis comprised a total of eleven articles encompassing 1,417 patients. The pooled results revealed that cancer patients with low GNRI levels exhibited shorter OS (HR: 2.64, 95% CI: 2.08–3.36, $p < 0.001$) and PFS (HR: 1.87, 95% CI: 1.46–2.41, $p < 0.001$), and lower ORR (OR: 0.46, 95% CI: 0.33–0.65, $p < 0.001$) and DCR (OR: 0.42, 95% CI: 0.29–0.61, $p < 0.001$). Sensitivity analyses confirmed that the above results were stable. Egger's and Begg's tests revealed that there was no publication bias in the above results.

Conclusion: Our results imply that the GNRI is a useful predictor of immunotherapy response in cancer patients.

KEYWORDS

biomarker, cancers, geriatric nutritional risk index, immune checkpoint inhibitors, outcomes

1. Introduction

With the rising use of immune checkpoint inhibitors (ICIs) in tumor treatment, there has been significant research on identifying novel biomarkers that can effectively predict the response to ICI therapy (1–3). Traditionally, PD-L1 expression in tumor tissue has been considered a prominent marker for PD-(L)1 therapy due to its mechanistic relevance (1, 4). Additionally, the tumor mutational burden, which reflects the total number of somatic mutations, has also emerged as a predictive sign for ICIs and has been authorized as a companion diagnostic test (1, 5, 6). In contrast to oncogenic driver mutations for targeted therapy, these biomarkers are insufficient to identify ICI responders. For instance, even individuals with NSCLC and strong PD-L1 expression only exhibit an ORR of 44.8% when treated with

pembrolizumab (7). Conversely, patients with low PD-L1 expression may also benefit from ICIs (8–10). This discrepancy indicates that tissue-based approaches alone are insufficient for predicting ICI therapy outcomes. ICIs stimulate antitumor responses through immune cells, in contrast to targeted treatments, which have direct antitumor effects on tumor cells. Thus, assessing host factors in addition to tumor characteristics may provide crucial information for accurately predicting the efficacy of ICIs.

It is well known that nutritional status is linked to immune function and influences the clinical consequences of various diseases, including cancer (11–13). The Geriatric Nutritional Risk Index (GNRI) is a simple and convenient nutritional assessment tool that utilizes serum albumin levels and the ratio of actual to ideal body weight (14–16). It has been associated with mortality in elderly patients as well as those with cardiovascular disease and various cancers (17–20). In the field of cancer treatment, GNRI has been related to survival following chemotherapy, surgery, or chemoradiotherapy in various malignancies (21–23). Additionally, although GNRI was initially created for older people, it can be used for younger populations as well (24–26).

However, the effectiveness of the GNRI in predicting the efficacy of ICI treatment remains a subject of debate. Therefore, the purpose of our study was to comprehensively assess the prediction value of GNRI in ICI-treated cancer patients. The outcomes of this research will contribute to the development of effective treatment strategies that enable precise and cost-effective therapies with minimal adverse effects.

2. Methods

2.1. Strategies for literature search

The current study followed the guidelines outlined in the PRISMA statement (27). On July 1, 2023, a comprehensive literature search was conducted using PubMed, EMBASE, and the Cochrane Library. Supplementary Table S1 provides a comprehensive description of the search strategies. In addition, Google Scholar was used to research grey literature, and the reference lists of eligible studies were manually screened.

2.2. Criteria for inclusion and exclusion

Strict inclusion criteria were applied in this study, focusing on articles that evaluated the prognostic value of GNRI in cancer patients undergoing ICI treatment. Only articles reporting relevant outcomes such as OS, PFS, ORR, and DCR were included. Conference abstracts were excluded from the analysis. We chose the trials with the most thorough data and robust methodology when studies had overlapping patients (28).

2.3. Data extraction and quality assessment

A comprehensive range of information was extracted from the selected articles, including author names, study design, duration and location of the study, drugs used for treatment, cancer type, sample size, patient demographics (age and gender), and outcomes. In cases where both univariate and multivariate analyses were conducted, greater emphasis was placed on the data from multivariate analyses. The quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS), with literature scoring 6 or above considered high-quality (29).

2.4. Statistical methods

For statistical analysis, Stata 15.0 software was used. We used the chi-squared test to determine heterogeneity, and when the p-value was less than 0.1, we selected a random-effects model; otherwise, we selected a fixed-effects model. To calculate publication bias, we used the Egger's and Begg's tests. We also conducted a sensitivity analysis, eliminating each study separately, to assess the validity of the results.

3. Results

3.1. Characteristics of studies

We were left with 23 publications to evaluate in full text after removing duplicates and analyzing titles and abstracts. A total of eleven studies with 1,417 patients were included in the final analysis (26, 30–39). Figure 1 uses a PRISMA flowchart to show the research selection process. Table 1 lists all of the specific characteristics of the accepted studies. Using the NOS, the risk of bias in each of the included studies was evaluated; scores between 6 and 8 denote a low risk of bias.

Three studies of urothelial cancer, two studies of non-small cell lung cancer, hepatocellular carcinoma, and head and neck squamous cell carcinoma were included in this study. Most of the studies were retrospective designs implemented in Japan. The timeframe for publication of the article is 2020–2023.

3.2. Baseline GNRI levels and OS

We sought to investigate the relationship between GNRI levels (as a binary categorical variable) and OS in patients with solid tumors receiving ICI by the analysis of data from seven studies involving 567 participants. We found patients with low GNRI had a shorter OS compared to patients with high GNRI (HR: 2.64, 95% CI: 2.08–3.36, $p < 0.001$, Figure 2A). The analysis above used a fixed effects model because there was no significant heterogeneity ($I^2 = 0\%$, $p = 0.529$). No publication bias in the aforementioned results was verified by Begg's and Egger's tests (Begg's: $p = 0.230$, Egger's: $p = 0.174$). By gradually removing each study and analyzing the effects on the combined findings, we carried out a sensitivity analysis to assess the reliability of our findings. Our findings showed that the pooled HR was not significantly affected by the deletion of any particular study, ranging from 2.46 [95% CI: 1.89–3.20, after removing Liu et al. (39)] to 2.89 [95% CI: 2.16–3.87, after removing Haas et al. (32), Figure 2B].

In addition, two studies with 320 patients analyzed the GNRI as a triple categorical variable based on cut-off values of 98 and 82. We found that the lower the GNRI, the shorter the OS of cancer patients (<82 vs. >98, HR: 3.21, 95% CI: 1.99–5.15, $p < 0.001$, Figure 3A; 98–82 vs. >98, HR: 1.86, 95% CI: 1.39–2.50, $p < 0.001$, Figure 3B).

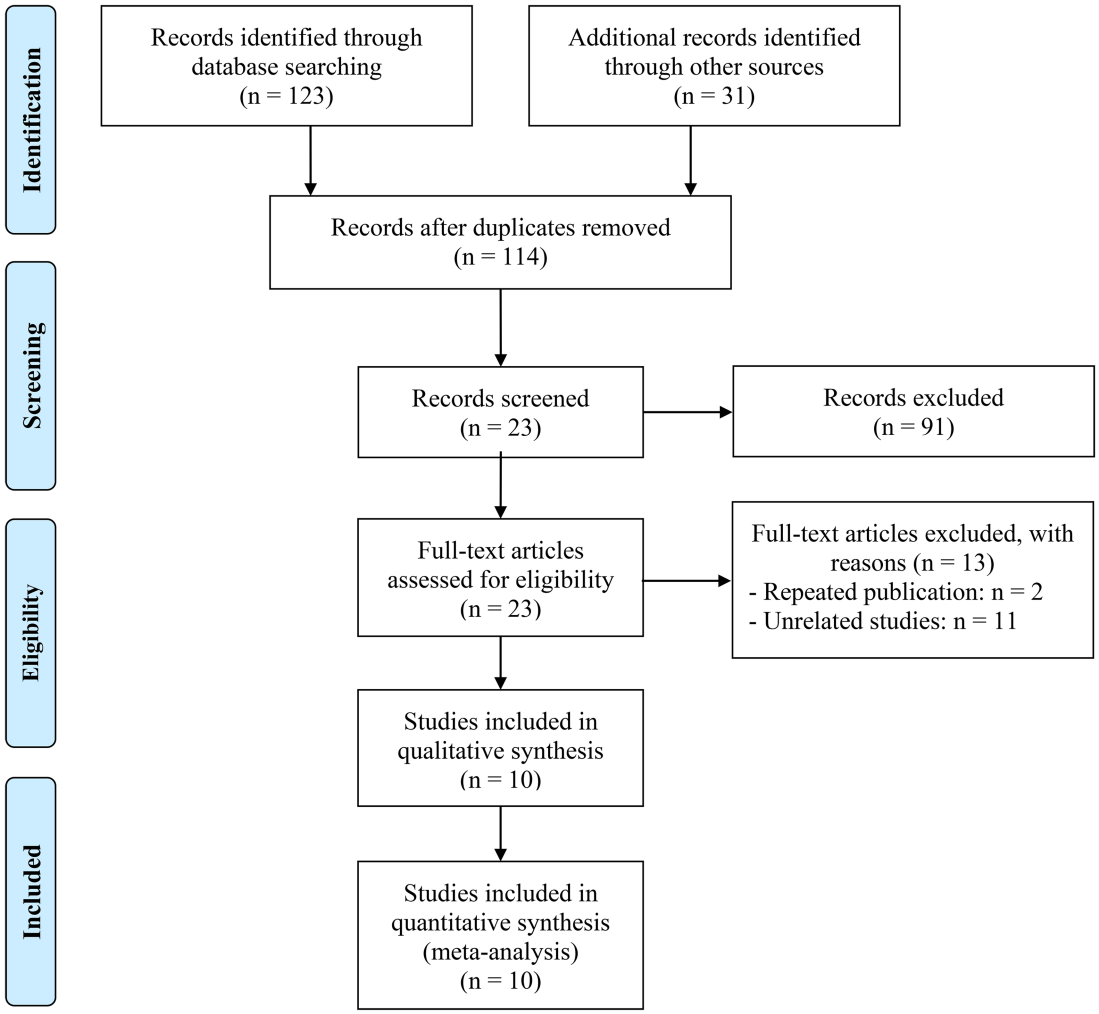

FIGURE 1
The flow diagram for identifying eligible studies.

3.3. Baseline GNRI levels and PFS

To determine the connection between GNRI levels and PFS in cancer patients receiving ICIs, we analyzed six studies involving 541 individuals. The results indicated that patients with low GNRI had a higher risk of progression (HR: 1.87, 95% CI: 1.46–2.41, $p < 0.001$, Figure 4A) than those with high GNRI. Because there was no significant heterogeneity ($I^2 = 6.8\%$, $p = 0.373$), the analysis presented above utilized a fixed effects model. Notably, no publication bias was found using the Begg's and Egger's tests (Begg's: $p = 0.452$, Egger's: $p = 0.294$). According to the findings of the sensitivity analysis, leaving out any of the studies had no significant effect on the pooled HR (Figure 4B).

3.4. Baseline GNRI levels and ORR

Using data from seven studies with a total of 1,037 participants, we analyzed the link between GNRI levels and ORR in cancer patients receiving ICI. Patients with low GNRI had lower ORR than patients with high GNRI (OR: 0.46, 95% CI: 0.33–0.65, $p < 0.001$, Figure 5A). Because there was no significant heterogeneity ($I^2 = 0\%$, $p = 0.446$), a fixed effects model was used in the analysis ($I^2 = 0\%$, $p = 0.446$). Begg's and Egger's tests showed no evidence of publication bias in the results mentioned above (Begg's: $p = 0.548$, Egger's: $p = 0.656$). We performed a sensitivity analysis to evaluate the stability of our results by gradually deleting each study and examining the implications for the overall findings. Our results showed that the pooled HR was not significantly impacted by the deletion of any individual research (Figure 5B).

3.5. Baseline GNRI levels and DCR

We then combined four studies with 814 individuals to investigate the relationship between GNRI levels and DCR in cancer patients. We used a fixed-effect model for our analysis because, as shown in Figure 6A ($I^2 = 0.0\%$, $p = 0.732$), there was no discernible heterogeneity in the results. Patients with low GNRI had a lower DCR than those with high GNRI (OR: 0.42, 95% CI: 0.29–0.61, $p < 0.001$, Figure 6A). No significant publication bias was discovered in the analysis (Begg's: $p = 1.000$; Egger's: $p = 0.467$). Sensitivity analyses confirmed no significant effect on the pooled results after deleting any of the studies (Figure 6B).

TABLE 1 Main characteristics of the studies included.

Study	Study design	Study period	Study region	ICI treatment	Cancer type	Sample size	Age (years)	Gender (male/female)	Outcome
Zheng et al. (38)	*R*	03/2020–06/2022	China	Tislelizumab	CC	115	54 (32–70)[a]	0/115	PFS, ORR
Liu et al. (39)	*R*	01/2018–12/2021	China	ICIs treatment	HCC	101	57.8 ± 9.29	83/18	OS, PFS
Tanaka et al. (37)	*R*	04/2017–12/2020	Japan	Nivolumab	HNSCC	42	60.5 (26–81)[d]	36/6	OS, ORR, DCR
Haas et al. (32)	*R*	2016–2021	Austria	Nivolumab or pembrolizumab	HNSCC	162	65 (28–85)[a]	115/47	OS, PFS, ORR, DCR
Hiraoka et al. (33)	*R*	09/2020–07/2022	Japan	Atezolizumab + Bevacizumab	HCC	525	74 (68–80)[b]	420/105	ORR, DCR
Fujiwara et al. (31)	*R*	09/2013–08/2020	Japan	Nivolumab	RCC	56	62 (56–69)[b]	42/14	OS, PFS, ORR
Karayama et al. (35)	*P*	07/2016–12/2018	Japan	Nivolumab	NSCLC	158	69 (40–83)[a]	129/29	OS, PFS
Isobe et al. (34)	*R*	07/2009–02/2021	Japan	Pembrolizumab	UC	94	72 (47–85)[a]	77/17	OS
Sonehara et al. (26)	*R*	02/2016–10/2020	Japan	Nivolumab, Pembrolizumab, Atezolizumab	NSCLC	85	39/46[c]	68/17	OS, PFS, ORR, DCR
Shimizu et al. (36)	*R*	12/2017–08/2019	Japan	Pembrolizumab	UC	27	73 (52–82)[a]	23/4	OS, PFS
Etani et al. (30)	*R*	01/2018–10/2019	Japan	Pembrolizumab	UC	52	71 (46–84)[a]	43/9	ORR

[a]Medians (ranges).
[b]Medians (interquartile range).
[c]≥ 70 vs. < 70.
[d]Mean(ranges); *R*, retrospective study; *P*, prospective study; CC, cervical cancer; HNSCC, head and neck squamous cell carcinoma; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; NSCLC, non-small cell lung cancer; UC, urothelial cancer; ICIs, immune checkpoint inhibitors; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate.

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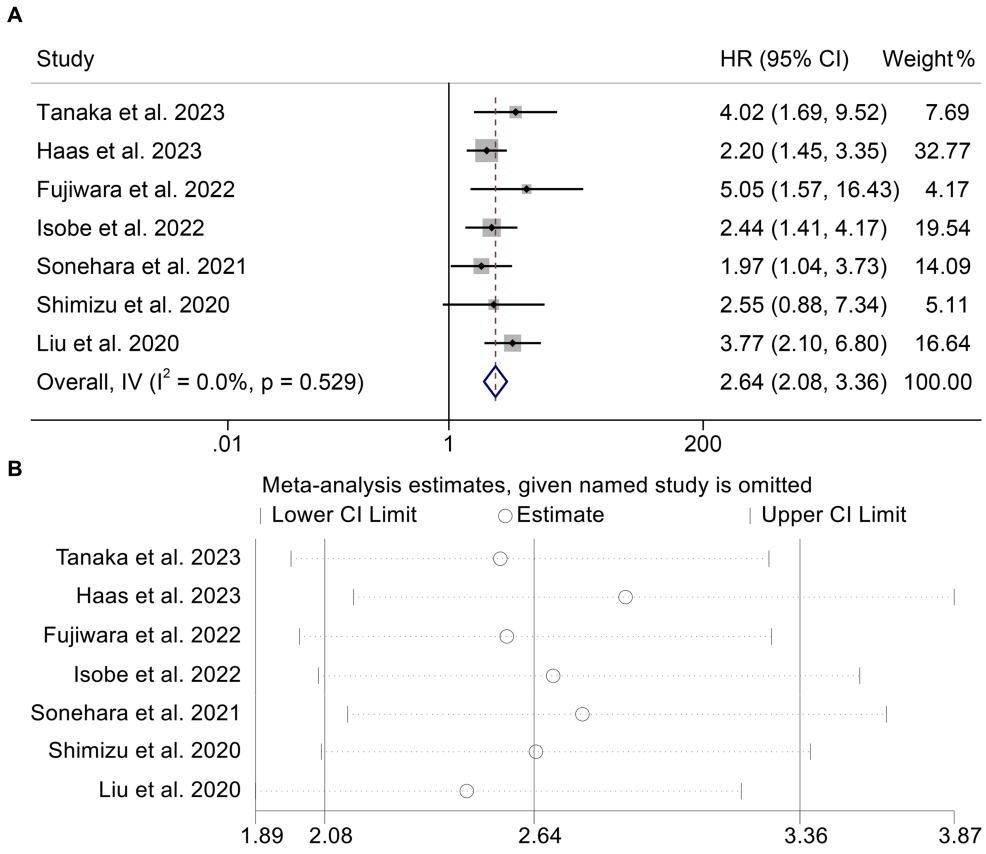

FIGURE 2
Forest plots of the relationship between geriatric nutritional risk index and overall survival **(A)**. Sensitivity analysis of the association between geriatric nutritional risk index and overall survival **(B)**. HR, hazard ratio; CL, confidence interval.

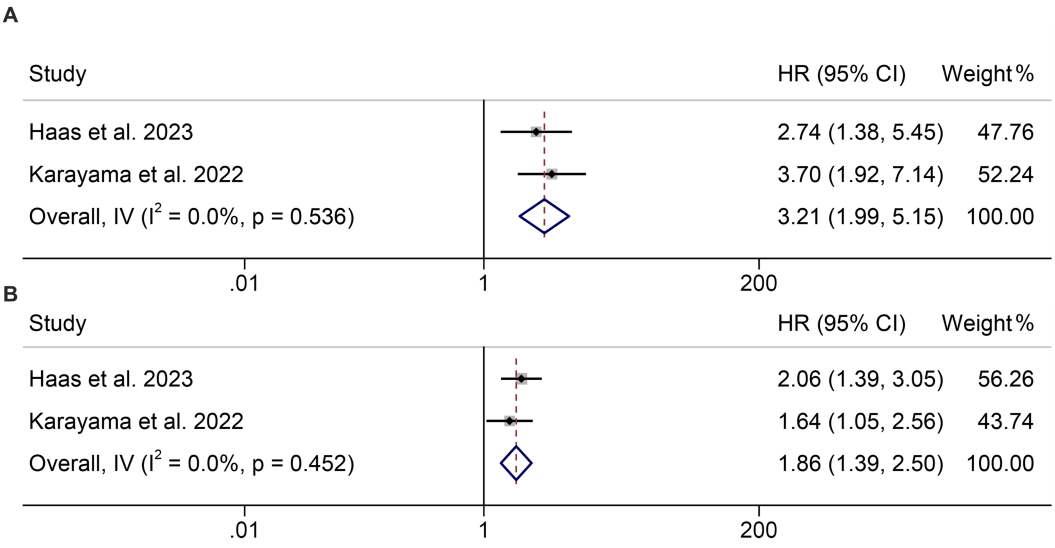

FIGURE 3
Forest plots of the relationship between geriatric nutritional risk index and overall survival. **(A)** <82 vs. >98; **(B)** 98–82 vs. >98. HR, hazard ratio; CL, confidence interval.

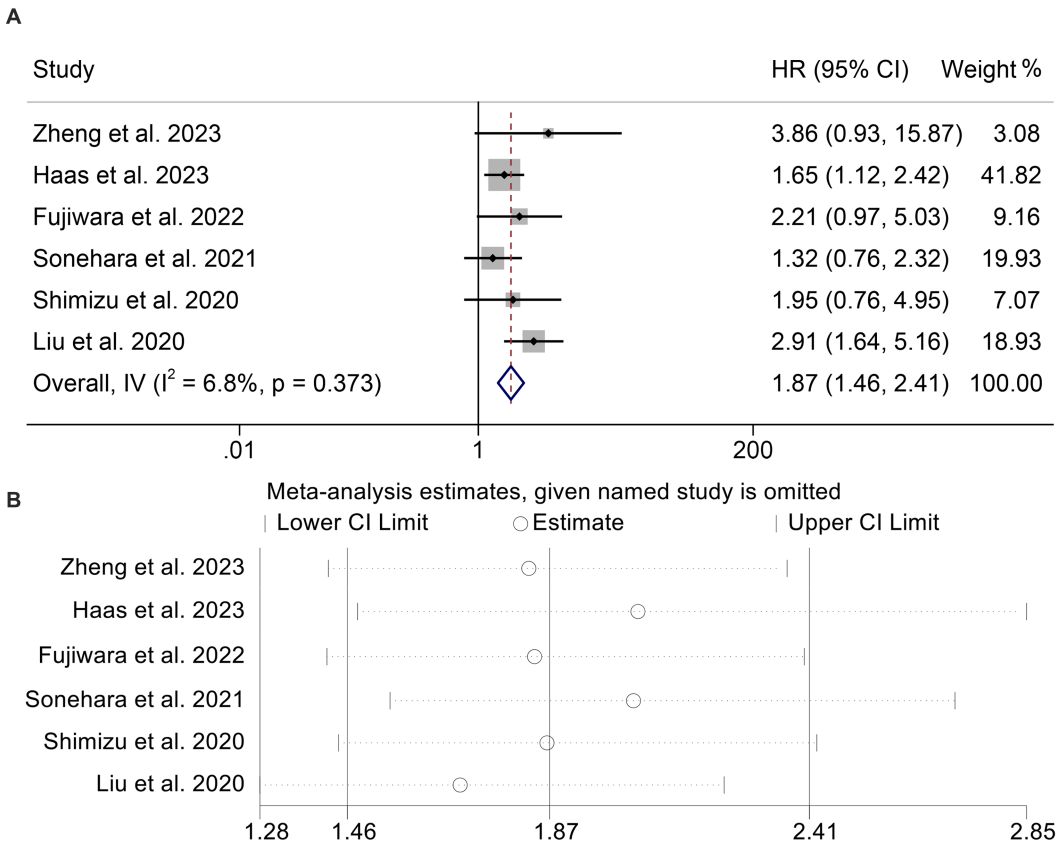

FIGURE 4
Forest plots of the relationship between geriatric nutritional risk index and progression-free survival **(A)**. Sensitivity analysis of the association between geriatric nutritional risk index and progression-free survival **(B)**. HR, hazard ratio; CL, confidence interval.

4. Discussion

The aim of our study was to examine the predictive value of GNRI in ICI-treated cancer patients. We found a robust correlation between low GNRI levels and poorer OS and PFS, as well as a lower ORR and DCR. GNRI can be measured cost-effectively, readily, and noninvasively to evaluate nutritional status. Our data suggested that the potential utility of GNRI in predicting the effectiveness of ICI therapy is worth considering.

Malnutrition is a prevalent issue affecting a considerable proportion of patients with advanced diseases, ranging from 30 to 85% (40). This complex condition encompasses reduced protein reserves, caloric depletion, and compromised immune defenses (40, 41). Despite the absence of defined criteria for malnutrition in cancer patients, various nutritional screening tools are currently used to estimate the outcomes of hemodialysis or the prognosis of patients with tumors or infections (42, 43). One well-established screening tool is the subjective global assessment, which has been validated and widely utilized for screening purposes. However, its subjective nature requires examiners to undergo extensive training to ensure consistent and reliable results, given the complexity of the assessment process. For elderly patients, malnutrition assessment has commonly relied on tools such as the Mini-Nutritional Assessment (MNA) or MNA-Short Form. These methods demand extended screening periods and lack specific biological factors (40, 44). In contrast, the GNRI offers a more straightforward approach, relying solely on serum albumin levels, height, and weight measurements for each individual. Prior studies have underscored the value of GNRI in evaluating the physical well-being of elderly patients with chronic illnesses (45). In our research, we found compelling evidence that the GNRI serves as a valuable and convenient predictive biomarker for survival outcomes in ICI-treated cancer patients.

Along with controlling osmotic pressure and transporting bioactive molecules, albumin, a GNRI component, is also recognized to have immunomodulatory properties. For instance, albumin prevents neutrophils from overreacting by inhibiting inflammation (46, 47). Albumin suppresses neutrophil extracellular trap formation in the tumor microenvironment, where neutrophils emit neutrophil extracellular traps, facilitating tumor development and metastasis (48–50). Furthermore, albumin possesses antioxidant capabilities and decreases oxidative stress in tissues (46, 47). Through altered cytokine signaling, increased immunosuppressive immune cell activity, and decreased cytotoxic lymphocytes, oxidative stress causes immunosuppression in the tumor microenvironment (51). It has been demonstrated that under oxidative stress, regulatory T cells cause significant immunosuppression, which eliminates the anticancer immunity response by PD-L1 inhibition *in vivo* (52). The

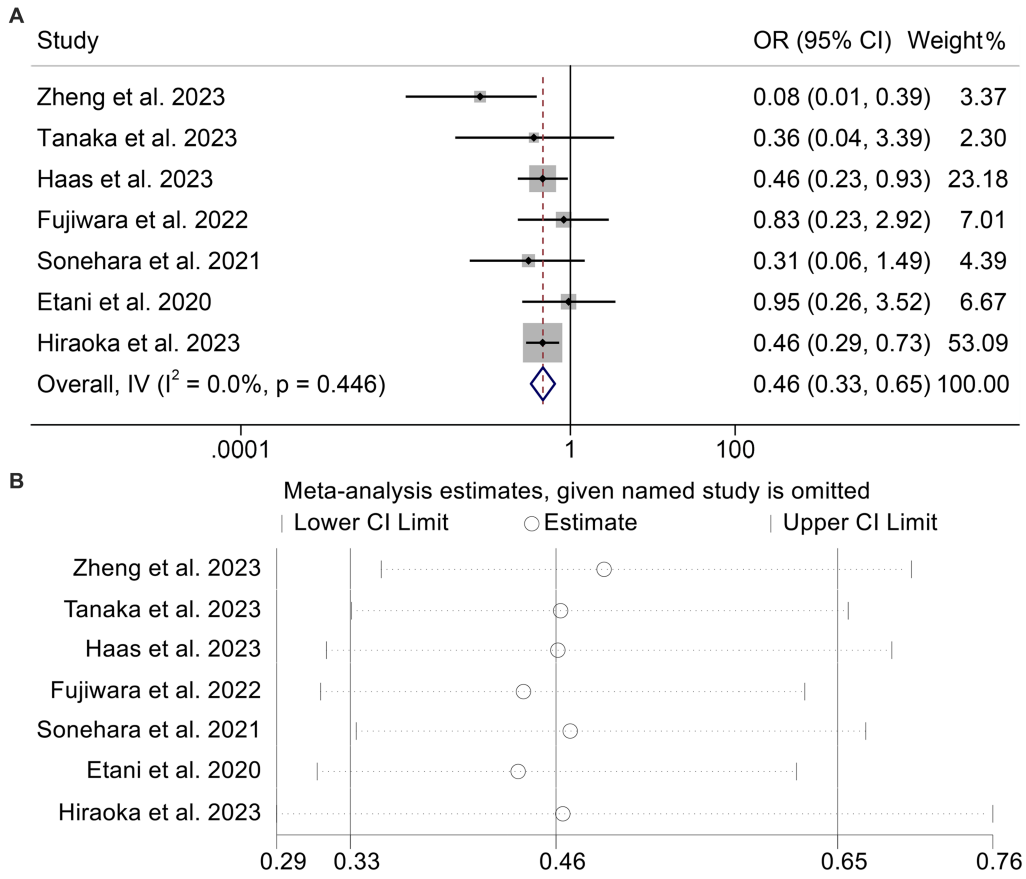

FIGURE 5
Forest plots of the relationship between geriatric nutritional risk index and objective response rate **(A)**. Sensitivity analysis of the association between geriatric nutritional risk index and objective response rate **(B)**. OR, odds ratio; CL, confidence interval.

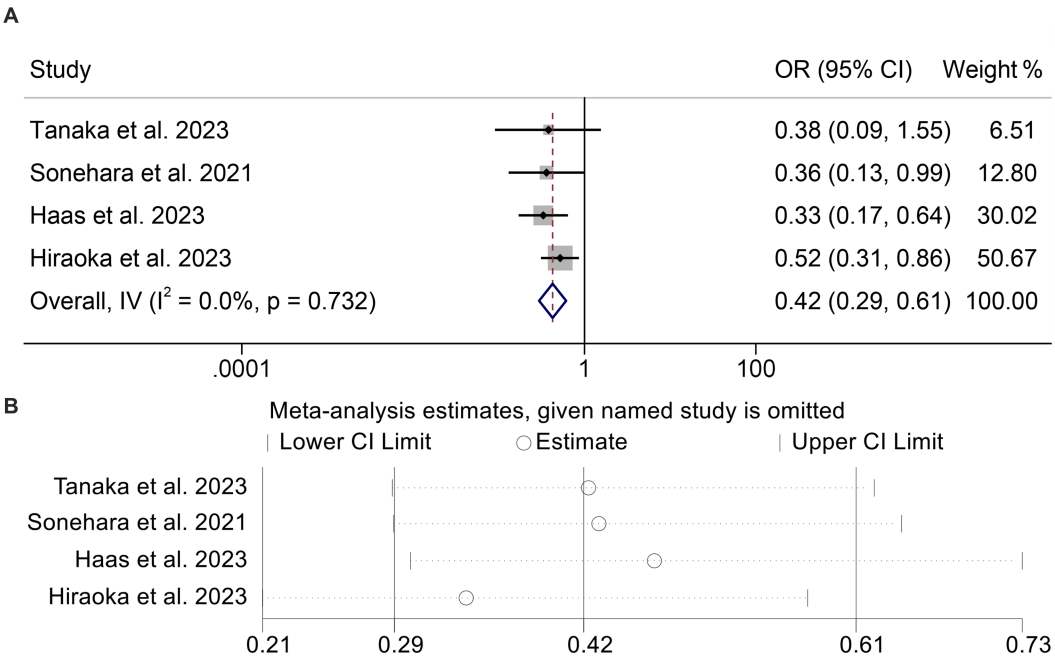

FIGURE 6
Forest plots of the relationship between geriatric nutritional risk index and disease control rate **(A)**. Sensitivity analysis of the association between geriatric nutritional risk index and disease control rate **(B)**. OR, odds ratio; CL, confidence interval.

immunomodulatory activity of albumin may favor tumor immunity in the tumor microenvironment.

Another element of GNRI, body weight, has drawn interest as a potential indicator of ICI effectiveness. As compared to control diet-fed mice, obese animals brought on by diet showed superior responses to anti-PD-1 therapy (52). It is believed that factors related to adipose tissue contribute to cancer immunity, despite the fact that the precise mechanisms underlying the increased efficacy of ICI therapy in obesity have not been elucidated (53). Furthermore, it has been demonstrated that improved survival outcomes in overweight patients can be attributed to the role of white adipose tissue as a source of cytokines and chemokines that induce and/or coordinate host defenses (54, 55). Adipose tissue can modulate the balance between helper T-cell (Th)1 and Th2 responses, downregulating regulatory T-cell activation through adiponectin, promoting the presence of pro-inflammatory macrophages, activating T-cells, and enhancing the inflammatory state through the CD40 pathway (56–58). Therefore, the preclinical studies mentioned above fully support the idea that high GNRI levels contribute to a better immune response.

Notably, in addition to PD-(L)1 and CTLA-4, TGF-β also promotes immune escape. In recent years, anti-TGF-β/PD-L1 bispecific antibodies such as YM101 and BiTP have been developed (59, 60). However, there are no studies examining the relationship between GNRI and the efficacy of anti-TGF-β/PD-L1 bispecific antibodies. Therefore, only cancer patients treated with PD-(L) or CTLA4 were included in this study, and the relationship between GNRI and anti-TGF-β/PD-L1 bispecific antibodies needs to be further investigated.

In conclusion, this study demonstrates that GNRI is an important prognostic biomarker for ICI-treated cancer patients. This simple classification may be useful in clinical practice. Our evidence of interrogative medicine needs to be validated by further external multicenter randomized controlled studies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

LZ: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. KW: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft. TK: Investigation, Software, Writing – original draft. WD: Supervision, Writing – review & editing. PH: Conceptualization, Methodology, Validation, Visualization, Writing – review & editing. WW: Investigation, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1286583/full#supplementary-material

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Effect of sarcopenia on survival in patients after pancreatic surgery: a systematic review and meta-analysis

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Background: Numerous studies have reported sarcopenia to be associated with unfavorable outcomes in patients who have undergone pancreatectomy. Therefore, in this meta-analysis, we examined the relationship between sarcopenia and survival after pancreatic surgery.

Methods: PubMed, Embase, and Cochrane Library were searched for studies that examined the association between sarcopenia and survival after pancreatic surgery from the inception of the database until June 1, 2023. Hazard ratio (HR) for overall survival (OS) and/or progression-free survival (PFS) of sarcopenia and pancreatic surgery were extracted from the selected studies and random or fixed-effect models were used to summarize the data according to the heterogeneity. Publication bias was assessed using Egger's linear regression test and a funnel plot.

Results: Sixteen studies met the inclusion criteria. For 13 aggregated univariate and 16 multivariate estimates, sarcopenia was associated with decreased OS (univariate analysis: HR 1.69, 95% CI 1.48–1.93; multivariate analysis: HR 1.69; 95% CI 1.39–2.05, I^2 = 77.4%). Furthermore, sarcopenia was significantly associated with poor PFS of pancreatic resection (Change to univariate analysis: HR 1.74, 95% CI 1.47–2.05; multivariate analysis: HR 1.54; 95% CI 1.23–1.93, I^2 = 63%).

Conclusion: Sarcopenia may be a significant prognostic factor for a shortened survival following pancreatectomy since it is linked to an elevated risk of mortality. Further studies are required to understand how sarcopenia affects long-term results after pancreatic resection.

Systematic review registration: Registration ID: CRD42023438208 https://www.crd.york.ac.uk/PROSPERO/#recordDetails.

KEYWORDS

sarcopenia, pancreatectomy, survival, cancer, meta-analysis

Introduction

Pancreatectomy is associated with good outcomes for numerous benign, premalignant, and malignant pancreatic tumors. However, it remains a challenging surgery with high morbidity due to postoperative complications and a low survival rate, particularly when performed for oncologic purposes (1, 2). These results can be attributed to the pancreatic gland texture (3), surgical nutritional support (4), the requirement for blood transfusions (5), and surgeon volume (6). Sarcopenia, meaning the degenerative loss of skeletal muscle mass, can be assessed through computed tomography (CT) measures of the psoas area and muscle density (7). Sarcopenia is linked to longer hospital stays, a higher risk of postoperative complications, and an increased risk of disability and recurrent hospitalization (8). Other detrimental effects of sarcopenia include mobility limitations, chronic illness, premature death, and frailty (9). Sarcopenia has recently been reported to possibly predict poor results in patients undergoing major abdominal surgeries (10–13). Despite some contradicting evidence, existing information on the relationship between sarcopenia and mortality in individuals after pancreatic surgery suggested that sarcopenia usually increases mortality in such patients (14–16). Moreover, a previously published International Study Group on Pancreatic Surgery Consensus Statement on Nutritional Support in Pancreatic Surgery reported that sarcopenia is a significant predictor of short-term and long-term outcomes and that long-term survival in patients with sarcopenia has consistently been low. However, the consensus statement is primarily based on observational research with a small sample size (17). Therefore, we conducted this systematic review and meta-analysis to further understand the effect of sarcopenia on patient survival following pancreatic resection.

Methods

The study has been reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines (18, 19).

Search strategy

PubMed, Embase, and the Cochrane Library databases were thoroughly searched for relevant papers released from the of date the database's inception till June 1, 2023. The search phrases were ('Sarcopenia' OR 'Muscular Atrophy') AND ('Pancreaticoduodenectomy' OR 'Pancreatectomy' OR 'Pancreaticojejunostomy'). Furthermore, all references in the eligible publications were carefully reviewed for new relevant studies. The search was conducted according to PRISMA Guidelines and included PICOs and cited references of PRISMA Guidelines (20).

Selection criteria

Articles with data on the HR with a 95% confidence interval (CI) of sarcopenia and survival of pancreatic surgery were included. When the same data were used in two or more studies, only the most detailed study was selected. Studies not published in English and letters, case reports, reviews, expert comments, or editorials were excluded. Two researchers (LZ and SL) reviewed the titles and abstracts of all selected studies. Next, both researchers separately downloaded and rescreened the entire texts of any possibly relevant articles. Additionally, the reference lists of those papers were also screened for additional relevant articles that could be included.

Data extraction

Every article was critically assessed by the two researchers (LZ and SL). For each article, we collected the following data: (1) study location, (2) sample size, (3) mean age of the sample, (4) sex ratio in every sample, (5) surgical procedures, (6) definitions of sarcopenia, (7) cut-off values of sarcopenia, (8) outcome of the research, including OS and/or PFS patients with sarcopenia who underwent pancreatic surgery, and (9) univariate and/or multivariate HR.

Quality assessment

This meta-analysis utilized the Newcastle Ottawa scale (NOS) (21) to evaluate the quality of the included studies. The scale rates three categories, namely selection, comparability, and outcome, with a total of nine stars. An appropriate participant selection for the exposure and non-exposure cohorts was represented by 4 stars, while the comparability of the cohort was reflected by 2 stars. Lastly, three stars reflected the evaluation of the result and follow-up. Studies that scored >5 stars had moderate-to-high quality.

Statistical analysis

Data on univariate and/or multivariate HR and 95% CI were extracted from the qualified studies and pooled to calculate an aggregating magnitude of effect by using fixed or random effect models according to the study's heterogeneity. Univariate and multivariate HR were analyzed separately. For studies that provided multivariate analysis data, the HR with the most adjusted factors was used. The I^2 statistic was applied to assess statistical heterogeneity between studies. The projected percentages of low, moderate, and high heterogeneity were 25, 50, and 75%, respectively. A sensitivity analysis was also performed to see if the excluded studies had a substantial influence on the result. When more than 10 original publications were included, publication bias was examined using funnel plotting and Egger's test. All analyses were performed using STATA (version 16.0), and statistical significance was set at $p < 0.05$.

Results

Search results

A flowchart depicting the literature screening procedure is shown in Figure 1. We identified 695 studies in the databases. After excluding studies that failed to meet the inclusion criteria and duplicate articles,

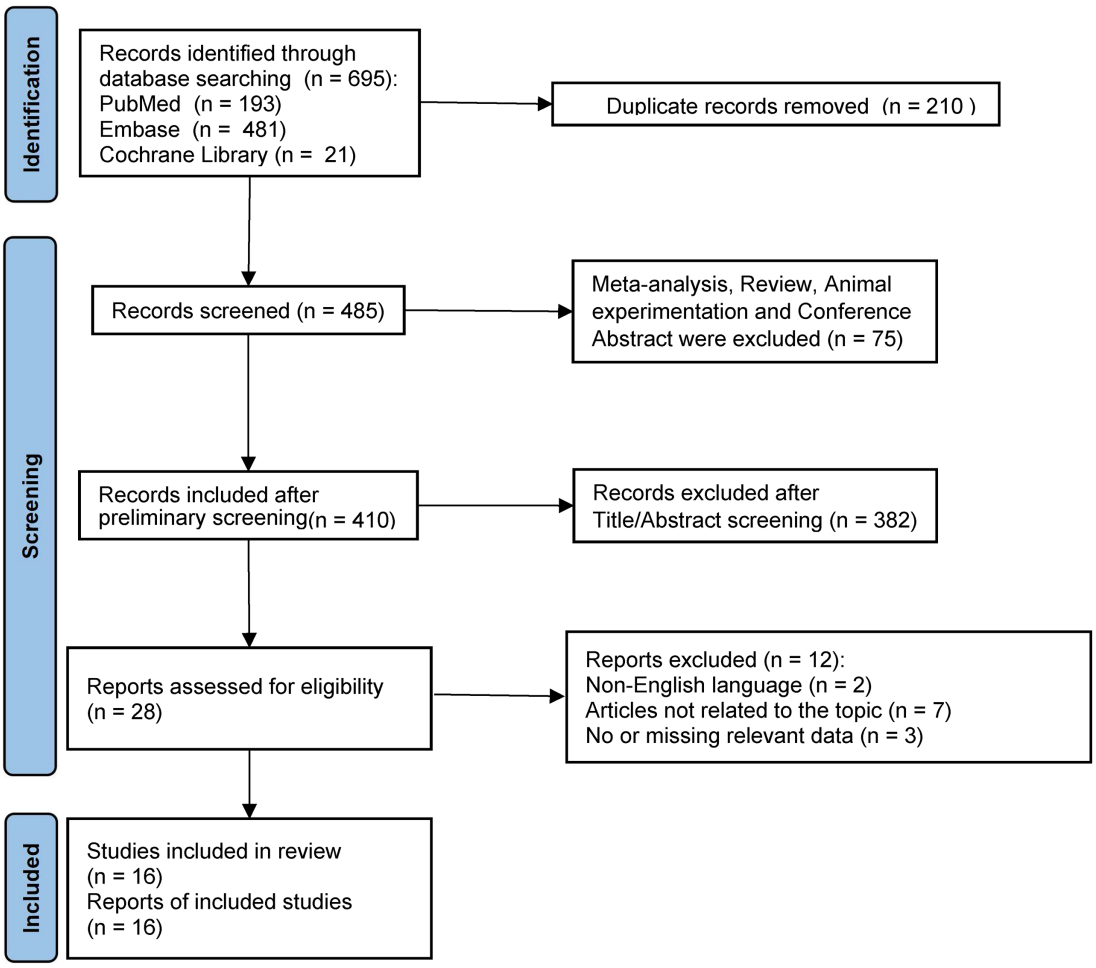

FIGURE 1
Process flow diagram for choosing studies for inclusion in the literature.

16 studies (13–16, 22–33) met the inclusion requirements for the analyses. A meta-analysis and systematic review were performed of these 16 studies.

Study characteristics

All 16 included studies were c cohort analyses comprising a total of 4,250 patients included between 1996 and 2022. The sample sizes ranged from 83–763, and these studies had an average quality scoring of 7.4 stars. In total, multivariate OS results for 16 studies [13 studies (13–16, 22, 23, 25–31) were assessed for univariate estimates only] and multivariate PFS results for 6 studies (16, 23, 26, 30, 31, 33) were analyzed [five studies (16, 23, 26, 30, 31)were assessed for univariate estimates only]. The three main surgical procedures performed in the included studies were distal pancreatectomy (DP), total pancreatectomy (TP), and pancreaticoduodenectomy (PD). In addition to malignant tumors, such as pancreatic adenocarcinoma (PDAC) and periampullary cancer, benign pancreatic lesions like pancreatitis in the studies were also examined. Table 1 summarizes the basic characteristics of each included study. The sources of funding for each study included in the review are shown in Supplementary Table S1.

Meta-analysis results

Overall survival of patients after pancreatic surgery

Sarcopenia was predictive of increased mortality risk among studies that provided a univariate HR (HR 1.69, 95% CI 1.48–1.93, $p < 0.001$, $I^2 = 38\%$; Figure 2). Additionally, sarcopenia was linked to a higher mortality risk according to the results of the aggregated multivariate HR (HR 1.69; 95% CI 1.39–2.05, $I^2 = 77.4\%$; Figure 3) analysis. To investigate potential causes of the high heterogeneity in the multivariate analyses, a subgroup analysis was performed. Both non-Asian (HR 1.82, 95% CI 1.28–2.58; Figure 4) and Asian (HR 1.59, 95% CI 1.26–2.00; Figure 4) studies demonstrated a pooled increased mortality risk associated with sarcopenia, and the impact of sarcopenia on OS after pancreatic surgery in non-Asians was more pronounced than in Asians.

Progression-free survival of patients with pancreatic cancer after pancreatic surgery

Six studies assessed the relationship between PFS and sarcopenia after pancreatic cancer surgery. Among the studies that reported a univariate HR, the results suggested that sarcopenia reduces PFS in patients after pancreatectomy (HR 1.74; 95% CI 1.47–2.05, $p < 0.001$,

TABLE 1 Characteristics of the included studies.

Study	Country	Average age	Sample size	percentage of sarcopenic patients	Male/ Female	Study interval	Disease	Types of resection	Overall survival (1,3,5 years)	Sarcopenia measure used and cut-off values	Study quality
Amini 2015	USA	67 (58–74)	763	152 (19.9%)	418/345	1996–2014	PDAC	PD, DP, TP	76.4, 34.9, 23.9%	TPV (cm^2/m^2) M: <17.2 *F* < 12.0	6★
Okumura 2015	Japan	67 (32–87)	230	64 (27.8%)	124/106	2004.1–2013.6	PDAC	PD, DP, TP, PPPD, SSPPD	–	PMI (cm^2/m^2) M: <5.9\u00B0F: <4.1	7★
Onesti 2016	USA	63.8 (18–93)	270	-	144/126	2005.7.1–2012.12.31	PDAC, DCC, Others	PD, DP, TP	–	LPMA (cm^2) M: 920–1896\u00B0F: 601–1,131	8★
Ninomiya 2017	Japan	65.4 ± 10.1	265	170 (64.2%)	164/101	2005.5–2014.11	PDAC	PD, DP, TP	63.0, 18.9, 5.2%	SMI (cm^2/m^2) M: <43.75\u00B0F: <38.5	8★
Okumura 2017	Japan	68 (61–74)	301	120 (39.9%)	168/133	2004–2015	PC	PD, DP, TP	70.8, 21.9, 10.0%	SMI (cm^2/m^2) M: <47.1\u00B0F: <36.6	7★
Choi 2018	Korea	64.4 ± 9.3	180	60 (33.3%)	98/82	2008–2015	PC	PD, DP	67.3, 23.9, 16.0%	SMI (cm^2/m^2) M: <45.3 F: <39.3	8★
El Amrani 2018	France	61 ± 12	107	50 (47.6%)	51/56	2011.5–2015.7	PDAC, DCC, Others	PD, DP, TP	–	SMI (cm^2/m^2) M: <52.4 F: <38.5	6★
Sugimoto 2018	USA	65 (38–88)	323	200 (61.9%)	176/147	2000.3–2015.2	PDAC	PD, DP, TP	–	SMI (cm^2/m^2) M: <55.4 F: <38.9	8★
Gruber 2019	Austria	68 (34–87)	133	78 (58.6%)	68/65	2005–2010	PDAC	PD, DP	–	SMI (cm^2/m^2) M: <52.4 F: <38.5	7★
Ryu 2020	Korea	62.51 (24–88)	548	252 (46.0%)	326/222	2007.1–2016.6	PC	PPPD, PD, SSPPD	–, 26.0%	PMI (cm^2/m^2) M: <50.18\u00B0F: <38.63	8★
Peng 2021	China	66.2 ± 11.9	116	20 (17.2%)	68/48	2005.10–2018.8	PDAC	PD	56.0, 4.3, 0.0%	SMI (cm^2/m^2) M: <42.2 F: <33.9	7★
Aoki 2022	Japan	72.35 ± 8	83	14 (16.9%)	47/36	2016.1–2020.3	PC	–	–	SMI (kg/m^2) M: <7 F: <6	7★
Kim 2022	Korea	63.6 ± 9.6	347	188 (54.2%)	202/145	2014.1–2017.1	PDAC	–	82.4, 45.8, 20.7%	SMI (cm^2/m^2) M: <42.2 F: <33.9	8★
Rom 2022	Israel	67 (61–75)	111	30 (27.0%)	59/52	2005–2017	PDAC	PD, DP	–	SMI (cm^2/m^2) M: <44.35\u00B0F: <34.82	7★
Shen 2023	China	59.9 ± 10.3	614	318 (61.6%)	368/246	2015.1–2022.5	PDAC	PD, DP, TP	–	SMI (cm^2/m^2) M: <52.4 F: <38.5	8★
Tazeoglu 2023	Turkey	60.45 ± 13.08	179	83 (46.3%)	105/74	2012.1–2022.1	PC	PD	–	PMI (cm^2/m^2) M: <5.3 F: <3.6	8★

PDAC, Pancreatic ductal adenocarcinoma; DCC, distal cholangiocarcinoma; PC, pancreatic cancer; Others: including ampullary cancer, solid-pseudopapillary tumor, chronic pancreatitis, intraductal papillary mucinous neoplasm, neuroendocrine tumor, gastrointestinal stromal tumor; PD, pancreatoduodenectomy; DP, Distal pancreatectomy; TP, total pancreatectomy; PPPD, pylorus-preserving PD, SSPPD, subtotal stomach-preserving PD; M, male; F, female; TPV, total psoas volume; PMI, psoas muscle mass index; LPMA, lean psoas muscle area; SMI, skeletal muscle mass index; –, not given or reported in the study.

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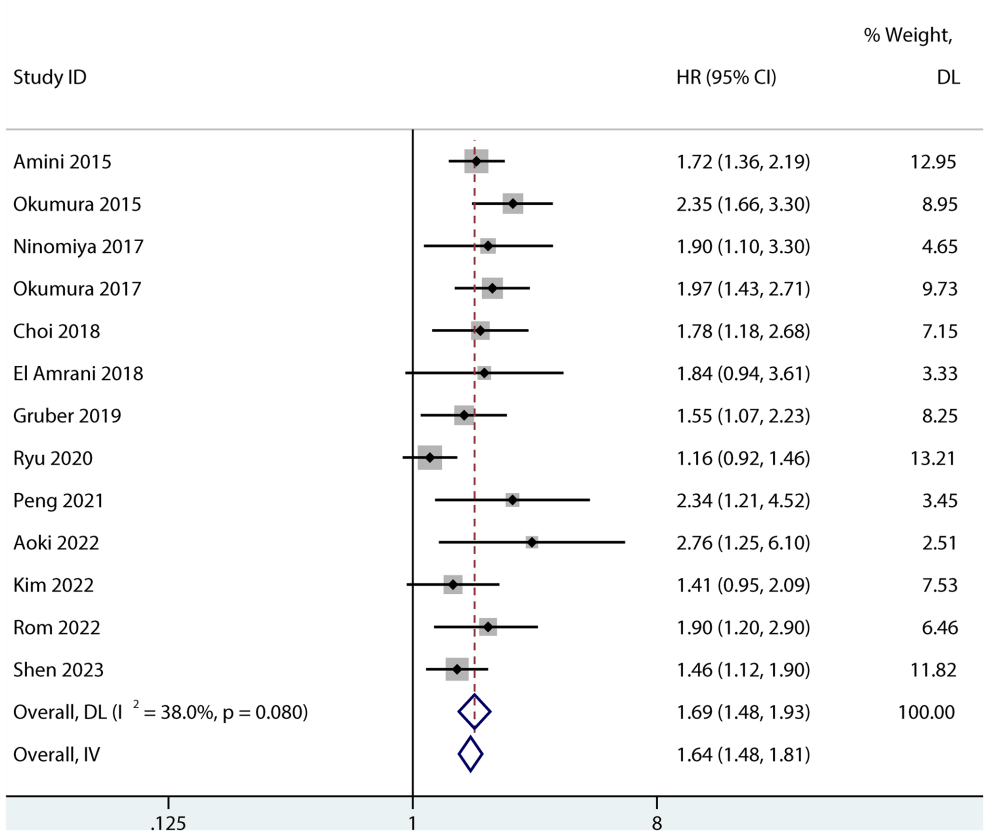

FIGURE 2
Forest plot of the univariate association between sarcopenia and OS for patients after pancreatic surgery.

$I^2 = 0.0\%$; Figure 5). Sarcopenia also had a negative influence on PFS after pancreatic surgery even after risk factor adjustment (1.54; 95% CI 1.23–1.93, $I^2 = 63\%$; Figure 6). However, no subgroup analysis for PFS was done due to the small number of primary studies.

Overall survival of patients with pancreatic adenocarcinoma after pancreatic surgery

The influence of sarcopenia on the postoperative OS of patients with PDAC was reported in nine studies (13, 22, 23, 25, 28–31, 33). The aggregated multivariate HR analysis indicated that sarcopenia was associated with lower postoperative OS of patients with PDAC (HR 1.47; 95% CI 1.27–1.72, $I^2 = 44.6\%$; Figure 7).

Sensitivity analysis and publication bias

Sensitivity analyses of studies that conducted univariate and multivariate analyses of the effect of sarcopenia on OS showed that arbitrary deletion of studies would not affect the results of this meta-analysis, indicating stable and reliable results (Supplementary Figures S1, S2). Either Egger's regression analysis ($p > 0.05$) or funnel plots (Supplementary Figures S3, S4) indicated the presence of possible publication bias for the univariate and multivariate analyses.

Discussion

Despite advancements in perioperative care and surgical techniques improving pancreatic surgery results, surgical morbidity and death are significant concerns (34, 35). Sarcopenia, which is traditionally characterized as decreased lean skeletal muscle mass coupled with impaired nutritional status and immune function, is an integrated, quantitative indication of body reserve (36–38). Recently research has shown that preoperative sarcopenia is linked to a worse OS for patients with PDAC (39–41). However, the effects of sarcopenia on patient survival following pancreatic surgery remain debatable. This is the first meta-analysis to investigate the predictive value of sarcopenia on post-pancreatectomy patient survival. Of note, this study included both benign and malignant pancreatic diseases, thereby incorporating all possible reasons for pancreatic resection. Consistent with most previous study findings (13, 32), the present meta-analysis demonstrates that sarcopenia was associated with a poor prognosis in patients who underwent pancreatic surgery. Patients with sarcopenia have significantly shorter long-term OS in univariate or multivariate analyses than those without sarcopenia. However, the multivariate meta-analysis evaluating the impact of sarcopenia on OS following pancreatic surgery revealed significant heterogeneity. The subgroup analysis identified the inclusion of various racial groups in the different studies as a possible source of heterogeneity and that sarcopenia had a more negative effect on OS in non-Asians following pancreatic surgery than in Asians. This is also the first meta-analysis to examine the impact of sarcopenia on the postoperative survival rate in patients undergoing pancreatic surgery in different populations. Postoperatively, in patients with pancreatic cancer, sarcopenia was associated with a reduced postoperative PFS. Moreover, postoperatively, in patients with PDAC, sarcopenia was linked to a poorer OS according to a meta-analysis of the results from nine trials.

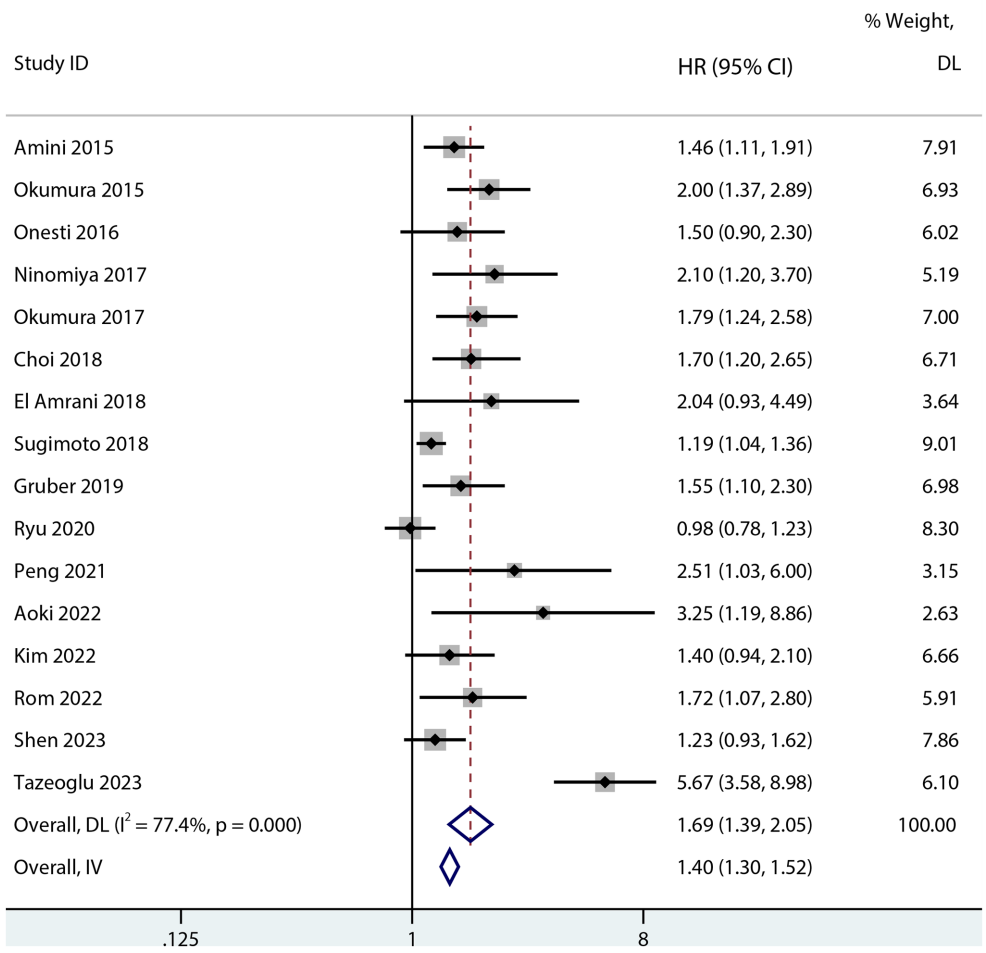

FIGURE 3
Forest plot of the multivariate association between sarcopenia and OS for patients after pancreatic surgery.

Several discrepancies have persisted between the definition and diagnostic criteria of sarcopenia in the last dozen years. Most original sarcopenia working groups in their definition and diagnosis criteria have defined sarcopenia as reduced muscle mass (42, 43). It was only later that researchers reported that muscle strength function could better predict sarcopenia and suggested adding them to the definition and diagnostic criteria of sarcopenia (44, 45). In the latest Sarcopenia Definitions and Outcomes Consortium diagnostic criteria, muscle mass has been removed, and instead, sarcopenia has been defined by muscle strength and function (46). The prevalence of sarcopenia varies widely across most meta-analyses, despite recent studies using relatively consistent definitions (47, 48). This is because the use of different cut-offs and measurements reveals different prevalence results. Although the studies included in our meta-analysis all used imaging methods to assess muscle mass, they used different cut-off values, possibly affecting the final analysis results.

In most studies, preoperative or baseline sarcopenia was linked to a higher risk of postoperative infection, longer hospital stays, and an elevated risk of short-and long-term death (49–52). Besides, the risks differed for various patient groups in terms of survival, death rates, and other unfavorable outcomes. Patients who had emergency laparotomies had the highest all-cause mortality (52), whereas those who underwent radical cystectomies had the lowest (51). These differences may be largely due to the different definitions of sarcopenia used and may also be influenced by different measurement methods for muscle mass, strength, and function. MRI and CT scans are the gold standard for the non-invasive assessment of muscle mass (53); nevertheless, their use in primary care and research is limited due to cost, accessibility, absence of portable equipment, and the need for highly skilled people (54). Clinically, grip strength is the most widely used, economical, and straightforward metric for assessing muscular strength (55), and gait speed is the most utilized tool for evaluating muscle function (56). Low grip strength and gait speed are good predictors of adverse outcomes, such as longer hospital stays, poor health-related quality of life, and all-cause mortality (57, 58). Hence, compared with CT or MRI, grip strength and gait speed are easier to measure. Additionally, similar to decreased muscle mass, decreased muscle strength and function are risk factors for adverse outcomes in several diseases. All studies included in our analysis used the criteria of low muscle mass to assess sarcopenia, which may reduce the comprehensiveness of our study.

Sarcopenia results in muscle weakness, decreased muscle mass, and impaired muscle function. These factors may raise the surgical risk, such as the difficulty of the surgical procedure, the higher

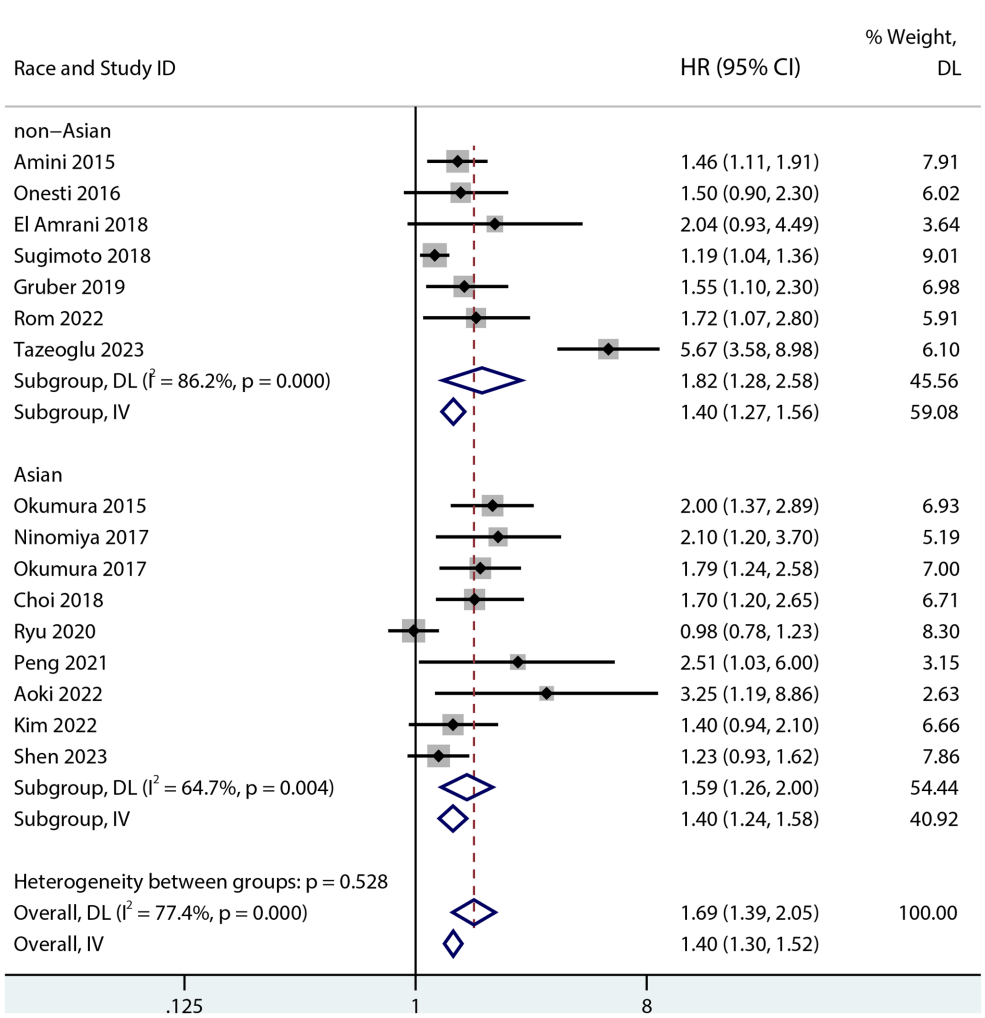

FIGURE 4
Forest plot of the association between sarcopenia and OS in both Asians and non-Asians after pancreatic surgery (multivariate analysis).

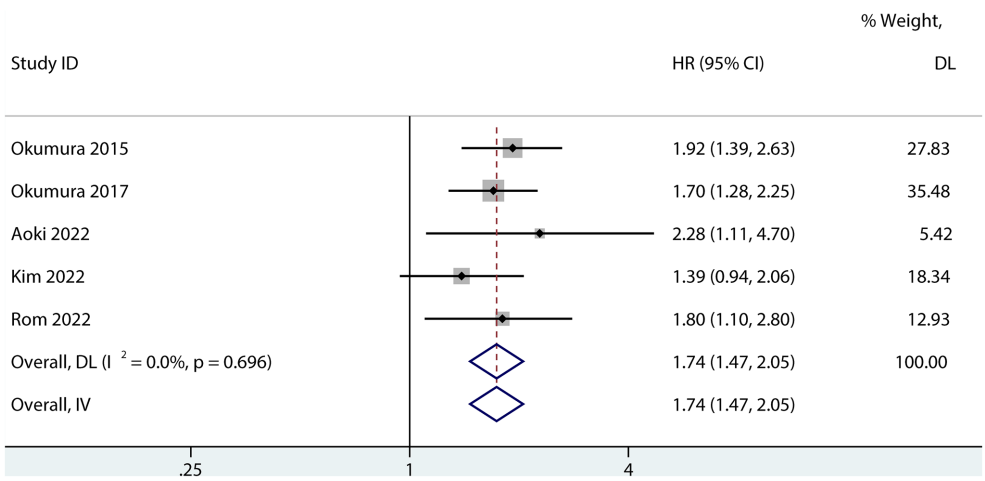

FIGURE 5
Forest plot of the univariate association between sarcopenia and PFS for patients with pancreatic cancer after pancreatic surgery.

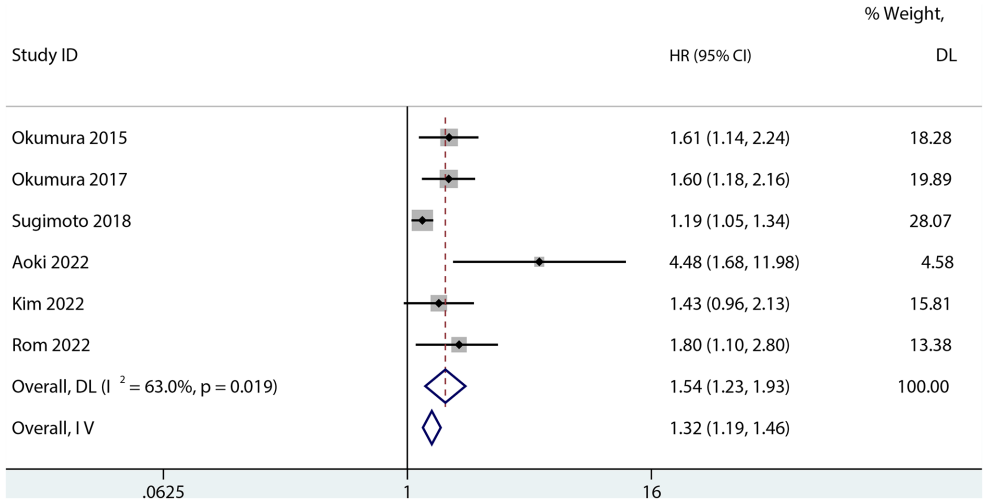

FIGURE 6
Forest plot of the multivariate association between sarcopenia and PFS for patients with pancreatic cancer after pancreatic surgery.

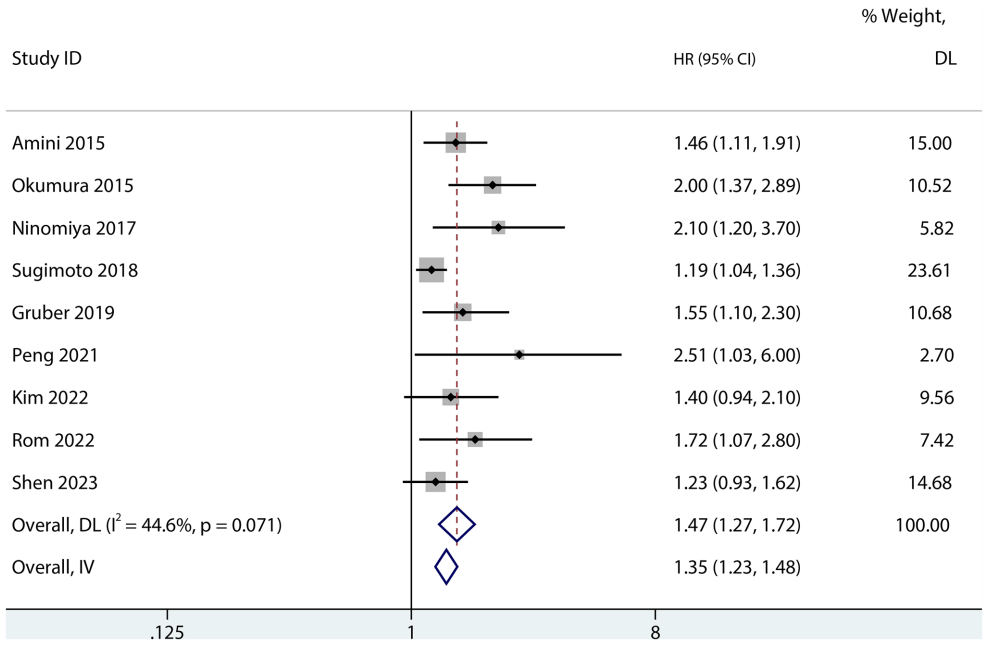

FIGURE 7
Forest plot of the association between OS in patients with PDAC after pancreatic surgery.

prevalence of postoperative complications, and make it more difficult for patients to recover postoperatively, which negatively affected patient survival (25, 59, 60). However, Chathura et al. (61) discovered that preoperative sarcopenia was not linked to a higher incidence of any particular postoperative complication. Aoki et al. performed a multivariate analysis and reported sarcopenia as the most significant risk factor for poor RFS and OS (16). Notably, muscle mass loss may lead to frailty. Although there are many similarities between the physical signs of sarcopenia and frailty, frailty as a complicated geriatric syndrome that covers a wider range of geriatric decline, including cognitive and social impairment linked to negative outcomes (62). When compared to non-frail patients, the preoperative presence of frailty was linked to a threefold increase in long-term mortality, a sixfold increase in the risk of early postoperative mortality, and a twofold increase in the chance of developing significant postoperative morbidity (63). Therefore, for patients with sarcopenia, a comprehensive assessment of the patient's physical condition preoperatively is necessary to increase the therapeutic effect of the surgery.

As we all know that poor prognostic factors for post-pancreatic surgery mainly included large tumor size, higher levels of CA 19–9, nodal involvement, involved resection margins, TNM stage, and the need for

neoadjuvant chemotherapy (64). Rom et al. (31) reported that sarcopenia was associated not only with the above adverse prognostic factors but also with poor survival after pancreatic surgery, supporting our findings that sarcopenia is an early surrogate radiological marker of aggressive tumor biology that predicts a poor prognosis. Furthermore, a recent study has reported that sarcopenia with differentiated degrees of PDAC has different prognostic values (13). Shen et al. speculated that this may be because tumor-associated sarcopenia is more severe in poorly differentiated PDAC than in moderate or highly differentiated PDAC and sarcopenia can be largely reversed in patients with moderate or highly differentiated PDAC but not in patients with poorly differentiated PDAC (13). However, more prospective studies are needed to confirm this.

Of note, postoperative radiotherapy and chemotherapy are routinely required for pancreatic malignancies (64). A recent study on the relationship between sarcopenia and prognosis after surgery for gastrointestinal cancer showed that there were significantly more patients undergoing postoperative chemotherapy radiation in the sarcopenic group than in the nonsarcopenic group and that patients with sarcopenia had significantly more chemotherapy changes, including delays, dose reduction, or termination (65). These findings indicate that following abdominal surgery for digestive tract cancer, sarcopenia had a negative impact on chemotherapy and radiation, particularly on the former. Interestingly, recent studies have also reported a significant reduction in skeletal muscle mass during chemotherapy (66), and sarcopenia is associated with major chemotherapy toxicities (such as diarrhea, infection, alopecia and neuro-pathy) (67, 68). Consequently, in light of the earlier discoveries, it is proposed that sarcopenia detection before, during, and following chemotherapy is crucial for focused nutritional intervention that is intended to enhance the results of chemotherapy treatment.

The mechanisms through which sarcopenia increases the risk of tumor recurrence and death remain unknown. However, it might be connected to the following factors. First, people with sarcopenia may have a poorer tolerance for chemotherapy according to a study that reported that sarcopenia is linked to lower chemotherapy tolerance in individuals with different cancers (69–71). Given that adjuvant chemotherapy is a significant independent protective factor for both OS and disease-free survival, lower chemotherapy tolerance may contribute to sarcopenia's detrimental effect on long-term survival. Second, sarcopenia may be a reflection of high metabolic activity due to a more aggressive tumor biology, leading to more serious systemic inflammation and, consequently, muscle wasting (72).

Sarcopenia can also affect patients with benign disease. Brittany et al. (73) reported an increased incidence of overall as well as major complications among patients with sarcopenia among individuals without a cancer diagnosis. One explanation is that major surgery is known to be associated with biochemical cytokine response, causing persistent inflammation and immunosuppression, leading to prolonged severe illness and poor survival (74). Moreover, patients with sarcopenic patients may be more "vulnerable" to negative outcomes as an impact of this reaction (75). However, to fully understand the association between sarcopenia and postoperative survival in non-tumor patients, further research is required.

To lower the risks, perioperative therapies are crucial. The complex etiology of sarcopenia significantly influences effective prevention and treatment of isolated drugs and/or nutritional strategies (76). To manage sarcopenia more effectively, multimodal solutions, such as a combination of exercise regimens and dietary treatments, need to be developed (77). Some studies have indicated that certain dietary patterns, such as sufficient protein, vitamin D, antioxidant elements, and long-chain polyunsaturated fatty acid intake, can help control sarcopenia (78). Additionally, a high total protein diet can also protect against frailty (79). In individuals who are already frail, protein-energy supplementation may reduce the progression of functional decline (80). Nevertheless, currently, no solid recommendations on nutrition therapy for sarcopenia and frailty exist because of heterogeneous data and a lack of major clinical trials (81, 82). Exercise therapies, particularly those based on resistance training, may be able to enhance athletic ability and increase muscle mass and power (83). Additionally, resistance training prevents sarcopenia development in the most cost-efficient manner and enhances multiple facets of overall wellness (84). Patients with pancreatic cancer might benefit from supportive treatment that emphasizes diet and exercise because malnutrition is a common occurrence in this population (85). Such supportive therapy would be best administered during neoadjuvant chemoradiation therapy, as patients undergoing these treatments are more likely to experience steatotic changes and lose muscle mass due to reduced oral intake and physical activity (26).

This study had some limitations. First, a subgroup analysis to assess how different definitions and cut-off values affected the final results could not be performed because the definitions of sarcopenia in the included studies and their cut-off values varied. Moreover, because the included study did not use muscle strength and function to assess sarcopenia, we could not comprehensively analyze the effects of sarcopenia and pancreatic postoperative prognosis; thus, future studies are required to explore this. Second, the analysis could have decreased credibility because of insufficient research on sarcopenia and PFS following pancreatic surgery. Third, the adjusted HR offered estimates after accounting for any confounding risk variables; however, most studies did not account for the same risk factors, such as changes in patient profiles, improvements in the perioperative patterns of care, and the balance between the safety and efficacy of adjuvant therapy, which might impact the final outcomes of this analysis. Fourth, due to insufficient data from the original study, no subgroup analysis was performed on tumor and non-tumor patients, which may have had some impact on the final results. Lastly, publication bias may be present, and research with no substantial impacts may not have been published. Hence, the given data may overestimate the genuine effect. Moreover, our study did not include studies that defined sarcopenia in terms of muscle strength and function, which may also have contributed to publication bias. Only English studies were included, possibly leading to selection bias. Therefore, we still need a large number of multicenter, prospective studies to verify the association between sarcopenia and survival after pancreatic surgery.

In summary, sarcopenia is related to poor OS after pancreatic surgery. Moreover, it can reduce the PFS in patients with pancreatic cancer after pancreatectomy. Moreover, for patients with PDAC, sarcopenia can negatively affect their OS postoperatively. More research is needed to validate our findings, and the causes underlying malnutrition in this population undergoing pancreatic surgery must be understood and improved in future studies.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

LZ: Data curation, Investigation, Methodology, Software, Writing – review & editing. JL: Writing – review & editing. SL: Writing – original draft. GT: Writing – review & editing. MX: Data curation, Methodology, Writing – review & editing. YZ: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2023.1315097/full#supplementary-material

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Relationship between skeletal muscle index at the third lumbar vertebra with infection risk and long-term prognosis in patients with acute-on-chronic liver failure

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Objective: Infection is a major cause of increased mortality in patients with acute-on-chronic liver failure (ACLF). This study aims to examine the potential correlation of the skeletal muscle index at the third lumbar vertebra (L3-SMI) with infections among ACLF patients and to evaluate its impact on the long-term survival.

Methods: This retrospective study included 126 patients who underwent abdominal computed tomography (CT) and were diagnosed with ACLF at our center between December 2017 and December 2021. L3-SMI was calculated using CT, and the clinical and biochemical data as well as MELD scores were also collected, so as to analyze the relationship between L3-SMI and infections in ACLF patients and the impact on long-term prognosis.

Results: Of the 126 ACLF patients enrolled, 50 had infections. In the multivariate logistic regression analysis, both L3-SMI [odds ratio (OR) = 0.89, 95% confidence interval (*CI*) = 0.81 – 0.97, $P = 0.011$] and hepatic encephalopathy (OR = 8.20, 95% *CI* = 1.70 – 39.59, $P = 0.009$) were independently associated with the risk of infection development. The overall survival (OS) estimates were obtained using Kaplan-Meier curves, and it was found that patients in the lowest tertile of L3-SMI had significantly lower 3-month, 6-month, 1-year, and 2-year survival rates than those in the highest tertile ($P = 0.014$; log-rank test).

Conclusion: Low L3-SMI is an independent risk factor for the development of infections and significantly influences the long-term survival in ACLF patients.

KEYWORDS

acute-on-chronic liver failure, sarcopenia, low skeletal muscle index, infection, long-term survival rate

1 Introduction

Acute-on-chronic liver failure (ACLF) is a clinical syndrome characterized by acute deterioration of liver function on the basis of chronic liver disease. It has a high case-fatality rate, with the 28- and 90-day mortality rates being up to 25% and 40%, respectively (1, 2). It was found that 52.2% of ACLF patients died of comorbid infection(s) (3). Identifying the risk factors that lead to infections in ACLF patients may aid in the formulation of multidisciplinary treatment protocols, ultimately reducing patient mortality rates.

Previous studies have demonstrated that hepatic encephalopathy, hepatorenal syndrome, and higher MELD scores increase the susceptibility to infection in patients with ACLF (4–6). However, these factors primarily rely on liver function indicators (7), and there is a lack of indicators for evaluating the association of general nutritional status with infections. Evidence suggests that nutritional status is closely associated with infections (8). A recent study shows that sarcopenia is a highly predictive nutritional indicator for the occurrence of hospital-acquired infections (9). Sarcopenia is a syndrome characterized by low skeletal muscle mass and progressive decline in strength and function (performance) with age (10, 11). Sarcopenia significantly increases the risk of developing infections in various conditions, including type 2 diabetes, post-gastric cancer surgery, and post-heart transplantation (12–14). Furthermore, critically ill cirrhotic patients with sarcopenia have a higher incidence of sepsis (15). Kaido et al. (16) found that low skeletal muscle index (SMI) was an independent risk factor for bacteremia after living donor liver transplantation. However, no study has yet demonstrated the effects of L3-SMI on infection and long-term survival in ACLF patients.

Patients with ACLF are often found to have sarcopenia (17–19). The SMI at the third lumbar vertebra (L3-SMI) reflects the skeletal muscle mass of the body and is also an important indicator for the diagnosis of sarcopenia (20, 21). Therefore, we assumed that L3-SMI might be a risk factor for infections and affect survivals in ACLF patients. The purpose of this study was to examine the potential correlation of L3-SMI with infections among ACLF patients, as well as to evaluate its impact on the long-term survival.

2 Materials and methods

2.1 Patients

A retrospective cohort study was conducted on ACLF patients aged ≥ 18 years who were hospitalized at Shanxi Bethune Hospital from December 2017 to December 2021. The inclusion criteria were as follows: (a) aged ≥ 18 years; (b) underwent computed tomography (CT) within 2 weeks before and after hospitalization; and (c) diagnosed with ACLF according to the diagnostic criteria of ACLF defined by the Asian Pacific Association for the Study of the Liver (APASL) (22). Patients with one of the following conditions were excluded: (a) severe underlying disease(s) affecting extrahepatic organ(s), such as respiratory failure and/or heart failure; (b) concomitant malignancies; (c) comorbid wasting diseases such as hyperthyroidism and active tuberculosis; (d) neuromuscular disorders and/or being bedridden; and (e) long-term administration of corticosteroids and other immunosuppressant drugs. A flowchart illustrating patient inclusion is shown in **Figure 1**.

All patient data were obtained from the electronic medical record, and all patients were followed up every 6 months after discharge from the hospital. The scheduled follow-up duration was 4 years. Follow-up information was collected through telephone interviews. The study was conducted in accordance with the Declaration of Helsinki, and the research protocol was approved by the Shanxi Bethune Hospital. Written informed consent was obtained from all patients or their families prior to participating in the study.

2.2 Clinical data

The basic demographic data and clinical information of the patients, including gender, age, body height, body weight, etiology, and comorbidities (e.g., ascites and hepatic encephalopathy), were collected during hospitalization. Laboratory data were also collected from each patient at the time of diagnosis, including routine blood tests, liver function test (including alanine aminotransferase, aspartate aminotransferase, and total bilirubin), renal function test (including creatinine and urea), albumin, and coagulation-related indices. The Model for End-Stage Liver Disease (MELD) score and Child-Pugh score were calculated. The death and survival information was also collected.

Acute-on-chronic liver failure patients usually have body fluid retention such as edema and ascites. In the present study, the dry weight of the ACLF patients with body fluid retention was calculated and corrected according to the clinical severity of ascites minus a certain amount of body weight (23) (mild severity 5%, moderate 10%, severe 15%, and 5% if there was peripheral edema). The body mass index (BMI) was calculated using the following formula: BMI = dry weight (kg)/height squared (m^2).

2.3 CT measurements of skeletal muscle area (SMA)

Abdominal CT examinations were performed in all patients within 2 weeks of admission. L3 intervertebral disk planar imaging was selected. Image analysis software (syngo.via Siemens AG) was used to calculate the sum of the cross-sectional areas of the skeletal muscles at the L3 level, including psoas major, erector spinae, transversus abdominis, internal abdominal oblique, external abdominal oblique, and quadratus lumborum. The SMA of the L3 cross-section was evaluated by two imaging physicians independently. When there was disagreement, a third physician was involved to reach an agreement. L3-SMI was calculated as follows: SMA at the L3 level divided by the square of height (cm^2/m^2) (24). In this study, patients were divided into gender-stratified L3-SMI tertiles to mitigate the known influence of gender on the outcome. Each tertile has a comparable proportion of males and females (25).

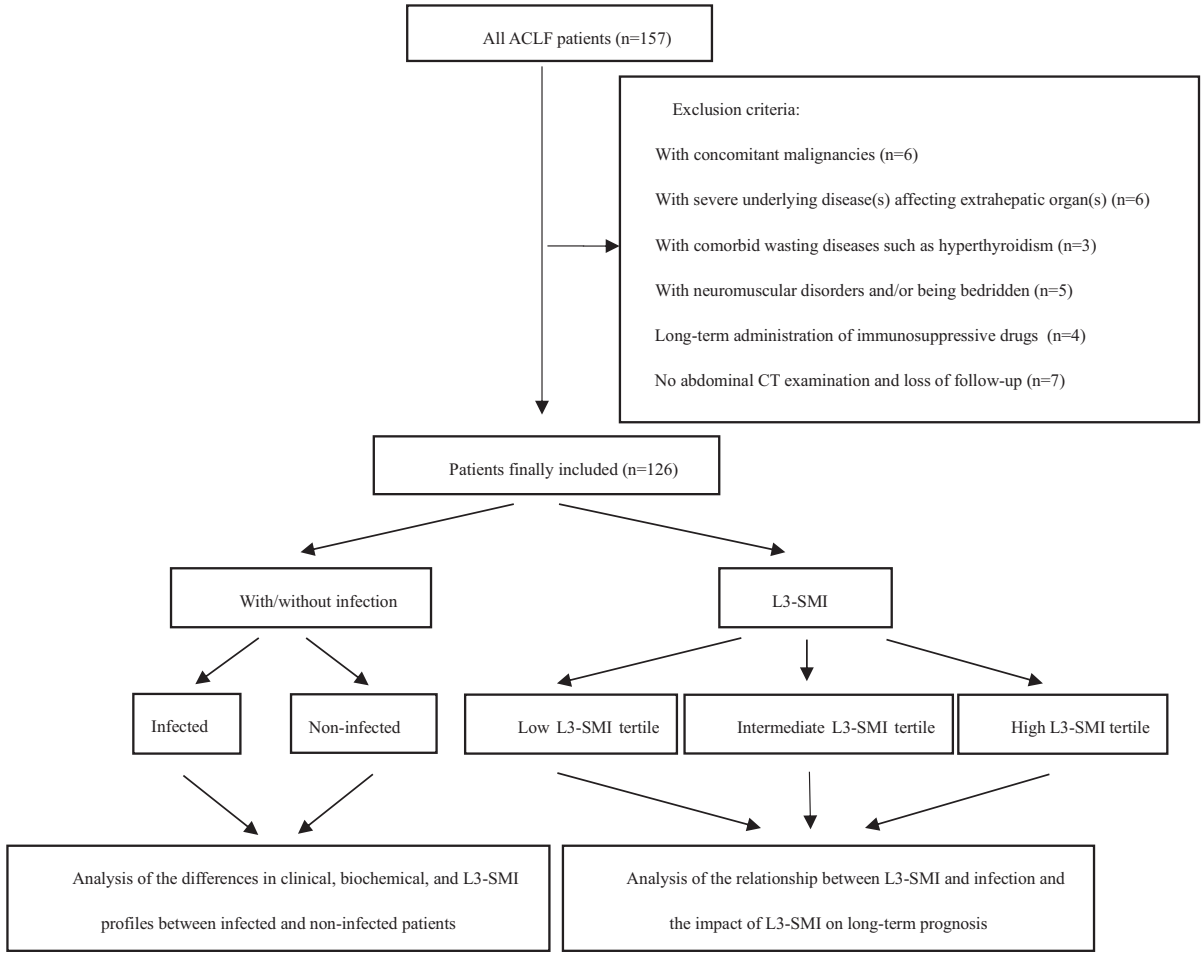

FIGURE 1
The flowchart of patient enrollment.

2.4 Diagnosis of infections

Pathogens were actively detected in the enrolled patients through the following examinations and tests: (1) history of an infection; (2) physical examination focusing on signs suggestive of an infection; (3) laboratory tests: such as erythrocyte sedimentation rate, C-reactive protein, white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), and procalcitonin; (4) analyses of ascitic fluid analysis, pleural fluid, and biochemistry; and (5) Chest X-ray or chest CT. Cultures of blood, urine, stool, sputum, ascites, pleural fluid, or purulent secretions were carried out to search for pathogenic microorganisms in cases of suspected co-infection (26).

Spontaneous bacterial peritonitis (SBP) was defined by the presence of $\geq$ 250 polymorphonuclear cells (PMN)/mm^3 in ascites. Pneumonia was defined as the presence of radiologic evidence of pulmonary consolidation plus at least two of the following criteria: fever above 38°C or temperature below 35°C; dyspnea; cough and sputum production; pleuritic chest pain; or signs of pulmonary consolidation on imaging. Urinary, biliary, and gastrointestinal tract infections were diagnosed by evaluating symptoms, biochemical and imaging parameters that met the established criteria (27). Positive blood culture result without a recognized site of infection was defined as spontaneous bacteremia.

According to the site of infection, standard guidelines and the results of cultures (if available), all patients with infection were assessed by infectious disease experts with expertise in nosocomial infections.

2.5 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software package (version 26) (IBM Corp, Armonk, NY, USA). Demographic data, clinical features, and laboratory findings were analyzed for patients in the L3-SMI tertiles. Continuous data with normal distribution are presented as mean ± standard deviation (SD) and analyzed using one-way ANOVA; non-normal variables are reported as median [interquartile range (IQR)] and analyzed using Kruskal-Wallis test. Categorical data are presented as percentages and analyzed using Pearson's chi-square test.

Differences in demographic characteristics, laboratory data, and L3-SMI between infected and uninfected patients were compared using unpaired *t*-tests and Mann-Whitney *U* tests (for continuous variables) or using either Pearson's chi-square tests or Fisher's exact tests (for categorical variables). Univariate and multivariate logistic regression analyses were conducted to

investigate the risk factors associated with infections in ACLF patients. Variables that showed a P value of less than 0.05 in the univariate analysis were included in the multivariate analysis. Furthermore, to investigate the association between L3-SMI tertiles and infections, logistic regression was used to calculate the unadjusted odds ratio and the adjusted odds ratio of L3-SMI tertiles to infections.

Overall survival estimates were obtained using the Kaplan-Meier curves. Survival analyses were carried out to compare L3-SMI tertiles using log-rank tests. Survival rates of 3, 6, 12, and 24 months were reported.

Significant predictors of mortality in patients evaluated for ACLF were determined using univariate and multivariate Cox proportional hazard models and the results were reported as hazard ratio (HR) and 95% CI. Baseline factors known to associate with mortality of patients with ACLF including age, cirrhosis, laboratory data, MELD score, Child-Pugh score, ascites, hepatic encephalopathy as well as L3-SMI were included in univariate analysis. Variables with $P < 0.10$ in the univariate analysis were included in the multivariate model. A two-sided P value of < 0.05 was considered statistically significant.

3 Results

3.1 Characteristics of the study population

A total of 126 patients diagnosed with ACLF, with a mean age of 50 ± 11 years, were included in this study. Most of them were males (n = 80, 63%). ACLF was most commonly caused by hepatitis B (n = 56, 44.4%), followed by alcohol-associated hepatitis (n = 36, 28.6%). Compared to patients with high L3-SMI, patients with low L3-SMI exhibited lower BMI (21.45 ± 2.97 kg/m^2 *vs.* 25.64 ± 3.49 kg/m^2, P = 0.001), higher Child-Pugh score (11.48 ± 1.47 *vs.* 9.95 ± 1.96, P = 0.023), and higher MELD score (26.75 ± 8.96 *vs.* 21.08 ± 6.25, P = 0.041). Patients with low L3-SMI had a higher incidence of ascites in terms of the complications (90.5% *vs.* 52.4%, P = 0.019), and were significantly more likely to develop infections than those with high L3-SMI (61.9% *vs.* 19.0%, P = 0.018). In addition, low L3-SMI was associated with a higher mortality (61.9% *vs.* 23.8%, P = 0.006). The characteristics of patients in the L3-SMI tertiles are shown in Table 1.

3.2 Characteristics of ACLF patients who developed infections

Of the 126 ACLF patients, 50 (40%) developed infections, among whom 16 patients were infected via more than 2 routes. Sixteen patients had more than two microbial infections. The lungs (n = 30) were identified as the most frequent site of infection, followed by the urinary tract (n = 10), bloodstream (n = 8), and intra-abdominal cavity (n = 6). There were acute cholecystitis (n = 6), acute cholangitis (n = 4), and intestinal infections (n = 2).

Table 2 shows the difference between ACLF patients who developed infection and those who did not. Compared with non-infected patients, infected patients had lower L3-SMI (39.40 cm/m^2 *vs.* 45.97 cm/m^2, P = 0.014) and were more likely to have comorbid hepatic encephalopathy (44.0% *vs.* 15.8%, P = 0.028). In addition, patients with infection had a significantly higher mortality rate than those without infection (48.0% *vs.* 26.3%, P = 0.012).

3.3 Risk factors for co-infections in ACLF patients

In the univariate and multivariate analyses, the following variables were determined to be independent risk factors for infections: hepatic encephalopathy (OR = 8.20, 95% *CI* = 1.70 – 39.59, P = 0.009) and L3-SMI (OR = 0.89, 95% *CI* = 0.81 – 0.97, P = 0.011). Table 3 summarizes the results of the binary logistic regression analysis.

As shown in Table 4, low L3-SMI was associated with an increased risk of developing infections (tertile 1 vs. tertile 3: adjusted Odds ratio = 10.88, 95% CI = 1.89–62.76, P = 0.008).

3.4 Survival rates

Survivals were assessed using Kaplan-Meier curves, which were compared using the log-rank test. The 3-month, 6-month, 1-year, and 2-year survival rates were 81, 67, 52, and 38%, respectively, for patients with low L3-SMI (Tertile 1), however, 93, 88, 83, and 81%, respectively, for patients with intermediate L3-SMI (Tertile 2) and 95, 86, 81, and 76%, respectively, for patients with high L3-SMI (Tertile 3), the survival rate of ACLF patients with low L3-SMI was significantly lower than that of ACLF patients with intermediate and high L3-SMI (P = 0.005, P = 0.014, log-rank test). The difference in survival rates between intermediate and high L3-SMI was not statistically significant (P = 0.706; Figure 2).

3.5 L3-SMI and long-term mortality in ACLF patients

To explore the independent relationship between L3-SMI and long-term mortality of ACLF patients, we performed univariate and multivariate Cox regression analyses of patients on the selected patients (Table 5). Univariate Cox regression analysis showed that age, creatinine, low albumin, INR, MELD score and Child-Pugh score were risk factors for long-term mortality of ACLF patients (24 months), while L3-SMI acted as a protective factor (hazard ratio (HR) = 0.876, 95%CI = 0.814–0.943, $P < 0.001$). After the variables of $P < 0.10$ in univariate analysis were included in the multivariate Cox regression model, it demonstrated that age (HR = 1.053, 95% CI = 1.004–1.104, P = 0.035), Child-Pugh score (HR = 1.785, 95%CI = 1.203–2.648, P = 0.004), L3-SMI (HR = 0.906, 95%CI = 0.841–0.976, P = 0.010) had an independent relationship with long-term mortality of ACLF patients.

4 Discussion

Acute-on-chronic liver failure is an independent clinical syndrome with a high mortality (1). Up to 80% of ACLF

TABLE 1 Characteristics of enrolled ACLF patients stratified by L3-SMI tertiles (n = 126).

Variables	Tertile 1 (n = 42)	Tertile 2 (n = 42)	Tertile 3 (n = 42)	P-value
Age (years)	51.62 ± 8.41	50.67 ± 12.54	48.29 ± 12.19	0.613
Weight (kg)	60.58 ± 8.10	61.54 ± 9.41	71.34 ± 10.90[b]	<0.001
BMI (kg/m^2)	21.45 ± 2.97	22.93 ± 3.03	25.64 ± 3.49[b]	0.001
Etiology				
HBV (%)	16 (38.1)	18 (42.9)	22 (52.4)	0.638
Alcohol (%)	18 (42.9)	8 (19.0)	10 (23.8)	0.195
Autoimmune (%)	2 (4.8)	4 (9.5)	6 (14.3)	0.864
Others (%)	6 (9.5)	12 (33.3)	4 (9.5)	0.343
Serum Indexes				
RBC (10^{12}/L)	3.26 ± 0.96	3.79 ± 0.74	3.32 ± 0.90	0.110
WBC (10^9/L)	7.50 (5.10, 11.05)	5.30 (3.75, 7.30)	6.30 (4.85, 10.65)	0.130
Neutrophil (10^9/L)	5.42 (3.29, 9.67)	3.38 (2.18, 5.16)	4.11 (2.65,7.19)	0.097
Hemoglobin (g/L)	110.10 ± 22.17	120.57 ± 20.93	113.48 ± 27.67	0.352
TBIL (mg/dL)	16.68 (11.08, 28.70)	17.11 (12.74, 22.51)	16.87 (12.39, 29.12)	0.861
Albumin (g/L)	27.07 ± 4.27	30.65 ± 6.43	28.90 ± 5.21	0.107
Scr (μmol/L)	86.40(66.70, 160.05)	77.20(68.90, 109.20)	82.05(69.50, 147.60)	0.631
INR	2.10 (1.83, 2.66)	1.82 (1.60, 2.33)	2.10 (1.66, 2.67)	0.311
Child-Pugh score	11.48 ± 1.47	9.95 ± 1.96[a]	10.57 ± 1.78	0.023
MELD scores	26.75 ± 8.96	21.08 ± 6.25[a]	25.57 ± 6.96	0.041
Ascites (%)	38 (90.5)	32 (76.2)	22 (52.4)	0.019
HE (%)	12 (28.6)	12 (28.6)	10 (23.8)	0.923
Infection (%)	26 (61.9)	16 (38.1)	8 (19.0)	0.018
Mortality (%)	26 (61.9)	8 (19.0)	10 (23.8)	0.006
L3-SMI: females (cm^2/m^2)	37.82 (31.33, 39.08)	42.27 (40.46, 43.08)	47.15 (46.61, 53.89)[b]	<0.001
L3-SMI: males (cm^2/m^2)	36.09 (34.24, 37.77)	43.83 (41.10, 45.74)	50.59 (48.18, 56.49)[b]	<0.001

[a] $P < 0.05$, Tertile 1 *vs.* Tertile 2;
[b] $P < 0.05$, Tertile 1 *vs.* Tertile 3. ALT, glutamic-pyruvic transaminase; AST, glutamic-oxalacetic transaminase; HE, hepatic encephalopathy; TBIL, total bilirubin; INR, international normalized ratio; MELD, model for end-stage liver disease; RBC, red blood cell; WBC, white blood cell; BMI, Body mass index; Scr, serum creatinine.

TABLE 2 Characteristics of ACLF patients with/without infection.

	With infection (n = 50)	Without infection (n = 76)	P-value
Age (years)	47.00 ± 10.19	52.29 ± 11.32	0.064
BMI (kg/m^2)	22.36 ± 3.59	23.58 ± 3.68	0.221
Weight (kg)	63.30 ± 10.80	65.63 ± 10.62	0.425
WBC (10^9/L)	7.50 (5.30, 12.20)	5.50 (4.33, 7.55)	0.012
Neutrophil (10^9/L)	5.49 (3.55, 9.69)	3.91 (2.41, 5.28)	0.007
TBIL (mg/dL)	19.07 (10.98, 27.80)	16.67 (12.87, 24.63)	0.837
Albumin (g/L)	27.27 ± 5.11	29.93 ± 5.54	0.059
Scr (μmol/L)	100.10 (72.45, 150.75)	77.20 (66.55, 128.05)	0.139
INR	2.10 (1.66, 2.56)	1.92 (1.64, 2.69)	0.643
Child-Pugh score	11.00 (10.00, 12.00)	11.00 (9.00, 12.00)	0.230
MELD score	26.00(22.50, 29.50)	23.00 (17.00, 27.25)	0.093
HE (%)	22 (44.0)	12 (15.8)	0.028
L3-SMI (cm^2/m^2)	39.40 (34.68, 43.89)	45.97 (39.98, 48.28)	0.014
Mortality (%)	24 (48.0)	20 (26.3)	0.012

TABLE 3 Logistic regression analysis of the risk factors of infections in ACLF patients.

	Univariate analysis		Multivariate analysis	
Variables	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
WBC (10^9/L)	1.13 (1.00–1.27)	0.046		
Neutrophil (10^9/L)	1.17 (1.01–1.35)	0.034		
Scr (μmol/L)	1.01 (1.00–1.02)	0.111		
Albumin (g/L)	0.91 (0.82–1.01)	0.065		
MELD score	1.03 (0.96–1.10)	0.380		
Child-Pugh score	1.27 (0.94–1.71)	0.116		
HE	4.19 (1.29–13.59)	0.017	8.20 (1.70–39.59)	0.009
L3-SMI (cm^2/m^2)	0.92 (0.85–0.99)	0.028	0.89 (0.81–0.97)	0.011

TABLE 4 Unadjusted odds ratio and adjusted odds ratio for infections among ACLF patients in three L3-SMI tertiles.

	Unadjusted Odds ratio		Adjusted Odds ratio	
L3-SMI Tertiles	(95%CI)	*P* value	(95%CI)	*P* value
First versus third	6.91 (1.70–28.03)	0.007	10.88 (1.89–62.76)	0.008
Second versus third	2.62 (0.64–10.61)	0.179	6.12(0.98–38.18)	0.053

Using L3-SMI tertiles as categorical variables, multivariate analysis adjusted for white blood cells, neutrophil, creatinine, albumin, ascites, hepatic encephalopathy, MELD score, Child-Pugh score, and L3-SMI Tertiles.

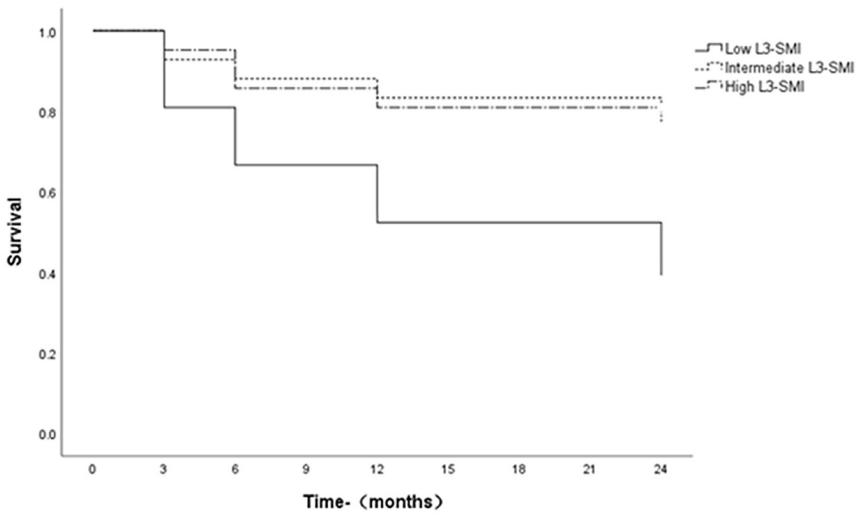

FIGURE 2
Survival curves of ACLF patients with L3-SMI tertiles. Survivals with time were assessed using Kaplan-Meier curves, which were compared using the log-rank test.

patients will develop bacterial infections, which are associated with worsening liver function and increased mortality (3). Therefore, it is crucial to identify risk factors for infection development and intervene promptly to minimize mortality risk. In the present study, L3-SMI was found to be an independent risk factor for infections in ACLF patients, and patients with low L3-SMI were more likely to develop infections than those with high L3-SMI. In addition, ACLF patients in the low L3-SMI quartile had significantly lower long-term survival rates than those in the high L3-SMI quartile.

The most important finding in this study is that low L3-SMI is strongly associated with the risk of developing infections in ACLF patients. Evidence suggests that sarcopenia is a risk factor for infections after liver transplantation (28). Similar to previous studies, our results indicated that the risk of developing infection was several times higher in the low L3-SMI tertile than in the high L3-SMI tertile. Further multivariate analysis showed that low L3-SMI was an independent risk factor for developing infections in ACLF patients. As for the cause of risk of infections increased by sarcopenia, we hypothesize that sarcopenia may impact the immune system, resulting in a higher risk of infection. Impaired immune response has been found in sarcopenia patients who had undergone surgery for esophageal cancer (29). Similarly, a worse systemic or local immune status

TABLE 5 Univariate and multivariate Cox regression models for ACLF patients.

	Univariate analysis		Multivariate analysis	
Variables	HR (95%CI)	*P*-value	HR(95%CI)	*P*-value
Age (years)	1.043(1.005–1.082)	0.025	1.053(1.004–1.104)	0.035
Cirrhosis	1.498(0.586–3.828)	0.399		
BMI (kg/m^2)	0.969(0.843–1.114)	0.660		
WBC ($10^9/L$)	1.041(0.979–1.108)	0.200		
Hemoglobin (g/L)	0.986(0.970–1.003)	0.115		
TBIL (mg/dL)	1.002(1.000–1.004)	0.065		
INR	1.966(1.039–3.720)	0.038		
Scr (μmol/L)	1.009(1.005–1.013)	<0.001		
Albumin (g/L)	0.902(0.824–0.988)	0.027		
MELD scores	1.117(1.057–1.181)	<0.001		
Child-Pugh score	1.811(1.330–2.465)	<0.001	1.785(1.203–2.648)	0.004
Ascites	4.249(0.992–18.195)	0.051		
HE	2.118(0.904–4.965)	0.084		
L3-SMI (cm^2/m^2)	0.876(0.814–0.943)	<0.001	0.906(0.841–0.976)	0.010

in patients with sarcopenia was confirmed in patients with extrahepatic cholangiocarcinoma (30). Meanwhile, the risk of infection significantly increased in patients with sarcopenia (12, 31, 32). Similar to these studies, our study revealed that low L3-SMI (sarcopenia) affected the risk of infections in ACLF patients, The possible mechanism is that muscle cytokines such as interleukin (IL)-6 and IL-15 have been shown to be to modulate the immune system (33). However, insufficient myokine signaling in patients with sarcopenia might result in the destruction of immune system function (34). In addition, sarcopenia often represents malnutrition, several studies have proved that malnutrition lead to decrease of immune response (35, 36). The finding that improves our understanding of the risks and outcomes of sarcopenia affecting individual patients and facilitate the development of more effective management measures.

We also demonstrated that ACLF patients with a low L3-SMI had a lower long-term survival rate. Similarly, Kaido et al. (37) used bioelectrical impedance analysis to assess sarcopenia in adult patients undergoing living liver transplantation and confirmed that the OS was lower in patients with low skeletal muscle mass. A possible explanation for the impact of L3-SMI on the prognosis of ACLF patients is that skeletal muscle influences systemic energy and protein metabolism and sarcopenia may reflect protein-energy malnutrition (PEM) (38–40). Previous studies indicated that PEM was a risk factor for poor prognosis in individuals with cirrhosis (41, 42). This study found that low L3-SMI affects the long-term survival rate of ACLF patients, strengthening the management of sarcopenia may improve the prognosis of ACLF patients. It has been shown that testosterone increased muscle mass and strength (43), and testosterone therapy increased muscle mass in male cirrhotic patients with low testosterone level (44). In addition, a leucine-enriched amino acid supplementation can increase muscle strength. Resistance exercise training is an effective intervention for preventing and even reversing sarcopenia (45). Nevertheless, more treatments to improve sarcopenia in ACLF patients warrant further investigations. In the enrollment study, we also found that second tertile MELD score and Child-Pugh score were better than third tertile. But, the results of this study indicate that low L3-SMI is an independent risk factor for infection and an influential factor for long-term prognosis. These results further validates our hypothesis that skeletal muscle plays a role in predicting infection and prognosis in ACLF patients independently of established liver factors. We will further explore this phenomenon in subsequent studies.

There are limitations in our study. First, the study was a single-center and retrospective study and sample size was small. More patients from multiple regions and centers are required in future studies. Secondly, this study assessed that low L3-SMI was one of the factors affecting the risk of death and infection in ACLF patients. However, there was a lack of comprehensive assessment of the factors affecting the mortality of ACLF. Further study should be comprehensively executed to evaluate the comprehensive risk factors including L3-SMI. Furthermore, we did not analyze the direct relationship between immune status and sarcopenia due to lack of baseline data. Finally, we did not attempt to investigate differences in microbiology or site of infection among different L3-SMI tertiles, nor did we explore the potential efficacy of antimicrobial therapy. Nevertheless, standard anti-infective therapy was administered to all infected patients.

5 Conclusion

In conclusion, the low L3-SMI is not only a risk factor for infections but also correlates significantly with poorer survival outcomes in ACLF patients. Therefore, the management of sarcopenia should be strengthened while treating the primary affection, which may improve the infection status and poor prognosis of ACLF. Further in-depth research is needed in the future.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Shanxi Bethune Hospital, Third Hospital of Shanxi Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JW: Formal analysis, Investigation, Software, Writing – original draft, Writing – review and editing. JB: Writing – original draft, Writing – review and editing. HW: Data curation, Formal analysis, Investigation, Writing – review and editing. GX: Data curation, Formal analysis, Investigation, Methodology, Writing – review and editing. RY: Data curation, Formal analysis, Investigation, Writing – review and editing. JL: Data curation, Funding acquisition, Writing – review and editing. WZ: Data curation, Formal analysis, Investigation, Software, Writing – review and editing. HW: Data curation, Formal analysis, Investigation, Methodology, Software, Writing – review and editing. JY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Supervision, Writing – review and editing, Writing – original draft. XR: Data curation, Formal analysis, Funding acquisition, Investigation, Software, Supervision, Writing – original draft, Writing – review and editing.

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We thank the participants of the study and hope that this study will be useful in improving the quality of life of acute-on-chronic liver failure patients.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Comparison of the cachexia index based on hand-grip strength (H-CXI) with the original CXI for the prediction of cancer cachexia and prognosis in patients who underwent radical colectomy for colorectal cancer

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Background and aims: The cachexia index (CXI) is a novel biomarker for estimating cancer cachexia. The cachexia index based on hand-grip strength (H-CXI) has been recently developed as a simple proxy for CXI. The present study aims to compare both the H-CXI and CXI for the prediction of cancer cachexia and postoperative outcomes in patients who underwent radical colectomy for colorectal cancer.

Methods: Patients who underwent radical operations for colorectal cancer were included in this study. Cancer cachexia was diagnosed according to the international consensus outlined by Fearon et al. The cachexia index (CXI) was calculated as [skeletal muscle index (SMI) × serum albumin/neutrophil-to-lymphocyte ratio (NLR)]. The H-CXI was calculated as [hand-grip strength (HGS)/height^2 × serum albumin/NLR]. The SMI was measured based on the preoperative CT images at the third lumbar vertebra (L3) level. HGS was measured before surgery.

Results: From July 2014 to May 2021, a total of 1,411 patients were included in the present study, of whom 361 (25.6%) were identified as having cancer cachexia. Patients with cachexia had a lower CXI ($p < 0.001$) and lower H-CXI ($p < 0.001$) than those without cachexia. A low CXI but not low H-CXI independently predicted cancer cachexia in the multivariate analysis (OR 1.448, $p = 0.024$). Both a low CXI (HR 1.476, $p < 0.001$ for OS; HR 1.611, $p < 0.001$ for DFS) and low H-CXI (HR 1.369, $p = 0.007$ for OS; HR 1.642, $p < 0.001$ for DFS) were independent predictors for overall survival (OS) and disease-free survival (DFS) after adjusting for the same covariates. A low H-CXI but not low CXI was an independent risk factor for postoperative complications (OR 1.337, $p = 0.044$). No significant association was found between cancer cachexia and postoperative complications.

Conclusion: The CXI and H-CXI exhibited better prognostic value than cancer cachexia for the prediction of postoperative outcomes in patients who underwent radical colectomy for colorectal cancer. The H-CXI was a superior index over the CXI in predicting short-term clinical outcomes, whereas the CXI demonstrated a closer correlation with Fearon's criteria for cancer cachexia. Ideal tools for the assessment of cancer cachexia should incorporate not only weight loss but also muscle mass, physical function, and inflammatory state.

KEYWORDS

cancer cachexia, cachexia index, muscle mass, hand-grip strength, colorectal cancer, prognosis

1 Introduction

Cancer cachexia is a multifactorial syndrome characterized by the ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support (1). Cancer cachexia is associated with impaired physical function (2), more treatment-related toxicity (3), and reduced survival (4). As indicated by a review from Haehling et al., cancer cachexia is believed to be the direct cause of mortality in more than 30% of patients with cancer, and more than 50% of patients with cancer may have died with cachexia being present (5). Colorectal cancer is the third most common malignancy and ranks second in cancer mortality worldwide (6). Cancer cachexia was detected in 55% of patients with stage IV colorectal cancer and was significantly associated with worse overall survival (7). Therefore, the early identification and management of cancer cachexia are significant, which could provide a potential strategy to improve the prognosis of patients with colorectal cancer.

The diagnostic criteria for cancer cachexia varied in the literature (1, 8, 9). In 2011, the international consensus for the definition of cancer cachexia was published by Fearon et al., and it has become the most accepted criteria so far (1). Weight loss was the most important element in the diagnosis of cancer cachexia shared by these criteria. However, several previous studies have found that cancer cachexia diagnosed by weight loss is not an optimal index for the prediction of clinical outcomes (7, 10). Cancer cachexia diagnosed by the Fearon criteria has been reported to have a low agreement with the clinical presentation of cachexia in patients with colorectal cancer (11). Reduced muscle mass and function and increased systemic inflammation are also significant characteristics of cancer cachexia. Therefore, new tools incorporating muscle mass/function and inflammatory indices are needed for the better monitoring of cachexia and prognosis in patients with cancer.

The cachexia index (CXI) was originally developed by Jafri et al. in 2015 to assess the degree of cachexia in patients with advanced non-small-cell lung cancer (NSCLC) (12). The CXI is an objective index calculated as skeletal muscle index (SMI) × serum albumin/neutrophil lymphocyte ratio (NLR). Jafri et al. reported that patients with a low CXI exhibited worse overall survival and progression-free survival (12). Subsequently, several studies from other groups demonstrated that CXI was significantly associated with prognosis in patients with malignancies, such as lung cancer (13) and lymphomas (14). A recent study showed that the CXI was better than the Fearon criteria for cancer cachexia in predicting overall survival in patients with colorectal cancer (15).

However, the measurement of the SMI is complex, and abdominal CT scans are not routinely performed for many types of malignancies, which impedes the clinical application of the CXI. In 2022, Xie et al. developed a hand-grip strength (HGS)-based cancer cachexia index (H-CXI) as a potential predictor of cancer cachexia and prognosis in patients with cancer. The H-CXI was calculated as [HGS (kg)/height $(m)^2$ × serum albumin (g/L)]/NLR. The authors included a nationwide cohort of 14,682 patients with cancer from 41 Chinese medical institutions and found that a low H-CXI was an independent risk factor predicting adverse short-term outcomes and cancer cachexia in patients with cancer (16). The H-CXI is a simple index that has an advantage over the CXI in clinical applications. However, no evidence proves the superiority of the H-CXI over CXI in terms of the prognostic value for clinical outcomes, which is partially due to the lack of high-quality studies investigating the two indices. The present study aims to compare the H-CXI and CXI for the prediction of cancer cachexia and postoperative outcomes in patients who underwent radical colectomy for colorectal cancer.

2 Materials and methods

2.1 Patients

Patients who underwent radical operations for colorectal cancer at the Gastrointestinal Surgical Department, The First Affiliated Hospital of Wenzhou Medical University, China, were included in this study from July 2014 to May 2021. This study included patients who (1) were ≥ 18 years old, (2) had an American Society of Anesthesiologists (ASA) grade not more than III, (3) planned to receive operations for colorectal cancer with curative intent, (4) had abdominal computed tomography (CT) scans available for review within 1 month before surgery, (5) had a blood routine examination within 1 week before surgery, and (6) agreed to take part in the study and sign an informed consent form. Patients with situations of emergency, such as acute abdomen, intestinal obstruction, and acute inflammation, were not included in the present study. We excluded patients who were unable to be measured for hand-grip strength before surgery and those who were confirmed with cancer metastasis during surgery or underwent palliative surgery. All patients were informed that their clinical information would be used anonymously

for research purposes and signed a consent form. This study protocol has been approved by the ethics review board of the First Affiliated Hospital of Wenzhou Medical University. The present study was part of a large-scale prospective study registered in the China Clinical Trial Registry (No. ChiCTR1800019717).

2.2 Data collection

The following data were prospectively collected by specialized investigators: (1) preoperative patient demographic and clinical features, including age, sex, body mass index (BMI), Nutritional Risk Screening 2002 (NRS2002) scores, an American Society of Anesthesiologists (ASA) grade, comorbidity, a previous abdominal operation, tumor location, hemoglobin and serum albumin concentration, and neutrophil and lymphocyte counts; (2) operative details, including laparoscopic surgery and combined organ resection; (3) postoperative pathological characteristics of tumor, including histopathology differentiation and tumor-node-metastasis (TNM) stage; (4) short-term postoperative outcomes, including postoperative complications within 30 days of surgery, length of postoperative hospital stay, and costs during hospitalization; and (5) long-term survival obtained by a follow-up after surgery. Postoperative complications classified as grade II or above according to the Clavien–Dindo classification were analyzed (17).

2.3 Diagnosis of cancer cachexia and the calculation of the cachexia index

Patients who met one of the three following criteria were diagnosed with cancer cachexia according to the international consensus by Fearon et al. (1): (1) weight loss >5% over the past 6 months; (2) BMI <20 and any degree of weight loss >2%; or (3) low skeletal muscle index (SMI) and any degree of weight loss >2%. A cutoff value for low SMI was referenced from the study by Zhuang et al. (18) based on the Chinese population, which was 34.9 cm^2/m^2 for women and 40.8 cm^2/m^2 for men. The cachexia index (CXI) was calculated based on the SMI (12) or hand-grip strength (HGS) (16) and was referred to as the CXI or H-CXI, respectively. The CXI was calculated as SMI (cm^2/m^2) × serum albumin (g/L)/neutrophil-to-lymphocyte ratio (NLR) (12). The H-CXI was calculated as HGS (kg)/height $(m)^2$ × serum albumin (g/L)/NLR (16). The cutoff values for a low CXI and H-CXI were defined using the sex-specific lower quartile, which were 483.25 for the CXI and 98.51 for the H-CXI in males, and 372.96 for the CXI and 66.32 for the H-CXI in females. To measure the SMI, CT images at the third lumbar vertebra (L3) level were analyzed using the image processing system (version 3.0.11.3 BN17 32 bit; INFINITT Healthcare Co., Ltd). To reduce the bias in the measurement of muscle mass, one specialized investigator (Z-Z Li) was trained to analyze the muscle mass under the supervision of an experienced radiologist (Z Zhang). Representative CT images of patients with and without skeletal muscle atrophy are shown in Supplementary Figure S1. Skeletal muscle was identified by Hounsfield unit (HU) thresholds within a range from −29 to +150 and normalized for height (m^2) to calculate the SMI. HGS was measured using electronic hand-grip dynamometers (EH101, Camry, China) before surgery. Patients were guided to grip the hand-grip dynamometers with the dominant hand with all their strength. The maximum value from three consecutive tests was recorded.

2.4 Follow-up

All patients were followed up 1 month after surgery, then every 3 months for the first 2 years, and every 6 months thereafter. The patients were kept in contact with specialized investigators through telephone calls. The patients were scheduled for outpatient visits on the dates of their follow-ups. The follow-up programs included physical examinations, laboratory tests, and radiological examinations such as CT, ultrasonography, and endoscopy as needed. The last follow-up date was January 2022. Overall survival (OS) was calculated from the date of surgery to the date of death from any cause. Disease-free survival (DFS) was calculated from the date of surgery to the date of cancer recurrence or death from any cause, whichever came first.

2.5 Statistical analysis

Continuous data were presented as medians with interquartile ranges (IQR). Categorical variables were presented as numbers and percentages. Differences between groups were analyzed using the Mann–Whitney U test or Kruskal–Wallis test for continuous variables and Pearson's chi-squared tests or Fisher's exact tests for categorical variables. Survival curves were estimated using the Kaplan–Meier method. Log-rank tests were used to test the difference between the groups for the survival data. Logistic regression analysis was conducted to identify risk factors for postoperative complications and cancer cachexia. Cox proportional hazards models were constructed to identify risk factors for OS and DFS. Variables that were considered clinically relevant and candidate variables with P of <0.1 in the univariate analysis were entered into multivariate analysis to identify independent risk factors. We conducted two separate multivariable analyses for complications, OS, DFS, and cancer cachexia including a low CXI or H-CXI, respectively. The cutoff values for the CXI and H-CXI were defined based on the sex-specific lower quartile. All variables were examined for their multicollinearity before inclusion in the multivariate analyses by calculating the variance inflation factor (VIF). Factors with variance inflation factors (VIF) ≥10 were excluded from the multivariate analysis (19). *Post-hoc* analysis for the sample size and power of the study was conducted based on postoperative complications as the main event using PASS software version 11.0. Based on our sample size, the power for a chi-squared test was 0.837 for a low CXI and 0.962 for a low H-CXI. The data were analyzed using SPSS statistics version 22.0 (IBM, United States) and Empower Stats software (version 2.0). *p*-values of <0.05 were considered statistically significant.

3 Results

3.1 Baseline characteristics

A total of 1,411 patients were included in the study, including 539 women and 872 men. The median age of the patients was 66 years. Based on the sex-specific lower quartile of the cachexia

index, there were 353 patients who were classified as low CXI and low H-CXI groups. Specifically, 255 patients had both a low CXI and low H-CXI, 98 patients had only a low CXI but not a low H-CXI, and 98 patients had only a low H-CXI but not a low CXI. The CXI and H-CXI showed a good agreement (kappa = 0.822, $p < 0.001$). Patients with a low CXI or low H-CXI were older, had a lower BMI, SMI, and HGS, lower levels of albumin and hemoglobin and higher NLR, and had a higher incidence of nutritional risk (NRS2002 ≥ 3) than patients with a high CXI or high H-CXI (Table 1).

3.2 Short-term postoperative outcomes

Of the 1,411 patients, postoperative complications occurred in 347 (24.6%) of them. Both a low CXI and low H-CXI showed a significant correlation with a higher incidence of postoperative complications. Details of short-term postoperative outcomes are listed in Supplementary Table S1. Patients with a low H-CXI had significantly longer postoperative hospital stays and more costs than those with a high H-CXI. However, no significant association was found between a low CXI and length of postoperative hospital stay or costs. The univariate analysis showed that a low CXI, a low H-CXI, age ≥ 75 years, ASA grade III, and TNM stage III were associated with the occurrence of postoperative complications, whereas laparoscopic surgery was negatively associated with postoperative complications. The multivariate analysis showed that age ≥ 75 years ($p < 0.001$) and ASA grade III ($p = 0.010$) were independent risk factors for postoperative complications, whereas laparoscopic surgery was an independent protective factor ($p = 0.032$). Notably, when a low H-CXI was included in the multivariate model instead of a low CXI, a low H-CXI was identified as a significant risk factor for postoperative complications in the multivariate analysis ($p = 0.044$) after adjusting for the same covariates (Table 2). Moreover, a low H-CXI showed better sensitivity (32.3% vs. 30.5%), specificity (77.3% vs. 76.8%), accuracy (66.5% vs. 65.4%), positive predictive value (PPV, 31.7% vs. 30.0%), negative predictive value (NPV, 77.8% vs. 77.2%), and larger area under the ROC curve (AUC, 0.548 vs. 0.537) in the prediction of postoperative complications (Table 3).

3.3 Long-term survival

The median follow-up period was 50.1 months. Among 1,411 patients in this cohort, 365 had died and 92 were lost to follow-up during this period. The deceased cohort was older than those lost to the follow-up, which is reasonable because age is the most significant risk factor for death. There was no significant difference between the two cohorts in the other baseline characteristics (Supplementary Table S2). Survival curves showed that both a low CXI and low CXI were significantly associated with worse OS and DFS (Figures 1A–D). When stratified by different TNM stages, a low CXI and low H-CXI were significantly associated with worse OS and DFS in patients with TNM stage II or stage III (Supplementary Figures S2, S3). The univariate analysis showed that age ≥ 75 years, a low CXI, a low H-CXI, cachexia, ASA grade III, low differentiation of tumor, and TNM stage III were associated with worse OS. The multivariate analysis including a low CXI showed that age ≥ 75 years ($p < 0.001$), low CXI ($p = 0.001$), ASA grade III ($p = 0.004$), low tumor differentiation ($p = 0.004$), and TNM stage III ($p = 0.032$) were independent prognostic factors for OS. When a low H-CXI was included in the multivariate model instead of a low CXI, the former remained a significant risk factor ($p = 0.007$). Other independent risk factors remained the same in both multivariate models (Table 4). The univariate analysis for DFS showed that age ≥ 75 years, a low CXI, a low H-CXI, cachexia, NRS2002 ≥ 3, ASA grade III, low differentiation of tumor, and TNM stage III were associated with worse DFS, whereas laparoscopic surgery was associated with better DFS. The multivariate analysis including a low CXI showed that age ≥ 75 years ($p < 0.001$), a low CXI ($p = 0.001$), ASA grade III ($p = 0.021$), low tumor differentiation ($p = 0.003$), and TNM stage III ($p < 0.001$) were independent prognostic factors for DFS. When a low H-CXI was included in the multivariate model instead of a low CXI, a low H-CXI remained a significant prognostic factor ($p < 0.001$) for DFS (Table 5).

3.4 Cancer cachexia

Cancer cachexia was identified in 361 (25.6%) of all the patients using Fearon's criteria. Patients with cachexia had a lower CXI ($p < 0.001$) and lower H-CXI ($p < 0.001$) than those without cachexia. Moreover, a higher TNM stage was associated with a lower CXI ($p = 0.015$) and lower H-CXI ($p = 0.006$). The univariate analysis showed that both a low CXI ($p = 0.001$) and low H-CXI ($p = 0.039$) were associated with cancer cachexia (Table 6). The multivariate analysis showed that a low CXI was an independent risk factor for cachexia ($p = 0.024$), whereas a low H-CXI cannot independently predict cachexia after adjusting for the same covariates ($p = 0.944$). Survival curves showed a worse OS and DFS in patients with cancer cachexia than those without cachexia (Figures 1E,F). Cancer cachexia was associated with worse OS and DFS in the univariate analyses but did not remain a significant risk factor in the multivariate analyses (Tables 4, 5). Moreover, no significant association was found between cancer cachexia and postoperative complications ($p = 0.192$) (Table 2).

4 Discussion

4.1 H-CXI vs. CXI for detecting baseline characteristics and cancer cachexia

The present study showed that both a low CXI and low H-CXI were associated with older age, a lower BMI, SMI, and HGS, lower levels of albumin and hemoglobin, and higher NLR, which indicated that both the CXI and H-CXI reflect body nutritional and functional status as well as systemic inflammation. However, a low CXI but not a low H-CXI was identified as an independent risk factor for cancer cachexia in the present study. Low skeletal muscle mass was one of the diagnostic criteria for cancer cachexia according to the international consensus, whereas HGS was not

TABLE 1 Baseline characteristics of the patients.

Characteristics	All (*n* = 1,411)	High CXI (*n* = 1,058)	Low CXI (*n* = 353)	*p*	High H-CXI (*n* = 1,058)	Low H-CXI (*n* = 353)	*p*
Age, median (IQR), years	66 (7)	64 (16)	69 (16)	<0.001*	64 (16)	71 (15)*	<0.001*
Sex				0.984			0.984
Female	539 (38.2)	404 (38.2)	135 (38.2)		404 (38.2)	135 (38.2)	
Male	872 (61.8)	654 (61.8)	218 (61.8)		654 (61.8)	218 (61.8)	
BMI, median (IQR), kg/m^2	22.7 (4.2)	22.8 (4.3)	22.2 (4.0)	<0.001*	22.8 (4.3)	22.2 (3.8)	<0.001*
Weight loss							
<2%	955 (67.7)	719 (68.0)	236 (66.9)	0.701	715 (67.6)	240 (68.0)	0.887
≥2%	456 (32.3)	339 (32.0)	117 (33.1)		343 (32.4)	113 (32.0)	
Albumin, median (IQR), g/L	38.1 (5.8)	38.4 (5.5)	36.3 (6.4)	<0.001*	38.6 (5.4)	36.1 (6.1)	<0.001*
Hemoglobin, median (IQR), g/L	124 (31)	127 (30)	117 (30.5)	<0.001*	127 (29)	116 (30.5)	<0.001*
NLR, median (IQR)	2.49 (1.75)	2.16 (1.08)	4.52 (2.49)	<0.001*	2.20 (1.19)	4.33 (2.94)	<0.001*
NRS2002 scores				0.043*			0.001*
<3	980 (69.5)	750 (70.9)	230 (65.2)		759 (71.7)	221 (62.6)	
≥3	431 (30.5)	308 (29.1)	123 (34.8)		299 (28.3)	132 (37.4)	
ASA grade				0.714			0.052
I	393 (27.8)	296 (28.0)	97 (27.5)		301 (28.4)	92 (26.1)	
II	863 (61.2)	642 (60.7)	221 (62.6)		653 (61.7)	210 (59.5)	
III	155 (11.0)	120 (11.3)	35 (9.9)		104 (9.8)	51 (14.4)	
Previous abdominal surgery				0.810			0.489
No	1,137 (80.6)	851 (80.4)	286 (81.0)		857 (81.0)	280 (79.3)	
Yes	274 (19.4)	207 (19.6)	67 (19.0)		201 (19.0)	73 (20.7)	
SMI, median (IQR), cm^2/m^2	43.2 (13.2)	44.5 (13.2)	39.9 (10.5)	<0.001*	43.9 (13.3)	41.2 (11.9)	<0.001*
HGS, median (IQR), kg	25.1 (13.7)	25.9 (13.2)	23.2 (13.5)	<0.001*	27.4 (12.8)	18.3 (13.2)	<0.001*
Tumor location				0.909			0.384
Colon	863 (61.2)	648 (61.2)	215 (60.9)		654 (61.8)	209 (59.2)	
Rectum	548 (38.8)	410 (38.8)	138 (39.1)		404 (38.2)	144 (40.8)	
Differentiation of tumor				0.538			0.437
Poorly differentiated	206 (14.6)	158 (38.8)	48 (13.6)		150 (14.2)	56 (15.9)	
Well differentiated	1,205 (85.4)	900 (61.2)	305 (86.4)		908 (85.8)	297 (84.1)	
TNM stage				0.375			0.171
I	351 (24.9)	273 (25.8)	78 (22.1)		276 (26.1)	75 (21.3)	
II	571 (40.5)	422 (39.9)	149 (42.2)		418 (39.5)	153 (43.3)	
III	489 (34.6)	363 (34.3)	126 (35.7)		364 (34.4)	125 (35.4)	
Laparoscopy-assisted surgery				0.246			0.017*
No	630 (44.6)	463 (43.8)	167 (47.3)		453 (42.8)	177 (50.1)	
Yes	781 (55.4)	595 (56.2)	186 (52.7)		605 (57.2)	176 (49.9)	
Combined organ resection				0.601			0.798
No	1,327 (94.0)	993 (93.9)	334 (94.6)		996 (94.1)	331 (93.8)	
Yes	84 (6.0)	65 (6.1)	19 (5.4)		62 (5.9)	22 (6.2)	
Follow-up time, median (IQR), months	50.1 (6.4)	50.3 (6.9)	48.3 (14.1)	0.298	50.3 (7.0)	48.3 (13.8)	0.825

CXI, cachexia index; IQR, interquartile range; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; NRS2002, Nutritional Risk Screening 2002; ASA, American Society of Anesthesiologists; SMI, skeletal muscle index; HGS, hand-grip strength; TNM, tumor-node-metastasis. The values in the table were number of patients and percentage unless indicated otherwise. *Statistically significant.

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TABLE 2 Univariate and multivariate analyses of factors associated with postoperative complications.

Factors	Univariate analysis		Multivariate analysis			
			Low CXI		Low H-CXI	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Age, years						
≥75/<75	2.298 (1.755–3.009)	< **0.001***	2.054 (1.548–2.724)	< **0.001***	2.009 (1.510–2.673)	< **0.001***
Sex						
Male/Female	1.042 (0.812–1.338)	0.745	1.056 (0.817–1.365)	0.676	1.055 (0.816–1.363)	0.683
BMI, kg/m^2						
≥25/<25	1.209 (0.914–1.599)	0.184	–	–	–	–
Low CXI						
Yes/No	1.455 (1.112–1.904)	**0.006***	1.298 (0.981–1.718)	0.068		
Low H-CXI						
Yes/No	1.628 (1.246–2.125)	< **0.001***	–	–	1.337 (1.008–1.772)	**0.044***
Cachexia						
Yes/No	1.199 (0.913–1.574)	0.192	–	–	–	–
Anemia						
Yes/No	1.237 (0.962–1.590)	0.098	0.955 (0.730–1.250)	0.739	0.950 (0.725–1.243)	0.707
NRS2002						
≥3/<3	1.074 (0.827–1.395)	0.591	–	–	–	–
ASA grade						
III/I, II	1.876 (1.318–2.670)	< **0.001***	1.618 (1.120–2.337)	**0.010***	1.575 (1.092–2.274)	**0.015***
Previous abdominal surgery						
Yes/No	0.943 (0.692–1.285)	0.710	–	–	–	–
Tumor location						
Rectum/Colon	1.070 (0.835–1.371)	0.591	–	–	–	–
Differentiation of tumor						
Low/median or high	1.314 (0.946–1.826)	0.103	–	–	–	–
TNM stage						
II/<I	1.307 (0.948–1.801)	0.102	1.200 (0.863–1.669)	0.279	1.198 (0.861–1.666)	0.284
III/<I	1.418 (1.022–1.967)	**0.037***	1.324 (0.946–1.854)	0.101	1.325 (0.946–1.854)	0.101
Combined organ resection						
Yes/No	1.243 (0.762–2.029)	0.383	–	–	–	–
Laparoscopic surgery						
Yes/No	0.691 (0.541–0.881)	**0.003***	0.758 (0.590–0.974)	**0.030***	0.761 (0.592–0.977)	**0.032***

OR, odds ratio; CI, confidence interval; BMI, body mass index; CXI, cachexia index; NRS2002, Nutritional Risk Screening 2002; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis. * Statistically significant.

TABLE 3 Sensitivity and specificity of a low CXI and low H-CXI for the prediction of postoperative complications.

Factors	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	AUC, 95% CI
Low CXI	30.5	76.8	65.4	30.0	77.2	0.537 (0.501–0.572)
Low H-CXI	32.3	77.3	66.5	31.7	77.8	0.548 (0.513–0.584)

PPV, positive predictive value; NPV, negative predictive value, AUC, area under the ROC curve. Postoperative complications classified as Grade II or above by the Clavien–Dindo classification were analyzed.

included in the current diagnostic criteria for cancer cachexia (1). The skeletal muscle index is a parameter in the calculation of CXI (12), which can explain the better predictive value of the CXI for cancer cachexia over the H-CXI. Our results indicated that HGS cannot fully substitute SMI in the detection of cancer cachexia. The measurement of skeletal muscle mass is still imperative for an accurate assessment of cachexia state based on the current diagnostic criteria for cancer cachexia.

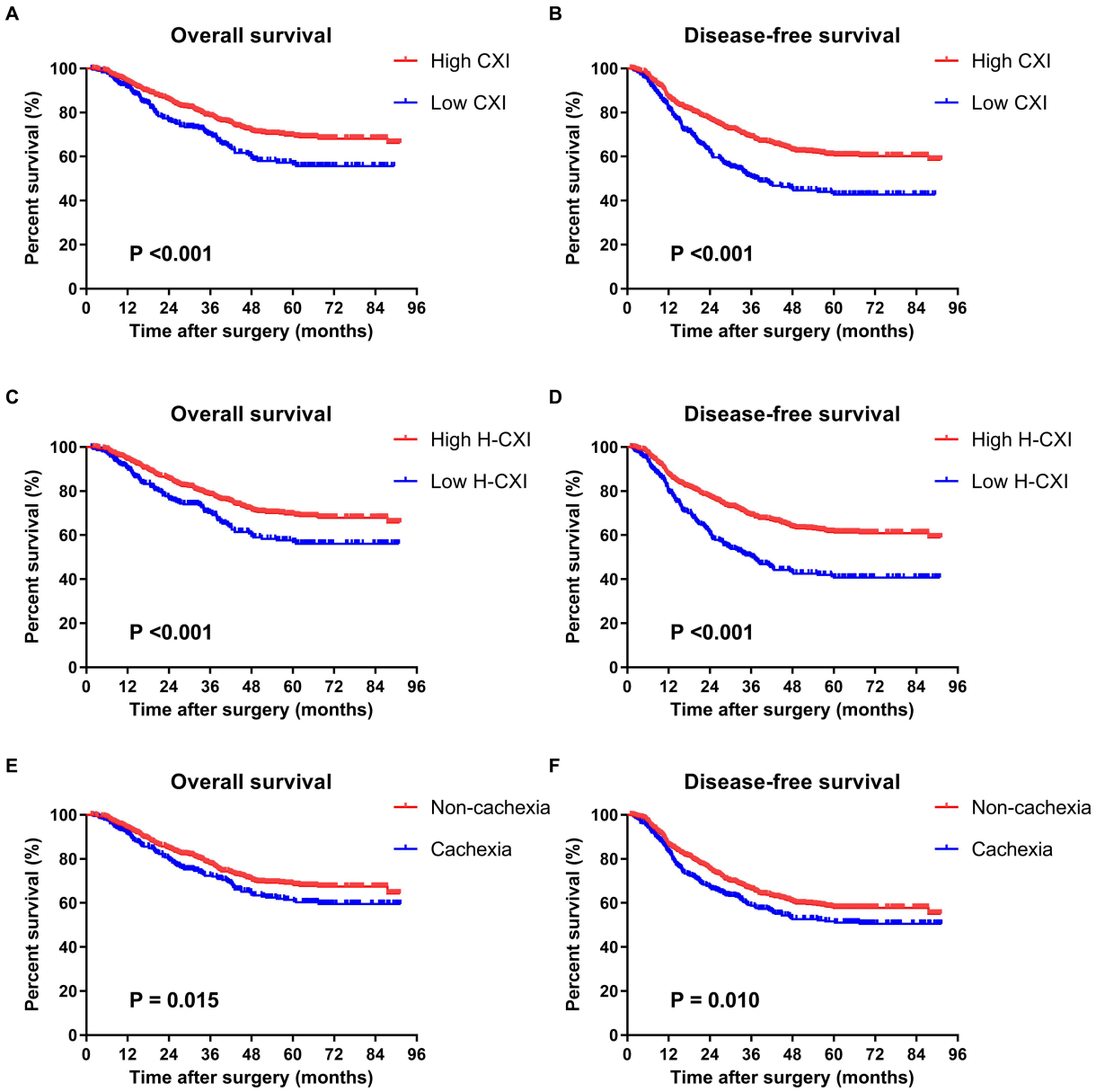

FIGURE 1
Kaplan–Meier survival curves for associations between survival and the CXI, H-CXI, or cancer cachexia. **(A)** Overall survival and **(B)** disease-free survival of patients with a high CXI and low CXI; **(C)** overall survival and **(D)** disease-free survival of patients with a high H-CXI and low H-CXI; and **(E)** overall survival and **(F)** disease-free survival of patients with and without cancer cachexia.

4.2 The H-CXI and CXI rather than cancer cachexia predicted clinical outcomes

Several previous studies have investigated the influence of cancer cachexia on postoperative outcomes in colorectal cancer, and the results were inconsistent (7, 10, 20). The present study showed that the CXI and H-CXI rather than cancer cachexia predicted worse postoperative outcomes. Our finding was consistent with a previous study, which showed that a low CXI instead of cachexia was associated with a decreased OS after surgery for colorectal cancer (15). The diagnosis of cancer cachexia requires the estimation of weight loss, which might be influenced by the subjectivity of patients' recall. On the contrary, the CXI and H-CXI were calculated based on objective parameters such as SMI, HGS, and the results of hematological examinations. The SMI and HGS were key elements for the diagnosis of sarcopenia, serum albumin reflected the nutritional status, and higher NLR indicated higher levels of systemic inflammation (12). Moreover, these three factors were closely correlated with each other. The chronic inflammatory state was the most important feature shared by sarcopenia and malnutrition (21). Both malnutrition and systemic inflammation played a key role in the development of sarcopenia (22). Sarcopenia (18), nutritional status (23), and systemic inflammation (24) were all associated with worse prognosis in patients with cancer. The CXI and H-CXI incorporated all three factors, which can explain their superior prognostic value for postoperative outcomes over cancer cachexia. Previous studies have indicated that current pharmacologic agents used in cancer cachexia

TABLE 4 Univariate and multivariate analyses of factors associated with overall survival[#].

Factors	Univariate analysis		Multivariate analysis			
			Low CXI		Low H-CXI	
	HR (95%CI)	*p*	HR (95%CI)	*p*	HR (95%CI)	*p*
Age, years						
≥75/<75	1.741 (1.393–2.177)	**<0.001***	1.545 (1.218–1.959)	**< 0.001***	1.543 (1.215–1.960)	**< 0.001***
Sex						
Male/Female	0.963 (0.780–1.187)	0.721	0.987 (0.800–1.219)	0.906	0.991 (0.803–1.224)	0.935
BMI, kg/m^2						
≥25/<25	0.982 (0.770–1.252)	0.883	–	–	–	–
Low CXI						
Yes/No	1.542 (1.237–1.922)	**<0.001***	1.476 (1.178–1.849)	**0.001***	–	–
Low H-CXI						
Yes/No	1.534 (1.230–1.913)	**<0.001***	–	–	1.369 (1.090–1.720)	**0.007***
Cachexia						
Yes/No	1.308 (1.052–1.626)	**0.016***	1.187 (0.915–1.540)	0.197	1.212 (0.936–1.570)	0.145
Anemia						
Yes/No	1.100 (0.889–1.360)	0.382	–	–	–	–
NRS2002						
≥3/<3	1.231 (0.995–1.523)	0.055	0.968 (0.748–1.254)	0.807	0.958 (0.741–1.239)	0.743
ASA grade						
III/I, II	1.688 (1.264–2.254)	**<0.001***	1.574 (1.168–2.121)	**0.003***	1.480 (1.100–1.992)	**0.010***
Previous abdominal surgery						
Yes/No	0.998 (0.768–1.297)	0.989	–	–	–	–
Tumor location						
Rectum/Colon	0.986 (0.800–1.216)	0.895	–	–	–	–
Differentiation of tumor						
Low/median or high	1.446 (1.108–1.889)	**0.007***	1.362 (1.036–1.791)	**0.027***	1.325 (1.008–1.742)	**0.044***
TNM stage						
II/<I	1.011 (0.764–1.337)	0.940	0.938 (0.708–1.244)	0.656	0.943 (0.711–1.249)	0.680
III/<I	1.479 (1.127–1.943)	**0.005***	1.332 (1.007–1.763)	**0.045***	1.345 (1.017–1.779)	**0.038***
Combined organ resection						
Yes/No	0.829 (0.523–1.316)	0.427	–	–	–	–
Laparoscopic surgery						
Yes/No	0.838 (0.682–1.031)	0.094	0.943 (0.763–1.165)	0.585	0.952 (0.770–1.176)	0.648

HR, hazard ratio; CI, confidence interval; BMI, body mass index; CXI, cachexia index; NRS2002, Nutritional Risk Screening 2002; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis. * Statistically significant. [#] Cox proportional hazards models were utilized.

may improve weight but not the prognosis (25, 26). The superior prognostic value of the CXI and H-CXI over Fearon's criteria for cancer cachexia recommended we recognize cachexia beyond weight loss alone, focusing more on muscle mass, physical function, and inflammatory state (25).

4.3 H-CXI vs. CXI for the prognostic value

The present study showed that both a low CXI and low H-CXI were independently associated with worse OS and DFS after surgery. Moreover, patients with a higher TNM stage had a lower CXI and lower H-CXI, indicating that both the CXI and H-CXI were good indicators for tumor progression in colorectal cancer. Notably, a low H-CXI but not a low CXI was identified as an independent risk factor for postoperative complications in the present study. Moreover, a low H-CXI but not a low CXI was associated with a longer hospital stay after surgery and costs. This finding indicated that the H-CXI was a better predictive factor for short-term postoperative outcomes than the CXI. Hand-grip strength is the most common measure for the assessment of muscle function (27), which has been proven to be an appropriate proxy for muscle status in many situations (27, 28). Some

TABLE 5 Univariate and multivariate analyses of factors associated with disease-free survival[#].

Factors	Univariate analysis		Multivariate analysis			
			Low CXI		Low H-CXI	
	HR (95%CI)	*p*	HR (95%CI)	*p*	HR (95%CI)	*p*
Age, years						
≥75/<75	1.933 (1.606–2.327)	**<0.001***	1.756 (1.437–2.145)	**<0.001***	1.710 (1.398–2.092)	**<0.001***
Sex						
Male/Female	0.906 (0.760–1.081)	0.275	0.942 (0.788–1.126)	0.511	0.939 (0.786–1.122)	0.489
BMI, kg/m^2						
≥25/<25	0.917 (0.744–1.130)	0.417	–	–	–	–
Low CXI						
Yes/No	1.705 (1.419–2.050)	**<0.001***	1.611 (1.334–1.946)	**<0.001***		
Low H-CXI						
Yes/No	1.838 (1.532–2.205)	**<0.001***	–	–	1.642 (1.357–1.986)	**<0.001***
Cachexia						
Yes/No	1.277 (1.060–1.539)	**0.010***	1.114 (0.891–1.392)	0.345	1.148 (0.920–1.431)	0.222
Anemia						
Yes/No	1.166 (0.974–1.394)	0.094	0.901 (0.745–1.089)	0.280	0.876 (0.723–1.062)	0.179
NRS2002						
≥3/<3	1.227 (1.024–1.471)	**0.026***	0.980 (0.787–1.220)	0.855	0.967 (0.778–1.201)	0.759
ASA grade						
III/I, II	1.478 (1.144–1.908)	**0.003***	1.376 (1.056–1.792)	**0.018***	1.269 (0.975–1.651)	0.076
Previous abdominal surgery						
Yes/No	1.132 (0.914–1.401)	0.257	–	–	–	–
Tumor location						
Rectum/Colon	0.958 (0.802–1.145)	0.640	–	–	–	–
Differentiation of tumor						
Low/median or high	1.529 (1.222–1.913)	**<0.001***	1.417 (1.124–1.785)	**0.003***	1.377 (1.093–1.735)	**0.007***
TNM stage						
II/<I	1.223 (0.960–1.557)	0.103	1.142 (0.894–1.458)	0.287	1.151 (0.902–1.470)	0.258
III/<I	1.772 (1.397–2.248)	**<0.001***	1.630 (1.277–2.082)	**<0.001***	1.646 (1.290–2.101)	**<0.001***
Combined organ resection						
Yes/No	1.076 (0.756–1.531)	0.684	–	–	–	–
Laparoscopic surgery						
Yes/No	0.839 (0.705–0.999)	**0.049***	0.938 (0.784–1.121)	0.480	0.951 (0.796–1.138)	0.584

HR, hazard ratio; CI, confidence interval; BMI, body mass index; CXI, cachexia index; NRS2002, Nutritional Risk Screening 2002; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis. * Statistically significant. [#] Cox proportional hazards models were utilized.

previous studies have demonstrated the superior prognostic value of HGS over skeletal muscle mass for the prediction of clinical outcomes (29, 30). The procedure for the measurement of the skeletal muscle index by CT scans is relatively complicated, requiring experienced technicians to determine the border of muscle mass with the assistance of specialized image processing software. The measurement of the skeletal muscle index is not a routine clinical practice in most medical centers, except for research purposes. The skeletal muscle index is not included in the formal report of CT examinations in routine clinical work. Moreover, abdominal CT scans were not routinely performed in many other types of cancers, except for gastrointestinal cancers. All the abovementioned factors impede the generalization of the skeletal muscle index in clinical practice. On the contrary, hand-grip strength can be easily measured in various types of patients. The results of hand-grip strength tests can be immediately acquired to promote rapid preoperative assessment and risk stratification. Therefore, the H-CXI is the most readily usable measure among the above three tools. Our study indicated that the H-CXI is a superior biomarker over the original CXI in terms of its better prognostic value for short-term postoperative outcomes and its convenience in clinical applications.

TABLE 6 Univariate and multivariate analyses of factors associated with cancer cachexia.

Factors	Univariate analysis		Multivariate analysis			
			Low CXI		Low H-CXI	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Age, years						
≥75/<75	1.572 (1.197–2.064)	**0.001***	0.753 (0.534–1.061)	0.105	0.795 (0.564–1.122)	0.192
Sex						
Male/Female	0.815 (0.639–1.040)	0.100	0.900 (0.674–1.201)	0.474	0.896 (0.672–1.195)	0.454
BMI, kg/m^2						
≥25/<25	0.396 (0.282–0.555)	**< 0.001***	0.529 (0.360–0.775)	**0.001***	0.509 (0.347–0.746)	**0.001***
Low CXI						
Yes/No	1.595 (1.224–2.078)	**0.001***	1.448 (1.049–1.998)	**0.024***	–	–
Low H-CXI						
Yes/No	1.326 (1.014–1.734)	**0.039***	–	–	1.012 (0.729–1.405)	0.944
Anemia						
Yes/No	1.891 (1.479–2.416)	**< 0.001***	1.439 (1.066–1.942)	**0.017***	1.481 (1.098–1.999)	**0.010***
NRS2002						
≥3/<3	11.476 (8.699–15.139)	**< 0.001***	11.394 (8.487–15.297)	**< 0.001***	11.287 (8.416–15.137)	**< 0.001***
ASA grade						
III/I, II	1.052 (0.720–1.536)	0.793	–	–	–	–
Previous abdominal surgery						
Yes/No	1.201 (0.894–1.613)	0.224	–	–	–	–
Tumor location						
Rectum/Colon	0.760 (0.592–0.976)	**0.032***	1.045 (0.774–1.411)	0.775	1.054 (0.780–1.422)	0.733
Differentiation of tumor						
Low/median or high	1.305 (0.942–1.806)	0.109	–	–	–	–
TNM stage						
II/<I	1.681 (1.202–2.351)	**0.002***	1.467 (0.994–2.166)	0.054	1.468 (0.955–2.164)	0.053
III/<I	2.230 (1.592–3.123)	**< 0.001***	2.120 (1.430–3.142)	**< 0.001***	2.131 (1.439–3.154)	**< 0.001***

OR, odds ratio; CI, confidence interval; BMI, body mass index; CXI, cachexia index; NRS2002, Nutritional Risk Screening 2002; ASA, American Society of Anesthesiologists; TNM, tumor-node-metastasis. * Statistically significant.

4.4 Advantages and limitations

Our present study was the first to compare the prognostic value between the CXI and H-CXI. The advantages of our study are the large sample size and the prospective data collection. However, the single-center study design may impede the generalization of our conclusion, which is a limitation of the present study. In addition, we determined the cutoff value for the cachexia index based on the sex-specific lower quartile. Therefore, our cutoff values may not be feasible for other studies, which is also a limitation of our study. However, there was no consensus on the optimal cutoff for the cachexia index. Previous studies set the cutoff values either by the receiver operating characteristic (ROC) curves (13, 15) or by the median CXI of men and women, respectively (31). Since the present study aimed to compare the prognostic value between the CXI and H-CXI, the same proportion of patients (1/4) below the cutoff values could make a rational comparison.

5 Conclusion

In conclusion, the present study showed that the CXI and H-CXI exhibited better prognostic value than cancer cachexia for the prediction of postoperative outcomes in patients who underwent radical colectomy for colorectal cancer. The H-CXI had a similar predictive value for long-term survival and a better predictive value for short-term postoperative outcomes than the original CXI, whereas the CXI had a closer correlation with Fearon's criteria for cancer cachexia. Ideal tools for the assessment of cancer cachexia should incorporate not only weight loss but also muscle mass, physical function, and inflammatory state.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by The Ethical Review Board of The First Affiliated Hospital of Wenzhou Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

X-LY: Writing – original draft, Writing – review & editing, Project administration, Data curation, Formal analysis. L-MW: Writing – review & editing, Formal analysis, Data curation. X-BT: Data curation, Writing – original draft, Writing – review & editing. Z-ZL: Writing – review & editing, Data curation, Formal analysis. ZZ: Data curation, Writing – review & editing, Formal analysis. H-JJ: Writing – review & editing, Data curation. Z-TC: Writing – review & editing, Data curation. D-HC: Writing – review & editing, Data curation. J-YL: Writing – review & editing, Data curation. XS: Conceptualization, Writing – review & editing. D-DH: Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1290299/full#supplementary-material

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Linear association of compound dietary antioxidant index with hyperlipidemia: a cross-sectional study

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Background: There is growing evidence that antioxidant-rich diets may prevent hyperlipidemia. However, the relationship between the Composite Dietary Antioxidant Index (CDAI) and hyperlipidemia is unclear. The CDAI is a composite score reflecting the antioxidant content of an individual's diet, and this study aimed to investigate the relationship between CDAI and hyperlipidemia.

Methods: The study used the 2003–2018 National Health and Nutrition Examination Survey (NHANES) database for cross-sectional analyses and included 27,626 participants aged 20 years and older. The CDAI, which includes vitamins A, C, and E, zinc, selenium, and carotenoids, was calculated based on dietary intake reported in a 24-h recall interview. Hyperlipidemia was defined by the National Cholesterol Education Program (NCEP). Covariates included age, sex, race, education, marriage, household poverty-to-income ratio (PIR), glomerular filtration rate (eGFR), body mass index (BMI), energy, carbohydrates, total fat, cholesterol, smoking, alcohol consumption, hypertension, diabetes mellitus, coronary heart disease, and lipid-lowering medications. The association between CDAI and hyperlipidemia was explored through multiple logistic regression analyses and smoothed curve fitting. We also performed subgroup analyses and interaction tests to verify the relationship's stability.

Results: After adjusting for potential confounders, CDAI was negatively associated with the risk of developing hyperlipidemia (OR 0.98, 95% CI 0.96–0.99, $p<0.01$). The results of weighted regression models stratified by quartiles of CDAI ($-8.664 \leq Q1 \leq -2.209$, $-2.209 < Q2 \leq -0.002$, $-0.002 < Q3 \leq 2.774$, $2.774 < Q4 \leq 124.284$), fully adjusted for confounding variables, indicated that compared with the bottom quartile (Q1) of the CDAI, Q2, Q3, and Q4 of participants had a lower advantage ratio (Q2: OR 0.91, 95% CI 0.78–1.06, $p<0.21$; Q3: OR 0.85, 95% CI 0.73–1.00, $p<0.05$; and Q4: OR 0.77, 95% CI 0.64–0.94, $p<0.01$), which was confirmed by a test for trend ($p<0.05$). Smoothed curve fit analysis showed linearity (p for non-linear=0.0912). In summary, there is a linear negative relationship between CDAI and the risk of developing hyperlipidemia. Subgroup analyses by age, sex, ethnicity, education level, marriage, tobacco status, alcoholic drinking, body mass index (BMI), hypertension, and diabetes did not indicate strong interactions.

Conclusion: In this large cross-sectional study, there was a linear negative association between CDAI and hyperlipidemia among US adults. Therefore increase antioxidant rich foods in your life as a prevention of hyperlipidemia.

KEYWORDS

CDAI, hyperlipidemia, relationship, a cross-sectional study, NHANES

1 Introduction

Hyperlipidemia is a metabolic disorder in which there is an abnormally high level of lipids in the blood and is clinically classified as hypercholesterolemia, hypertriglyceridemia, mixed hyperlipidemia, and low HDL cholesterolemia, depending on the type of elevated lipoprotein (1, 2). Hyperlipidemia has been a widespread concern in Europe, America, and other developing countries. According to epidemiologic surveys, it was found that in the United States, about 12% of adults ≥20 years of age had total cholesterol levels higher than 240 mg/dL, and about 17% had high-density lipoprotein (HDL) cholesterol levels <40 mg/dL between 2015 and 2018 (3). Hyperlipidemia is one of the risk factors for several vascular diseases (4). Thus, it increases the risk of disease in the elderly (5). The prevalence of hyperlipidemia continues to grow as the world faces an increasingly aging population (6). Hyperlipidemia is associated with a variety of diseases such as stroke, diabetes, coronary heart disease, and other chronic diseases (7), severely reducing the quality of life, shortening the lifespan of the patients, and causing a substantial economic burden. Based on this fact, finding effective treatments to address this problem is essential.

Current research has identified the key to oxidative stress as reactive oxygen species (ROS), and the overproduction of ROS has been linked to pathological diseases such as obesity, insulin resistance, hyperglycemia, chronic inflammation and dyslipidemia (8–10). During physiological circumstances, ROS are readily modulated by counter-oxidants. However, counter-oxidants can be obtained *in vivo* and *in vitro* (11). When antioxidant deficiencies and malnutrition result in the body being more susceptible to oxidative stress, thus improving the risk of an adverse reaction (12). There is evidence of an association between hyperlipidemia and oxidative stress (13). Vitamin A (VA) as a dietary antioxidant, Wang et al. (14). In an intervention experiment in diabetic adipose rats, administration of VA for 8 weeks was able to improve fat metabolism to reduce hyperlipidemia. Vitamin E (VE) derives its antioxidant activity mainly from α-tocopherol and γ-tocopherol. In a study in children and adolescents, administration of micronutrients VE and VA was shown to reduce blood lipids through antioxidant properties (15). Administration of zinc alone in type 2 diabetic rats improved lipid levels (16), in addition to dietary zinc reducing oxidative stress (17). It is apparent that numerous studies have confirmed the effect of single antioxidants on hyperlipidemia, but the relationship between combined dietary antioxidant intake and hyperlipidemia still needs to be explored.

In recent years, the role of antioxidants has become prominent in global dietary patterns, and the impact of total nutritional antioxidant capacity on health has become increasingly common in all sectors (18). Dietary antioxidant supplementation through consuming fruits, vegetables, whole grains, nuts, and legumes has been suggested (19), and the intake of adequate antioxidants may help reduce the burden of oxidative stress (20). CDAI was proposed by Wright et al. (21) as a composite score reflecting antioxidant capacity of one's diet, which includes vitamins A, C, and E, zinc, selenium, and carotenoids. Previous studies have found that CDAI improves heart failure, hypertension, depression, and atherosclerotic cardiovascular disease and reduces the risk of morbidity (18, 22–24). However, there are no studies on the relationship between CDAI and hyperlipidemia.

In this study, we explored the association between CDAI and hyperlipidemia for the first time using a large-sample cross-sectional design. Based on previous studies, it was hypothesized that there may be a negative association between CDAI and hyperlipidemia, intending to prevent hyperlipidemia and reduce the risk of its onset through diet, with important clinical implications.

2 Materials and methods

2.1 Study participants

The National Health and Nutrition Examination Survey (NHANES) is a United States population census intended to accurately estimate health and nutritional status, applying stratified, multistage, and probability sampling methods to obtain comprehensive data. This survey utilized a database of 80,312 participants from 8 cycles of NHANES in the United States from 2003 to 2018. After excluding participants with age < 20 years ($n = 35{,}522$) and missing or incomplete data on hyperlipidemia ($n = 1871$), CDAI ($n = 7{,}890$), and covariates ($n = 7{,}403$), we ultimately included 27,626 participants. Figure 1 shows a flow diagram of the entire sample selection process. The National Center for Health Statistics (NCHS) Ethics Review Committee approved the research, and all subjects signed an informed consent form.

2.2 Measurement of CDAI

During the NHANES survey, a professional statistician conducted two 24-h recall dietary interviews to collect information on the intake of nutritional antioxidants and other food components. The primary recollection interview was performed at the Mobile Screening Center, and the secondary recollection interview was obtained 3–10 days later through a telephone inquiry. Participants were asked to recall the specifics of all diets over 24 h, and dietary supplement intake, including dose, frequency, and duration, was determined (25). The Composite Dietary Antioxidant Index (CDAI) includes six dietary antioxidants: vitamins A, C, and E, zinc, selenium, and carotenoids. This dietary antioxidant access excludes antioxidants in nutritional supplements, medications, or drinking water. The CDAI was calculated by subtracting the mean and dividing by the standard deviation of an individual's intake, and the results were as follows:

$$CDAI = \sum_{i=1}^{6} \frac{Individual\ Intake - Mean}{SD}.$$

2.3 Definition of hyperlipidemia

Relying on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III), we estimated the Hyperlipidemia status. We defined Hyperlipidemia as (1) triglycerides (TG) ≥ 150 mg/dL (1.7 mmol/L), (2) total cholesterol (TC) ≥ 200 mg/dL (5.18 mmol/L), (3) low-density lipoprotein (LDL-C) ≥ 130 mg/dL (3.37 mmol/L), (4) high-density lipoprotein (HDL-C<), ≤40 mg/dL (1.04 mmol/L) for men or ≤ 50 mg/dL (1.30 mmol/L) for women, and (5) a participant that reported the use of lipid-lowering drugs was at

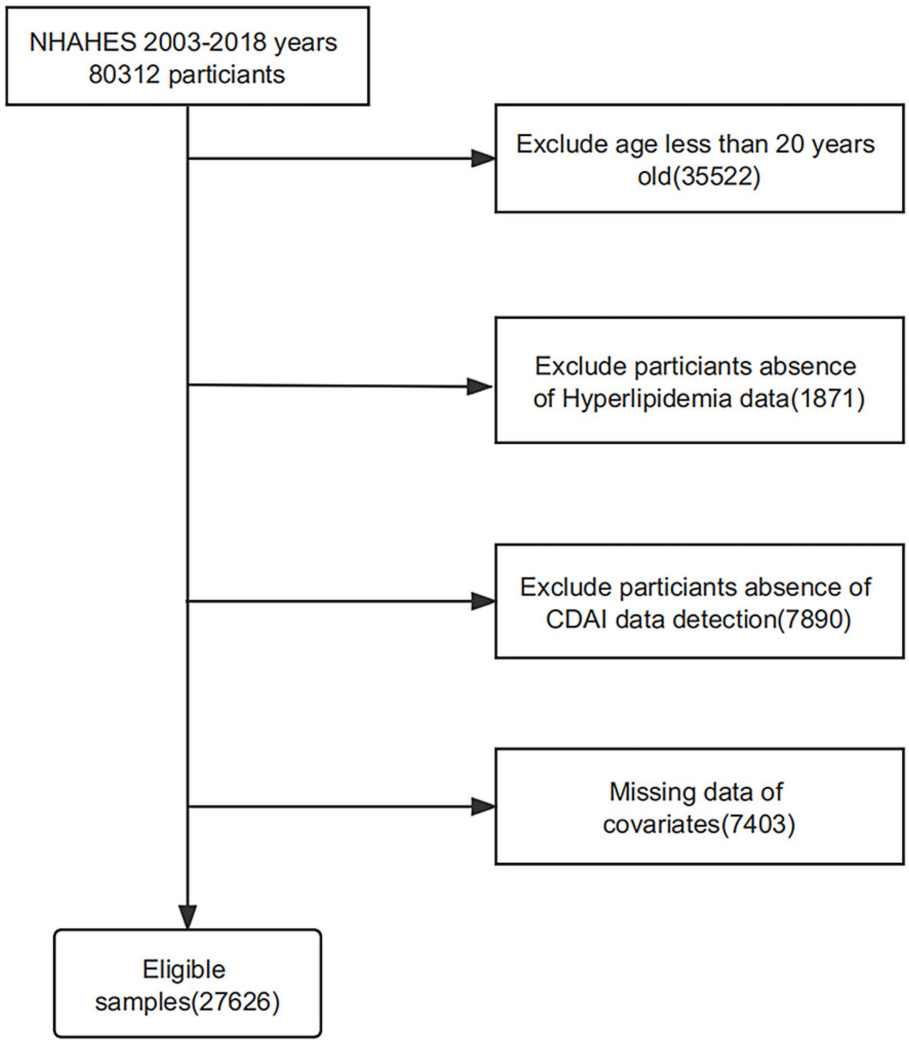

FIGURE 1
Flowchart depicting participant selection in the study.

the same time defined as having hyperlipidemia (3, 26–28). Hyperlipidemia was diagnosed if any of these five conditions were met.

2.4 Assessment of covariates

Based on previous studies and confounders, we selected the following covariates including age, sex (male/female), race (Mexican American/other Hispanic/non-Hispanic white/non-Hispanic black/other race), educational attainment (less than 9th grade, 9th–11th grade, high school graduation, some college graduation, and college and beyond), marital status (married, widowed, divorced, separated, unmarried, living with a partner), and household poverty-to-income ratio (PIR, <1.3, 1.3–3.5, ≥3.5); income-to-poverty ratios were calculated based on the US Department of Health and Human Services (DHHS) Family Income Poverty Guidelines (29). Smoking was categorized as (1) non-smoking (2) former tobacco (3) current smoking. Alcohol consumption was categorized as (1) no alcohol consumption, (2) previous alcohol consumption, (3) mild alcohol consumption, (4) moderate alcohol consumption, (5) heavy alcohol consumption. Body mass index (BMI) is weight (Kg) divided by the square of height (m). The glomerular filtration rate (eGFR) was calculated based on the serum creatinine equation (30). Energy, carbohydrate, total fat, and cholesterol intake were determined by averaging dietary recall over 2 days; coronary artery disease and lipid-lowering medications were obtained by a questionnaire that recorded whether participants were told by a physician that they had coronary artery disease and were taking lipid-lowering medications. The definition of diabetes was sufficient to satisfy any of the following: (1) self-reported physician diagnosis of diabetes mellitus, (2) current use of glucose-lowering medications or insulin injections, an (3) randomized Blood glucose ≥11.1 mmol/L, (4) Glycated hemoglobin (HbA1c) level ≥ 6.5%, (5) Fasting blood glucose (FPG) level ≥ 7.0 mmol/L, and (6) 2-h OGTT blood glucose level ≥ 11.1 mmol/L. The definition of hypertension can be satisfied with any one of the following: (1) self-reported high blood pressure, (2) patients taking antihypertensive medication, (3) mean systolic blood pressure (SBP) ≥140 mmHg and/or mean diastolic blood pressure (DBP) ≥90 mmHg; detailed measurement procedures for all covariates are available at www.cdc.gov/nchs/nhanes/index.htm.

2.5 Statistical analysis

All data in this study were statistically analyzed using the R language (version 4.3.1) and followed the guidelines established by the Centers for Disease Control and Prevention (CDC). We weighted the data in the data analysis, applying mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Differences between categorical variables were analyzed using the chi-square test, while continuous variables conforming to normal distribution were tested with the weighted Student's *t*-test; otherwise, they were tested with the Man-Whitney *u*-test. The correlation between CDAI and hyperlipidemia was studied using multifactor logistic regression modeling. CDAI was transformed into categorical variables by quartiles, and the linear trend test and *p*-value of the trend were calculated to determine the consistency of the relationship. Three models were constructed for this research: Model 1, a crude model without adjusting for any variables; Model 2, adjusted for sex, age, and race; and Model 3, which continued to change for education, marriage, PIR, eGFR, BMI, energy, carbohydrates, total fat, cholesterol, smoking, alcohol, hypertension, diabetes mellitus, coronary artery disease, and lipid-lowering medications based on Model 2. Smoothed curve fitting was applied to explore further whether there was a linear relationship between CDAI and hyperlipidemia. In addition, to investigate whether there were interactions and stability between subgroups, we performed subgroup-stratified analyses for age, gender, race, education level, marriage, smoking status, alcohol consumption, BMI, hypertension, and diabetes mellitus. A *p*-value of below 0.05 was recognized as statistically significant.

3 Results

3.1 Characteristics of participants

This research included 27,626 participants, with a mean age of 47.42 ± 0.24 years, of which 51.23% were female and 48.77% were male. Baseline characteristics of participants by CDAI quartiles are shown in Table 1, differences between quartiles were statistically significant ($p < 0.05$) for age, sex, race, education, marriage, PIR, smoking, alcohol consumption, BMI, eGFR, energy, carbohydrates, total fat, cholesterol, hypertension, diabetes mellitus, coronary artery disease, and use of lipid-lowering drugs. Compared to Q1, Q4 tended to be younger, male, non-Hispanic white, with lower BMI, better economic standard, and higher education status. Non-smoking and mild alcohol consumption had greater levels of CDAI. The higher the CDAI level, the more energy, carbohydrates, total fat, and cholesterol they consume. Hypertension, diabetes mellitus, coronary heart disease, and hyperlipidemia decreased with increasing CDAI.

3.2 Relationship between CDAI and hyperlipidemia

The multivariate logistic regression model, as shown in Table 2, demonstrates the correlation between CDAI and the risk of hyperlipidemia. In model 3, CDAI scores were negatively associated with the risk of developing hyperlipidemia (OR 0.98, 95% CI 0.96–0.99). This negative correlation was more pronounced in participants with a lower predominance ratio of hyperlipidemia than in Q1 according to quartile stratification in Q2 (OR 0.91, 95% CI 0.78–1.06), Q3 (OR 0.85, 95% CI 0.73–1.00), and Q4 (OR 0.77, 95% CI 0.64–0.94) and was also confirmed by a test of trend in each model using Q1 as control this ($p < 0.05$). We also used smoothed curve fitting to assess the association between the two; as shown in Figure 2, the correlation between CDAI and hyperlipidemia was negative and linear (p for non-linear = 0.0912).

3.3 Subgroup analysis

As shown in Figure 3, we stratified age, gender, race, education level, marriage, smoking status, alcohol consumption, BMI, hypertension, and diabetes to explore the stability of the relationship between CDAI and hyperlipidemia and the presence or absence of interaction. In subgroup analyses, no significant interactions were found between CDAI and these stratified variables ($p > 0.05$), and the relationship was very stable.

4 Discussion

The study analyzed the most representative US population data and, after adjusting for several covariates, found that CDAI was negatively associated with the prevalence of hyperlipidemia in the population, which confirms our hypothesis. These results suggest that appropriate dietary modification and increased antioxidant intake can help prevent and treat hyperlipidemia. Although previous studies have demonstrated the effect of dietary antioxidants such as VA, VE, and zinc on hyperlipidemia, most of them applied a single class of antioxidants for correlation analysis and did not consider them in combination. However, the intake of a single antioxidant is difficult to achieve in the daily diet, and it is more likely that a wide range of foods and a wide range of antioxidants will be consumed. In addition, there is no single antioxidant component in foods that are rich in multiple antioxidants. Therefore, there is a need to investigate the relationship between combined dietary antioxidant intake and hyperlipidemia.

Oxidative stress plays a vital role in hyperlipidemia. Wu et al. (31) found that the substrates of *G. frondosa* decreased glutathione (GSH) and catalase activity, increased GSH peroxidase activity, inhibited oxidative stress, and increased bile acid synthesis to improve hypercholesterolemia. Feng et al. (32) administered hawthorn fructofuranic acid (HFA) to rats. Found that activation of Nrf2/HO-1 signaling pathway could inhibit oleic acid (OA)-induced oxidative damage in a hepatocellular carcinoma cell line (HepG2), which in turn reduced oxidative stress damage in rats, effectively reduced triglyceride and cholesterol levels, attenuated hepatic steatosis and intervened in hyperlipidemia. Pretreatment with *M. charantia* polysaccharides for 25 days in a rat model was found to inhibit oxidative stress via nuclear factor κB (NF-kB), lowering lipid indices, and consequently ameliorating hyperlipidemia (33). Ji et al. (34) further found that consumption of propolis by rabbits with hypercholesterolemia lowered the lipid levels and enhanced antioxidant activity by a mechanism which may be the inhibition of the TLR4-mediated NF-κB signaling pathway. Puerarin was found to reduce ROS production and increase antioxidant capacity by modulating the phosphorylated

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TABLE 1 The characteristics of participants.

Variable	Total	Q1 (−8.664, −2.209)	Q2 (−2.209, −0.002)	Q3 (−0.002, 2.774)	Q4 (2.774, 124.284)	*p*-value
N	27,626	6,907	6,906	6,907	6,906	
Age, year	47.42 ± 0.24	47.88 ± 0.36	48.10 ± 0.34	47.35 ± 0.38	46.56 ± 0.35	0.001
Gender, *n* (%)						<0.0001
Female	14,008 (51.23)	3,792 (57.88)	3,471 (51.40)	3,416 (49.84)	3,329 (47.33)	
Male	13,618 (48.77)	3,115 (42.12)	3,435 (48.60)	3,491 (50.16)	3,577 (52.67)	
Race, *n* (%)						<0.0001
Mexican American	4,231 (8.01)	1,074 (8.06)	1,135 (8.70)	1,040 (7.89)	982 (7.50)	
Non-Hispanic Black	5,558 (10.22)	1,741 (14.35)	1,398 (11.06)	1,214 (8.39)	1,205 (8.09)	
Non-Hispanic White	13,160 (70.38)	2,959 (65.68)	3,238 (68.75)	3,449 (72.52)	3,514 (73.30)	
Other race	2,423 (6.70)	498 (6.51)	586 (7.05)	637 (6.41)	702 (6.81)	
Others	2,254 (4.70)	635 (5.40)	549 (4.44)	567 (4.78)	503 (4.30)	
Education, *n* (%)						<0.0001
9–11th grade	3,702 (9.76)	1,218 (14.87)	955 (10.00)	815 (8.41)	714 (6.94)	
College graduate or above	6,635 (30.26)	932 (17.00)	1,474 (26.45)	1,926 (34.22)	2,303 (39.83)	
High school graduate	6,409 (23.38)	1,813 (29.28)	1,670 (25.17)	1,535 (21.87)	1,391 (18.79)	
Less than 9th grade	2,543 (4.49)	1,012 (7.36)	689 (5.09)	507 (3.86)	335 (2.38)	
Some college	8,337 (32.12)	1,932 (31.49)	2,118 (33.29)	2,124 (31.64)	2,163 (32.06)	
Marital status, *n* (%)						<0.0001
Divorced	3,050 (10.52)	882 (12.70)	749 (10.31)	701 (9.79)	718 (9.73)	
Living with partner	2,108 (7.67)	539 (8.59)	517 (8.44)	506 (7.08)	546 (6.87)	
Married	14,731 (56.21)	3,312 (48.69)	3,708 (55.97)	3,875 (58.99)	3,836 (59.53)	
Never married	4,691 (17.87)	1,220 (19.69)	1,133 (17.33)	1,118 (16.66)	1,220 (18.11)	
Separated	848 (2.15)	262 (3.16)	220 (1.96)	190 (2.04)	176 (1.64)	
Widowed	2,198 (5.57)	692 (7.17)	579 (5.99)	517 (5.44)	410 (4.11)	
PIR						<0.0001
<1.30	8,094 (20.25)	2,653 (28.63)	2,077 (21.98)	1,734 (17.07)	1,630 (15.41)	
1.30–3.50	10,537 (35.16)	2,734 (38.80)	2,703 (36.25)	2,616 (33.93)	2,484 (32.63)	
≥3.50	8,995 (44.59)	1,520 (32.57)	2,126 (41.77)	2,557 (49.00)	2,792 (51.96)	
Smoking status, *n* (%)						<0.0001
Former	7,085 (25.20)	1,648 (21.57)	1,824 (25.33)	1,808 (26.29)	1,805 (26.82)	
Never	14,972 (54.80)	3,376 (48.47)	3,736 (53.90)	3,871 (56.40)	3,989 (58.87)	
Now	5,569 (20.00)	1,883 (29.96)	1,346 (20.76)	1,228 (17.31)	1,112 (14.30)	
Alcohol use, *n* (%)						<0.0001
Former	4,807 (13.85)	1,453 (16.96)	1,256 (14.40)	1,090 (12.60)	1,008 (12.21)	
Heavy	5,331 (20.95)	1,366 (23.09)	1,333 (21.73)	1,278 (19.91)	1,354 (19.66)	
Mild	9,497 (36.80)	1,955 (29.90)	2,394 (36.38)	2,541 (37.82)	2,607 (41.47)	
Moderate	4,294 (17.72)	993 (16.73)	1,002 (16.57)	1,144 (19.22)	1,155 (18.00)	
Never	3,697 (10.68)	1,140 (13.31)	921 (10.92)	854 (10.46)	782 (8.67)	
BMI, kg/m^2	28.97 ± 0.09	29.25 ± 0.12	29.23 ± 0.13	28.93 ± 0.14	28.58 ± 0.15	0.001
eGFR, mL/min/1.73 m2	93.63 ± 0.32	93.04 ± 0.45	92.66 ± 0.45	93.80 ± 0.49	94.77 ± 0.44	<0.001
Energy, kcal	2117.91 ± 8.49	1442.51 ± 10.46	1898.05 ± 10.80	2226.76 ± 11.80	2716.42 ± 17.52	<0.0001
Carbohydrate, g	252.27 ± 1.06	179.44 ± 1.71	227.01 ± 1.64	263.32 ± 1.83	318.78 ± 2.27	<0.0001
Total fat, g	81.79 ± 0.42	52.32 ± 0.43	72.58 ± 0.52	87.10 ± 0.61	107.03 ± 0.88	<0.0001

(Continued)

TABLE 1 (Continued)

Variable	Total	Q1 (−8.664, −2.209)	Q2 (−2.209, −0.002)	Q3 (−0.002, 2.774)	Q4 (2.774, 124.284)	*p*-value
Cholesterol, mg	292.17 ± 1.87	183.38 ± 2.14	261.21 ± 2.61	311.55 ± 3.55	383.03 ± 4.41	<0.0001
Hypertension						<0.001
No	15,695 (62.47)	3,617 (60.15)	3,798 (60.08)	4,061 (64.00)	4,219 (64.81)	
Yes	11,931 (37.53)	3,290 (39.85)	3,108 (39.92)	2,846 (36.00)	2,687 (35.19)	
CHD						0.001
No	26,415 (96.37)	6,538 (95.67)	6,581 (95.83)	6,625 (96.54)	6,671 (97.19)	
Yes	1,211 (3.63)	369 (4.33)	325 (4.17)	282 (3.46)	235 (2.81)	
DM						<0.0001
No	22,650 (86.78)	5,426 (84.59)	5,546 (84.47)	5,778 (88.33)	5,900 (88.93)	
Yes	4,976 (13.22)	1,481 (15.41)	1,360 (15.53)	1,129 (11.67)	1,006 (11.07)	
AntiHyperlipidemic						<0.001
No	21,984 (82.28)	5,387 (82.05)	5,360 (79.89)	5,520 (82.78)	5,717 (83.99)	
Yes	5,642 (17.72)	1,520 (17.95)	1,546 (20.11)	1,387 (17.22)	1,189 (16.01)	
Hyperlipidemia						<0.0001
No	7,623 (28.91)	1,716 (26.27)	1,787 (27.11)	1,939 (29.38)	2,181 (32.00)	
Yes	20,003 (71.09)	5,191 (73.73)	5,119 (72.89)	4,968 (70.62)	4,725 (68.00)	
CDAI	1.02 ± 0.06	−3.74 ± 0.03	−1.10 ± 0.01	1.25 ± 0.01	6.24 ± 0.07	<0.0001
Vitamin A, ug	650.77 ± 6.49	287.55 ± 3.57	480.49 ± 4.12	654.27 ± 5.15	1069.26 ± 14.72	<0.0001
Vitamin C, mg	83.00 ± 0.94	35.67 ± 0.55	60.93 ± 0.83	85.27 ± 1.10	135.69 ± 1.75	<0.0001
Vitamin E, mg	8.42 ± 0.08	4.17 ± 0.04	6.36 ± 0.05	8.51 ± 0.07	13.33 ± 0.14	<0.0001
Zinc, mg	11.79 ± 0.08	6.76 ± 0.05	9.80 ± 0.07	12.19 ± 0.09	16.92 ± 0.18	<0.0001
Selenium, ug	114.08 ± 0.59	70.51 ± 0.54	99.12 ± 0.56	119.80 ± 0.67	154.57 ± 1.26	<0.0001
Carotenoid, ug	9990.59 ± 136.86	3558.74 ± 62.66	6485.76 ± 85.01	9735.40 ± 112.53	18118.56 ± 276.35	<0.0001

PIR, Income to poverty ratio; BMI, body mass index; eGFR, estimated glomerular filtration rate; CHD, coronary heart disease; DM, diabetes mellitus; CDAI, composite dietary antioxidant index.

TABLE 2 The association between CDAI and hyperlipidemia.

Character	Model 1		Model 2		Model 3	
	95%CI	*p*	95%CI	*p*	95%CI	*p*
CDAI	0.97 (0.97, 0.98)	<0.0001	0.97 (0.97, 0.98)	<0.0001	0.98 (0.96, 0.99)	0.01
CDAIQ						
Q1	1 (ref)		1 (ref)		1 (ref)	
Q2	0.96 (0.84, 1.09)	0.50	0.93 (0.81, 1.06)	0.28	0.91 (0.78, 1.06)	0.21
Q3	0.86 (0.76, 0.97)	0.01	0.84 (0.74, 0.95)	0.01	0.85 (0.73, 1.00)	0.05
Q4	0.76 (0.67, 0.86)	<0.0001	0.75 (0.66, 0.85)	<0.0001	0.77 (0.64, 0.94)	0.01
p for trend	<0.0001		<0.0001		0.01	

Model 1: non-adjusted.
Model 2: adjusted age, gender, race.
Model 3: adjusted age, gender, race, education, marital, PIR, smoke, alcohol, eGFR, BMI, energy, carbohydrate, total, cholesterol, DM, hypertension, CHD, antiHyperlipidemic.

Jun N-terminal kinase (JNK)/phosphorylated c-Jun protein/cholesterol 7a-hydroxylase (CYP7A1) pathway in mouse liver, which in turn inhibited hyperlipidemia (35). Fan et al. (36) used baicalein to intervene in hyperlipidemic rats and showed results of enhanced activation of PI3K/AKT and activation of Nrf2, thereby increasing the expression of HO-1 and NQO1, inhibiting oxidative stress and preventing hyperlipidemia. Honey pretreatment given to rats before feeding them a high-fat diet was found to be able to attenuate oxidative stress and exert anti-hyperlipidemia effects more significantly by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (37). Antunes et al. (38) experimented with different combinations of phenolic compounds from purple grape bark, both *in vitro* and *in vivo*, and all of the results showed an antioxidant effect, thereby reducing hypercholesterolemia. Administration of p-coumaric

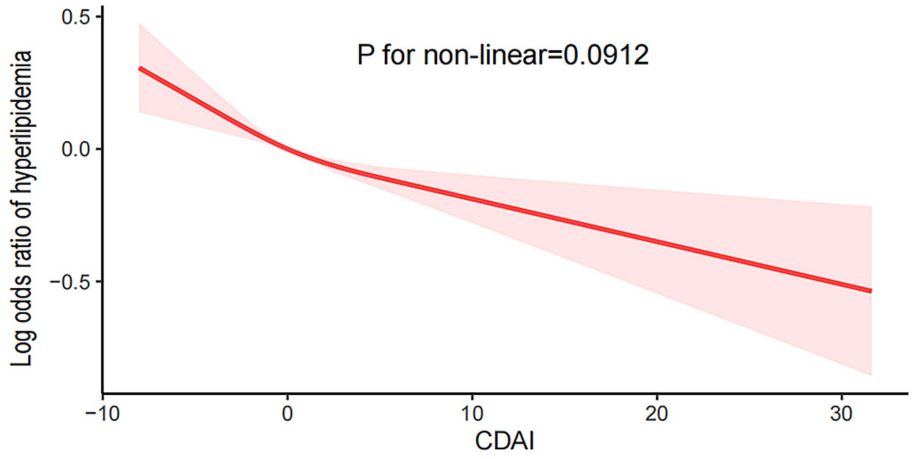

FIGURE 2
The smooth curve fitting analysis of CDAI and hyperlipidemia.

acid (p-CA) in mouse experiments revealed an increase in the expression of Nrf2, HO-1, glutathione peroxidase (Gpx), and superoxide dismutase (SOD-1), which in turn exerted an antioxidant and potentially therapeutic effect in the treatment of hyperlipidemia (39). In conclusion, inhibition of oxidative stress, which can treat hyperlipidemia, is the same as the conclusions of cross-sectional studies on the relationship between CDAI and hyperlipidemia.

This study also found that the prevalence of hypertension, diabetes mellitus, and coronary heart disease decreased progressively with increasing CDAI. Previous analyses of the NHANES database found that the prevalence of hypertension, coronary heart disease, and diabetes mellitus were negatively correlated with CDAI (18, 23, 40), which is consistent with our findings. Control variables such as energy, carbohydrates, total fat, and cholesterol, which may affect the results of the study, were added to the previous ones. In addition, instead of using the traditional Dietary Antioxidant Quality Score (DAQS) for assessing dietary antioxidant indices in this study, the more accurate CDAI was used for correlation analyses because of its applied advantages and validity proved in epidemiological studies.

Diet is essential in treating hyperlipidemia by containing antioxidants that reduce oxidative stress damage and promote health (41). Antioxidants are biologically active compounds that neutralize free radicals and reduce oxidative damage (42). Although there are no studies on the relationship between CDAI and hyperlipidemia, the use of dietary antioxidant properties to intervene in hyperlipidemia has become a hot research topic. The vitamins (A, D, and E) and carotenoids in CDAI are fat-soluble and vitamin C is water-soluble, which is relevant for absorption, transport and action. Feeding a VA-rich (52 mg/kg) diet for 20 weeks in hypercholesterolemic obese rats increased plasma lecithin cholesterol acyltransferase activity and expression of ATP-binding cassette transporter protein A1, which, in turn, led to normalization of plasma HDL-C levels (43). Vitamin C (VC) is an essential nutrient for humans and the effect of administration is highly dose dependent (44), maximizing neutrophil concentration, reducing ROS production and inhibiting LDL-C oxidation through dietary intake (45, 46). Kumar et al. (47) administered VC (0.5 g/kg) once daily for 30 days in a male rat model of hyperlipidemia. It showed a decrease in triglycerides, cholesterol, ROS, malondialdehyde (MDA), and reduced GSH, the mechanism of which may be to prevent hyperlipidemia by inhibiting oxidative stress and maintaining redox balance. In a randomized double-blind crossover study, VC (1,000 mg) in combination with dietary nitrates given to untreated hypercholesterolemic subjects for 4 weeks was found to reduce oxidized low-density lipoprotein (oxLDL), triglycerides and inhibit oxidative stress by increasing the total plasma NO metabolites (48). Selenium was able to maintain the anti-oxidative stress function of glutathione peroxidation and selenoprotein P (49). Guo et al. (50) fed selenium nanoparticles (SeNPs) 50 μg/d in apolipoprotein E-deficient (ApoE) mice, and showed that it was able to alleviate hyperlipidemia in ApoE mice by regulating cholesterol metabolism through antioxidant selenoenzymes/selenoproteins and reducing oxidative stress, and additionally metabolomics selenium-enriched kiwifruit was also found to be able to treat hyperlipidemia (51). Carotenoids (Crt) act as antioxidants in lipid-rich environments (52), mainly through (i) electron transfer between free radicals (R-) and Crt, leading to the formation of Crt radical cation (Crt-+) or Crt radical anion (Crt-); and (ii) radical adducts (R-), leading to the formation of Crt radical cation (Crt-+) or Crt radical anion (Crt-). (-); (ii) radical adduct formation (RCrt-); and (iii) hydrogen atom transfer leading to neutral Crt radicals (Crt-) three pathways to scavenge free radicals, which can also effectively scavenge ROS and play an antioxidant role (53). Lycopene, a water-soluble carotenoid, intervenes in hyperlipidemia by down-regulating oxidative stress induced by the preprotein convertase *Bacillus subtilis* protease/kexin type 9 (PCSK-9) targeting lipopolysaccharide (LPS) (54). This study concluded that the difference between single serum antioxidant and hyperlipidemia was statistically significant, and the more intake, the greater the CDAI and the lower the prevalence of hyperlipidemia, which is in line with the results of the above study.

The following four limitations exist in this research. First, the study was a cross-sectional analysis, and we could not determine a causal relationship between CDAI and hyperlipidemia. Second, since the population studied was Americans, special people such as minors were omitted. Third, some unknown covariates may affect the relationship between CDAI and the risk of hyperlipidemia. Fourth, CDAI data are self-reported and will be subject to recall bias.

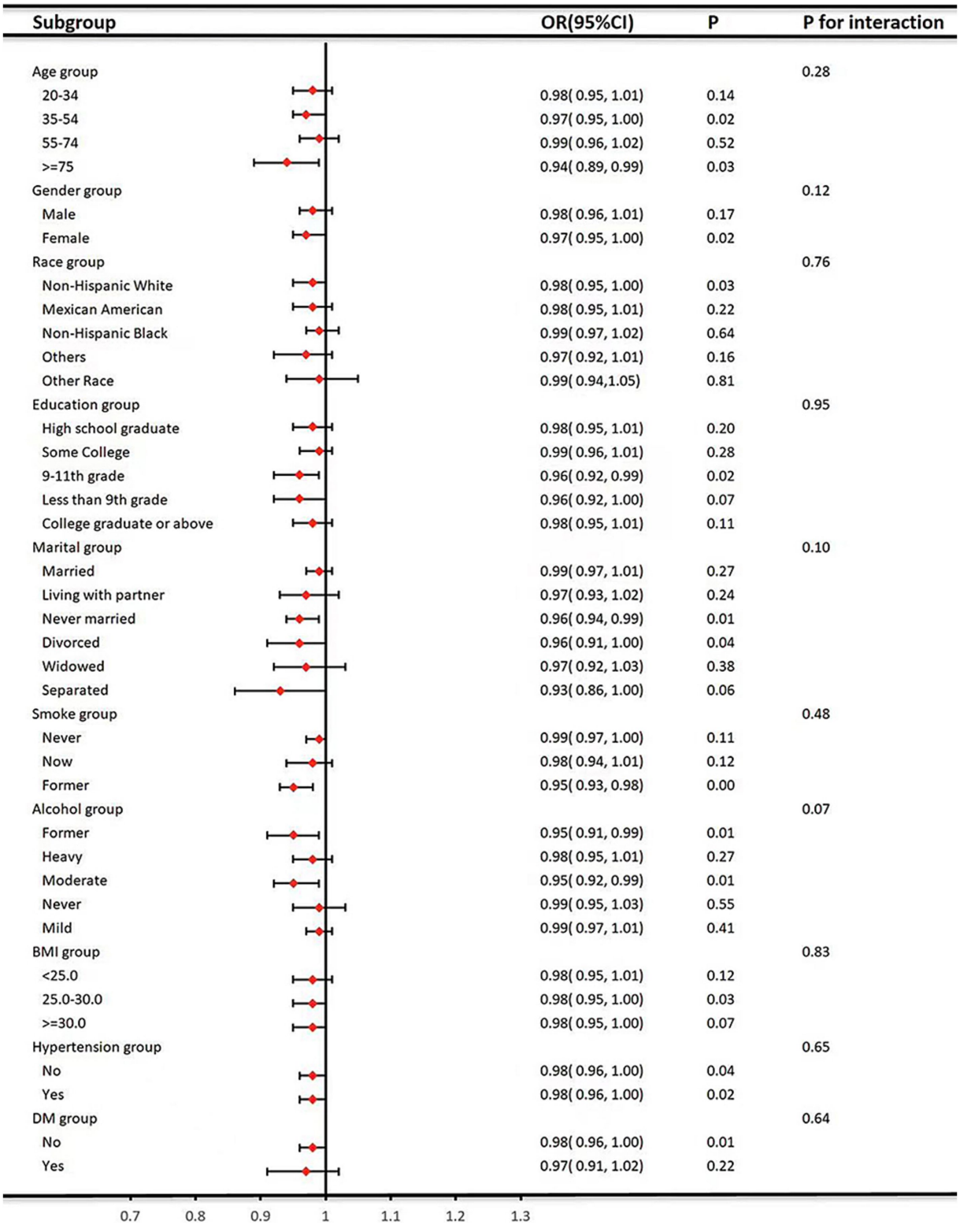

FIGURE 3
Subgroup analysis for the association between CDAI and hyperlipidemia.

5 Conclusion

There is a linear negative association between CDAI and the risk of hyperlipidemia. Therefore, intake of foods rich in CDAI components, which are mainly rich in VC and VE, may reduce the risk of hyperlipidemia. In the future, prospective studies and basic experiments are needed to further explore the mechanism of action, tap into the diet of each component of CDAI to exclude the effect of individual variability, and additionally explore the relationship between more antioxidants in the diet and hyperlipidemia to guide the

diet. Living with balanced nutrition, reasonable diet, strengthening physical exercise, improving body metabolism, strengthening hyperlipidemia prevention and reducing the occurrence of the disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The Research Ethics Review Board at the National Center for Health Statistics (NCHS). The patients/participants provided their written informed consent to participate in this study. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HZ: Data curation, Formal analysis, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. TL: Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. JL: Conceptualization, Methodology, Visualization, Writing – review & editing. DZ: Formal analysis, Software, Visualization, Writing – review & editing. JY: Conceptualization, Methodology, Validation, Visualization, Writing – review & editing. XZ: Data curation, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Comparative analysis of four nutritional scores in predicting adverse outcomes in biopsy-confirmed diabetic kidney Disease

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Malnutrition is associated with adverse outcomes in patients with diabetic kidney disease (DKD). However, it is uncertain which nutritional assessment tools are most effective in predicting the adverse outcomes of DKD. This retrospective study was conducted at a single center and included 367 patients diagnosed with DKD based on biopsy results between August 2009 and December 2018. Four nutritional assessment indices, namely the Prognostic Nutritional Index (PNI), Geriatric Nutritional Risk Index (GNRI), Triglycerides (TG) × Total Cholesterol (TC) × Body Weight (BW) Index (TCBI), and Controlling Nutritional Status (CONUT) score, were selected and calculated. We aimed to assess the association between these nutritional scores and adverse outcomes, including progression to end-stage kidney disease (ESKD), cardiovascular diseases events (CVD), and all-cause mortality. Univariate and multivariate Cox regression analyses, Kaplan–Meier analysis, along with Restricted cubic spline analysis were used to examine the relationship between nutritional scores and adverse outcomes. Furthermore, the area under the curve (AUC) was calculated using time-dependent receiver operating characteristics to determine the predictive value of the four nutritional scores alone and some combinations. Lastly, ordered logistic regression analysis was conducted to explore the correlation between the four nutritional scores and different renal histologic changes. The incidence of ESKD, CVD, and all-cause mortality was significantly higher in patients with DKD who had a lower PNI, lower GNRI, and higher CONUT score. Additionally, The TCBI performed the worst in terms of grading and risk assessment. The PNI offer the highest predictive value for adverse outcomes and a stronger correlation with renal histologic changes compared to other nutritional scores. Patients diagnosed with DKD who have a worse nutritional status are more likely to experience higher rates of adverse outcomes. The PNI might offer more valuable predictive values and a stronger correlation with different renal histologic changes compared to other nutritional scores.

KEYWORDS

prognostic nutritional index, geriatric nutritional risk index, triglycerides × total cholesterol × body weight index, controlling nutritional status, end-stage kidney disease, cardiovascular disease, all-cause mortality, renal histologic changes

1 Introduction

Diabetic kidney disease (DKD) has become a major public health concern, with a high incidence rate, high mortality, and high medical costs (1, 2). Nutritional status is closely related to the progression of end-stage kidney disease (ESKD), cardiovascular events (CVD), and all-cause mortality (3, 4). Therefore, evaluating the nutritional status of DKD patients and using it to assess the occurrence, development, and prognosis of DKD is extremely important. Currently, four objective nutritional scores have been used in previous studies to evaluate the prognosis of patients with DKD. These scores include the Prognostic Nutrition Index (PNI) (5), Geriatric Nutritional Risk Index (GNRI) (6), Triglycerides (TG) × Total cholesterol (TC) × Body weight (BW) index (TCBI) (7), and controlling nutritional status (CONUT) score (8). Previous studies have found that GNRI and PNI are effective tools in assessing the prognosis of patients with chronic kidney disease (CKD) (9, 10). CONUT score has also been identified as an independent risk factor for ESKD, CVD events, and overall death in patients with DKD (11). According to a recent study comparing GNRI, PNI, and TCBI, PNI has the most significant predictive value for all-cause and cardiovascular mortality in the general population (12). Additionally, previous studies have shown that renal histological changes are good predictors of ESKD (13). However, the relationship between these four nutritional scores and adverse outcomes remains elusive in patients with DKD. It is also still unclear which score or combination is more valuable in predicting the adverse outcomes. Additionally, the correlation between nutritional status and renal histologic changes in patients with DKD is largely unknown. Therefore, this study aims to introduce four nutritional scores to evaluate the nutritional status of DKD patients with different renal histologic changes. It also aims to analyze in-depth the correlation between nutritional status and ESKD, CVD events and all-cause death, and the correlation between nutritional status and different renal histologic changes in DKD patients. The ultimate goal is to provide new ideas for the prevention and treatment measures of disease occurrence, development, and prognosis in clinical DKD patients.

2 Materials and methods

2.1 Data source and case selection

This retrospective study included 367 patients with biopsy-confirmed DKD from Xinqiao Hospital of the Army Medical University in China between August 2009 and December 2018. DKD was diagnosed based on criteria established by the Renal Pathology Society in 2010 (14). All participants were followed up from the screening date until 31 December 2021 or until their death. The study protocol was approved by the ethical committee of Xinqiao Hospital (No. 2018-006-02). Inclusion criteria were: (1) biopsy-confirmed DKD; (2) adults aged 18 years or older; (3) complete medical information and follow-up data. Exclusion criteria were: (1) end-stage kidney disease (ESKD), cardiovascular (CVD) events and all-cause death took place within 1 month of follow-up after enrollment; (2) patients with incomplete pathological information or blood routine examination; (3) patients with malignancies (e.g., breast, lung, gastrointestinal, hematologic cancers), infectious diseases (e.g., pneumonia, viral hepatitis) (Figure 1).

2.2 Clinical information acquisition

We extracted baseline demographic characteristics and laboratory values from the Electronic Medical Record System of Xinqiao Hospital at the time of the patient's first renal biopsy. This included demographic data such as age and gender, medical history including hypertension and history of coronary heart disease, and laboratory data such as lymphocyte count, hemoglobin, serum creatinine, blood urea nitrogen (BUN), uric acid, intact parathyroid hormone (iPTH), calcium, magnesium, phosphate, albumin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), proteinuria, and pathological information. We determined the estimated glomerular filtration rate (eGFR) using the cystatin C-based chronic kidney disease (CKD)-EPI equation and combined by serum creatinine (CKD-EPIscr-cys) which incorporates the Chinese eGFR racial factor.

2.3 Preliminary data processing

We calculated body mass index (BMI) by dividing weight in kilograms by height in meters squared based on the obtained height and weight measurements. In addition, the PNI was defined by the following formula: PNI = serum albumin (g/L) + 5 × total lymphocyte count (10^9/L). The GNRI was calculated by using the following formula: GNRI = [1.489 × serum albumin (g/l)] + [41.7 × weight (kg)/ideal body weight (kg)]. The calculation of the ideal body was as follows: 22 × square of height because of its validity. The ratio of weight-to-ideal body weight was set to 1 if the actual body weight exceeded the ideal body weight (15). The TCBI was calculated using the formula: serum level of TG (mg/dL) × TC (mg/dL) × body weight (kg)/1,000. The CONUT score was described in Supplementary Table S1 (8). Nutritional scores (including GNRI, PNI, TCBI, CONUT) were divided into four groups according to the mean four nutritional scores of the quartiles: Q1 (GNRI <82.35), Q2(GNRI:82.35–92.92), Q3 (GNRI:92.92–102.90) and Q4 (GNRI >102.90) GNRI groups; Q1 (PNI < 35.26), Q2 (PNI: 35.26–42.75), Q3 (PNI:42.75–50.19) and Q4(PNI > 50.19) PNI groups; and Q1 (TCBI <1,210.17), Q2 (TCBI: 1,210.17–2079.83), Q3 (TCBI:2079.83–3451.43) and Q4(TCBI >3451.43) TCBI groups. For the CONUT score, a score of 0 was considered Q1, scores of 1 to 2 were considered Q2, scores of 3 to 4 were considered Q,2 and scores of≥5 were considered Q4 CONUT groups.

2.4 Clinical outcomes

The study evaluated three outcomes: ESKD, CVD events, and all-cause mortality, each of which was considered separately. ESKD was defined as an eGFR less than 15 mL/min/1.73 m^2 or the need for maintenance renal replacement therapy due to irreversible deterioration of renal function, including hemodialysis, peritoneal dialysis, or kidney transplantation. CVD events were defined as the occurrence of new CVD events, such as coronary heart disease, heart failure, cerebrovascular events, and severe arrhythmia. All-cause mortality was defined as death from any cause. The study obtained clinical outcomes primarily through telephone follow-up or patient medical record reports.

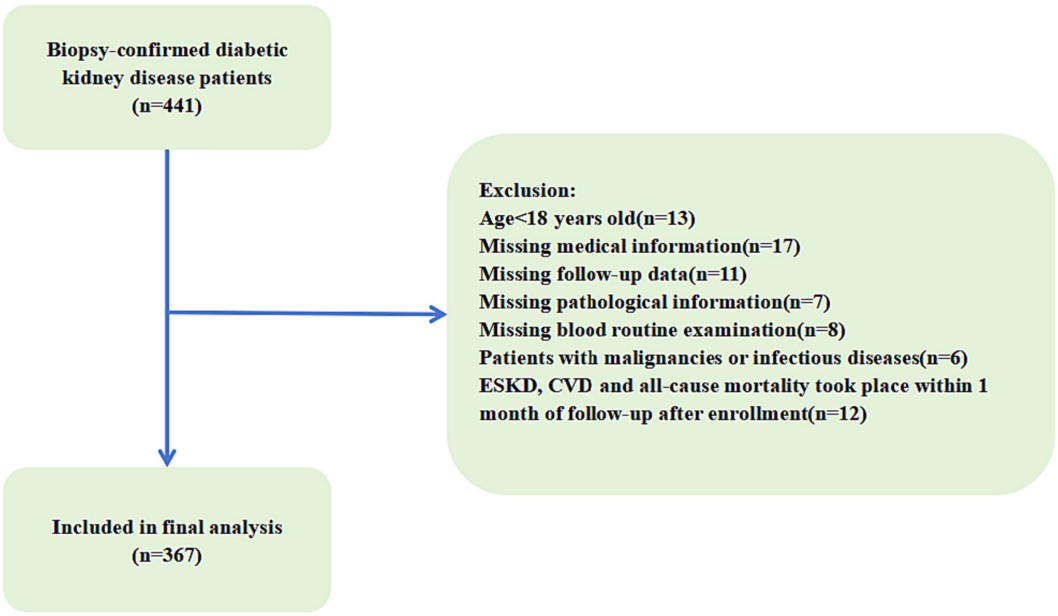

FIGURE 1
Flowchart of included patients in this study. ESKD, end-stage kidney disease; CVD, cardiovascular disease.

2.5 Statistical analysis

The data analysis involved the use of SPSS (version 27.0), GraphPad Prism (version 10.0.3) or R version 4.3.1. All the data used were checked for normality of distribution using the Kolmogorov–Smirnov test. Normally distributed data were expressed as mean ± standard deviation while non-normally distributed data were expressed as median (interquartile range). The differences between groups were tested using *t*-tests, Mann–Whitney U tests, and chi-square tests. The Kaplan–Meier curve was used to compare the outcomes of the patients according to the mean four nutritional scores (including PNI, GNRI, TCBI, and CONUT) of the quartiles, and the log-rank test was used to compare the differences between each group. Furthermore, the independent relationships between four nutritional scores and end-stage renal disease, cardiovascular, and all-cause mortality were investigated by univariate and multivariate Cox regression models. The initial confounding factors were selected based on previous studies, data availability, and established associations. If these factors changed the estimates of four nutritional scores on end-stage renal disease, cardiovascular, and all-cause mortality by more than 10% or were significantly associated with endpoint events after adjustment for sociodemographic factors (age), they were included as the covariates in multivariate Cox regression analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) are provided. Additionally, restricted cubic splines (RCS) and threshold effect analysis were applied using the R package "rms" based on the Cox proportional hazards models to further explore the relationship between the nutritional scores and endpoint events. Moreover, the time-dependent receiver operating characteristic (td-ROC) curve was constructed to compare the diagnostic accuracy of PNI, GNRI, TCBI, and CONUT, alone or in different combinations with PNI, in predicting end-stage renal disease, cardiovascular and all-cause mortality. Combine four nutritional scores in the following different ways: PNI + CONUT, PNI + TCBI, PNI + GNRI, PNI + TCBI+CONUT, PNI + GNRI+CONUT, PNI + GNRI+TCBI, and PNI + TCBI+CONUT+GNRI. Then, the area under the curve (AUC) was calculated for different groups. The correlation heatmap was generated using R software (v.4.2.2) package "corrplot" (v.0.92) (16) and "ggplot2" (v3.4.2) (17). To explore the correlation between four nutritional scores and different renal histologic changes (glomerular lesions, IFTA, interstitial inflammation, arteriolar hyalinosis, and arteriosclerosis) in patients with diabetic kidney disease, we used X-tile software (v3.6.1) to calculate the optimum cutoff value for converting the continuous variables (PNI, GNRI) into categorical variables (the low-level group and the high-level group) according to end-stage renal disease. Patients were divided into two groups based on median CONUT score. Then, we use ordered logistic regression analysis to investigate the factors affecting different renal histologic changes in patients with diabetic kidney disease. Ordered logistic regression analysis: The model meets the parallelism by parallel test, and multivariate analysis was performed by ordinal logistic regression. It is important to note that a p value of <0.05 was considered statistically significant during the analysis.

3 Results

3.1 Baseline characteristics

A total of 367 patients with DKD were recruited for the current study. The mean age of the patients was 51.30 ± 10.35 years, and 63.2% (232) were male. Among the patients, 34.1% (125) were smokers, 70.8% (260) had hypertension, and 20.7% (76) had a history of coronary heart disease. Then, the PNI, GNRI, TCBI, and CONUT score were calculated. The baseline characteristics of the study population according to different glomerular lesions are shown in

Table 1. According to our findings, serum creatinine, uric acid, blood urea nitrogen, Cystatin C, LPA, TNF-α, and CONUT increased in proportion to the severity of glomerular lesions, and patients with more severe glomerular lesions were more likely to suffer from coronary heart disease and diabetes retinopathy. They also have lower levels of hemoglobin, eGFR, albumin, GNRI, and PNI. In addition, we found that significant differences in interstitial fibrosis and tubular atrophy (IFTA), interstitial inflammation, arteriolar hyalinosis, and arteriosclerosis. The distribution of the PNI, GNRI, TCBI, and CONUT score among DKD patients with different glomerular lesions is shown in Figure 2.

3.2 Association between four nutritional scores and adverse outcomes

During a median follow-up period of 5.1 years, about 114 (31.1%) of ESKD, 115 (31.3%) of CVD events, and 54 (14.7%) of deaths occurred. The Kaplan–Meier curve showed that, PNI, GNRI, and COUNT score were all significantly associated with renal progression, CVD events and all-cause mortality except for TCBI (Figure 3). Then, we performed the Cox regression analysis (Tables 2, 3). In the univariate Cox proportional hazards analysis, patients with lower GNRI, PNI and higher CONUT score had increased risks of ESKD ($p < 0.001$), CVD events ($p < 0.001$) and all-cause mortality ($p < 0.001$). Moreover, age, hypertension, diabetic retinopathy, eGFR, serum creatinine, cystatin C, calcium, hemoglobin, iPTH, albumin, LDL, IFTA, and arteriosclerosis were also significantly associated with adverse outcomes (Table 2). In a multivariate Cox regression model (Model 3), the GNRI and PNI were still associated with the incidence of adverse outcomes. In addition, the CONUT score was still an independent predictor of CVD events (HR = 1.113, 95% CI 1.029–1.203, $p = 0.007$), and all-cause mortality (HR = 1.208, 95% CI 1.033–1.411, $p = 0.018$) in Model 3, but the positive effect size of ESKD was non-significant (Table 3).

Next, we also used restricted cubic splines to model and visualize the relation of predicted nutritional scores (PNI, GNRI, TCBI, and CONUT) with ESKD in DKD patients (Figures 4A–D). For PNI, the risk of ESKD was relatively flat until it reached 34–35 and then started to decrease rapidly afterwards but the P for nonlinearity was non-significant (P for overall = 0.016, P for nonlinear = 0.146). For GNRI, regarding the strong N-shaped relation between predicted GNRI and ESKD, the plot showed an increase of the risk within the lower range of predicted GNRI until around 75 and HR exceeded the horizontal line with HR = 1, which reached the highest risk around 55–56 and then substantially decreased thereafter until it until it reached 92–93 (P for overall<0.001, P for nonlinear<0.001). In addition, the nonlinear relationship between nutrition scores and cardiovascular death was weakened and no apparent correlation was found between the nutrition scores and cardiovascular death (Figures 4E–H). An L-shaped relationship between the HR of all-cause mortality and nutritional scores (PNI, GNRI, and TCBI) was indicated in DKD patients. However, the nonlinear relationship between nutrition scores and all-cause mortality was weakened and no apparent correlation was found between the nutrition scores and all-cause mortality (Figures 4I–L). After adjusting for various adverse events using Model 3 in the Cox analysis, the restricted spline curve indicates a potential linear correlation between the four nutritional scores and the outcomes.

Furthermore, we investigated nutrition scores that exhibit a notable non-linear relationship with outcomes. We employed threshold effect analysis to identify critical inflection point that influence the correlation between variables. Subsequently, we assessed the correlation between the independent and dependent variables both before and after these turning points. The relationship between GNRI and ESKD reveals a critical inflection point at 71.629, indicating a significant threshold effect. When the GNRI falls below 71.629, a positive correlation with ESKD becomes evident (HR = 1.835, 95% CI 1.170–2.878, $p = 0.008$), while exceeding 71.629 leads to a negative association with ESKD (HR = 0.946, 95% CI 0.925–0.968, $p < 0.001$). However, there is no significant threshold effect in TCBI (HR = 1.000, 95% CI 1.000–1.000, $p = 0.6631$) (Table 4).

Overall, compared with TCBI and CONUT score, GNRI and PNI have a stronger correlation with ESKD, CVD events and all-cause mortality, which is similar to the results of the time-dependent receiver operating characteristic (td-ROC). Therefore, it showed that individual PNI has the best diagnostic accuracy and the strongest correlation with the disease, making it an independent risk factor for ESKD, CVD events, and all-cause death in patients with DKD.

3.3 Diagnostic accuracy of four nutritional scores and different combinations with PNI in predicting outcomes

The prediction of clinical outcomes by the PNI, GNRI, TCBI, CONUT score and different combinations with PNI was evaluated using the time-dependent receiver operating characteristic (td-ROC) of the subjects. Then, the ROC curves were constructed to calculate the area under curve (AUC) (Figures 5A-I). For the prediction of ESKD, the PNI score had slightly higher AUC than GNRI, whereas the TCBI and the CONUT score had similar AUC. Diagnostic accuracy of PNI + TCBI+CONUT (AUC = 0.7305) was slightly higher than that of other combined scores and slightly higher than that of PNI (AUC = 0.7209) alone. Other combinations is not significantly improved or lower than the individual PNI scores (Figures 5B,C). We also obtained similar results in the AUC for cardiovascular death and all-cause mortality. However, the AUC of PNI + TCBI+CONUT+GNRI (AUC = 0.6320) was slightly higher than PNI (AUC = 0.6261) for CVD events (Figure 5F), and the AUC of PNI + GNRI+TCBI (AUC = 0.7226) was slightly higher than PNI (AUC = 0.7208) for all-cause mortality (Figure 5I). Overall, compared with PNI, the diagnostic accuracy of other nutritional scores alone or different combinations with PNI performed worse on ESKD, CVD events and death.

3.4 Correlation between four nutritional scores and different renal histologic changes in patients with diabetic kidney disease

We detected the correlation analysis between four nutritional scores and different renal histologic changes in patients with DKD, and our results showed PNI was negatively correlated with glomerular

TABLE 1 Baseline characteristics of patients with diabetic kidney disease.

valuable	ALL (*n* = 367)	Class I (*n* = 60)	Class II a (*n* = 81)	Class II b (*n* = 60)	Class III (*n* = 158)	Class IV (*n* = 8)	*p* value
Gender (Male, %)	232 (63.2%)	35 (58.3%)	49 (60.5%)	36 (60.0%)	109 (69.0%)	3 (37.5%)	0.224
Age (years)	51.30 ± 10.35	50.55 ± 11.76	53.44 ± 10.13	49.55 ± 10.21	51.20 ± 10.01	50.5 ± 7.31	0.234
Smoking (%)	125 (34.1%)	18 (30.0%)	28 (34.6%)	24 (40.0%)	54 (34.2%)	1 (12.5%)	0.550
Hypertension (%)	260 (70.8%)	27 (45.0%)	50 (61.7%)	41 (68.3%)	135 (85.4%)	7 (87.5%)	<0.001
Coronary disease (%)	76 (20.7%)	7 (11.7%)	18 (22.2%)	9 (15.0%)	39 (24.7%)	3 (37.5%)	0.126
Diabetic retinopathy (%)	211 (57.5%)	17 (28.3%)	34 (42.0%)	41 (68.3%)	114 (72.2%)	5 (62.5%)	<0.001
Neutrophil (%)	65.40 (59.40–71.60)	64.80 (58.13–69.80)	64.40 (58.30–68.60)	66.85 (60.43–71.75)	66.40 (61.38–72.48)	71.35 (64.98–76.83)	0.040
Medication							
Statin use (%)	75 (20.4%)	8 (13.3%)	11 (13.6%)	11 (18.3%)	43 (27.2%)	2 (25.0%)	0.063
Anti-platelet drug use (%)	51 (13.9%)	7 (11.7%)	7 (8.6%)	5 (8.3%)	31 (19.6%)	1 (12.5%)	0.091
Laboratory data							
Lymphocyte (%)	24.30 (18.60–29.10)	24.40 (21.93–32.98)	25.10 (21.00–31.65)	22.95 (18.15–26.65)	23.90 (17.80–27.63)	19.75 (16.45–24.20)	0.025
Proteinuria (g/day)	2.48 (0.74–5.28)	0.81 (0.23–3.98)	0.96 (0.29–2.98)	1.89 (0.91–4.13)	4.32 (2.17–7.20)	2.63 (1.34–4.86)	<0.001
Fasting glucose (mmol/L)	6.82 (5.30–9.10)	7.00 (5.78–8.62)	6.29 (4.95–8.94)	7.04 (5.00–9.15)	6.89 (5.30–9.49)	5.02 (3.53–7.96)	<0.001
HbA1c (%)	7.30 (6.50–8.80)	7.55 (6.43–8.58)	7.10 (6.50–8.25)	7.20 (6.50–8.45)	7.55 (6.50–9.34)	7.10 (6.34–9.28)	<0.001
SBP (mmHg)	144.40 ± 22.96	132.02 ± 17.02	138.21 ± 22.88	142.67 ± 18.14	152.78 ± 23.54	147.63 ± 23.56	<0.001
DBP (mmHg)	84.00 (77.00–93.00)	82.00 (73.00–89.00)	82.00 (75.00–90.00)	84.00 (78.25–90.00)	86.00 (78.00–96.00)	90.00 (80.50–95.00)	0.044
Height (cm)	163.31 ± 7.78	162.84 ± 8.29	163.96 ± 7.73	161.98 ± 7.76	163.92 ± 7.49	158.31 ± 8.64	0.145
Weight (kg)	67.19 ± 11.49	68.23 ± 11.72	68.80 ± 11.64	64.48 ± 11.67	67.18 ± 11.13	63.55 ± 12.52	0.183
BMI (kg/m^2)	25.10 ± 3.30	25.61 ± 3.04	25.52 ± 3.55	24.45 ± 3.13	24.92 ± 3.23	25.32 ± 4.44	0.229
Hemoglobin (g/L)	116.24 ± 27.20	130.97 ± 19.31	127.86 ± 24.05	116.17 ± 35.26	104.98 ± 22.67	110.88 ± 24.67	<0.001
eGFR (ml/min/1.73 m^2)	64.00 (37.00–97.85)	95.97 (71.58–112.59)	90.92 (62.84–110.67)	66.15 (36.52–102.56)	43.04 (27.48–64.27)	32.50 (24.74–73.62)	<0.001
Serum creatinine (μmol/L)	110.00 (71.40–155.20)	72.00 (57.18–94.78)	77.50 (63.25–101.95)	109.75 (71.05–151.55)	144.25 (111.08–216.45)	185.25 (92.13–203.48)	<0.001
Uric acid (μmol/L)	384.70 ± 105.81	347.85 ± 112.07	371.78 ± 112.12	398.79 ± 116.17	398.09 ± 93.25	421.63 ± 79.01	0.010
BUN (mmol/L)	7.33 (5.52–9.99)	5.53 (4.80–7.63)	6.28 (5.07–7.94)	7.43 (5.38–9.88)	8.66 (6.58–10.86)	8.41 (6.72–11.68)	<0.001
Cystatin C (mg/L)	1.49 (1.03–2.20)	1.00 (0.75–1.38)	1.08 (0.88–1.54)	1.39 (1.04–2.17)	1.92 (1.45–2.66)	1.90 (1.52–2.90)	<0.001
Calcium (mmol/L)	2.18 (2.05–2.30)	2.20 (2.09–2.34)	2.25 (2.10–2.36)	2.21 (2.08–2.32)	2.15 (2.03–2.24)	2.13 (1.96–2.34)	<0.001
Phosphorus (mmol/L)	1.16 (1.03–1.34)	1.13 (1.02–1.29)	1.06 (0.92–1.24)	1.15 (1.03–1.34)	1.23 (1.09–1.40)	1.19 (0.99–1.36)	<0.001
iPTH (pg/mL)	64.30 (39.60–92.30)	56.30 (39.00–64.30)	61.20 (37.10–77.50)	53.15 (36.04–72.10)	67.45 (41.80–125.73)	93.70 (53.28–153.43)	0.002
Albumin (g/L)	34.53 ± 8.86	37.30 ± 9.74	37.27 ± 10.17	35.38 ± 8.59	31.62 ± 7.03	37.00 ± 6.41	<0.001
Lpa (mg/L)	275.00 (113.00–597.0)	131.00 (40.75–300.75)	248.00 (83.00–458.00)	264.00 (124.25–524.00)	387.00 (169.00–781.75)	394.00 (157.00–1006.00)	<0.001

(Continued)

TABLE 1 (Continued)

valuable	ALL (*n* = 367)	Class I (*n* = 60)	Class II a (*n* = 81)	Class II b (*n* = 60)	Class III (*n* = 158)	Class IV (*n* = 8)	*p* value
APOA1 (g/L)	1.32 (1.12–1.56)	1.27 (1.09–1.58)	1.28 (1.09–1.49)	1.32 (1.11–1.55)	1.37 (1.14–1.58)	1.31 (1.08–1.75)	<0.001
APOB (g/L)	1.02 (0.82–1.25)	0.95 (0.74–1.12)	1.04 (0.87–1.24)	1.01 (0.82–1.31)	1.09 (0.84–1.34)	0.87 (0.78–1.15)	<0.001
APOE (mg/dL)	3.86 (3.00–4.37)	3.91 (3.20–5.24)	3.91 (3.06–4.11)	3.74 (2.91–4.04)	3.86 (2.89–4.24)	3.82 (3.04–5.75)	<0.001
Triglycerides (mmol/L)	1.70 (1.19–2.54)	1.82 (1.16–3.12)	1.84 (1.28–2.70)	1.70 (1.15–2.56)	1.64 (1.08–2.36)	1.64 (1.29–6.36)	<0.001
LDL (mmol/L)	3.10 (2.49–4.02)	2.74 (2.31–3.59)	3.18 (2.47–4.00)	2.98 (2.39–3.96)	3.27 (2.61–4.27)	2.53 (2.21–3.03)	0.034
HDL (mmol/L)	1.17 (0.94–1.46)	1.12 (0.91–1.55)	1.07 (0.93–1.34)	1.20 (0.95–1.47)	1.22 (0.97–1.53)	1.00 (0.85–1.87)	<0.001
Total cholesterol (mmol/L)	5.20 (4.19–6.47)	4.88 (4.02–6.01)	5.00 (4.16–6.01)	5.30 (4.25–6.51)	5.51 (4.37–6.98)	5.35 (3.99–6.81)	<0.001
CRP (mg/L)	4.70 (2.50–6.80)	5.00 (2.23–6.80)	5.40 (2.95–6.80)	3.00 (2.05–6.80)	5.10 (2.50–6.80)	3.85 (2.95–6.40)	0.091
TNF-α	10.70 (8.10–11.10)	9.60 (7.00–10.70)	10.40 (8.10–10.80)	10.70 (8.15–11.85)	10.70 (8.48–11.55)	8.65 (7.85–10.68)	0.033
PNI	42.75 (35.26–50.19)	49.49 (37.91–54.50)	46.88 (38.42–54.15)	45.11 (37.54–48.74)	39.81 (33.29–44.16)	43.63 (40.22–47.44)	<0.001
GNRI	92.92 (82.35–102.90)	102.82 (86.93–107.89)	99.62 (87.45–108.74)	95.60 (83.09–104.35)	88.08 (80.67–94.89)	94.56 (91.69–101.13)	<0.001
TCBI	2079.83 (1210.17–3451.43)	2071.94 (1121.05–3907.08)	2281.74 (1414.59–3792.47)	2227.59 (1068.87–2850.11)	1987.10 (1157.46–3448.97)	1681.74 (1189.77–8983.92)	0.791
CONUT score ≥ 3 (%)	195 (53.3%)	23 (38.3%)	33 (40.2%)	30 (51.7%)	106 (67.1%)	3 (37.5%)	<0.001
IFTA							
0	44 (12.0%)	34 (56.7%)	10 (12.20%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	<0.001
1	116 (31.7%)	22 (36.7%)	53 (64.6%)	24 (41.4%)	17 (10.8%)	0 (0.0%)	
2	93 (25.4%)	4 (6.7%)	14 (17.1%)	25 (43.1%)	49 (31%)	1 (12.5%)	
3	113 (30.9%)	0 (0.0%)	5 (6.1%)	9 (15.5%)	92 (58.2%)	7 (87.5%)	
Interstitial inflammation							
0	49 (13.4%)	33 (55.0%)	14 (17.1%)	1 (1.7%)	1 (0.6%)	0 (0.0%)	<0.001
1	115 (31.4%)	15 (25.0%)	52 (63.4%)	24 (41.4%)	24 (15.2%)	0 (0.0%)	
2	202 (55.0%)	12 (20.0%)	16 (19.5%)	33 (56.9%)	133 (84.2%)	8 (100.0%)	
Arteriolar hyalinosis							
0	14 (3.8%)	5 (8.3%)	7 (8.5%)	2 (3.4%)	0 (0.0%)	0 (0.0%)	<0.001
1	92 (25.1%)	37 (61.7%)	27 (32.9%)	16 (27.6%)	10 (6.3%)	2 (25.0%)	
2	260 (71.0%)	18 (30.0%)	48 (58.5%)	40 (69.0%)	148 (93.7%)	6 (75.0%)	
Arteriosclerosis							
0	94 (25.7%)	36 (60.0%)	31 (37.8%)	17 (29.3%)	10 (6.3%)	0 (0.0%)	<0.001
1	141 (38.5%)	17 (28.3%)	33 (40.2%)	24 (41.4%)	64 (40.5%)	3 (37.5%)	
2	131 (35.8%)	7 (11.7%)	18 (22.0%)	17 (29.3%)	84 (53.2%)	5 (62.5%)	

Data are presented as mean ± SD, *N* (%) or median (IQR). HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone; Lpa, Lipoprotein a; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Risk Index; TCBI, Triglycerides × Total Cholesterol × Body Weight Index; CONUT score, Controlling Nutritional Status score; IFTA, interstitial fibrosis and tubular atrophy.

lesions ($r = -0.290$, $p < 0.001$), IFTA ($r = -0.234$, $p < 0.001$), interstitial inflammation ($r = -0.226$, $p < 0.001$), arteriolar hyalinosis ($r = -0.168$, $p = 0.001$) and arteriosclerosis ($r = -0.212$, $p < 0.001$). For PNI, we also found similar results. For CONUT score, the positive correlation was found with glomerular lesions ($r = 0.224$, $p < 0.001$), IFTA ($r = 0.176$, $p = 0.001$), interstitial inflammation ($r = 0.197$, $p < 0.001$), arteriolar hyalinosis ($r = 0.128$, $p = 0.014$) and arteriosclerosis ($r = 0.189$, $p < 0.001$). No significant correlation between TCBI and renal histologic changes was found in patients with diabetic kidney disease (Figure 6A).

To further explore the underlying correlations between PNI, GNRI and CONUT score and different renal histologic changes in patients with DKD, patients were divided into two groups (the low level group and the high level group) based on X-tile software and

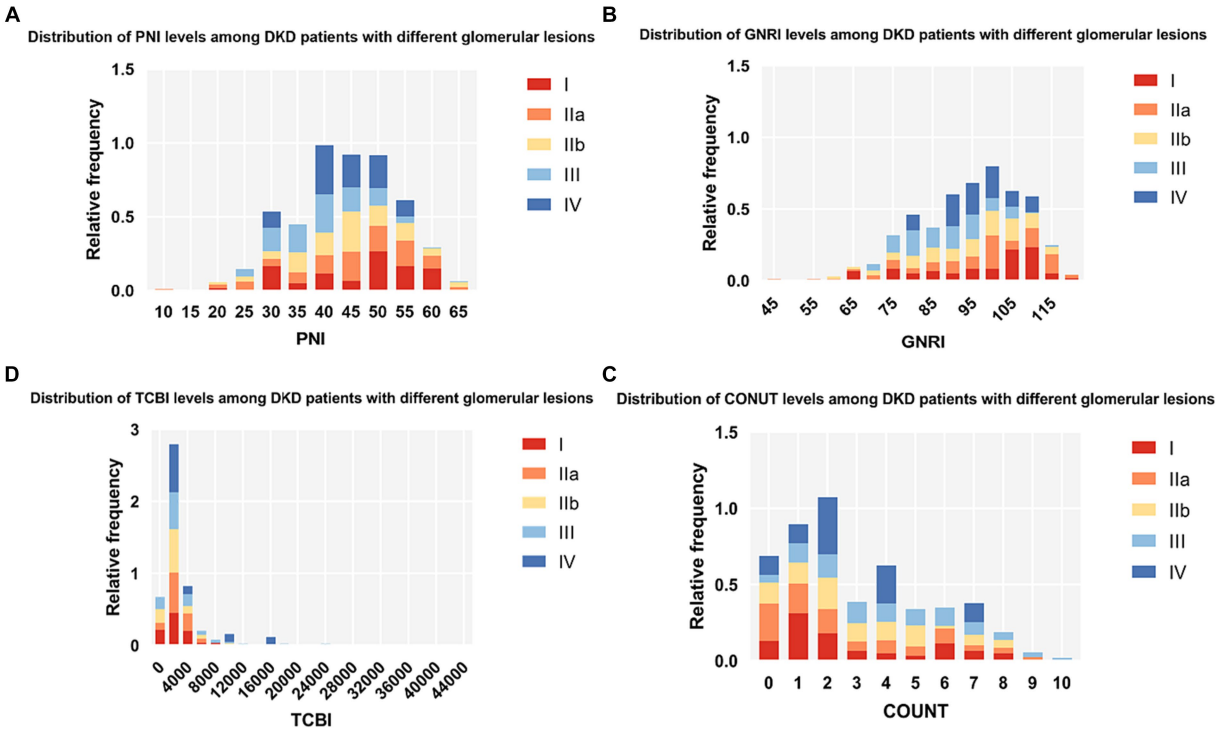

FIGURE 2
Histograms show the population distribution of nutritional scores. **(A)** PNI; **(B)** GNRI; **(C)** TCBI; **(D)** COUNT score. PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Risk Index; CONUT score, Controlling Nutritional Status score; TCBI, Triglycerides×Total Cholesterol×Body Weight Index.

median CONUT score. The variable "PNI" was grouped as "<44.0" and "≥44.0" under end-stage renal disease (Figures 6B,D); "GNRI" was categorized into "<92.9" and "≥92.9" under cardiovascular (Figures 6C,E). Patients were divided into two groups based on median CONUT score: the low CONUT score group (CONUT score < 3) and the high CONUT score group (CONUT score ≥ 3). Then, we use ordered logistic regression analysis to investigate the factors affecting different renal histologic changes in patients with DKD.

After adjusting proteinuria in the ordered logistic regression analysis, we found that high PNI level was an adverse factor for obtaining the higher glomerular lesions grade ($p < 0.001$, OR = 2.532, 95%CI 1.645–3.892), IFTA ($p < 0.001$, OR = 2.303, 95%CI 1.508–3.515), interstitial inflammation ($p = 0.010$, OR = 1.800, 95%CI 1.148–2.824), arteriolar hyalinosis ($p = 0.026$, OR = 1.800, 95%CI 1.075–3.016), arteriosclerosis ($p = 0.008$, OR = 1.795, 95%CI 1.168–2.757) (Figure 6F). GNRI was also inversely correlated with glomerular lesions ($p = 0.013$, OR = 1.725, 95%CI 1.121–2.656). There is no significant correlation between GNRI and IFTA, interstitial inflammation, arteriolar hyalinosis and arteriosclerosis (Figure 6G). Besides, a lower CONUT score was linked to improved renal histologic changes in glomerular lesions, interstitial inflammation, and arteriosclerosis grade (Figure 6H). Compared with GNRI and CONUT score, PNI have a stronger correlation with different renal histologic changes and higher PNI may be related to a lower risk of different renal histologic changes in patients with diabetic kidney disease. The PNI remained best incremental values for predicting the order of severity of different renal histologic changes.

4 Discussion

In this study, we used four nutritional scores to assess the nutrition status of patients with DKD under different renal histologic changes, analyzed the relationship of nutritional status with ESKD, CVD events, and all-cause mortality in patients with DKD and detected the correlation analysis between four nutritional scores and different renal histologic changes.

The major conclusions are as follows: (1) Malnourished patients were at a higher risk of adverse outcomes. Moreover, GNRI, PNI, and CONUT score had higher predictive value for all-cause mortality than other adverse outcomes. (2) Compared with other nutritional scores, the PNI alone had the highest predictive value in biopsy-confirmed diabetic kidney disease. However, TCBI showed the worst performance on risk assessment and prediction. Moreover, the predictive value of certain combinations with PNI is slightly higher than PNI alone for various adverse outcomes. (3) Malnourished patients were found to have a heightened risk of experiencing significant renal histologic changes. However, no clear correlation could be found between TCBI and renal histologic change. Furthermore, the PNI remained the most accurate predictor of the severity order of various renal histologic changes.

In recent years, it has been widely suggested by numerous studies that CKD patients exhibit abnormal protein-energy metabolism, with significant muscle and fat wasting. In 2008, the International Society of Renal Nutrition and Metabolism (ISRNM) expert group named this condition protein-energy wasting (PEW), which refers to the reduced protein and energy reserves in the body, resulting in a state of malnutrition characterized by decreased protein and fat content (3).

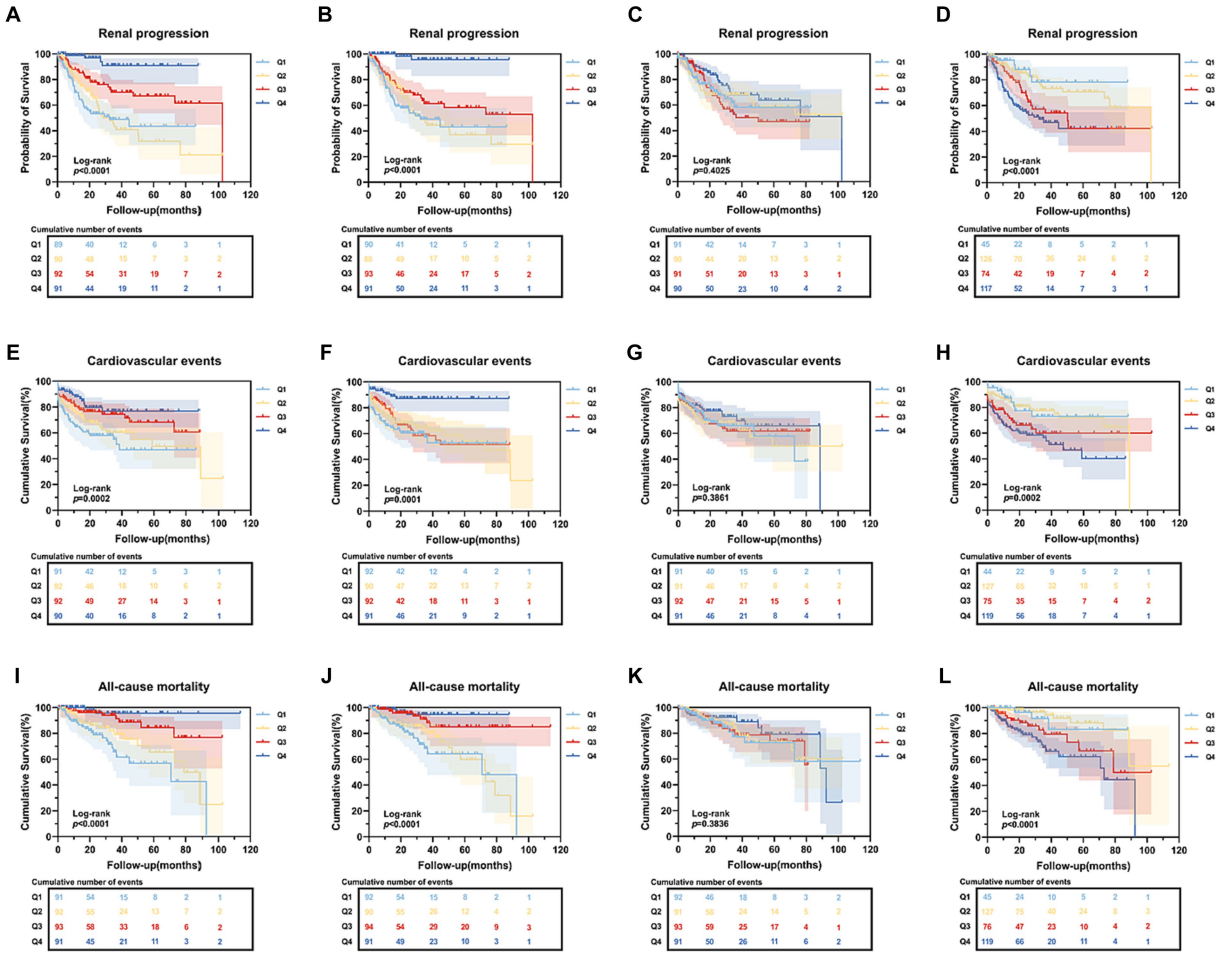

FIGURE 3
Kaplan–Meier curves of end-stage renal disease, cardiovascular events and all-cause mortality based on four nutritional scores. **(A–D)** Kaplan–Meier curves of end-stage renal disease categorized by PNI, GNRI, TCBI, COUNT score; **(E–H)** Kaplan–Meier curves of cardiovascular death categorized by PNI, GNRI, TCBI, COUNT score; **(I–L)** Kaplan–Meier curves of all-cause mortality categorized by PNI, GNRI, TCBI, COUNT score. PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Risk Index; TCBI, Triglycerides×Total Cholesterol×Body Weight Index; CONUT score, Controlling Nutritional Status score.

Nutrition plays a crucial role in reducing the risk of cardiovascular disease and slowing the decline in kidney function (4). Currently, PEW is highly prevalent among elderly individuals and those with ESKD, and it is closely associated with poor clinical outcomes due to the breakdown of body proteins and reduced energy caused by metabolic inflammation responses (3, 18). In dialysis patients, malnutrition may increase the risk of cardiovascular and all-cause mortality through factors such as chronic inflammation and oxidative stress (19). Malnutrition is a common complication in CKD stages 4–5 and also influence the severity and progression of DKD (20–22). Therefore, the nutritional status is closely related to the progression and prognosis of DKD, and the prevention and treatment of malnutrition in DKD can improve patient outcomes.

Four nutritional scores include two or three of the following elements: serum albumin, lymphocytes count, TC, TG, and body weight. Serum albumin and weight loss are strong independent risk factors for mortality in older persons. Low albumin or weight loss was correlated with increased mortality in older persons (23, 24). Meanwhile, the synthesis of albumin is influenced by chronic inflammation and malnutrition, and lower levels of albumin may be a marker of continuous arterial injury, as well as the progression of atherosclerosis and thrombosis (25). High cholesterol is a common risk factor for CVD. However, low cholesterol is a high risk factor for CVD events in dialysis patients (26). The reason for this paradox may be that the inflammatory or malnutrition state of the organism leads to a disturbance in lipid metabolism, which increases the risk of adverse outcomes. In addition, age related lymphopenia is well described in the literature and an association between lymphopenia and mortality has recently been reported (27). The occurrence of diabetes is accompanied by an increase in reactive oxygen species, which in turn leads to an increase in oxidative stress (28). This oxidative stress (29), along with protein energy consumption (30), are both potential causes of CKD inflammation, and may represent the mechanisms underlying DKD inflammation. Consequently, low serum albumin and low lymphocyte count may contribute to ESKD.

Our study found that a higher risk of adverse outcomes was associated with lower GNRI and PNI, as well as higher CONUT score. GNRI is based on measurements of serum albumin and weight loss, which are strong independent risk factors for mortality in older persons. The utilization of both indicators in the GNRI minimizes

TABLE 2 Univariate Cox analysis of adverse outcomes in patients with diabetic kidney disease.

Variable	ESKD		CVD		All-cause mortality	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Male	0.663 (0.463–0.949)	0.025	0.730 (0.501–1.065)	0.102	1.203 (0.754–1.919)	0.437
Age	1.006 (0.988–1.023)	0.526	1.036 (1.015–1.056)	<0.001	1.037 (1.009–1.066)	0.009
Smoking	1.208 (0.830–1.757)	0.325	1.071 (0.708–1.619)	0.746	1.254 (0.731–2.151)	0.412
Hypertension	2.680 (1.578–4.551)	<0.001	2.156 (1.260–3.688)	0.005	2.754 (1.240–6.119)	0.130
Coronary disease	1.471 (0.973–2.226)	0.067	5.009 (3.341–7.511)	<0.001	1.381 (0.757–2.520)	0.292
Diabetic retinopathy	2.623 (1.692–4.066)	<0.001	1.799 (1.165–2.780)	0.008	2.161 (1.153–4.051)	0.016
CKD stage	1.488 (1.298–1.706)	<0.001	1.326 (1.148–1.531)	<0.001	1.235 (1.028–1.484)	0.024
Statin use	1.646 (1.076–2.518)	0.022	2.504 (1.636–3.833)	<0.001	0.920 (0.445–1.900)	0.822
Anti-platelet drug use	1.342 (0.808–2.230)	0.256	2.262 (1.378–3.712)	0.001	0.991 (0.422–2.327)	0.984
eGFR	0.965 (0.958–0.973)	<0.001	0.985 (0.978–0.991)	<0.001	0.980 (0.972–0.989)	<0.001
Serum creatinine	1.007 (1.006–1.008)	<0.001	1.003 (1.002–1.004)	<0.001	1.004 (1.003–1.006)	<0.001
Uric acid	1.002 (1.000–1.004)	0.012	1.002 (1.001–1.004)	0.110	1.001 (0.999–1.004)	0.294
BUN	1.001 (0.996–1.007)	0.629	1.000 (0.992–1.008)	0.996	1.001 (0.992–1.010)	0.783
Cystatin C	2.429 (2.081–2.837)	<0.001	1.514 (1.267–1.809)	<0.001	1.797 (1.424–2.267)	<0.001
Calcium	0.089 (0.035–0.226)	<0.001	0.269 (0.095–0.760)	0.013	0.88 (0.024–0.320)	<0.001
Phosphorus	1.447 (1.116–1.874)	0.005	1.076 (0.668–1.734)	0.763	1.236 (0.742–2.060)	0.416
Hemoglobin	0.960 (0.951–0.970)	<0.001	0.990 (0.982–0.998)	0.012	0.973 (0.961–0.985)	<0.001
iPTH	1.009 (1.007–1.011)	<0.001	1.006 (1.003–1.008)	<0.001	1.006 (1.002–1.010)	0.007
Albumin	0.942 (0.923–0.962)	<0.001	0.962 (0.941–0.984)	<0.001	0.919 (0.889–0.951)	<0.001
TCH	1.075 (0.976–1.184)	0.141	1.020 (0.910–1.143)	0.732	1.278 (1.114–1.466)	<0.001
TG	0.880 (0.765–1.012)	0.073	0.963 (0.861–1.078)	0.517	0.863 (0.695–1.072)	0.184
Lpa	1.001 (1.000–1.001)	<0.001	1.001 (1.000–1.001)	<0.001	1.001 (1.000–1.001)	0.003
APOA1	0.905 (0.648–1.265)	0.559	0.789 (0.485–1.283)	0.789	1.086 (0.828–1.425)	0.551
APOB	0.943 (0.608–1.463)	0.792	1.081 (0.680–1.719)	0.743	1.456 (0.8116–2.599)	0.203
APOE	0.973 (0.873–1.086)	0.629	0.949 (0.836–1.078)	0.422	1.061 (0.904–1.246)	0.467
HDL-C	1.006 (0.682–1.485)	0.975	0.974 (0.627–1.513)	0.974	1.925 (1.193–3.105)	0.007
LDL-C	1.037 (0.900–1.196)	0.615	0.928 (0.780–1.103)	0.394	1.225 (1.007–1.490)	0.042
CRP	1.000 (0.994–1.005)	0.900	1.001 (0.997–1.006)	0.545	1.001 (0.994–1.008)	0.738
IL-6	1.006 (0.998–1.013)	0.136	1.001 (0,991–1.012)	0.804	1.004 (0.992–1.017)	0.493
TNF-α	1.042 (1.007–1.079)	0.019	1.019 (0.974–1.065)	0.417	1.057 (1.003–1.114)	0.037
IL-8	1.004 (0.995–1.014)	0.378	1.011 (1.003–1.019)	0.004	0.995 (0.965–1.026)	0.763
Glomerular lesions	2.121 (1.719–2.617)	<0.001	1.244 (1.053–1.471)	0.010	1.269 (0.993–1.621)	0.057
IFTA	2.326 (1.860–2.908)	<0.001	1.360 (1.106–1.672)	0.004	1.357 (1.038–1.774)	0.026
Interstitial inflammation	2.540 (1.855–3.476)	<0.001	1.650 (1.212–2.246)	0.001	1.537 (1.023–2.310)	0.390
Arteriolar hyalinosis	2.605 (1.552–4.373)	<0.001	1.286 (0.866–1.910)	0.212	1.811 (0.952–3.447)	0.070
Arteriosclerosis	1.755 (1.361–2.262)	<0.001	1.672 (1.271–2.198)	<0.001	1.764 (1.219–2.552)	0.003

Data are presented as HR (hazard ratios), 95% CI (confidence intervals), and *p* value. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone; TCH, total cholesterol; TG, triglycerides; Lpa, Lipoprotein a; HDL, High-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; TNF-α, tumor necrosis factor-α; IFTA, interstitial fibrosis and tubular atrophy; ESKD, end-stage kidney disease; CVD: cardiovascular.

confounding variables such as hydration status. Therefore, the GNRI is a reliable prognostic indicator of adverse outcomes in patients with DKD. The CONUT score, a combination of cholesterol, lymphocyte count, and serum albumin, may serve as a reliable indicator for identifying high-risk CVD patients. Early assessment of the CONUT score can provide a preliminary understanding of the nutritional, immune, inflammatory, and lipid metabolism status of patients. Consequently, it can be used as a reference for clinical management.

In addition, we presumed that the PNI may be a better predictor than GNRI and CONUT to predict the ESKD in DKD patients, most likely because the PNI is a more comprehensive marker that reflects nutrition, immune and inflammation (31), all of which are closely

TABLE 3 Multivariate Cox analysis of adverse outcomes in patients with diabetic kidney disease.

	Model 1		Model 2		Model 3	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
ESKD						
PNI	0.942 (0.924–0.961)	<0.001	0.941 (0.923–0.959)	<0.001	0.963 (0.938–0.989)	0.006
GNRI	0.963 (0.950–0.976)	<0.001	0.961 (0.949–0.974)	<0.001	0.974 (0.956–0.992)	0.004
TCBI	1.000 (1.000–1.000)	0.453	1.000 (1.000–1.000)	0.382	1.000 (1.000–1.000)	0.477
CONUT	1.206 (1.125–1.293)	<0.001	1.207 (1.126–1.295)	<0.001	1.087 (0.997–1.185)	0.059
CVD						
PNI	0.965 (0.947–0.983)	<0.001	0.970 (0.951–0.989)	0.002	0.976 (0.954–0.998)	0.036
GNRI	0.976 (0.962–0.989)	<0.001	0.978 (0.964–0.992)	0.002	0.978 (0.963–0.995)	0.009
TCBI	1.000 (1.000–1.000)	0.598	1.000 (1.000–1.000)	0.728	1.000 (1.000–1.000)	0.273
CONUT	1.149 (1.074–1.230)	<0.001	1.124 (1.049–1.205)	<0.001	1.113 (1.029–1.203)	0.007
All-cause mortality						
PNI	0.919 (0.890–0.948)	<0.001	0.921 (0.892–0.952)	<0.001	0.945 (0.897–0.995)	0.032
GNRI	0.942 (0.921–0.963)	<0.001	0.943 (0.922–0.965)	<0.001	0.954 (0.918–0.990)	0.013
TCBI	1.000 (1.000–1.000)	0.775	1.000 (1.000–1.000)	0.951	1.000 (1.000–1.000)	0.664
CONUT	1.323 (1.188–1.473)	<0.001	1.317 (1.176–1.474)	<0.001	1.208 (1.033–1.411)	0.018

Data are presented as HR (hazard ratios), 95% CI (confidence intervals), and *p* value. PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Risk Index; CONUT score, Controlling Nutritional Status score; TCBI, Triglycerides × Total Cholesterol × Body Weight Index; ESKD, end-stage kidney disease; CVD, cardiovascular disease event.
ESKD: Model 1, adjusted none; Model 2, adjusted gender (male) and age; Model 3, adjusted gender (male), age, hypertension, diabetic retinopathy, CKD stage, eGFR, serum creatinine, cystatin C, phosphorus, hemoglobin, iPTH, glomerular lesions, IFTA, interstitial inflammation, arteriolar hyalinosis, arteriosclerosis.
CVD: Model 1, adjusted none; Model 2, adjusted gender (male) and age; Model 3, adjusted gender (male), age, hypertension, coronary disease, diabetic retinopathy, CKD stage, statin use, anti-platelet drug use, eGFR, serum creatinine, cystatin C, hemoglobin, iPTH, IL-8, IFTA, interstitial inflammation, arteriosclerosis.
All-cause mortality: Model 1, adjusted none; Model 2, adjusted gender (male) and age; Model 3, adjusted gender (male), age, eGFR, serum creatinine, cystatin C, calcium, hemoglobin, iPTH, TCH, Lpa, HDL-C, arteriosclerosis.

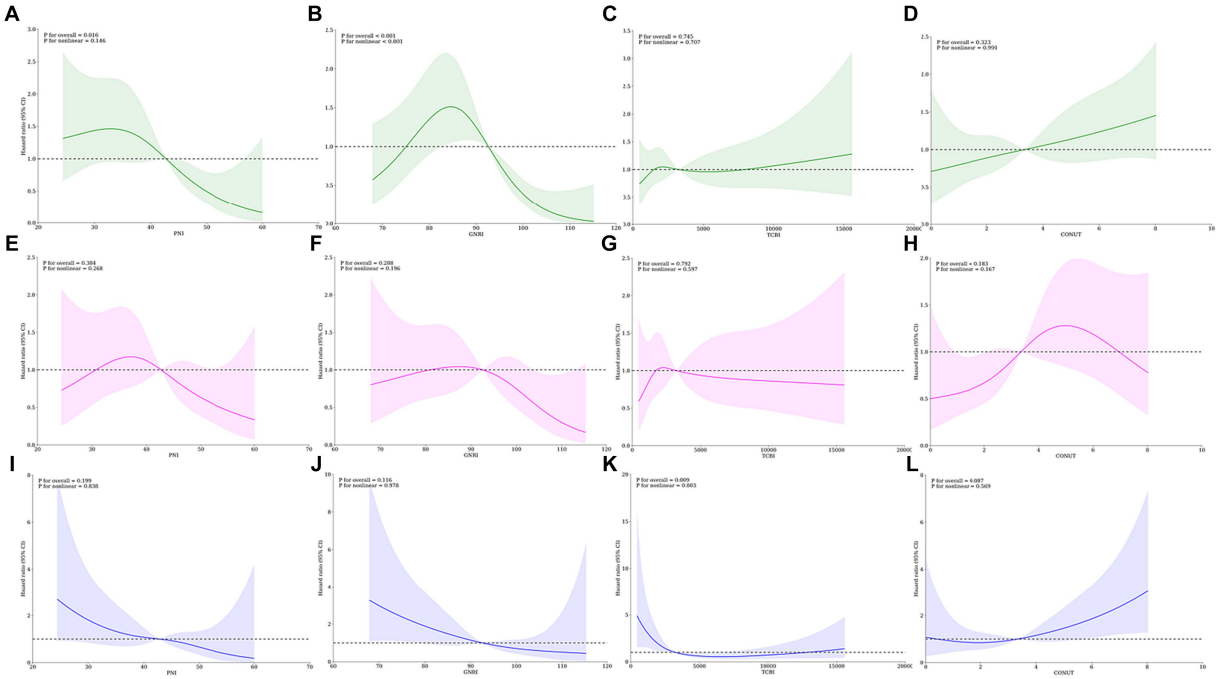

FIGURE 4
Restricted spline curves for the associations between four nutritional scores and adverse events in DKD patients. Lines represent the HR (hazard ratio), and transparent areas represent the 95% confidence intervals. HR (95% CI) were adjusted for various adverse events in Cox analysis using Model 3. **(A–D)** Associations between PNI, GNRI, TCBI, COUNT score and end-stage renal disease; **(E–H)** Association between PNI, GNRI, TCBI, COUNT score and cardiovascular death; **(I–L)** Association between PNI, GNRI, TCBI, COUNT score and all-cause mortality. PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Risk Index; CONUT score, Controlling Nutritional Status score; TCBI, Triglycerides×Total Cholesterol×Body Weight Index.

TABLE 4 Threshold effect analysis of nutritional scores on adverse events.

		Adjusted HR (95% CI)	*p* value
ESKD			
Fitting by standard lincar model	GNRI	0.971 (0.952–0.989)	0.002
Fitting by two-piecewise linear model			
	Inflection point of GNRI	71.629 (69.991–78.478)	
	GNRI<71.629	1.835 (1.170–2.878)	0.008
	GNRI>71.629	0.946 (0.925–0.968)	<0.001
	Log likelihood ratio		<0.001
All-cause mortality			
Fitting by standard lincar model	TCBI	1.000 (1.000–1.000)	0.6631
Fitting by two-piecewise linear model			
	Inflection point of TCBI	4942.720 (3560.630–7792.496)	
	TCBI<4942.720	0.999 (0.999–1.000)	0.002
	TCBI>4942.720	1.000 (1.000–1.000)	0.057
	Log likelihood ratio		<0.001

Data are presented as HR (hazard ratios), 95% CI (confidence intervals), and *p* value. PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Risk Index; CONUT score, Controlling Nutritional Status score; TCBI, Triglycerides × Total Cholesterol × Body Weight Index; ESKD, end-stage kidney disease; CVD, cardiovascular disease event.

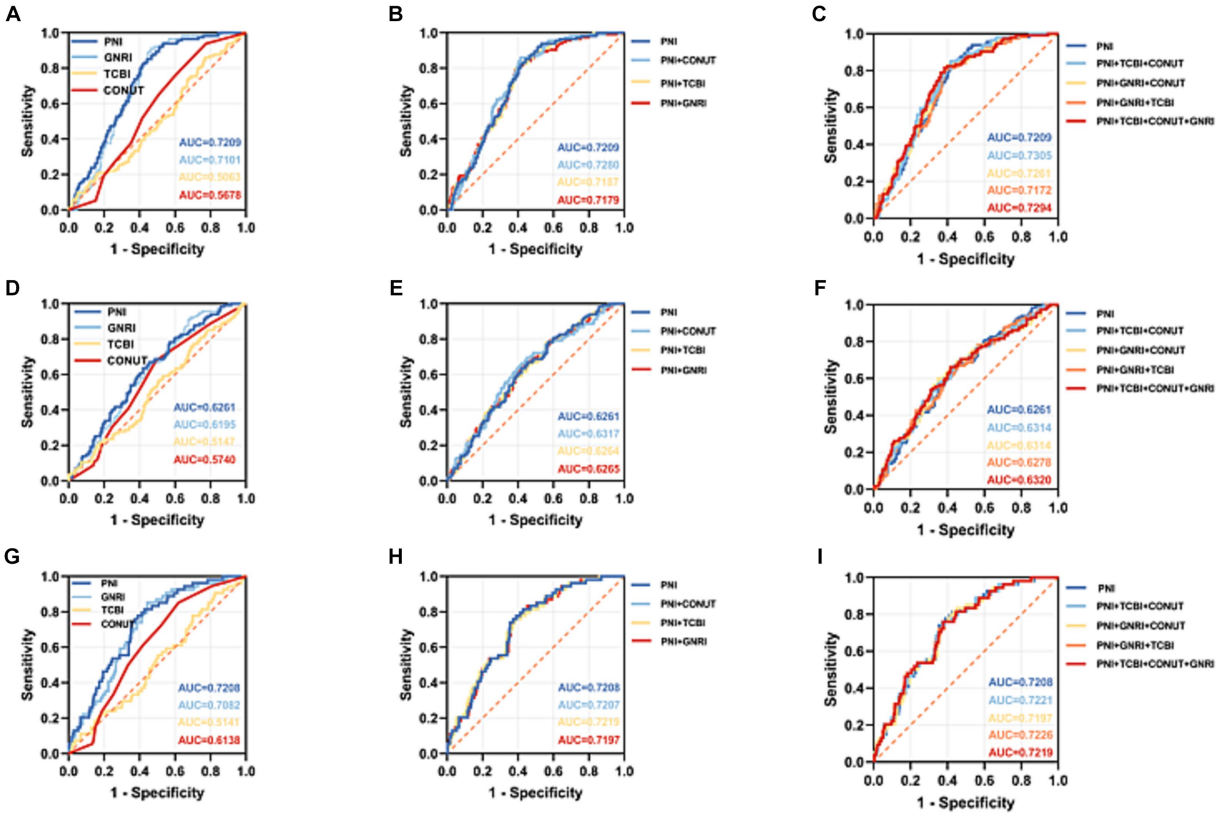

FIGURE 5
Comparison of the receiver operating characteristic (ROC) curves of four nutritional scores and different combinations with PNI in predicting adverse events in DKD patients. **(A–C)** ROC curves for predicting end-stage renal disease plotted by four nutritional scores and different combinations with PNI in DKD patients. **(D–F)** ROC curves for predicting cardiovascular mortality plotted by four nutritional scores and different combinations with PNI in DKD patients. **(G–I)** ROC curves for predicting all-cause mortality plotted by four nutritional scores and different combinations with PNI in DKD patients. ROC, Receiver operating characteristic; AUC, area under the curve. PNI, Prognostic Nutritional Index; GNRI, Geriatric Nutritional Risk Index; CONUT score, Controlling Nutritional Status score; TCBI, Triglycerides×Total Cholesterol×Body Weight Index.

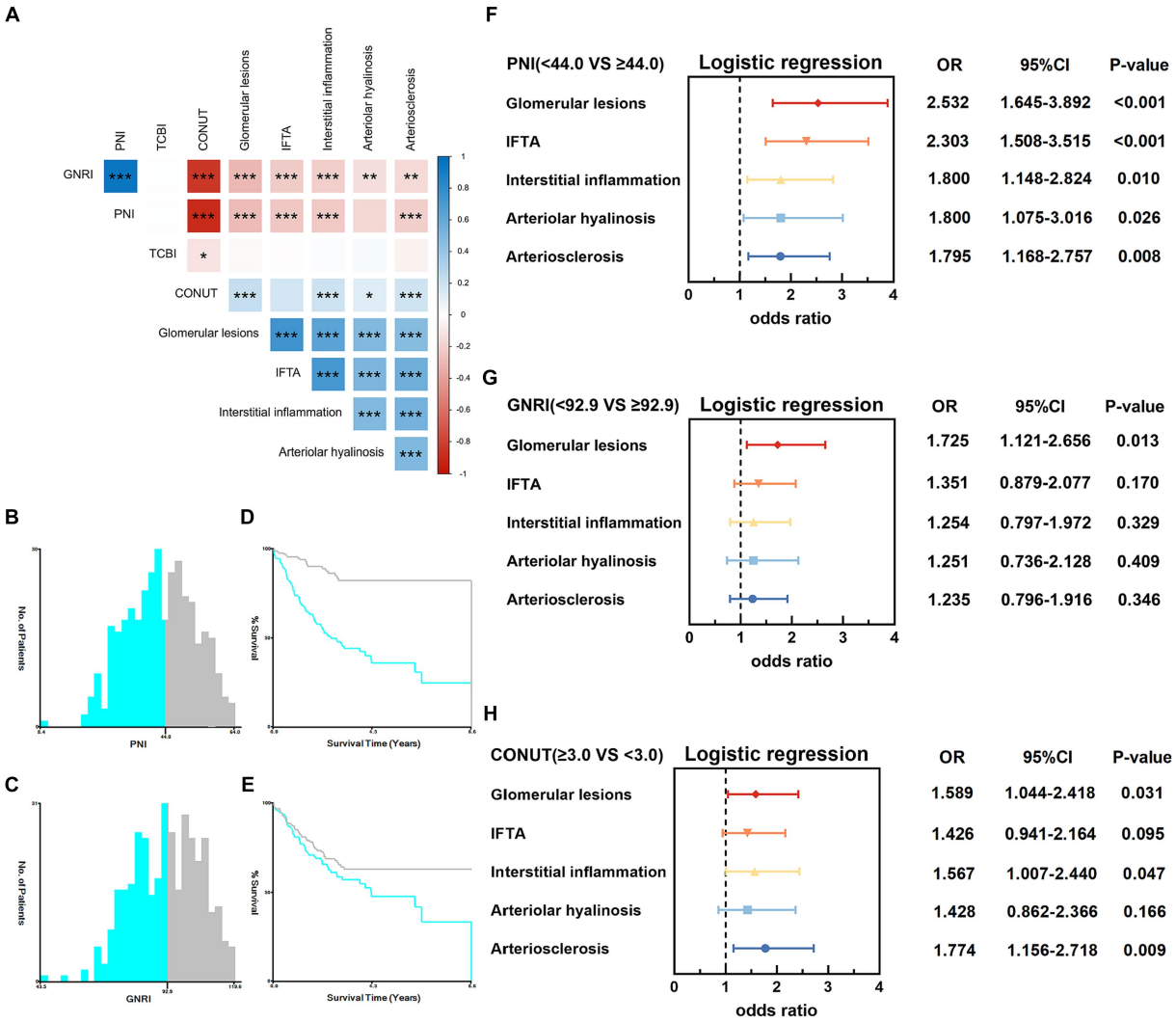

FIGURE 6
Correlation between four nutritional scores and different renal histologic changes in patients with diabetic kidney disease. **(A)** Correlation heatmap showing the correlation between four nutritional scores and different renal histologic changes. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. **(B,C)** Histograms of patient distribution according to the PNI and GNRI. **(D,E)** The Kaplan–Meier curves of the PNI and GNRI to calculate the optimum cutoff value. **(F)** Ordered logistic regression analysis to identify the relationship between PNI (<44.0 vs. ≥44.0) and different renal histological changes. **(G)** Ordered logistic regression analysis to identify the relationship between GNRI (<92.9 vs. ≥92.9) and different renal histological changes. **(H)** Ordered logistic regression analysis to identify the relationship between CONUT (≥3.0 vs. <3.0) score and different renal histological changes. OR, odds ratio; 95%CI, 95% confidence interval.

related with DKD. Moreover, lymphocyte count proves to be a more consistent measure of body composition over extended periods. In contrast, the markers used in calculating GNRI and TCBI, which include body weight, TC, and TG, are greatly influenced by factors like age, diet, drugs, smoking, drinking, and lifestyle choices. The TCBI score is calculated from variables reflecting lipid metabolism as well as immune function measured from blood tests. We presumed that TCBI may be the worst predictor to predict ESKD in DKD patients, most likely because TC and TG cannot effectively assess the body's nutritional status, inflammation level, and immune response.

A recommended treatment approach for DKD is the comprehensive management of blood glucose, blood pressure, and blood lipids, aiming to delay DKD progression to ESKD and cardiovascular diseases. High protein intake can further impair kidney function, increasing the risk of DKD progression and cardiovascular events. Carbohydrates, as a readily available source of energy, are one of the main influencing factors of blood glucose. Therefore, many renal experts suggest that DKD patients adopt a low-carbohydrate diet (energy intake of 25–35 kcal/kg/day) and minimize the risk of high protein intake (low protein diet, protein intake of 0.6–0.8 g/kg/day) (22). The new guidelines also differentiate between pre-dialysis diabetes patients and non-diabetes patients, providing specific protein ranges for each group. For clinically stable stage 3–5 CKD patients without diabetes, the new recommendations set a range of 0.55–0.60 g/kg/day or an extremely low protein diet of 0.28–0.43 g/kg/day (32). A lower protein intake reduces readily available energy in the body, thus requiring more carbohydrates to meet energy demands. However, a high carbohydrate intake may worsen blood glucose control in diabetes (33). From an energy perspective, low-carbohydrate and low-protein diets fundamentally contradict each other. Strict dietary

restrictions may lower the quality of life in DKD patients and significantly increase the risk of malnutrition. Therefore, it is especially important to comprehensively evaluate the nutritional status of DKD patients and utilize it to restrict protein intake and regulate blood glucose levels. We presumed that the diagnostic accuracy of PNI + TCBI+CONUT+GNRI was slightly higher than PNI alone for cardiovascular death, and the diagnostic accuracy of PNI + GNRI+TCBI was slightly higher than PNI alone for all-cause mortality, most likely because the combinations including more serum nutritional indicators and other factors can comprehensively evaluate the nutritional status of DKD patients.

Recent meta-analysis of kidney biopsies in diabetes patients has shown a wide range of changes in kidney disease (34). Autopsy studies have also indicated that pathological changes in diabetic kidney disease can occur before clinical manifestations like proteinuria and eGFR decline (35–38). Previous research has suggested that some renal histological changes are good predictors of end-stage renal disease, cardiovascular and all-cause mortality (39, 40). Therefore, evaluating the renal histological changes of DKD patients is clinically significant. However, even when clinical manifestations are present, renal biopsies are rarely conducted in routine clinical practice for DKD patients. Interestingly, we did not find any correlation between renal histological changes and all-cause mortality in both the low PNI group and the high PNI group in our study, which may be due to insufficient follow-up time. Moreover, albumin also has anti-inflammatory, antioxidant, and antithrombotic properties. Inflammatory states and conditions that increase capillary permeability can cause low serum albumin concentration, resulting in the expansion of interstitial space and an increase in albumin distribution volume (41). In our study, we found that DKD patients with more severe renal histological changes had a higher risk of adverse outcomes, particularly in low PNI group, where the relationship between renal histological changes (glomerular lesions, IFTA, interstitial inflammation) and end-stage renal disease was more pronounced. We hypothesized that DKD patients with low PNI have lower serum protein concentrations, indicating an increase in the excretion of renal amino acids that activate the RAS (42–44). The activation of the RAS induces glomerulosclerosis and interstitial fibrosis through various mechanisms, ultimately leading to renal histological changes. Therefore, integrating nutritional status and histological changes is crucial, particularly focusing on DKD patients with poor nutritional status (low PNI group), as it may help predict ESKD in these patients.

Despite the crucial findings being mentioned, our study has some limitations: (1) To begin with, our study was conducted at a single center and encompassed a small sample size comprising exclusively of patients with confirmed DKD through renal biopsy. This inclusion criteria might have introduced some degree of selective bias into our findings. We speculated that this was the reason why we found an N-shaped relationship between the nutritional score GNRI and ESKD, rather than an L-shaped relationship. (2) Certain factors that could potentially disrupt the results, including dietary factors and the use of various types of therapeutic medications, were not taken into account. (3) Due to the difficulty of repeated renal biopsies and reassessments, we only evaluated four nutritional scores at the time of patient enrollment, without investigating the impact of changes in renal histology and nutritional assessments overtime on the prognosis of DKD patients. (4) A more comprehensive assessment tool that incorporates additional nutrients, such as blood lipids and glucose, is necessary due to the limited nutritional content of the four nutritional scores.

5 Conclusion

In summary, our study demonstrated that the nutritional status of patients with DKD significantly influences their outcomes. We reported an association between end-stage kidney disease, cardiovascular, and all-cause mortality, and four nutritional scores (PNI, GNRI, TCBI, and COUNT). Moreover, our findings indicate that the PNI may provide more accurate predictive values for adverse outcomes and display stronger correlations with various renal histologic changes compared to other nutritional scores.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the data presented in this study are available on request from the corresponding author. The data are not publicly available due to the protection of patient's rights of privacy. Requests to access these datasets should be directed to chenling@cqmu.edu.cn.

Ethics statement

The studies involving humans were approved by the ethical committee of Xinqiao Hospital (No. 2018-006-02). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LX: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Data curation, Conceptualization. JX: Writing – review & editing, Validation, Supervision, Investigation, Data curation, Conceptualization. QH: Writing – review & editing, Project administration, Methodology, Data curation. WL: Writing – review & editing, Supervision, Investigation. LC: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1352030/full#supplementary-material

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Impact of the geriatric nutritional risk index on long-term outcomes in patients undergoing hemodialysis: a meta-analysis of observational studies

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Background: This meta-analysis aimed to synthesize current evidence on the association between the Geriatric Nutritional Risk Index (GNRI) and long-term outcomes in patients undergoing hemodialysis.

Methods: Electronic databases were systematically searched for relevant studies that investigated the association between GNRI and long-term outcomes in hemodialysis patients until November 2023. The primary outcome was the association between the GNRI (i.e., low versus high) and overall mortality risk, while the secondary outcome was the relationship between the GNRI and cardiovascular mortality risk.

Results: Thirty cohort studies involving 55,864 patients were included. A low GNRI was found to be significantly associated with increased overall mortality (hazard ratio [HR]: 2.42, 95% confidence interval [CIs]: 2.10–2.79, $p < 0.00001$, $I^2 = 65\%$). Each unit increase in GNRI corresponded to a 5% reduction in mortality risk (HR: 0.95, 95% CI: 0.93–0.96, $p < 0.00001$, $I^2 = 79\%$). The association remained consistent across Asian (HR = 2.45, 95% CI: 2.08–2.88, $p < 0.00001$, $I^2 = 70\%$) and non-Asian subgroups (HR = 2.3, 95% CI: 1.72–3.06, $p < 0.00001$, $I^2 = 23\%$). Meta-regression analysis of patient age (coefficient: −0.002; $p = 0.896$), male proportion (coefficient: 0.002; $p = 0.875$), percentage of diabetes mellitus (coefficient: −0.003; $p = 0.605$), and follow-up duration (coefficient: −0.003; $p = 0.431$) revealed that these moderator variables did not significantly influence the association between GNRI and overall mortality risk. Cardiovascular mortality risk also increased with low GNRI (HR, 1.93; 95%CI: 1.51–2.45, $p < 0.00001$; $I^2 = 2\%$). Similarly, an inverse association was observed between the GNRI values and cardiovascular mortality risk (HR, 0.94; 95% CI: 0.91–0.97; $p < 0.0001$; $I^2 = 65\%$) (per unit increase).

Conclusion: The GNRI is a simple nutritional screening tool that can be used to effectively stratify patients undergoing hemodialysis globally. Further studies are warranted to determine whether nutrition optimization based on the GNRI improves long-term outcomes.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, CRD42023483729.

KEYWORDS

geriatric nutritional risk index, hemodialysis, overall mortality, meta-analysis, renal failure

1 Introduction

End-stage renal disease (ESRD) is a global public health problem, with increasing prevalence rates worldwide in conjunction with population aging and increasing incidences of diabetes mellitus (DM), hypertension, and chronic kidney disease (1–4). The average number of new ESRD diagnoses worldwide is 144 individuals per million populations (5). However, the incidence of ESRD varies significantly across countries. In China, the estimated number of patients undergoing hemodialysis is expected to increase to 629.67 individuals per million populations in 2025 (6). Hemodialysis is the predominant form of renal replacement therapy in patients with ESRD (7). Compared with the general population, patients with ESRD undergoing hemodialysis have multiple comorbidities, impaired quality of life, malnutrition, and dramatically increased risks of cardiovascular events and premature mortality (8–10). The first-year mortality rate in elderly patients undergoing dialysis was reported to range from 30 to 54.5% (11). Protein-energy wasting is a multifaceted metabolic condition characterized by diminished mass of muscle and adipose tissue, frequently accompanied by reduced appetite and nutritional status (12). It is a common issue among patients undergoing hemodialysis, with its prevalence varying between 28 and 54% in patients undergoing regular dialysis treatment (9, 13–15). Current evidence suggests that protein energy wasting or malnutrition is a potential predictor of morbidity and mortality in this population (12, 16).

The Geriatric Nutritional Risk Index (GNRI) was developed as a simplified nutritional screening tool for assessing the risk of nutrition-related complications and nutritional status in patients undergoing maintenance hemodialysis (17–20). This tool is calculated based on serum albumin levels, body weight, and ideal body weight (18, 21). A previous meta-analysis of 10,739 patients from 19 cohort studies published between 2010 and 2018 revealed that GNRI was significantly associated with overall mortality and cardiovascular events in hemodialysis patients (22). However, the findings from the meta-analysis might not fully represent the long-term risk associated with clinical outcomes, as the associations were assessed at a single point in time—for instance, displaying results as odds ratios (ORs)—without considering the potential effects of interactions over time (22). Additional evidence is warranted to elucidate the association between the GNRI and long-term mortality risk in hemodialysis patients through time-to-event analyses. Recently, there has been a growing trend in the number of studies conducted to examine the association between the GNRI and long-term mortality risk in patients on maintenance hemodialysis, providing an opportunity to update the existing pool of knowledge (23–33). This meta-analysis aimed to synthesize the current evidence and provide a quantitative estimate of the association between GNRI and mortality risk in hemodialysis patients.

2 Materials and methods

The study protocol was registered with PROSPERO under registration number CRD42023483729, and the meta-analysis was executed in compliance with the PRISMA guidelines (34).

2.1 Data sources and search strategies

To achieve a comprehensive review of the relevant literature, we rigorously searched multiple electronic databases, including MEDLINE, Embase, Cochrane Library, and Google Scholar, to identify observational studies that investigated the association between the GNRI and long-term mortality risk in hemodialysis patients. The search period spanned from the inception of these databases until November 17, 2023. Our search strategy involved a combination of terms associated with "geriatric nutritional risk index," "mortality," and "hemodialysis," and no language restrictions were imposed. In addition to electronic databases, we explored the reference lists of the included studies or relevant review articles for any additional pertinent publications. Table 1 presents a summary of the detailed search strategy for one of the databases (i.e., MEDLINE).

2.2 Study selection process

To ensure a systematic approach in selecting relevant studies, a two-step screening process was used. First, two independent reviewers screened the titles and abstracts of retrieved records to assess their potential eligibility. Second, full-text assessments of the selected records were conducted to determine final inclusion in the study. Any discrepancies or disagreements between the reviewers were promptly addressed by consulting a third reviewer, thereby ensuring uniformity and minimizing the potential for bias. The study selection adhered to

TABLE 1 Search strategy for MEDLINE.

#1	("Dialysis, Renal" or "Hemodialysis" or "Hemodialyses" or "Extracorporeal Dialyses" or "Extracorporeal Dialysis" or "Kidney Dialysis" or "Renal Dialysis" or "Blood Dialysis" or "Artificial Kidney Treatment" or "End-Stage Renal Disease "or "End-Stage Kidney Disease" or "Chronic Kidney Failure" or "End-Stage Renal Failure" or "Renal Failure, Chronic" or "Chronic Renal Failure" or "ESRD").mp.
#2	exp "Renal Dialysis"/ or exp. "Kidney Failure, Chronic"/
#3	("geriatric nutritional risk index" or "GNRI").mp.
#4	("Mortality" or "Cardiovascular mortality" or "Survival" or "Survival Analysis" or "Kaplan–Meier Survival Curves").mp.
#5	exp "Mortality"/ or exp. "Survival"/ or exp. "Kaplan–Meier Estimate"/
#6	(#1 or #2) and #3 and (#4 or #5)

a predefined protocol and specific selection criteria, ensuring transparency and replicability in the study selection process.

2.3 Inclusion and exclusion criteria

The following inclusion criteria were used for study selection: (1) studies involving adult patients undergoing maintenance hemodialysis therapy regardless of hemodialysis vintage; (2) studies assessing or reporting on the GNRI as a prognostic factor; (3) studies reporting on the association between the GNRI and time-dependent variables, including overall and cardiovascular mortality risk; and (4) cohort studies. The exclusion criteria were as follows: (1) case reports, reviews, editorials, and studies that did not provide relevant outcome data; (2) cross-sectional studies (excluded due to the lack of time-dependent variables); and (3) studies focused on patients undergoing peritoneal dialysis or those suffering from acute kidney injury.

2.4 Data collection

Relevant data were extracted independently by two team members using a standardized form, including study characteristics, participant demographics (e.g., age and male proportion), sample size, hemodialysis duration, percentage of patients with DM, GNRI cutoff values (low/high), follow-up duration, country in which the study was conducted, and mortality outcomes. For mortality outcomes, we only collected time-dependent variables (i.e., HR). In cases where information was missing, we contacted the corresponding authors of the article to request necessary details.

2.5 Outcomes and definition

The primary outcome was overall mortality, defined as death from any cause, while the secondary outcome was cardiovascular mortality. Low GNRI was the main exposure variable, as defined by the individual study. We conducted subgroup analyses to explore the impact of the geographical location of the study populations (i.e., Asian and non-Asian) on the primary outcome.

2.6 Quality assessment of included studies

The quality of the included studies was assessed using the Newcastle–Ottawa Scale, which consists of three main components: selection, comparability, and outcome of interest. Studies were awarded stars in each category, with more stars indicating a higher quality. Each study was awarded a maximum of nine stars, with studies receiving six or more stars deemed high quality. This threshold was set to distinguish studies with a lower risk of bias and robust methodological approach. Disagreements were resolved by consensus or consultation with a third reviewer.

2.7 Statistical analysis

Statistical analyses were conducted using Comprehensive Meta-Analysis software (Version 4, Biostat, Englewood, NJ). Owing to the anticipated clinical and methodological heterogeneity among the included studies, a random-effects model was used. Heterogeneity among studies was quantified using the I^2 statistic, which describes the percentage of total variation across studies caused by heterogeneity rather than by chance. An I^2 value exceeding 50% indicated considerable heterogeneity among studies. Sensitivity analyses were conducted to evaluate the impact of each study on combined effect size. Furthermore, funnel plots were created to assess publication bias for outcomes reported in more than 10 studies. A meta-regression analysis was conducted to explore the potential sources of heterogeneity and assess the impact of the moderator variables on the effect size. The variables included age, male proportion, percentage of patients with DM, and follow-up duration. These variables were selected based on their clinical relevance and likelihood of influencing the association between the GNRI and long-term mortality. The statistical significance of the pooled estimates and meta-regression coefficients was set at $p < 0.05$.

3 Results

3.1 Study selection and characteristics of studies

The selection process for the meta-analysis is illustrated in Figure 1. Database searches, including PubMed, Embase, Cochrane Library, and Google Scholar, initially yielded 403 records. After removing 80 duplicates and 362 records based on titles and abstracts, 41 records were retrieved for full-text review. All of these were assessed for eligibility, and various reports were excluded for reasons such as review articles or irrelevant to the study population. Ultimately, 30 studies were deemed suitable and included in the meta-analysis (23–33, 35–53).

Table 2 presents data from 30 studies published between 2010 and 2023 that examined the association between GNRI and mortality in hemodialysis patients. These studies were conducted globally across countries, including Turkey, Japan, Korea, China, Taiwan, Israel, Italy, the Netherlands, Iran, and Brazil. The mean or median age of the patients ranged from 49 to 72 years, with the percentage of males ranging from 42.5 to 69.4%. The sample sizes varied significantly across studies, with a minimum of 75 patients and a maximum of 34,933 patients, accumulating in a combined total of 55,864 patients. The hemodialysis vintage varied from 6.4 to 110.4 months in 26 studies, while four studies did not provide relevant information. The percentage of patients with DM as a comorbidity ranged from 15 to 61.5%. The mean GNRI scores ranged from 91.2 to 109.2. The follow-up period for mortality analysis ranged from 12 to 120 months. All 30 studies assessed in the analysis were considered to be of high quality with a low risk of bias, as each scored seven or higher on the Newcastle–Ottawa Scale.

3.2 Outcomes

3.2.1 Primary outcomes

Of the 30 included studies, 25 provided categorical GNRI data (low versus high GNRI groups), allowing them to be pooled for the primary meta-analysis. The other five studies only provided continuous GNRI data and did not have categorical cutoff values.

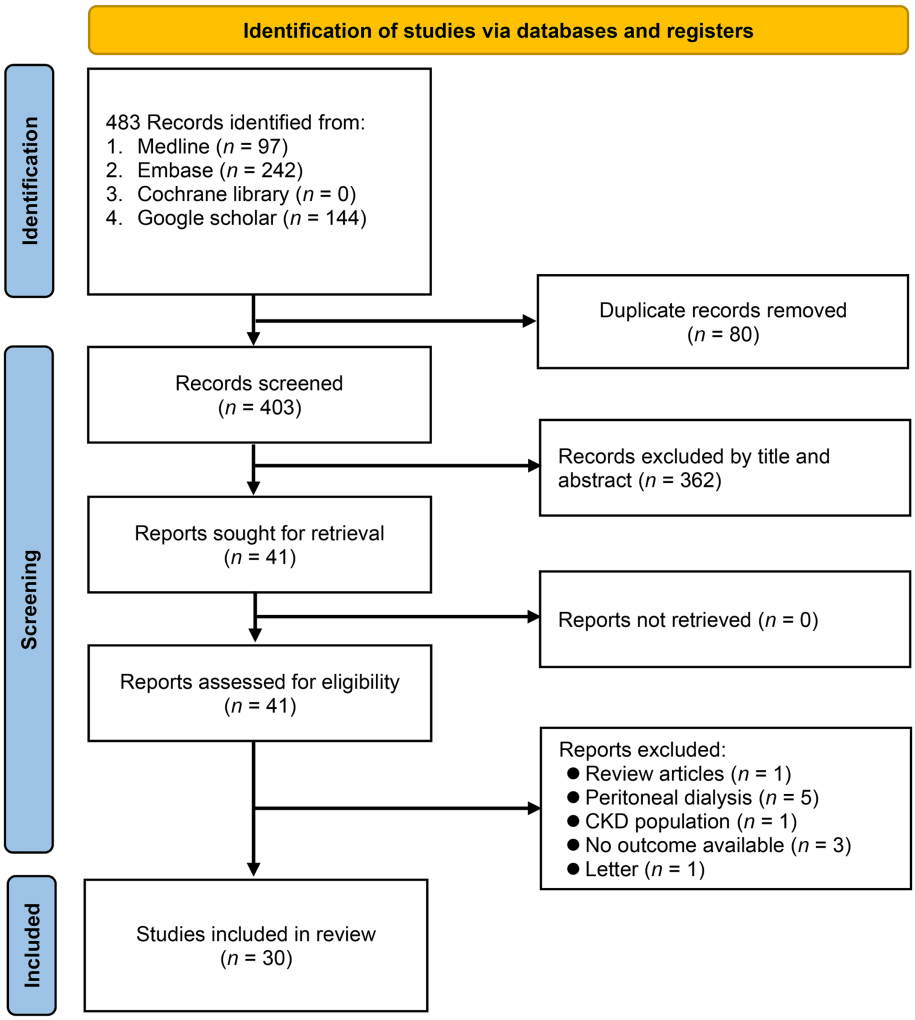

FIGURE 1
The flowchart outlining the study selection process for current meta-analysis. CKD, chronic kidney disease.

These five studies were not excluded, as we utilized them in a separate analysis to examine the impact of the GNRI on mortality risk when treating the GNRI as a continuous variable.

In our meta-analysis on 25 studies, we found a significant association between lower GNRI and increased long-term mortality risk, with a combined HR of 2.42 (95% CI, 2.10–2.79, $p < 0.00001$), indicating a more-than-twofold-higher risk of mortality (Figure 2) (23–33, 35, 36, 38–42, 45, 46, 48, 50–53). Sensitivity analysis revealed that this association was evident across multiple studies despite moderate to high heterogeneity ($I^2 = 65\%$), reinforcing the value of the GNRI as a prognostic indicator for this patient population. Additional analysis revealed that with each unit increase in GNRI, there was a corresponding decrease in the overall mortality risk (HR: 0.95, 95% CI: 0.93–0.96, $p < 0.00001$, $I^2 = 79\%$), suggesting an inverse association (Figure 3) (23–25, 27, 28, 32, 35–37, 43, 44, 47, 49, 52, 53). The funnel plot shows a largely symmetrical spread of studies around the combined effect estimate, suggesting minimal publication bias (Figure 4) (23–33, 35, 36, 38–42, 45, 46, 48, 50–53).

Subgroup analyses revealed a significant association between lower GNRI and increased overall mortality risk (HR = 2.3, 95% CI: 1.72–3.06, $p < 0.00001$, $I^2 = 23\%$) in non-Asian population (Figure 5) (23–33, 35, 36, 38–42, 45, 46, 48, 50–53). For Asian studies, this association was also significant and slightly stronger (HR = 2.45, 95% CI: 2.08–2.88, $p < 0.00001$), albeit with substantial heterogeneity ($I^2 = 70\%$) (Figure 5) (23–33, 35, 36, 38–42, 45, 46, 48, 50–53). This finding suggests that the GNRI is a consistent predictor of mortality across different ethnic populations.

Meta-regression analysis of patient age (coefficient: −0.002; $p = 0.896$) (Figure 6) (23–33, 35, 36, 38–42, 45, 46, 48, 50–53), male proportion (coefficient: 0.002; $p = 0.875$) (Figure 7) (23–33, 35, 36, 38–42, 45, 46, 48, 50–53), percentage of patients with DM (coefficient: −0.003; $p = 0.605$) (Figure 8) (23–33, 35, 36, 38–42, 45, 46, 48, 50–53), and follow-up duration (coefficient: −0.003; $p = 0.431$) (Figure 9) (23–33, 35, 36, 38–42, 45, 46, 48, 50–53) revealed that these moderator variables did not significantly impact the association between GNRI and mortality outcomes.

3.2.2 Secondary outcomes

Meta-analysis on cardiovascular mortality among hemodialysis patients revealed a significant association between lower GNRI scores and increased cardiovascular mortality risk, with a combined HR of

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TABLE 2 Characteristics of 30 studies involving 55,864 hemodialysis patients.

Studies	Age (years)†	Male (%)	*n*	Hemodialysis (m)	DM (%)	GNRI	Cut-off (low/high)	Follow-up (m)	Country	NOS
Ayerden Ebinc 2022	57	50.3	169	33	15	105.9 ± 16.6	104.2	12	Turkey	7
Beberashvili 2013	64.8	57	75	41	46.7	na	113	46.8	Israel	7
Beberashvili 2016	67.4	62	352	23.0	57	109.2 ± 12.4	na§	30	Israel	8
Chen 2019	53.9	57	1,025	24.5	27	95.0 ± 6.9	82/98	28.1	China	7
Cho 2022	62	62	2,313	na	54	96.9 ± 6.91	92	37.2	Korea	8
de Roij van Zuijdewijn 2015	63.3	61	489	24	24	na	na‖	35.6	Netherlands	8
Edalat-Nejad 2015	60	53	145	60	33	102.6 ± 5.5	100	18	Iran	7
Fujioka 2022	68.3	54	183	97	41	91.2 ± 10.9	91.6	60	Japan	8
Ishii 2017	64	63	973	24	48	94.1 ± 8.8	91.2	96	Japan	9
Jung 2014	55.7	42.5	120	65.2	23	99.8 ± 9.9	90	120	Korea	8
Kim 2023	60.2	58.8	34,933	67.2	61.5	98.7	90.8	53.7	Korea	9
Kobayashi 2010	60	59.8	490	88	25	98.0 ± 6.0	na§	60	Japan	9
Komatsu 2015	65.4	64.2	332	67.2	47.9	96.8 ± 8.9	na§	36	Japan	8
Lin 2020	56.5	47	151	na	41	101 ± 6.3	94/98	60	Taiwan	8
Machiba 2022	61.0	62.9	518	110.4	21.2	95.2 (90.8–98.3)	92.3/96.8	60	Japan	9
Matsukuma 2019	68.9	49.5	3,436	58.8	26.9	na	90.8/100.2	48	Japan	8
Naito 2022	65	67	499	64	37	95 (90–100)	92	60	Japan	9
Panichi 2014	65.7	60.7	753	70.4	18.8	93.4 ± 10.7	90.6	84	Italy	9
Park 2012	56.2	42.5	120	54.9	48.3	100.4 ± 9.0	na§	90	Korea	8
Ren 2020	50.2	55.4	1,804	31.8	18.7	92.96 ± 9.15	82/98	33.7	China	8
Rodrigues 2019	69.4	65	173	34.7	38	na	91.2	23.6	Brazil	7
Takahashi 2014	64	66.9	1,568	na	52	na	84.9/97.3	63	Japan	9
Takahashi 2017	64	55.3	409	8	31.8	93.2 ± 5.6	na§	52	Japan.	8
Tsai 2014	49	48.7	318	na	26.7	na	92	54	Taiwan	8
Tsai 2016	72	51.9	104	65	36.5	na	92	38.5	Taiwan	7
Yajima 2022	63.8	66.5	263	18	42.6	93.1 ± 7.6	91.2	37.2	Japan	8
Yajima 2020	63.6	69.4	229	6.4	45.8	94.0 ± 7.0.	91.2	44.4	Japan	8
Yajima 2021	63.4	68.3	180	7.2	46.7	94.5 ± 6.9	91.2	55.2	Japan	7
Yajima 2019	65.1	69.2	234	9.6	45.3	93.5 ± 6.5	94.5	33.6	Japan	8
Yamada 2020	66	65	3,536	50.4	39.9	na	89.3/98.8	26.4	Japan	8

†Mean or median; na, not available; ‖The GNRI value was classified into four distinct groups; §The relationship between GNRI and mortality was examined by treating GNRI as a continuous variable. NOS, Newcastle–Ottawa Scale; m, months.

1.93 (95% CI, 1.51–2.45, $p < 0.00001$, $I^2 = 2\%$) (Figure 10) (25–27, 35, 41, 51, 53). The sensitivity analysis revealed a consistent finding using the leave-one-out approach. Similarly, an inverse association was observed between GNRI values and cardiovascular mortality risk (HR: 0.94, 95% CI: 0.91–0.97, $p < 0.0001$, $I^2 = 65\%$) (per unit increase) (Figure 11) (25, 27, 35, 37, 44, 53).

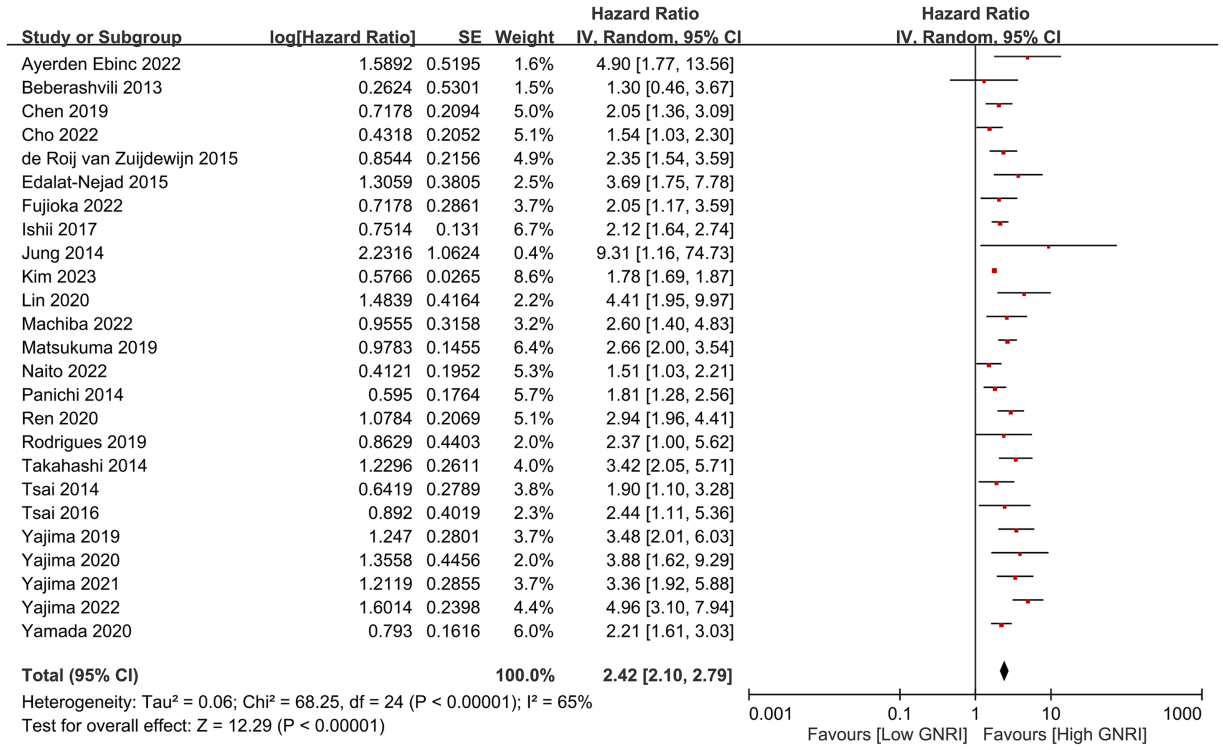

FIGURE 2
Forest plot showing the association between the Geriatric Nutritional Risk Index (GNRI) and overall mortality. CI, confidence intervals.

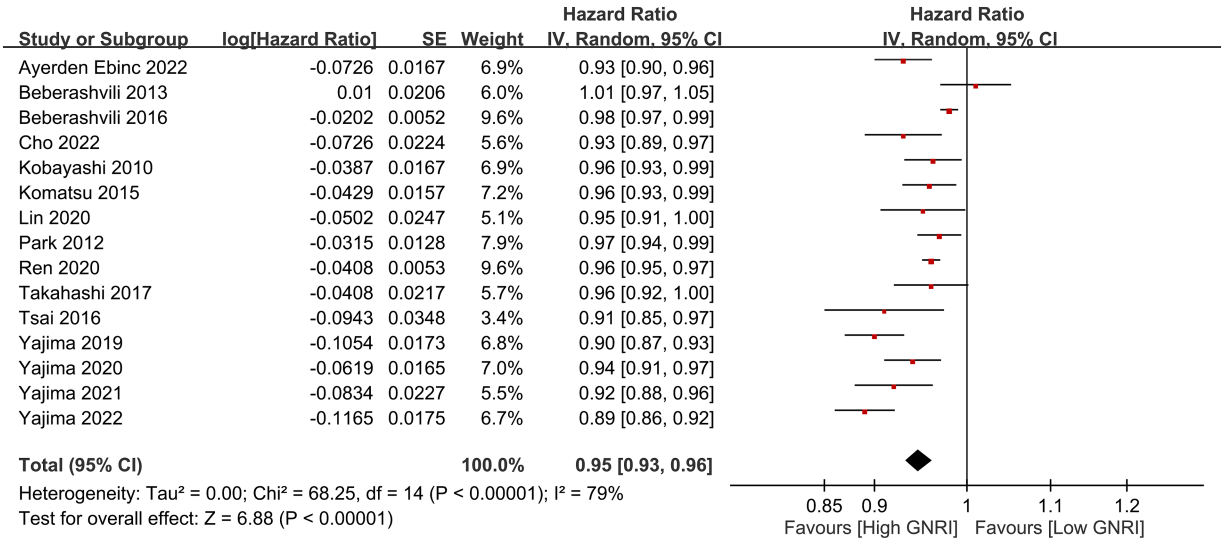

FIGURE 3
Forest plot showing that with each unit increase in Geriatric Nutritional Risk Index (GNRI), there was a corresponding decrease in overall mortality risk. CI, confidence intervals.

4 Discussion

Assessment of the prognostic value of the GNRI can facilitate evidence-based practices to optimize the delivery of nutritional interventions and improve risk stratification for targeted care in high-risk hemodialysis populations. In the meta-analysis of 30 studies involving a total of 55,864 patients, a notable correlation was observed between a lower GNRI and an increase in overall mortality risk (HR: 2.42). Furthermore, it was found that each increment in GNRI corresponded with a reduced overall mortality risk (HR: 0.95). The funnel plot showed negligible publication bias. Subgroup analyses have revealed that the GNRI consistently predicts overall mortality

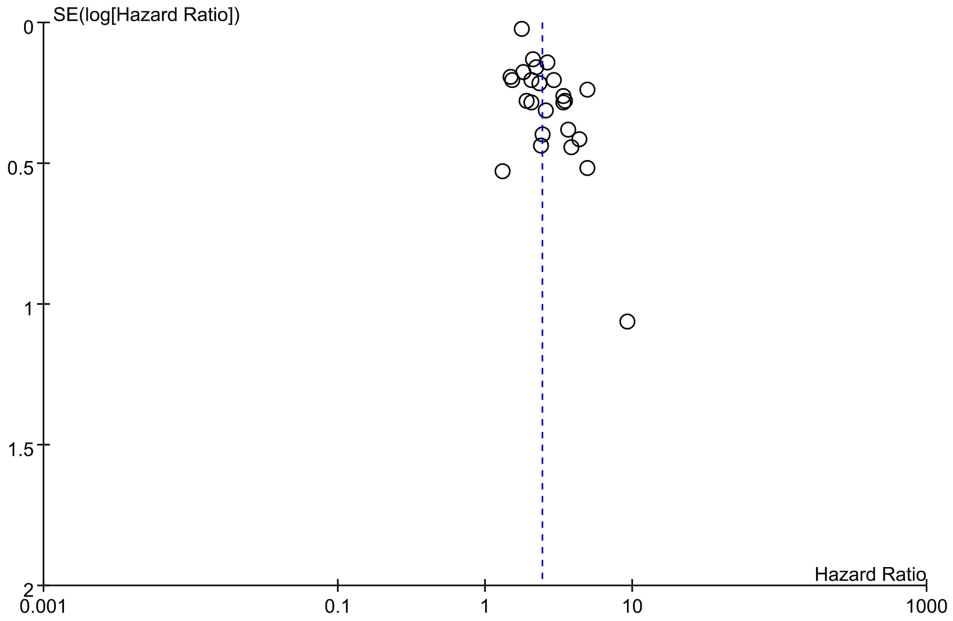

FIGURE 4
Funnel plot showing the publication bias in studies examining the association between the geriatric nutritional risk index (GNRI) and overall mortality.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.5.1 Non-Asian				
Ayerden Ebinc 2022	1.5892	0.5195	1.6%	4.90 [1.77, 13.56]
Beberashvili 2013	0.2624	0.5301	1.5%	1.30 [0.46, 3.67]
de Roij van Zuijdewijn 2015	0.8544	0.2156	4.9%	2.35 [1.54, 3.59]
Edalat-Nejad 2015	1.3059	0.3805	2.5%	3.69 [1.75, 7.78]
Panichi 2014	0.595	0.1764	5.7%	1.81 [1.28, 2.56]
Rodrigues 2019	0.8629	0.4403	2.0%	2.37 [1.00, 5.62]
Subtotal (95% CI)			**18.2%**	**2.30 [1.72, 3.06]**
Heterogeneity: Tau² = 0.03; Chi² = 6.53, df = 5 (P = 0.26); I² = 23%				
Test for overall effect: Z = 5.65 (P < 0.00001)				
1.5.2 Asian				
Chen 2019	0.7178	0.2094	5.0%	2.05 [1.36, 3.09]
Cho 2022	0.4318	0.2052	5.1%	1.54 [1.03, 2.30]
Fujioka 2022	0.7178	0.2861	3.7%	2.05 [1.17, 3.59]
Ishii 2017	0.7514	0.131	6.7%	2.12 [1.64, 2.74]
Jung 2014	2.2316	1.0624	0.4%	9.31 [1.16, 74.73]
Kim 2023	0.5766	0.0265	8.6%	1.78 [1.69, 1.87]
Lin 2020	1.4839	0.4164	2.2%	4.41 [1.95, 9.97]
Machiba 2022	0.9555	0.3158	3.2%	2.60 [1.40, 4.83]
Matsukuma 2019	0.9783	0.1455	6.4%	2.66 [2.00, 3.54]
Naito 2022	0.4121	0.1952	5.3%	1.51 [1.03, 2.21]
Ren 2020	1.0784	0.2069	5.1%	2.94 [1.96, 4.41]
Takahashi 2014	1.2296	0.2611	4.0%	3.42 [2.05, 5.71]
Tsai 2014	0.6419	0.2789	3.8%	1.90 [1.10, 3.28]
Tsai 2016	0.892	0.4019	2.3%	2.44 [1.11, 5.36]
Yajima 2019	1.247	0.2801	3.7%	3.48 [2.01, 6.03]
Yajima 2020	1.3558	0.4456	2.0%	3.88 [1.62, 9.29]
Yajima 2021	1.2119	0.2855	3.7%	3.36 [1.92, 5.88]
Yajima 2022	1.6014	0.2398	4.4%	4.96 [3.10, 7.94]
Yamada 2020	0.793	0.1616	6.0%	2.21 [1.61, 3.03]
Subtotal (95% CI)			**81.8%**	**2.45 [2.08, 2.88]**
Heterogeneity: Tau² = 0.07; Chi² = 60.03, df = 18 (P < 0.00001); I² = 70%				
Test for overall effect: Z = 10.86 (P < 0.00001)				
Total (95% CI)			**100.0%**	**2.42 [2.10, 2.79]**
Heterogeneity: Tau² = 0.06; Chi² = 68.25, df = 24 (P < 0.00001); I² = 65%				
Test for overall effect: Z = 12.29 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%				

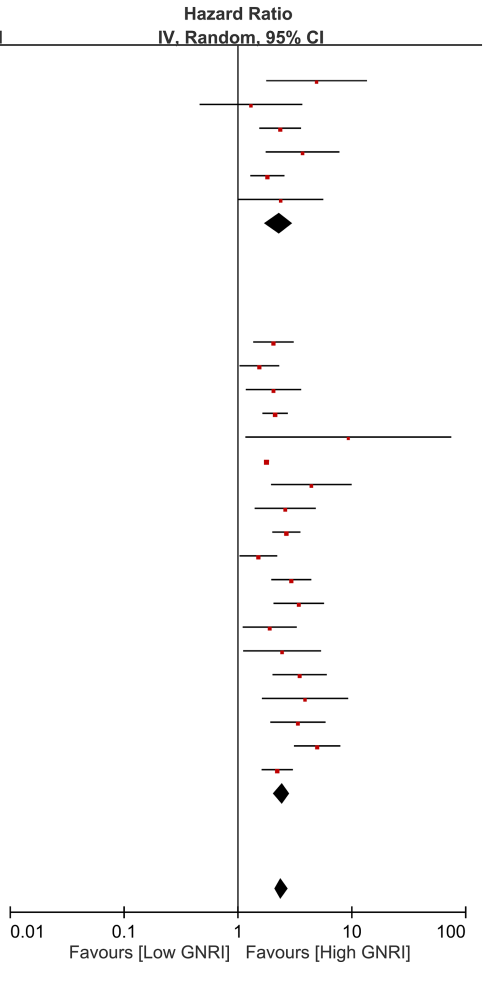

FIGURE 5
Subgroup analysis showing the association between the geriatric nutritional risk index (GNRI) and overall mortality across different ethnic populations. CI, confidence intervals.

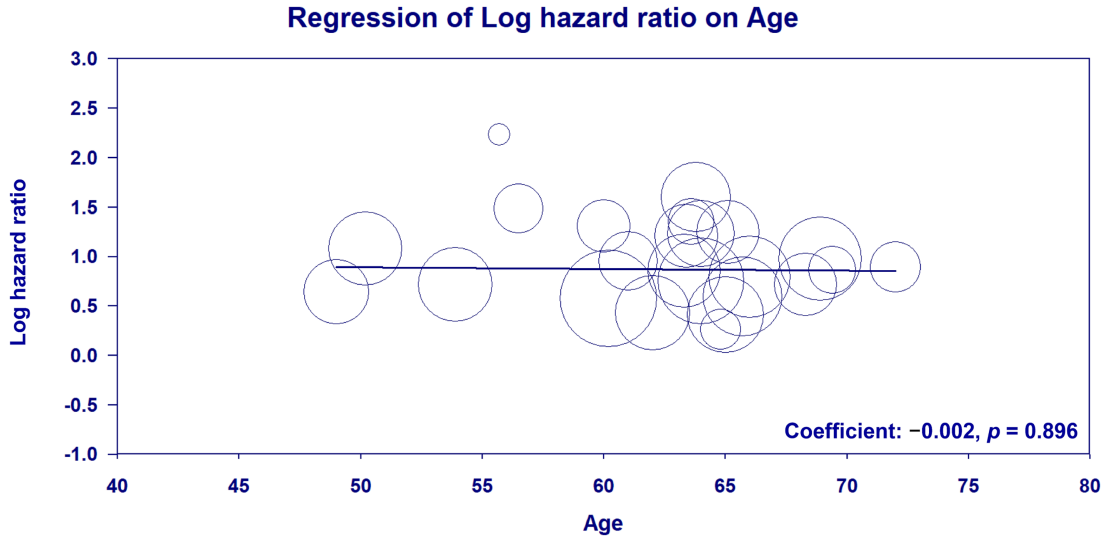

FIGURE 6
Meta-regression plot analyzing the impact of the age on the effect size on the association between the geriatric nutritional risk index (GNRI) and overall mortality.

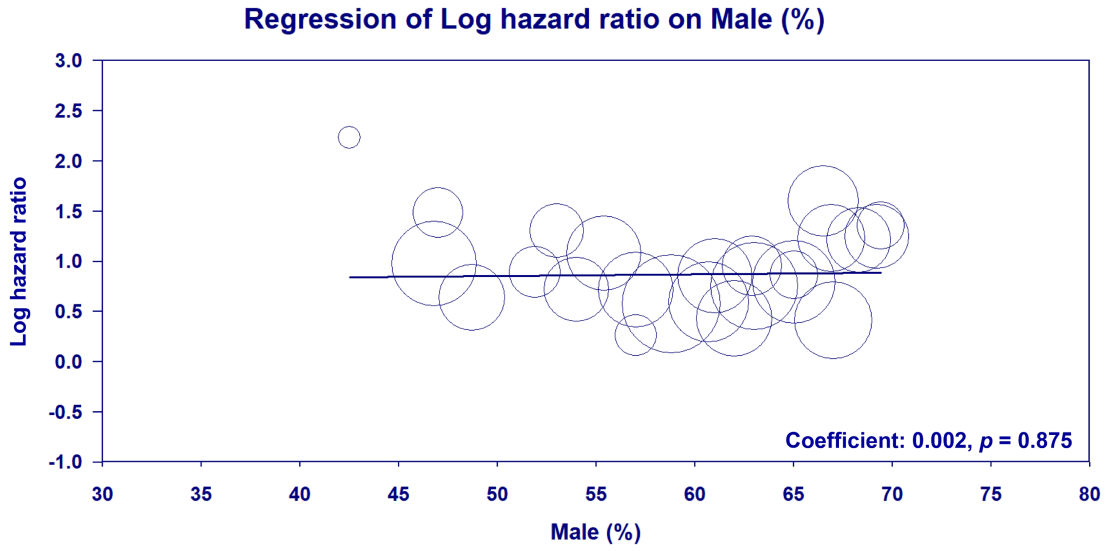

FIGURE 7
Meta-regression plot analyzing the impact of the male proportion on the effect size of the association between the geriatric nutritional risk index (GNRI) and overall mortality.

risk across diverse ethnic groups. In addition, meta-regression analyses revealed that variables such as patient age, male proportion, percentage of patients with DM, and follow-up duration did not significantly affect the association between the GNRI and overall mortality risk. In relation to cardiovascular mortality among hemodialysis patients, a significant association was observed between lower GNRI scores and an increased risk (HR: 1.93). Similarly, it was found that each increment in GNRI corresponded with reduced cardiovascular mortality risk (HR: 0.94).

Our findings indicate a significant association between lower GNRI scores and increased overall mortality risk. Having a simple and objective tool for identifying patients at a greater risk of mortality based on their nutritional status is of great clinical value for the following reasons. First, earlier nutritional interventions in patients on hemodialysis may improve outcomes (54, 55). The use of the GNRI as a screening tool may help effectively identify these high-risk patients and enable the implementation of preventive strategies. Second, the association between the GNRI and overall mortality risk contributes to better-informed discussions with patients regarding their expected health outcomes. However, the analyzed studies were observational; therefore, causal conclusions cannot be drawn regarding the effect of nutritional status improvements on mortality. Nevertheless, the consistency of the association, despite the population differences, supports the reliability of the findings. Overall, this

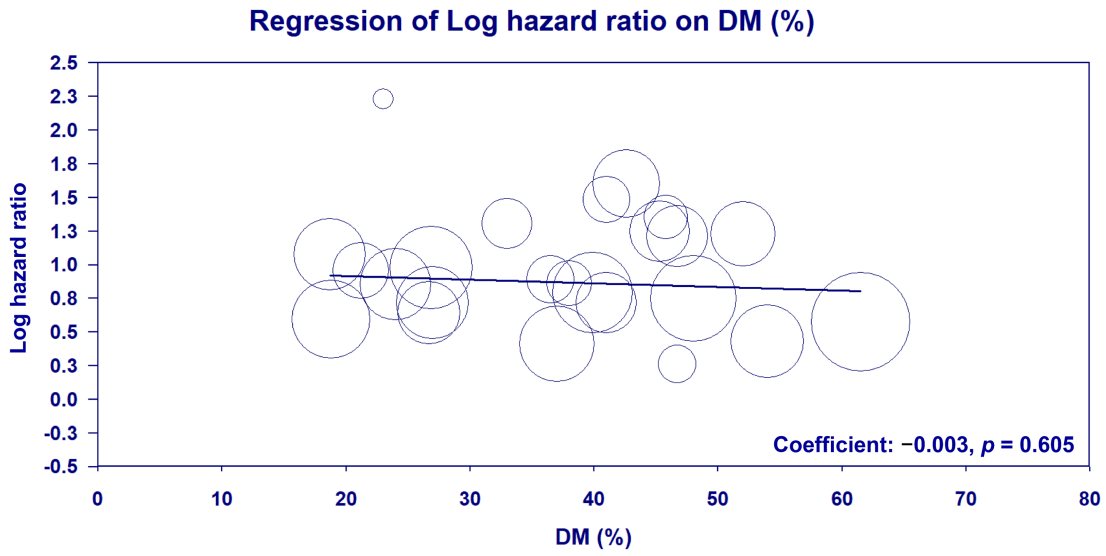

FIGURE 8
Meta-regression plot analyzing the impact of percentage of patients with diabetes mellitus (DM) on the effect size on the association between the geriatric nutritional risk index (GNRI) and overall mortality.

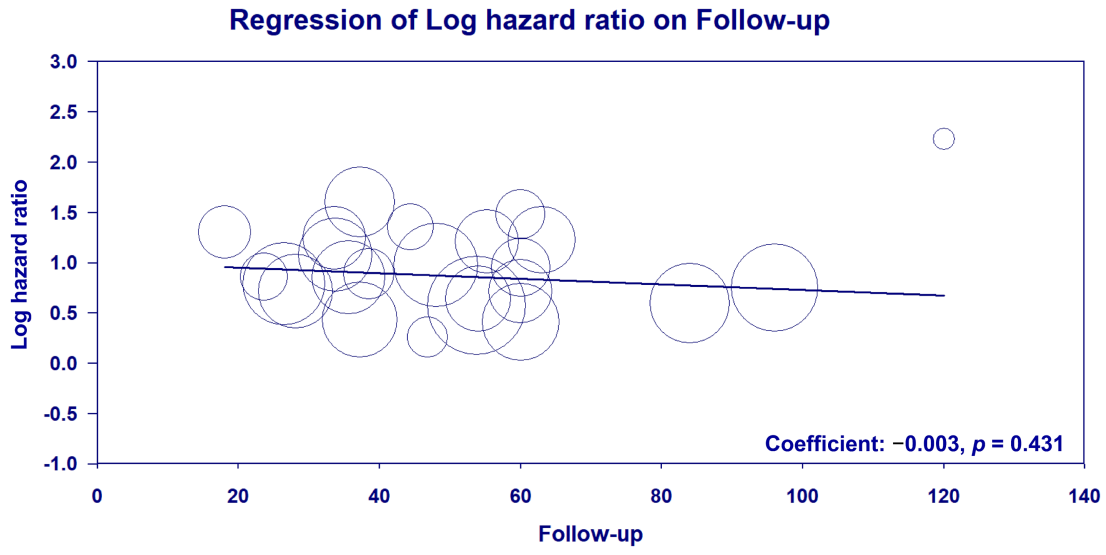

FIGURE 9
Meta-regression plot analyzing the impact of follow-up duration on the effect size on the association between the geriatric nutritional risk index (GNRI) and overall mortality.

meta-analysis provides robust evidence that the GNRI could be a practical nutritional assessment tool that can be incorporated into the care of hemodialysis patients globally to identify those with a higher mortality risk. Additional studies are warranted to determine the effects of nutritional support guided by GNRI scores on patient-centered outcomes.

An important strength of this meta-analysis was the inclusion of data solely from patients undergoing hemodialysis. Patients receiving other forms of dialysis such as peritoneal dialysis were excluded. Combining data across different dialysis modalities could potentially impact mortality outcomes (56) and limit the generalizability of the findings to specific populations. By focusing our meta-analysis specifically on patients receiving hemodialysis, we were able to evaluate the GNRI-mortality association in a distinct patient group with shared characteristics. Compared with a previous meta-analysis of 19 studies involving 10,739 patients (22), the present analysis significantly expands the evidence base, encompassing 30 studies with a cumulative total of 55,864 patients. The increase in sample size enhanced the statistical robustness and confidence in the outcomes. Furthermore, our analysis benefits from the incorporation of studies published within a more contemporary window from 2010 to 2023, providing insights from data collected over the last decade, whereas

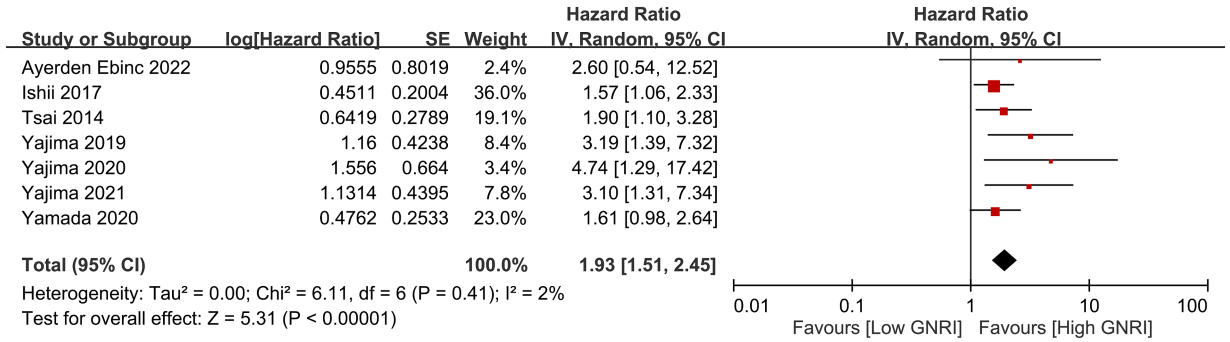

FIGURE 10
Forest plot illustrating the association between the geriatric nutritional risk index (GNRI) and cardiovascular mortality. CI, confidence intervals.

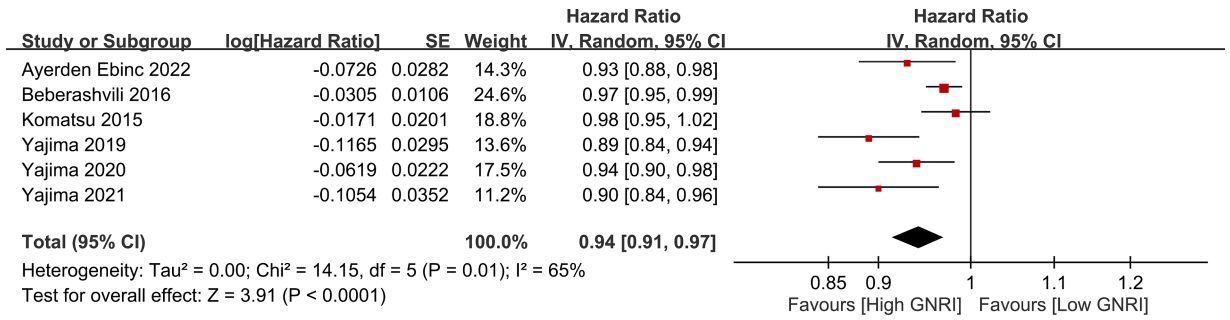

FIGURE 11
Forest plot showing that with each unit increase in Geriatric Nutritional Risk Index (GNRI), there was a corresponding decrease in cardiovascular mortality risk. CI, confidence intervals.

the previous analysis included studies published up to 2018 (22). Analytically, our meta-analysis advances by using time-to-event data such as HRs, which are more indicative of longitudinal trends in patient health, as opposed to the single point ORs previously used (22). Finally, the robustness of our research findings is bolstered by the thorough methodology used, including meta-regression and subgroup analysis, which adds to the overall strength of our results.

Compared with other clinical predictors, the GNRI may serve as a stronger prognostic factor. A previous meta-analysis of 28 studies revealed that geriatric impairments such as functional and cognitive decline, as well as falls, were associated with a higher mortality risk in elderly dialysis patients (OR: 1.14–1.45), in addition to traditional factors such as age and comorbidities (57). A review of nine cohort studies demonstrated that low handgrip strength was significantly associated with an increased mortality risk in dialysis patients (risk ratio [RR]: 1.88) (58). Furthermore, a meta-analysis of eight observational studies involving 190,163 patients revealed a paradoxical association between low body mass index and a higher mortality risk (RR: 1.22) in dialysis patients (59). Another meta-analysis of 38 studies highlighted serum albumin as having a strong inverse association with mortality in patients on dialysis (HR: 0.7038) (60). Our finding that a lower GNRI is associated with increased overall mortality risk, as indicated by a combined HR of 2.42, highlights the utility of this predictor in clinical settings.

The efficacy of the GNRI in predicting overall mortality may vary across populations. For the general population, a previous meta-analysis of 26 observational studies involving 17,097 participants revealed a significant association between low GNRI and an increased risk of both all-cause (HR: 1.32) and cardiovascular (HR: 2.10) mortalities (61). For elderly patients with heart failure, a meta-analysis of nine studies involving 7,659 patients revealed that low GNRI was predictive of all-cause mortality (HR: 1.56) compared to high GNRI (62). In addition, low GNRI values have been associated with an increased overall mortality risk in patients with head and neck, gastrointestinal, or lung cancer, with HRs ranging from 2.39 2.84 (63–65). Considering our findings and previous research, it appears that using the GNRI as a prognostic tool in patients on hemodialysis or suffering from cancer is more beneficial than in other clinical situations.

Despite the focus of our meta-analysis on studies predominantly from Asian countries, there is evidence that the use of nutritional indices to predict long-term outcomes is equally feasible and effective in non-Asian populations. A recent study that examined 101,616 hemodialysis patients in the United States found that higher Prognostic Nutritional Index (PNI) quartiles were associated with stepwise reductions in all-cause mortality (66). For instance, compared with the lowest PNI quartiles, patients in the highest quartile had a 64% lower mortality (66). Furthermore, a higher PNI predicted mortality better than albumin or lymphocyte count alone (66). A key distinction between the GNRI and PNI is that the former relies on serum albumin, body weight, and ideal weight, whereas the latter incorporates albumin and lymphocyte count. Although both use

distinct formulations, recent research (66) and our meta-analysis have demonstrated that nutritional indices are effective in predicting the clinical outcomes of hemodialysis patients regardless of their ethnicity. Compared to the PNI, the simplicity of the GNRI, owing to its exclusion of cell counts, makes it a practical and valuable tool in clinical settings.

This meta-analysis had several limitations that need to be acknowledged. First, all the included studies were observational in nature, which prevented the determination of causal associations between the GNRI and mortality outcomes. Residual confounding factors may still be present despite adjustments made in the analyses of individual studies. Second, there was moderate to substantial heterogeneity among the studies for the primary outcome, indicating variability in effects and populations. We addressed this by using a random-effects model and conducting meta-regression; however, some heterogeneity was likely due to differences in the study design and patient factors that could not be accounted for. Potential sources of heterogeneity include differences in patient characteristics, such as comorbidities and dialysis vintages, variation in ethnicities and healthcare systems across countries, and lack of standardized cut-off values used for categorizing high and low GNRI groups. Third, the majority of studies were conducted in Asian countries, with relatively few focusing on Western populations. Additional research may be warranted to confirm the generalizability of these findings to diverse ethnic groups globally. Finally, publication bias is a concern in meta-analyses, although we did not find evidence of significant bias based on visual inspection of funnel plots. However, studies with small sample sizes and null findings may be underrepresented. Overall, this meta-analysis provides strong evidence for the utility of the GNRI as a prognostic marker in hemodialysis patients; however, the limitations highlight the need for cautious interpretation and further high-quality longitudinal studies.

5 Conclusion

This meta-analysis of 30 studies involving 55,864 patients revealed an inverse association of the GNRI with overall and cardiovascular mortalities, highlighting the potential of the GNRI as a predictor of patient outcomes. Consistent findings across ethnicities and the lack of influence of age, sex, DM, and follow-up duration on this association highlight the reliability of the GNRI as a prognostic tool. These results underscore the importance of nutritional assessment in patient care and advocate for future research to explore the GNRI as a guide for nutritional interventions to enhance patient survival.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

K-CH: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. C-LK: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. C-WH: Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. C-HY: Methodology, Software, Writing – original draft, Writing – review & editing. C-ML: Methodology, Writing – original draft, Writing – review & editing. H-TC: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. Y-JC: Methodology, Writing – original draft, Writing – review & editing. S-WL: Investigation, Methodology, Writing – original draft, Writing – review & editing. I-WC: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

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ALTA: a simple nutritional prognostic score for patients with hepatitis B virus-related acute-on-chronic liver failure

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Background: Malnutrition, despite being a common complication, is often neglected in patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF). The objective of this study was to develop a simplified nutritional prognostic score to accurately predict mortality in HBV-ACLF patients.

Methods: In this multicenter retrospective study, clinical data from 530 HBV-ACLF patients were used to create a new prognostic score, which was then validated in two external cohorts (n = 229 and 248).

Results: Four independent factors were significantly associated with 28-day mortality in HBV-ACLF patients, forming a novel prognostic score (ALTA score = 0.187 × age−0.849 × lymphocyte count−2.033 × total cholesterol−0.148 × albumin−0.971). Notably, the AUROC of ALTA score for 28/90-day mortality (0.950/0.967) were significantly higher than those of three other ACLF prognostic scores (COSSH-ACLF II, 0.864/0.734; MELD, 0.525/0.488; MELD-Na, 0.546/0.517; all $P < 0.001$), and three known nutritional scores (CONUT, 0.739/0.861; OPNI, 0.279/0.157; NRS-2002, 0.322/0.286; all $P < 0.001$). The prediction error rates of ALTA score for 28-day mortality were significantly lower than COSSH-ACLF II (7.3%), MELD (14.4%), MELD-Na (12.7%), CONUT (9.0%), OPNI (30.6%), and NRS2002 (34.1%) scores. Further classifying ALTA score into two strata, the hazard ratios of mortality at 28/90 days were notably increased in the high-risk groups compared to the low-risk group (15.959 and 5.740). These results were then validated in two external cohorts.

Conclusion: ALTA, as a simplified nutritional prognostic score for HBV-ACLF, demonstrates superiority over the COSSH-ACLF II and other scores in predicting short-term mortality among HBV-ACLF patients. Therefore, it may be used to guide clinical management, particularly in primary care settings.

KEYWORDS

acute-on-chronic liver failure, hepatitis B virus, prognostic score, nutrition, mortality

Introduction

Acute-on-chronic liver failure (ACLF) is a clinical syndrome characterized by an exacerbation of chronic liver disease, associated with a significantly elevated short-term mortality rate (1). The development of early and accurate prognostic indicators, as well as scoring systems, is crucial for optimizing the management of patients presenting with ACLF (2).

To date, numerous prognostic scores have been developed to evaluate the prognosis of ACLF. These scores primarily fall into two categories: the first is based on organ failures (OF), such as the Chronic Liver Failure Consortium Organ Failure (CLIF-C OF) (3), CLIF-C ACLF (4) and the Chinese Group on the Study of Severe Hepatitis B-ACLF (COSSH-ACLF) (2) scores. The second category is derived from liver and kidney function, coagulation, or clinical manifestations, including the Child-Pugh (5), model of end-stage liver disease (MELD) (6), and Asian Pacific Association for the Study of the Liver ACLF research consortium ACLF (AARC-ACLF) (7) scores. Moreover, several modified or simplified scores have been constantly proposed, such as the MELD-Na (8) and COSSH-ACLF II (9) scores. However, most of these scores are not widely applicable, particularly in primary hospitals, due to their complex assessment processes or the inaccuracy of subjective judgments. Consequently, there is an urgent need to develop a simpler, more accessible ACLF prognostic scoring system that utilizes easily obtainable metrics.

Notably, malnutrition is a frequently overlooked yet common complication in advanced liver diseases, which is associated with unfavorable clinical outcomes (10). Some nutritional scoring systems have been employed to assess prognoses in hospitalized patients, such as the Nutritional Risk Screening 2002 (NRS-2002) (11), the Onodera Prognostic Nutritional Index (OPNI) (12), and the Controlling Nutritional Status (CONUT) (13) scores. The primary components of these scoring systems include lymphocyte count, albumin, and total cholesterol level. However, the ability of these nutritional indices to more effectively identify ACLF patients with poor prognoses remains unknown.

Given that hepatitis B virus (HBV) infection is the primary etiology of ACLF in China (14), hence, the current study aims to develop a new simple nutritional prognostic score to accurately predict short-term mortality in patients with HBV-ACLF.

Patients and methods

Study design

Retrospectively enrolling patients with HBV-ACLF from January 2021 to June 2023 at the Second Affiliated Hospital of Chongqing Medical University, we utilized a two-step approach to develop a novel prognostic score for HBV-ACLF patients. Firstly, clinical data and selected nutritional indices from these patients were employed to identify predictive factors associated with short-term (28-day and 90-day) mortality, laying the foundation for the construction of the new prognostic score. Secondly, a comprehensive external validation was conducted using two independent cohorts of HBV-ACLF patients from the Fifth People's Hospital of Chongqing (January 2015 to June 2023) and the Ninth People's Hospital of Chongqing (January 2018 to June 2023). This study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University and two other hospitals (Ratification No. 87/2023), and adhered to the ethical guidelines stipulated by the Declaration of Helsinki. Due to the retrospective nature of the study, patient informed consent was waived by the Committees.

Patients

The inclusion criteria were as follows: (i) aged 18 years or older; (ii) positivity of serum hepatitis B surface antigen for at least 6 months; (iii) fulfilling the ACLF criteria of APASL (15) {previously diagnosed or undiagnosed chronic liver disease/cirrhosis, characterized by jaundice [serum total bilirubin (TBil) $\geq$ 5 mg/dl] and coagulation disorder [international normalized ratio (INR) $\geq$ 1.5 or prothrombin activity (PTA) $<$ 40%], with concurrent ascites and/or hepatic encephalopathy (HE) within 4 weeks}; (iv) availability of baseline data for lymphocyte count, total cholesterol, and albumin. Exclusion criteria: (i) presence of acute (an illness duration of $<$ 26 weeks duration in a patient without preexisting liver disease or cirrhosis associated with any degree of HE and INR $\geq$ 1.5) (16) or chronic liver failure (a slow progressive decline and decompensation of liver function on the basis of cirrhosis) (17); (ii) chronic liver diseases of other etiology; (iii) hepatic or extra-hepatic malignancies; (iv) use of immunosuppressants or corticosteroids; (v) incomplete clinical data. All patients underwent standard medical treatments, including antiviral agents for HBV-DNA positive patients, management for ascites, HE, and/or bacterial infections. Artificial liver support was administered after comprehensive evaluation and informed consent. Clinical data were collected at admission, encompassing demographic information, medical history, clinical parameters, and laboratory indicators. The 28-day and 90-day liver transplant-free survival rates of each patient were also assessed.

Scoring models

The MELD score (6) was calculated using the following formula: MELD = 3.78 $\times$ ln[TBil, (mg/dL)] + 11.2 $\times$ ln(INR) + 9.57 $\times$ ln[serum creatinine (mg/dL)] + 6.43.

The MELD-Na score (8) was derived from the MELD score using the formula: MELD-Na = MELD—Na—[0.025 $\times$ MELD $\times$ (140—Na)] + 140, with the serum sodium concentration ranging between 125 and 140 mmol/L.

The COSSH-ACLF II score (9) was calculated based on the formula: COSSH-ACLF II = 1.649 $\times$ ln(INR) + 0.457 $\times$ HE score + 0.425 $\times$ ln(neutrophil) + 0.396 $\times$ ln(TBil) + 0.576 $\times$ ln(serum urea) + 0.033 $\times$ age.

The NRS-2002 score (11) was assessed through three components: impaired nutritional status, disease severity, and age $\geq$ 70 years, with a score of $\geq$ 3 indicating nutritional risk.

The OPNI score (12) was calculated as 10 $\times$ albumin (g/L) + 5 $\times$ lymphocyte count (10^9/L).

The CONUT score (13) was derived from the sum of the albumin score, lymphocyte count score, and total cholesterol score.

All scores were applied at the time of admission for each patient in this study. Due to the arterial blood gas analysis not being performed in most ACLF patients at admission, the scores related to SOFA or lactate level could not be evaluated in this study.

Statistical analysis

Appropriate statistical methods were employed based on the type of data, with categorical variables represented as percentages (%), and continuous variables reported as median with interquartile range (IQR). Comparisons between categorical variables were conducted using the Chi-Square test or Fisher's exact test, while the Mann–Whitney U test was applied for continuous variables. Logistic regression analysis was utilized to identify the independent prognostic predictors of 28-day mortality. Variance inflation factors (VIFs) were calculated to assess collinearity, and variables with a VIF exceeding 10 were excluded. Variables with a $P < 0.1$ value in the univariate logistic regression analysis were advanced to a multivariate analysis using stepwise regressions. Receiver operator characteristic (ROC) curves were generated for predictors, and the area under ROC curve (AUROC) was employed to evaluate their predictive value. AUROCs were compared using the DeLong method. The probability density function (PDF) was utilized to define an integral of the survival and non-survival densities within a specified range of each score, while the difference in overlapping coefficient between ALTA and other scores was assessed using the Chi-Square test. The optimal cut-off value of the new prognostic score was determined based on selecting the largest v2 value using X-tile software (18) (version 3.6.1) to categorize patients into low-risk and high-risk groups for mortality. Hazard ratios (HRs) of 28-day and 90-day mortality among the three groups were calculated by Cox regression analysis. Cumulative survival rates were compared using the Kaplan-Meier method. Decision curve analysis (DCA) was employed to assess the new prognostic score in clinical practice by examining the theoretical relationship between the threshold probability of an event occurring and the relative value of false-positive and false-negative results. This method could determine if predictive models are clinically effective (19). A two-sided p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS (version 24.0.0), and graphs were created using GraphPad Prism (version 8.0.2) and R (version 4.3.2).

Results

Characteristics of patients with HBV-ACLF

In this study, a total of 967 ACLF patients were recruited. Following screening, 530 eligible HBV-ACLF patients were selected for the ultimate analysis (**Supplementary Figure 1**). **Table 1** summarizes the clinical features of HBV-ACLF patients at the time of admission. Of the 530 patients, the median age was 65.0 years, with males comprising over 50% (68.1%). Most patients presented with cirrhosis (65.7%), followed by ascites (only), HE (only) and ascites +HE (43.0, 33.2 and 17.4%, respectively). Regarding hepatitis B, 36.4% of HBV-ACLF patients were HBeAg-positive, while 79.8% were receiving antiviral therapy [entecavir (47.3%), tenofovir (47.5%), and entecavir+tenofovir (5.2%)]. According to the CONUT score, all patients exhibited varying degrees of malnutrition, i.e., 56 (10.1%), 275 (51.9%), and 202 (39.1%) patients had mild, moderate, and severe malnutrition, respectively. Among the 530 HBV-ACLF patients, no liver transplantation was performed, and the mortality rates at 28/90 days were 40.6 and 61.7%, respectively. As depicted in **Table 1**, 28-day survivors tended to be younger, slighter malnutrition, and exhibit higher lymphocyte count, albumin, and total cholesterol compared to non-survivors. A similar trend was also observed in the 90-day analysis (**Table 1**).

Development of a new prognostic score

To develop a simplified, practicable nutritional prognostic score for patients with HBV-ACLF, we collected clinical and laboratory indices at admission to identify the most significant risk factors associated with 28-day mortality. After excluding collinearity variables using VIF (**Supplementary Table 1**), univariate analysis revealed that age, HE, lymphocyte count, albumin, TBil, and total cholesterol were significantly associated with 28-day prognosis in patients with ACLF (**Supplementary Table 2**). But antiviral history was not associated with short-term mortality. Finally, multivariate analysis identified four independent risk factors for the final prognostic score: albumin, lymphocyte count, total cholesterol, and age (**Supplementary Table 2**). Based on the multivariate logistic regression analysis, the novel prognostic model for patients with HBV-ACLF (ALTA score) was calculated using the following formula: ALTA score = 0.187 × age (years)—0.849 × lymphocyte count (10^9/L)—2.033 × total cholesterol (mmol/L)—0.148 × albumin (g/L)—0.971.

Evaluation of the new score

First, we evaluated the discriminative ability of the new ALTA score. As shown in **Figure 1**, the area under the receiver operating characteristic curve (AUROC) for 28-day and 90-day mortality of the ALTA score demonstrated a higher predictive accuracy (0.950 and 0.967, respectively), compared to the three other ACLF prognostic scores (COSSH-ACLF II: 0.845 and 0.814, MELD: 0.521 and 0.519, MELD-Na: 0.606 and 0.571; all $P < 0.001$), as well as three established nutritional scores (CONUT: 0.739 and 0.861, OPNI: 0.279 and 0.157, and NRS-2002: 0.322 and 0.286; all $P < 0.001$; **Table 2**). Furthermore, ALTA demonstrated the highest prognostic accuracy for 28-day mortality compared to COSSH-ACLF II (7.3%), MELD (14.4%), MELD-Na (12.7%), CONUT (9.0%), OPNI (30.6%), and NRS2002 (34.1%), as evidenced by the corresponding percent improvement in prediction error rates obtained with ALTA when compared to other scores (**Figure 2A**). The improvement in prediction error rates for 90-day mortality was more obvious by ALTA. Further subgroup analysis in cirrhosis revealing that the ALTA score exhibits robust predictive performance across both patients with and without cirrhosis (**Supplementary Figure 3** and **Supplementary Table 4**).

The results of PDF analysis revealed a positive correlation between increasing ALTA score and the proportion of patients

TABLE 1 Baseline characteristics of patients with HBV-ACLF in the derivation cohort.

Characteristics	Total (*n* = 530)	28-day survivor (*n* = 315)	28-day non-survivor (*n* = 215)	*p*-value	90-day survivor (*n* = 203)	90-day non-survivor (*n* = 327)	*p*-value
Age, (years)	65.0 (47.0–65.0)	49.0 (46.5–55.0)	67.0 (55.5–71.0)	< 0.001	47.0 (45.0–53.0)	56.0 (53.0–69.0)	< 0.001
Gender, (male)	361 (68.1)	217 (68.9)	144 (67.0)	0.704	152 (74.9)	209 (63.9)	0.032
Current smoking	258 (48.7)	144 (45.7)	114 (53.0)	0.111	103 (50.7)	155 (47.4)	0.475
Current drinking	187 (35.3)	115 (36.5)	72 (38.6)	0.517	71 (35.0)	116 (35.5)	0.926
HBeAg positive	193 (36.4)	110 (34.9)	83 (34.9)	0.409	64 (31.5)	129 (39.4)	0.078
Cirrhosis	348 (65.7)	207 (65.7)	141 (65.6)	1.000	117 (57.6)	231 (70.6)	0.003
Ascites (only)	228 (43.0)	106 (33.7)	122 (56.7)	0.185	33 (16.3)	195 (59.6)	< 0.001
HE (only)	176 (33.2)	81 (27.0)	95 (44.2)	< 0.001	58 (28.6)	118 (36.1)	0.074
Ascites+HE	92 (17.4)	25 (7.9)	67 (31.1)	< 0.001	12 (6.0)	80 (24.5)	< 0.001
Antiviral history				0.179			0.911
Absent	107 (20.2)	60 (19.0)	47 (21.9)		40 (19.7)	67 (20.5)	
Present	423 (79.8)	255 (81.0)	168 (78.1)		163 (80.3)	260 (79.5)	
Antiviral agents using				0.353			0.444
Entecavir	200 (47.3)	136 (48.6)	62 (43.4)		79 (48.5)	121 (46.5)	
Tenofovir	201 (47.5)	130 (46.4)	71 (49.7)		77 (47.2)	124 (47.7)	
Entecavir+tenofovir	22 (5.2)	12 (4.3)	10 (7.0)		7 (4.3)	15 (5.8)	
Laboratory examination							
RBC (10^{12}/L)	3.3 (2.6–3.9)	3.3 (2.6–4.1)	3.3 (2.8–3.8)	0.891	3.3 (2.6–4.1)	3.3 (2.7–3.8)	0.944
WBC (10^9/L)	5.7 (4.3–8.4)	5.4 (4.2–8.9)	5.9 (4.7–7.7)	0.704	4.6 (4.0–9.2)	6.6 (4.8–8.4)	0.001
Lymphocyte (10^9/L)	0.9 (0.5–1.4)	1.3 (0.7–1.8)	0.5 (0.4–0.9)	< 0.001	1.4 (1.2–2.2)	0.5 (0.3–0.9)	< 0.001
Neutrophil (10^9/L)	6.3 (3.2–8.9)	6.4 (3.5–9.0)	6.1 (2.8–8.7)	0.062	6.4 (3.8–9.7)	6.1 (3.2–8.7)	0.166
Platelet (10^9/L)	83.5 (51.3–114.0)	74.0 (55.5–114.0)	84.0 (48.0–111.0)	0.300	60.0 (53.0–111.0)	84.0 (51.0–114.0)	0.001
Albumin (g/L)	30.0 (27.1–32.5)	30.1 (27.5–36.0)	29.0 (25.8–32.4)	< 0.001	31.2 (29.9–36.6)	29.0 (25.0–32.3)	< 0.001
ALT (U/L)	111.0 (42.5–285.0)	86.0 (27.0–188.0)	129.0 (58.0–625.0)	< 0.001	65.0 (19.0–188.0)	115.0 (56.0–583.0)	< 0.001
TB (mg/dL)	11.4 (5.1–16.3)	12.0 (5.1–17.4)	11.4 (5.2–15.6)	0.811	7.6 (4.9–13.6)	12.7 (5.2–17.4)	0.001
Serum creatinine (μmol/L)	60.8 (48.0–73.9)	62.6 (51.40–72.9)	54.9 (47.4–76.6)	0.001	62.0 (51.4–73.0)	57.5 (45.9–73.9)	0.013
BUN (mmol/L)	6.6 (4.1–10.3)	6.7 (4.4–10.3)	6.5 (3.8–9.5)	0.289	6.4 (4.0–10.3)	6.8 (4.2–10.3)	0.747

(Continued)

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TABLE 1 (Continued)

Characteristics	Total (n = 530)	28-day survivor (n = 315)	28-day non-survivor (n = 215)	p-value	90-day survivor (n = 203)	90-day non-survivor (n = 327)	p-value
Serum sodium (mmol/L)	133.1 (125.0–140.9)	133.3 (125.1–140.2)	132.9 (124.9–142.6)	0.735	133.9 (124.8–140.9)	132.9 (125.1–132.9)	0.656
PT	22.7 (19.1–24.6)	21.5 (18.2–24.0)	23.2 (21.5–26.2)	< 0.001	20.8 (18.0–23.3)	24.0 (21.9–26.1)	< 0.001
INR	1.7 (1.1–1.9)	1.5 (1.0–1.6)	1.7 (1.0–1.9)	< 0.001	1.4 (1.0–1.4)	1.8 (1.0–1.9)	< 0.001
TC (mmol/L)	2.3 (1.8–3.0)	2.7 (2.2–3.8)	1.8 (1.6–2.0)	< 0.001	3.0 (2.6–4.2)	1.9 (1.6–2.5)	< 0.001
Nutrition index[#]				< 0.001			< 0.001
Normal	0	0	0		0	0	
Mild malnutrition	56 (10.1)	56 (17.8)	0		50 (24.6)	3 (0.9)	
Moderate malnutrition	275 (51.9)	182 (57.8)	93 (43.3)		152 (74.9)	123 (37.6)	
Severe malnutrition	202 (39.1)	77 (24.4)	122 (56.7)		1 (0.5)	201 (61.5)	

Data are presented in n (%) or median (IQR) as appropriate. [#]The nutrition status was classified by the CONUT scoring system. ALT, alanine aminotransferase; BUN, blood urea nitrogen; HE, hepatic encephalopathy; IQR, interquartile range; PT, prothrombin time; RBC, red blood cell; TB, total bilirubin; TC, total cholesterol; WBC, white blood cell.

with poor outcomes, with distinct peaks observed for surviving and non-surviving patients (Figure 3A). Notably, PDF analysis demonstrated significantly lower overlapping coefficients for ALTA in relation to 28-/90-day mortality (28.2%/17.3%) compared to COSSH-ACLF II (47.6%/63.8%), MELD (85.8%/86.5%), MELD-Na (87.7%/87.9%), CONUT (69.9%/45.6%), OPNI (66.3%/55.2%), and NRS2002 (66.9%/65.9%) scores (all $P < 0.001$), indicating superior prognostic accuracy of the new ALTA score through reduced similarity between probability distributions for surviving and non-surviving patients.

Last, we assessed the clinical utility of the ALTA score. The decision curve analysis (DCA) demonstrated a substantial net benefit for the ALTA score across a broad range of threshold probabilities in predicting 28-day and 90-day mortality, which was larger than other scores (Figure 4).

Taken together, the ALTA score demonstrates superior discriminative ability, accuracy, and enhances clinical decision-making compared to other prognostic scores.

Risk stratification of the new score

Subsequently, we interrogate whether the novel scoring system has the capacity to effectively stratify the short-term mortality of HBV-ACLF patients. As depicted in the X-tile plot (Supplementary Figure 2), HBV-ACLF patients were hierarchically categorized into two risk strata for death within 28 days, based on one optimal cut-off values (−0.2): low-risk (≤ -0.2) and high-risk (> -0.2). The 28/90-day mortality rates for each group exhibited a pronounced discrepancy (low-risk, 4.9%/25.2%; high-risk, 56.4%/77.9%; Figure 5). In comparison to the low-risk group, the hazard ratios (HRs) for mortality at 28/90 days were notably elevated in the high-risk groups (15.96/5.74, all $P < 0.001$; Figure 5).

External validation of the new score

Patients with HBV-ACLF from two other hospitals (n = 229 and 248) were utilized as two external cohorts to validate the novel scoring system (Supplementary Table 3). The ALTA score outperformed all other scores such as COSSH-ACLF II, MELD, MELD-Na, CONUT, OPNI, and NRS-2002 (all $P < 0.01$) in terms of AUROC (Figure 1 and Table 2). The new ALTA score showed a significant improvement in the prediction errors for 28-/90-day mortality compared to other scores (4.0 to 41.4%; Figures 2B, C).

The PDF analysis also revealed a reduced overlapping coefficient of the ALTA score between the surviving and non-surviving patients in the validation cohorts (all $P < 0.001$; Figures 3B, C). In addition, the DCA cure analysis demonstrated that the ALTA score possesses the largest net benefit for predicting 28/90-day mortality than other scores in validation cohorts (Figure 4). The HRs of death at 28/90-day in the high-risk groups of the validation cohorts resembled those in the derivation group compared to the low-risk group (validation cohort 1: 7.70/7.52, all $P < 0.001$; validation cohort 2: 17.70/7.55, all $P < 0.001$; Figure 5).

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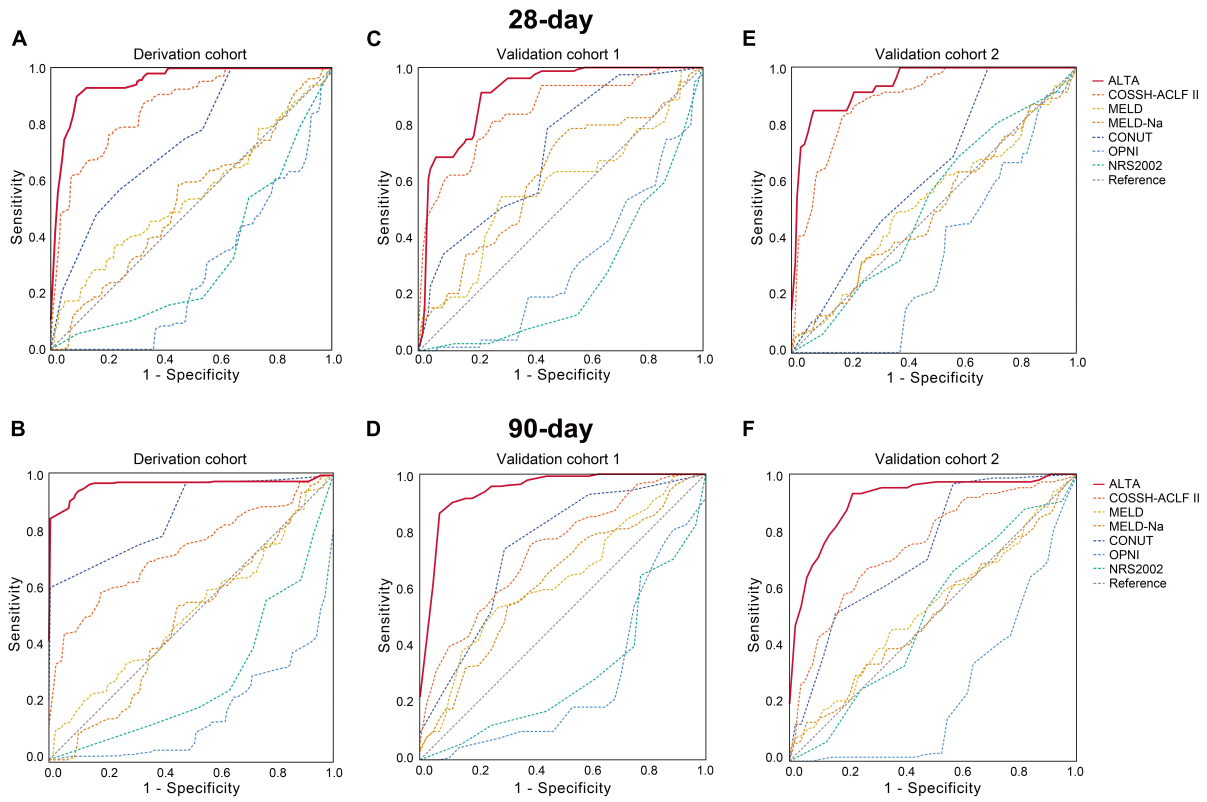

FIGURE 1
AUROC of the ALTA score for predicting mortality of HBV-ACLF patients in the derivation and validation cohorts. The AUROC of the ALTA score for predicting 28-day and 90-day mortality of patients in the derivation cohort **(A,B)**, the validation cohort 1 **(C,D)**, and the validation cohort 2 **(E,F)**.

TABLE 2 The AUROC of ALTA for predicting 28-/90-day mortality of patients with HBV-ACLF.

Model	ALTA	COSSH-ACLF II	MELD	MELD-Na	CONUT	OPNI	NRS2002
Derivation cohort							
28-day mortality	0.950	0.864	0.525	0.546	0.739	0.279	0.322
p-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
90-day mortality	0.967	0.734	0.488	0.517	0.861	0.157	0.286
p-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Validation cohort 1							
28-day mortality	0.909	0.848	0.573	0.616	0.705	0.301	0.248
p-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
90-day mortality	0.950	0.733	0.624	0.633	0.742	0.277	0.307
p-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Validation cohort 2							
28-day mortality	0.941	0.888	0.502	0.525	0.632	0.345	0.519
p-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
90-day mortality	0.913	0.751	0.512	0.529	0.735	0.248	0.510
p-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

In brief, our findings indicate an enhancement in the predictive efficacy of the novel ALTA score for short-term (28/90-day) mortality, as compared to other generic prognostic scores and nutritional assessment tools.

Discussion

Malnutrition, an important yet frequently overlooked factor, significantly impacts the prognosis of patients with end-stage liver

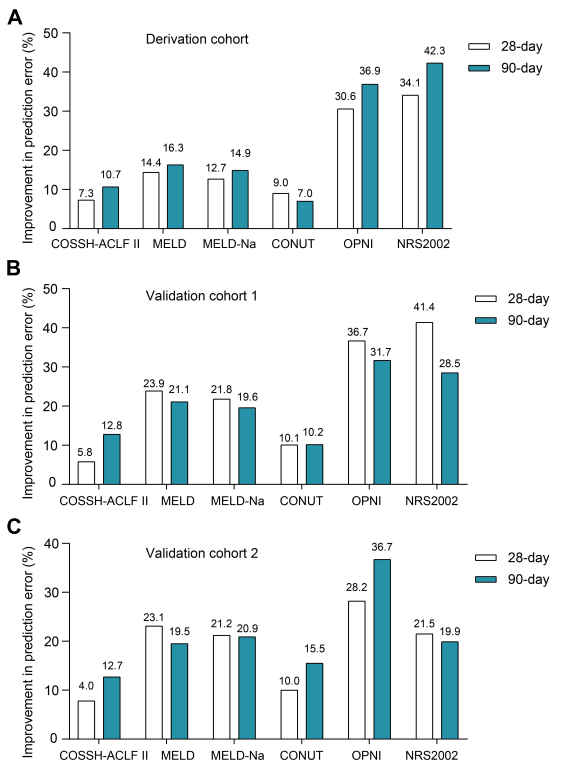

FIGURE 2
The improvement prediction error rates for 28-/90-day mortality of HBV-ACLF patients for the ALTA score. Compared to other scores, percent reduction in the prediction error rates for 28-/90-day mortality of the ALTA score in the derivation cohort **(A)**, the validation cohort 1 **(B)** and the validation cohort 2 **(C)**.

disease, particularly those with ACLF (10). Even though numerous prognostic scores have been developed for ACLF patients, those related to nutrition remain scarce. In this multicenter retrospective study, we concentrated on the nutrient status of patients with HBV-ACLF and their short-term prognosis, and accordingly, developed a novel, simple, and user-friendly score, the ALTA, which accurately predicts the 28/90-day mortality of HBV-ACLF patients.

Early prognosis determination in ACLF patients can guide clinical management to reduce short-term mortality (2). Consequently, numerous new scoring models have been proposed to better achieve this goal. The MELD score, initially developed to evaluate cirrhosis patients' prognosis after TIPS, has been used for organ allocation (6). However, several studies have shown that the MELD score and its derivative (MELD-Na) have a relatively low accuracy in predicting short-term mortality in ACLF patients (20–22), consistent with our observations. Additionally, organ failure-based scores like the CLIF-ACLF score (4), COSSH-ACLF score (2) and AARC-ACLF score (7), have demonstrated good prognostic abilities in ACLF patients. However, these scores cannot be widely used in primary hospitals due to complexity in organ failure scoring or lack of arterial blood gas data. Therefore, it's crucial to develop a simplified prognostic score for ACLF patients.

The recently proposed COSSH-ACLF II score is a simplified version of the COSSH-ACLF score, containing six independent risk factors reflecting HBV-ACLF pathophysiology. This score has better predictive power in predicting the prognosis of HBV-ACLF patients compared to the COSSH-ACLF and CLIF-C ACLF scores (9). However, it doesn't consider HBV-ACLF patients' nutrition status. In this study, we developed a simple, nutrition-based ALTA score for HBV-ACLF patients, consisting of four indices (albumin, lymphocyte count, total cholesterol, and age). Notably, the ALTA score outperformed the COSSH-ACLF II score in predicting 28/90-day mortality in HBV-ACLF patients, which showed in higher AUROC value and DCA net benefit, and lower prediction error rate for 28/90-day mortality and overlapping coefficient in distributions for surviving and non-surviving patients. However, arterial blood gases at admission were not determined in most ACLF patients, hindering direct comparison of these scores. The ALTA score might be superior to these organ failure-based scores, based on the comparison results of the COSSH-ACLF II scores.

The NRS-2002 score, a widely used nutritional screening tool for inpatients (11), demonstrated low predictive ability for short-term mortality in HBV-ACLF patients in our study. This suggests that general nutritional scores might not be suitable for HBV-ACLF patients. The OPNI score, a simple prognostic tool for preoperative nutritional status (12), and the CONUT score, another nutritional risk screening tool (13), both showed limited predictive value in HBV-ACLF patients. Similarly, in this study, OPNI and CONUT scores showed low and intermediate abilities in predicting the mortality of HBV-ACLF patients, respectively. Therefore, it's crucial to develop a more accurate nutritional prognostic score tailored to HBV-ACLF patients. Surprisingly, the new ALTA score, which only added age factor compared to the CONUT score (12), exhibited significantly higher predictive ability for HBV-ACLF patients compared to the other three widely used nutritional scores.

The ALTA score, differing from previous prognostic scores based on ACLF pathophysiology, primarily focused on the nutritional status of patients with HBV-ACLF. Low serum albumin levels may result in specific antioxidant function or systemic protein metabolism and inflammation abnormalities (23, 24), which can lead to an increase in infections, renal dysfunction, refractory ascites, and accelerate the progress of ACLF and mortality rates (25, 26). Decreased lymphocyte count, reflecting reduced immune and inflammatory status (27), which may exacerbate the immunosuppression in ACLF (28). The lymphocyte count, especially for $CD8^+$ T cell, have been found significantly decreased in non-survivors compared with survivors of HBV-ACLF (29). Similarly, studies suggest that decreased total cholesterol represents deterioration of nutritional status and exacerbates inflammation, posing a higher risk of death in older patients (30, 31). Interestingly, a previous study found hypercholesterolemia was associated with well-preserved hepatic function and decreased mortality in patients with cirrhosis (32). On the other hand, a recent study showed that HBV-ACLF patients with lower high-density lipoprotein cholesterol level had a worse prognosis than those with higher HDL-C levels (33). Increased age also raises the risk of mortality due to a higher incidence of comorbidities and poor hepatic regeneration in response to acute insults (34). These mechanisms, at least in part, explain the accuracy of the ALTA score in predicting the prognosis of patients with HBV-ACLF. As the ACLF pathophysiology involves no unique factors, the ALTA score (or an optimized version) may prove universal for other ACLF etiologies or end-stage liver diseases (e.g., hepatocellular carcinoma), and even for patients with malignant tumors. Further studies to validate this hypothesis are greatly appreciated.

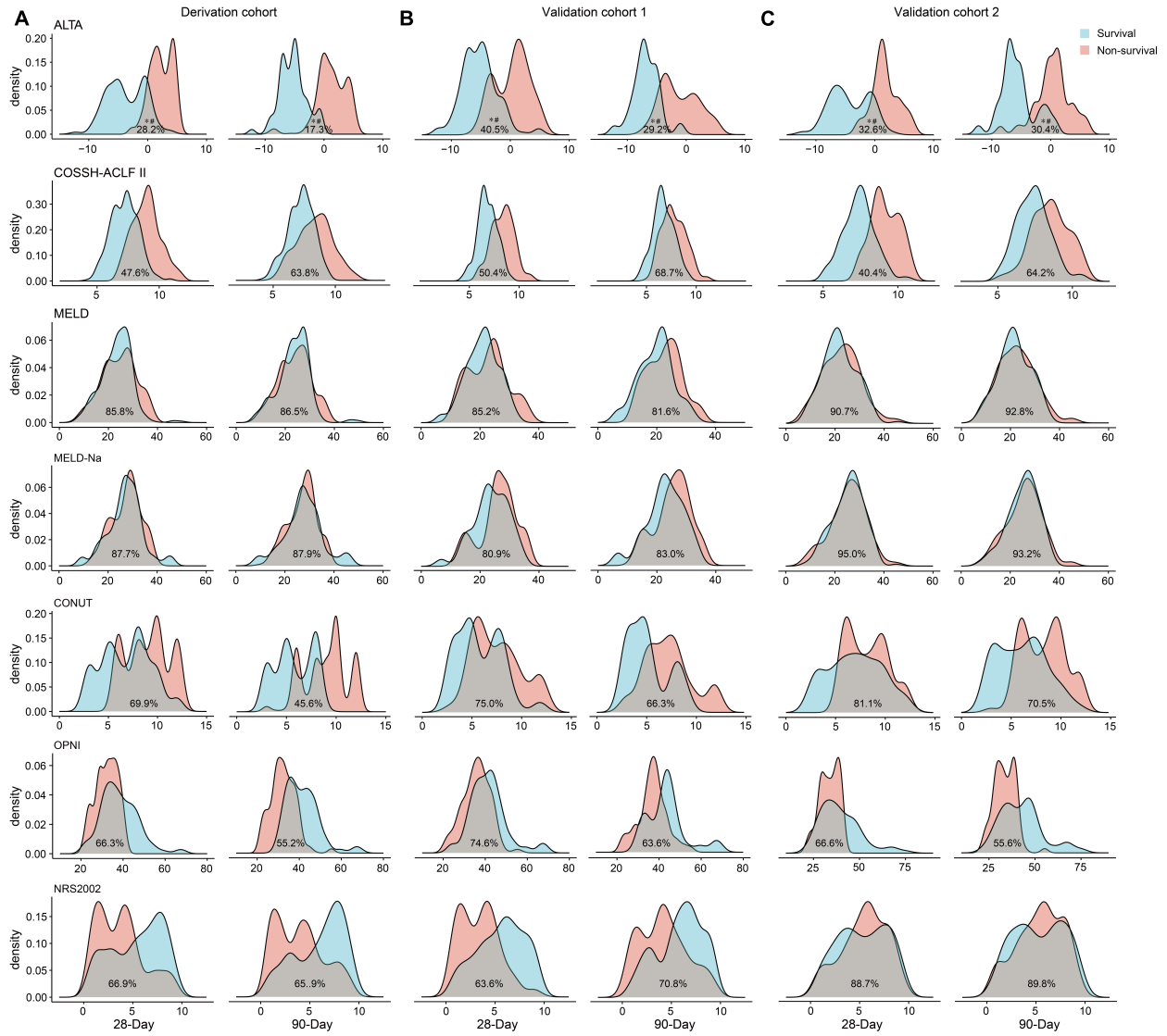

FIGURE 3
Probability density function of the ALTA score for the 28-/90-day prognosis of surviving and non-surviving patients. The derivation cohort **(A)**, the validation cohort 1 **(B)**, and the validation cohort 2 **(C)**. $^{*}p < 0.001$ for comparisons of the overlapping coefficient between ALTA score and the other scores. $^{\#}p < 0.001$ for comparisons of the ALTA score between surviving and non-surviving patients.

Cirrhosis is closely associated with the development of ACLF. The impact of cirrhosis on mortality in ACLF patients remains controversial, previous study suggesting that cirrhosis independently predicts short-term mortality in ACLF patients (35), while others argue that it is not an independent risk factor for ACLF-related death (36). In our study, we observed no significant correlation between the presence of cirrhosis and the risk of death at 28 or 90 days. Additionally, we evaluated ALTA score comprising both cirrhotic and non-cirrhotic patients, demonstrating their effective predictive performance in both cohorts, which hint that the ALTA score may be widely applicable for patients with ACLF. In addition, whether antiviral therapy is associated with HBV-ACLF survival remains controversial (37, 38). In this study, antiviral therapy was not an independent risk factor of HBV-ACLF short-term survival. More studies with large sample size are highly appreciated to verify our results.

To our knowledge, the ALTA score is the first nutrition-based prognostic score specific to HBV-ACLF patients, accurately predicting short-term mortality. However, the study has limitations. Firstly, despite being a multicenter study, the retrospective nature inherently lead to an unavoidable selection bias. And most patients were recruited from Chongqing in this study, which cannot represent other region of China and the world. Large-sample, prospective, and national studies are needed. Additionally, arterial blood gases at admission were not determined in most patients, hindering direct comparison with organ failure-based scores. However, indirect comparison was made through the COSSH-ACLF II study. Lastly, we cannot evaluate the effect of early intervention for high-risk HBV-ACLF patients identified by the ALTA score. A well-designed prospective study is highly appreciated.

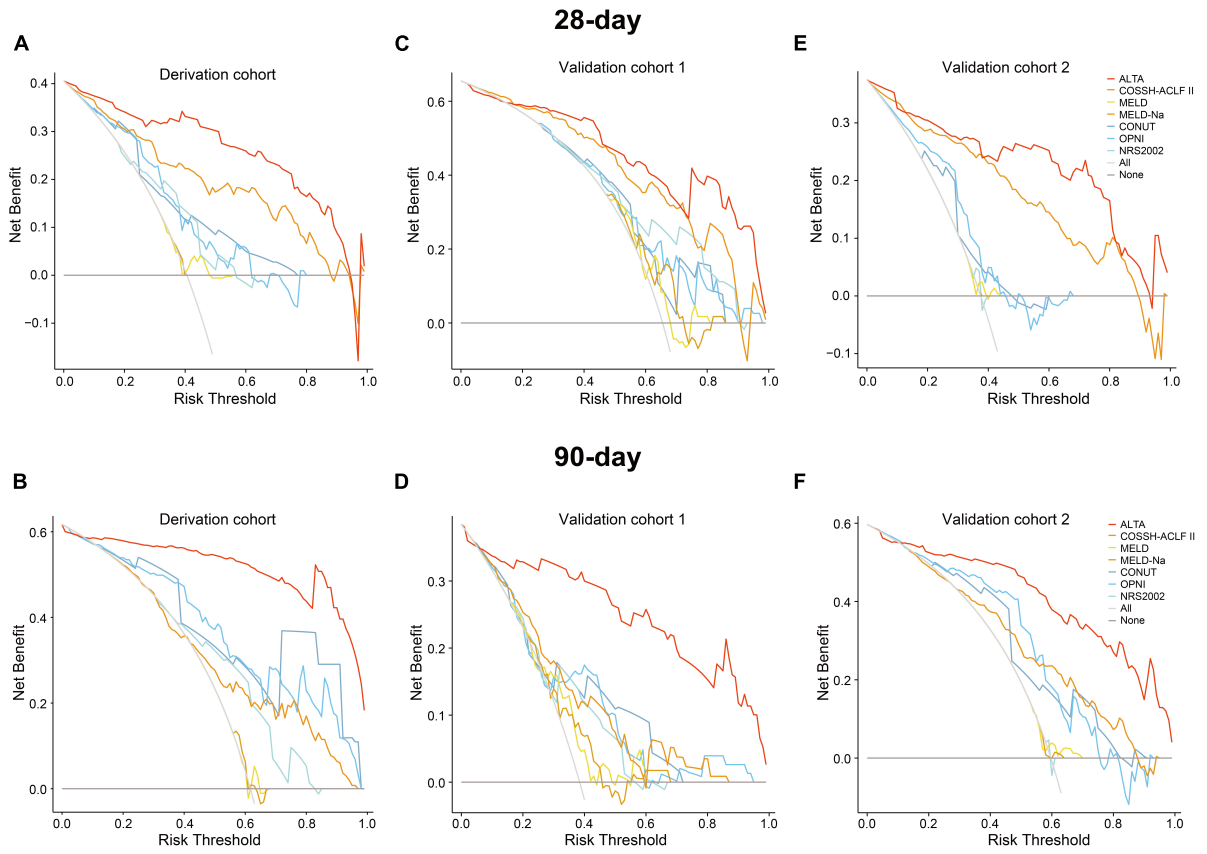

FIGURE 4
Decision curve analysis of the ALTA score for predicting mortality of HBV-ACLF patients in the derivation and validation cohorts. The decision curve analysis of the ALTA score for predicting 28-day and 90-day mortality of patients in the derivation cohort **(A,B)**, the validation cohort 1 **(C,D)**, and the validation cohort 2 **(E,F)**.

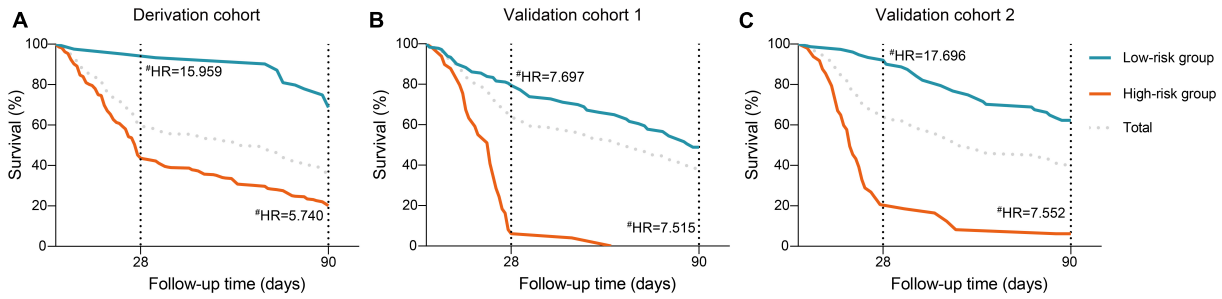

FIGURE 5
Risk stratification of the ALTA score. Cumulative incidence of mortality at 28- and 90-day stratified according to the ALTA classification rule (low-/high-risk: ALTA score $\leq -0.2/> -0.2$) in the in the derivation cohort **(A)**, the validation cohort 1 **(B)**, and the validation cohort 2 **(C)**, $^{\#}P < 0.001$ for hazard ratios of death in the high-risk groups compared with those in the low-risk group. HR, hazard ratio.

Conclusion

In summary, we have successfully devised the ALTA score, a concise and accurate predictive tool capable of stratifying the short-term mortality risk of HBV-ACLF patients. This score, which employs only four readily accessible predictor factors, could holds promise for guiding the management of patients diagnosed with HBV-ACLF, particularly for clinicians in primary hospitals. However, further validation and assessment of the ALTA score's clinical utility are necessary, which may be achieved through larger, prospective studies in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/Institutional Review Board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because due to the retrospective nature of the study, patient informed consent was waived by the Committees.

Author contributions

RS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. XW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. ZL: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – review & editing. HW: Data curation, Formal analysis, Methodology, Project administration, Software, Writing – review & editing. JiT: Data curation, Formal analysis, Methodology, Software, Supervision, Validation, Writing – review & editing. JuT: Data curation, Investigation, Validation, Writing – review & editing. HL: Data curation, Formal analysis, Software, Validation, Writing – review & editing. TZ: Conceptualization, Data curation, Software, Writing – review & editing. HR: Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. ZC: Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1370025/full#supplementary-material

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Body composition assessment with ultrasound muscle measurement: optimization through the use of semi-automated tools in colorectal cancer

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Colorectal cancer (CRC) is a disease with a high prevalence and major impact on global health. Body composition (BC) data are of great importance in the assessment of nutritional status. Ultrasound (US) is an emerging, accessible and non-invasive technique that could be an alternative when it is not feasible to perform computed tomography (CT). The aim of this study is to evaluate the correlation between CT, as a reference technique, and US of the rectus femoris (RF) as a "proof of concept," in a cohort of patients with CRC and assess the optimisation of results obtained by US when performed by our new semi-automated tool. A single-centre cross-sectional study including 174 patients diagnosed with CRC and undergoing surgery was carried out at the Vall d'Hebron Hospital. We found a strong correlation between CT and US of the RF area ($r = 0.67$; $p < 0.005$). The latter, is able to discriminate patients with worse prognosis in terms of length of hospital stay and discharge destination (AUC-ROC = 0.64, p 0.015). These results improve when they are carried out with the automatic tool (area AUC-ROC = 0.73, p 0.023), especially when normalised by height and eliminating patients who associate overflow. According to our results, the US could be considered as a valuable alternative for the quantitative assessment of muscle mass when CT is not feasible. These measurements are improved when measuring software is applied, such as "Bat" software.

KEYWORDS

ultrasound, rectus femoris, computed tomography, colorectal cancer, body composition

1 Introduction

Muscle plays a fundamental role in the patient's prognosis and its measurement is now necessary to make a correct nutritional assessment (1). Body composition (BC) evaluation is fundamental for the identification of hidden muscle abnormalities despite adequate, excess or stable weight (2–4). As stated in several recent clinical guidelines, body composition assessment is emphasised as an integral part of daily clinical practise in nutritional assessment (1, 5–7).

In the context of two highly prevalent conditions, such as malnutrition related to the disease (MRD) and sarcopenia, measurement of muscle mass is critical for optimal assessment and identification (1, 7).

Malnutrition related to the disease (MRD) is defined as a subacute or chronic nutritional state in which a combination of varying degrees of over-or undernutrition and inflammatory activity has resulted in altered body composition and reduced function (8, 9).

Sarcopenia is defined as a progressive and generalised loss of skeletal muscle mass, strength and/or physical function, which is associated with an increased risk of adverse outcomes, such as physical disability, poor quality of life, increased mortality (7) and metabolic syndrome (10–14). The presence of sarcopenia at diagnosis or its onset during treatment has been widely associated with poorer outcomes in terms of prognosis, higher rates of surgical complications, poorer response to chemotherapy and greater toxicity, longer hospital stay, and mortality (15–17).

Malnutrition and sarcopenia are very common in patients with oncological pathology (18). Their presence is closely associated with poor clinical outcomes and prognosis. Therefore, the study of BC is important to facilitate diagnoses and allow early intervention (19, 20).

Nowadays, there are several techniques to assess BC and muscle mass, and it is important to recognise the strengths and limitations for an optimal application. Currently, bioelectrical impedance analysis (BIA), muscle ultrasound (US), dual-energy X-ray absorptiometry (DXA), magnetic resonance image (MRI) and computed tomography (CT) are recognised as diagnostic methods for sarcopenia (5, 7).

On the one hand, BIA is a simple, non-invasive, fast and inexpensive method that estimates the BC by measuring the resistance to a low-power alternating current through the body (21). BIA estimates BC as a bicompartmental model: fat free mass (FFM) and fat mass (FM) in kilogrammes and percentage (22). The use of predictive equations is the main limitation of the BIA as it requires a constant hydration and population references that do not always correspond to the clinical reality of the patient (23–25).

Furthermore, DXA is considered to be a precise technique that, provides results from three compartments. It is important to note that since there are only specific attenuation factors for bone and fat, the DXA technique measures only two compartments (bone mass and fat mass) and estimates the third (lean mass) (26, 27). The need for dedicated space for the equipment, trained personnel and exposure to X-ray radiation (even at low doses) are some of the limitations (28).

In addition, US is an emerging accessible bedside, portable, and non-invasive technique as it does not involve ionising radiation for the patient (29, 30). It is able to provide not only quantitative information but also qualitative information by grey scale (31–33). Several skeletal muscle groups have been studied with US, and most of them showed a strong correlation with total muscle mass (32, 34). The quadriceps femoris is the most studied muscle group, especially the rectus femoris (32, 35). Quantitative analysis shows a strong correlation with reference techniques such as MRI or CT (36–38).

CT is emerging as a widely used technique in clinical practise, providing very accurate information for the assessment of BC (39–41). Regional analysis of adipose tissue and muscle at the third lumbar vertebra has been shown to have a high correlation with total BC, and provides significant additional information on tissue quality based on the Hounsfield units (HU) (26, 40, 42).

The assessment of BC by CT image has been widely used in clinical research, especially in those pathologies where CT evaluation is part of the protocol, such as some types of cancer or abdominal pathologies (43). Colorectal cancer (CRC) is a disease of high prevalence and great impact on global health, being the third most commonly diagnosed cancer worldwide and the second leading cause of cancer death (44). Abdominal CT must be routinely performed in colorectal cancer for diagnosis, staging and follow-up (17, 45, 46).

It is crucial to highlight the fluctuations of BC during the evolution of the disease, especially during the active treatment process, which indicates the importance of monitoring its evolution (45, 46). Therefore, an easy to perform and accessible technique is needed to allow us to study BC at any time during the patient's evolution, taking into account that it does not cause any harm or discomfort to the patient. In this scenario, the US could be a good alternative to CT when the latter is unfeasible to carry out.

In this context, this study is proposed with the aim of assessing: (a) the strength of correlation between the measurements made by ultrasound at the level of the rectus femoris in relation to abdominal CT (as a reference technique) and clinical variables of evolution; (b) to determine which ultrasound variables are significantly associated with clinical evolution; (c) the use of our semi-automated tool would optimise the results obtained by US; (d) whether the use of semi-automatic tools in ultrasound better represents the patient's clinical reality than manual measurements.

2 Materials and methods

2.1 Patient selection

We performed a single-centre cross-sectional study including consecutive patients diagnosed with colorectal cancer who underwent oncological surgery at the Vall d'Hebron University Hospital, between May 2021 and September 2023.

The study was approved by the local ethics committee PR (AG) 489/2021 and was conducted in accordance with the Declaration of Helsinki.

All the patients signed the informed consent form before participating in the study. Inclusion criteria: (a) more than 18 years of age; (b) diagnosis of colorectal cancer confirmed by biopsy; (c) patients recruited 48 h after colorectal oncology surgery; (d) acceptance and return of the signed informed consent form signed after clarification of doubts. Exclusion criteria: (a) unable to perform CT scan; (b) unable to undergo ultrasound in the rectus femoris (i.e., amputations); (c) abdominal CT scan performed 30–40 days before recruitment.

2.2 Clinical data collection

Patients were recruited 48 h after colorectal oncology surgery. At this time, anthropometric measurements of current weight and height

were performed, and anthropometric history (usual weight and weight loss in the previous 6 months) was obtained. Patients' performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) scale. The remaining demographic and oncological variables were obtained from the clinical history. At the time of recruitment, a tetrapolar bioimpedance was performed using the Bodystat quadscan 4,000.

In this study, we evaluated the potential use of rectus femoris muscle measurement, via ultrasound, as a prognostic criterion for clinical outcomes in patients, specifically considering length of hospital stay and discharge destination.

After discharge, return home from the hospital was considered a natural progression. The need for hospitalisation at home, referral to a social health centre or death was considered an unfavourable outcome with a poor prognosis.

The hospital stay considered favourable in our centre for this type surgery is 3–5 days. Therefore, two hospital stay groups were identified, those with a normal or expected hospital stay (less than 5 days) and those with a prolonged hospital stay (>10 days). The exclusion of patients with stays between 6 and 9 days was a deliberate methodological choice. This decision was informed by the clinical observation that within this range, the reasons for prolonged hospitalisation can vary widely, encompassing both medical complications and non-medical, logistical factors (such as weekend discharge policies, availability of the discharging physician, or unexpected systemic demands on hospital resources). As such, including this group in either the positive or negative outcome categories could introduce significant variability and potential bias into the analysis, undermining the clarity and interpretability of our findings. Our approach aligns with the principle of maximising the interpretability of the study's outcomes by focusing on patient groups with clear clinical trajectories.

We scored these two prognostic variables together as "good" (good outcome) or "poor" (poor outcome). In this way, those individuals who have a "normal" stay (up to 5 days) and who return home upon discharge are considered to have a good prognosis. This allows for biases such as those patients with a short stay who end up dying.

2.3 Rectus femoris ultrasound

Ultrasound measurements of the unilateral right quadriceps rectus femoris (RF) were performed in all patients. Ultrasound imaging and manual measurements were performed by an experienced medical sonographer on the same day of recruitment. A linear portable ultrasound transducer (UProbe L6C Ultrasound Scanner, Guangzhou Sonostar Technologies Co., China) was used, and all the images were acquired with 10 kHz.

Thigh muscle measurements were performed with the patient in the supine position with knees extended and relaxed. The acquisition site was located two-thirds of the way along the femur length, measured between the anterior superior iliac spine and the upper edge of the patella (29). The transducer was placed perpendicular to the long axis of the thigh with abundant use of contact gel and minimal pressure to avoid muscle compression (Figure 1A).

All parameters were taken as the average of two consecutive measurements in the dominant leg. We took an image in a transversal section, and then measured the cross-sectional area (CSA) in cm^2, the *X*-axis and *Y*-axis in cm, which corresponded to the linear measurement of the distance between the muscle limits of the rectus femoris (lateral and anteroposterior), and the total fat subcutaneous tissue in cm (Figure 1B). All US parameters were also standardised by the height squared (in cm^2 for the rectus femoris) (29).

In order to optimise the measurements obtained manually from the US, our group has developed a semi-automatic tool called "Bat." All the images in crude format (".dcom"), obtained from the US were first manually marked with the "Bat" tool. Later, the tool generated the same metrics of the RF area obtained manually, adding the grayscale value (0: Black, 255: white) (31, 32).

To analyse these images, a combination of advanced digital techniques, including pixel labelling, Principal Component Analysis (PCA) and centroid identification were used. The latter involves calculating the "centre" of the labelled pixels, similar to determining the equilibrium point of the muscle's shape within the image. Besides, PCA is also a sophisticated statistical method used to identify patterns in data. Its purpose is to express data in a way that highlights both its similarities and its differences. In simple terms, envisioning the muscle as an ellipse, these axes can be visualised as lines passing through its centre. The first principal axis (major eigenvector) is the direction with the highest variance in the data (pixels) and corresponds to the "longest" diameter of the ellipse. The second principal axis (minor eigenvector) is perpendicular to the first and represents the direction with the next highest variance, corresponding to "shortest" diameter of the ellipse (Figure 1D).

Manual area marking using "Bat" tool was performed by a different researcher to the one who initially measured the image (Figure 1C). It is important to note that both researchers remained blind to any additional clinical or body composition data during both the image acquisition and analysis stages.

In addition, occasionally, the image of the rectus femoris exceeds the dimensions of the transducer, making it impractical to include the entire area in a single image. This circumstance, referred to as "overflow" (Figure 1C), presents a challenge at the image analysis level. When the image has overflow, the area calculation is estimated according to the trajectory of the rectum. As it is not possible to fully analyse the area completely manually or automatically, the level of precision or adjustment of this variable to the reality of the patient is artefactual. Therefore, we categorised the sample into two groups based on the presence or absence of image overflow to assess its potential impact on clinical outcomes.

2.4 Computed tomography analysis

Skeletal computed tomography (CT) images focused on the L3 vertebrae were obtained using a multidetector computed tomography scanner (Aquilion Prime SP, Canon Medical Systems, Japan), with the following technical parameters: 135 kV (tube voltage), 1 mm 80 row (detector configuration), tube current modulation, and 0.8 s/rotation (gantry rotation). The following variables were recorded: skeletal muscle mass area or SMA (cm^2 and %), skeletal muscle mass index or SMI (cm^2/m^2), intramuscular adipose tissue area or IMAT (cm^2 and %), intramuscular adipose tissue index or IIMAT (cm^2/m^2), area of visceral fat mass (VFA) (cm^2 and %), subcutaneous fat (SFA) (cm^2 and %), visceral fat mass index (VFI) (cm^2/m^2), and subcutaneous fat (SFI)

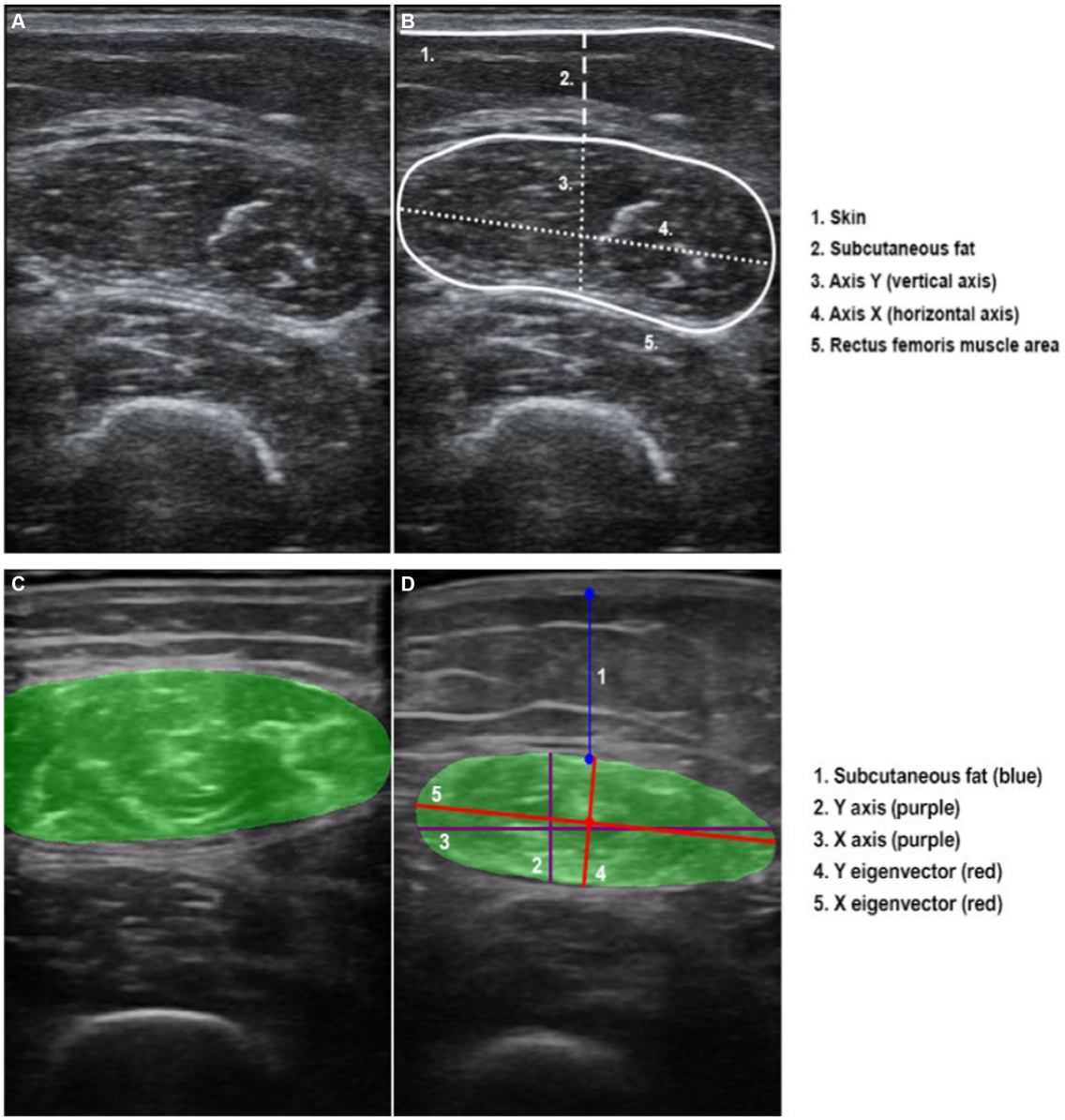

FIGURE 1
Ultrasound transversal section of rectus femoris. **(A)** Rectus femoris image without overflow. **(B)** Rectus femoris manual measures and scheme of the anatomical structures. **(C)** Image of rectus femoris with overflow. **(D)** Rectus femoris "Bat" measures, representing the "classic *X* and *Y* axes" and the reorientation using the automatic variables of the "*X* and *Y* eigenvector".

(cm^2/m^2), and average Hounsfield Units (HU) for each segmented tissue. The CT images centred on the third lumbar vertebra (L3) were analysed using FocusedON-BC software. Tissue quality was assessed based on its average Hounsfield Units (HU) value. Standard thresholds were used as follows: −29 to 150 HU for skeletal muscle, −190 to−30 for subcutaneous adipose tissue and−150 to−50 for visceral adipose tissue (41, 42, 47).

2.5 Statistical analyses

Statistical analyse were performed using Python 3. Continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables and median ± interquartile range (IQR) for non-normally distributed variables. Categorical variables are presented as percentages. Statistical significance was accepted at $p < 0.05$.

To assess whether a given numerical variable can be used as a predictive criterion for a patient's clinical outcome, the separability of groups associated with treatment success or failure was assessed. Treatment success or failure was determined on the basis of several clinical variables, such as length of hospital stay or discharge destination. Group separability was assessed using the Student's t-test when the two groups had a normal distribution and equivalent variances. The Mann–Whitney U test was used when neither condition applied. The Anderson-Darling method was used to evaluate the normality of the distribution of the numerical variables. The Levene's test was used to confirm the equivalence of variances.

In addition, ROC curves were used to quantify the overall precision of each method by measuring the area under the curve (AUC).

Given the innovative nature of the methodology being tested, our study was designed as a proof-of-concept (PoC) investigation. Primarily to explore the feasibility and potential efficacy of this new approach, rather than to provide definitive evidence of its effectiveness. This inherent uncertainty in the expected outcomes and effect sizes made traditional sample size calculation methods challenging to apply effectively. In this context, the sample size for our PoC study was determined based on practical considerations, including the availability of subjects and resources, with an emphasis on obtaining a preliminary assessment of the methodology's feasibility and potential signals of effectiveness.

Moreover, various graphs and images were generated to better illustrate the statistical results.

3 Results

3.1 Study population

We recruited 174 patients (see Table 1), predominantly male, with a mean age of 68.91 ± 11.52 years old. All participants had colorectal neoplasia, with the colon and sigmoid colon being the most commonly affected sites. Notably, 65% of the recruited patients presented with stage II-III disease at the time of diagnosis, although an overwhelming 95% maintained a good baseline functional status (ECOG≤1). According to the GLIM criteria (assuming that all patients have an etiologic criteria + at least 1 phenotypic criteria including weight loss >5% during the last 6 months, BMI < 20 kg/m2 if <70 years old or < 22 kg/m2 if >70 years old and a reduction in muscle mass measured by BIA), 21% of the patients met the criteria for malnutrition, although the average BMI was above the normal range (BMI 26 kg/m2) (5). Sarcopenia was screened screening using the SARC-F questionnaire, which showed a 9% risk of sarcopenia within in the sample.

TABLE 1 Patients' demographic, clinical and anthropometric characteristics.

Characteristics	Study population (n = 174)
Sex	
Female	64 (37%)
Male	105 (60%)
Age (years)	68.91 ± 11.52
Tumour location	
Colon	78 (45%)
Sigmoid	53 (30%)
Rectum	23 (13%)
Cecum	15 (9%)
Anus	1 (1%)
TNM stage	
I	31 (18%)
II	54 (31%)
III	60 (34%)
IV	10 (6%)
ECOG	
0	141 (81%)
1	25 (14%)
2	4 (2%)
3	1 (1%)
4	1 (1%)
BMI (kg/m^2)	26.27 ± 4.61
Malnutrition by GLIM criteria	36 (21%)
Suspicion sarcopenia by SARC-F	16 (9%)
Ultrasound RF area (cm^2)	3.89 ± 1.35
CT muscle area – SMA (cm^2)	112.59 ± 28.52
Discharge destination	
Home	160 (92%)
No home	14 (8%)
Length hospital stay (days)	7.72 ± 10.12
≤5 (n = 112)	3.56 ± 0.78
≥10 (n = 31)	22.35 ± 15.44

BMI, body mass index; GLIM: Global leadership Initiative of Malnutrition, ECOG, Eastern Cooperative Oncology Group scale; RF, rectus femoris; CT, computed tomography; SMA, skeletal muscle area.

3.2 Quantifying muscle mass: US vs. CT

The amount of muscle measured by the rectus femoris present a strong and statistically significant correlation with the results of the CT muscle area, especially in the variables "Y axis" and "area" (Table 2). In Figure 2 a graphical representation illustrates the correlation between the results of the RF ultrasound area and the results of the abdominal CT muscle area. The graphic presentation clearly shows a remarkable correlation between both CT and US findings. In particular, patients without overflow (represented by blue dots) are closer to 0, indicating a smaller muscle mass. The graph also highlights a noticeable clustering of the samples within a narrower numerical range, which represents a challenge in separating patients based on their clinical evolution.

3.3 US quantification of muscle mass and clinical evolution

The averages of the main variables obtained by ultrasound have been obtained and presented in Table 3. It can be seen that the possibility of having a good or bad prognosis is related to the manual area (p = 0.041), and especially when we normalise this measurement by the square of the height (m^2), improving the ability to predict the patient's outcome. In addition, other manual and automatic variables also improve their prognosis capabilities when normalised by patient's height. In example, muscle area improves its AUC from 0.62 to 0.64 and Y axis from 0.59 to 0.61.

Similarly, when the patient's whit overflow was removed from the sample, muscle area improves its AUC from 0.64 to 0.71.

On the other hand, the use the software tool, which allows carrying the analysis in a more automatic and user independent way,

TABLE 2 Correlation between CT muscle area and US RF variables (area, *X* and *Y* axis).

CT variable	US variable	*N*	R^2	IC (95%)	*p* value
CT Muscle area (cm^2)	US RF Muscle area (cm^2)	166	0.67	(0.57, 0.74)	$p < 0.005$
CT Muscle area (cm^2)	US RF Muscle X (cm)	166	0.53	(0.41, 0.63)	$p < 0.005$
CT Muscle area (cm^2)	US RF Muscle Y (cm)	166	0.66	(0.56, 0.74)	$p < 0.005$

CT, computed tomography; US, ultrasound; RF, rectus femoris.

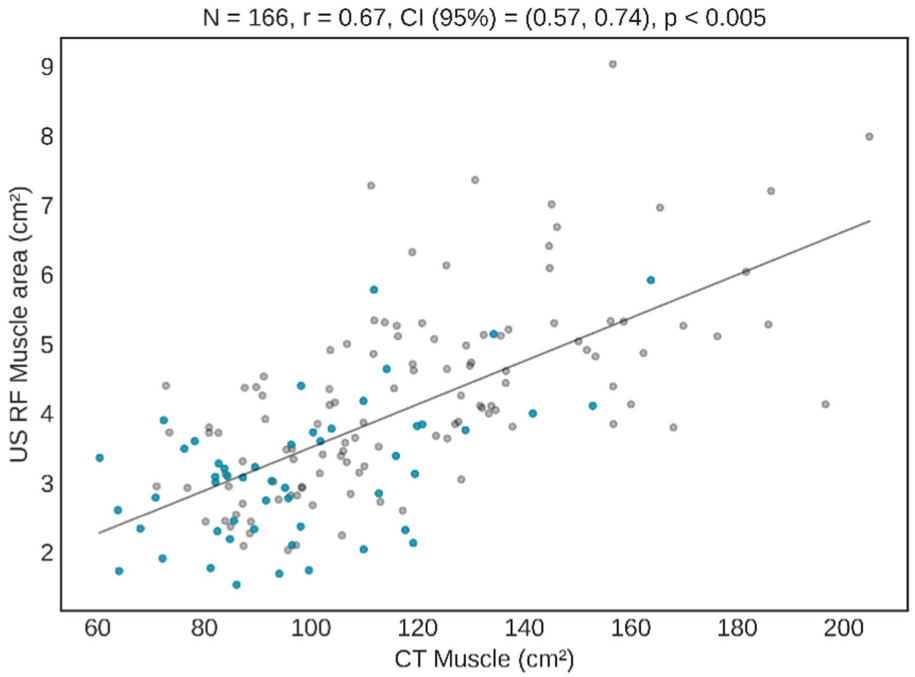

FIGURE 2
Correlation between CT muscle area and US RF area. Blue dots represent subjects with overflow in US image, and grey dots patients without overflow.

also increases the performance of the different metrics. For instance, muscle *Y* axis improves from 0.56 to 0.68, and even to 0.72 when using the y-eigenvector. Similarly, muscle area improves from 0.71 (after normalised by height and remove overflow) to 0.73 using semiautomatic tool. This improvement can be observed in the ROC curves displayed in Figure 3.

Although this trend can be clearly seen in the results, the difference between the manual and automatic metrics is not statistically significant (*p*-value >0.05).

4 Discussion

This study is, to our knowledge, the first to use a semi-automatic tool in the evaluation of muscle ultrasound (US) in rectus femoris.

US has gained widespread acceptance and is nowadays included in several influential body composition guidelines (1, 7, 48). Positioned as the "stethoscope of body composition," US is valued for its accessibility, cost-effectiveness, and bedside applicability (49). In our study, measurement of muscle mass using US at the RF showed a robust correlation when compared to quantification using CT as the reference technique ($r = 0.67$, IC 0.57–0.74, $p < 0.001$). These results are similar or superior to those reported in other studies, such as Paris et al. shows ($r = 0.45$, $p < 0.01$) or Lambell et al. (0.7, $p < 0.01$) (50, 51). However, the paucity of published evidence comparing ultrasound with CT is probably due to the logical challenge of synchronising both tests at clinically comparable times.

Taking into account the previously presented information, patients with colorectal cancer emerge as particularly suitable candidates, as they require CT scans as part of their follow-up, staging and overall assessment (45, 52). This positioning allows CT to be used as an "opportunistic" technique to analyse BC with a high degree of precision, thus providing a valuable validation platform for emerging techniques, such as US (53, 54). The results derived from this study contribute significantly to our understanding, endorsing US as a technique with acceptable results for screening and diagnosis of muscle alterations, validated against CT, in patients with colorectal cancer. Thus, it would be an alternative tool for use in the future when TC is not feasible.

It should be noted that muscle ultrasound is a technique that provides us quantitative (area and *Y* axis) and qualitative muscle information (grey scale) (29). This information is obtained directly from muscle mass and has been shown to have a very good correlation with the patient's functional capacity and prognosis (55, 56). In the case of bioimpedance, a doubly indirect method of assessing body composition, quantitative information on muscle

TABLE 3 Clinical evolution using US RF variables using all the image, and separating those with and without overflow, normalised or not by height.

	With overflow	Unnormalized by height						Normalised by height (/m^2)					
Manual metrics	US variable	All (*n*=143)	Good outcomes (*n*=111)	Poor outcomes (*n*=32)	*p* value	ROC (AUC)	SE	All (*n*=143)	Good outcomes (*n*=111)	Poor outcomes (*n*=32)	*p* value	ROC (AUC)	SE
	US RF muscle area (cm^2)	3.92	4.06	3.45	0.041	0.62	0.06	1.4	1.45	1.22	0.015	0.64	0.05
	US RF muscle x (cm)	3.65	3.67	3.56	0.315	0.56	0.06	1.32	1.33	1.28	0.095	0.57	0.06
	US RF muscle y (cm)	1.32	1.35	1.24	0.087	0.59	0.06	0.47	0.49	0.44	0.064	0.61	0.05
	Without overflow	Unnormalized by height						Normalised by height (/m^2)					
	US variable	All (*n*=42)	Good outcomes (*n*=33)	Poor outcomes (*n*=9)	*p* value	ROC (AUC)	SE	All (*n*=42)	Good outcomes (*n*=33)	Poor outcomes (*n*=9)	*p* value	ROC (AUC)	SE
	US RF muscle area (cm^2)	3.12	3.24	2.7	0.178	0.65	0.1	1.16	1.21	0.99	0.099	0.71	0.1
	US RF muscle x (cm)	3.32	3.37	3.14	0.19	0.68	0.1	1.25	1.28	1.15	0.065	0.68	0.12
	US RF muscle y (cm)	1.18	1.2	1.13	0.522	0.55	0.11	0.44	0.45	0.41	0.248	0.56	0.1
Software metrics	US RF muscle area-s (cm^2)	3	3.12	2.52	0.061	0.7	0.1	1.12	1.17	0.93	0.023	0.73	0.1
	US RF muscle y-s (cm^2)	1.15	1.18	1.04	0.152	0.66	0.09	0.43	0.44	0.38	0.053	0.68	0.09
	US RF x-eigenvector (cm)	3.29	3.33	3.16	0.374	0.6	0.13	1.24	1.26	1.16	0.253	0.59	0.14
	US RF Muscle y-eigenvector (cm)	1.16	1.19	1.03	0.085	0.69	0.08	0.43	0.45	0.38	0.024	0.72	0.09

US, ultrasound; RF, rectus femoris; SE, standard error.

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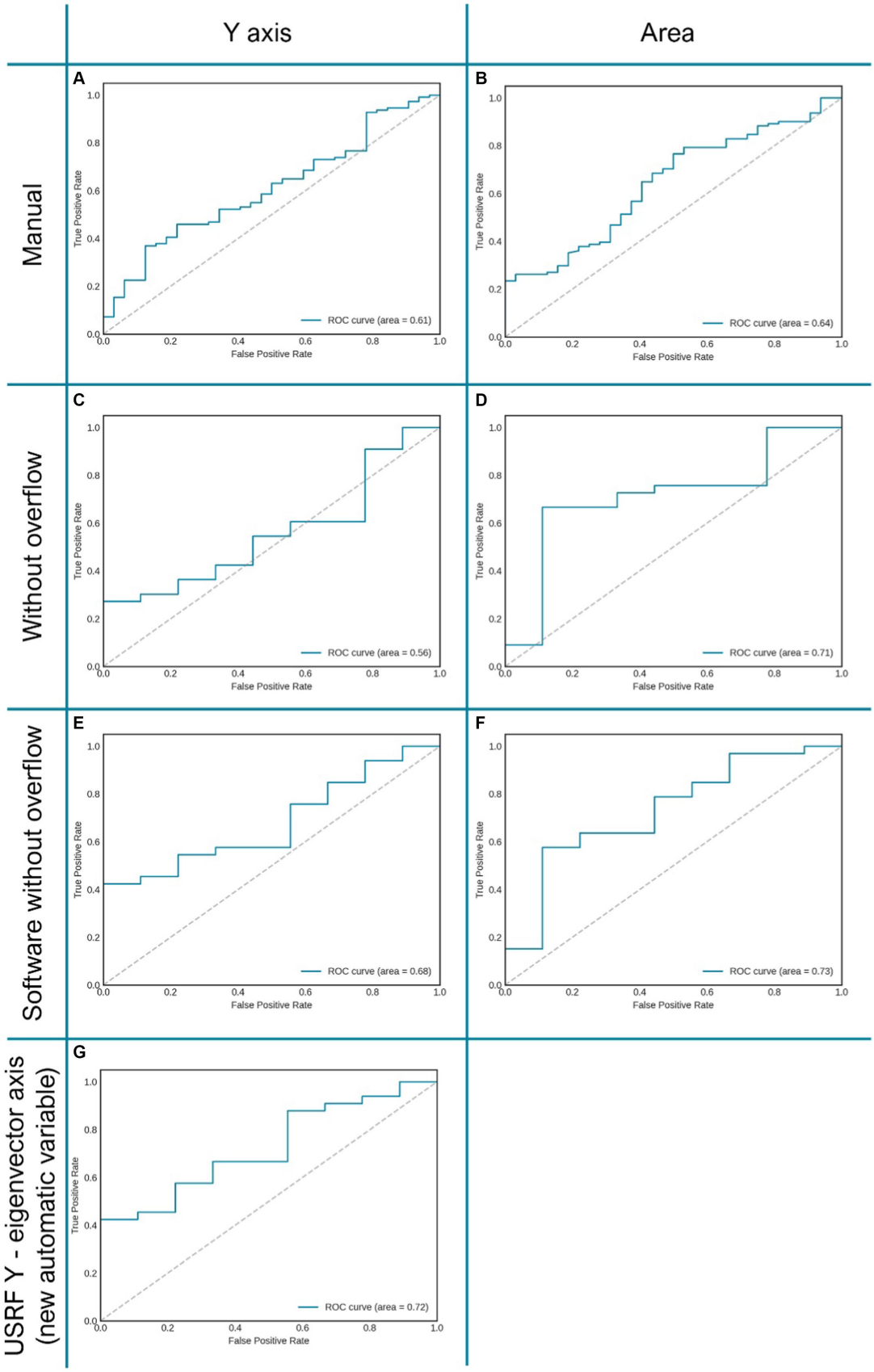

FIGURE 3
Graphic representation of several AUC of ROC curves of the variables "*Y* axis" and "area" related to clinical prognosis. Allows assessing the improvement of the same variable when changing the measurement method (manual or automatic). **(A,B)** RF area and "*Y* axis" measured manually; **(C,D)** RF "*Y* axis" and area measured manually in patients without overflow. **(E,F)** RF "*Y* axis" andarea measured automatically with "Bat" tool in patients without overflow. **(G)** "Eigenvector *Y* axis," proposed vector obtained automatically through image analysis with the "BAT tool".

mass can be obtained through fat free mass, but not qualitative information on muscle mass (22). The phase angle is a parameter that we can obtain from the BIA that has a highly impactful prognostic value (57, 61). However, it is a parameter that comes from a complete body evaluation, not from muscle mass in particular. On the other hand, DXA is a highly accurate technique for evaluating body composition, but it is not a particularly good technique for evaluating muscle status since it does not provide information on muscle quality (26). Furthermore, it is an expensive and inaccessible technique.

Reduction in muscle mass (MM) is strongly associated with a prognosis in terms of postoperative complications, prolonged hospital stays, discharge outcomes, treatment response and mortality (61). Consistent with this premise, our study results confirm that lower MM, as measured by US, associated with longer hospital stays and decreased likelihood of discharge home, essentially indicating a more difficult prognosis for the patient. Given the accessibility of US as a technique, serious consideration should be given to its more frequent incorporation into protocols for prevention and clinical optimization in patients with colorectal cancer. Furthermore, the results obtained can play a key role in tailoring multimodal treatments in cases where low muscle mass is evident or its deterioration is observed over time.

On the other hand, one of the weaknesses of muscle ultrasound is its operator-dependent nature, requiring skilled personnel to perform it accurately (39, 59, 60). It is also necessary to implement standardised protocols so that their results are comparable (32). A key factor contributing to the variability of findings is the manual nature of quantitative measurements, such as the area or the X and Y axes, which are subject to the operator interpretation. There are various software programmes that allows us to obtain the grey scale through manual measurements, but currently, there are no tools for the rest of the ultrasound metrics at the RF level that are automatic (31).

In this study, we begin to develop a near automatic tool that simplifies the process by requiring only the manual marking of the RF area. This innovative approach facilitates the automatic derivation of other variables from the initial manual marking. Several processes in medicine have shown that the automation of measurements and the use of software that reduces the intervention of the "researcher's hand" is superior and optimises results (61–63). When performing ultrasound imaging, for example of the rectus femoris muscle, there's a common challenge related to the orientation of the ultrasound probe. Even a slight rotation or tilt of the probe can alter the appearance of the muscle in the image. However, the described method, based on principal axes (eigenvectors), significantly mitigates this problem by incorporating principal component analysis (PCA) to identify the principal axes of the muscle image effectively addresses this challenge. Regardless of the probe's orientation, the principal axes of the muscle's image will consistently adjust. This means that the major and minor axes of the ellipse representing the muscle are consistently aligned with the directions of maximum variance in the image, regardless of how the ultrasound probe is held.

This technique featly reduces the reliance on the operator skill or consistency in probe placement. Different observers can perform the scan, and the main axes will remain consistent for the same anatomical structure, ensuring more objective and reproducible measurements. By focusing on the intrinsic geometric properties of the muscle tissue, as represented by the ellipse in the image, measurements become more reflective of the actual dimensions of the muscle and less dependent on the probe positioning. Consequently, this approach leads to more accurate and objective assessments of muscle size, shape, and potentially its health status.

Firstly, we carefully analysed the correlation between our measurements and those performed manually, and found robust and statistically significant associations for all variables (refer to Table 3). RF area (cm^2) emerged as the variable with the strongest correlation with CT, although results were also noted for the *Y* axis (see Table 2). This may be related to the fact that the favourable performance of the axis due to its vertical measurement, which is not affected by possible image displacement from the screen. In this sense, we observed that a significant percentage of the images (62%) acquired according to our protocol in the lower third of the leg showed an area that extended beyond the edges of the screen. This overflow situation, where the area extends beyond the edges of the screen, introduces a potential source of imprecision in area measurements compared to situations where the area is fully displayed. We therefore, stratified the sample into two groups, with and without overflow. We re-run the clinical correlation in the group without overflow, and observed an improvement in the ROC curves, indicating a lower rate of false positives and false negatives. An increase in the correlation with clinical complications, discharge destination and hospital stay were also observed. However, it is recognised that these results may be influenced by the fact that many patients without overflow generally have worst muscle mass.

A limitation of our tool is its partial automation, which requires a manual measurement by a researcher. However, it has been shown that a reduction in manual measurement leads to significantly better results. It is necessary to carry out studies with a larger sample size to fully automate the tool. In addition, it would have been interesting to measure the RF area a few centimetres closer to the patella to see if this would provide an improvement that we should definitely include in our protocols when eliminating the overflow. Furthermore, assessing the usefulness of these measurements in patient follow-up and exploring other prognostic variables such as post-operative complications or mortality is an interesting avenue for further research. Our ongoing studies are designed to a comprehensively address these issues.

5 Conclusion

In conclusion, the significant correlation levels observed in our study prompt led to consider the US as an alternative for the quantitative assessment of muscle mass when CT is not feasible. It is noteworthy to highlight the pioneering role of "Bat," the first software to allow semi-automatic derivation of metrics in rectus femoris measurements. The application of principal axis analysis in ultrasound imaging is proving to be a powerful approach to standardising muscle tissue measurements. This methodology effectively overcomes the challenges associated with variable probe orientation, thereby improving the accuracy, objectivity, and reproducibility of measurements. Such improvements are of paramount importance in clinical settings, contributing significantly to accurate diagnosis and monitoring. In addition, the approach reduces inter and intra-observer dependencies, further enhancing the precision and objectivity of the results. This not only improves their separability but

also partially compensates for one of the recognised weaknesses of muscle ultrasound.

Whilst acknowledging these advances, it is prudent to emphasise the need for additional studies to fully automate the "Bat" tool and thoroughly reassess its clinical utility. This ongoing research is critical for refining and optimising muscle assessment methodologies, and ensuring continued progress in the field.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Comité de Ética de la Investigación con medicamentos del Instituto de Investigación Vall d'Hebron. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FP: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing, Validation. FM: Investigation, Writing – review & editing. MR: Investigation, Writing – review & editing. AL: Investigation, Writing – review & editing. AZ: Investigation, Writing – review & editing. JM: Investigation, Software, Writing – review & editing. RG: Formal analysis, Software, Writing – review & editing. AR: Resources, Writing – review & editing. NR: Resources, Writing – review & editing. AC: Writing – review & editing. RB: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The prognostic value of prognostic nutritional index in postoperative onset of PAH in children with isolated VSD: a prospective cohort study based on propensity score matching analysis

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Background: The mechanism of pulmonary arterial hypertension (PAH) after surgery/intervention for isolated venticlular septal defect (VSD) in children is unknown. Reliable prognostic indicators for predicting postoperative PAH are urgently needed. Prognostic nutration index (PNI) is widely used to predict postoperative complications and survival in adults, but it is unclear whether it can be used as an indicator of prognosis in children.
Methods: A total of 251 children underwent VSD repair surgery or interventional closure in Hunan Children's Hospital from 2020 to 2023 were collected. A 1:1 propensity score matching (PSM) analysis was performed using the nearest neighbor method with a caliper size of 0.2 Logistics regression analysis is used to examine factors associated with the development of PAH.
Results: The cut-off value for PNI was determined as 58.0. After 1:1 PSM analysis, 49 patients in the low PNI group were matched with high PNI group. Children in the low PNI group had higher risk of postoperative PAH ($P = 0.002$) than those in the high PNI group. Multivariate logistics regression analysis showed that PNI (RR: 0.903, 95% CI: 0.816–0.999, $P = 0.049$) and tricuspid regurgitation velocity (RR: 4.743, 95% CI: 1.131–19.897, $P = 0.033$) were independent prognostic factors for the development of PAH.
Conclusion: PNI can be used as a prognostic indicator for PAH development after surgery/intervention in children with isolated VSD.

KEYWORDS

pulmonary arterial hypertension, prognostic nutrition index, propensity score matching, prognosis, ventricular septal defect, pediatric

1 Introduction

Congenital malformations are an important cause of death in children whose important component is congenital heart disease (CHD) (1). Congenital heart disease is considered the most common and serious abnormality at birth, with a prevalence of 6–13 cases per 1,000 births (2, 3). Venticlular septal defect (VSD) is a congenital heart disease that causes communication between the left and right ventricles due to

embryonic ventricular septal dysplasia, resulting in horizontal ventricular shunting, accounting for about 40 percent of congenital heart disease and is the most common congenital heart disease (4, 5).

Surgery is an effective treatment for children with VSD which includes repair surgery and interventional closure. The development of pulmonary arterial hypertension (PAH) is an important factor affecting the prognosis of children after VSD surgery. Pulmonary hypertension crises lead to significantly increased perioperative mortality in children, and on the other hand, life expectancy in VSD patients with postoperative PAH is even lower than in patients with unoperated complex VSD and Eisenmenger syndrome (6). Therefore, early screening of patients who may have PAH after surgery/intervention is of great significance to improve the success rate of treatment. Recognized risk factors influencing the development of PAH after VSD repair surgery or interventional closure include age, defect size, and pulmonary vascular resistance (7). However, these factors did not take into account the nutritional status of the child.

Malnutrition is a common problem in children born with dysplasia or prematurity. Malnutrition can affect the patient's response to treatment, resulting in a poorer quality of life. Assessment of systemic nutritional status is achieved by introducing the prognostic nutration index (PNI), a continuous variable based on serum albumin concentration and total peripheral blood lymphocyte count (8). PNI was originally designed to assess perioperative immunotrophic status and surgical risk in patients undergoing gastrointestinal surgery (9). Several studies have demonstrated the prognostic value of PNI in a variety of malignancies and in adult patients with pulmonary hypertension (10–12). However, it is unclear whether it is an indicator of the prognostic development of PAH in children after VSD repair surgery or interventional closure.

Confounding factors always impair the accuracy and objectivity of cohort studies. Propensity score matching analysis (PSM) is commonly used to overcome selection bias, adjust for confounders, improve comparability between groups by increasing the level of evidence in cohort studies, and simulate randomization of observed covariates (13–15). This prospective cohort study first performed PSM analysis to assess the prognostic value of PNI for postoperative PAH development in children with acute VSD repair or interventional closure.

2 Materials and methods

2.1 Ethics statement and cohort selection

This is a prospective cohort study of children who attended the Department of Cardiology of Hunan Children's Hospital from January 2020 to January 2023. The study was approved by the Ethics Committee of Hunan Children's Hospital. Written informed consent signatures were obtained from the parents of children included in the studies, and all data were de-identified for analysis. Children undergoing VSD repair surgery or interventional closure who met the following inclusion criteria were included in the study: (1) transthoracic echocardiography for isolated ventricular septal defect without other cardiac malformations; (2) did not undergo any cardiac surgery or interventional procedures prior to admission; (3) were aged 3 months–18 years; (4) had complete clinical data and detection indicators. Exclusion criteria: (1) concurrent pulmonary hypertension caused by left heart disease, lung disease, hypoxia, chronic thromboembolic pulmonary hypertension or other diseases within 1 week before surgery/intervention; (2) incomplete case data; (3) unwilling to participate in the investigation. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

2.2 Data collection

Pediatric clinical data were collected from electronic medical records. During admission, the following variables were considered: age, sex, body mass index (BMI), VSD defect size, preoperative New York Heart Association (NYHA) functional class, postoperative development of PAH, echocardiographic indicators including tricuspid regurgitation velocity (TRV), right ventricular end-diastolic diameter (RVEDd), left ventricular end-diastolic diameter (LVEDd) and right atrial diameter (RAd), electrocardiography (PR interval, QRS wave) at 1 week before surgery/intervention, and serum albumin and complete blood lymphocyte count within 1 week before surgery/intervention. VSD defect size is divided into 3 grades. Small defects are those with a defect diameter of less than 5 mm; defect of medium size refers to the defect diameter between 5 and 9 mm; Large defects are those that are larger than 9 mm in diameter. The preoperative NYHA functional class has four grades: Grade I refers to unrestricted physical activity. Preschoolers are able to participate in physical education classes and to move around the same as children of the same age in this grade. Grade II refers to mild limitation of physical activity without any discomfort at rest, but general activity can cause fatigue, palpitations, or dyspnea. School-age children are able to participate in physical education but are less active than children their age and may have secondary growth disorders in this grade. Grade III refers to obvious limitation of physical activity, less than usual general activities can appear symptoms. School-age children cannot participate in physical activities and there are secondary growth disorders in this grade; Grade IV refers to the inability to engage in any physical activity, heart failure symptoms at rest, and worsening after activity, and secondary growth disorders. TRV is divided into 3 grades. The low tricuspid regurgitation velocity tricuspid is <2.8 m/s. The modorate tricuspid regurgitation velocity is 2.8–3.4 m/s. The remaining is moderate grade.

2.3 Follow up and endpoints

We followed all children until 31 August 2023 or when PAH developed. Postoperative follow-up examination of hemodynamics lasted for more than half a year. The diagnosis of PAH meets the

criteria of the 2021 Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension Associated with Congenital Heart Disease in Children (16): mean pulmonaryartery pressure (mPAP) >20 mmHg measured by standard right heart catheterization, pulmonary artery wedge pressure (PAWP) ≤15 mmHg, pulmonary vascular resistance index (PVRI)≥ 3 WU·m^2. If right heart catheterization was not performed, TRV >3.4 m/s is measured by echocardiography.

2.4 Assessment and calculation of PNI

PNI is a scoring system that reflects a patient's nutritional and immune status. It is calculated based on serum albumin and lymphocyte. PNI = albumin (g/L) + 5 × lymphocyte count (10^9/L).

2.5 Statistical analyses

Data for continuous variables that conform to a normal distribution are expressed as mean (standard deviation, SD) and otherwise by median (interquartile range, IQR). Data for categorical variables are expressed as numbers (percentage, %). The comparison of continuous variables that do not conform to the normal distribution is analyzed by rank-sum test (Mann-Whitney test), otherwise the t-test is used. The χ^2 test was used to analyze the differences in clinical factors. The nearest neighbor method was used for 1:1 PSM to reduce selection bias and confounding factors caused by different covariate distributions between low and high PNI groups. Matching factors included clinical features of baseline unequivalence between the two groups, including age, gender, BMI, NYHA functional class, VSD defect size, TRV, RAd, RVEDd, NT-pro BNP and PR interval. The caliper size is 0. 2 to determine the effect of PNI on the development of PAH in children with isolated VSD after surgery/intervention. After the 1:1 propensity score matching, continuous variables were compared using the Mann-Whitney *U*-test and categorical variables were compared using the χ^2 test. The logistics model was used to analyze the univariate correlation between prognostic factors and postoperative PAH development. In multivariate analysis, all variables with $P < 0.1$ in univariate analysis are included in the model. All statistical tests were two-sided and statistically significant set to $P < 0.05$. All statistical analyses were performed using SPSS 26.0 software (IBM).

3 Results

3.1 Characteristics of included patients before and after PSM

143 children were excluded from this study due to concurrent pulmonary hypertension within 1 week before surgery/intervention. The characteristics of included 251 children with isolated VSD who underwent repair surgery or interventional closure are detailed in Table 1. The cut-off value is obtained as 58.0 according to the Receiver Operating Characteristic (ROC) curve, at which point the Jordon index reaches its maximum (Supplementary Figure S1). A PNI greater than 58.0 was in the high PNI group, and vice versa in the low PNI group. A total of 56 children were in the low PNI group and 195 in the high PNI group. The median age in the low PNI group was 2.3 (IQR: 3.1) years, of whom 28 (50.0%) were male. The median age of children in the high PNI group was 1.9 (IQR: 2.6) years, of whom 95 (48.7%) were male. Children in the high PNI group had a higher BMI ($P = 0.025$). A higher proportion of children in the low PNI group had high-grade NYHA functional class ($P = 0.037$), VSD defect size ($P = 0.005$), and TRV ($P = 0.003$). NT-pro BNP ($P = 0.012$) was larger in the low PNI group than those in the high PNI group. A greater proportion of children in the low PNI group developed PAH underwent VSD after surgery/intervention (15.0% vs. 7.0%, $P < 0.001$).

After PSM, a total of 49 children in the low PNI group were matched with a high PNI group. After PSM, there was a good balance between the two groups, as there was no longer a significant difference between each confounding factor ($P > 0.05$, Table 1). Patient characteristics after PSM are detailed in Table 1. After PSM, a higher proportion of children in the low PNI group developed PAH after VSD surgery/intervention compared with high PNI group (22.4% vs. 2.0%, $P = 0.002$).

3.2 Univariable and multivariable analysis of included patients

After PSM, univariate analysis showed that high PNI was a protective factor for postoperative PAH in children after VSD surgery/intervention (RR = 0.893, $P = 0.022$, Table 2). Children with moderate ($P = 0.027$) TRV are more likely to develop postoperative PAH than low TRV. Right atrial diameter ($P = 0.037$) was risk factors for postoperative PAH in children after VSD surgery/intervention. Multivariate analysis showed that high PNI remained an independent prognostic protective factor for postoperative PAH in children after VSD surgery/intervention (RR = 0.903, $P = 0.049$). The other factor include VSD defect size ($P = 0.066$), TRV ($P = 0.033$) and RVEDd ($P = 0.067$).

4 Discussion

The development of PAH is an important factor affecting the prognosis of children after CHD surgery/intervention (17). As VSD is the most common congenital heart disease, early identification of VSD patients who may develop pulmonary hypertension after surgery/intervention is important to improve the success rate of treatment (18). In this prospective single-center cohort study, we analyzed the value of PNI in predicting postoperative PAH in children with VSD. For making the results more convincing, we used PSM analysis to reduce confounding effects, balance the differences of clinicopathological confounding factors for the groups. This method allows us to use non-randomized grouping data to estimate the relationship between PNI and postoperative onset of PAH. These clinicopathological

TABLE 1 Associations between PNI and clinicopathological factors before and after PSM.

Variables	Before propensity matching		*P*	After propensity matching		*P*
	PNI ≤58	PNI >58		PNI ≤58	PNI >58	
	(*n* = 56)	(*n* = 195)		(*n* = 49)	(*n* = 49)	
Age (y)	2.3 (3.1)	1.9 (2.6)	0.431	1.9 (2.3)	1.9 (2.5)	0.964
Gender (male)	28 (50.0)	95 (48.7)	0.866	24 (49.0)	26 (53.1)	0.686
BMI	13.9 (2.0)	14.7 (2.3)	0.025*	13.9 (2.0)	13.9 (2.2)	0.114
NYHA functional class			0.037*			0.997
I	16 (28.6)	112 (42.6)		14 (28.6)	19 (30.6)	
II	26 (46.4)	144 (46.7)		24 (49.0)	40 (46.9)	
III	10 (17.9)	22 (7.7)		9 (18.4)	6 (18.4)	
IV	14 (7.1)	7 (3.1)		2 (4.1)	5 (4.1)	
Defect size			0.005*			0.226
Small	3 (5.4)	27 (13.8)		3 (6.1)	1 (2.0)	
Medium	12 (21.4)	73 (37.4)		12 (24.5)	19 (38.8)	
Large	41 (73.2)	95 (48.7)		34 (69.4)	29 (59.2)	
TRV			0.003*			0.507
Low	34 (60.7)	156 (80.0)		33 (67.3)	36 (73.5)	
Modorate	22 (39.3)	39 (20.0)		16 (32.7)	13 (26.5)	
RAd	20.8 (7.0)	20.4 (7.0)	0.671	20.8 (5.3)	19.2 (7.0)	0.863
RVEDd	18.3 (4.0)	18.1 (4.0)	0.746	18.2 (4.2)	17.3 (5.0)	0.646
RVEDd/LVEDd	0.62 (0.15)	0.60 (0.14)	0.355	0.62 (0.15)	0.58 (0.15)	0.830
NT-pro BNP	4,193.2 (4,405.6)	1,499.7 (1,979.0)	0.012*	2,335.6 (2,731.6)	3,027.5 (4,644.8)	0.754
PR interval	112.5 (21.7)	110.1 (24.0)	0.438	110.9 (22.0)	110.9 (32.0)	0.762
QRS wave	84.5 (22.0)	83.82 (14.0)	0.912	82.2 (20.0)	95.2 (26.0)	0.244
PAH	15 (26.8)	7 (3.6)	<0.001*	11 (22.4)	1 (2.0)	0.002*

BMI, body weight index; NYHA, New York Heart Association; TRV, tricuspid regurgitation velocity; Rad, right atrial diameter; RVEDd, right ventricular end-diastolic diameter; LVEDd, left ventricular end-diastolic diameter; PAH, pulmonary hypertension.
*$p < 0.05$.

TABLE 2 Univariable and multivariable analysis after 1:1 ratio PSM.

Variables	Univariable analysis			Variables	Multivariable analysis		
	RR	95% CI	*P*		RR	95% CI	*P*
PNI	0.893	0.810–0.984	0.022*	PNI	0.903	0.816–0.999	0.049*
Age	1.070	0.886–1.291	0.484	Age			
Gender (male)	0.435	0.122–1.533	0.200	Gender (male)			
BMI	0.911	0.609–1.363	0.651	BMI			
NYHA functional class			0.303	NYHA functional class			
I	reference			I			
II	4.098	0.467–35.918	0.203	II			
III	8.000	0.816–78.471	0.074	III			
IV	9.333	0.457–190.626	0.1447	IV			
Defect size (large)	0.139	0.017–1.127	0.065	Defect size (large)	7.934	0.875–71.939	0.066
TRV (modorate)	4.073	1.172–14.154	0.027*	TRV (modorate)	4.743	1.131–19.897	0.033*
RAd	1.138	1.008–1.286	0.037*	RAd			
RVEDd	1.162	0.995–1.356	0.058	RVEDd	1.17	0.989–1.400	0.067
RVEDd/LVEDd	1.692	0.028–103.693	0.802	RVEDd/LVEDd			
NT-pro BNP	1.000	1.000–1.000	0.655	NT-pro BNP			
PR interval	1.028	0.998–1.058	0.064	PR interval			
QRS wave	0.999	0.987–1.011	0.887	QRS			

BMI, body weight index; NYHA, New York Heart Association; TRV, tricuspid regurgitation velocity; RAd, right atrial diameter; RVEDd, right ventricular end-diastolic diameter; LVEDd, left ventricular end-diastolic diameter.
*$P < 0.05$.

confounding factors including age, gender, BMI, NYHA functional class, VSD defect size, TRV, RAd, RVEDd, NT-pro BNP and PR interval were well adjusted, and no differences were demonstrated between the low and high PNI groups after PSM. After PSM, factors including PNI and TRV remain independent association with the development of postoperative PAH in multivariate analysis model. To our knowledge, this is the first study to assess the effect of PNI on the prognostic effect of PAH after surgery/

intervention for congenital heart disease by scoring matching analysis, and we demonstrated that PNI is an independent prognostic factor.

Nutritional status can affect the prognosis of PAH. Malnutrition is a complex problem with many causes. The causes of malnutrition in patients with PAH are multifactorial and include loss of appetite, malabsorption due to right heart failure, side effects of specific medications, increased metabolic rate, and dyspnea. Malnutrition is thought to be more likely to be the result of PAH. Studies have shown that children with young, low-weight congenital heart disease associated with pulmonary arterial heart disease have a higher incidence of PAH after surgery (19). It is thought that the possible cause is the large congenital heart disease defect in children with young age and low weight. Large defects cause a large number of left-to-right shunts that affect the blood circulation of organs and tissues, as well as the growth and development of the child, resulting in low body weight. In addition, large shunts due to large defects can lead to early pulmonary vascular remodeling and dynamic PAH. At the same time, large shunts may also hinder the transition of pulmonary circulation to adult form in some children after birth, and pulmonary artery pressure is persistently high. Thus, low body weight and malnutrition may be due to major defects and subsequent pulmonary hemodynamic disturbances and pulmonary vascular remodeling. However, this study found that nutritional status can influence the occurrence of postoperative PH in children with isolated VSD, not just the consequences of PAH. There may be a vicious circle between malnutrition and PAH. Therefore, nutritional status assessment is an important part of predicting prognosis. Assessment of nutritional status is multidimensional. Although nutritional indicators such as hypoalbuminemia are associated with the risk of mortality in patients with PAH (9), their single evaluation criteria limit the scope of application. Nutritional status can be assessed using the PNI, which combines an assessment of metabolic status and an assessment of inflammatory status. Inflammation and immune imbalance are thought to be involved in the development of pulmonary vascular remodeling in PAH, which is an important pathological feature of PAH (20). PNI is a viable tool to assess the relationship between immunotrophic status and prognosis and has been widely used in acute heart failure, esophageal cancer, and lymphoma (21–24). In fact, the prognostic value of PNI index for survival in adult patients with PAH has also been reported (12). Low PNI was associated with an increased risk of death in PH patients. However, the prognosis of whether PNI indices can be used for PAH in children is unclear. In this study, we used the PNI to assess the nutritional status of children with VSD after VSD surgery/intervention and confirmed that PNI is an independent prognostic factor predicting the development of PAH. The optimal cut-off point for PNI was determined to be 58.0. This value is larger compared to the results of other studies in adults (8, 25). This may be due to the shorter period of disease attrition in children than in adults.

TRV can be used as both a diagnostic and prognostic indicator of PAH.The use of TRV as a key variable in echocardiography for the diagnosis of PAH has been recommended (26). Studies have shown that there are different criteria for the diagnosis of pulmonary hypertension based on TRV in different inclusion criteria and study participants (27, 28). The 2022 ESC guidelines for pulmonary hypertension state that the likelihood of pulmonary hypertension is low when TRV $\leq$2.8 m/s, and that PAH should be highly suspected at 2.8 m/s <TRV <3.4 m/s (29). If TRV >3.4 m/s, PAH should be taten into consideration clinically (29). After balancing the confounding factors, this study found that TRV is associated with the development of PAH, and high TRV is more dangerous than low TRV. TRV marks a high afterload of the right heart, and its value also depends on the adaptive capacity of the right heart, which means TRV is not necessarily large when pulmonary artery blood pressure is high. RVEDd is also an important prognostic factor for the development of PAH. In the development of PAH, the right heart changes from compensatory hypertrophy to decompensatory hypertrophy and even failure in the process of adapting to increased afterload, accompanied by right heart fibrosis, metabolic disorders, apoptosis of cardiomyocytes and inflammatory damage (30, 31). The increase in RVEDd marks the right heart reconstruction process after increased afterload.

There are some advantages to this study. Firstly, this study proposes for the first time the application of PNI in predicting the development of PAH in children with CHD after surgery/intervention. Children with low PNI can be alerted early to the development of a PAH crisis and the development of PAH. Second, the laboratory indicators involved in PNI are simple, practical, and effective biomarkers in routine examinations in hospitalized children, because these indicators can be assessed by routine blood and liver function tests without causing greater financial pressure.

However, there are some limitations in this study that cannot be ignored. First, this was a cohort study design conducted at a single center with a limited number of patients. A multicentre study and more patients should be included. Second, selection bias could not be ruled out, even if consecutive patients were included and eligibility criteria were implemented to reduce bias. Third, PNI is a non-specific tumor marker that can be confused with other non-cancer and cancerous diseases. Further validation of a large prospective study is needed to further evaluate the prognostic and predictive value of future PNI for the development of PAH after VSD surgery/intervention.

5 Conclusion

In conclusion, by using propensity score matching analysis, we confirmed that adjusted PNI is a valid prognostic factor for the postoperative development of PAH in children with VSD. However, due to inherent flaws in the retrospective design, more prospective studies are needed to confirm this result in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Hunan Children's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ZZ: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. JS: Conceptualization, Formal Analysis, Methodology, Writing – original draft. CL: Data curation, Formal Analysis, Methodology, Software, Writing – review & editing. SC: Data curation, Formal Analysis, Methodology, Writing – review & editing. CS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing. QL: Conceptualization, Data curation, Formal Analysis, Methodology, Visualization, Writing – review & editing. HL: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Supervision, Writing – review & editing. ZX: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Supervision, Writing – review & editing. YX: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – review & editing. QL: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2024.1292786/full#supplementary-material

SUPPLEMENTARY FIGURE S1
(A) PNI score is higher in patients with no PAH after surgery (n = 229) than in patients with PAH (n = 22; 65.65 vs 58.44, P = 0.003); (B) Receiver Operating Characteristic (ROC) curve shown that area under the curve (AUC) is 0.695 and P value of 0.003; (C) The Jordon index achieves its maximum when the PNI index is equal to 58.0.

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A novel nomogram integrating body composition and inflammatory-nutritional markers for predicting postoperative complications in patients with adhesive small bowel obstruction

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Background: Postoperative complications in adhesive small bowel obstruction (ASBO) significantly escalate healthcare costs and prolong hospital stays. This study endeavors to construct a nomogram that synergizes computed tomography (CT) body composition data with inflammatory-nutritional markers to forecast postoperative complications in ASBO.

Methods: The study's internal cohort consisted of 190 ASBO patients recruited from October 2017 to November 2021, subsequently partitioned into training ($n = 133$) and internal validation ($n = 57$) groups at a 7:3 ratio. An additional external cohort comprised 52 patients. Body composition assessments were conducted at the third lumbar vertebral level utilizing CT images. Baseline characteristics alongside systemic inflammatory responses were meticulously documented. Through univariable and multivariable regression analyses, risk factors pertinent to postoperative complications were identified, culminating in the creation of a predictive nomogram. The nomogram's precision was appraised using the concordance index (C-index) and the area under the receiver operating characteristic (ROC) curve.

Results: Postoperative complications were observed in 65 (48.87%), 26 (45.61%), and 22 (42.31%) patients across the three cohorts, respectively. Multivariate analysis revealed that nutrition risk score (NRS), intestinal strangulation, skeletal muscle index (SMI), subcutaneous fat index (SFI), neutrophil-lymphocyte ratio (NLR), and lymphocyte-monocyte ratio (LMR) were independently predictive of postoperative complications. These preoperative indicators were integral to the nomogram's formulation. The model, amalgamating body composition and inflammatory-nutritional indices, demonstrated superior performance: the internal training set exhibited a 0.878 AUC (95% CI, 0.802–0.954), 0.755 accuracy, and 0.625 sensitivity; the internal validation set displayed a 0.831 AUC (95% CI, 0.675–0.986), 0.818 accuracy, and 0.812 sensitivity. In the external cohort, the model yielded an AUC of 0.886 (95% CI, 0.799–0.974), 0.808 accuracy, and 0.909 sensitivity. Calibration curves affirmed a strong concordance between predicted outcomes and actual events. Decision curve analysis substantiated that the model could confer benefits on patients with ASBO.

Conclusion: A rigorously developed and validated nomogram that incorporates body composition and inflammatory-nutritional indices proves to be a valuable tool for anticipating postoperative complications in ASBO patients, thus facilitating enhanced clinical decision-making.

KEYWORDS

body composition, inflammatory-nutritional markers, adhesive small bowel obstruction, postoperative complications, prediction

Introduction

Adhesive small bowel obstruction (ASBO) ranks as a leading cause of emergency hospital admissions and surgeries (1). Despite advancements in surgical methods, treatment for ASBO patients may lead to extended hospital stays, increased healthcare costs, and notably high morbidity (48%) and mortality rates (5%) (2, 3). The incidence of postoperative complications significantly impacts patients' postoperative quality of life, an essential metric in evaluating therapeutic effectiveness. Clavien et al. introduced a surgical complications classification system that aids in accurately assessing outcomes across different treatment approaches (4). While the American College of Surgeons National Surgical Quality Improvement Project (NSQIP) is a prevalent risk prediction tool, its complexity and potential inaccuracies render it less suitable for specific patient populations (5).

To date, no universally accepted risk prediction system exists for ASBO patients. Developing a model to forecast postoperative complications and identify risk factors is crucial. Growing evidence suggests that the prognosis and progression of bowel obstruction are linked not only to bowel dysfunction but also to systemic inflammatory responses (6–8). The persistent obstruction leads to digestive tract dilation, intestinal barrier compromise, microbial translocation, and infiltration of inflammatory cells like neutrophils, lymphocytes, platelets, and monocytes, indicative of inflammatory responses in clinical settings (9, 10). Recent research has explored the connection between patient outcomes and various inflammatory-nutritional scores in small bowel obstruction cases (11, 12). These studies have examined scores such as the neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), monocyte–lymphocyte ratio (MLR), the albumin–alkaline phosphatase ratio (ALP), systemic immune-inflammation index (SII), and prognostic nutritional index (PNI). These calculated indicators, including NLR and PLR, have proven more sensitive than singular hematological markers like C-reactive protein (CRP) or lymphocyte count in reflecting the inflammatory response and predicting disease progression (13).

Nutritional status is a critical determinant for ASBO, influencing disease progression and patient prognosis (14, 15). Lee et al. demonstrated that nutritional data, such as body mass index (BMI) and weight loss, are correlated with an increased risk of major complications in ASBO patients (16). However, this study did not provide detailed quantitative insights into nutritional status. The widespread adoption of computed tomography (CT) has advanced body composition research, offering more granular insights than traditional metrics like BMI and weight fluctuation (17). CT-based multiple body composition parameters are usually obtained from the images at the level of third lumbar vertebra (L3), which focus on skeletal muscle and adipose tissue (18). These parameters offer superior informativeness in defining nutrition related disorders such as sarcopenia, visceral obesity and sarcopenic obesity, and are associated with adverse outcomes in several gastrointestinal diseases (19, 20).

Despite numerous studies exploring the links between individual nutritional and inflammatory markers and surgical outcomes, comprehensive research integrating laboratory and CT-derived body composition data for ASBO patients is scant. We conducted a systematic and thorough collection of body composition and systemic inflammatory markers (NLR, PLR, LMR, SII, PNI) data to explore their associations. Furthermore, a nomogram was developed to ascertain their predictive capacity for postoperative complications in ASBO patients.

Materials and methods

Patients

This study adheres to the principles of the Declaration of Helsinki. We retrospectively reviewed cases of ASBO from October 2017 to November 2021, utilizing our center's clinicopathologic database. The inclusion criteria were: (1) diagnosis of ASBO based on clinical or radiological evidence; (2) undergoing emergent surgery due to ASBO; (3) availability of abdominal CT scans and comprehensive hematological indices during hospitalization preoperatively. Exclusion criteria included: (1) conditions that could affect peripheral blood cell counts, such as autoimmune diseases, leukemia, and other hematological malignancies; (2) small bowel obstruction due to primary tumors, hernias, or inflammatory bowel disease; (3) lack of complete clinical data; and (4) age under 18 years. The participants were subsequently divided into training ($n = 133$) and internal validation ($n = 57$) cohorts at a 7:3 ratio. A total of 52 patients were enrolled in the external validation cohort from the Central Hospital Affiliated to Shandong First Medical University between January 2022 and January 2023. Figure 1 illustrates the flowchart of patient selection.

Date collection

This retrospective study extracted basic clinical data, including age, sex, BMI, symptoms, comorbidities, nutritional risk score (NRS), American Society of Anesthesiologists (ASA) score, intraoperative findings, and related laboratory indicators from the de-identified

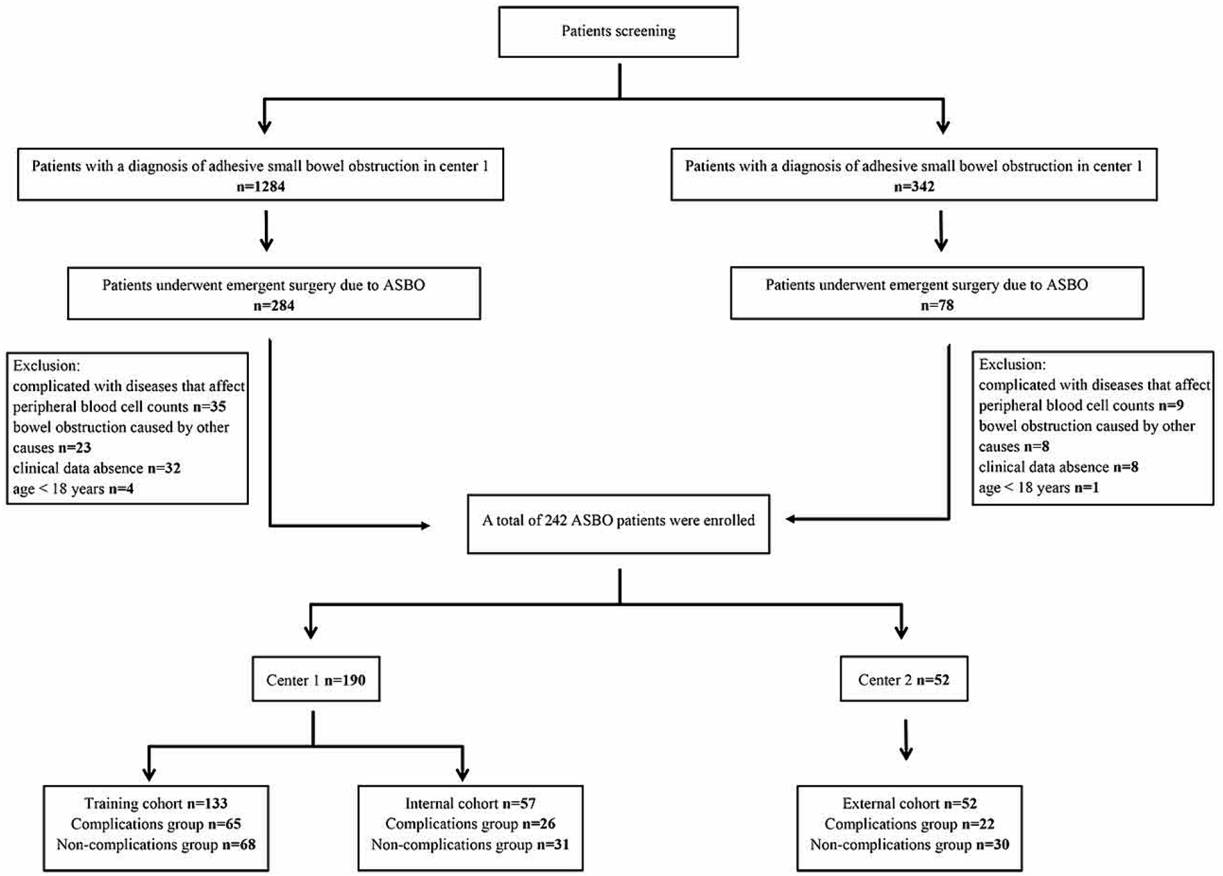

FIGURE 1
Flowchart for selecting the study population.

database and electronic medical record system. Inflammatory-nutritional markers were determined as follows: NLR = N/L, PLR = P/L, LMR = L/M; SII=P × N/L; PNI = albumin (g/L) +5 × L (109/L), where N: neutrophil count, L: lymphocyte [109]/L; P: platelet count, M: monocyte count (21, 22).

Evaluation of CT-based body composition

Using the institutional PACS (Picture Archiving and Communication System), postoperative L3 CT images were obtained for each patient. Slicer O Matic software (version 5.0)[1] was used for assessing body composition. The CT Hounsfield units (HU) thresholds were set at −190 to −30 for intermuscular and subcutaneous adipose tissue, −150 to −50 for visceral adipose tissue, and −29 to +150 for skeletal muscle area (23). The evaluation areas were delineated by two experienced radiologists who were blinded to the clinical characteristics of the patients. The body composition indexes (cm^2/m^2), including skeletal muscle index (SMI), subcutaneous fat index (SFI), visceral fat index (VFI), and intermuscular adipose tissue index (IFI), were defined as the body composition area (cm^2) by height squared (m^2). Figure 2 presents a schematic diagram of the study workflow.

Definitions of postoperative complications

Postoperative complications were classified according to the Clavien–Dindo classification (4). Our analysis focused on complications that occurred within 1 month after the surgical procedure. In cases where a patient experienced multiple complications either simultaneously or sequentially, the most severe complication was selected as the primary outcome for this study.

Statistical analysis

Statistical analysis was conducted using R software version 3.6.3[2] and SPSS version 25.0. We utilized the Kolmogorov–Smirnov test to assess the normal distribution of texture features. Intergroup categorical variables were examined using Fisher's exact tests and Chi-square tests, while independent-sample *t*-tests were applied for

1 http://www.tomovision.com

2 https://www.r-project.org

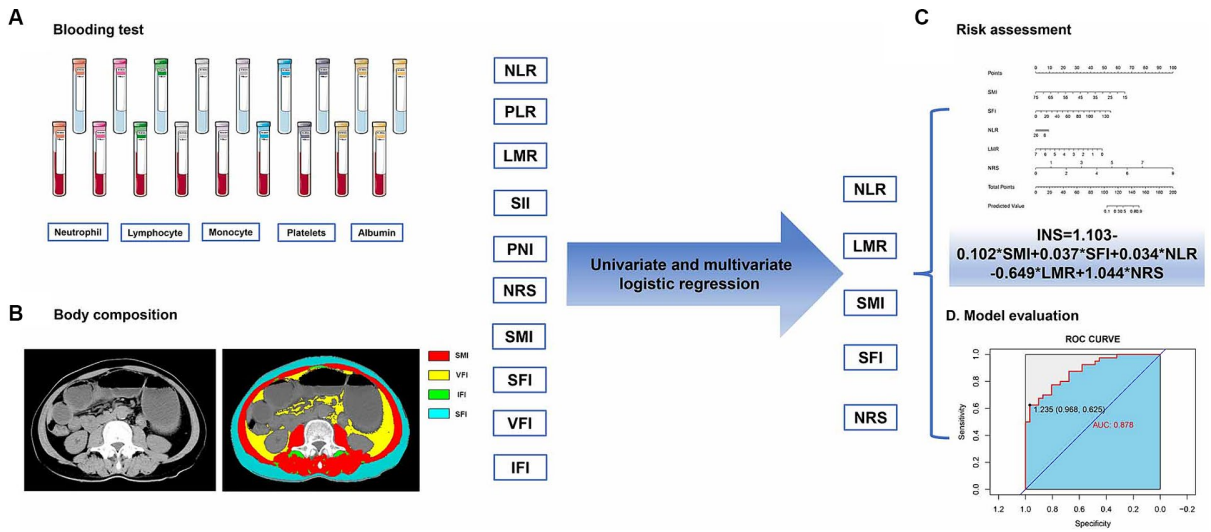

FIGURE 2
The process of analyzing inflammatory-nutritional markers, from data collection to model creation, involves: **(A)** blood test, **(B)** body composition, **(C)** risk assessment, and **(D)** model evaluation.

continuous variables. The "rms" R package facilitated the generation of ROC curves, areas under the curves (AUCs), a nomogram, and corresponding calibration curves (24, 25). The "rmda" package was employed for decision curve analysis (DCA) (26). A *p*-value of less than 0.05 was considered statistically significant.

Results

Characteristics of enrolled patients

In total, 190 patients with ASBO were included in the study (96 men and 94 women; average age 62.48 ± 13.50 years). They were randomized into training ($n = 133$) and internal validation ($n = 57$) cohorts at a 7:3 ratio. An external validation cohort comprised 52 patients from another center. Basic characteristics of the three cohorts are presented in Table 1. In the training cohort, 65 patients (48.87%; 35 men and 30 women; average age 63.20 ± 13.73 years) experienced complications, compared to 26 patients (45.61%; 15 men and 11 women; average age 67.46 ± 15.85 years) in the internal validation cohort. The external validation cohort included 22 patients (42.31%; 12 men and 10 women; average age 61.23 ± 10.70 years) with complications. Factors such as preoperative infection, ASA score, NRS, intestinal strangulation, CRP, NLR, PLR, LMR, SII, PNI, SMI, and SFI showed a significant correlation with postoperative complications in the training set ($p < 0.05$).

Overview of complications

The incidence of complications across different grades did not significantly differ among the three cohorts ($p > 0.05$) (Table 2). There were 37 (27.82%), 14 (24.56%), and 13 (25%) patients who experienced severe complications (Grade III or higher) in training, internal validation, and external validation cohorts, demonstrating comparable rates of severe complications.

Univariate and multivariate analysis of inflammatory-nutritional markers

Table 3 indicates significant differences between the two groups in preoperative infection, ASA score, NRS, intestinal strangulation, CRP, NLR, PLR, LMR, SII, PNI, SMI, and SFI, as identified by univariate regression in the training cohort ($p < 0.05$). These variables with *p*-values less than 0.05 were subsequently included in the multivariate regression analysis. Our findings reveal that NRS (OR = 21.731, $p = 0.002$), intestinal strangulation (OR = 401.665, $p = 0.008$), NLR (OR = 4.264, $p = 0.029$), LMR (OR = 0.183, $p = 0.034$), SMI (OR = 0.708, $p = 0.008$), and SFI (OR = 1.115, $p = 0.014$) are independent predictors of postoperative complications.

Inflammatory-nutritional model construction and verification

Figure 3 presents a correlation matrix of inflammatory-nutritional biomarkers, with correlation coefficients ranging from −1 (red) to 1 (blue) in training and validation sets. Hemoglobin (HB) was found to be correlated with SMI in both the training [Pearson Correlation Coefficient (PCC) = 0.196, $p = 0.023$] and internal validation sets (PCC = 0.348, $p = 0.008$), as shown in Supplementary Tables S1–S3. To avoid multicollinearity, the inflammatory-nutritional model was constructed using indicators with a PCC below 0.7 (27).

A nomogram derived from the multivariate analysis was developed, incorporating NRS, NLR, PLR, SMI, and SFI. Each patient's total score was calculated by summing the scores of these five predictive factors, which were then used to evaluate the risk of postoperative complications. A higher total score correlated positively with an increased probability of postoperative complications (Figure 4A). The inflammatory-nutritional score (INS) was calculated as 1.103–0.102*SMI + 0.037*SFI + 0.034*NLR-0.649*LMR + 1.044*NRS. Calibration curves demonstrated good agreement in three

TABLE 1 Clinical characteristics of patients in this study.

	Training set		*p* value	Internal validation set		*p* value	External validation set		*p* value
	Complications group (*n* = 65)	Non-complications group (*n* = 68)		Complications group (*n* = 26)	Non-complications group (*n* = 31)		Complications group (*n* = 22)	Non-complications group (*n* = 30)	
Age (years), mean (SD)	63.20 (13.73)	60.93 (12.48)	0.319	67.46 (15.85)	60.23 (12.46)	0.059	61.23 (10.70)	59.37 (11.61)	0.558
Gender, *n* (%)			0.300			0.790			0.575
Male	35 (53.85%)	30 (44.12%)		15 (57.69%)	16 (51.61%)		12 (54.55%)	13 (43.33%)	
Female	30 (46.15%)	38 (55.88%)		11 (42.31%)	15 (48.39%)		10 (45.45%)	17 (56.67%)	
BMI (kg/m^2), mean (SD)	20.97 (3.48)	22.01 (3.39)	0.122	21.86 (3.69)	21.54 (3.25)	0.745	21.81 (3.83)	22.11 (2.95)	0.779
Manifestations									
Obstruction time (d), mean (SD)	7.32 (9.67)	9.33 (12.95)	0.313	5.77 (6.25)	6.39 (6.66)	0.724	5.68 (6.64)	5.13 (5.79)	0.752
Vomit, *n* (%)	40 (61.54%)	47 (69.12%)	0.369	14 (53.85%)	20 (64.52%)	0.432	18 (81.82%)	20 (66.67%)	0.344
Abdominal pain, *n* (%)	58 (89.23%)	66 (97.06%)	0.092	23 (88.46%)	30 (96.77%)	0.322	22 (100%)	28 (93.33%)	0.502
Abdominal distention, *n* (%)	53 (81.54%)	50 (73.53%)	0.304	20 (76.92%)	25 (80.65%)	0.755	16 (72.73%)	18 (60%)	0.390
No exhaust or defecation, *n* (%)	36 (55.38%)	33 (48.53%)	0.489	18 (69.23%)	16 (51.61%)	0.278	12 (54.55%)	11 (36.67%)	0.262
Commodities									
Hypertension, *n* (%)	13 (20.00%)	18 (26.47%)	0.417	7 (26.92%)	6 (19.35%)	0.541	7 (31.82%)	8 (26.67%)	0.762
Diabetes mellitus, *n* (%)	7 (10.77%)	4 (5.88%)	0.358	5 (19.23%)	3 (9.68%)	0.448	1 (4.55)	2 (6.67%)	0.999
Coronary disease, *n* (%)	4 (6.15%)	4 (5.88%)	0.999	5 (19.23%)	2 (6.45%)	0.228	3 (13.64%)	2 (6.67%)	0.639
Preoperative infection, *n* (%)	10 (15.38%)	2 (2.94%)	0.015*	6 (23.08%)	1 (3.23%)	0.045*	4 (18.18%)	2 (6.67%)	0.382
ASA score, mean (SD)	2.97 (0.59)	2.72 (0.54)	0.012*	3.15 (0.73)	2.74 (0.51)	0.016*	3.00 (0.44)	2.77 (0.43)	0.062
NRS, mean (SD)	4.08 (1.80)	2.13 (1.33)	0.001*	3.56 (1.67)	2.59 (1.04)	0.050*	4.09 (1.27)	3.17 (0.70)	0.004*
Intraoperative findings									
Enterotomy, *n* (%)	35 (53.85%)	25 (36.76%)	0.056	17 (65.38%)	15 (48.39%)	0.284	11 (50%)	8 (26.67%)	0.144
Intestinal strangulation, *n* (%)	21 (32.31%)	11 (16.18%)	0.042*	12 (46.15%)	6 (19.35%)	0.045*	7 (31.82%)	4 (13.33%)	0.169
HB (g/L), mean (SD)	116.83 (20.68)	116.04 (24.41)	0.841	121.15 (17.93)	124.65 (20.87)	0.505	117.91 (24.86)	125.70 (23.32)	0.253
CRP (mg/L), mean (SD)	45.50 (47.83)	22.36 (34.62)	0.003*	47.45 (53.73)	34.71 (57.33)	0.405	86.04 (102.24)	10.63 (18.05)	0.002*
NLR, mean (SD)	6.83 (5.83)	4.78 (4.27)	0.022*	8.41 (7.21)	5.09 (3.28)	0.037*	9.79 (8.64)	3.34 (4.23)	0.001*
PLR, mean (SD)	318.43 (226.02)	231.24 (111.59)	0.006*	296.09 (191.32)	224.65 (108.02)	0.099	321.80 (315.97)	181.19 (117.61)	0.058
LMR, mean (SD)	2.19 (1.43)	2.83 (1.45)	0.011*	2.27 (1.93)	2.75 (2.04)	0.367	2.44 (2.22)	4.30 (2.32)	0.005*
SII, mean (SD)	1734.83 (1692.46)	1126.24 (1060.17)	0.015*	2228.30 (2185.85)	1101.10 (729.05)	0.018*	2018.78 (1623.55)	839.09 (1494.27)	0.010*
PNI, mean (SD)	39.12 (6.48)	41.73 (8.17)	0.044*	40.31 (9.40)	40.44 (7.48)	0.953	40.16 (12.06)	45.59 (7.66)	0.053
SMI (cm^2/m^2), mean (SD)	33.58 (8.76)	38.86 (10.07)	0.002*	32.40 (8.64)	39.30 (9.59)	0.007*	32.87 (7.25)	40.58 (9.01)	0.002*
IFI (cm^2/m^2), mean (SD)	3.03 (2.37)	2.75 (2.31)	0.500	3.02 (2.88)	2.48 (2.39)	0.442	3.29 (3.25)	2.54 (2.15)	0.353
SFI (cm^2/m^2), mean (SD)	39.72 (25.02)	31.51 (18.59)	0.034*	42.44 (19.43)	28.06 (16.51)	0.004*	39.59 (16.98)	30.11 (14.54)	0.035*
VFI (cm^2/m^2), mean (SD)	23.16 (19.98)	23.29 (17.75)	0.968	26.12 (23.44)	24.17 (18.24)	0.726	26.44 (19.66)	18.63 (13.53)	0.095

*$p < 0.05$.

BMI, body mass index; ASA, American Society of Anesthesiologists; NRS, nutritional risk score; HB, hemoglobin; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; SMI, skeletal muscle index; IFI, intermuscle fat index; SFI, subcutaneous fat index; VFI, visceral fat index.

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TABLE 2 Thirty-day postoperative complications.

	Training set (n = 133)	Internal validation set (n = 57)	External validation set (n = 52)	p value
Overall postoperative complication	65 (48.87%)	26 (45.61%)	22 (42.31%)	0.711
Grade I	11 (8.27%)	5 (8.77%)	4 (7.69%)	0.979
Superficial wound infection	3	1	0	
Electrolyte imbalance	8	4	4	
Grade II	17 (12.78%)	7 (12.28%)	5 (9.62%)	0.835
Ileus (treated conservatively)	4	0	0	
Intraperitoneal hemorrhage (necessitating transfusion)	2	2	1	
Fever with antibiotics	4	2	3	
Respiratory infection	6	2	1	
Urinary infection	1	1	0	
Grade III	24 (18.05%)	6 (10.53%)	5 (9.62%)	0.214
Wound infection (necessitating reoperation)	7	1	3	
Intraperitoneal hemorrhage (necessitating reoperation)	2	2	0	
Intraperitoneal infection (necessitating reoperation)	8	1	0	
Ileus (necessitating reoperation)	3	2	1	
Intestinal fistula (necessitating reoperation)	4	0	1	
Grade IV	11 (8.27%)	7 (12.28%)	8 (15.38%)	0.340
Respiratory failure	1	1	2	
Cardiac failure	2	1	1	
Renal failure	0	1	1	
Multiple organ dysfunction syndrome	8	4	4	
Grade V	2 (1.50%)	1 (1.75%)	0	0.594
Death	2	1	0	

The definition of complications was given in the article.

cohorts (Figures 4B–D). Validation was conducted using the bootstrap method, and model performance was assessed over 1,000 iterations.

Evaluating predictive performance of the three models

Based on inflammatory-nutritional markers, we established an inflammatory model (NLR, PLR, LMR, SII, PNI) and nutritional model (SMI, IFI, SFI, VFI). ROC analysis revealed that the nomogram achieved AUCs of 0.878 (95% CI, 0.802–0.954) in the training set, 0.831 (95% CI, 0.675–0.986) in the internal validation set, and 0.886 (95% CI, 0.799–0.974) in the external validation set. These results surpassed those of the inflammatory model (0.648, 95% CI 0.554–0.742) and the nutritional model (0.674, 95% CI 0.583–0.766) in the training set, 0.655 (95% CI 0.508–0.802) and 0.766 (95% CI 0.642–0.889) in the internal validation set, and 0.814 (95% CI 0.695–0.933) and 0.811 (95% CI 0.689–0.932) respectively (Figures 5A–C) in the external validation set. Decision curve analysis (DCA) indicated that our nomogram achieved greater net benefits at optimal threshold probabilities in predicting complications in ASBO cases (Figures 5D–F). Table 4 details the predictive performance of the inflammatory model, nutritional model, and nomogram in three cohorts.

Discussion

The choice between conservative management and surgical intervention for ASBO patients continues to be debated. Previous research indicated that the method of treatment correlates with postoperative complications in ASBO patients (28, 29). In our study, 113 of the 242 ASBO patients (46.69%) encountered complications (30). This significant rate of postoperative complications adversely affects ASBO patient outcomes, underscoring the necessity for a predictive model to foresee these complications and assist in clinical decision-making (31). Our current research, involving 242 ASBO patients, validated the efficacy of a nomogram that incorporates CT-based body composition and inflammatory-nutritional markers. This model, easy to compute, holds broad applicability in clinical practice.

Increasing evidence suggests that poor nutritional status is a prognostic risk factor for various gastrointestinal disorders, encompassing both malignancies and benign conditions (14, 32, 33). In ASBO cases, impaired intestinal function curtails the efficacy of standard enteral interventions in swiftly rectifying malnutrition, elevating the risk of severe malnutrition and impeding potential enhancements in nutritional status due to acute gastrointestinal failure (34). Consequently, clinicians are in pursuit of reliable indicators to accurately evaluate the nutritional status of ASBO patients (35).

TABLE 3 Univariate and multivariate analysis of patients with complications versus those without in the training set.

	Univariate analysis				Multivariate analysis			
	SE	Exp(B)	*p* value	95%CI	SE	Exp(B)	*p* value	95%CI
Preoperative infection, *n* (%)	0.796	6.000	0.024	1.261–28.547	2.360	69.815	0.072	0.684–7122.731
ASA score, mean (SD)	0.340	2.268	0.016	1.166–4.414	1.363	2.077	0.592	0.144–30.020
NRS, mean (SD)	0.219	2.278	0.001	1.484–3.497	0.995	21.731	0.002	3.092–152.746
Intestinal strangulation, *n* (%)	0.423	2.473	0.032	1.080–5.665	2.262	401.665	0.008	4.774–33797.868
CRP (mg/L), mean (SD)	0.005	1.014	0.005	1.004–1.024	0.019	1.036	0.065	0.998–1.075
NLR, mean (SD)	0.038	1.086	0.028	1.009–1.169	0.663	4.264	0.029	1.162–15.648
PLR, mean (SD)	0.001	1.004	0.008	1.001–1.006	0.005	1.004	0.388	0.994–1.015
LMR, mean (SD)	0.129	0.728	0.014	0.566–0.938	0.800	0.183	0.034	0.038–0.879
SII, mean (SD)	0.000	1.000	0.020	0.999–1.000	0.004	1.004	0.074	1.000–1.009
PNI, mean (SD)	0.025	0.952	0.049	0.906–1.000	0.112	0.834	0.105	0.670–1.039
SMI (cm^2/m^2), mean (SD)	0.020	0.940	0.003	0.903–0.979	0.131	0.708	0.008	0.547–0.915
SFI (cm^2/m^2), mean (SD)	0.008	1.018	0.037	1.001–1.035	0.044	1.115	0.014	1.022–1.217

ASA, American Society of Anesthesiologists; NRS, nutritional risk score; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-monocyte ratio; SII, systemic immune inflammation index; PNI, prognostic nutritional index; SMI, skeletal muscle index; SFI, subcutaneous fat index.

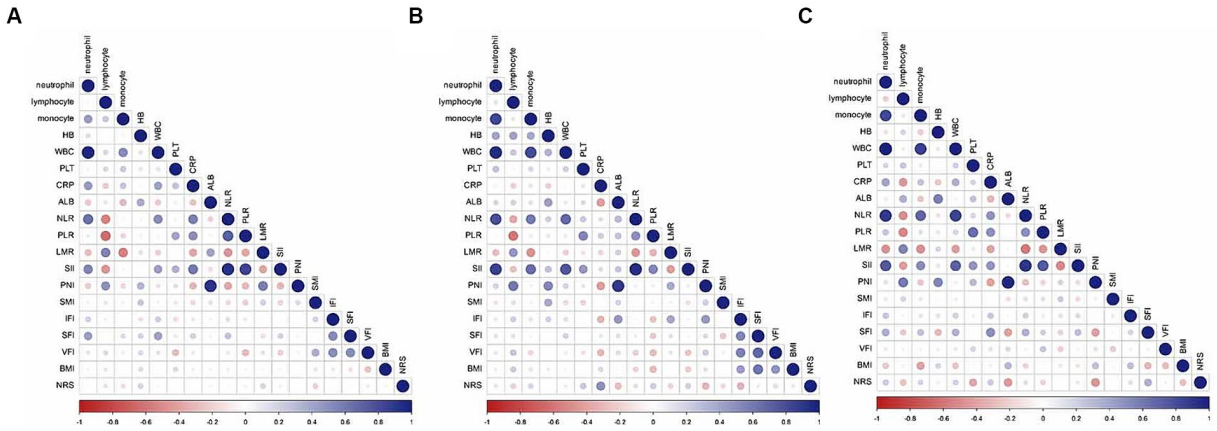

FIGURE 3
Correlation matrix of nutritional inflammatory biomarkers in the training **(A)**, internal validation **(B)**, and external validation **(C)** sets.

Although traditional nutritional assessment tools like body weight and BMI offer a general insight into an individual's nutritional status, they do not provide specific details on body composition, such as muscle mass or regional fat distribution. Recent research has increasingly acknowledged the pivotal role of body composition in determining a patient's nutritional state and postoperative outcomes (36, 37). Our study also showed that the SMIs of ASBO patients with complications were significantly lower than those of patients without complications ($p < 0.05$), and multivariable analysis confirmed this protective factor (OR = 0.708). This association indicated the importance of maintaining skeletal muscle mass quality for postoperative recovery of ASBO patients (38). Patients at a heightened risk of sarcopenia may undergo a persistent inflammatory response that disrupts normal nitrogen metabolism, increasing the likelihood of postoperative complications. This is consistent with prior findings that surgical patients with reduced skeletal muscle mass have poorer prognoses, encounter more postoperative complications, require more intensive care, and exhibit higher mortality rates (39, 40). Furthermore, our observations indicate that a high SFI correlates with postoperative complications in ASBO patients, adding to the discourse on the "obesity paradox" and supporting the notion that sarcopenic obesity is as indicative of surgical outcomes as sarcopenia alone, as several studies have previously reported (41, 42).

ASBO is often associated with acute inflammatory process, a key marker of disease progression. Mueller et al. discovered that as obstruction advances and intestinal barrier dysfunction ensues, luminal flora can penetrate the mucosal layer, triggering host immune responses (43). This uncontrolled inflammatory response is characterized by immune cells infiltration and the release of inflammatory mediators. Numerous systemic inflammatory response indicators, derived from serum biomarkers, have been developed to assess the extent of this response. In our study, systemic inflammatory response indicators, including CRP, PLR, NLR, LMR, PNI and SII, were examined. We found that patients with higher NLR and lower LMR values were more likely to experience

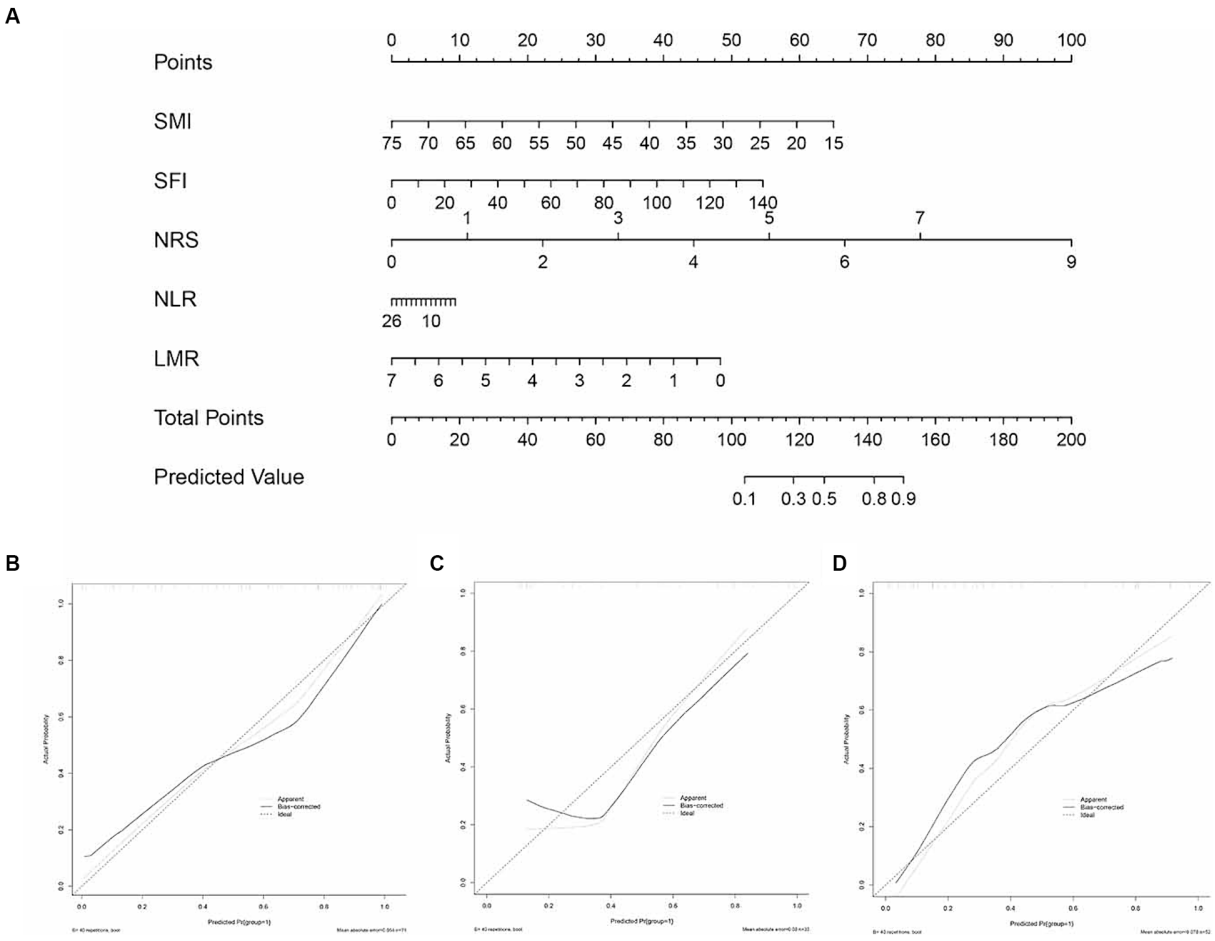

FIGURE 4
The inflammatory-nutrition nomogram and its calibration curves. **(A)** Development of the inflammatory-nutrition nomogram in the training set, incorporating SMI, SFI, NLR, PLR, and NRS. Calibration curves for the nomogram in the training **(B)**, internal validation **(C)**, and external validation **(D)** sets.

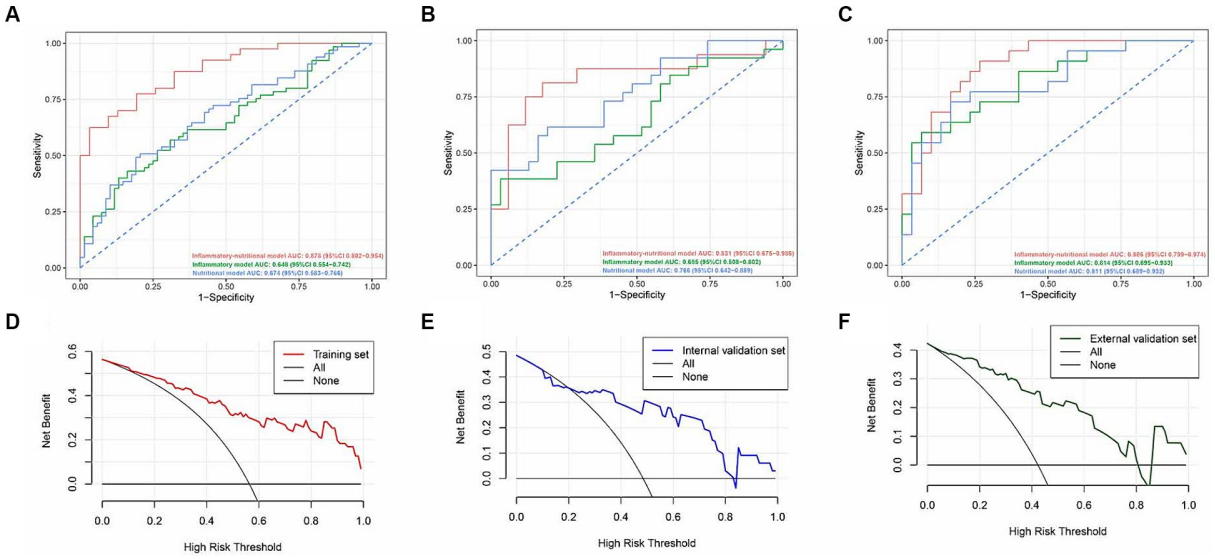

FIGURE 5
Receiver operating characteristic curves of the inflammatory-nutrition model, the inflammatory model, and the nutritional model in the training **(A)**, internal validation **(B)**, and external validation **(C)** sets. Decision curve analysis for the inflammatory-nutrition model in the training **(D)**, internal validation **(E)**, and external validation **(F)** sets.

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TABLE 4 Predictive performance of the three models in the training and validation sets.

	Training set (n = 133)						Internal validation set (n = 57)						External validation set (n = 52)					
	AUC (95%CI)	ACC	SEN	SPE	PPV	NPV	AUC (95%CI)	ACC	SEN	SPE	PPV	NPV	AUC (95%CI)	ACC	SEN	SPE	PPV	NPV
Inflammatory model	0.648 (95%CI 0.554–0.742)	0.639	0.431	0.838	0.718	0.606	0.655 (95%CI 0.508–0.802)	0.702	0.385	0.968	0.909	0.652	0.814 (95%CI 0.695–0.933)	0.788	0.591	0.933	0.867	0.757
Nutritional model	0.674 (95%CI 0.583–0.766)	0.654	0.508	0.794	0.702	0.628	0.766 (95%CI 0.642–0.889)	0.737	0.423	0.999	0.999	0.674	0.811 (95%CI 0.689–0.932)	0.788	0.727	0.833	0.762	0.806
Inflammatory-nutritional model	0.878 (95%CI 0.802–0.954)	0.755	0.625	0.968	0.962	0.667	0.831 (95%CI 0.675–0.986)	0.818	0.812	0.824	0.812	0.824	0.886 (95%CI 0.799–0.974)	0.808	0.909	0.733	0.714	0.917

AUC, area under the curve; CI, confidence interval; ACC, accuracy; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value.

postoperative complications, corroborating previous findings that NLR and LMR are crucial indicators for predicting disease severity and prognosis in cancer patients (12, 44, 45). NLR and LMR calculations involve neutrophils, lymphocytes, and monocytes. Changes in NLR and LMR values generally reflect disturbances in these immune cell types and their prognostic significance, linked to the effects of such cells. Neutrophil and monocyte activation, a response to infection signals, is a fundamental component of the innate immune response phase and is implicated in the pathogenesis of various diseases (46). A decrease in lymphocyte count, indicating impaired immune function, hampers the body's ability to combat persistent infections (11, 47, 48). In recent years, the interplay between inflammation and nutrition has gained significant attention. The volume of research examining the impact of nutrition on the immune system is continuously expanding (49, 50). On correlation analysis, we also found HB and SMI were positively correlated (Supplementary Table S1) which implied the underlying mechanistic association between anemia and sarcopenia in ASBO settings. Consistent with the findings of Hirani's study, lower HB levels might contribute to a decrease in skeletal muscle volume, through biological pathways generally involving decreased oxygenation of skeletal muscle tissues (51). Anemia caused by ASBO may impair oxygen delivery and expenditure within muscle tissues, creating hypoxia within the local microenvironment that undermines the function of skeletal muscle cells, ultimately leading to skeletal muscle loss and sarcopenia.

The findings from our multivariate and correlation analyses have paved the way for the development of a practical predictive model for postoperative complications in ASBO patients. This model aims to identify those at heightened risk for such complications. While most previous studies have focused on the predictive power of single inflammatory–nutritional scores or CT composition indices on prognosis (45, 52), these singular measures often fail to provide a comprehensive and accurate representation of a patient's entire inflammatory-nutritional status, thereby limiting their practical accuracy (21). Recently, there has been a trend toward developing prognostic scores based on multiple inflammatory-nutrition indices. For instance, Wang et al. created a prognostic score incorporating LMR, NLR, and PLR to predict outcomes for gastrectomy patients' post-chemotherapy, with their nomogram demonstrating superior predictive performance (C-index 0.707) compared to single-index models (53). Our previous research utilized multiple inflammatory-nutritional scores to construct a model for predicting postoperative quality of life in gastric cancer patients (22). In this study, we initially attempted to create an inflammation-based model (Inflam-model) using inflammatory scores (Inflam-scores) and a radiography-based model (Radio-model) using body composition parameters. However, both models exhibited suboptimal performance. Consequently, we explored whether combining various inflammatory factors with nutrition-related indicators could enhance the predictive accuracy for ASBO patients. We selected significant inflammatory-nutritional and radiographic indicators from the multivariable analysis to construct a combined predictive model. Our risk predictive model, integrating two Inflam-scores, two Radio-scores, and NRS, showed improved performance in both cohorts. These Radio-scores and Inflam-scores, derived from routine clinical practice, make this multiparametric model practical, particularly in preoperative settings. Identifying patients with a high inflammatory state and low nutritional status preoperatively is crucial in clinical practice. Accordingly, prognosis may be improved through prompt and effective therapeutic interventions.

This study has several limitations. Firstly, the sample size was comparatively small, indicating the necessity for subsequent multicenter studies with expanded sample sizes. Secondly, the expansion of the intestine lumen within the abdominal cavity may affect the accuracy of visceral adipose tissue detection on CT images. Relying solely on measurements of visceral adipose tissue in single CT slides may not sufficiently predict postoperative outcomes. Dynamic and comprehensive assessments of whole-body composition warrant further study. Thirdly, although the correlation between the inflammatory and nutritional factors identified in ultimate model was investigated initially, the causal relationship of these factors is unknown, which might have impact on clinical management. Some promising new statistical methods could assist in quantifying robustness of causal inferences in future research (54).

Conclusion

In summary, we have developed and validated a nomogram that incorporates CT body composition data and inflammatory–nutritional scores to predict postoperative complications in patients with ASBO. Given its usability and the positive results achieved in our initial cohort, this model demonstrates potential as an effective tool for guiding nutritional treatment and decision-making in ASBO cases in future clinical settings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

ZW: Data curation, Writing – original draft. BS: Formal analysis, Methodology, Writing – original draft. YY: Formal analysis, Writing – original draft. JL: Validation, Writing – original draft. DL: Formal analysis, Writing – review & editing. YL: Writing – review & editing. RL: Funding acquisition, Writing – review & editing.

Ethics statement

The studies involving humans were approved by The Affiliated Hospital of Qingdao University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1345570/full#supplementary-material

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Glossary

ASBO	Adhesive small bowel obstruction
NLR	Neutrophil-lymphocyte ratio
PLR	Platelet–lymphocyte ratio
LMR	Lymphocyte-monocyte ratio
SII	Systemic immune-inflammation index
PNI	Prognostic nutritional index
CRP	C-reactive protein
BMI	Body mass index
CT	Computed tomography
ASA	American society of anesthesiologists
NRS	Nutritional risk score
SMI	Skeletal muscle index
SFI	Subcutaneous fat index
IFI	Intermuscular fat index
VFI	Visceral fat index
INS	Inflammatory-nutritional score
ROC	Receiver-operating characteristic
DCA	Decision curve analysis
OR	Odds ratio

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The relationship between baseline nutritional status with subsequent parenteral nutrition and clinical outcomes in cancer patients undergoing cytoreductive surgery: a retrospective study

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Introduction: Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with Cytoreductive Surgery (CRS) is the preferred treatment for peritoneal malignancies. This highly complex operation is associated with a high incidence of complications, particularly due to malnutrition. This study aimed to investigate the potential association between preoperative nutritional status and postoperative clinical outcomes in adult cancer patients who underwent CRS/HIPEC for peritoneal malignancy.

Methods: A retrospective study with 140 adult cancer patients, on parenteral nutrition (PN) (n=40) and not on PN (n=100) who underwent CRS with or without HIPEC, was conducted.

Results: Patients who received PN had significantly longer post-operative, hospital, and ICU LOS than those who did not (p=0.001). ICU admission was significantly higher in the non-PN receiving group compared to the PN receiving group. When compared to the PN group, the majority of patients not receiving PN were at low risk of malnutrition (91% vs. 75%, p=0.020), whereas 17.5% of PN patients were at risk of malnutrition during hospitalization. Multiple regression analyses revealed a strong positive relationship between patients with increased risk of malnutrition and ICU LOS (p=0.047).

Discussion: Routine preoperative nutrition assessment is essential to identify patients who are at higher nutritional risk, and nutrition support should be provided preoperatively.

KEYWORDS

nutritional status, cancer, parenteral nutrition, cytoreductive surgery, hyperthermic

1 Introduction

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with Cytoreductive Surgery (CRS) is the preferred treatment for peritoneal mesothelioma, pseudomyxoma peritonei, peritoneal carcinomatosis, and other peritoneal malignancies (1). The CRS aims to reduce the residual tumor volume by the aggressive resection of visceral and peritoneal components, followed by HIPEC administration to minimize the incidence of postoperative adverse events. This complex medical operation is associated with a high incidence of significant gastrointestinal complications. Patients with abdominopelvic malignancy, who undergo CRS/HIPEC, experience high risk of mortality, prolonged hospital length of stay (LOS), and morbidity, particularly due to malnutrition (2). Multiple evidence have also revealed a 0.9–5.8% mortality rate and a 12–60% morbidity rate following the implementation of the CRS/HIPEC procedure (3). Most importantly, chemotherapy can further add to the incidence of systemic toxicity and postoperative complications. Evidence have demonstrated that these outcomes have a detrimental impact on the overall health-related quality of life and nutritional status of the treated patients (4).

Peritoneal carcinomas have been reported to be associated with 60–80% incidence of malnutrition. This emphasizes the significance of providing appropriate nutrition support to minimize the risk of clinical complications (5, 6). Nonetheless, evidence in the current literature concerning the clinically significant relationship between postoperative outcomes and the nutrition status of patients treated with CRS/HIPEC is scarce (7). Recent retrospective study has demonstrated enteral nutrition to be a protective factor for LOS in patients with pseudomyxoma peritonei treated with CRS/HIPEC (8). The conclusion from another real-world study has also indicated the possible association of the postoperative parenteral nutrition (PN) requirement with the operative and nutritional factors in the setting of CRS (9). Furthermore, findings from other studies emphasized poor nutritional status as a preoperative factor, which deteriorates the postoperative clinical outcomes after CRS/HIPEC administration (10). A prospective observational study has additionally reported a clinically significant relationship between postoperative outcomes, such as LOS and infections, and preoperative malnutrition in patients with peritoneal malignancies (2). This great amount of evidence claimed the importance of optimizing perioperative nutritional support to reduce the incidence of postoperative complications and improve postoperative recovery in patients undergoing CRS/HIPEC (11). This could be potentially established by statistically comparing preoperative and postoperative nutritional parameters. To the best of our knowledge, no real-world studies have yet established a statistically meaningful association between PN and postoperative adverse events, comparing PN-related versus non-PN-related complications and their correlation with patients' preoperative (baseline) nutritional status in patients undergoing CRS/HIPEC. This virgin area of research could significantly enhance nutrition-based risk stratification, prognosis, and recovery patterns in patients requiring CRS/HIPEC. Furthermore, the assessment of the relationship between postoperative PN duration/optimal timing and patient's baseline nutrition levels is paramount to determining the high-risk patients (i.e., those with an increased predisposition for postoperative/hospital/intensive care unit (ICU) LOS and mortality). Improved clinical decision-making through nutritional screening could also effectively minimize postoperative outcomes in CRS/HIPEC patients, including the occurrence of serious/life-threatening complications. This single-center study was aimed to investigate the possible association between the preoperative nutritional status and postoperative clinical outcomes, as well as the incidence of PN-related and non-PN-related postoperative complications in adult cancer patients who underwent CRS/HIPEC for peritoneal malignancy.

2 Materials and methods

2.1 Study design and population

This single-center retrospective study has enrolled adult cancer patients (age > 18 years) who underwent CRS with or without HIPEC monotherapy, between January 2017 and December 2022 at King Saud University Medical City (KSUMC), Kingdom of Saudi Arabia. All included study participants had a clinician confirmed diagnosis of colorectal, gynecologic, appendiceal, and/or peritoneal malignancies. Study participants were divided into two groups: patients who received PN after procedure (i.e., PN group $n = 40$) and patients who did not receive PN after procedure (i.e., non-PN group $n = 100$). Patients started PN after being screened for their nutritional status using validated tools such as the Nutrition Risk Screening (NRS)-2002. Patients deemed at high risk of malnutrition based on their NRS scores were considered candidates for PN therapy to optimize their nutritional status during the perioperative period. Moreover, clinician discretion played a role in the decision-making process, with healthcare providers considering various clinical factors and patient-specific variables including severity and extent of disease, surgical complexity and duration, pre-existing nutritional deficiencies and comorbidities, anticipated postoperative recovery, and potential risks associated with inadequate oral intake. Approval of the study protocol was obtained from KSUMC Institutional Review Board (E-23-7718) before the commencement of the study, and all procedures were performed in accordance with the Declaration of Helsinki.

2.2 Clinical data and assessment tools

After screening, data on patients' demographics, baseline NRS, cancer site, type of surgery, postoperative and hospital LOS, ICU admission, oral intake, and enteral feeding were collected for all study participants. The primary outcome of interest was the association between baseline nutritional status and clinical outcomes in CRS/HIPEC patients who either received or did not receive PN. The secondary outcomes were postoperative PN-related complications, non-PN-related complications, and ICU admissions.

PN-related complications were defined as the composite of one or more of the following complications: hyperglycemia [fasting blood glucose>180 mg/dL (10 mmol/L)]; electrolyte imbalances, including Hyponatremia (Sodium <135 mmol/L), Hypernatremia (Sodium >145 mmol/L), Hypomagnesemia (Magnesium <0.7 mmol/L), Hypermagnesemia (Magnesium >1.10 mmol/L), Hypokalemia (Potassium <3.5 mmol/L), Hyperkalemia (Potassium >5.5 mmol/L), Hypophosphatemia (Phosphorus <0.8 mmol/L), Hyperphosphatemia (Phosphorus >1.45 mmol/L), Hypocalcemia (Calcium <2.2 mmol/L), and Hypercalcemia (Calcium >2.7 mmol/L); hypertriglyceridemia

(Triglycerides >150 mg/dL); hepatic steatosis (diagnosed as elevation in biochemical markers: aspartate transaminase (AST), alanine transaminase (ALT) >2x UNL or imaging Studies); or cholestasis [defined as increasing in biochemical markers, such as Total bilirubin (>2 mg/dL), Alkaline phosphatase (>1.5 x ULN), and gamma-glutamyl transpeptidase (GGT) (>3 x ULN) in patients receiving PN, and not due to other liver diseases or biliary obstruction].

Non-PN-related complications have also been assessed, which were defined as the composite of one or more of the following complications: catheter-related [catheter related bloodstream infection (CRBSI), cerebral venous thrombosis (CVT), pulmonary embolism (PE), or occlusion], infectious [wound related infection, bacteremia, or urinary tract infection (UTI)], hematological (leukopenia, leukocytosis, thrombocytopenia, or thrombocytosis) gastrointestinal (intra-peritoneal complications or chyle leaks), renal (AKI or azotemia), or death.

2.3 Nutritional status

The Nutrition Risk Screening (NRS)-2002, a simple and well-validated tool had been used to assess patients' nutritional status (12). It represented the sum of the nutritional, disease severity, and age adjustment scores. Scoring is categorized as Low-risk (score = 0–3: indicating weekly rescreening requirement), at-risk (score = 4, indicating the need to initiate nutritional care plan) (food, oral supplements, tube feeding, and/or parenteral nutrition as appropriate), and high-risk (score = 5–7, indicating the need to initiate early intervention nutritional care plan).

2.4 Statistical analysis

The patients' characteristics were summarized according to PN status and measured using descriptive statistics. The continuous variables were expressed as mean ± standard deviation or median [interquartile range (IQR)] depending on the data distribution. While categorical variables were expressed as numbers (percentages). The student's *t*-test was used to compare age, body mass index (BMI), and albumin level, whereas Mann–Whitney U-test was used to compare postoperative, hospital, and ICU LOS. Linear and logistic regression analyses were performed to measure the association between NRS and clinical outcomes in both PN groups. All data were analyzed using Statistical Package for Social Studies (SPSS v. 29; IBM Corp., New York, NY, United States).

3 Results

3.1 Baseline characteristics

A total of 140 patients who underwent CRS with or without HIPEC monotherapy or their combinations and met the study inclusion criteria were admitted in the study. Participants in the study were divided into two groups: PN group ($n = 40$) and non-PN group ($n = 100$). Demographic variables including age, gender, and BMI did not differ significantly between the two groups. However, significant difference was found in albumin levels ($p = 0.029$) among both groups. Colorectal cancer cases were higher and statistically significant in the non-PN group than in the PN group (62% vs. 37.5%, $p = 0.002$), however, appendix cancer cases were higher and statistically significant in the PN group ($p = 0.002$). The type of surgery performed in neither group was significantly different ($p = 0.712$). All the baseline characteristics of the study participants are presented in Table 1.

3.2 Postoperative nutritional and surgical outcomes

The postoperative nutritional and surgical outcomes for both study groups are shown in Table 2. Patients who received PN had significantly longer post-operative, hospital, and ICU LOS ($p = 0.001$) than those who did not receive PN. However, the number of ICU admission was considerably greater in the non-PN than in the PN group. When compared to those on PN, the majority of patients in the non-PN group were at low risk of malnutrition according to the NRS criteria (91% vs. 75%, $p = 0.020$). On the other hand, 17.5% of PN patients were at risk of malnutrition during hospitalization, compared to 4% of non-PN patients.

Subgroup analysis of the PN group for the parenteral nutrition formula composition revealed that the median duration of the PN was

TABLE 1 Baseline characteristics of the study participants receiving and not receiving PN.

	Total ($n = 140$)	PN ($n = 40$)	Non-PN ($n = 100$)	*p*-value*
Age (years)[a]	53.14 ± 13	52 ± 12	53 ± 13	0.413
Gender, *N* (%)				0.280
Male	60 (42.9)	20 (50)	40 (40)	
Female	80 (57.1)	20 (50)	60 (60)	
BMI (Kg/m^2)[a]	27.75 ± 6.15	25.71 ± 6.50	28.43 ± 6.03	0.326
Albumin level (g/l)[a]	25.56 ± 6.32	22.46 ± 7.071	26.8 ± 5.88	0.029*
Cancer Site, *N* (%)				0.002*
Colorectal	77 (55)	15 (37.5)	62 (62)*	
Gynecologic	19 (13.9)	7 (17.5)	12 (12)	
Appendix	28 (20)	14 (35)*	14 (14)	
Peritoneal/ mesothelioma	2 (1.4)	2 (5)	0	
Others[b]	14 (10)	2 (5)	12 (12)*	
Type of Surgery, *N* (%)				0.712
CRS	20 (14.3)	6 (15)	14 (14)	
CRS + HIPEC	108 (77.1)	30 (75)	78 (78)	
HIPEC	1 (0.7)	1 (2.5)	0	
CRS + IORT	7 (5)	2 (5)	5 (5)	
CRS+ HIPEC + IORT	4 (2.9)	1 (2.5)	3 (3)	

PN, parenteral nutrition; BMI, body mass index; CRS, Cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; IORT, Combined Intraoperative Radiotherapy; ICU, intensive care unit; LOS, length of study; N, number; NRS, Nutrition Risk Screening 2002. *Statistically significant difference between the PN groups ($p < 0.05$).

[a]Data are presented as mean ± standard deviation. Student's *t* test was used in the comparison.

[b]Others, include: (Omentum, small intestine, stomach, neuroendocrine, unknown).

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TABLE 2 Postoperative nutritional and surgical outcomes among PN and non- PN groups.

	Total (n = 140)	PN (n = 40)	Non-PN (n = 100)	p-value*
Post-operative LOS (days)[a]	16.50 (10–30)	32 (21–48)	14 (9–21)	<0.001*
Hospital LOS (days)[a]	21 (14–38)	44 (28–70)	18 (13–28)	<0.001*
ICU LOS (days)[a]	2 (1–3)	4 (2–6)	1 (0–2)	<0.001*
ICU admission, *N* (%)	109 (77.9)	38 (95)	71 (71)	<0.001*
NRS, *N* (%)				0.020*
Low risk	121 (86.4)	30 (75)	91 (91)*	
At risk	11 (7.9)	7 (17.5)*	4 (4)	
High risk	8 (5.7)	3 (7.5)	5 (5)	
Oral intake, *N* (%)	58 (41.4)	10 (25)	48 (48)	0.014*
Enteral Feeding, *N* (%)	18 (12.9)	4 (10)	14 (14)	0.370

PN, parenteral nutrition; ICU, intensive care unit; LOS, length of study; N, number; NRS, Nutrition Risk Screening 2002. *Statistically significant difference between the PN groups ($p < 0.05$).
[a]Data are presented as median (p25-p75). Mann–Whitney U test was used in the comparison.

TABLE 3 Composition of parenteral nutrition formula among PN group.

	PN + (N = 40)
PN duration (days)[a]	11 (7–17)
Volume (mL/day)[a]	1920 (1807–2,395)
Dextrose (gm/day)[b]	256.10 ± 84.77
Protein (gm/day)[b]	84.75 ± 24.05
Fat (gm/day)[a]	36 (24–48)
Kcal/kg/day[b]	27.33 ± 5.48
Reached Target, *N* (%)	19 (47.5)

PN, parenteral nutrition; Kcal, kilocalories; N, number.
[a]Data are presented as median (p25–p75).
[b]Data are presented as mean ± standard deviation.

11 (1, 7–16) days, with nearly 50% of the patients reaching the PN goal (Table 3).

3.3 PN and non-PN related complications

Electrolyte imbalance, metabolic, and hepatic complications were the most reported PN-related complications (Table 4). Hypernatremia, hypokalemia, hypophosphatemia, hypomagnesemia, and hypocalcemia were evident in the PN group. In 35% of the patients, PN was associated with hyperglycemia and, to a lesser extent, hypertriglyceridemia (10%). The most prevalent hepatic complications in the PN group were cholestasis and steatosis, with nearly 50% of patients on PN developing cholestasis.

Non-PN related complications have also been observed in both PN and non-PN patients, as shown in Table 5. Complications include catheter related, infectious, hematological, gastrointestinal, and renal complications. In comparison to the non-PN group, PN was associated with more incidents of catheter-related bloodstream infection ($p = 0.006$), wound-related infection ($p = 0.002$), bacteremia ($p = 0.014$), leukopenia ($p = 0.005$), thrombocytopenia ($p = 0.029$), intra-peritoneal abscess ($p = 0.009$), acute kidney injury, and azotemia. Deaths were also recorded in both groups, with the PN group having more cases ($p = 0.047$) than the non-PN group.

3.4 Nutritional status and patient's clinical outcome

As presented in Table 6, the association between the patients' NRS and clinical outcomes including postoperative, hospital, and ICU LOS and death have been assessed in multiple regression analyses. Unadjusted models demonstrated a non-significant association between nutritional risk and LOS in all settings except the ICU. This demonstrates a strong positive relationship between increased risk of malnutrition and ICU LOS ($p = 0.047$). A stratified analysis based on PN status revealed a non-significant correlation between the patients' NRS and clinical outcomes in the PN group only. However, in the non-PN group, the risk of malnutrition was positively linked with the ICU LOS ($p = 0.008$) but not with other outcomes.

4 Discussion

This single-center retrospective study investigated the potential association between the preoperative nutritional status and postoperative clinical outcomes, as well as the incidence of PN and non-PN-related postoperative complications in adult cancer patients who underwent CRS/HIPEC for peritoneal malignancy. Patients who received PN had significantly longer post-operative, hospital, and ICU LOS compared to those who did not receive PN. Number of ICU admissions in the non-PN group was significantly higher than in the PN group. During hospitalization, the majority of the patients who did not receive PN were at low risk of malnutrition, whereas the majority of patients on PN were at risk of malnutrition. The association between the patients' nutritional status and clinical outcomes showed a strong positive relationship between an increased risk of malnutrition and ICU LOS. Furthermore, the risk of malnutrition was positively linked with the ICU LOS in the non-PN group.

Preoperative nutrition status can have a significant impact on predicting postoperative outcomes (7) and complications in cancer patients undergoing CRS/HIPEC (10). The findings from several studies have suggested the significant association between clinical outcomes and PN use (2, 13, 14). Furthermore, a recent study by Khan et al. has suggested the importance of focusing on nutrition and improving its quality to limit the complications associated with the CRS/HIPEC (9). PN have also been found to influence the outcomes in terms of length of stay and survival, especially since patients after

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TABLE 4 PN-related complications among patients receiving PN ($n = 40$).

PN related complications			
	Normal	Hypo	Hyper
Electrolyte imbalance[a], *N (%)*			
Sodium	25 (62.5)	6 (15)	9 (22.5)
Potassium	23 (57.5)	13 (32.5)	4 (10)
Phosphorous	21 (52.3)	13 (52.5)	6 (15)
Magnesium	23 (57.5)	11 (27.5)	6 (15)
Calcium	28 (70)	9 (22.5)	3 (7.5)
Metabolic complications, *N (%)*			
Hyperglycemia[b]		14 (35)	
Hypertriglyceridemia[c]		4 (10)	
Hepatic complications, *N (%)*			
Cholestasis		20 (50)	
Steatosis		12 (30)	

[a]Electrolyte Imbalances: Sodium (Na+): Normal (135–145) mmol/L, Hypo <135 mmol/L, Hyper >145 mmol/L; Magnesium (Mg): Normal (0.7–1.10)mmol/L, Hypo <0.7 mmol/L, Hyper >1.10 mmol/L; Potassium (K): Normal (3.5–5.5) mmol/L, Hypo <3.5 mmol/L, Hyper >5.5 mmol/L; Phosphorus (Ph): Normal (0.8–1.45)mmol/L, Hypo <0.8 mmol/L, Hyper >1.45 mmol/L; Calcium (Ca): Normal (2.2–2.7) mmol/L, Hypo <2.2 mmol/L, Hyper >2.7 mmol/L.
[b]Fasting Blood Glucose Level > 180 mg/dL (10 mmol/L).
[c]Triglyceride level > 150 to 499 mg/dL (1.7 to 5.6 mmol/L).

TABLE 5 Non- PN related complications among both PN groups.

	PN ($n = 40$)	Non-PN ($n = 100$)	p-value*
Catheter related complication, *N* (%)			
CRBSI	8 (20)	5 (5)	0.006*
CVT	0	0	
PE	1 (2.5)	0	0.113
Occlusion	1 (2)	2 (2)	0.854
Infectious complications, *N* (%)			
Wound-related infection	21 (52.5)	25 (25)	0.002*
Bacteremia	14 (35)	16 (16)	0.014*
UTI	2 (5)	7 (7)	0.663
Hematological complications, *N* (%)			
WBC (cells/mm^3)[a]	5,950 (3300–9,450)	9,000 (6100–12,500)	0.005*
Normal	17 (42.5)	56 (56)	0.012*
Leukopenia	14 (35)*	13 (13)	
Leukocytosis	9 (22.5)	31 (31)	
Platelets (cells/mm^3)			0.029*
≥100,000	28 (70)	89 (89)*	
75,000-99,000	6 (15)*	4 (4)	
50,000-74,000	3 (7.5)	6 (6)	
25,000-49,000	2 (5)	1 (1)	
<25,000	1 (2.5)	0	
Bleeding	19 (47.5)	43 (43)	0.628
GI abnormality, *N* (%)			
Intra-peritoneal abscesses	15 (37.5)	17 (17)	0.009*
Chyle leak	1 (2.5)	2 (2)	0.854
Renal complications, *N* (%)			
AKI	11 (27.5)	13 (13)	0.038*
Azotemia	10 (25)	8 (8)	0.010*
Death, *N* (%)	6 (15)	5 (5)	0.047*

PN, parenteral nutrition; N, number; CRBSI, Catheter-related bloodstream infection; CVT, Cerebral Venous Thrombosis (CVT); PE, Pulmonary Embolism; UTI, urinary tract infection; WBC, white blood cells; AKI, acute kidney injury. *Statistically significant difference between the PN groups ($p < 0.05$).[a]WBC: Data are presented as median (p25–p75) and N (%). Normal 4,000-11,000, Leukopenia <4,000, Leukocytosis >11,000.

the surgeries suffer from an intolerance of oral intake within the first week. Therefore, optimizing and receiving the most adequate perioperative nutrition is required to enhance clinical outcomes. According to the systematic review of Gearing et al., Subjective Global Assessment (SGA) and sarcopenia assessment had significantly predict the nutritional status of the study patients (1). Our study results, however, demonstrated a non-significant correlation between the patients' NRS and clinical outcomes in the PN group. Despite the observation that nutritional status risk did not seem to influence PN decision-making, a similar distribution of at-risk and high-risk patients between the PN and non-PN groups were found, it is important to consider that the decision to initiate PN is multifaceted and may be influenced by additional clinical factors beyond nutritional risk alone.

In addition, the risk of malnutrition in the non-PN group was positively linked with the ICU LOS ($p = 0.008$). Moreover, patients who received PN had significantly longer post-operative, hospital, and ICU LOS ($p = 0.001$) than those who did not receive PN. The ICU admission was also relatively higher in the non-PN group than the PN group. Nutritional status of the patients can also have a significant impact on the outcomes of the surgeries (15, 16). Previous investigations have demonstrated that a preoperative albumin level below 3.5 g/dL has a direct impact on severe morbidity (17). In this study there was a strong significant difference in the albumin level ($p = 0.029$) between the PN and non-PN groups, which could have an influence on the management of the complications for the non-PN group.

The Prognostic Nutritional Index, Nutrition Risk Screening 2002, and Prealbumin represent viable and reliable screening assessments for accurately predicting postoperative nutritional status (18). Malnutrition is a silent and hidden disease that can lead to severe complications for patients who undergo major surgeries (19). Gupta et al. findings have demonstrated that cancer patients often suffer from a decline in nutrition status as a consequence of disease progression and chemotherapy side effects (18). Williams and Wischmeyer have highlighted that cancer patients after major surgeries are at risk of malnutrition (20). Furthermore, Solanki et al. have reported the PN influences the outcomes in terms of length of stay and survival (21). The findings of these studies were consistent with our own findings which demonstrated the relationship between LOS and PN. This study also revealed a relationship between increased risk of malnutrition and ICU LOS, demonstrating a significant correlation between the patients' NRS and clinical outcomes ($p = 0.008$). Moreover, Kim et al. have suggested the association between preoperative malnutrition

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TABLE 6 Association between patients NRS and clinical outcomes in multiple regression analyses and among PN groups individually.

Outcomes		Post-operative LOS[a]			Hospital LOS[a]			ICU LOS[a]			Death[b]		
		B	Pvalue	95% CI	B	Pvalue	95% CI	B	Pvalue	95% CI	B	Pvalue	95% CI
PN group													
NRS	Low risk		1(Ref)			1(Ref)			1(Ref)			1(Ref)	
	At risk	−0.023	0.787	−50.574, 38.392	0.154	0.071	−1.673, 40.285	0.052	0.538	−3.589, 6.845	1.244	0.843	0.143, 10.844
	High risk	−0.053	0.539	−67.644, 35.485	0.032	0.704	−19.638, 28.999	0.1619	0.047*	0.069, 12.165	1.778	0.605	0.196, 16.086
Non-PN group													
NRS	Low risk		1(Ref)			1(Ref)			1(Ref)			1(Ref)	
	At risk	−0.145	0.381	−115.656, 45.256	0.019	0.908	−42.422, 47.565	−0.075	0.639	−14.897, 9.259	1.083	0.947	0.102, 11.523
	High risk	−0.084	0.609	−145.599, 86.532	0.002	0.992	−64.574, 65.241	0.279	0.087	−2.290, 32.557	3.250	0.378	0.236, 44.691
NRS	Low risk		1(Ref)			1(Ref)			1(Ref)				
	At risk	0.009	0.931	−56.660, 61.864	0.171	0.092	−2.323, 30.460	0.263	0.008*	0.781, 5.186			
	High risk	−0.061	0.551	−69.332, 37.235	0.010	0.923	−14.019, 15.456	−0.051	0.606	−2. 497, 1.464			

[a]Beta coefficient computed using linear regression analysis.
[b]Beta coefficient representing the adjusted odd ratio (AOR) computed using logistic regression analysis.
*Statistically significant association ($p < 0.05$).

status and poor outcomes. The researchers demonstrated that the recovery group who were receiving good nutrition pre- and post-operatively demonstrated an increase in their nutrition status in a period of 3 to12 months after the operation, while the patients who were suffering from malnutrition pre- and post-operation demonstrated a decreased status of nutrition during the same period. The studies also suggest that BMI scores postoperatively remained relatively low in all the groups (malnourished, risk-of-malnutrition, and well-nourished groups) after the 12 months period compared with preoperative levels (21.3 ± 2.8 vs. 22.1 ± 2.5 vs. 24.5 ± 2.4, respectively; $p < 0.001$) (22). Dineen et al. (23) reported similar findings. Nevertheless, our study revealed that the BMI scores for the non-PN group were higher than those of the PN group, although the difference did not achieve statistical significance ($p = 0.326$).

Efficient nutrition routine screening prior to any operation plays a key role in enhancing patients' clinical outcomes (20). Parenteral nutrition provides cancer patients with essential macronutrients and micronutrients, that contribute to nitrogen balance, muscle mass, surgical recovery time, and immunological function. Furthermore, PN helps minimize complications and the incidence of PN- and non-PN-related complications (24). In the present study, patients in the PN group experienced a variety of complications, including hepatic cholestasis and steatosis, with approximately 50% of PN patients developing cholestasis. PN was also associated with hyperglycemia in 35% of the patients and, to a lesser extent, hypertriglyceridemia in 10%. Although non-PN complications occurred in both groups, the frequency of catheter-related bloodstream infection ($p = 0.006$), wound-related infection ($p = 0.002$), bacteremia ($p = 0.014$), leukopenia ($p = 0.012$), intra-peritoneal abscess ($p = 0.009$), acute kidney injury, and azotemia were more prevalent in the PN group. In terms of mortality rates, our study findings indicate that death cases in the PN group were considerably higher than in the non-PN group ($p = 0.047$). Only one prospective study in malnourished gastric and colorectal cancer patients revealed that preoperative PN led to a lower mortality rate (7 days preoperative PN and 7 days postoperative PN), compared to the control group (2.1% vs. 6%, $p = 0.003$) (24).

This study has several limitations that need to be acknowledged. The study's retrospective nature prohibits making any inferences about the causal relationship between PN and clinical outcomes. The inclusion of patients from a single medical center limits the generalizability of the findings. The limited duration of the follow-up period restricts the findings to the immediate postoperative period and does not provide insight into postoperative nutrition decline. The NRS-2002 is susceptible to bias due to its emphasis on the assessor's capacity to collect and interpret data. Despite these limitations, this study, to the best of our knowledge, represents a pioneering effort within the local context examining the prognostic significance of nutritional assessment and intervention in cancer patients undergoing CRS and HIPEC. This highlights the necessity for robust, high-quality randomized controlled trials in this field.

In conclusion, routine preoperative nutrition assessment is essential for identifying patients who are at increased nutritional risk, and nutrition support should be provided preoperatively. The study demonstrated a significant relationship between nutritional risk and ICU LOS. In comparison to the non-PN group, the PN group experienced more complications. Further randomized clinical trials in these patient population, should investigate the

systematic provision of PN to all malnourished patients in the preoperative period for at least 7–10 days, with PN continued in the postoperative period.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Institutional Review Board at King Saud University Medical City. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because there was no direct patient contact or intervention used, the blood collected was obtained from the patients routinely as usual patients' care.

Author contributions

EA: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. NK: Data curation, Formal analysis, Writing – original draft, Writing – review & editing. SoA: Data curation, Investigation, Writing – review & editing. FA: Writing – review & editing. SuA: Writing – review & editing. TB: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association of composite dietary antioxidant index with mortality in adults with hypertension: evidence from NHANES

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Objective: The objective of this study is to assess the correlation between composite dietary antioxidant index (CDAI) with all-cause mortality and cause-specific mortality in adults with hypertension.

Methods: The cohort study comprised adult participants with hypertension from the NHANES database, spanning 9 cycles from 2001 to 2018. Follow-up was conducted until December 31, 2019. Multi-variable Cox regression analysis was utilized to ascertain hazard ratios (HR) and their corresponding 95% confidence intervals, evaluating the relationship between CDAI and the risks of all-cause and cause-specific mortality. To further investigate the association between CDAI and mortality rates in adults with hypertension, Kaplan–Meier survival curves, restricted cubic splines (RCS), subgroup analyses and sensitivity analyses were employed.

Results: The analysis included 16,713 adults with hypertension (mean age 56.93±0.23years, 8,327 [49.61%] male). During the mean follow-up time 102.11±1.22months, with 3,908 (18.08%) all-cause mortality occurred, 1,082 (4.84%) cardiovascular mortality and 833 (3.80%) cancer mortality. Compared to the lowest quartile of CDAI, the weighted multivariate hazard ratios of participants in the highest quartile was 0.77 (95% CI, 0.68–0.87) for all-cause mortality, 0.83 (95% CI, 0.67–1.04) for cardiovascular mortality, and 0.64 (95% CI, 0.50–0.82) for cancer mortality. RCS analysis demonstrated a nonlinear association of CDAI with all-cause and cancer mortality, and a linear association between CDAI and cardiovascular mortality. The results were robust in subgroup analyses and sensitivity analyses.

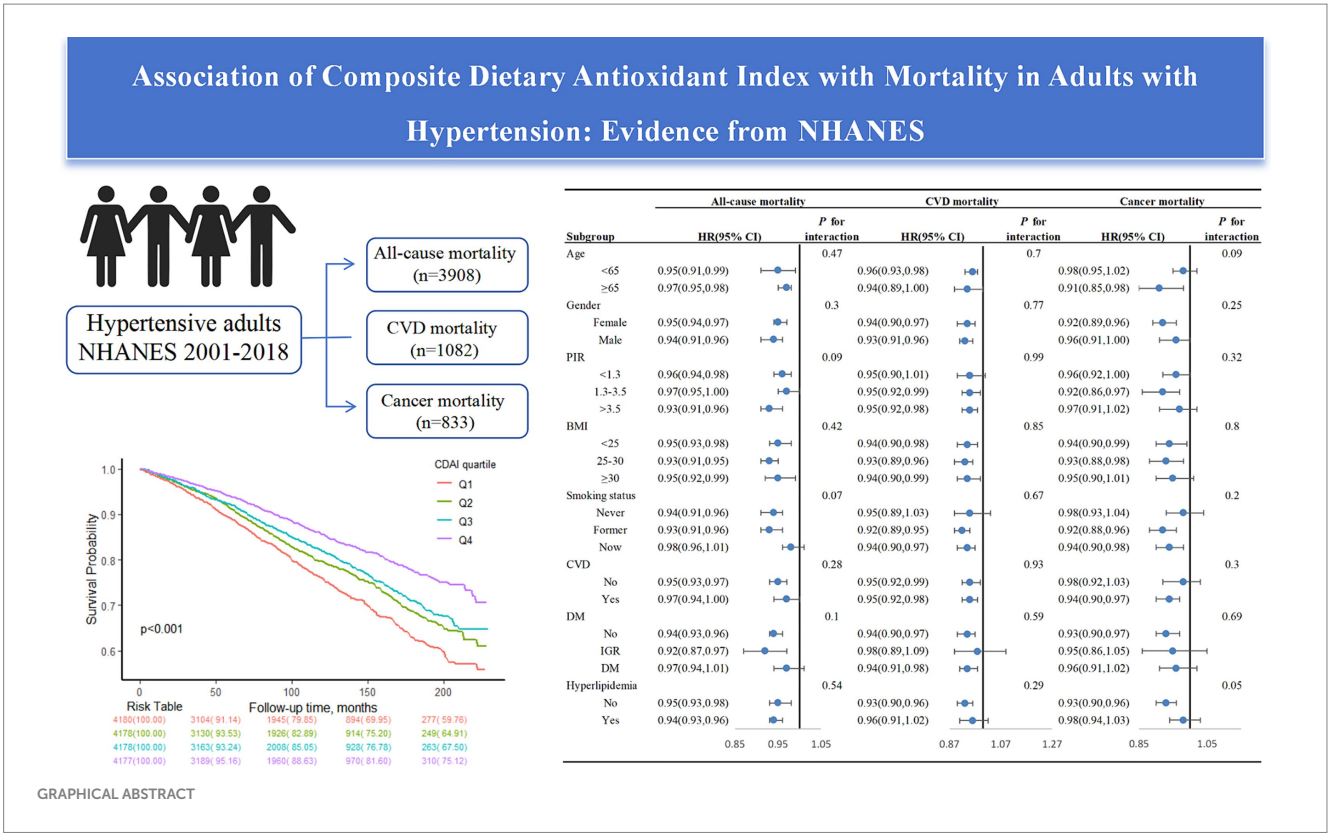
Conclusion: Higher CDAI is associated with reduced all-cause mortality, cardiovascular mortality, and cancer mortality in hypertensive adults. Our findings highlight the importance of an antioxidant diet in improving outcomes in adults with hypertension.

KEYWORDS

CDAI, all-cause mortality, cardiovascular mortality, cancer mortality, hypertension

1 Introduction

The prevalence of hypertension is a major public health concern worldwide, affecting a significant proportion of the global population (1). The prevalence of hypertension tends to increase with aging, with approximately 1.39 billion individuals (31.1%) diagnosed with hypertension as of 2010 (2). There are several vital organs affected by this chronic condition,



GRAPHICAL ABSTRACT

including the heart, cerebrovascular system, and kidneys. It is also a primary cause of cardiovascular disease-related deaths (3). Identification of reversible risk factors is therefore clinically important, as it can delay or even prevent hypertension-associated damage to target organs.

The pathogenesis of hypertension is greatly influenced by oxidative stress (4). It involves an excessive generation of reactive oxygen species (ROS) and impairment of antioxidative homeostasis, resulting in post-translational modifications of proteins and aberrant signal transduction (5). These processes contribute to endothelial dysfunction, inflammation, and vascular remodeling (4). The influence of eating patterns on cardiometabolic status has long been a significant concern in public health (6). Research findings indicate that dietary antioxidants may have a significant impact on reducing blood pressure and preventing cardiovascular disease-related mortality (7–9).

Composite Dietary Antioxidant Index (CDAI) assesses the daily intake of antioxidants, including vitamins A, C, E, zinc, selenium, and carotenoids (9). CDAI was developed with the purpose of assessing and quantifying the overall health benefits of dietary antioxidants. Study has shown that an elevated CDAI level could potentially lower the risk of death in cancer survival individuals (10). Wu et al. (8) emphasized that higher levels of CDAI reduce the risk of hypertension. However, as long-term studies are lacking, it is unclear that if CDAI are associated with a decreased hazard of overall and disease-specific mortality in those identified as having hypertension. We examined the potential correlation between CDAI and total and disease-specific mortality in adults diagnosed with hypertension using NHANES data from 2001 to 2018.

2 Methods

2.1 Study population

NHANES employs a multiple-stage, cluster sampling strategy to ensure that samples are nationally representative. Information from the NHANES study is gathered via surveys that inquire about characteristics, financial status, eating habits, and medical concerns. Each year, approximately 5,000 nationally representative participants participate in the survey. The survey protocol at the Centers for Disease Control and Prevention (CDC) has been approved by the Institutional Review Board of the National Center for Health Statistics (NCHS). Before any participant is enrolled in the study, they are required to provide written informed consent.

A nine-cycle NHANES survey spanning 2001–2018 was used in our study. We selected individuals with available data on dietary antioxidant intake, survival status, demographics and history of disease. Individuals with incomplete or unidentified information were not included in the study. In the end, 16,713 individuals aged 18 years or older with hypertension met the criteria for inclusion after applying the specified criteria for inclusion and exclusion. These participants represented 75,258,953 non-institutionalized U.S. residents. Figure 1 demonstrates the process of including and excluding participants.

2.2 Dietary assessment

The evaluation of CDAI utilized the index established by Wright et al. (11). A 24-h dietary recall was conducted for each participant in

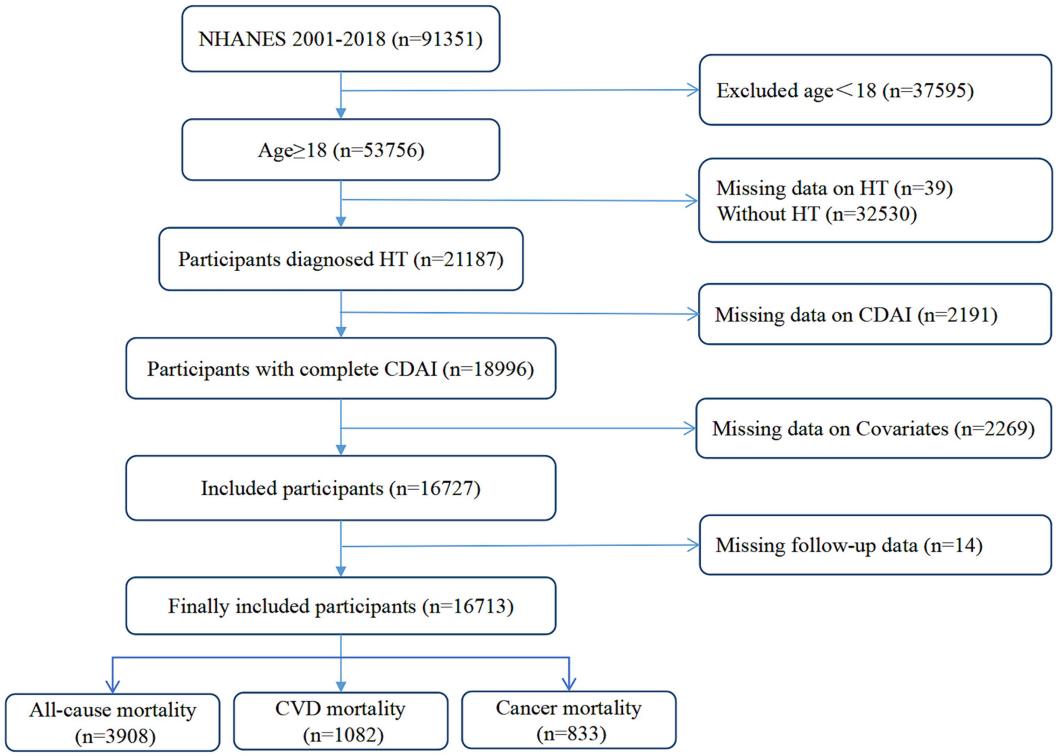


FIGURE 1
Flowchart of NHANES participants with hypertension enrolled in this study.

NHANES in order to obtain information about their dietary antioxidant intake and other food components. Dietary antioxidant intake data was obtained from NHANES participants through in-person interviews. Investigators normalized the amount six dietary antioxidants, such as vitamins A, C, E, zinc, selenium, and total carotenoids, without including supplements, drugs, or water, in order to determine the CDAI.

2.3 Definition of hypertension

To identify hypertension, one or more of these criteria were utilized: Patients self-report that they have hypertension or taking medications to lower blood pressure currently. The systolic and diastolic blood pressure readings are taken three times to ensure accuracy and are considered high if they exceed the standard reference range.

2.4 The collection of survival data

The NCHS connects data from population surveys with death certificates from the NDI to understand mortality rates and causes for specific outcomes. The term "all-cause mortality" referred to all types of deaths that occurred in this study. To identify and classify the specific subcategories of causes of death, the study relied on the NDI data and followed the coding guidelines outlined in the International Classification of Diseases. During the observation period that ended on December 31, 2019, or the date of death, a total of 3,908 deaths were recorded, out of which 1,082 were attributed to cardiovascular diseases and 833 were attributed to cancers.

2.5 Covariates

This study has identified various significant covariates. The data related to these covariates was collected through baseline questionnaires, which were administered by trained health technicians, interviewers, and physicians.

Covariates included: age, sex, ethnicity, marital status, level of education, poverty-to-income ratio (PIR), body mass index (BMI), energy consumption, carbohydrate consumption, dietary fiber consumption, smoking habits and tobacco exposure (serum cotinine), alcohol consumption, caffeine consumption. BMI was stratified as "<25, 25–30, or ≥30," indicating normal weight, overweight, and obese, respectively. The classification for smoking status were based on criteria used during previous research (12). Serum cotinine was determined by liquid chromatography/mass spectrometry. CVD status was determined by self-reported diagnosis. Diabetes mellitus can be identified by meeting any of the following conditions: a prior diagnosis, HbA1C level of 6.5% or above, fasting plasma glucose ≥7.0 mmol/L, random plasma glucose level ≥11.1 mmol/L, 2 h OGTT ≥11.1 mmol/L, or taking glucose-lowering medications. Impaired Glucose Regulation is defined as exceeding the standard reference limit but not meeting the above criteria. Hyperlipidemia was defined as blood lipids exceeding the upper reference limit or using lipid-lowering drugs.

2.6 Statistical analysis

The data from the NHANES project were collected and processed using the nhanesR package. To ensure accurate nationwide estimates in the United States, all analyses were conducted using sample weights. Continuous variables are presented in Mean ± standard error format, and categorical variables are presented in frequency (%). One-way ANOVA was employed to analyze the continuous variables, while the χ^2 test was used to analyze the categorical variables across the four quartiles.

To evaluate the relationship of CDAI with overall and disease-specific mortality in hypertensive adults, three Cox proportional hazards models were employed. Three models were as follows: Crude Model: This model was unadjusted. Model 1: Adjusted for age, sex, ethnicity, marital status, education level and PIR. Model 2 was modified to account for age, sex, ethnicity, marital status, level of education, PIR, caloric intake, BMI, alcohol consumption, caffeine consumption, serum cotinine, cardiovascular disease, DM, and hyperlipidemia.

We utilized restricted cubic spline models to examine the relationship between CDAI and mortality. Furthermore, we conducted subgroup analysis, interaction testing, and sensitivity analyses to evaluate the credibility of the results. Statistical analyses were conducted using R version 4.2.1 software, with significance determined by *p*-values below 0.05.

3 Results

3.1 Baseline profiles

Participants' sociodemographic and health conditions were weighted and presented in Table 1 according to the quartiles of CDAI. The study population comprised a total of 16,713 participants with hypertension. Their average age was 56.93 ± 0.23 years, consisted of 8,327 (49.61%) male and 8,386 (50.39%) female. In comparison to people in the lowest quartile, individuals with the highest CDAI level exhibited the following characteristics: younger, more commonly male and non-Hispanic White, more educated and higher family income, and were more likely to be coupled. In terms of dietary intake, individuals in the first quartile had lower intakes of energy, dietary carbohydrates and fiber. Moreover, subjects with higher CDAI had a lower incidence of cardiovascular disease and DM. Supplementary Table S1 showed that compared with survivors, participants who died were more likely to take lower level of dietary vitamins E, zinc, selenium, and total carotenoids, while dietary vitamins A, C increased slightly but without statistically significant.

3.2 Kaplan–Meier survival curve

Among these participants, during a median follow-up period of 102.11 ± 1.22 months, there were 3,908 (18.08%) all-cause mortality occurred, 1,082 (4.84%) and 833 (3.80%) deaths specifically attributed to cardiovascular disease and cancer among adults with hypertension, respectively (Supplementary Table S2). As illustrated in Figure 2, survival was shown by weighted Kaplan–Meier survival curves in different groups according to CDAI quartiles. In comparison to Q1 (the lowest quartile), Q2, Q3, and Q4 exhibited significantly lower overall and disease-specific mortality (all $p < 0.01$). According to the Log-rank tests, subjects with lower CDAI display a tendency toward a higher risk of both all-cause and disease-specific mortality.

3.3 Relationship of CDAI with overall and disease-specific mortality

Table 2 and Supplementary Table S3 presented survey-weighted multivariate Cox regression results. As a continuous variable, CDAI demonstrated an inverse relationship with mortality in unadjusted models. The adjusted hazard ratios for overall mortality, cardiovascular mortality, and cancer-related mortality were 0.95, 0.94, and 0.94, respectively. In the Model 2 adjusted for all covariates, CDAI was significantly negative correlated with overall and cancer-related death, rather than CVD mortality. As a categorical variable, fully adjusted model 2 demonstrated a continued adverse correlation between CDAI and mortality in hypertensive adults. The hazards ratios for total death, CVD death, and cancer death were 0.77, 0.83, and 0.64, respectively, for participants in the highest quartile of the CDAI (Q4), as compared to those in the lowest quartile (Q1).

According to Figure 3, there was a clear correlation between CDAI and mortality that follows a dose-dependent pattern. It's worth noting that a nonlinear connection between CDAI and both all-cause ($p < 0.001$, P for nonlinear = 0.0056) and cancer mortality ($p = 0.004$, P for nonlinear = 0.016). Furthermore, the correlation between CDAI and CVD mortality was more closely aligned with a linear pattern.

3.4 Relationship of CDAI components with overall and disease-specific mortality

Multivariate Cox regression analysis revealed the effects of CDAI components on overall and disease-specific mortality in hypertensive adults (Table 3). The weighted hazard ratios of vitamin E was found to be 0.98 for overall mortality, 0.97 for cardiovascular mortality, and 0.96 for cancer-related mortality.

To further explore the relationship of vitamin E with overall and disease-specific mortality, RCS analysis was conducted. Figure 4 illustrated that an inverse linear correlation between vitamin E and CVD mortality ($p < 0.001$, *P* for nonlinear = 0.9711). Additionally, the association of vitamin E between overall and cancer-related mortality displayed a nonlinear pattern ($p < 0.001$, *P* for nonlinear < 0.05). These findings suggest that certain dietary antioxidants, particularly Vitamin E may have an impact on reducing the likelihood of all-cause and cause-specific mortality in hypertensive adults.

3.5 Subgroups analyses and sensitivity analyses

In subgroup analyses, we noticed that CDAI had a stronger negative correlation with all-cause mortality in most subgroups except

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TABLE 1 Baseline characteristic of participants by CDAI levels quartiles among adults with HT in NHANES 2001–2018, weighted.

Variables	Total (*n* = 16,713)	CDAI				*p* value
		Q1 (*n* = 4,180)	Q2 (*n* = 4,178)	Q3 (*n* = 4,178)	Q4 (*n* = 4,177)	
CDAI range	(−7.06, 48.29)	(−7.06, −2.51)	(−2.51, −0.67)	(−0.67, 1.74)	(1.74, 48.29)	
Age, years	56.93 (0.23)	57.58 (0.38)	57.93 (0.38)	57.28 (0.36)	55.27 (0.36)	<0.0001
PIR	2.96 (0.03)	2.51 (0.04)	2.90 (0.04)	3.09 (0.04)	3.23 (0.04)	<0.0001
Energy, kcal/d	2071.51 (11.93)	1297.73 (12.46)	1789.88 (14.57)	2184.62 (17.38)	2788.48 (24.75)	<0.0001
Carbohydrate, g/d	244.09 (1.46)	162.87 (1.89)	214.38 (2.13)	255.36 (2.35)	320.01 (3.23)	<0.0001
Fiber, g/d	16.21 (0.14)	8.45 (0.11)	13.39 (0.14)	17.12 (0.20)	23.62 (0.25)	<0.0001
Caffeine, mg/d	180.51 (3.23)	167.76 (5.62)	179.38 (5.31)	184.88 (5.09)	187.02 (4.96)	0.02
Alcohol, g/d	11.07 (0.40)	9.66 (0.65)	9.74 (0.60)	11.69 (0.70)	12.70 (0.81)	0.01
Cotinine, ng/ml	58.84 (0.98)	72.94 (1.99)	59.31 (1.86)	56.02 (1.87)	50.46 (1.48)	<0.0001
Age, *n* (%)						<0.0001
<65	9,742 (66.30)	2,312 (64.03)	2,308 (63.21)	2,432 (65.63)	2,690 (71.26)	
≥65	6,971 (33.70)	1,868 (35.97)	1,870 (36.79)	1,746 (34.37)	1,487 (28.74)	
Gender, *n* (%)						0.14
Male	8,327 (49.61)	2,100 (47.51)	2,053 (48.73)	2,092 (50.52)	2,082 (51.10)	
Female	8,386 (50.39)	2,080 (52.49)	2,125 (51.27)	2,086 (49.48)	2,095 (48.90)	
Race, *n* (%)						<0.0001
Non-Hispanic White	7,886 (71.37)	1,752 (65.70)	1,994 (71.59)	2,076 (73.37)	2,064 (73.60)	
Non-Hispanic Black	4,304 (13.24)	1,286 (17.77)	1,063 (13.26)	955 (11.32)	1,000 (11.58)	
Mexican American	2,161 (5.55)	560 (5.72)	536 (5.51)	545 (5.48)	520 (5.52)	
Other	2,362 (9.84)	582 (10.81)	585 (9.64)	602 (9.83)	593 (9.30)	
Marital status, *n* (%)						<0.0001
Singled	6,897 (36.91)	1,904 (41.93)	1,737 (37.14)	1,657 (35.36)	1,599 (34.38)	
Coupled	9,816 (63.09)	2,276 (58.07)	2,441 (62.86)	2,521 (64.64)	2,578 (65.62)	
Education level, *n* (%)						<0.0001
<High school	4,711 (18.39)	1,599 (27.25)	1,177 (18.80)	1,053 (16.67)	882 (12.94)	
High school	4,164 (26.08)	1,062 (29.37)	1,103 (28.92)	1,006 (24.11)	993 (23.02)	
>High school	7,838 (55.53)	1,519 (43.38)	1,898 (52.28)	2,119 (59.21)	2,302 (64.04)	
PIR, *n* (%)						<0.0001
<1.3	5,189 (21.63)	1,697 (31.01)	1,284 (21.57)	1,131 (18.23)	1,077 (17.74)	
1.3–3.5	6,645 (37.53)	1,631 (39.70)	1,715 (39.61)	1,728 (38.39)	1,571 (33.35)	
>3.5	4,879 (40.84)	852 (29.30)	1,179 (38.83)	1,319 (43.38)	1,529 (48.91)	
BMI, *n* (%)						0.04
<25	3,320 (19.01)	918 (21.34)	772 (17.33)	785 (18.52)	845 (19.14)	
25–30	5,523 (32.86)	1,343 (30.71)	1,437 (34.30)	1,444 (34.34)	1,299 (31.88)	
≥30	7,870 (48.13)	1,919 (47.95)	1,969 (48.37)	1,949 (47.14)	2,033 (48.98)	
Smoking status, *n* (%)						<0.0001
Never	8,242 (49.00)	1,905 (44.82)	2,048 (48.14)	2,089 (49.28)	2,200 (52.62)	
Former	5,315 (31.83)	1,268 (29.47)	1,362 (32.52)	1,383 (32.89)	1,302 (32.05)	
Now	3,156 (19.17)	1,007 (25.70)	768 (19.35)	706 (17.83)	675 (15.33)	
CVD, *n* (%)						<0.0001
No	13,259 (82.51)	3,143 (78.01)	3,263 (81.58)	3,379 (83.39)	3,474 (85.86)	
Yes	3,454 (17.49)	1,037 (21.99)	915 (18.42)	799 (16.61)	703 (14.14)	
DM, *n* (%)						<0.0001
No	10,222 (66.26)	2,482 (63.99)	2,488 (63.98)	2,604 (66.58)	2,648 (69.62)	
IGR	1,530 (9.32)	360 (8.00)	379 (9.83)	392 (9.84)	399 (9.41)	
DM	4,961 (24.42)	1,338 (28.01)	1,311 (26.18)	1,182 (23.58)	1,130 (20.98)	
Hyperlipidemia, *n* (%)						0.14
No	3,400 (19.23)	849 (18.85)	844 (20.03)	801 (17.61)	906 (20.33)	
Yes	13,313 (80.77)	3,331 (81.15)	3,334 (79.97)	3,377 (82.39)	3,271 (79.67)	

CDAI, composite dietary antioxidant index; PIR, income-poverty-ratio; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; IGR, impaired glucose regulation.
Data are presented as the mean (SE) for continuous variables and frequencies (percentages) for categorical variables.
One-way ANOVA was used for continuous variable and χ^2 test was used for categorical variables among the four quartiles.

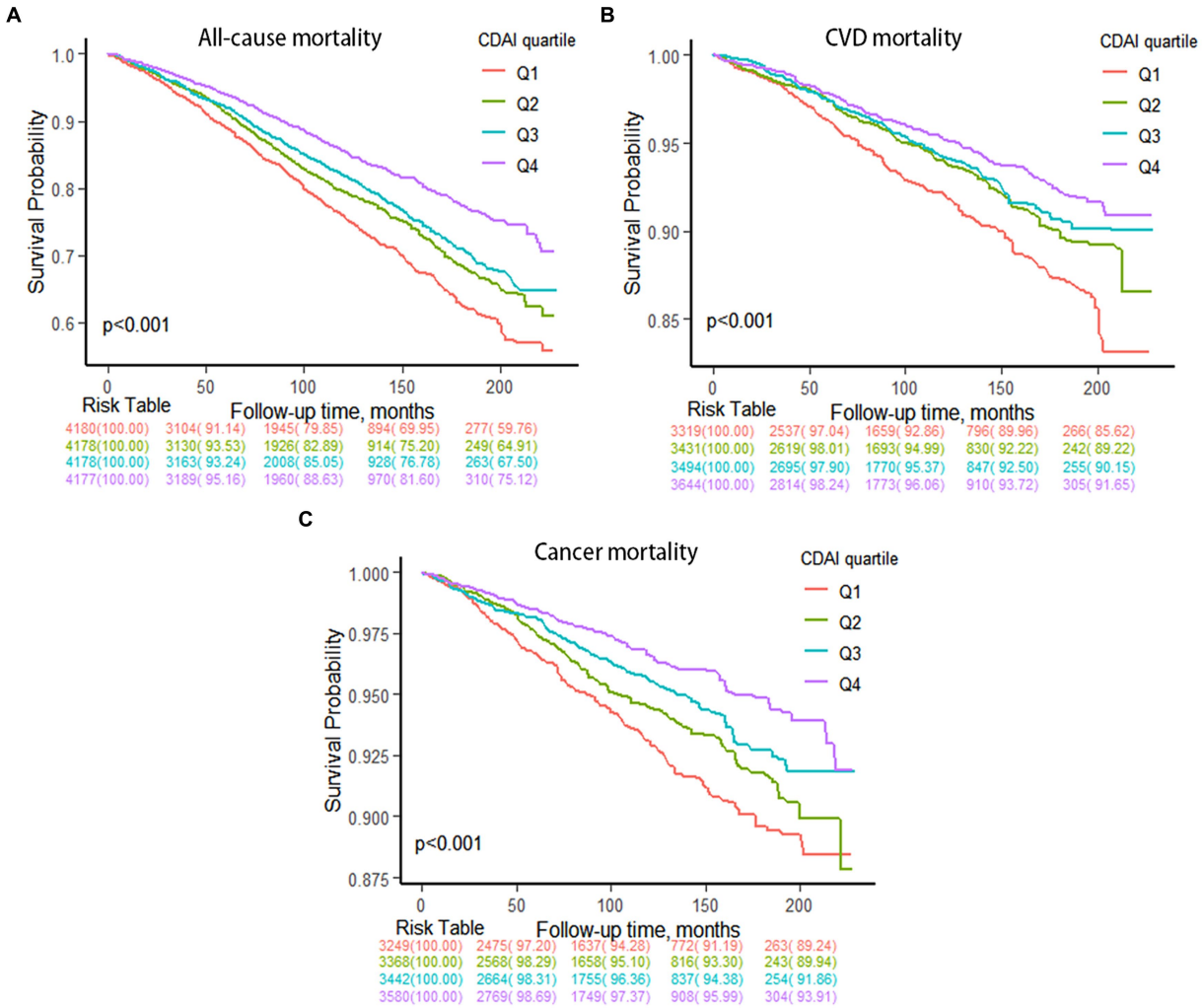

FIGURE 2
Kaplan–Meier survival curves of CDAI quartiles with mortality. **(A)** All-cause mortality. **(B)** CVD mortality. **(C)** Cancer mortality.

current smokers, CVD and DM participants. For cause-specific mortality, CDAI was negatively linked with cardiovascular and cancer-related mortality in female, non-obese, smokers and CVD participants (Figure 5). It is worth mentioning that there were no notable interactions detected among the subgroup variables (all *P* for interaction >0.05). These findings suggest that the effect of CDAI on mortality in adults with hypertension is consistent across various demographic and health-related subgroups, with no significant influence from these variables.

Two sensitivity analyses were performed to assess robustness, as detailed in Supplementary Table 4. After excluding participants who deceased within the first 2 years of follow-up, the relationship between CDAI and mortality from all causes, CVD, and cancer was found to be consistent with the findings in Table 2.

4 Discussion

This observational cohort study examined the relationship between dietary antioxidants and mortality rates in hypertensive adults in the United States. The results showed a significant association between the consumption of antioxidants, specifically CDAI and dietary Vitamin E, and both all-cause and cause-specific mortality. Even in the fully adjusted Cox model, higher CDAI levels were found to be linked to lower risks of mortality. The findings suggest that increasing intake of dietary antioxidants, especially Vitamin E, could potentially reduce mortality rates among individuals with hypertension. These results underscore the importance of including antioxidant-rich foods in the diets of hypertensive individuals to enhance health outcomes and mitigate mortality risks.

The CDAI functions as a thorough instrument to evaluate the diet's overall antioxidant level, enabling the identification and categorization of possible sources of antioxidants derived from intricate dietary elements (11). This allows for classifying individual dietary patterns based on antioxidant consumption, promoting the development of healthier dietary habits and lifestyles. Previous research has documented connections between antioxidant intake and the occurrence of hypertension (8, 13, 14). Some studies have utilized NHANES data to

TABLE 2 Cox proportional hazards models for all-cause and cause-specific mortality by CDAI, weighted.

Status	HR (95% CI) *p* value				
	Q1	Q2	Q3	Q4	*P* for trend
All-cause mortality					
Crude model	Reference	0.82 (0.72,0.93) 0.002	0.74 (0.65, 0.85) <0.0001	0.55 (0.49, 0.63) <0.0001	<0.0001
Model 1	Reference	0.88 (0.77, 0.99) 0.03	0.85 (0.75, 0.98) 0.02	0.72 (0.64, 0.81) <0.0001	<0.0001
Model 2	Reference	0.88 (0.77, 1.00) 0.05	0.89 (0.78, 1.02) 0.11	0.77 (0.68, 0.87) <0.0001	<0.001
CVD mortality					
Crude model	Reference	0.74 (0.59, 0.93) 0.01	0.67 (0.54, 0.83) <0.001	0.56 (0.44, 0.72) <0.0001	<0.0001
Model 1	Reference	0.78 (0.63, 0.96) 0.02	0.74 (0.60, 0.91) 0.01	0.70 (0.56, 0.88) 0.002	0.002
Model 2	Reference	0.81 (0.64, 1.01) 0.06	0.84 (0.67, 1.04) 0.11	0.83 (0.67, 1.04) 0.10	0.13
Cancer mortality					
Crude model	Reference	0.80 (0.63, 1.02) 0.08	0.67 (0.52, 0.86) 0.001	0.50 (0.39, 0.64) <0.0001	<0.0001
Model 1	Reference	0.82 (0.64, 1.04) 0.10	0.71 (0.55, 0.92) 0.01	0.58 (0.46, 0.75) <0.0001	<0.0001
Model 2	Reference	0.84 (0.65, 1.08) 0.18	0.75 (0.58, 0.99) 0.04	0.64 (0.50, 0.82) <0.001	<0.001

CDAI, composite dietary antioxidant index; PIR, income-poverty-ratio; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; CI, confidence interval.
Crude model unadjusted.
Model 1 adjusted for age, gender, race, marital status, education level and PIR.
Model 2 adjusted for age, gender, race, marital status, education level, PIR, energy intake, BMI, alcohol, caffeine intake, cotinine exposure, CVD, DM, and hyperlipidemia.

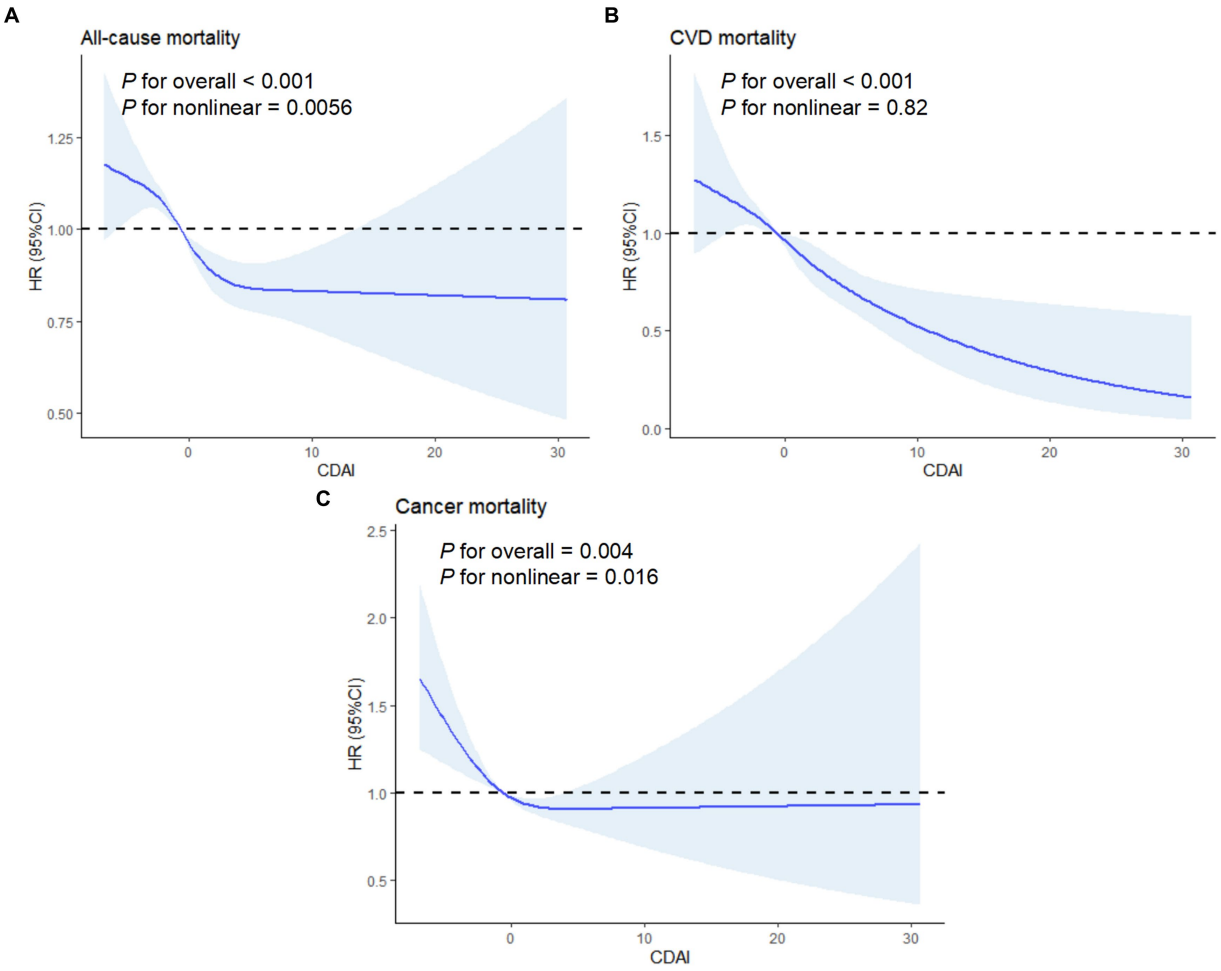

FIGURE 3
Association between CDAI and mortality using a restricted cubic spline regression model. **(A)** All-cause mortality. **(B)** CVD mortality. **(C)** Cancer mortality. Graphs show HRs for status according to CDAI adjusted for age, gender, race, marital status, education level, PIR, energy intake, BMI, alcohol, caffeine intake, cotinine exposure, CVD, DM and hyperlipidemia. Data were fitted by a restricted cubic spline Cox proportional hazards regression model. Solid lines indicate HRs, and shadow shape indicate 95% CIs. HR, hazard ratio; CI, confidence interval.

TABLE 3 Effects of CDAI components on all-cause and cause-specific mortality by multivariate cox proportional hazards regression analysis, weighted.

Components	HR (95% CI) *p* value		
	All-cause mortality	Cardiovascular mortality	Cancer mortality
Vitamin A	1.00 (1.00, 1.00) 0.43	1.00 (1.00, 1.00) 0.30	1.00 (1.00, 1.00) 0.10
Vitamin C	1.00 (1.00, 1.00) 0.004	1.00 (1.00, 1.00) 0.03	1.00 (1.00, 1.00) 0.31
Vitamin E	0.98 (0.97, 0.99) <0.0001	0.97 (0.95, 0.98) <0.001	0.96 (0.94, 0.99) <0.001
Zinc	0.99 (0.98, 1.00) 0.03	0.99 (0.98, 1.00) 0.12	0.99 (0.97, 1.00) 0.28
Selenium	1.00 (0.99, 1.00) 0.02	1.00 (0.99, 1.00) 0.39	1.00 (0.99, 1.00) 0.01
Carotenoids	1.00 (1.00, 1.00) 0.02	1.00 (1.00, 1.00) 0.85	1.00 (1.00, 1.00) 0.71

HR, hazard ratio; CI, confidence interval.
Fully adjusted for age, gender, race, marital status, education level, PIR, energy intake, BMI, alcohol, caffeine intake, cotinine exposure, CVD, DM, and hyperlipidemia.

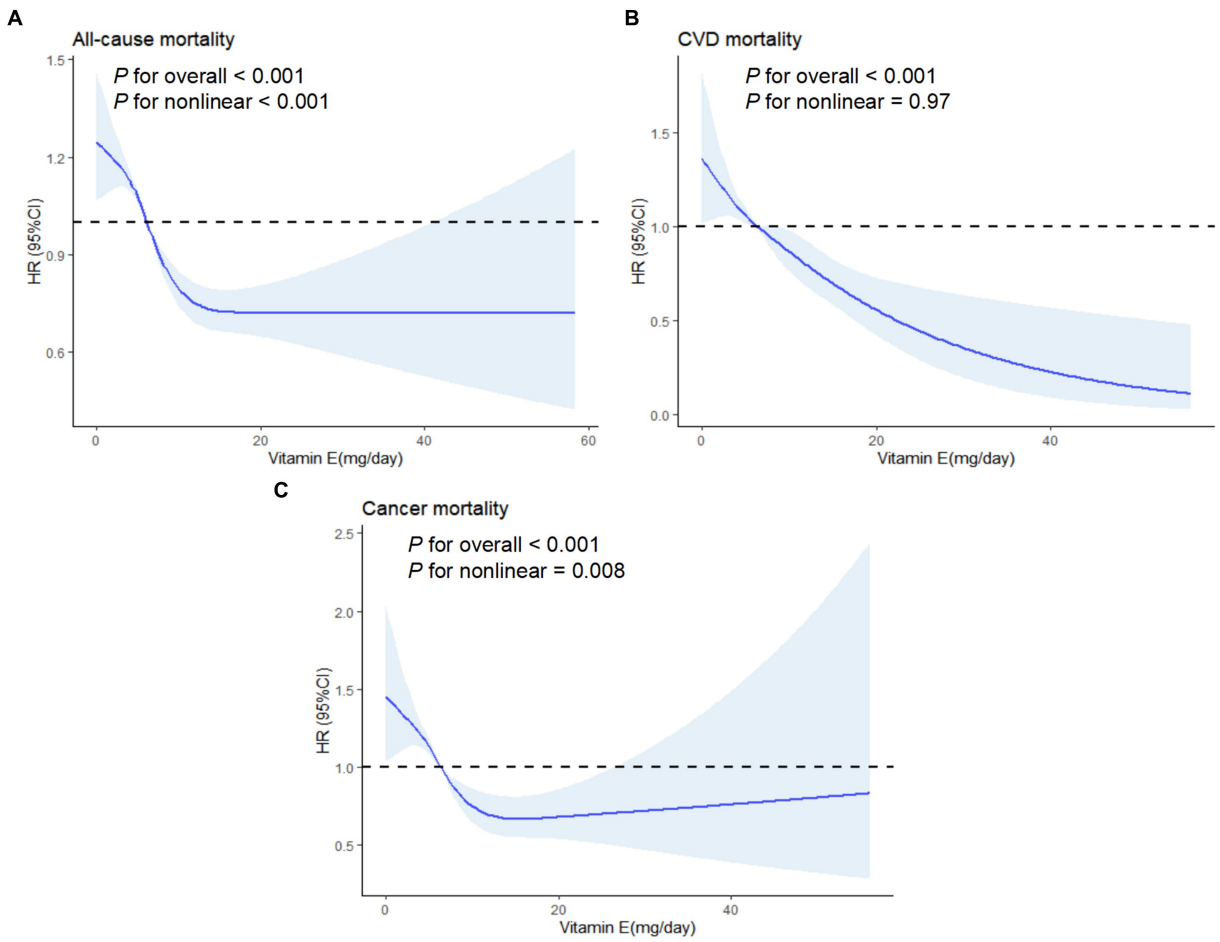

FIGURE 4
Association between vitamin E and mortality using a restricted cubic spline regression model. **(A)** All-cause mortality. **(B)** CVD mortality. **(C)** Cancer mortality. Graphs show HRs for status according to CDAI adjusted for age, gender, race, marital status, education level, PIR, energy intake, BMI, alcohol, caffeine intake, cotinine exposure, CVD, DM and hyperlipidemia. Data were fitted by a restricted cubic spline Cox proportional hazards regression model. Solid lines indicate HRs, and shadow shape indicate 95% CIs. HR, hazard ratio; CI, confidence interval.

investigate the correlation between CDAI and mortality across various populations. Wang et al.'s research indicates that elevated levels of CDAI in the general population are linked to a substantial reduction in the likelihood of both overall and CVD-related death (15). Specifically, in contrast to the Q1 group, the Q4 group showed a 10% decrease in the risk of overall mortality and a 19% reduction in CVD death. Among individuals with diabetes, those in the highest CDAI quartile experienced a 53% reduction in both overall and CVD mortality (12, 15). Furthermore, higher CDAI levels in patients with early-stage

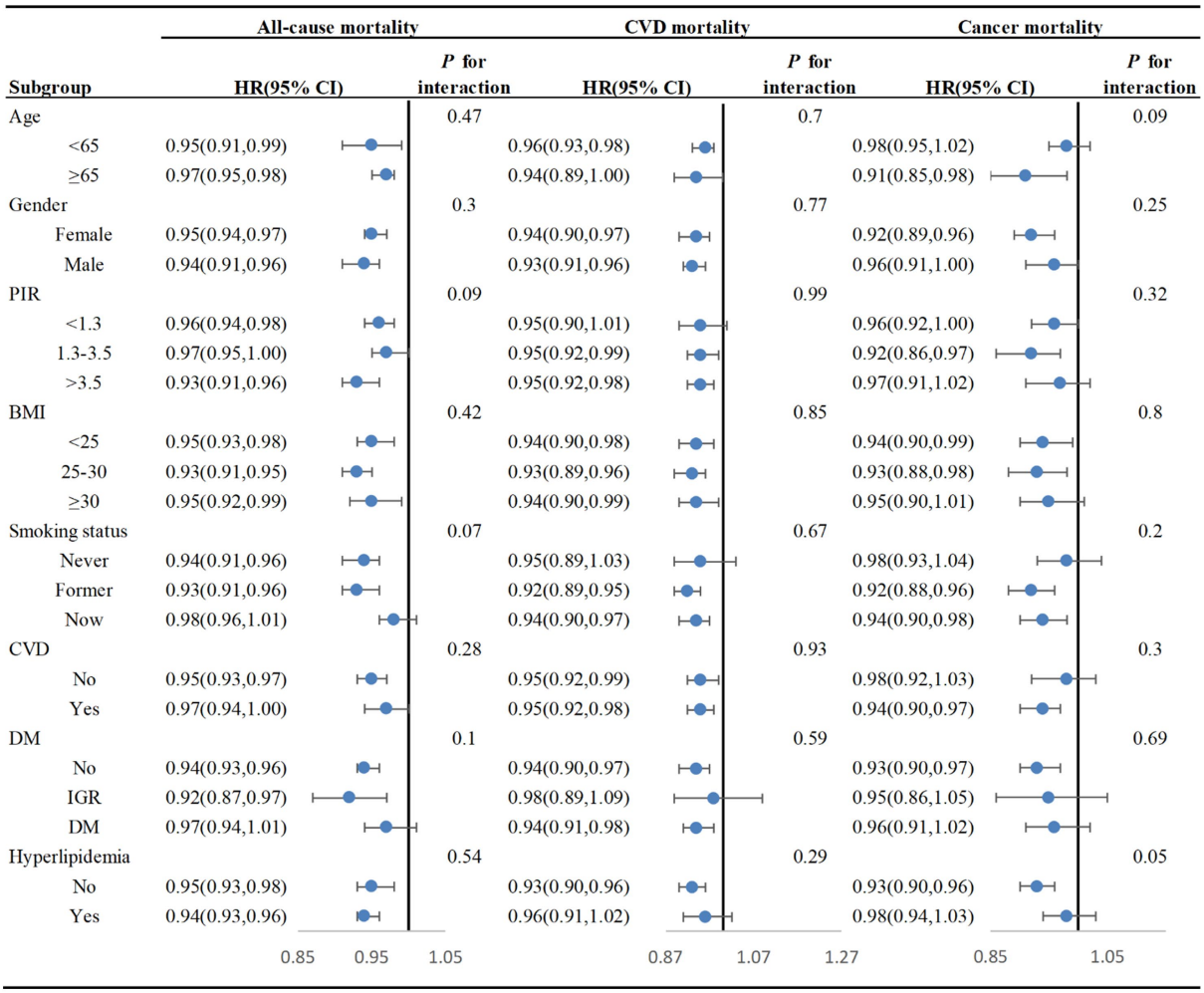

FIGURE 5
Subgroup analyses of the relationship between CDAI and mortality among adults with HT in NHANES 2001–2018, weighted. Cox proportional hazards models adjusted for age, gender, race, marital status, education level, PIR, energy intake, BMI, alcohol, caffeine intake, cotinine exposure, CVD, DM, and hyperlipidemia. In the subgroup analysis, the model is not adjusted for age, gender, poverty-to-income ratio (PIR), body mass index (BMI), cotinine exposure, cardiovascular disease (CVD), diabetes mellitus (DM), and hyperlipidemia, respectively.

CKD were linked to a notable decrease in the risk of all-cause death (16). Xu highlighted the protective impact of CDAI on individuals suffering from post-stroke depression, as well as the favorable influence of CDAI on the recovery outlook of stroke survivors (17). A recent survey has also highlighted the inverse correlation between CDAI levels and poor prognosis in patients with osteoarthritis (18). Studies observed significant inverse correlation between consuming antioxidants like carotenoids and vitamin E and decreased risk of death from heart disease and overall mortality (19, 20). In line with prior research, our study also revealed that higher level of CDAI was linked to reduced hazards of mortality from all causes and specific causes in adults with hypertension. Maintaining a balanced and adequate dietary intake of antioxidants, including Vitamin E, is crucial for optimizing health outcomes in this population.

There are many factors involved in the etiology of hypertension (21). Oxidative stress notably in a similar way plays a vital part in developing hypertension (4, 22). ROS produced in vascular smooth muscle cells (VSMCs) contribute to oxidative stress, resulting in peroxidation of lipids and proteins, DNA damage, and the initiation of a transition in the VSMC phenotype from a contractile to a synthetic state (23, 24). These mechanisms contribute to the pathological remodeling of arteries, potentially worsening hypertension. In summary, the interaction of these elements forms a intricate network of mechanisms that contribute to the onset and development of hypertension. Grasping these processes is vital in devising effective strategies for preventing and treating this prevalent public health issue.

Previous studies has revealed a positive correlation between biomarkers of oxidative stress, including methylmalonic acid (MMA) and malondialdehyde (MDA), and the likelihood of cardiovascular disease (CVD) and hypertension (25, 26). On the contrary, dietary antioxidants, widely present in various diets, possess the capability to strengthen the body's defense mechanisms against oxidative stress. They achieve this by scavenging surplus free radicals, thereby diminishing oxidative stress. Additionally, the close association between chronic low-grade inflammation and hypertension development is evident, given its contribution

to arterial stiffness and pathological remodeling (22). Elevated levels of CDAI have been shown to significantly reduce levels of pro-inflammatory cytokines (27). Hence, dietary antioxidants can alleviate the disturbance of tissue homeostasis induced by oxidative stress and decrease the infiltration of inflammatory factors. This presents potential advantages for preventing and treating hypertension. This partly explained the negative relationship between CDAI and total and disease-specific mortality in adults with hypertension. Through the reduction of oxidative stress and inflammation, dietary antioxidants may significantly contribute to promoting cardiovascular health and enhancing outcomes for individuals managing hypertension. Numerous studies underscore a noteworthy correlation between the consumption of essential trace elements, including zinc, iron, copper, and selenium, and the likelihood of developing hypertension (28–30). Additionally, a recent cross-sectional study focusing on 5,067 women revealed a significant negative correlation between hypertension and dietary antioxidant intake (31).

Based on the rigorous standardized procedures and quality control measures of NHANES, our study's findings can be applied to 75,258,953 non-institutionalized US residents. By incorporating nutritional factors, specifically CDAI into the realm of chronic disease management, we examined the association between CDAI and overall mortality, as well as CVD and cancer related death among individuals with hypertension. While conventional medical research has primarily focused on pharmaceutical treatments and clinical interventions, our study underscores the significance of dietary antioxidants in mitigating mortality risk within this specific demographic. Moreover, our analysis uncovers intricate relationships between specific dietary antioxidants and mortality from different causes, resulting in a more comprehensive understanding and a foundation for creating customized preventive measures. By delving into the distinct roles of various antioxidants in lowering mortality risk, our study provides practical guidance for future nutritional interventions, enabling healthcare professionals and patients to make more informed dietary choices. Through subgroup analysis and interaction detection, we further explored the impact of CDAI on mortality risk across different subgroups, confirming the robustness and applicability of our findings. In essence, our research underscores the crucial role of antioxidant-rich diets in reducing overall mortality and cause-specific deaths among hypertensive individuals, contributing valuable insights to public health initiatives and clinical practices in hypertension management.

Our study has some limitations. Firstly, in this observational cohort study, we can only analyze the correlation between dietary antioxidant intake and the risk of all-cause and cause-specific mortality in individuals with hypertension, and causality cannot be determined. Secondly, the reliance on self-reported data for both dietary questionnaires and disease status, as obtained from the NHANES database, may introduce recall bias and discrepancies between reported and actual conditions. Although NHANES employs rigorous data collection protocols, there remains a possibility of measurement error in the self-reported information. Thirdly, as our study comprises only Americans and excludes special groups such as minors, we are unable to conduct specific subgroup analyses for other ethnicities or diverse populations due to the constraints of sample size and representativeness. In order to thoroughly comprehend the connection between CDAI and the hazards of overall mortality as well as mortality from specific causes among people with hypertension, it is crucial to confirm our findings through larger prospective studies.

5 Conclusion

In summary, this research discovered that hypertensive adults with high CDAI levels had a lower risk of overall mortality as well as mortality from specific causes. These results established a crucial groundwork for comprehending the possible role of dietary antioxidants in managing hypertension and reducing mortality risk. Additional research will be essential to validate the observed associations and ascertain potential therapeutic implications for individuals grappling with hypertension.

Data availability statement

The National Health and Nutrition Examination Survey dataset is publicly available at the National Center for Health Statistics of the Center for Disease Control and Prevention (https://www.cdc.gov/nchs/nhanes/index.htm). The mortality data were sourced from the National Death Index (NDI) database (https://www.cdc.gov/nchs/data-linkage/mortality-public.htm).

Ethics statement

The studies involving humans were approved by The National Center for Health Statistics Research Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

HQ: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. LS: Writing – review & editing, Supervision, Funding acquisition. DX: Writing – review & editing, Supervision, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1371928/full#supplementary-material

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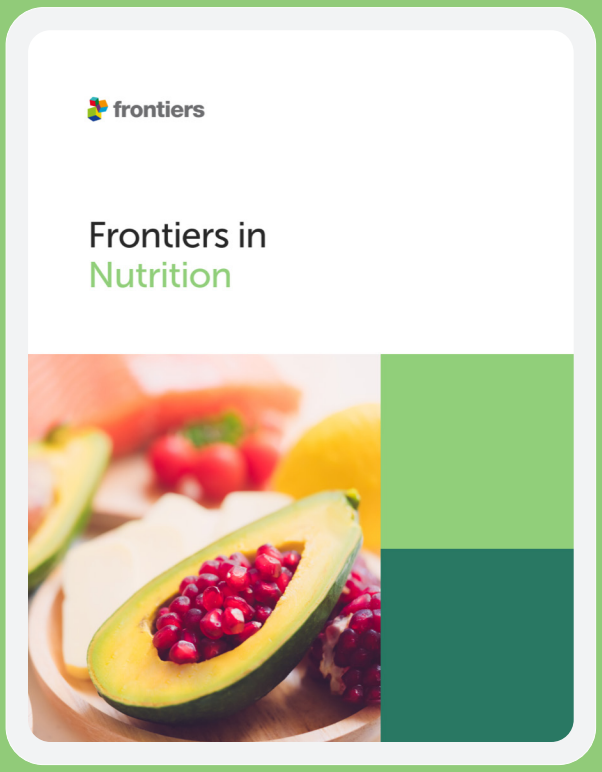

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