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Body composition changes and nutrition therapy in surgical oncology patients

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Body composition changes and nutrition therapy in surgical oncology patients

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Table of contents

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The geriatric nutritional risk index is an effective tool to detect GLIM-defined malnutrition in rectal cancer patients

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Background: This study aimed to investigate the value of the Geriatric Nutritional Risk Index (GNRI), prognostic nutritional index (PNI), and advanced lung cancer inflammation index (ALI) scores in detecting malnutrition in patients with rectal cancer; the Global Leadership Initiative on Malnutrition (GLIM) was used as the reference criterion.

Materials and methods: This study included patients with rectal cancer who underwent proctectomy. GNRI, PNI, and ALI were calculated to detect the GLIM-defined malnutrition using the Receiver operating characteristic (ROC) curves. Univariate and multivariate logistic regression analyses were used to evaluate the association between the nutritional tools and postoperative complications. Kaplan-Meier survival curves, log-rank tests, and univariate and multivariate Cox regression analyses were used to clarify the relationship between nutritional tools and overall survival (OS).

Results: This study enrolled 636 patients with rectal cancer. The GNRI demonstrated the highest sensitivity (77.8%), pretty specificity (69.0%), and the largest AUC (0.734). The GNRI showed good property in predicting major postoperative complications. All three nutritional tools were independent predictors of OS.

Conclusion: The GNRI can be used as a promising alternative to the GLIM and is optimal in perioperative management of patients with rectal cancer.

KEYWORDS

GLIM, GNRI, PNI, ALI, malnutrition, rectal cancer

Introduction

The third most common form of cancer is colorectal cancer (CRC), but the CRC-related mortality rate ranks second. In 2020, an estimated 1.9 million cases and 935,000 deaths will be attributed to colorectal cancer (including anal cancer), representing approximately one in 10 cancer cases and deaths (1). Patients with cancer often experience malnutrition, which is related with increased postoperative complications and mortality (2, 3). Thus, the nutritional status of patients with cancer should be assessed, and nutritional interventions should be provided as necessary in the perioperative period.

Many approaches have been used to screen and assess malnutrition. Additionally, quantitative nutritional tools have been developed to predict adverse outcomes. The geriatric nutritional risk index (GNRI) is an easy screening nutritional tool that combines serum albumin levels with ideal body weight to assess nutritional risk (4). The GNRI is related with poor prognosis in various malignancies and can be applied not only in elderly patients but also in young patients (5). The prognostic nutritional index (PNI), based on total lymphocyte counts and serum albumin levels, has been shown to be a prognostic indicator in many types of malignancies (6). The advanced lung cancer inflammation index (ALI), which is composed of serum albumin levels, neutrophil-lymphocyte ratio (NLR) and body mass index (BMI), is related with the poor outcomes in patients with different types of cancer (7–9). Based on the routine examination of biochemical and anthropometric measurements, all quantitative and objective nutritional tools facilitate the simplification of nutritional assessment and dynamic surveillance.

Despite the fact that malnutrition poses a major global health concern linked to an increased risk of morbidity, mortality, and costs, the clinical diagnostic criteria have not been universally agreed upon. To find an approach to secure broad global acceptance, the Global Leadership Initiative on Malnutrition (GLIM) has established a new consensual criteria report to build universal criteria for malnutrition diagnosis (10). GLIM is a two-step model for risk screening and diagnostic assessment. Since its introduction, the GLIM has been validated in a variety of diseases, including cancer, chronic liver disease, chronic kidney disease, and heart failure (11–14).

Quantitative nutritional tools have not been validated with the standard malnutrition diagnosis criteria as a reference for patients with rectal cancer. Therefore, we aimed to investigate the value of the GNRI, PNI, and ALI scores in detecting malnutrition using the GLIM as a reference criterion in patients with rectal cancer.

Materials and methods

Patients

This study included patients with rectal cancer who underwent proctectomy between January 2013 and April 2019 at the Anorectal Surgery Department of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University. Inclusion criteria included the following: (1) age $\geq$ 18 years, (2) American Society of Anesthesiologists (ASA) grade $\leq$ III, and (3) available preoperative abdominal CT scans. Patients with metastatic cancer were excluded from this study. The data collection protocol for this study was approved by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (LCKY2020–209). Informed consent was obtained from all participants.

Data collection

Data was collected on the following parameters: (1) general features, including age, gender, height, weight, BMI, Charlson comorbidity index (CCI) score, ASA grade, and previous abdominal surgery; (2) laboratory features, including hemoglobin, albumin, neutrophil, lymphocyte, and NLR; (3) clinicopathological features, including tumor size, tumor location, tumor differentiation, tumor stage, node stage, and pathological tumor node metastasis (TNM); and (4) postoperative short-term and long-term outcomes, including postoperative major complications [major complications classified as Clavien–Dindo classification grade $\geq$ II. Complications of the highest grade were recorded when more than one type of complication occurred (15)] and mortality.

Assessment of skeletal muscle index

Using specialized imaging software (INFINITT Healthcare Co, Ltd), preoperative abdominal CT images at the third lumbar vertebra (L3) level were obtained to determine skeletal muscle mass. Muscle tissues were identified using a Hounsfield unit (HU) threshold ranging from −29 to 150. Skeletal muscle index (SMI) was calculated as the cross-sectional area of the skeletal muscle mass divided by the square of the height (m). SMI cut off values were determined by our previous study (16).

Nutritional assessment

GLIM is a two-step model for diagnosing malnutrition. The first step is to perform malnutrition risk screening to identify

at-risk individuals. In this study, we used the Nutritional Risk Screening 2002 (NRS 2002). NRS 2002 $\geq$ 3 was considered to at risk of malnutrition. The second step requires at least one of the three phenotypic criteria [non-volitional weight loss, low BMI and reduced muscle mass] and one of the two etiologic criteria (reduced food intake or assimilation and disease burden/inflammation) for the diagnosis of malnutrition (10). The definition of non-volitional weight loss is exceeding 5% within 6 months or more than 10% beyond 6 months. Low BMI was defined as BMI <18.5 kg/m^2 if patients aged $\geq$ 70 years, or BMI $<$ 20 kg/m^2 if patients aged $<$ 70 years. Reduced muscle mass was defined as low SMI. Malnutrition was diagnosed based on the phenotypic criteria in this study, because one of the etiologic criteria (disease burden) had already been met.

GNRI was calculated as follows: GNRI = 1.489 $\times$ albumin (g/L) + 41.7 $\times$ present body weight/ideal body weight (the ideal body weight was calculated using Lorentz equations) (4). PNI formula was as follows: PNI = albumin (g/L) + 5 $\times$ total lymphocyte count (10^9/L) (17). ALI was calculated using the following formula: ALI = BMI $\times$ albumin (g/dL) / NLR (9). According to Youden's index, a GNRI $<$ 98, PNI$<$ 45.5, or ALI $<$ 40 were defined as malnutrition.

Follow-up

Follow-up with patients *via* telephone or outpatient visits was regularly conducted from enrollment until death, or until the end of the study in August 2022, or for more than 8 years. Patients were followed up 1 month after surgery, every 3 months for 2 years, and every 6 months thereafter. From the date of surgery until the date of death, overall survival (OS) was calculated.

Statistical analysis

In continuous variables, mean and standard deviation (SD) or median and interquartile range (IQR) are shown. The categorical variable is presented as number and proportion. The optimal cutoff thresholds for the GNRI, PNI, and ALI are determined by receiver operating characteristic (ROC) curves with Youden's index correction. Univariate and multivariate logistic regression analyses are preformed to evaluate the relationship between the nutritional tools and postoperative complications. Kaplan-Meier survival curves, log-rank tests, and univariate and multivariate Cox regression analyses are used to clarify the association between nutritional tools and OS. Multivariate analysis is conducted on factors with $P < 0.10$ in the univariate analysis. Statistics assume significance when both sides of the *P*-value are lower than 0.05. The data were analyzed

TABLE 1 The patients' clinical characteristics.

Characteristics	Overall ($n = 636$)
General feature	
Age, median (IQR), years	65 (17)
<65	305 (48.0)
≥65	331 (52.0)
Gender	
Male	385 (60.5)
Female	251 (39.5)
Height, median (IQR), m	1.64 (0.08)
Weight, median (IQR), kg	60.99 (10.22)
SMI, mean (SD), cm^2/m^2	42.57 (8.49)
BMI, median (IQR), kg/m^2	22.41 (4.07)
<18.5	72 (11.3)
18.5–23.9	369 (58.0)
≥24	195 (30.7)
Charlson comorbidity index	
0	436 (68.6)
≥1	200 (31.4)
ASA grade	
I	64 (10.1)
II	469 (73.7)
III	103 (16.2)
Previous abdominal surgery	
No	578 (90.9)
Yes	58 (9.1)
Laboratory feature	
Hemoglobin, median (IQR), g/L	130 (21)
Albumin, median (IQR), g/L	39.1 (5.4)
Neutrophil, median (IQR), 10^9/L	3.69 (1.61)
Lymphocyte, median (IQR), 10^9/L	1.74 (0.73)
Neutrophils/lymphocytes ratio, median (IQR)	2.12 (1.34)
Clinicopathological feature	
Tumor size, median (IQR), cm	4.0 (2.0)

(Continued)

TABLE 1 (Continued)

Characteristics	Overall ($n = 636$)
Tumor location	
Upper	501 (78.8)
Lower	135 (21.2)
Tumor differentiation	
Well differentiated	554 (87.1)
Poorly differentiated	82 (12.9)
Tumor stage	
Tis, T1	58 (9.1)
T2	158 (24.8)
T3	353 (55.5)
T4	67 (10.5)
Node stage	
N0	370 (58.2)
N1	162 (25.5)
N2	104 (16.3)
TNM stage	
I, Tis	175 (27.5)
II	192 (30.2)
III	269 (42.3)
Nutrition-related feature	43.22 (8.58)
NRS-2002	
No nutritional risk	450 (70.8)
Nutritional risk	186 (29.2)
Phenotypic criteria	
Weight loss	54 (8.5)
Low BMI	99 (15.6)
Low skeletal muscle index	192 (30.2)
GLIM	114 (11.4)
Normal	478 (75.2)
Malnutrition	158 (24.8)
GNRI	
Normal	365 (57.4)
Malnutrition	271 (42.6)
PNI	
Normal	439 (69.0)
Malnutrition	197 (31.0)
ALI	
Normal	338 (53.1)
Malnutrition	298 (46.9)

Values are shown as number (%) unless otherwise indicated. IQR, interquartile range; SD, standard deviation; SMI, skeletal muscle index; BMI, body mass index; ASA, American Society of Anesthesiologists; TNM, tumor node metastasis; GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; ALI, advanced lung cancer inflammation index.

using SPSS version 26.0 and R software (version 4.2.1, https://cran.r-project.org).

Results

This study enrolled 636 patients with rectal cancer. As shown in Table 1, the median age was 65 years, median height was 1.64 m, median weight was 60.99 kg, mean SMI was 42.57 cm^2/m^2, and median BMI was 22.41 kg/m^2; furthermore, there were 385 (60.5%) male patients, and 200 (31.4) patients with CCI $\geq$1; the median tumor size was 4.0 cm, with 135 (21.2%) cases of lower location, and 82 (12.9%) cases of poor differentiation. There were 175 (27.5%) patients with TNM stage 0/I, 192 (30.2%) with stage II, and 269 (42.3%) with stage III. 158 (24.8%) patients were GLIM-defined malnutrition, and the malnutrition prevalence rates of GNRI, PNI, and ALI were 42.6, 31.0, and 46.9%, respectively.

Figure 1 shows the relationship between the nutritional tools and GLIM-defined malnutrition. Of the 24.8% of the cohort with GLIM-defined malnutrition, 19.3% were categorized as malnutrition by the GNRI, 10.5% were categorized as malnutrition by the PNI, and 16.4% were categorized as malnutrition by the ALI. A cross-tabulation of the nutritional tools and GLIM-defined malnutrition results is provided in Table 2.

Table 3 illustrates the sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and area under the curve (AUC) of the nutritional tools for identifying GLIM-defined malnutrition. The GNRI demonstrated the highest sensitivity (77.8%), pretty specificity (69.0%), and the largest AUC (0.734).

As shown in Table 4, GLIM [odds ratio (OR): 1.735, 95% confidence interval (CI): 1.165–2.585; $P = 0.007$] and GNRI (OR: 1.647, 95% CI: 1.143–2.373; $P = 0.007$) were associated with postoperative complications in the univariate analysis. In the subsequent multivariate analysis, GLIM (OR: 1.865, 95% CI: 1.243–2.797; $P = 0.003$) and GNRI (OR: 1.669, 95% CI: 1.154–2.415; $P = 0.007$) were still associated with postoperative complications. Details of postoperative complications are shown in Supplementary Table 1.

There were 135 deaths (21.2%) during follow-up. The median follow-up time was 4.94 years (IQR: 3.38–6.70). Figure 2 showed the Kaplan-Meier curves for overall survival by the category of each tool in rectal cancer. As shown in Table 5, GLIM (OR: 2.129, 95% CI: 1.542–2.872; $P < 0.001$), GNRI (OR: 1.975, 95% CI: 1.404–2.778; $P < 0.001$), PNI (OR: 1.871, 95% CI: 1.330–2.631; $P < 0.001$), and (OR: 1.862, 95% CI: 1.321–2.625; $P < 0.001$) were associated with worse OS. Considering the confounding factors in the multivariate analysis, GLIM (OR: 1.650, 95% CI: 1.147–2.375; $P = 0.007$), GNRI (OR: 1.478, 95% CI: 1.037–2.107; $P = 0.031$), PNI (OR: 1.539, 95% CI:

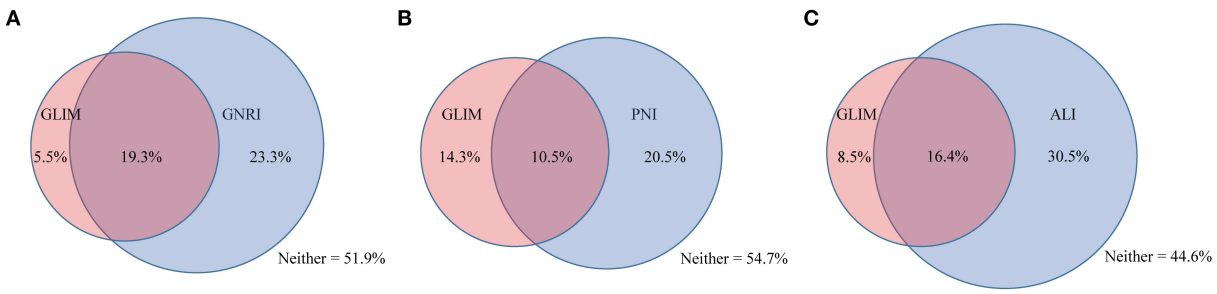

FIGURE 1
The relationship between GLIM and other nutritional tools. The relationship between GLIM and **(A)** GNRI, **(B)** PNI, **(C)** ALI. GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; ALI, advanced lung cancer inflammation index.

TABLE 2 Cross tabulation of the results of nutritional tools and GLIM.

Nutrition screening tool	GLIM-malnutrition	Normal
GNRI		
Score < 98 (malnutrition)	123 (19.3)	148 (23.3)
Score ≥ 98 (normal)	35 (5.5)	330 (51.9)
PNI		
Score < 45.5 (malnutrition)	67 (10.5)	130 (20.5)
Score ≥ 45.5 (normal)	91 (14.3)	348 (54.7)
ALI		
Score < 400 (malnourished)	104 (16.4)	194 (30.5)
Score ≥ 400 (normal)	54 (8.5)	284 (44.6)

Values are shown as number (%). GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; ALI, advanced lung cancer inflammation index.

TABLE 3 Statistical evaluations of the nutritional tools compared with GLIM criteria for the diagnosis of malnutrition.

	GNRI	PNI	ALI
Sensitivity (%)	77.8	42.4	65.8
Specificity (%)	69.0	72.8	59.4
Positive predictive value (%)	45.4	34.0	34.9
Negative predictive value (%)	90.4	79.3	84.0
Positive likelihood ratio	2.5	1.6	1.6
Negative likelihood ratio	0.3	0.8	0.6
AUC	0.734	0.576	0.626

GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; ALI, advanced lung cancer inflammation index. AUC, area under the curve.

1.082–2.189; $P = 0.016$), and ALI (OR: 1.620, 95% CI: 1.143–2.297; $P = 0.007$) were still associated with worse OS.

Discussion

To our knowledge, this is the first study to investigate three nutritional tools GNRI, PNI, and ALI in detecting GLIM-defined malnutrition in patients with rectal cancer. The GNRI

TABLE 4 Univariate and multivariate logistic regression analysis of the association between the nutritional tools and postoperative complications.

Tools	Univariate analysis HR (95% CI)	*P*	Multivariate analysis[a] HR (95% CI)	*P*
GLIM				
Normal	Reference		Reference	
Malnutrition	1.735 (1.165–2.585)	0.007*	1.865 (1.243–2.797)	0.003*
GNRI				
Normal	Reference		Reference	
Malnutrition	1.647 (1.143–2.373)	0.007*	1.669 (1.154–2.415)	0.007*
PNI				
Normal	Reference			
Malnutrition	1.096 (0.743–1.617)	0.645		
ALI				
Normal	Reference			
Malnutrition	1.403 (0.975–2.018)	0.068		

*Statistically significant ($P < 0.05$). GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; ALI, advanced lung cancer inflammation index. [a]Adjusted by age, gender, Charlson Comorbidity Index, ASA grade, previous abdominal surgery, tumor size, tumor location, tumor differentiation, TNM stage.

demonstrated the highest sensitivity (77.8%), pretty specificity (69.0%), and the largest AUC (0.734). GNRI is associated with postoperative complications and OS. Furthermore, all three nutritional tools were independent predictors of OS. The GNRI performs optimally among three nutritional tools, and we anticipate that it will substitute for the GLIM in specific situations.

The prevalence of GLIM-defined malnutrition ranged widely from 11.9 to 87.9% (11). Different subgroups of patients and different combinations of criteria in the GLIM criteria can explain these variations. In this study, the prevalence of GLIM-defined malnutrition was 24.8%, and other nutritional tools classified 31.0–46.9% of patients with rectal cancer as malnourished. Recently, Song et al. (3) reported that the

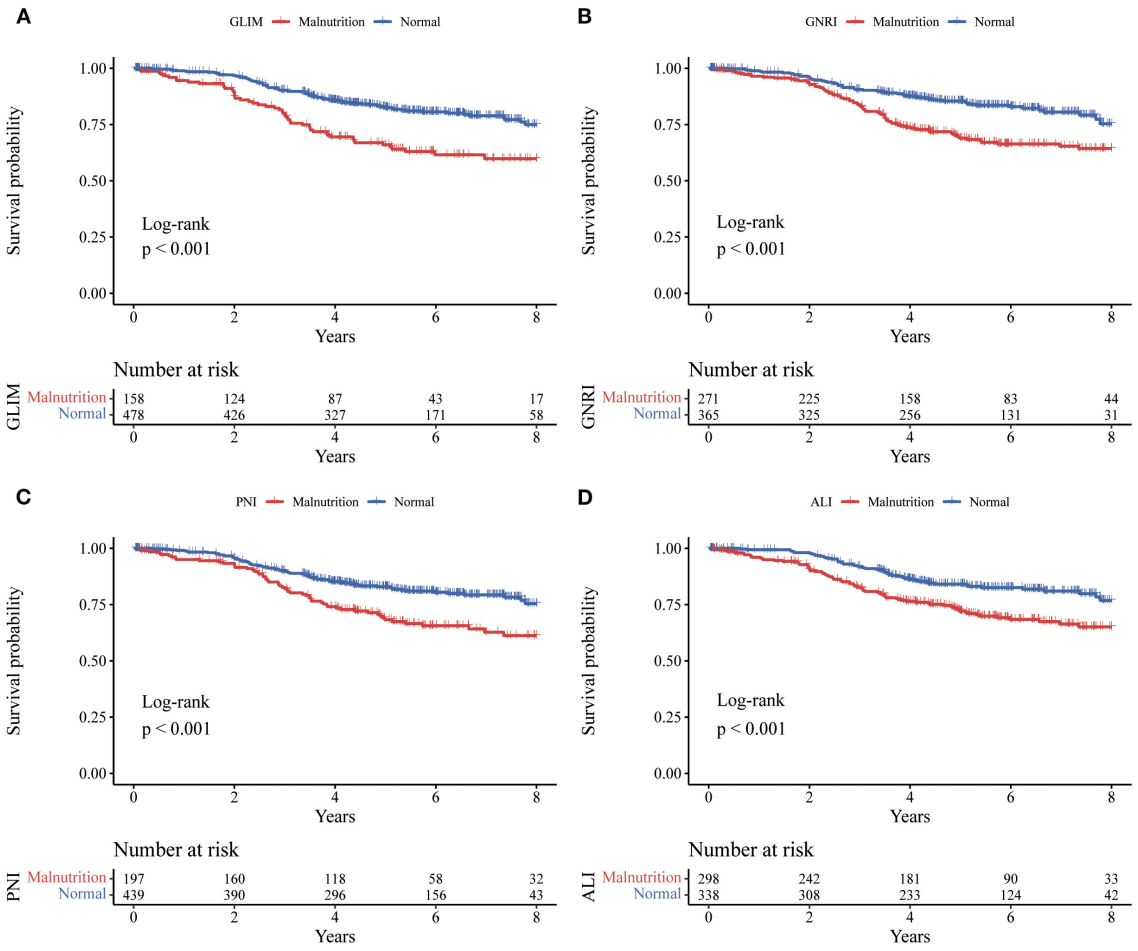

FIGURE 2
Kaplan-Meier curves for overall survival by the category of each tool in rectal cancer. Kaplan-Meier curves **(A)** for the GLIM, **(B)** for the GNRI, **(C)** for the PNI, and **(D)** for the ALI. GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; ALI, advanced lung cancer inflammation index.

prevalence of GLIM-defined malnutrition was 23.6% in patients with colorectal cancer, which is similar to the prevalence of GLIM-defined malnutrition in this study. Many previous studies have demonstrated that malnutrition is both a short and long-term risk factor. Malnutrition is a risk factor for postoperative complications and mortality in various malignancies, because malnutrition can affect the progression and therapeutic responses of cancer (18–20). Malnutrition is estimated to be responsible for 10–20% of deaths in patients with cancer rather than the tumor itself (21). Therefore, it is essential to assess the nutritional status of patients with cancer.

Previous studies compare the malnutrition risk screening tools that identify whether patients "at risk" status, like the NRS-2002, Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment Short Form (MNA-SF) Patient-generated Subjective Global Assessment (PG-SGA) with the GLIM criteria in patients with cancer (22, 23). However, we do not believe that this is appropriate. GLIM emphasizes that identifying "at risk" status using a validated screening tool is the first key step in evaluating nutritional status. However, Zhang et al. (22) diagnosed GLIM-defined malnutrition without a first-step malnutrition risk screening. Huang et al. (23) reported no clear indication of which nutritional risk screening tool was used. Henriksen et al. (24) showed that different numbers of patients were diagnosed with malnutrition when different screening tools were used during the first step of the GLIM process. Thus, we compared three quantitative nutritional tools using the GLIM criteria in patients with rectal cancer. During the current COVID-19 pandemic, it has become more difficult to conduct traditional nutritional assessments and interventions because of social segregation and recommendations for reducing close contact. Quantitative and objective nutritional tools facilitate simplification of nutritional assessments and dynamic

TABLE 5 Univariate and multivariate Cox regression analysis of the association between the nutritional tools and overall survival.

Tools	Univariate analysis HR (95% CI)	*P*	Multivariate analysis[a] HR (95% CI)	*P*
GLIM				
Normal	Reference		Reference	
Malnutrition	2.129 (1.542–2.872)	< 0.001*	1.650 (1.147–2.375)	0.007*
GNRI				
Normal	Reference		Reference	
Malnutrition	1.975 (1.404–2.778)	< 0.001*	1.478 (1.037–2.107)	0.031*
PNI				
Normal	Reference		Reference	
Malnutrition	1.871 (1.330–2.631)	< 0.001*	1.539 (1.082–2.189)	0.016*
ALI				
Normal	Reference		Reference	
Malnutrition	1.862 (1.321–2.625)	< 0.001*	1.620 (1.143–2.297)	0.007*

*Statistically significant ($P < 0.05$). GLIM, Global Leadership Initiative on Malnutrition; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; ALI, advanced lung cancer inflammation index. [a]Adjusted by age, gender, BMI, Charlson Comorbidity Index, ASA grade, previous abdominal surgery, tumor size, tumor location, tumor differentiation, TNM stage.

surveillance. Therefore, it is important to validate these nutritional tools.

In the present study, the GNRI was in good agreement with the GLIM. This association may be explained by the factors that constitute the indices. The GNRI is composed of serum albumin, present body weight and ideal body weight. Serum albumin levels have traditionally been considered to reflect the nutritional status and protein reserves of a person (25). There is also a close relationship between serum albumin levels and systemic inflammation in patients with cancer. Inflammatory cytokine levels surge as cancer cells progress, resulting in the albumin synthesis suppression, degradation promotion, and capillary escape (26). Therefore, serum albumin as a supportive proxy measure of inflammation is one of the etiologic criteria of GLIM (10). As for the other factors of the GNRI, the parameter of present body weight/ideal body weight cannot reflect the body composition precisely, while it may describe skeletal muscle mass macroscopically (4). In this study, the prevalence of reduced mass index was 30.2%, which was the most predominant of the three phenotypic criteria. This may explain why the GNRI has high agreement with the GLIM. Consistent with previous literature (5), we found that a low GNRI was negatively associated with postoperative complications and OS.

The PNI includes only two laboratory indicators (serum albumin and lymphocytes), without any anthropometric measurements. Serum albumin is a reflection of nutritional status and inflammation. Similar to serum albumin, lymphocytes reflect not only nutritional status, but also systemic inflammation (27). Accordingly, poor agreement with the GLIM for identifying malnutrition may be reasonable. In the present study, we found that PNI was associated with OS, but not with postoperative complications.

ALI, consisting of BMI, albumin, and NLR, is a recently described new tool for evaluating the nutritional status of patients with tumors. The specific feature of this index is a comprehensive formula that evaluates both nutritional status and inflammation because covariates of both aspects are included. Although BMI is used as a traditional nutritional indicator is used in the etiologic criteria for GLIM, the prevalence of low BMI is 15.6%. Huang et al. (28) reported that the prevalence of GLIM-defined malnutrition cannot be neglected by 11.9% of patients with obesity who have cancer. These factors may have contributed to the poor agreement between ALI and GLIM. Yin et al. (9) reported that ALI is associated with postoperative surgical site infection. Unfortunately, we did not classify postoperative complications as infectious or non-infectious in this study. In line with previous evidence, our study demonstrated that ALI is an independent prognostic marker for OS in patients with cancer.

This study has some limitations that should be considered. Firstly, even though we successfully validated our internal results, we did not conduct an external validation. Second, the nutritional tools were evaluated only once on admission. Dynamic changes in nutritional tools, which may be a better predictor of worse outcomes, were not examined in our study. Third, despite our attempts to minimize confounding factors, the retrospective nature of our analysis posed a risk of selection bias. Finally, this was a retrospective study among Chinese patients with rectal cancer, which may not be applicable to other ethnic populations and regions. In the future, a multicenter prospective study in different populations is required to validate our findings.

Conclusion

In conclusion, this study demonstrated the superiority of GNRI in identifying GLIM-defined malnutrition and predicting postoperative complications in patients with PNI, and ALI. Regardless of the nutritional tools used to assess the nutritional status of the patients with rectal cancer, the OS of patients with malnutrition was worse than that of patients without malnutrition. Therefore, nutritional assessments should be highlighted in the management of patients with rectal cancer. In particular, the GNRI can be used as a promising alternative

to the GLIM in some special situations, such as the current COVID-19 pandemic.

Data availability statement

The datasets presented in this article are not readily available because the data presented in this study are available on request from the corresponding authors. The data are not publicly available due to patients' privacy. Requests to access the datasets should be directed to C-GZ, zhengchenguo_80@163.com.

Ethics statement

This study was approved by the Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (LCKY2020–209). Informed consent was obtained from all participants.

Author contributions

C-GZ and C-JZ designed and revised the study. S-YY, X-CZ, and Y-TS collected the data. X-YC and K-KC did the analysis and interpretation of data. X-YC and YL did the drafting of manuscript. All authors contributed to the article and approved the submitted version.

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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.2022.1061944/full#supplementary-material

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Muscle loss 6 months after surgery predicts poor survival of patients with non-metastatic colorectal cancer

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Background: Muscle loss is a common characteristic of cancer-related malnutrition and a predictor of poorer prognosis in oncological patients. This study evaluated the association between altered body composition 6 months after surgery and the prognosis in patients with non-metastatic colorectal cancer.

Materials and methods: A total of 314 patients who underwent elective curative surgery were enrolled in the study. The third lumbar CT images on preoperative and 6-months postoperative were collected to calculate the skeletal muscle index (SMI), visceral adiposity index (VATI), and subcutaneous adiposity index (SATI). Sarcopenia was defined by the cut-off values reported in the literature, and risk factors affecting overall survival (OS) and disease-free survival (DFS) in CRC were analyzed using Cox regression models.

Results: Eighty-two of 314 patients (26.1%) with CRC were diagnosed with sarcopenia before surgery, the preoperative sarcopenia was not significantly associated with the prognosis of CRC patients. There were significant differences in frequency of complications between patient groups according to sarcopenia (41.5 vs. 21.4%, $p = 0.004$). The Postoperative LOS (11.21 ± 3.04 vs. 8.92 ± 2.84, $p < 0.001$) was longer in the sarcopenia group than in the non-sarcopenia group, and 30-d readmission (24.4 vs. 6.0%, $p < 0.001$) was higher in the sarcopenia group compared to the non-sarcopenia group. In multivariate analysis, 6-months SMI loss > 10% after surgery was independently associated with poorer OS [hazard ratio (HR) = 3.74; 95% confidence interval (CI) 1.96 to 7.12; $P < 0.001$] and DFS (HR = 3.33; 95% CI,

1.71 to 6.47; $P < 0.001$). SMI changes were moderately correlated with changes in body mass index (BMI) ($R = 0.47$, $P < 0.001$).

Conclusion: 6-months muscle loss after surgery may affect overall and disease-free survival and was an independent predictor of prognosis in patients with CRC.

KEYWORDS

colorectal cancer, sarcopenia, skeletal muscle loss, visceral adipose tissue, survival

Introduction

Colorectal cancer (CRC) is one of the common malignancies of the gastrointestinal tract in China, with the third-highest incidence and the fifth-highest mortality rates among all cancers in China (1). Compared to the average population, the incidence of malnutrition in CRC patients is even higher at 40 to 80% (2). Cancer cachexia is defined as body weight loss of $\geq$ 5% during the previous 6 months, or $\geq$ 2% if body mass index $<$ 20 kg/m^2 (3). It's a disease characterized by weight loss, specifically loss of skeletal muscle and adipose tissue, which may lead to weight loss and sarcopenia. Adipose tissue is strongly associated with the development of CRC, and obesity not only increases the risk of CRC but has also been shown to be an independent risk factor for CRC prognosis (4). In addition, some researchers have concluded that the presence of preoperative sarcopenia affects the prognosis of many malignancies, including CRC (5), but some studies (6, 7) have contradicted this finding and thus remains doubtful. This may be due to the fact that most of the previous studies were based on the body composition of the patients before treatment. However, the body composition in patients with malignancy is dynamic and skeletal muscle and adipose tissue may increase or decline as the disease progresses or treatment is administered. Therefore, it is worth considering whether body composition observations at a particular period are sufficiently descriptive or representative of predicting patient outcomes. However, there is a lack of data on the potential impact of changes in skeletal muscle and adipose tissue during treatment on the prognosis of CRC patients.

In terms of methods to assess the nutritional status of patients, studies have shown that the cross-sectional areas of skeletal muscle and adipose tissue at the level of the third lumbar vertebra (L3) on abdominal computed tomography (CT) are strongly correlated with the total body skeletal muscle and fat masses, and that CT images can provide objective qualitative and quantitative measurements of the patient's body composition (8, 9). CT images are widely used in the diagnostic examination, radiotherapy (RT) planning and long-term follow-up of CRC patients; clinicians can easily access body composition change during treatment. The ease of use and safety of the method and no additional expenses to the patient has made CT-based measurement of body composition one of the most popular research methods in recent years.

We hypothesized that sarcopenia, skeletal muscle loss, and adipose tissue change during treatment would affect patient outcomes. Therefore, This study collected abdominal CT images data from CRC patients before and after surgery to assess the impact of skeletal muscle and adipose tissue changes on clinical outcomes in CRC patients.

Patients and methods

We retrospectively analyzed a total of 514 patients with CRC who underwent surgical resection with curative intent at Xuzhou Central Hospital from January 2015 and May 2017. Patients were excluded if they were died within 6 months after surgery (n = 21), did not have a preoperative or postoperative CT scan (n = 81), or if they had metastatic disease (n = 26), or missing visit (72). The final sample size was 314 patients. The study was conducted after review and approval by the Ethics Committee of Xuzhou Central Hospital.

The same board-certified colorectal surgeons treated all patients, and all enrolled patients underwent radical surgery. We obtained data regarding patients' sex, age, height, weight, pathological TNM stage, and CT images from medical records. These were used to calculate BMI and body composition. A routine preoperative CT image was obtained before surgery, and a postoperative CT image was obtained close to 6 months after surgery.

Body composition measurement and data collection

The third lumbar (L3) vertebra was selected as a standardized landmark. Preoperative and postoperative CT scans were extracted from each patient. Each image was segmented in MATLAB software for analysis. Skeletal muscle area in this plane was calculated by using Hounsfield unit (HU) thresholds of −29 and + 150, the subcutaneous fat area was calculated from extra muscular tissue with a

density between −190 and −30 HU and visceral adipose tissue from non-subcutaneous tissue with a density between −150 and −50 HU. For assessment of inter-rater reliability, a random sample of 20 patients selected from this cohort was performed by two independent researchers. The intraobserver coefficients of variation were 0.6, 1.0, and 0.8% for the skeletal muscle area, and VAT area, SAT area respectively, which is regarded to be low. The cross-sectional skeletal muscle area (SMA), subcutaneous adipose tissue area (SATA), and visceral adipose tissue area (VATA) were measured in cm^2 and normalized by the patient's height (m^2) to calculated indexes (cm^2/m^2) for skeletal muscle (SMI), subcutaneous adipose tissue (SATI), and visceral adipose tissue (VATI).

Definitions of skeletal muscle index, subcutaneous adiposity index, and visceral adiposity index

The optimal cut-off values for SMI, SATI, and VATI have not been clearly defined, and in this study, sarcopenia was defined as an SMI of < 41.0 cm^2/m^2 according to the definition of Martin et al. (10). The cut-off values for SATI and VATI were set at the highest tertile for SATI and VATI as performed by other studies with similar population sizes (6, 11). We assessed the magnitude of change in skeletal muscle and adipose tissue before and after surgery, and patients with an increase or reduction in SMI, SATI, and VATI of > 10% were classified as having "SMI gain," "SATI gain," "VATI gain" or "SMI loss," "SATI loss," "VATI loss," respectively.

Outcome parameters

The primary endpoints of the study were OS and DFS. Overall survival was defined as the time from surgery to death from any cause for expired patients or the last follow-up for live patients. Disease-free survival was defined as the time from surgery to the time of recurrence. Secondary endpoints were postoperative complications (Clavien-Dindo Surgical Complication classification system) and hospital length of stay.

Method of follow-up

Patients are followed up from the end of treatment until September 2020. The main components of the follow-up are: whether the patient is surviving, whether the tumor has recurred, their living status and whether they have any discomfort or complications arising from the treatment received. The duration of follow-up ranged from 0.6 to 6.75 years, with a median duration of 3.9 years.

TABLE 1 Clinical characteristics and perioperative outcomes according to the preoperative SMI category (n = 314).

	Overall (n = 314)	Sarcopenia (n = 82)	Non-sarcopenia (n = 232)	p-value
Sex				< 0.001
Female	111 (35.4%)	58 (70.7%)	53 (22.8%)	
Male	203 (64.6%)	24 (29.3%)	179 (79.2%)	
Age	58.91 ± 11.48	60.87 ± 11.58	58.22 ± 11.55	0.07
BMI	23.36 ± 3.28	21.19 ± 2.81	24.16 ± 3.07	< 0.001
CRP (mg/L)				0.11
>10	36 (11.5%)	14 (17.1%)	22 (9.5%)	
<10	262 (83.4%)	65 (79.3%)	197 (84.9%)	
Missing	16 (5.1%)	3 (3.6%)	13 (5.6%)	
ALB (g/L)				0.006
>35	301 (95.9%)	74 (90.2%)	227 (97.8%)	
<35	13 (4.1%)	8 (9.8%)	5 (2.1%)	
ASA score				0.63
I	178 (56.7%)	43 (52.4%)	135 (58.2%)	
II	102 (32.5%)	30 (36.6%)	72 (31.0%)	
III	34 (10.8%)	9 (11.0%)	25 (10.8%)	
30-d Any complications				0.004
No	224 (71.3%)	48 (58.5%)	176 (75.9%)	
YES	90 (28.7%)	34 (41.5%)	56 (24.1%)	
30-d Major complications (Clavien Dindo score)				
I-II	70 (22.2%)	27 (32.9%)	43 (18.5%)	0.66
III-IV	20 (6.4%)	6 (7.3%)	14 (6.0%)	
Operation				0.32
Right hemi-colectomy	28 (8.9%)	11 (13.4%)	17 (7.3%)	
LEFT hemi-colectomy	62 (19.7%)	12 (14.6%)	50 (21.6%)	
Dixon	204 (65.0%)	51 (62.2%)	153 (65.9%)	
Miles	20 (6.4%)	8 (9.8%)	12 (5.2%)	
TNM stage				0.341
I	46 (14.6%)	15 (18.3%)	31 (13.3%)	
II	150 (47.8%)	34 (41.5%)	116 (50.0%)	
III	118 (37.6%)	33 (40.2%)	85 (36.7%)	
Neoadjuvant therapy afterpreoperative scan				0.009
No	206 (95.1%)	53 (91.8%)	185 (96.8%)	
Yes	108 (4.9%)	29 (8.2%)	47 (3.2%)	
Postoperative LOS, days	9.71 ± 2.41	11.21 ± 3.04	8.92 ± 2.84	< 0.001
≤7	165 (52.5%)	30 (36.6%)	135 (58.2%)	
>7	149 (47.5%)	52 (63.4%)	97 (41.8%)	
30-d Readmission				
No	280 (89.2%)	62 (75.6%)	218 (94.0%)	< 0.001
Yes	34 (10.8%)	20 (24.4%)	14 (6.0%)	
Incisional hernia				1
No	298 (94.9%)	78 (95.1%)	220 (94.8%)	
Yes	16 (5.1%)	4 (4.9%)	12 (5.2%)	

Statistical analysis methods

All data was statistically processed with R.4.1.0 software. The measurement data were expressed according to the type of data, with mean ± standard deviation if normally distributed and median and interquartile spacing when not normally distributed. The *t*-test was used for measurement data, the χ^2 test was used to compare count data, and the rank-sum test was used for rank data. Survival curves were plotted using the Kaplan-Meier method, and differences were analyzed using the log-rank test (Log-Rank). Survival analyses were first performed using one-way analysis of variance. Single factors with $P < 0.05$ or substantiated by evidence were further included in Cox regression for multi-factor analysis. For testing correlations between BMI changes and body composition changes, Pearson correlation and one-way analysis of variance (ANOVA) were used, where appropriate. Pearson correlation factors of > 0.7 were considered a good correlation between datasets. A correlation was considered moderate at 0.4–0.7, and poor at < 0.4. The test level was set as a two-sided test, and differences were considered statistically significant at $P < 0.05$.

Results

Patient characteristics

In total, 314 patients with biopsy-proven AJCC stage I-III colorectal cancer who had received surgical resection with curative intent were enrolled. Clinical characteristics and perioperative outcomes according to the preoperative SMI category are summarized in Table 1. The mean age of all patients was 58.91 ± 11.48 years. Eighty-two patients (26.1%) had preoperative sarcopenia. The preoperative BMI (21.19 ± 2.81 vs. 24.16 ± 3.07, $p < 0.001$) were significantly lower in the sarcopenia group than in the non-sarcopenia group. Sarcopenia was noted more frequently in female patients (70.7 vs. 22.8%, $p < 0.001$) than in male patients.

Body composition change during treatment

The body composition changes during 6 months after surgery were summarized in Table 2. Forty-nine (15.6%), 213 (67.8%), and 52 (16.6%) patients were diagnosed with SMI loss, stable SMI, or SMI gain, respectively. VATI stable, VATI loss, VATI gain was seen in 96 (30.6%), 117 (37.3%), and 101 (32.1%) patients, respectively. SATI stable, SATI loss, SATI gain occurred in 108 (34.4%), 90 (28.7%), and 116 (36.9%) patients, respectively. The prevalence of SMI loss (19.0 vs. 6.1%, $p < 0.05$) was higher in patients with non-sarcopenia than in patients with sarcopenia. The prevalence of SATI and VATI changes were not significantly different between sarcopenia and non-sarcopenia groups. Patients in the sarcopenia group had a lower SMI than the non-sarcopenia group (36.58 ± 3.38 vs. 50.21 ± 7.07, $p < 0.05$), while VATI and SATI was higher in the non-sarcopenia group, with a statistically significant difference (43.21 ± 23.55 vs. 37.08 ± 21.80, $p < 0.05$; 43.93 ± 19.70 vs. 34.53 ± 17.93, $p < 0.001$). The changes in BMI were correlated to the changes in SMI ($R = 0.47$, $P < 0.001$), SATI ($R = 0.4$, $P < 0.001$), VATI ($R = 0.33$, $P < 0.001$) (Figure 1).

TABLE 2 The body composition changes during 6 months after surgery ($n = 314$).

	Overall ($n = 314$)	Sarcopenia (82)	Non-sarcopenia (232)	*p*-value
SMI	46.65 ± 8.71	36.58 ± 3.38	50.21 ± 7.07	< 0.001
SMI change				0.0019
SMI stable (±10.0%)	213 (67.8%)	56 (68.3%)	157 (67.7%)	
SMI loss (> −10.0%)	49 (15.6%)	5 (6.1%)	44 (19.0%)	
SMI gain (> +10.0%)	52 (16.6%)	21 (25.7%)	31 (13.3%)	
SATI	41.48 ± 19.69	34.53 ± 17.93	43.93 ± 19.70	< 0.001
Pre-treatment SATI, categorical				0.012
< 47.28	207 (65.9%)	66 (80.5%)	141 (60.8%)	
> 47.28	107 (34.1%)	16 (19.5%)	91 (39.2%)	
SATI change				0.89
SATI stable (± 10.0%)	108 (34.4%)	27 (32.9%)	81 (34.9%)	
SATI loss (> −10.0%)	90 (28.7%)	23 (28.0%)	67 (28.9%)	
SATI gain (> +10.0%)	116 (36.9%)	32 (39.1%)	84 (36.2%)	
VATI	41.61 ± 23.27	37.08 ± 21.80	43.21 ± 23.55	0.04
Pre-treatment VATI, categorical				0.005
< 47.54	207 (65.9%)	65 (79.3%)	142 (61.2%)	
> 47.54	107 (34.1%)	17 (20.7%)	90 (38.8%)	
VATI change				0.13
VATI stable (± 10.0%)	96 (30.6%)	28 (34.0%)	68 (29.3%)	
VATI loss (> −10.0%)	117 (37.3%)	23 (28.0%)	94 (40.5%)	
VATI gain (> +10.0%)	101 (32.1%)	31 (38.0%)	70 (30.2%)	
Pre-treatment BMI	23.36 ± 3.28	21.19 ± 2.81	24.16 ± 3.07	< 0.001
BMI change				0.23
BMI stable (± 10.0%)	221 (70.4%)	53 (64.6%)	168 (72.4%)	
BMI loss (> −10.0%)	49 (15.6%)	13 (15.9%)	36 (15.5%)	
BMI gain (> +10.0%)	44 (14.0%)	16 (19.5%)	28 (12.1%)	

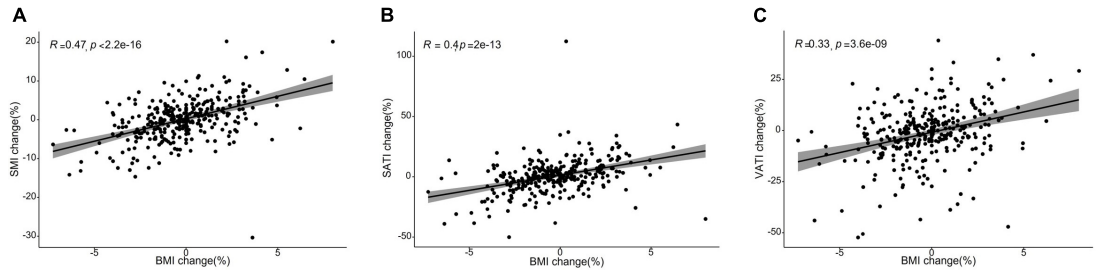

FIGURE 1
Scatter plots showing a correlation between the changes in body mass index (BMI) and body composition parameters from baseline to 6 months after treatment completion. **(A)** Skeletal muscle index (SMI) changes were moderately correlated with changes in body mass index (BMI) (R = 0.47, $P < 0.001$). **(B)** Subcutaneous adiposity index (SATI) changes were weakly correlated with changes in body mass index (BMI) (R = 0.4, $P < 0.001$). **(C)** Visceral adiposity index (VATI) changes were weakly correlated with changes in body mass index (BMI) (R = 0.33, $P < 0.001$).

Body composition change and postoperative recovery

The association between body composition and perioperative outcomes according to the preoperative SMI category were shown in Table 1. A total of 90 postoperative complications occurred in this study, of which 20 (6.4%) cases of moderate to severe (Clavien-Dindo grade III-V) complications occurred. There were significant differences in frequency of complications between patient groups according to sarcopenia (41.5 vs. 21.4%, $p = 0.004$). The Postoperative LOS (11.21 ± 3.04 vs. 8.92 ± 2.84, $p < 0.001$) was longer in the sarcopenia group than in the non-sarcopenia group, and 30-d readmission (24.4 vs. 6.0%, $p < 0.001$) was higher in the sarcopenia group compared to the non-sarcopenia group. Clinical characteristics and perioperative outcomes according to muscle change are shown in Supplementary Table 1. No significant differences were found between patients according to skeletal muscle loss in terms of postoperative outcomes, including complications, length of postoperative stay and readmission after discharge. Patients with SMI loss seemed to be more likely to have experienced incisional hernia (18.4 vs. 2.6%, $p < 0.001$) after surgery than the patients with non-SMI loss, and the results were statistically significant.

Body composition change and survival

The length of follow-up ranged from 0.6 to 6.75 years, with a median duration of 3.9 years. The 5-year overall survival (OS) and disease-free survival (DFS) rates for overall patients were 75.4 and 74.8%, respectively. No significant difference in 5-year OS (77.7 vs. 74.7%, respectively; $p = 0.90$) and DFS (72.1 vs. 76.0%, respectively; $p = 0.99$) rate between the preoperative sarcopenia and the non-sarcopenia groups (Supplementary Figures 1A,B). The 5-year OS and DFS in SMI loss, SMI stable and SMI gain groups were 52.2, 79.5, and 80.1% (Figure 2A, $p < 0.001$) and 54.8, 78.5, and 85.5% (Figure 2B, $p < 0.001$), respectively. There were no significant differences in OS and DFS between the two groups according to preoperative SATI (5-year OS: 76.1 vs. 75.1%, $p = 0.87$; 5-year DFS: 74.8 vs. 78.2%, $p = 0.52$) (Supplementary Figures 1C,D). Grouped by preoperative VATI, we found no significant difference in OS (5-year OS: 73.8 vs. 78.6%, $p = 0.41$) and DFS (74.8 vs. 78.1%, $p = 0.46$) (Supplementary Figures 1E,F). In a subgroup analysis, patients with SMI loss had worse OS and DFS in both the preoperative sarcopenia and non-sarcopenia groups (Figures 2C–F). The change in VATI, SATI and BMI were not associated with survival (Supplementary Figure 2).

Skeletal muscle index (SMI) change, TNM stage as risk factors for OS and DFS in the univariate analysis (Supplementary Table 2). After multivariate analysis, SMI change and TNM stage were independently associated with OS (HR: 3.74, 95% CI: 1.96 to 7.12, $p < 0.001$; HR: 3.08, 95% CI: 1.87 to 5.06, $p < 0.001$) and DFS (HR = 3.33; 95% CI, 1.71 to 6.47, $P < 0.001$; HR: 3.05, 95% CI: 1.82 to 5.09, $p < 0.001$) (Table 3). The preoperative BMI, SATI, VATI, and changes in VATI during treatment were not associated with OS or DFS.

Discussion

In the present study, we demonstrated that skeletal muscle loss negatively impacted oncological outcomes by decreasing OS and DFS in patients with CRC. Patients who had both preoperative sarcopenia and subsequent skeletal muscle loss had the worst OS and DFS. However, preoperative sarcopenia was not a prognostic factor of worse OS and DFS. Which, in line with the recent studies (12, 13), suggesting progressive skeletal muscle loss may be a more potent prognostic factor than a single pre-treatment measurement and highlighting the importance of preserving skeletal muscle mass during treatment in patients with CRC. According to our results, sarcopenic patients were more often readmission after discharge and with

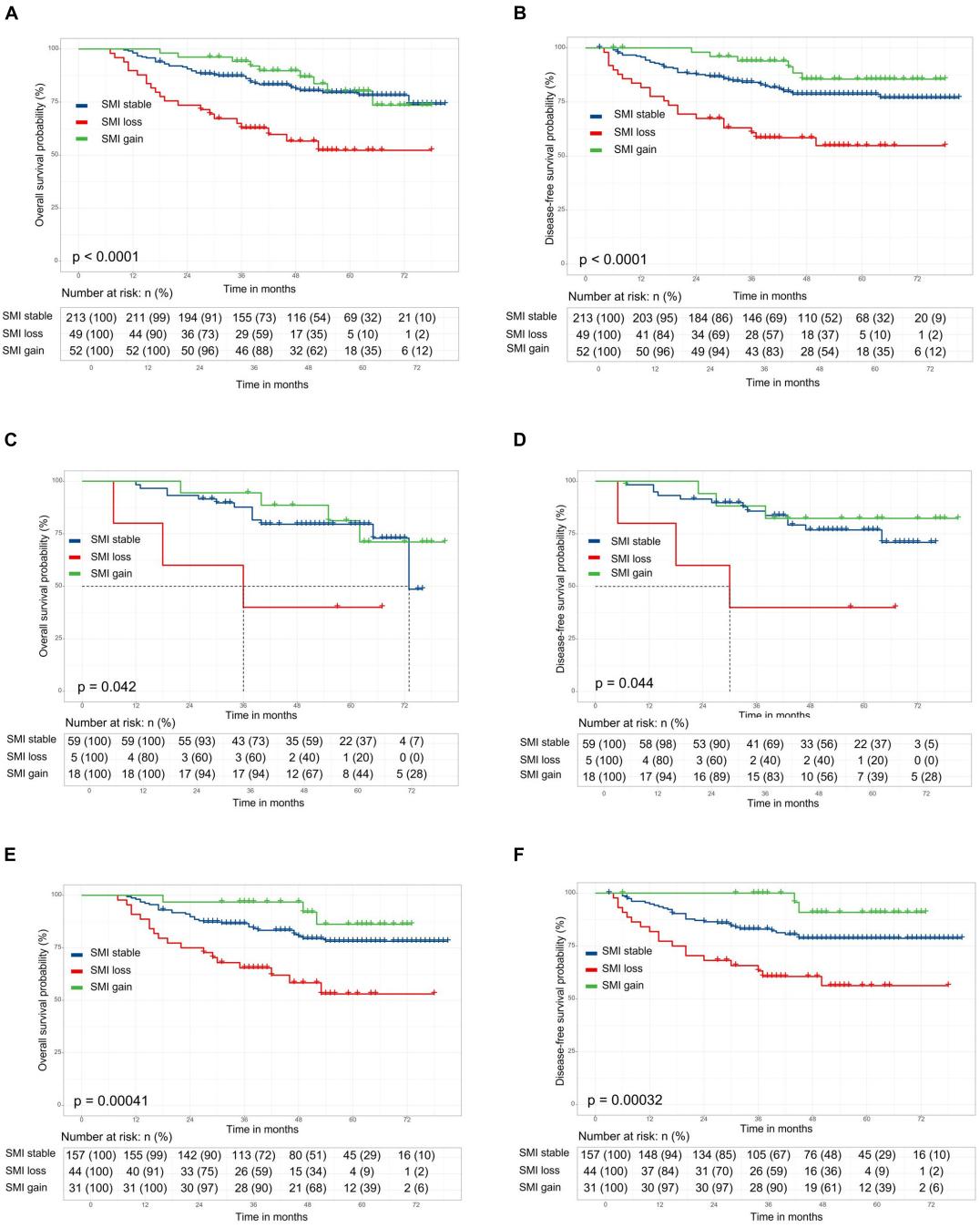

FIGURE 2
Kaplan–Meier curve demonstrating overall survival and disease-free survival according to skeletal muscle index (SMI) change. The 5-year overall survival (OS) and disease-free survival (DFS) in stocktickerSMI loss, stocktickerSMI stable, and stocktickerSMI gain groups were 52.2, 79.5, and 80.1% [**(A)**, $p < 0.001$] and 54.8, 78.5, and 85.5% [**(B)**, $p < 0.001$], respectively. In a subgroup analysis, patients with stocktickerSMI loss had worse OS and stocktickerDFS in both the preoperative sarcopenia [**(C,D)** and non-sarcopenia groups **(E,F)**].

a longer length of postoperative LOS than patients without sarcopenia. However, sarcopenia did not increase the rates of Major complications (Clavien Dindo III-V). It suggested that sarcopenia have a negative impact on recovery after colorectal cancer surgery, which is in line with the previous results (14, 15).

In terms of body composition change, we found non-sarcopenic patients were more likely to exhibit skeletal muscle loss during treatment. Because skeletal muscle area changes were used primarily to evaluate skeletal loss in this study, there was a lack of evaluation of skeletal muscle density

TABLE 3 Multivariate analysis for overall survival and disease-free survival (n = 314).

	Overall survival		Disease-free survival	
	HR and 95% CI	***P*-value**	**HR and 95% CI**	***P*-value**
SMI change				
SMI stable (± 10.0%)	Reference		Reference	
SMI loss (> −10.0%)	3.74 (1.96–7.12)	< 0.001	3.33 (1.71–6.47)	< 0.001
SMI gain (> +10.0%)	0.60 (0.27–1.35)	0.22	0.39 (0.16–0.89)	0.06
TNM stage				
I–II	Reference		Reference	
III	3.08 (1.87–5.06)	< 0.001	3.05 (1.82–5.09)	< 0.001
BMI change				
BMI stable (± 10.0%)	Reference		Reference	
BMI loss (> −10.0%)	2.04 (1.03–4.05)	0.04	1.72 (0.34–3.52)	0.14
BMI gain (> +10.0%)	1.23 (0.59–2.58)	0.58	1.15 (0.52–2.53)	0.73

changes, and in related studies it was also found that patients with sarcopenia were more likely to have decreased skeletal muscle density and fat infiltration. We also found a similar situation in our clinical study. We therefore hypothesize that the reduction in skeletal muscle area precedes the decline in skeletal muscle density and is followed by fatty infiltration. This is an interesting point for subsequent study. Therefore, In addition to advocating skeletal muscle protection for patients with sarcopenia, it is essential to preserve skeletal muscle in patients with non-sarcopenia to minimize the rate of skeletal muscle loss, thereby further blocking the change in skeletal muscle density. Though nutritional intervention combined with physical training programs is broadly accepted as therapeutic options (16) to prevent sarcopenia. The CRC patient's cohort almost consists of older patients who are not able, sometimes only for a certain period, to be included in physical activity programs. Thus, new pharmaceutical and nutritional interventions and tailor-made physical training for older people need to be explored.

Sarcopenia is considered by most to be an inevitable part of aging. However, the quality and quantity of muscle are dependent upon various factors (17, 18). Such as disease, inactivity, and poor nutrition. Our analysis found no significant differences between patients with SMI loss and non-SMI loss in terms of postoperative outcomes, including complications, length of postoperative stay, and readmission after discharge. Though preoperative sarcopenia has a negative impact on recovery after colorectal cancer surgery, the postoperative skeletal muscle loss does not appear to be related to postoperative recovery in our study. This implies that there are factors other than the postoperative recovery that impact skeletal muscle loss. However, as the interval between pre- and post-treatment CT scans was 6 months, without additional measurements during this interval, it is difficult to assess the exact relationship between postoperative recovery and skeletal muscle loss.

In addition, Ji-Bin Li et al. (19) suggested that a decrease in BMI of more than 5% showed a significantly increased risk of all-cause mortality among CRC patients. In our study, we found the same results. However, we also found that changes in BMI were much less effective in responding to patients' long-term survival prognosis compared to changes in skeletal muscle, especially with regard to DFS. In the correlation analysis, changes in BMI were moderately correlated with changes in SMI but weakly correlated with changes in SATI and VATI. It may suggest that change in BMI is not sufficiently sensitive to identify clinically meaningful alteration in body composition promptly. There is an emerging viewpoint (20–22) that sarcopenia may be obscured within the bulk of body weight, the patients with identical BMI can have various skeletal muscle. Thus, Body composition quantified using clinically acquired CT images may provide a vital sign to identify patients at increased risk of death.

Higher adiposity increases the risk of colorectal cancer (CRC) and has a negative impact on overall survival (OS) and progression-free survival (PFS) (23, 24). However, in our study, the preoperative SATI and VATI have no association with OS. Although the patients lost SATI and VATI during treatment, the adipose change was not associated with OS and DFS. This discrepancy may be attributed to the small size of our sample, the lack of an optimal cut-off value and the different treatment modalities.

In addition, this study focused on changes in skeletal muscle mass and the absence of the assessment of skeletal muscle strength and function. The lack of consideration of data such as mean skeletal muscle radial decay, patient walking speed, grip strength, and the small sample size are shortcomings of this study. Despite these limitations, the power of this study is that the included cases with detailed treatment and follow-up records, tumors were treated consistently according to clinical treatment guidelines and we conducted a multi-subgroup analysis of the data. Some of our findings are consistent with those of previous studies. Taken together, our results add to the body of evidence linking postoperative skeletal muscle loss to reduced survival.

Conclusion and implications

In summary, this retrospective study showed that 6-months muscle loss after surgery might affect overall survival and disease-free survival and was an independent predictor of prognosis in patients with CRC. Muscle loss after surgery may be a potential risk factor for incisional hernia. Adequate knowledge of changes in patient body composition by CT during CRC

treatment can help clinicians predict outcomes and target nutritional interventions, which may be beneficial in improving the prognosis of CRC patients.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Xuzhou Central Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

LZ and LG: conception and design of the study. JG and CD: imaging data analysis. LZ: drafting of the manuscript. LZ and CD: statistical analysis. All authors: acquisition, analysis, or interpretation of data, and critical revision of the manuscript for important intellectual content.

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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.2022.1047029/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Kaplan–Meier curve demonstrating overall survival and disease-free survival according to preoperative skeletal muscle index (SMI) **(A,B)**, subcutaneous adiposity index (SATI) **(C,D)**, and visceral adiposity index (VATI) **(E,F)**.

SUPPLEMENTARY FIGURE 2
Kaplan–Meier curve demonstrating overall survival and disease-free survival according to the change in visceral adiposity index (VATI) **(A,B)**, subcutaneous adiposity index (SATI) **(C,D)**, and body mass index (BMI) **(E,F)**.

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Development and validation of a radiomics-based nomogram for the prediction of postoperative malnutrition in stage IB1-IIA2 cervical carcinoma

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Objective: In individuals with stage IB1-IIA2 cervical cancer (CC) who received postoperative radiotherapy±chemotherapy (PORT/CRT), the interaction between sarcopenia and malnutrition remains elusive, let alone employing a nomogram model based on radiomic features of psoas extracted at the level of the third lumbar vertebra (L3). This study was set to develop a radiomics-based nomogram model to predict malnutrition as per the Patient-Generated Subjective Global Assessment (PG-SGA) for individuals with CC.

Methods: In total, 120 individuals with CC underwent computed tomography (CT) scans before PORT/CRT. The radiomic features of psoas at L3 were obtained from non-enhanced CT images. Identification of the optimal features and construction of the rad-score formula were conducted utilizing the least absolute shrinkage and selection operator (LASSO) logistic regression to predict malnutrition in the training dataset (radiomic model). Identification of the major clinical factors in the clinical model was performed by means of binary logistic regression analysis. The radiomics-based nomogram was further developed by integrating radiomic signatures and clinical risk factors (combined model). The receiver operating characteristic (ROC) curves and decision curves analysis (DCA) were employed for the evaluation and comparison of the three models in terms of their predictive performance.

Results: Twelve radiomic features in total were chosen, and the rad-score was determined with the help of the non-zero coefficient from LASSO regression. Multivariate analysis revealed that besides rad-score, age and Eastern Cooperative Oncology Group performance status could independently predict malnutrition. As per the data of this analysis, a nomogram prediction model was constructed. The area under the ROC curves (AUC) values of the radiomic and clinical models were 0.778 and 0.847 for the training and 0.776 and 0.776 for the validation sets, respectively. An increase in the AUC was observed up to 0.972 and 0.805 in the training and validation sets, respectively, in the combined model. DCA also confirmed the clinical benefit of the combined model.

Conclusion: This radiomics-based nomogram model depicted potential for use as a marker for predicting malnutrition in stage IB1-IIA2 CC patients who underwent PORT/CRT and required further investigation with a large sample size.

KEYWORDS

malnutrition, radiomics, nomogram, prediction, cervical cancer

Introduction

Cervical cancer (CC) remains an important health problem worldwide that is responsible for more than 600,000 new cases and 342,000 cancer-associated deaths based on the statistics of the GLOBOCAN 2020 study (1). For individuals diagnosed with International Federation of Gynecology and Obstetrics (FIGO, 2014 version) stage IB1-IIA2 CC, radical hysterectomy with lymph node dissection is the optimal therapeutic option (2). The pathological findings after surgery indicate that patients having intermediate-risk factors (such as deep stromal invasion, enlarged tumor size, or lymphatic vascular space involvement) or high-risk factors (such as positive surgical margins, lymph node metastasis, and parametrial invasion) for recurrence are recommended to receive adjuvant pelvic radiotherapy (RT) and/or platinum (cisplatin or carboplatin)-based chemoradiotherapy (CRT) to reduce the risk of tumor recurrence (3). However, around 30% of individuals with CC will still eventually develop tumor relapse, necessitating the investigation of better supportive care to improve therapeutic tolerance and reduce adverse responses in these patients (4).

Meanwhile, sarcopenia, or loss of skeletal muscle, is one of the most prevalent symptoms of malnutrition (5), and has been frequently reported as a negative factor in cancer patients at any disease stage (6, 7). In a meta-analysis, Li et al. reported that about half of the females having cancer had sarcopenia, which was significantly worse for Asian patients (8). Among the indices representing sarcopenia, the psoas parameter at the third lumbar vertebra (L3) was considered a valid indicator for identifying skeletal muscle depletion and malnutrition (9–11). In individuals with advanced lung cancer, retrospective research explored that alterations in the L3 skeletal muscle index (SMI) were consistent with the scores investigated *via* the Patient-Generated Subjective Global Assessment (PG-SGA) (12). This instrument has been considered useful for detecting malnutrition in individuals with cancer and validated on different levels (13–15). However, there are still concerns associated with patients failing to respond well to PG-SGA. In a recent surgery, Balstad and his co-authors found that an overwhelming majority of patients could complete the PG-SGA Short Form instrument properly. Though, participant- and questionnaire-linked sources of misinterpretation were still detected in some of the patients, which could lead to unfavorable results and could severely impact clinical decision-making (16, 17).

Typically, the gold standard determining skeletal muscle mass is acquired from a computed tomography (CT) scan (18) and benefits from the progress of radiomic within image processing. This study was designed to predict postoperative malnutrition assessed by means of PG-SGA with radiomic features retrieved at the psoas of L3 in individuals with FIGO stage IB1-IIA2 CC.

Patients, materials, and methods

Patients

Between July 2020 and June 2022, 120 patients with CC were retrospectively reviewed at the cancer center of Zhejiang Provincial People's Hospital (ZJPPH). The eligible patients complied with the following criteria were included: (I) they underwent pelvic lymphadenectomy and radical hysterectomy and pathological diagnosis of CC; (II) they had stage IB1-IIA2 CC based on the 2014 FIGO staging system; (III) they received PORT/CRT within 1 week after admission at the ZJPPH; IV) they had Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2 with no evidence of severe organ dysfunction. The exclusion criteria are mentioned below: (I) they received any anti-neoplastic treatments prior to surgery; (II) they had other malignant tumors that were contraindicated for RT; (III) poor image quality or visible artifacts around the L3 psoas. The patients' body mass index (BMI, kg/m^2) was adopted based on the Chinese cohort cut-off values for the identification of overweight and obesity (<24 vs. ≥ 24) (19). The ZJPPH institutional review committee granted its approval for this study (ZJPPH No. 2022-191), and informed consent was not required.

Treatment work-up and nutritional assessment

After surgery, patients were recommended to undergo adjuvant pelvic RT/CRT based on their pathological risk factors (3). The patients were immobilized in an immobilization device prior to PORT, and a scheduled abdomen–pelvis CT scan was routinely conducted to plan RT. The GE Discovery CT590 RT scanner was used to obtain CT scans. The main parameters are mentioned below: CT tube voltage and current were 120 kV and 250–400 mA, respectively. The thickness and spacing of the layer were both 5 mm. To eliminate any bias caused by iodinated contrast agents, non-enhanced CT images were used to derive the radiomic features.

The trained nutrition support team used the Chinese version of PG-SGA in the ward to investigate the nutritional status of the patients included in this study prior to PORT/CRT. During this research, the study subjects were classified into two groups based on previous studies (20, 21): the well-nourished group containing individuals with a PG-SGA score between 1 and 3 and the malnourished group containing individuals with a PG-SGA score ≥ 4.

Texture feature extraction and selection

The 3D-Slicer software (v4.11, Stable Release) was used to process the non-enhanced CT images and delineate the left and right L3 psoas

[volume of interest (VOI)]. This was carried out independently by one radiation oncologist (TS). Any voxel with an attenuation of < -30 or > 100 Hounsfield units was eliminated to prevent adjacent fat, bone, and surrounding organs (Supplementary Figure S1) (22).

Extraction of radiomic features was done using Pyradiomics (v3.6.2) package. In addition, 1,874 original features in total were extracted. For every VOI, 107 original, 465 Laplacian of Gaussian filter, 744 wavelet, 93 Square, 93 SquareRoot, 93 Logarithm, 93 Exponential, 93 Gradient, and 93 LocalBinaryPattern2D features were collected (Supplementary Table S1). Prior reports have mathematically defined these radiomic features (23), and these definitions can be explored at: https://pyradiomics.readthedocs.io/en/latest/features.html. After extraction, all radiomic features were subjected to further processing to conduct dimension reduction. Standardization and normalization of the features were done by means of the *Z*-score method before feature dimension reduction, thus removing unit limits from the data of every feature (24). In this study, the least absolute shrinkage and selection operator (LASSO) regression was employed to discover the most crucial features for predicting malnutrition to balance between over-fitting and under-fitting among variables (25).

The intra-observer and inter-observer agreements for feature extraction were determined with the help of the intra-class correlation coefficient (ICC) by comparing imaging data of 30 randomly selected L3 psoas from the study group (26). For the purpose of computing the intra-observer ICC, the extracted data between the two independent reader ones (TS) were compared. A second reader (HX) extraction was compared with the extraction of TS to determine the inter-observer ICC. Only the features having ICC values of ≥ 0.85 were chosen to conduct more investigations, while the rest of the segmentations were implemented by TS.

Development of the radiomics-based nomogram

A 7:3 ratio was used to randomly classify all eligible patients into training and validation sets. Within the training set, 15% of data was applied for inter-verification. LASSO logistic regression algorithm, with penalty parameter tuning carried out by 10-fold cross-validation, was utilized to evaluate the most significant features with non-zero coefficients to predict malnutrition (PG-SGA 1–3 vs. PG-SGA ≥ 4) in the training cohort. For each patient, the radiomic feature score (rad-score) was further calculated on the basis of the LASSO binary regression model in the training cohort. The LASSO regression is formulated below:

$$\text{Rad} - \text{score} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \ldots + \beta_n X_n$$

where $X_1, X_2 \ldots X_n$ are the different radiomic features demonstrated by the LASSO, and β_0 represented the intercept in the regression model. $\beta_1, \beta_2 \ldots \beta_n$ are the regression coefficients of the corresponding features determined in the LASSO. This score was computed individually for every patient from both sets (27).

Steps for constructing the nomogram-based predictive model have been detailed in a previous study conducted by us (28). The clinical factors identified with a *p*-value of ≤ 0.05 in the univariate analysis combined with the rad-score value were incorporated into the multivariate analysis using a logistic binary regression model with a backward model selection procedure. $p < 0.05$ indicated a statistically significant level in the model. A nomogram model that incorporated the independent clinical parameters was constructed using the multivariate analysis, and the rad-score was generated for clinical reference in the training dataset.

The predictive performances of these models (radiomics, clinical, and combined models) were further evaluated both in the training and validation cohorts using the receiver operating characteristic (ROC) curves and decision curve analyses (DCAs). Calibration curves and concordance index (C-index) were utilized for the assessment of the agreement between the malnutrition probabilities predicted by the nomogram and the actual outcomes. The methods for performing univariate and multivariate binary logistic regression and comparing the area under the ROC curves (AUCs) using Delong's test have been detailed in previous studies (29, 30).

Statistical analysis

Python programming language (v3.7.0) was used for radiomic feature extraction and data dimension reduction. Missing data (< 5%) were processed using mean substitution (31). Further statistical analysis procedures were carried out with the help of the R software v3.6.2[1] with the '*readr*, "*glmnet*, "*nomogramFormula*, "*pROC*, "*rms*, "*corrplot*' and '*rmda*' packages and the SPSS 21 (SPSS, Armonk, New York, NY, United States). Two-tailed $p < 0.05$ was considered statistically significant.

Results

Patients' clinical characteristics

This study enrolled 120 individuals with FIGO stage IB1-IIA2 CC who underwent PORT/CRT. Clinical features of subjects in the training set ($n = 84$) and validation set ($n = 36$) are enlisted in Table 1. At the time of diagnosis, the median age was 54 years (interquartile range, 47–62 years), and a total of 47 (39.2%) individuals were diagnosed with malnutrition (PG-SGA score ≥ 4) with 32 (38.1%) subjects in the training and 15 (41.7%) in the validation datasets. The distribution of the baseline features across these two cohorts showed no remarkable variations.

Radiomic feature selection

The intra-observer ICC measured according to two extractions of reader one ranged between 0.875 and 0.932. The inter-observer agreement among two readers (TS and HX) varied from 0.837 to 0.904. Favorable intra- and inter-observer feature extraction agreements were observed in the findings.

In the training cohort, the student's t-test, Levene's test, and the LASSO logistic regression analysis extracted 12 significant radiomic features with non-zero coefficients (Figures 1A,B). Further, the calculation of the rad-score was done as the sum of each feature multiplied by the non-zero coefficient from LASSO: Rad-score = −0.56187734 + 0.20554658 × wavelet.HHL_gldm_DependenceVariance +0.12534366 × log.sigma.3.0.mm.3D_glszm_LowGrayLevelZoneEmphasis + 0.09748077 × squareroot_glszm_SizeZoneNonUniformityNormalized + 0.07989539 × wavelet.

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

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TABLE 1 Baseline characteristics of 120 patients with FIGO stage IB1-IIA2 CC who underwent postoperative RT/CRT.

Characteristic	Frequency (*n*, %)	Training set (*n*, %)	Validation set (*n*, %)	*p* Value
Age at diagnosis (years)				0.098
Median (IQR)	54 (47–62)			
≤65	103 (85.8)	75 (89.3)	28 (77.8)	
>65	17 (14.2)	9 (10.7)	8 (22.2)	
ECOG PS				0.545
0–1	91 (75.8)	65 (77.4)	26 (72.2)	
2	29 (24.2)	19 (22.6)	10 (27.8)	
HPV infection				0.935
Negative and unknown	46 (38.3)	32 (38.1)	14 (38.9)	
Positive	74 (61.7)	52 (61.9)	22 (61.1)	
BMI (kg/m2)				0.898
<24	81 (67.5)	57 (67.9)	24 (66.7)	
≥24	39 (32.5)	27 (32.1)	12 (33.3)	
PG-SGA				0.430
1–3	77 (64.2)	52 (61.9)	25 (69.4)	
≥4	43 (35.8)	32 (38.1)	11 (30.6)	
Histology				
SCC	98 (81.7)	71 (84.5)	27 (75.2)	
AC and others	22 (18.3)	13 (15.5)	9 (25.0)	
Differentiation				0.905
Well and fairly	61 (50.8)	43 (51.2)	18 (50.0)	
Poorly and undifferentiated	59 (49.2)	41 (48.8)	18 (50.0)	
FIGO stage				0.300
IB	62 (51.7)	46 (54.8)	16 (44.4)	
IIA	58 (48.3)	38 (45.2)	20 (55.6)	
Surgery approach				0.931
Abdominal	84 (70.0)	59 (70.2)	25 (69.4)	
Laparoscopic	36 (30.0)	25 (29.8)	11 (30.6)	
Tumor volume (mm)				0.842
≤40	65 (54.2)	46 (54.8)	19 (52.8)	
>40	55 (45.8)	38 (45.2)	17 (47.2)	
LN metastasis				0.412
Negative	83 (69.2)	60 (71.4)	23 (63.9)	
Positive	37 (30.8)	24 (28.6)	13 (36.1)	
Margin				0.164[a]
Negative	110 (91.7)	79 (94.0)	31 (96.1)	
Positive	10 (8.3)	5 (6.0)	5 (13.9)	
Deep stromal invasion				0.276[a]
<1/2	9 (7.5)	8 (9.5)	1 (2.8)	
≥1/2	111 (92.5)	76 (90.5)	35 (97.2)	
LVSI				0.602
Negative	36 (30.0)	24 (28.6)	12 (33.3)	
Positive	84 (70.0)	60 (71.4)	24 (66.7)	

FIGO: International Federation of Gynecology and Obstetrics; CC: cervical cancer; CRT/RT: chemo-radiotherapy; IQR: IQR, interquartile range; ECOG PS: eastern cooperative oncology group performance status; HPV: human papillomavirus; BMI: body mass index; PG-SGA: patient-generated subjective global assessment; SCC: squamous cell carcinoma; AC: adenocarcinoma; LN: lymph node; LVSI: lymphatic vascular space involvement. [a]Fisher's exact test.

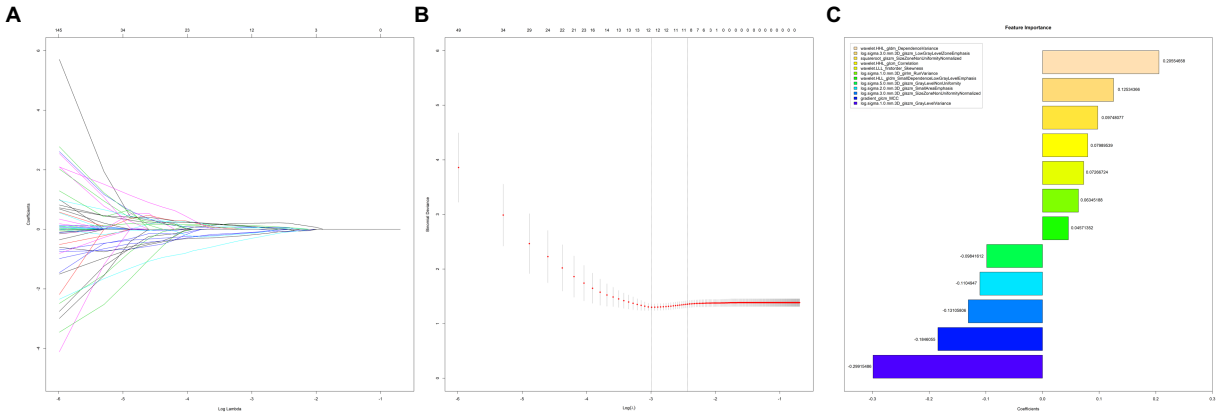

FIGURE 1
Radiomic features selection using the LASSO logistic regression model. **(A)** LASSO coefficient profiles of the 157 radiomics features. The coefficients (y-axis) were plotted against log (lambda), and the radiomics signature was constructed utilizing the selected 12 radiomic features with non-zero coefficients; **(B)**. Plotting the partial likelihood deviance against log (lambda). The upper and lower x-axis indicate the average number of predictors and the log (lambda), respectively. The y-axis denotes the partial likelihood of deviance. Utilizing the minimum criteria and one standard error of the minimum criteria, vertical lines (dotted) were created at the optimal values. The minimum criteria-based 10-fold cross-validation was utilized for the selection of the tuning parameter (λ) in the LASSO model; **(C)**. Feature importance analysis based on LASSO regression).

HHL_glcm_Correlation + 0.07266724 × wavelet.LLL_firstorder_Skewness + 0.06345188 × log.sigma.1.0.mm.3D_glrlm_RunVariance + 0.04571352 × wavelet.HLL_gldm_SmallDependenceLowGrayLevelEmphasis + −0.09841612 × log.sigma.5.0.mm.3D_glszm_GrayLevelNonUniformity + −0.1104947 × log.sigma.2.0.mm.3D_glszm_SmallAreaEmphasis + −0.13105806 × log.sigma.3.0.mm.3D_glszm_SizeZoneNonUniformityNormalized + −0.18466055 × original_glcm_MCC + −0.29915486 × log.sigma.1.0.mm.3D_glszm_GrayLevelVariance (Figure 1C).

Construction and performance of a rad-score-based nomogram

Univariate and multivariate binary logistic regression analyses were performed for the identification of predictive variables for malnutrition in the training set. Multivariate logistic binary regression analysis demonstrated that age [< 65 vs. ≥ 65, $p = 0.042$, odds ratio (OR) = 10.922] and ECOG PS (0–1 vs. 2, $p = 0.008$, OR = 8.672) were clinical factors significantly associated with malnutrition scored by PG-SGA (Table 2).

A nomogram for predicting malnutrition that integrated two clinical parameters, as demonstrated by the logistic regression and the rad-score, was further developed (Figure 2). The rad-score was regarded as the most significant prognostic parameter for malnutrition, followed by ECOG PS, and age.

The calibration plots and the C-index (0.887 for the training cohort; 0.855 for the validation cohort) revealed moderate to good agreement between the predicted and actual nutritional status between these two cohorts (Supplementary Figures S2A,B).

Performance comparison of predictive models

With the training set depicting an AUC of 0.778 [95% confidence interval (CI), 0.339–1.000] and validation set depicting 0.776 AUC (95% CI, 0.623–0.930), the radiomics model revealed a moderate to good predictive efficacy. The respective AUC values of the clinical model were 0.847 (95% CI, 0.577–1.000) in the training set and 0.776 (95% CI, 0.607–0.946) in the validation set. The respective AUC values of the combined predictive model were 0.972 (95% CI, 0.895–1.000) and 0.855 (95% CI, 0.713–0.996) for the training and validation sets. Incorporating the rad-score model into the clinical model improved prediction efficacy (Figures 3A,B). The DCAs also revealed similar results indicating that the combined prediction model yielded more net benefits for predicting malnutrition than the 'radiomics model' and 'clinical model' (Figures 4A,B). However, Delong's tests indicated no significant differences between the models.

Discussion

This research determined the predictive capability of a radiomics-based nomogram for malnutrition in patients with FIGO stage IB1-IIA2 CC. This nomogram incorporated two readily available clinical parameters and significant radiomic features extracted from indispensable CT scans of individuals with CC who were planning to receive PORT/CRT. The results revealed that the combined prediction model incorporating significant radiomic features and clinical factors exhibited superior prediction ability compared with the other two models, indicating a considerable significance in predicting malnutrition based on medical imaging findings.

Malnutrition, as measured by PG-SGA, was reported not only to be a predictor of the high incidence of treatment-related adverse events but to have a negative impact on patient survival. Recent prospective observational research involving 391 patients with CC assessed the PG-SGA score and its link to the incidence of RT/CRT toxicity. Over half of the patients in this cohort were diagnosed with stage I-II diseases. Malnutrition was observed in 47.6% of the total population. Multivariate analysis indicated malnutrition (PG-SGA score ≥ 4) to be an independent predictor related to grade 3–4 toxicities and toxicity-associated dose modifications (32). When comparing baseline nutritional status among 207 patients with CC in Mexico, Laura et al. observed that malnutrition was an

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TABLE 2 Univariate and multivariate analyses to predict malnutrition using a binary logistic regression model.

Factor	PG-SGA							
	Univariate				Multivariate			
	p Value	OR	95% CI Lowers	95% CI Upper	*p* Value	OR	95% CI Lower	95% CI Upper
Age, < 65 vs. ≥ 65	0.009	17.000	2.011	143.729	0.042	10.922	1.095	108.925
ECOG PS, 0–1 vs. 2	0.001	7.311	2.300	23.244	0.008	8.672	1.765	42.608
HPV infection, No and unknown vs. Yes	0.708	0.841	0.341	2.077	-			
BMI, < 24 vs. ≥ 24	0.118	0.448	0.164	1.227	-			
Histology, SCC vs. AC and others	0.556	0.683	0.192	2.431	-			
Differentiation, well and fairly vs. poorly and undifferentiated	0.535	1.322	0.547	3.197	-			
Stage, IB vs. IIA	0.114	2.057	0.841	5.031	-			
Surgery approach, abdominal vs. laparoscopic	0.797	0.880	0.334	2.322	-			
Tumor volume, ≤ 40 vs. > 40	0.830	0.907	0.374	2.201	-			
LN metastasis, negative vs. positive	0.045	0.322	0.106	0.975	0.494	0.584	0.125	2.732
Margin, negative vs. positive	0.313	2.586	0.408	16.395	-			
Deep stromal invasion, < 1/2 vs. ≥ 1/2	0.150	0.331	0.073	1.491	-			
LVSI, negative vs. positive	0.670	0.811	0.308	2.131	-			
Radscore	< 0.001	0.112	0.040	0.317	< 0.001	0.132	0.045	0.392

OR, odds ratio; CI: confidence interval.

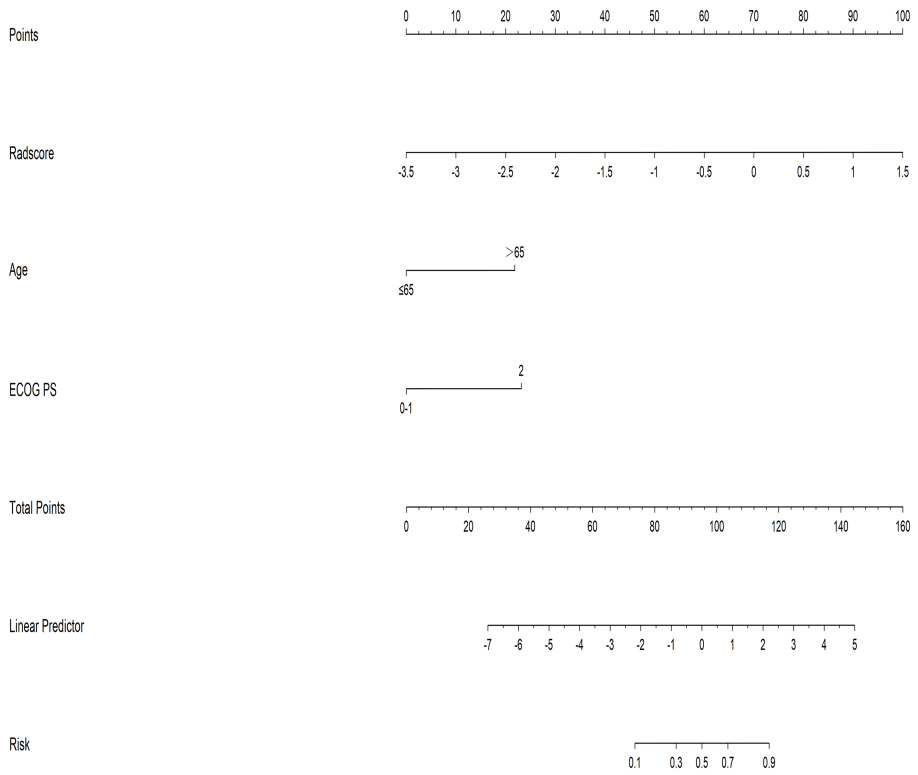

FIGURE 2
A nomogram prediction model integrated the rad-score and two clinical factors to detect malnutrition. The rad-score value is represented by the number. Every variable was located on the axis, and the corresponding point was obtained by drawing a straight line upwards to the points' axis. The summation of all the points and identification of the location on the bottom line could be utilized to determine the estimated probability of malnutrition.

independent parameter linked to severe gastrointestinal toxicities after treatment (OR = 3.6; 95% CI, 1.46–9.2; $p < 0.001$) (33). Furthermore, a prospective study revealed that CC patients with PG-SGA score ≥ 4 had a higher mortality risk [Hazard Ratio = 3.12; 95% CI, 1.23–7.86] than patients with PG-SGA score < 4 (34).

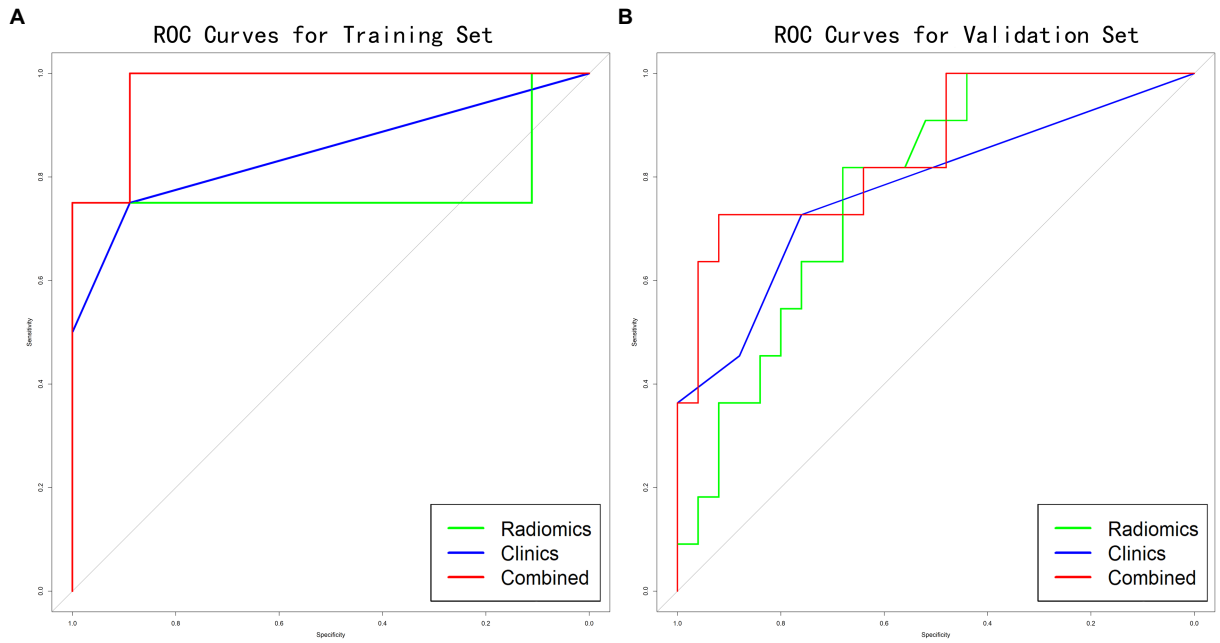

FIGURE 3
Comparing the prediction abilities of malnutrition in the training **(A)** and validation **(B)** sets. The performance of the combined prediction model (respective AUC values of0.972 and 0.855 in the training and validation set) was greater than the radiomics or clinical model.

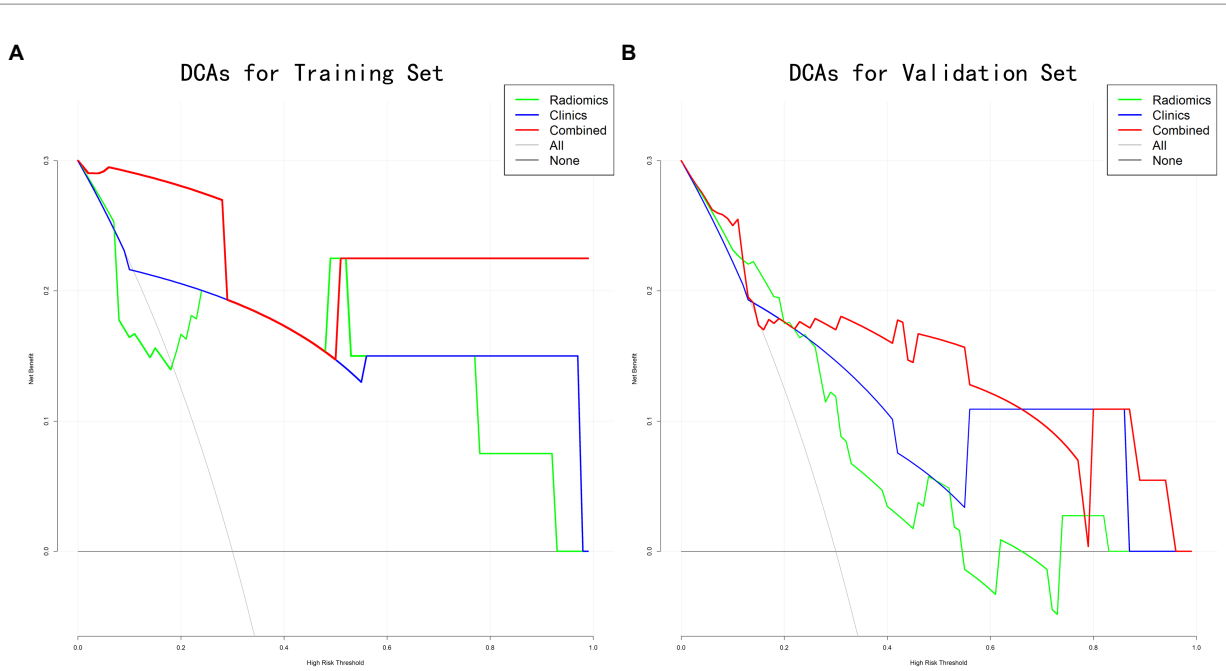

FIGURE 4
Decision curve analysis presenting the predictions of the radiomics, clinical, and combined models. **(A)** The training set; **(B)** the validation set. The threshold probability and net benefit are presented by *x*-axis and *y*-axis, respectively. The variance between the expected benefit and expected harm of the decision serves as a representation of the net benefit. The decision curve indicated that, in contrast to the other models, the combined model provided a higher net benefit.

Considering the aforementioned findings, the determination of malnutrition on the basis of objective parameters is a significant clinical challenge (15). Lee et al. conducted multiple studies in this field to demonstrate the impact of skeletal muscle loss in gynecologic patients who received RT. The skeletal muscle alterations were assessed by SMI on CT images defined at the L3 spinal level in a retrospective research involving 210 patients. The authors discovered that SMI alterations were substantially related to PG-SGA score (1–3 vs. ≥ 4) at the end of RT ($p < 0.001$). As per the multivariate analysis, PG-SGA ≥ 4 assessed at the end of RT was revealed to be an independent factor associated with

increased risk of muscle loss ($p < 0.001$; OR = 72.96; 95% CI, 9.45–563.18) (35). A similar result was obtained in another observational retrospective study that enrolled 133 patients with stage IB1-IIA2 CC who received adjuvant RT/RCT. The rate of muscle loss, which was determined by SMI at the L3 vertebral level, was reported to be higher in patients with PG-SGA score ≥ 4 than in patients with PG-SGA score < 4 (71.4% vs. 2.2%, $p < 0.001$). In addition, survival analysis indicated that patients with muscle loss were significantly associated with a lower 3-year overall survival rate than patients with retained muscle (65.6 vs. 93.9%, $p < 0.001$) (36). Several other studies reported similar results regarding the association and clinical significance of skeletal muscle changes, including total adipose tissue index, SMI, skeletal muscle density, and bowel RT dose-volume (37) or distant recurrence-free survival (38) in individuals with locally advanced CC who received CRT.

Nevertheless, available literature reveals that limited studies have documented sarcopenia or malnutrition based on radiomic findings and incorporating clinical factors for nutritional prediction. A previous retrospective study from Netherlands has examined the link between radiomic features and skeletal muscle loss in 116 individuals diagnosed with stage IV non-small cell lung cancer (NSCLC). Radiomic features were also derived from CT images of the L3 vertebrae. Following feature selection, 1,298 radiomic features were extracted, and 193 of them were used to build a prediction model for muscle loss. The average AUC for radiomic features to develop the prediction model with muscle loss as the result after 100 repetitions were calculated to be only 0.49 (95% CI, 0.36–0.62). The authors concluded the inability of skeletal muscle radiomics to predict sarcopenia during chemotherapy in NSCLC (39). Kim, in contrast, expressed a different viewpoint. The radiomic features were reported to be reliable predictors of sarcopenia in patients with NSCLC by means of various machine-learning algorithms (40). Compared with the present study focused on FIGO stage IB1-IIA2 CC patients, differences in cancer types and substantial heterogeneities among patients might cause the inconsistency between the prior Dutch study (39) and the present analysis. In addition, the incorporation of significant clinical factors was carried out in an attempt to improve the prediction power, as has been done in other studies. In a retrospective study employing a radiomics-based nomogram to predict lymphovascular space invasion, 149 patients with CC undergoing surgical resection were examined, and radiomics data were collected using T2-weighted imaging. The radiomics prediction model depicted considerably better performance compared to the clinical model in both training and validation datasets. The combined nomogram prediction model incorporating radiomic features and clinical parameters yielded better performance (training cohort, AUC = 0.943; validation cohort, AUC = 0.923) than other prediction models (41). Similar studies have demonstrated that radiomics-based nomogram has robust performance in predicting lymph node metastasis (42) and survival (43) in patients with CC.

Some limitations are present in this research. First, owing to the retrospective design of the research and small sample size, prospective external validation with a large sample size is required to be conducted in the future. Second, some important parameters, such as biochemical indicators, like albumin, pre-albumin, and other clinical indicators that may potentially influence the prediction of malnutrition, were not presented. The predictive ability of the combined nomogram prediction model can be further improved. Third, there was a difference in identifying skeletal muscles at the L3 vertebral level. Some investigations have also included axial cross-sections of the skeletal muscles, which included the rectus abdominis, erector spinae, and psoas. Accuracy and repeatability in this study were guaranteed by employing the population psoas at the L3 vertebral level with an ICC of ≥ 0.85. Interestingly, Naser et al. developed a deep learning-based auto-segmentation model of cervical skeletal muscle for detecting sarcopenia in head and neck cancers (44). Several excellent nutritional risk screening instruments, except PG-SGA, were also widely employed in the clinic. These tools may provide a future direction to examine the clinical potential of a nomogram prediction model that was based on radiomics. In addition, the new Global Leadership Initiative on Malnutrition (GLIM) criteria have also revealed a promising ability to detect malnutrition and warrant further investigation (45).

Conclusion

In summary, this study analyzed the radiomics features of psoas at the L3 level retrieved from planned CT scans of patients with FIGO stage IB1-IIA2 CC who received PORT/CRT. Furthermore, an effective and feasible nomogram prediction model on the basis of the rad-score and two clinical factors was constructed and verified for the prediction of malnutrition in patients with CC based on their PG-SGA scores. This combined nomogram prediction model presented a new strategy utilizing medical imaging data for more accurate and individualized malnutrition prediction in patients with CC, which might also be used for advanced CC and other types of malignancies 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 author.

Ethics statement

The studies involving human participants were reviewed and approved by the institutional review board of Zhejiang Provincial People's Hospital (ZJPPH No. 2022-191). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

WY: conception and design, and writing original draft. HX: provision of study materials, collection data, and review of the literature. FC and HX: collection and assembly of data and writing original draft. HS and JD: collection and assembly of data and writing original draft. YC and YJ: data analysis and interpretation and writing original draft. HZ and YW: interpretation and writing original draft. TS: conception and design, provision of study materials, collection and assembly of data, drafting, final approval, and accountable for aspects. All authors contributed to the article and approved the submitted version.

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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.2023.1113588/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Axial **(a)** and coronal **(b)** cross-sectional regions areas of the left and right psoas (green) on CT images at the L3 vertebral level.

SUPPLEMENTARY FIGURE S2
The calibration curves for predicting malnutrition in the **(a)** training set and **(b)** validation set, respectively. The predicted probability (from the nomogram) and the actual probability of malnutrition are represented by the x-axis and y-axis, respectively. Results were plotted via bootstrapping with 1000 resamples. Greater prediction accuracy of the model is indicated when the bias-corrected calibration curve (black line) is close to the diagonal line. The closer the line the higher the accuracy.

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Development of sarcopenia-based nomograms predicting postoperative complications of benign liver diseases undergoing hepatectomy: A multicenter cohort study

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Background: Sarcopenia has a remarkable negative impact on patients with liver diseases. We aimed to evaluate the impact of preoperative sarcopenia on the short-term outcomes after hepatectomy in patients with benign liver diseases.

Methods: A total of 558 patients with benign liver diseases undergoing hepatectomy were prospectively reviewed. Both the muscle mass and strength were measured to define sarcopenia. Postoperative outcomes including complications, major complications and comprehensive complication index (CCI) were compared among four subgroups classified by muscle mass and strength. Predictors of complications, major complications and high CCI were identified by univariate and multivariate logistic regression analysis. Nomograms based on predictors were constructed and calibration cures were performed to verify the performance.

Results: 120 patients were involved for analysis after exclusion. 33 patients were men (27.5%) and the median age was 54.0years. The median grip strength was 26.5kg and the median skeletal muscle index (SMI) was 44.4cm^2/m^2. Forty-six patients (38.3%) had complications, 19 patients (15.8%) had major complications and 27 patients (22.5%) had a CCI≥26.2. Age (p =0.005), SMI (p =0.005), grip strength (p =0.018), surgical approach (p=0.036), and operation time (p=0.049) were predictors of overall complications. Child-Pugh score (p=0.037), grip strength (p=0.004) and surgical approach (p=0.006) were predictors of major complications. SMI (p=0.047), grip strength (p<0.001) and surgical approach (p=0.014) were predictors of high CCI. Among the four subgroups, patients with reduced muscle mass and strength showed the worst short-term outcomes. The nomograms for complications and major complications were validated by calibration curves and showed satisfactory performance.

Conclusion: Sarcopenia has an adverse impact on the short-term outcomes after hepatectomy in patients with benign liver diseases and valuable sarcopenia-based nomograms were constructed to predict postoperative complications and major complications.

KEYWORDS

sarcopenia, hepatectomy, nutrition, benign liver disease, complication

1. Introduction

Along with the change of diet habit and life style, many people are diagnosed with benign liver diseases, such as focal nodular hyperplasia, hepatolithiasis and hemangioma (1). Liver resection remains the main curative treatment and many factors are related to the postoperative outcomes after hepatectomy (2, 3). Identifying predictive factors is important to minimize the risk of adverse outcomes and improve the quality of life of patients.

Sarcopenia, defined as a degenerative loss of muscle mass, strength and function, has gained increasing interest and is associated with adverse outcomes in patients with malignancies (4–6). Many patients with liver disease would experience sarcopenia, which is closely associated with poor clinical outcomes including survival, quality of life and complications (7, 8). Sarcopenia had an important impact on postoperative morbidity and overall survival (OS) after hepatectomy or liver transplantation (9–12). However, most studies defined sarcopenia only based on radiological images without assessing muscle strength, which was a better predictor affecting postoperative outcomes than muscle mass (13). Our previously published studies have confirmed the adverse impact of sarcopenia on the outcomes in hepatocellular carcinoma and intrahepatic cholangiocarcinoma following surgery, and identified the importance of muscle strength in defining sarcopenia (14, 15).

However, limited works have been reported on the impact of sarcopenia on benign liver diseases. Therefore, we performed this prospective study to assess the impact of sarcopenia on short-term outcomes in patients with benign liver diseases undergoing hepatectomy.

2. Materials and methods

2.1. Patients

Between May 2021 and April 2022, 558 patients with hepatobiliary diseases who admitted to the first affiliated hospital of Wenzhou Medical University and the first affiliated hospital of Zhejiang Chinese Medical University were prospectively enrolled. All patients received muscle strength test (grip strength and chair stand test), physical performance (gait speed), and imaging evaluation before treatment following the European Working Group on Sarcopenia in Older People (EWGSOP) standard (13). The study protocol was detailed in Supplementary data 1. Clinical data and follow-up information within 90 days after surgery were collected. The inclusion criteria were: (1) pathologically diagnosed benign liver disease, (2) receive liver resection, (3) without other diseases affecting muscle weakness, (4) Eastern Cooperative Oncology Group performance status (ECOG-PS) 0–2, (5) Child-Pugh grade A-B, (6) computed tomography (CT) performed within 1 month before surgery, (7) complete clinical and follow-up information. The flowchart of the study was shown in Figure 1.

Multidisciplinary meeting and essential supportive therapies were performed before surgery to optimize the treatment strategy. The relevant clinical data were collected, including epidemiological characteristics, laboratory tests, operation-related factors, image data, physical tests and postoperative outcomes (complications, major complications and mortality).

The study was approved by the Ethics Committee of local institutional review boards (Number 2021–066) and adhered to the Declaration of Helsinki. Written informed consents were obtained from each patient before research.

2.2. Definition of short-term outcomes

Patients were followed up once every 1 month after surgery through out-patient service. The primary outcomes of the study were postoperative complications and major complications. The postoperative complications were classified according to the Clavien-Dindo classification system and major complications were defined as grade III or higher (16). In addition, we used comprehensive complication index (CCI) to evaluate the burden of complications, which is calculated based on the Clavien–Dindo classification grade (17). We used an online tool provided at https://www.assessurgery.com to calculate CCI score and a CCI ≥26.2 was used as a threshold to define the severity of complications according to the previous studies (18, 19). Specifically, the complications included cardiovascular complications (e.g., heart insufficient and atrial fibrillation), infectious complications (e.g., wound infections, abdominal abscess, peritonitis and sepsis), pulmonary complications (e.g., pleural effusion, pneumonia and respiratory insufficiency), gastrointestinal complications (e.g., intestinal obstruction, vomit, diarrhea and biliary leakage), and others (e.g., fever, ascites, abdominal hemorrhage, organ failure and death). Postoperative biliary leak, bleeding, and organ failure were defined according to the international study group of liver surgery and other studies (18, 20, 21).

The secondary outcomes were hospital stay, hospital cost and unplanned 90-day readmission rate. Hospital cost was extracted from the electronic medical records database, which contains the cost associated with the treatment (e.g., surgery, anesthesia, and medication) and basic care of patients during hospitalization.

2.3. Definition of sarcopenia and clinical factors

Preoperative abdominal CT images at the third lumbar (L3) vertebra level were acquired. Image J software was used to segment the region of interest including the area of skeletal muscle, area of visceral adipose tissue (VAT) and area of subcutaneous adipose tissue (SAT) according to the tissue Hounsfield unit (HU) thresholds (Figure 2). The threshold of attenuation value was-29 to 150 HU for skeletal muscle tissue, −150 to −50 HU for VAT, and −190 to −30 HU for SAT. The muscle density was evaluated by the mean CT attenuation value (HU) of the muscle tissue at the L3 level. Skeletal muscle index (SMI) was used to define reduced muscle mass, which was calculated as the total cross-sectional area of skeletal muscle in the L3 plane (cm^2) /height (m^2) based on the CT image. Two researchers who were blinded to the clinical information segmented the CT images independently and discordance was resolved by consultation. According to the receiver operating characteristic (ROC) curve based on complications, the optimal cut-off values of SMI were defined as 51.1 cm^2/m^2 in males and 37.1 cm^2/m^2 in females. Handgrip strength, gait speed, and chair stand test data were recorded with a standardized protocol prior to surgery (22). According to the Asian consensus of sarcopenia, a cut-off value of less than 28 kg in men and less than 18 kg in women was used to define reduced muscle strength (23).

Body mass index (BMI) was calculated as weight (kg) /height^2 (m^2). Controlling nutritional status (CONUT) score was calculated and classified based on serum albumin concentration, total lymphocyte count, and total cholesterol concentration (24) (Supplementary Table S1). Prognostic nutritional index (PNI) score was calculated according to the formula: 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (/mm^3) (25). Albumin-bilirubin (ALBI) score was calculated according to the formula: ($\log_{10}$ bilirubin × 0.66) + (albumin × −0.085) (26). Major resection was

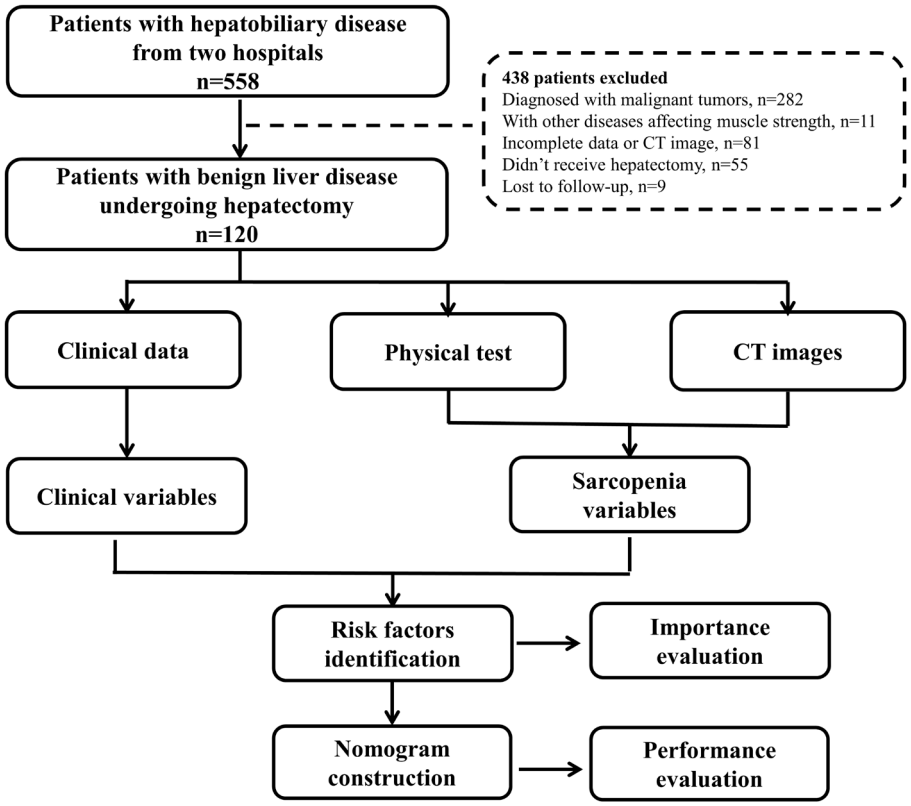

FIGURE 1
Flowchart of the study.

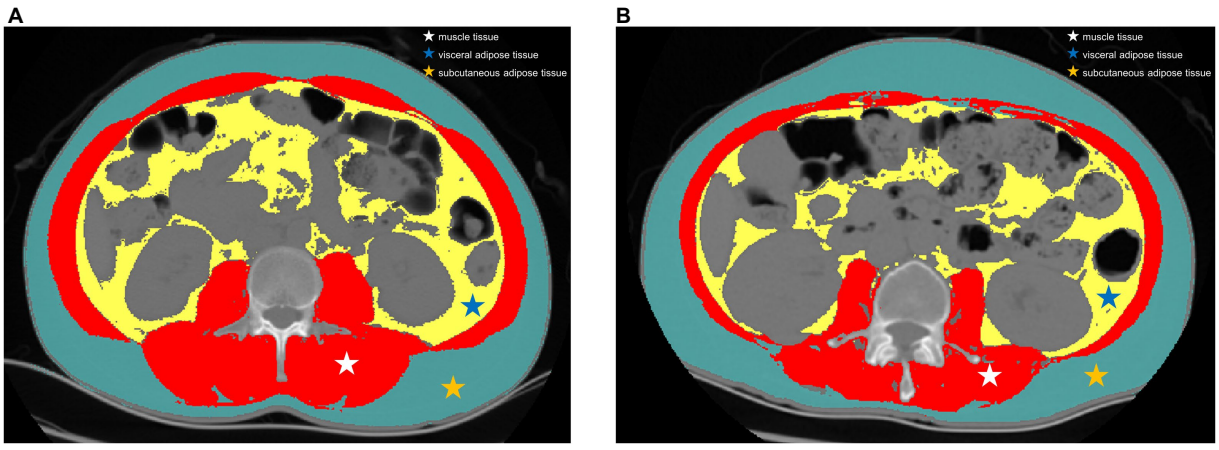

FIGURE 2
Representative computed tomography scans at the third lumbar vertebra level in patients with and without sarcopenia. **(A)** a patient with high skeletal muscle index and **(B)** a patient with low skeletal muscle index. Red region: skeletal muscle mass, assessed using thresholds of-29 to 150 Hounsfield units; yellow region: visceral adipose tissue, assessed using thresholds of-150 to-50 Hounsfield units; green region: subcutaneous adipose tissue, assessed using thresholds of −190 to −30 Hounsfield units.

defined as the resection of three or more segments, and minor resection was defined as the removal of less than three segments (18).

2.4. Statistical analysis

SPSS software (version 25.0) and R software (version 4.2.1) were used to perform statistic analysis and draw nomograms. Python (version 3.10.5) software was used to perform random forest algorithm and Shapley additive explanation (SHAP) analysis. PASS 15 software was used to calculate the sample size. Continuous data were presented as mean ± standard deviation (SD) or medians (interquartile range, IQR). Categorical data were presented as count (percentage). ROC curves using complication as a marker of endpoint were used to determine the optimal cut-off values of factors. T test or Mann–Whitney U test was used to analyze continuous data and Chi-square test or Fisher exact test

was used for categorical data. Univariate and multivariate logistic regression analysis were performed to identify risk factors. Random forest algorithm was used to evaluate the importance of each feature and SHAP values were used to provide a local explanation for the direction of each feature's effect. Nomogram was established according to the results of multivariate logistic analysis. C-index and calibration curve were performed to evaluate the predictive performance. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

A total 120 patients with benign liver diseases undergoing hepatectomy were enrolled for analysis after exclusion. Sixteen patients had focal nodular hyperplasia, four patients had hepatic cyst, 53 patients had hepatolithiasis and 47 patients had hepatic hemangioma. Forty-six patients (38.3%) had postoperative complications and 19 patients (15.8%) developed major complications. The baseline characteristics of patients with and without complications are shown in Table 1. There were 33 men (27.5%) and most patients (95.8%) had a Child-Pugh class A. The median age was 54.0 years (IQR, 44.3–62.0 years) and mean BMI was 22.7 ± 3.2 kg/m^2. The median grip strength was 26.5 kg (IQR, 21.4–33.8 kg) and the median SMI was 44.4 cm^2/m^2 (IQR, 39.1–52.1 cm^2/m^2). Thirty-three patients (27.5%) experienced low SMI and 28 patients (23.3%) experienced low grip strength. Seventy-seven patients (64.2%) underwent laparoscopic hepatectomy and 43 patients (35.8%) underwent open surgery. The mean operation time was 154.3 ± 61.6 min for all patients, 175.0 ± 62.5 min for patients with complications, and 141.4 ± 57.7 for patients without complications ($p = 0.003$). Five patients (4.2%) converted from laparoscopic operation to open surgery according to the following reasons: one case had severe abdominal adhesion, two cases had an unsuitable lesion location and two cases had serious intraoperative bleeding. One patient (0.8%) died because of postoperative multiple organ failure (MOF). All the other 119 patients went home for rehabilitation after discharge. Twenty-seven patients (22.5%) had a high CCI ≥26.2 and 16 patients (13.3%) had unplanned 90-day readmission. Patients with complications had a higher readmission rate ($p = 0.033$), a higher hospital cost ($p < 0.001$) and a longer hospital stay ($p < 0.001$) than patients without complications.

3.2. Predictors of overall complications

According to the univariate logistic regression analysis, age, PS score, SMI, grip strength, chair stand test, muscle density, albumin (ALB), aspartate transaminase (AST), prothrombin time, CONUT score, ALBI score, surgical approach and operation time were associated with overall complications (Table 2). Then variables with p value <0.05 were brought into the subsequent multivariate logistic regression analysis, which showed that age ($p = 0.005$), SMI ($p = 0.005$), grip strength ($p = 0.018$), surgical approach ($p = 0.036$), and operation time ($p = 0.049$) were independent risk factors of overall complications. The nomogram based on the results of multivariate logistic analysis were developed and the calibration plot showed favorable performance (Figures 3A,B). The C-index of the nomogram was 0.889 [95% confidence interval (CI), 0.827–0.951].

3.3. Predictors of major complications

Through univariate logistic regression analysis, Child-Pugh grade, SMI, grip strength, total bilirubin (TBIL), ALB, alanine aminotransferase (ALT), AST and surgical approach were associated with major complications (Table 3). Through multivariate logistic analysis, Child-Pugh grade ($p = 0.037$), grip strength ($p = 0.004$) and surgical approach ($p = 0.006$) were independent risk factors of major complications. Then the nomogram based on Child-Pugh grade, grip strength and surgical approach was developed to predict major complications (Figure 3C). The C-indexes was 0.883 (95% CI, 0.805–0.961) and the calibration plots showed good agreement between observed outcomes and predicted outcomes (Figure 3D).

3.4. Predictors of high comprehensive complication index ≥26.2

According to the previous studies, we also identified risk factors of high CCI ≥26.2. As shown in Supplementary Table S2, PS score, Child-Pugh grade, SMI, grip strength, chair stand test, TBIL, ALB, ALT, AST, surgical approach and operation time were associated with high CCI score. Multivariate logistic regression analysis showed that SMI ($p = 0.047$), grip strength ($p < 0.001$) and surgical approach ($p = 0.014$) were independent risk factors of high CCI score.

3.5. Subgroup analysis according to muscle mass and muscle strength

Based on the thresholds of SMI and grip strength to define sarcopenia, patients were further divided into four subgroups: patients with normal muscle mass and strength (77/120), patients with reduced muscle mass (15/120), patients with reduced muscle strength (10/120), and patients with reduced muscle mass and strength (18/120). As shown in Table 4, there are significant differences in overall complication, major complication, high CCI score, hospital cost, hospital stay and 90-day readmission rate among these four groups. Patients with reduced muscle mass and strength experienced the worst postoperative outcomes. No difference was seen in conversion rate among the four groups ($p = 0.662$).

3.6. Evaluation of feature importance associated with major complication

In order to evaluate the importance of factors obtained from the results of univariate logistic analysis which are recognized clinically important to major complication, we performed random forest algorithm which is a conventional machine learning algorithm. The importance matrix plot revealed the importance of the eight clinical factors (Figure 4A). Then we used SHAP method to elaborate the specific role of each feature on the risk of major complication. As shown in the SHAP summary plot (Figure 4B), each dot corresponds to the SHAP value for each feature in a given patient. Dots are colored based on the values of features for individual patient. Red indicates higher feature values and blue indicates lower feature values. The X-axis coordinate of each dot was determined by the SHAP value, and the dots are stacked along each feature to show the density. Each SHAP value indicates how much each feature contributes, either positively or

TABLE 1 Baseline characteristics of patients with and without postoperative complications.

Variables	All patients	With complications	Without complications	Value of *p*
	n=120	*n*=46	*n*=74	
Gender, *n* (%)				0.488
male	33 (27.5)	11 (23.9)	22 (29.7)	
female	87 (72.5)	35 (76.1)	52 (70.3)	
Age, year, median (IQR)	54.0 (44.3–62.0)	61.5 (49.8–71.0)	51.5 (42.0–58.0)	<0.001
BMI, kg/m^2, mean ± SD	22.7 ± 3.2	22.2 ± 3.0	23.1 ± 3.3	0.176
ECOG PS, *n* (%)				<0.001
0	74 (61.7)	18 (39.1)	56 (75.7)	
≥1	46 (38.3)	28 (60.9)	18 (24.3)	
ASA grade, *n* (%)				<0.001
1	74 (61.7)	18 (39.1)	56 (66.2)	
≥2	46 (38.3)	28 (60.9)	18 (33.8)	
Smoke, *n* (%)	14 (11.7)	6 (13.0)	8 (10.8)	0.711
Alcohol, *n* (%)	14 (11.7)	5 (10.9)	9 (12.2)	0.830
Diabetes, *n* (%)	16 (13.3)	4 (8.7)	12 (16.2)	0.239
Hypertension, *n* (%)	28 (23.3)	15 (32.6)	13 (17.6)	0.058
HBV, *n* (%)	14 (11.7)	7 (15.2)	7 (9.5)	0.339
Child-Pugh grade, *n* (%)				0.050
A	115 (95.8)	42 (91.3)	73 (98.6)	
B	5 (4.2)	4 (8.7)	1 (1.4)	
SMI,cm^2/m^2, *n* (%)				<0.001
low	33 (27.5)	24 (52.2)	9 (12.2)	
normal	87 (72.5)	22 (47.8)	65 (87.8)	
Grip strength, kg, *n* (%)				<0.001
low	28 (23.3)	23 (50.0)	5 (6.8)	
normal	92 (76.7)	23 (50.0)	69 (93.2)	
Chair stand test, s, median (IQR)	13.0 (11.5–15.8)	13.8 (12.1–16.2)	12.5 (11.2–14.3)	0.026
Gait speed, m/s, median (IQR)	1.1 (1.0–1.1)	1.0 (0.9–1.2)	1.1 (1.0–1.1)	0.334
Muscle density, HU, mean ± SD	50.0 ± 7.7	44.9 ± 8.2	48.2 ± 7.2	0.023
VAT, cm^2, mean ± SD	97.5 ± 58.5	100.8 ± 58.9	95.4 ± 58.6	0.623
SAT, cm^2, median (IQR)	130.7 (97.6–173.0)	135.6 (82.1–182.4)	129.3 (103.3–171.2)	0.383
TBIL, μmol/L, median (IQR)	11.08 (8.0–15.8)	11.5 (8.8–23.5)	10.5 (7.8–14.3)	0.076
ALB, g/L, mean ± SD	40.1 ± 3.9	38.5 ± 4.4	41.1 ± 3.2	0.001
ALT, U/L, median (IQR)	16.0 (12.0–30.0)	20.5 (14.0–39.8)	16.0 (11.0–27.3)	0.030
AST, U/L, median (IQR)	22.0 (18.0–27.8)	23.0 (20.0–42.8)	20.5 (18.0–23.5)	0.001
Prothrombin, s, median (IQR)	13.1 (12.7–13.6)	13.2 (12.9–13.8)	13.0 (12.6–13.3)	0.050
CONUT score, *n* (%)				0.046
0–1	71 (59.2)	22 (47.8)	49 (66.2)	
≥2	49 (40.8)	24 (52.2)	25 (33.8)	
PNI score, *n* (%)				0.045
<50	78 (65.0)	35 (76.1)	43 (58.1)	
≥50	42 (35.0)	11 (23.9)	31 (41.9)	
ALBI score, *n* (%)				<0.001
<−2.6	81 (67.5)	22 (47.8)	59 (79.7)	

(Continued)

TABLE 1 (Continued)

Variables	All patients	With complications	Without complications	Value of *p*
	n=120	*n*=46	*n*=74	
≥−2.6	39 (32.5)	24 (52.2)	15 (20.3)	
Surgical approach, *n* (%)				<0.001
laparoscopy	77 (64.2)	19 (41.3)	58 (78.4)	
laparotomy	43 (35.8)	27 (58.7)	16 (21.6)	
Type of hepatectomy, *n* (%)				0.144
major	9 (7.5)	6 (13.0)	3 (4.1)	
minor	111 (92.5)	40 (87.0)	71 (95.9)	
Blood loss, mL, median (IQR)	50.0 (50.0–80.0)	70.0 (50.0–200.0)	50.0 (50.0–50.0)	<0.001
Blood transfusion, *n* (%)	9 (7.5)	5 (10.9)	4 (5.4)	0.454
Pringle maneuver, min, median (IQR)	0.0 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–15.8)	0.173
Operation time, min, mean ± SD	154.3 ± 61.6	175.0 ± 62.5	141.4 ± 57.7	0.003
Conversion, *n* (%)	5 (4.2)	3 (6.5)	2 (2.7)	0.370
90-d readmission, *n* (%)	16 (13.3)	10 (21.7)	6 (8.1)	0.033
Major complication, *n* (%)	19 (15.8)	19 (41.3)	reference	
CCI, mean ± SD	10.6 ± 16.8	27.8 ± 16.2	reference	
CCI, *n* (%)				
<26.2	93 (77.5)	19 (41.3)	reference	
≥26.2	27 (22.5)	27 (58.7)	reference	
Hospital cost, €, median (IQR)	5696.3 (4591.7–6687.7)	6811.9 (6072.5–8572.5)	5049.8 (4129.9–5896.5)	<0.001
Hospital cost, $, median (IQR)	5999.1 (4835.8–7043.1)	7174.0 (6395.2–9028.1)	5318.2 (4349.4–6209.9)	<0.001
Hospital stay, day, median (IQR)	9.0 (7.3–13.0)	13.0 (10.0–17.0)	8.0 (6.0–10.0)	<0.001

Major complications were defined as Clavien-Dindo classification III-V. Abbreviations: IQR, inter quartile range; SD, standard deviation; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance status; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; SMI, skeletal muscle index; HU, Hounsfield units; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; CONUT, controlling nutritional status; PNI, prognostic nutritional index; ALBI score, albumin-bilirubin score; CCI, comprehensive complication index.

negatively, to the risk of major complication. The higher SHAP value of a feature is given, the higher risk of postoperative major complication the patient would have. For example, open surgery, low grip strength, low SMI and Child-Pugh class B are associated with a higher risk of major complication.

4. Discussion

Liver resection remains the curative treatment for benign liver diseases, but postoperative complications seriously threaten the recovery and quality of life of patients. Preoperative identification of risk factors for complication is significantly important to optimize the treatment strategy and improve postoperative outcomes. In this study, we first conducted a prospective cohort study to evaluate the impact of sarcopenia on the short-term outcomes after hepatectomy in benign liver diseases. We comprehensively defined sarcopenia by muscle mass and muscle strength, and directly delineated the adverse impact of both muscle mass and muscle strength on postoperative outcomes. We propose that sarcopenia is a critical factor affecting the short-term outcomes in patients with benign liver diseases undergoing hepatectomy.

As a major component of malnutrition, sarcopenia has been widely investigated in various liver diseases, including hepatocellular carcinoma (HCC), cholangiocarcinoma, liver cirrhosis and non-alcoholic fatty liver disease (27–30). But the impact of sarcopenia on benign liver disease undergoing hepatectomy has never been investigated before. In our study, we evaluated the impact of sarcopenia on the short-term outcomes after hepatectomy and showed that sarcopenia is negatively associated with major complications, overall complications and high CCI score in patients with benign liver diseases following surgery. We also built valuable sarcopenia-based nomograms to predict major complications and overall complications, which showed favorable performance. In addition to sarcopenia, we also evaluated the role of other clinical indicators such as CONUT score, PNI score and ALBI score. CONUT score is a valuable biomarker which can reflect the patient's immune-nutritional status. Previous studies have shown that CONUT score is closely associated with postoperative complications and survival prognosis in patients with hepatocellular carcinoma undergoing hepatectomy (31, 32). Spoletini et al. identified CONUT score as a predictor of morbidity after liver transplantation (33). Une et al. showed that CONUT score and sarcopenia are both valuable prognostic factors affecting the prognosis of patients with advanced urothelial carcinoma (34). Another study by Kodama et al. also

TABLE 2 Univariate and multivariate logistic regression analysis of predictors of overall complications.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	Value of *p*	OR (95% CI)	Value of *p*
Gender				
male	0.743 (0.320–1.723)	0.489		
female				
Age, year	1.072 (1.035–1.110)	<0.001	1.068 (1.020–1.119)	0.005
BMI，kg/m^2	0.921 (0.818–1.038)	0.177		
ECOG PS				
0	0.207 (0.093–0.458)	<0.001		
≥1				
ASA grade				
1	0.607 (0.286–1.291)	0.195		
≥2				
Smoke	1.237 (0.400–3.827)	0.711		
Alcohol	0.881 (0.276–2.812)	0.830		
Diabetes	0.492 (0.149–1.630)	0.246		
Hypertension	2.270 (0.961–5.362)	0.061		
HBV	1.718 (0.561–5.263)	0.343		
Child-Pugh grade				
A	0.144 (0.016–1.330)	0.087		
B				
SMI, cm^2/m^2				
low	7.879 (3.185–19.493)	<0.001	5.310 (1.656–17.031)	0.005
normal				
Grip strength, kg				
low	13.800 (4.705–40.479)	<0.001	5.033 (1.313–19.290)	0.018
normal				
Chair stand test, s	1.128 (1.001–1.271)	0.049		
Gait speed, m/s	0.220 (0.026–1.882)	0.167		
Muscle density, HU	0.945 (0.899–0.994)	0.027		
VAT, cm^2	1.002 (0.995–1.008)	0.620		
SAT, cm^2	0.996 (0.990–1.002)	0.204		
TBIL, μmol/L	1.027 (0.998–1.057)	0.066		
ALB, g/L	0.827 (0.739–0.926)	0.001		
ALT, U/L	1.010 (0.999–1.020)	0.065		
AST, U/L	1.015 (1.001–1.030)	0.034		
Prothrombin, s	1.690 (1.049–2.723)	0.031		
CONUT score				
0–1	0.468 (0.220–0.993)	0.048		
≥2				
PNI score				
<50	2.294 (1.010–5.208)	0.047		
≥50				
ALBI score				
<−2.6	0.233 (0.104–0.524)	<0.001		

(Continued)

TABLE 2 (Continued)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	Value of *p*	OR (95% CI)	Value of *p*
≥−2.6				
Surgical approach				
laparoscopy	0.194 (0.087–0.435)	<0.001	0.329 (0.117–0.929)	0.036
laparotomy				
Type of hepatectomy				
major	3.550 (0.842–14.969)	0.084		
minor				
Blood loss, mL	1.001 (1.000–1.002)	0.129		
Blood transfusion	2.134 (0.542–8.400)	0.278		
Pringle maneuver, min	0.970 (0.936–1.006)	0.099		
Operation time，min	1.009 (1.003–1.016)	0.005	1.008 (1.000–1.017)	0.049

Major complications were defined as Clavien-Dindo classification III-V. Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance status; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; SMI, skeletal muscle index; HU, Hounsfield units; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; CONUT, controlling nutritional status; PNI, prognostic nutritional index; ALBI score, albumin-bilirubin score.

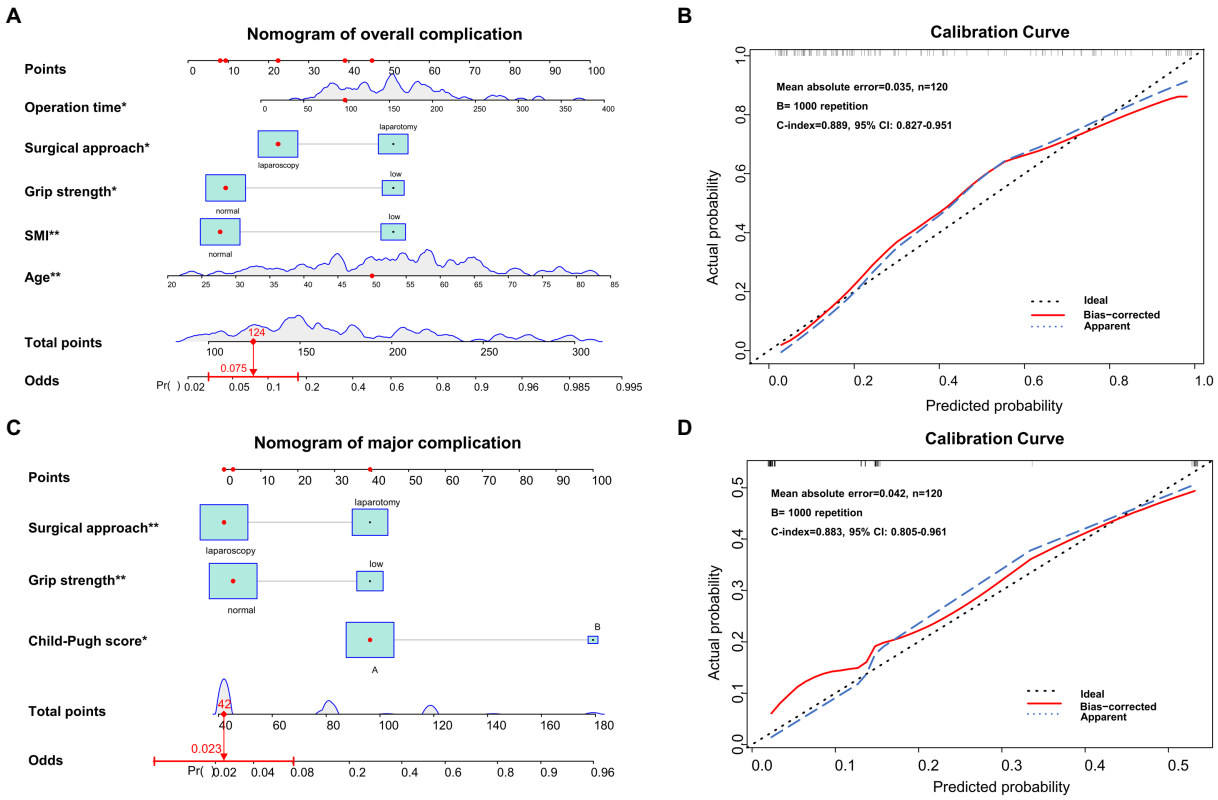

FIGURE 3
Nomograms and calibration curves for predicting overall complication and major complication after hepatectomy. **(A)** the nomogram predicting overall complications, **(B)** the calibration curve of the complication prediction model, **(C)** the nomogram predicting major complications, and **(D)** the calibration curve of the major complication prediction model.

confirmed the prognostic roles of CONUT score and skeletal muscle mass in patients with abdominal aortic aneurysm following open surgical repair (35). In our study, we found that postoperative complications were associated with a high CONUT score ≥ 2, a low PNI score < 50, and a high ALBI score ≥ −2.6, which were in accordance with previous studies. The clinicians should comprehensively assess the immune-nutritional status before surgery to minimize adverse postoperative outcomes.

There have been a variety of methods to evaluate sarcopenia, among which radiological evaluation is a most commonly used method (8, 36). The guidelines of EWGSOP propose that the definition of sarcopenia should be multidimensional, including

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TABLE 3 Univariate and multivariate logistic regression analysis of predictors of major complications (Clavien-Dindo classification III-V).

Variables	Univariate analysis		Multivariate analysis	
	OR(95% CI)	Value of *p*	OR(95% CI)	Value of *p*
Gender				
male	0.662 (0.203–2.164)	0.495		
female				
Age, year	1.027 (0.988–1.068)	0.172		
BMI，kg/m^2	0.881 (0.747–1.039)	0.131		
ECOG PS				
0	0.386 (0.142–1.047)	0.062		
≥1				
ASA grade				
1	1.078 (0.391–2.974)	0.884		
≥2				
Smoke	0.873 (0.179–4.254)	0.866		
Alcohol	0.376 (0.046–3.059)	0.360		
Diabetes	0.319 (0.040–2.568)	0.283		
Hypertension	0.856 (0.259–2.824)	0.798		
HBV	1.534 (0.385–6.116)	0.544		
Child-Pugh grade				
A	0.038 (0.040–0.358)	0.004	0.048 (0.003–0.832)	0.037
B				
SMI, cm^2/m^2				
low	3.768 (1.368–10.382)	0.010		
normal				
Grip strength, kg				
low	12.422 (4.086–37.768)	<0.001	6.473 (1.797–23.324)	0.004
normal				
Chair stand test, s	1.094 (0.944–1.268)	0.232		
Gait speed, m/s	0.293 (0.022–3.873)	0.351		
Muscle density, HU	0.982 (0.923–1.045)	0.567		
VAT, cm^2	1.000 (0.992–1.009)	0.919		
SAT, cm^2	0.997 (0.989–1.004)	0.387		
TBIL, μmol/L	1.029 (1.004–1.054)	0.021		
ALB, g/L	0.819 (0.720–0.933)	0.003		
ALT, U/L	1.013 (1.003–1.023)	0.014		
AST, U/L	1.017 (1.004–1.030)	0.011		
Prothrombin, s	1.254 (0.709–2.219)	0.437		
CONUT score				
0–1	0.439 (0.162–1.187)	0.105		
≥2				
PNI score				
<50	2.262 (0.699–7.318)	0.173		
≥50				
ALBI score				
<−2.6	0.469 (0.173–1.272)	0.137		

(Continued)

TABLE 3 (Continued)

Variables	Univariate analysis		Multivariate analysis	
	OR(95% CI)	Value of *p*	OR(95% CI)	Value of *p*
≥−2.6				
Surgical approach				
laparoscopy	0.068 (0.018–0.253)	<0.001	0.136 (0.033–0.572)	0.006
laparotomy				
Type of hepatectomy				
major	0.646 (0.076–5.485)	0.689		
minor				
Blood loss, mL	1.001 (1.000–1.002)	0.059		
Blood transfusion	1.580 (0.302–8.261)	0.588		
Pringle maneuver, min	0.943 (0.876–1.015)	0.119		
Operation time，min	1.007 (0.999–1.014)	0.089		

Major complications were defined as Clavien-Dindo classification III-V. Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance status; ASA, American Society of Anesthesiologists; HBV, hepatitis B virus; SMI, skeletal muscle index; HU, Hounsfield units; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase; CONUT, controlling nutritional status; PNI, prognostic nutritional index; ALBI score, albumin-bilirubin score.

TABLE 4 Postoperative outcomes after hepatectomy in patients with benign liver diseases classified by muscle mass and muscle strength.

Variables	total	normal muscle mass and strength	reduced muscle mass	reduced muscle strength	reduced muscle mass and strength	Value of *p*
	n=120	*n*=77	*n*=15	*n*=10	*n*=18	
Overall complications, *n* (%) <0.001						
yes	46 (38.3)	16 (20.8)	7 (46.7)	6 (60.0)	17 (94.4)	
no	74 (61.7)	61 (79.2)	8 (53.3)	4 (40.0)	1 (5.6)	
Major complications, *n* (%) <0.001						
yes	19 (15.8)	5 (6.5)	1 (6.7)	4 (30.0)	9 (55.6)	
no	101 (84.2)	72 (93.5)	14 (93.3)	6 (70.0)	9 (44.4)	
CCI, *n* (%)						<0.001
<26.2	93 (22.5)	72 (93.5)	13 (86.7)	5 (50.0)	3 (16.7)	
≥26.2	27 (77.5)	5 (6.5)	2 (13.3)	5 (50.0)	15 (83.3)	
Conversion, *n* (%)	5 (4.2)	3 (3.9)	1 (6.7)	0 (0.0)	1 (5.6)	0.662
Hospital cost, €, median (IQR)	5696.3 (4591.7–6687.7)	5480.7 (4526.3–6465.2)	5777.9 (3829.0–6410.3)	6266.8 (4461.4–9069.5)	6649.2 (5298.5–7912.9)	0.045
Hospital cost, $, median (IQR)	5999.1 (4835.8–7043.1)	5772.0 (4766.8–6808.8)	6084.9 (4032.5–6751.0)	6599.9 (4698.5–9551.5)	7002.6 (5580.1–8333.5)	0.045
Hospital stay,day, median (IQR)	9.0 (7.3–13.0)	9.0 (7.0–11.5)	8.0 (7.0–10.0)	12.5 (8.0–16.3)	16.0 (9.8–20.0)	<0.001
90-d readmission, *n* (%)						
yes	16 (13.3)	5 (6.5)	2 (13.3)	2 (20.0)	7 (38.9)	0.003
no	104 (86.7)	72 (93.5)	13 (86.7)	8 (80.0)	11 (61.1)	

Major complications were defined as Clavien-Dindo classification III-V. Abbreviations: CCI, comprehensive complication index; IQR, inter quartile range.

both muscle mass and muscle strength (37). Muscle strength has been demonstrated to be a better predictor than muscle quantity, which can be assessed by handgrip strength, chair stand test and gait speed (23, 38). In accordance to the guidelines, we comprehensively assessed the muscle mass and strength to define sarcopenia in our study. We found that muscle mass and muscle strength are all significant predictors of postoperative complications. Patients with reduced muscle mass and strength experienced the worst short-term outcomes than patients with individual reduced muscle mass or patients with individual reduced muscle strength.

We also evaluated the impact of other clinical factors except muscle mass and muscle strength in our study. We found that surgical approach was an independent predictor of major complication and high CCI. In addition, age, surgical approach and operation time were independent risk factors of overall complications. Previous studies has demonstrated the favorable benefit of laparoscopic procedure versus open surgery for patients undergoing hepatectomy (39, 40). And operation time was also demonstrated to be associated with adverse outcomes after surgery (41–43). Interestingly, another study by Wijk et al. showed that older age, open surgery and longer operation time were associated with muscle quality loss, leading to a shorter OS in patients following liver resection (44).

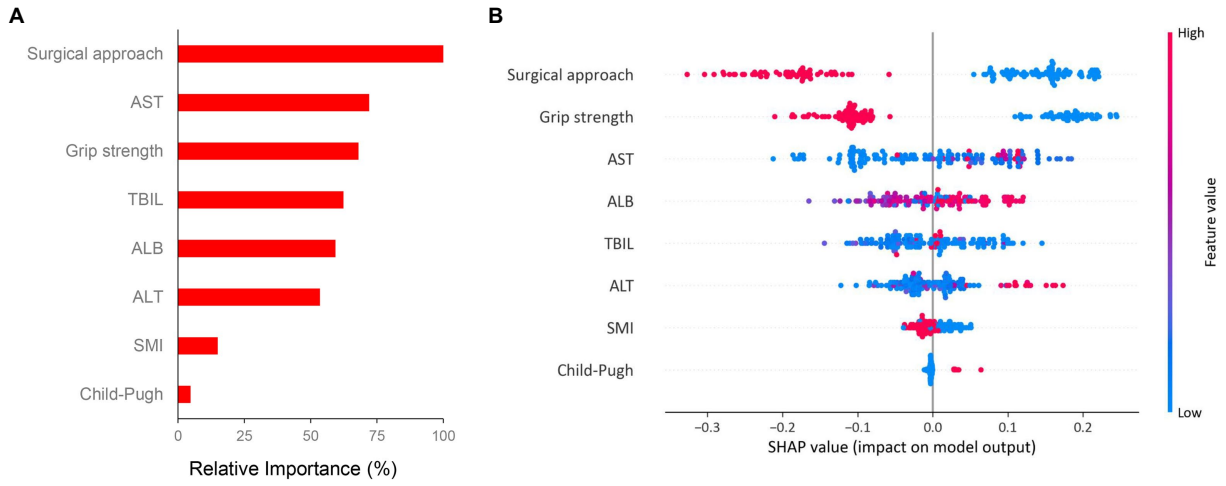

FIGURE 4
Importance matrix plot and SHAP summary plot of eight clinical features associated with major complication. **(A)** The importance ranking of eight clinical features using the random forest algorithm and **(B)** The SHAP summary plot of the eight feature clusters. Each patient is allocated one dot on the line for each feature and the dots are colored based on the values of features. Red indicates higher feature values and blue indicates lower feature values. A feature's SHA*p* value (x-axis) represents the contribution of the specific feature to the risk of major complication. The higher SHAp value of a feature is given, the higher risk of postoperative major complication the patient would have. Abbreviations: SHAP, Shapley additive explanation; SMI, skeletal muscle index; TBIL, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate transaminase.

Considering the adverse impact of sarcopenia on the short-term outcomes after hepatectomy, urgent efforts are needed to meliorate sarcopenia. According to our results, improving muscle mass and muscle strength are all important in revising sarcopenia. Deutz et al. found that adding leucine to high protein supplements could stimulate muscle protein synthesis and improve muscle mass in cancer patients (45). Smith et al. showed that resistance training was an effective method to improve muscle mass and muscle strength in clinical populations (46). The guidelines of EWGSOP suggested that supplementation of amino acids, vitamin D, testosterone, and growth hormone could improve muscle mass and muscle function (37). However, there has been no standard "pre-habilitation" strategy widely applied in clinical practice. A comprehensive understanding of molecular and metabolic mechanism of sarcopenia may provide new insights in finding novel therapeutic targets for sarcopenia in the future.

There are also some limitations in the study. Firstly, the sample size is relatively small, which may lead to some bias to the results. Prospective large-scale studies are needed to validate the results. Secondly, we only evaluate the impact of sarcopenia on postoperative complications after hepatectomy. It is still necessary to conduct further researches focusing on both short-term and long-term outcomes (e.g., recurrence and survival). Thirdly, the change in skeletal muscle after surgery has been identified as a significant predictor of outcomes in patients undergoing hepatectomy (47, 48). But the changes in sarcopenia-related factors have not been investigated in this study and we will pay more attention to the dynamic changes of sarcopenia in the further study. Lastly, although confirming the negative impact of sarcopenia, this study is an observational study without any interventions. Prospective interventional clinical trials are still necessary to find effective strategies for counteracting sarcopenia.

In conclusion, preoperative sarcopenia is closely associated with adverse short-term outcomes after hepatectomy in patients with benign liver diseases. Defining sarcopenia by muscle mass and muscle strength is more accurate and applicable to implement risk classification for patients following hepatectomy. In addition, valuable sarcopenia-based nomograms were built to predict major complications and overall complications for patients with benign liver diseases undergoing hepatectomy, which may provide new insights in clinical decision making.

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 human participants were reviewed and approved by Institutional Review Board of the First Affiliated Hospital of Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZB, ZC, BC, JY, ZZ, QH, HY, CZ, and KC contribute to data acquisition. ZB, ZC, and ZZ contribute to draft of the manuscript. ZB, GC, and YW contribute to study concept and design. ZB, YY, JM, and BC contribute to data analysis. ZB, ZC, GC, and YW contribute to draft revising and study supervision. All authors contributed to the article and approved the submitted version.

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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.2023.1040297/full#supplementary-material

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Body composition parameters, immunonutritional indexes, and surgical outcome of pancreatic cancer patients resected after neoadjuvant therapy: A retrospective, multicenter analysis

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Background and aims: Body composition parameters and immunonutritional indexes provide useful information on the nutritional and inflammatory status of patients. We sought to investigate whether they predict the postoperative outcome in patients with pancreatic cancer (PC) who received neoadjuvant therapy (NAT) and then pancreaticoduodenectomy.

Methods: Data from locally advanced PC patients who underwent NAT followed by pancreaticoduodenectomy between January 2012 and December 2019 in four high-volume institutions were collected retrospectively. Only patients with two available CT scans (before and after NAT) and immunonutritional indexes (before surgery) available were included. Body composition was assessed and immunonutritional indexes collected were: VAT, SAT, SMI, SMA, PLR, NLR, LMR, and PNI. The postoperative outcomes evaluated were overall morbidity (any complication occurring), major complications (Clavien-Dindo ≥ 3), and length of stay.

Results: One hundred twenty-one patients met the inclusion criteria and constituted the study population. The median age at the diagnosis was 64 years (IQR16), and the median BMI was 24 kg/m^2 (IQR 4.1). The median time between the two CT-scan examined was 188 days (IQR 48). Skeletal muscle index (SMI) decreased after NAT, with a median delta of -7.8 cm^2/m^2 ($p < 0.05$). Major complications occurred more frequently in patients with a lower pre-NAT SMI ($p = 0.035$) and in those who gained in subcutaneous adipose tissue (SAT) compartment during NAT ($p = 0.043$). Patients with a gain in SMI experienced fewer major postoperative complications ($p = 0.002$).

The presence of Low muscle mass after NAT was associated with a longer hospital stay [Beta 5.1, 95%CI (1.5, 8.7), $p = 0.006$]. An increase in SMI from 35 to 40 cm^2/m^2 was a protective factor with respect to overall postoperative complications [OR 0.43, 95% (CI 0.21, 0.86), $p < 0.001$]. None of the immunonutritional indexes investigated predicted the postoperative outcome.

Conclusion: Body composition changes during NAT are associated with surgical outcome in PC patients who receive pancreaticoduodenectomy after NAT. An increase in SMI during NAT should be favored to ameliorate the postoperative outcome. Immunonutritional indexes did not show to be capable of predicting the surgical outcome.

KEYWORDS

pancreatic cancer, nutrition–clinical, body composition, postoperative complications, inflammation

Introduction

Pancreatic cancer (PC) remains a lethal malignancy (1), with a 5-year survival rate of around 30% after surgical resection and multimodal treatment (2). Furthermore, pancreatic surgery's morbidity and mortality rates are still high (3, 4), making the scenario even more problematic.

Pancreatic resections are recognized as one of the most challenging operations due to the magnitude of dissection and resection, the resultant global stress, and the high morbidity rate. Major surgery produces an intense metabolic response and nutritional status changes by activating an inflammatory cascade and releasing stress hormones. Appropriate tissue healing and recovery/maintenance of organ function after such operations necessitate adequate qualitative and quantitative nutritional substrates to be effective. Furthermore, when PC is cephalic, obstructive jaundice is almost invariably present and associated with impaired absorption, nutritional state, and homeostasis (5).

The preoperative identification of patients at risk of malnutrition, and the adoption of nutritional corrective actions, especially in patients receiving systemic therapy before surgery, provides a window of intervention (6) that may mitigate the risk of poor postoperative outcome. Sarcopenia, a progressive decline in skeletal muscle mass, strength, and performance (7), is a direct consequence of impaired nutritional and metabolic status. Based on the patients' populations considered and the cutoff used, the prevalence of sarcopenia in PC patients at diagnosis is variable (8). Research on the association of sarcopenia with surgical outcomes after pancreatic surgery has produced conflicting results (9–11).

Computed tomography (CT) is an accurate tool to quantify whole-body composition (12); moreover, it is routinely used for staging and restaging of PC. Therefore, it is readily available without additional cost, radiation exposure, or inconvenience to the patient. In PC patients, the effects of neoadjuvant therapy (NAT) on body composition have been increasingly investigated, with contrasting results (13–16). In general, lean muscle mass depletion is typical in patients with energetic imbalance and metabolic derangement and may be the driver of a worse surgical outcome.

Chronic systemic inflammation is the theoretical substrate of muscle depletion, sarcopenia, and cachexia (17), and many immunonutritional biochemical parameters have been developed to quantify it (18). Cutoff values of such immunonutritional indexes might serve as a proxy for immunonutritional impairment. Thus, they may help identify fragile patients with an increased pro-inflammatory status, assign patients to appropriate therapies, and even identify early pre-cachexia by offering a multimodal treatment. Among these indexes, the prognostic nutritional index (PNI) (19), the neutrophil-to-lymphocyte ratio (NLR) (20), the platelet-to-lymphocyte ratio (PLR) (21), and the lymphocyte-to-monocyte ratio (LMR) (22) have all been shown to be predictive of surgical or oncological outcome of PC patients.

The current study investigated whether changes in body composition during NAT and multiple preoperative nutritional indexes predict the surgical outcome of locally advanced PC patients who underwent pancreaticoduodenectomy after NAT.

Methods

Study design, patient population, and management

The prospective institutional electronic databases of the General and Pancreatic Surgery Unit, Pancreas Institute, University of Verona (Verona, Italy), Milano-Bicocca University at San Gerardo Hospital (Monza, Italy), Pancreatic Surgery Unit, University of Bologna (Bologna, Italy), and of the Pancreatic Surgery Unit of Humanitas University (Milan, Italy) were searched for adult PC patients with NCCN-defined (23) "borderline resectable" or "locally advanced" PC receiving pancreaticoduodenectomy after NAT, between January 2012 and December 2019, of whom two cross-sectional imaging examinations (before and after NAT) and immunonutritional indexes (before surgery) were available.

Regarding individual patient management, each Institution managed each case independently but with a common pathway. Briefly, the chemotherapy choice was left at the oncologist's discretion, and regular multidisciplinary reassessments were made. When the tumor shrunk and/or the Ca 199 levels normalized or at least halved, if radical resection was deemed feasible and the patient was fit, surgery was optioned, and the tumor was ultimately resected. The postoperative care was conducted according to the ERAS recommendations (24).

Given this study's retrospective, observational, and anonymous nature, ethical approval was not required. The study was carried out following the Declaration of Helsinki.

Body composition assessments and definitions

Weight and height obtained from the patient's chart were recorded by hospital staff. Body mass index (BMI) was obtained by dividing actual weight by height squared (kg/m^2), and the WHO classification was used for interpretation (25). Skeletal muscle area (SMA), skeletal muscle index (SMI), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) were analyzed from CT images. A single DICOM image was extracted from pre- (at the time of diagnosis/staging) and post-NAT (at restaging before surgery) CT images at the level of the third lumbar vertebra (L3) (26), an area chosen as the best correlate to whole-body composition (27).

DICOM images were then exported to dedicated software, such as CoreSlicer® (28) (Verona and Milan Centers) and ImageJ (29) (Bologna Center). All software, using pre-established Hounsfield unit (HU) thresholds (30), identified and quantified in cm^2 areas of specific tissues as follows: −29– +150 HU for SM, −190– −30 HU for SAT, and −150– −50 HU for VAT. The skeletal muscle index (SMI) was calculated by normalizing the skeletal muscle area to squared height (in m^2). Body composition measurements' variation (delta, Δ, calculated as post- minus pre-NAT values) has been calculated.

Acknowledging that the evaluation of muscle quality is mandatory to describe the presence of sarcopenia, and this parameter was not evaluated in the present study, the commonly used term "sarcopenia" has been substituted with "Low muscle mass," referring to the depletion of lean muscle mass, and the cutoff value proposed by Martin et al. (31) has been adopted.

Immunonutritional indexes

The immunonutritional indexes were calculated using the laboratory data available at preoperative clinical assessment, typically performed 1–3 weeks before surgery. NLR, PNI, PLR, and LMR were considered continuous variables.

Surgical outcome

Overall morbidity was the main outcome. It was evaluated considering the rate of postoperative complications (any kind). Secondary metrics for surgical outcome evaluation were:

- Major Complications [defined as Clavien-Dindo (32) grade ≥ 3],
- Length of stay (days).

Statistical analysis

Descriptive statistics were used to summarize the data from the study variables. Median and interquartile ranges were considered for continuous variables, while, for categorical ones, absolute and relative frequencies were used to synthesize the data. Comparisons of patient characteristics between independent groups were made by calculating the Wilcoxon rank-sum test for continuous variables and the Chi-square test or Fisher's exact test, wherever appropriate, for

TABLE 1 Study population's general characteristics (n = 121).

Variable	Total, n (%)
Age (years, mean, SD)	61 (10)
Sex (Female)	61 (50.4%)
ASA score III-IV, yes	24 (19.8%)
CACI >4, yes	71 (58.7%)
Diabetes mellitus, yes	27 (22.3%)
NLR (median, IQR)	2.1 (2)
PLR (median, IQR)	140 (59.8)
LMR (median, IQR)	2.6 (2)
PNI (median, IQR)	41 (4.8)
Albumin (g/L, median, IQR)	41 (5.2)
Stage at diagnosis	
Borderline resectable	92 (76)
Locally advanced	29 (24)
Tumor size (mm, mean, SD)	
Pre-neoadjuvant therapy	30.6 (8.9)
Post-neoadjuvant therapy	24.3 (9.6)
Neoadjuvant therapy scheme	
FOLFIRINOX	55 (45.4)
Gemcitabine/Nab-Paclitaxel	33 (27.3)
Other	23 (27.3)
Chemotherapy duration (cycles, median, IQR)	5 (5)
Time diagnosis to surgery (mo, median, IQR)	6 (5)
Vascular resection, yes	24 (19.8%)
T-status at pathology	
Tx	15 (12.4)
T1	31 (25.6)
T2	58 (47.9)
T3	4 (3.3)
T4	13 (10.7)
N-status at pathology	
N0	47 (38.8)
N1	46 (38)
N2	28 (23.2)
R0 resection, yes	68 (56.2)
Length of stay (days), median (IQR)	11 (9)
Postoperative morbidity (overall), yes	61 (50.4%)
Major complications (Clavien-Dindo ≥ 3), yes	15 (12.4%)

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lympho-cyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index.

categorical ones. The effect of SMI on the primary study endpoint was evaluated *via* a logistic regression model accounting for non-linear effects by estimating a restricted cubic spline. The models were adjusted for the characteristics of the patients, such as "sex" and "age." The SMI cutoff was estimated by identifying the inflection point of the morbidity risk prediction curve. The SMI effects on the morbidity risk are reported in intervals of 5 SMI variations around the inflection point. The effect of SMI on the length of stay has been assessed using the ordinary least squares method with a restricted cubic spline. The Huber-White robust standard error sandwich estimator accounted for the correlation within the repeated pre- and post-measurements. The effect of age on SMI has been assessed using the ordinary least squares method with a linear regression model, adjusted for sex. The 1,000 runs bootstrap 95% confidence intervals have been reported for the prediction plots. The univariable linear regression model results, considering the effect of body composition parameters on the length of stay have been also reported with the estimated effects (Beta) and the 95% confidence intervals.

Analyses were performed with the R system (33) and the rms libraries (34).

Results

Patient characteristics

A total of 121 patients met the inclusion criteria and were enrolled in the study. Females and males were almost equally distributed (50.4%/49.6%), the median age at diagnosis was 64 (IQR 16), and the median BMI was 24 kg/m^2 (IQR 4.1). At diagnosis, 92 (76%) cases were borderline resectable cancer, and the remaining 29 (24%) were locally advanced. The most common chemotherapy regimen was FOLFIRINOX (Fluorouracil-Folinic Acid-Irinotecan-Oxaliplatin, 45.4%), and the median duration of chemotherapy was five cycles (IQR 5). Thirty patients (24.8%) received additional stereotaxic radiation therapy before surgery. At restaging, 63 (52%) and 54 (44.7%) patients had stable and partial/complete responses, respectively. Table 1 reports the general characteristics of the study population, including chemotherapy, surgical, pathologic, and relevant postoperative data.

TABLE 2 Body composition parameters changes during neoadjuvant therapy.

Parameter	Pre NAT	Post NAT	Delta	95% CI	*p*-value
BMI, kg/m^2	24.0 (4.1)	23.8 (4.0)	−0.14 (1.46)	−1.3, 0.60	0.5
SMA, cm^2	133 (58)	134 (51)	1.2 (16)	−12, 8.5	0.7
SMI, cm^2/m^2	52 (32)	49 (16)	0.34 (13.54)	−13, −2.6	**0.003**
VAT, cm^2	121 (124)	103 (108)	−8.7 (40.1)	−30, 9.4	**<0.001**
SAT, cm^2	167 (108)	166 (98)	−8.7 (55.3)	−29, 9.7	0.054

†Median (IQR); %; n (%).

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index. SMA, skeletal muscle area; SMI, skeletal muscle index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue. Bold values indicate statistical significance.

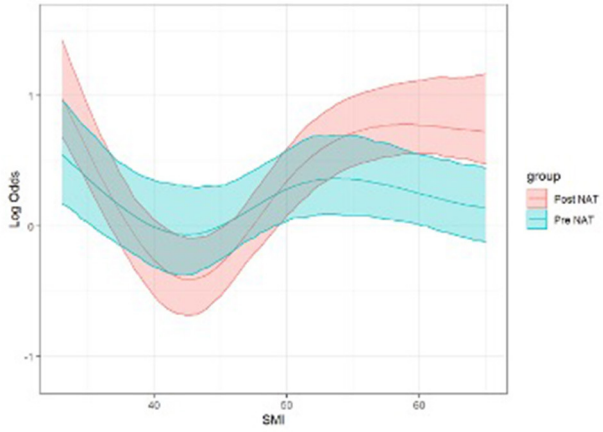

FIGURE 1
Logistic regression model for postoperative morbidity risk (log-OR) according to SMI (Pre- and Post-NAT) adjusted per gender and age ($p < 0.001$, see text). Both linear ($p = 0.01$) and non-linear ($p = 0.02$) effects are significant. NAT, Neoadjuvant therapy; SMI, skeletal muscle index (cm^2/m^2).

Body composition changes after NAT

Table 2 shows the changes in body composition after the completion of NAT. The median time between the two CT scans was 188 days (IQR 48). Before NAT, 36 patients (32.1%) reported low muscle mass, and this percentage increased slightly after NAT ($N = 41$, 33.9%). Muscle components (SMI) or adipose tissue (VAT) components decreased after NAT (all $p < 0.05$). The regression model found that for an increase in age from 54 to 70 years, a decrease in SMI of 5 cm^2/m^2 is expected [95%CI (−9.9, −0.2), $p = 0.04$].

Body composition changes and surgical outcome

Regarding the main study's outcome, general postoperative complications were not associated with changes in the body compartment (Supplementary Table 1). The SMI effects on the morbidity risk are reported in intervals of 5 SMI variations (30–50) around the 42 SMI inflection point. We found that an increase in SMI from 35 to 40 cm^2/m^2 reduced the probability of developing any postoperative complications [Log-OR 0.43, 95% CI (0.21, 0.86), $p < 0.001$, Figure 1]. As concern major postoperative complications, they occurred more frequently in patients who had a pre-NAT lower SMI ($p = 0.035$) and a gain in the SAT compartment ($p = 0.043$), and less frequently in patients who had a gain in SMI ($p = 0.002$, Table 3).

When it comes to the length of stay, an increase in VAT (pre- and post-NAT), and the presence of low muscle mass after NAT were associated with a longer stay [Beta 0.03, 95%CI (0.01, 0.05), $p = 0.010$; Beta 0.04, 95%CI (0.02, 0.06), $p = 0.019$; and Beta 5.1, 95%CI (1.5, 8.7), $p = 0.006$, respectively], while an increase in albumin predicted a shorter stay [Beta −0.24, 95%CI (−0.47, −0.02), $p = 0.039$]; Table 4 shows a selection of the variables of the analysis, while Supplementary Table 3 provides the complete list.

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TABLE 3 Body composition changes and major postoperative complications.

	Major Complications ($n = 15$)	No major Complications ($n = 101$)	p-value
SMA, cm^2 (median, IQR)			
Pre-NT	126 (54)	134 (58)134 (58)	0.8
Post-NT	125 (43)	136 (50)	0.7
Δ	15 (24)	1 (12)	0.066
SMI, cm^2/m^2 (median, IQR)			
Pre- NT	44 (10)	53 (35)	**0.035**
Post- NT	49 (16)	50 (12)	0.7
Δ	0 (17)	6 (5)	**0.002**
SAT, cm^2 (median, IQR)			
Pre- NT	140 (112)	168 (107)	0.7
Post- NT	183 (89)	164 (99)	0.5
Δ	12 (48)	−11 (51)	**0.043**
VAT, cm^2 (median, IQR)			
Pre- NT	81 (119)	121 (122)	0.5
Post- NT	96 (90)	107 (109)	0.9
Δ	−1 (43)	−10 (39)	0.2
Low muscle mass (32)			
Pre-neoadjuvant therapy	40%	28%	0.432
Post-neoadjuvant therapy	33%	34%	0.961

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index. SMA, skeletal muscle area; SMI, skeletal muscle index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue. Bold values indicate statistical significance.

Immunonutritional indexes and surgical outcome

None of the immunonutritional indexes proved predictive of a worse postoperative outcome (Table 4, Supplementary Tables 2, 3). In addition, no differences were found when comparing each immunonutritional index in sarcopenic vs. non-sarcopenic patients (data not shown).

Discussion

Body composition analysis and a careful nutritional assessment are invaluable tools that help identify cancer patients at risk of major postoperative complications. PC patients are not an exception. Typically, they are malnourished and sarcopenic, already at diagnosis. In this study, about one-third of the included patients had a low muscle mass at diagnosis, and this rate remained substantially stable after NAT. The absence of a worsening of sarcopenia, reported by other surgical series (9), may be due to the always increased awareness among patients, caregivers, and healthcare providers of the importance of nutritional status in oncology, especially in PC patients (the majority of the present study patients were enrolled during the last year of the study period).

Regarding the body composition changes that occur during NAT, it was found that both the muscular and the fat compartments were significantly impacted by NAT. These findings have already been reported for PC patients receiving chemotherapy (14, 35–39), demonstrating energetic dyshomeostasis. Therefore, attention must be paid to the body composition changes that occur during NAT in an attempt to maintain patients' body homeostasis, energetic balance, and appropriate metabolism. Radiological reevaluations performed periodically during NAT allow clinicians to achieve it.

When it comes to the study's primary endpoint, while any body composition parameter change did not influence the occurrence of any complications, patients experiencing major complications had a lower pre-NAT SMI value compared with those not facing major complications ($p < 0.05$); additionally, patients having a positive delta SMI (those who gained lean muscle mass) were less likely to experience major postoperative complications. The opposite was true for patients gaining subcutaneous fat tissues after NAT that were more exposed to major complications (all $p < 0.05$). These results align with the fact that the presence of sarcopenia post-NAT predicts a longer length of stay (11). That gaining SAT exposed patients to a greater risk of major postoperative complications is not easily explained because, despite being non-statistically significant, a tendency toward fat tissue loss during NAT was found for both VAT and SAT (Table 1). This finding is likely to be clinically meaningless.

A longer stay was also associated with high VAT values. This finding may be explainable by some factors or events not collected for this study (surgical site infections and, in general, infectious complications), so that patients with a high component of adipose tissue experience a longer hospitalization and, in general, failure to rescue. Instead, an increase in albumin was

TABLE 4 Univariable analysis and length of stay (extracted from Supplementary Table 3).

Variable	Beta	95% CI	*p*-value
Albumin, g/L	−0.24	−0.47, −0.02	**0.039**
NLR	0.58	−0.17, 1.3	0.13
PNI	−0.07	−0.42, 0.27	0.7
PLR	0.01	−0.01, 0.02	0.4
LMR	−0.50	−1.5, 0.47	0.3
SMA pre-NAT, cm^2	0.01	−0.03, 0.05	0.6
SMI pre-NAT, cm^2/m^2	−0.01	−0.09, 0.07	0.8
VAT pre-NAT, cm^2	0.03	0.01, 0.05	**0.010**
SAT pre-NAT, cm^2	0.00	−0.02, 0.02	>0.9
SMA post-NAT, cm^2	−0.03	−0.07, 0.02	0.2
SMI post-NAT, cm^2/m^2	−0.07	−0.17, 0.04	0.2
VAT post-NAT, cm^2	0.04	0.02, 0.06	**0.019**
SAT post-NAT, cm^2	0.01	−0.01, 0.03	0.4
Low muscle mass (32) pre-NAT	2.3	−1.5, 6.1	0.2
Low muscle mass (32) post-NAT	5.1	1.5, 8.7	**0.006**

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PNI, prognostic nutritional index. SMA, skeletal muscle area; SMI, skeletal muscle index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue. Bold values indicate statistical significance.

associated with a shorter length of stay. This recalls previous reports that associated low preoperative albumin levels with a worse postoperative outcome after pancreatic surgery (43–45). However, other studies did not report the same finding (46), and a recent randomized controlled trial demonstrated that the routine correction of preoperative hypoalbuminemia did not lead to a better postoperative outcome (40).

This study presents a novel dynamic model that can identify patients with the greater benefit of gaining lean muscle mass, namely those who move from an SMI of 35 to an SMI of 40 cm^2/m^2. This positive change may reduce the odds of experiencing any postoperative complication by about 60%. This aspect points attention to the need to identify patients at high risk of postoperative complications, focusing on those with low SMI who can concretely benefit from a tailored nutritional intervention to reduce the probability of postoperative complications, following a nutritional path, and setting a goal. The other fluctuations of the SMI to values >40 did not show any protective factor vs. major postoperative complications, since at these values of the SMI it is likely that the body can better resist surgical stress and sooner reach homeostasis. However, our results need to be confirmed prospectively.

Among the immunonutritional values, none predicted the postoperative outcome. This result probably reflects the heterogeneity of the study population when it comes to neutrophil and lymphocyte values with respect to having suffered from inflammatory, infectious events before and close to surgery that could have altered these values in the preoperative period (65% of patients had a biliary stent, 25% received multiple endoscopic procedures in the biliary tract, and 15% had had cholangitis).

Of note, we found that a decrease in SMI has to be expected with the increase in age (Supplementary Figure 1). About one-third of 60-year-old patients are sarcopenic (41), and a decrease in lean muscle mass must be expected at a rate of 15% per decade over 70 years (42). Considering that the highest peak of PC incidence occurs between 60 and 80 years, our results underline that nutritional evaluation at the time of diagnosis and during NAT may be fundamental, especially in elderly patients. Pre-habilitation regimens based on exercise (aerobic and resistance activity) and nutritional support focused on maximizing energy and protein intake should focus especially on these subgroups of patients to improve the outcome.

This study has some limitations. First, its retrospective nature does not allow avoiding a selection bias. Second, while the study covers a long period, there was an imbalance toward the last year, when more than half of the cases were recruited. This may have generated a selection and management bias. Third, it cannot be excluded that the enrolled patients could have received nutritional counseling and support during chemotherapy, thus creating another source of bias. Fourth, the assessment of muscle quality (strength or performance) was not done nor feasible, highlighting that muscle mass was evaluated in terms of quantity (low muscle mass) and not quality. Fifth, comparing the results of the present study with the available literature might be inaccurate, as populations are very heterogeneous in terms of disease stages and treatments. Last, the study population is heterogeneous in terms of neoadjuvant treatment and stage disease, and this may impact the results obtained.

Conclusions

In conclusion, in our experience, the muscle compartment may decrease during NAT, and the delta of variation may provide useful predictive information for the preoperative risk assessment analysis of PC patients undergoing pancreaticoduodenectomy after NAT. For the first time, we identified a subset of patients that may benefit the most from a gain in SMI during NAT, creating a nutritional trajectory to follow and a goal for clinicians to optimize postoperative outcomes. This study failed to prove the ability of the immunonutritional indexes to predict the postoperative outcome; their application may be more appropriate in non-cephalic PC.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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.2023.1065294/full#supplementary-material

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Relationship between preoperative malnutrition, frailty, sarcopenia, body composition, and anthropometry in elderly patients undergoing major pancreatic and biliary surgery

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Objective: To analyze the correlation between preoperative nutritional status, frailty, sarcopenia, body composition, and anthropometry in geriatric inpatients undergoing major pancreatic and biliary surgery.

Methods: This is a cross-sectional study of the database from December 2020 to September 2022 in the department of hepatopancreatobiliary surgery, Beijing Hospital. Basal data, anthropometry, and body composition were recorded. NRS 2002, GLIM, FFP 2001, and AWGS 2019 criteria were performed. The incidence, overlap, and correlation of malnutrition, frailty, sarcopenia, and other nutrition-related variables were investigated. Group comparisons were implemented by stratification of age and malignancy. The present study adhered to the STROBE guidelines for cross-sectional study.

Results: A total of 140 consecutive cases were included. The prevalence of nutritional risk, malnutrition, frailty, and sarcopenia was 70.0, 67.1, 20.7, and 36.4%, respectively. The overlaps of malnutrition with sarcopenia, malnutrition with frailty, and sarcopenia with frailty were 36.4, 19.3, and 15.0%. There is a positive correlation between every two of the four diagnostic tools, and all six p-values were below 0.002. Albumin, prealbumin, CC, GS, 6MTW, ASMI, and FFMI showed a significantly negative correlation with the diagnoses of the four tools. Participants with frailty or sarcopenia were significantly more likely to suffer from malnutrition than their control groups with a 5.037 and 3.267 times higher risk, respectively (for frailty, 95% CI: 1.715–14.794, p = 0.003 and for sarcopenia, 95% CI: 2.151–4.963, p<0.001). Summarizing from stratification analysis, most body composition and function variables were worsen in the ≥70 years group than in the younger group,

and malignant patients tended to experience more intake reduction and weight loss than the benign group, which affected the nutrition diagnosis.

Conclusion: Elderly inpatients undergoing major pancreatic and biliary surgery possessed high prevalence and overlap rates of malnutrition, frailty, and sarcopenia. Body composition and function deteriorated obviously with aging.

KEYWORDS

malnutrition, frailty, sarcopenia, body composition, surgery

1. Introduction

The geriatric syndrome refers to a range of multifactorial health conditions representing the accumulation of multiple system impairments in older adults. Malnutrition, frailty, and sarcopenia are three common geriatric syndromes, which can substantially lead to poor outcomes, such as disability, dysfunction, falls, and perioperative complications, and thereby increase the length of hospital stay (LOS) and the cost of hospitalization, and result in long-term care or even mortality (1–5).

Malnutrition or undernutrition refers to deficiencies in nutritional intake resulting in altered body composition, and approximately 1/3 of Chinese geriatric inpatients experience malnutrition (6). In the department of hepatopancreatobiliary surgery, the prevalence of nutritional risk and malnutrition are as high as 69.7 and 56.6% in our former study (7). Frailty is characterized by a cumulative decline in the physiological capacity of multiple organ systems and increased vulnerability to endogenous and exogenous stressors, with an estimated prevalence ranging from 18.8 to 41.9% in geriatric surgical patients and from 10.4 to 37.0% in general surgical patients (8, 9). Sarcopenia is an age-related syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, which accounts for 17.4% of Chinese community-dwelling and hospitalized elderly (10). In pancreatic surgery, the prevalence is 38.8% determined by the total psoas area index in CT scan (7).

Frailty, sarcopenia, and malnutrition have independent diagnostic criteria, but share many components, such as weight loss, muscle mass, or strength loss, and often coexist or overlap in elderly inpatients (11). In a recent systematic review, it was concluded that about half of the hospitalized older patients suffer from 2 or perhaps 3 of these debilitating conditions, and standardized screening for these conditions is highly controversial to guide nutritional and physical interventions (12). Due to the significant influence of these three clinical problems on outcomes, respectively, it is important to understand the current situation and provide basal data for further cohort study. So our study aims to investigate the prevalence and overlap of these conditions in the elderly who are going to receive major pancreatic and biliary surgery.

2. Materials and methods

2.1. Participants

This study is a cross-sectional study analyzing the daily database of the Department of hepatopancreatobiliary surgery, Beijing Hospital. From December 2020 to September 2022, 205 consecutive patients undergoing major pancreatic and biliary surgery were screened, and then, 140 elderly patients were recruited in this study.

The inclusion criteria of this study are as follows: (1) age ≥60 years old, which is the age cut-off of older adults defined by the Nation Health Commission of China (13); (2) major pancreatic and biliary surgery, containing pancreatectomy (Whipple procedure, distal pancreatectomy, and local pancreatectomy), bile-enteral bypass due to malignant obstructive, and bile duct exploration; (3) voluntary enrollment and signed informed consent. Exclusion criteria contain (1) emergency operation; (2) cancer patients who underwent adjuvant therapy before operation; (3) severe disability or dementia, inability to cooperate with frailty and sarcopenia assessment or effective communication; (4) refusal of informed consent. The Ethics Committee of Beijing Hospital approved the study protocol and written informed consents were obtained from all participants. (Approval letter No. 2020BJYYEC-218-01). The present study adhered to the STROBE guidelines for cross-sectional study. **Figure 1** shows the flowchart of this study.

2.2. Basal characteristics, anthropometry, and body composition

The basal data include sex, age, height, weight, body mass index (BMI), co-morbidities, and serum examination (complete blood count, liver function, renal function, albumin, glucose, et al.). According to the standard of the guidelines for prevention and control of overweight and obesity in Chinese adults, a BMI < 18.5 kg/m^2 was defined as underweight, 18.5 kg/m^2 $\leq$ BMI $<$ 24 kg/m^2 was normal weight, 24 kg/m^2 $\leq$ BMI $<$ 28 kg/m^2 was considered overweight, and BMI $\geq$ 28 kg/m^2 was considered obesity (14).

A diet survey was conducted after admission. We recorded the change of diet before and after the diagnosis of the original disease, and calculated the contents composition, containing protein, carbohydrate, fat, and total energy.

Anthropometry was done 1 to 2 days after admission, including calf circumference (CC) and grip strength (GS), both of which, we used the average value of the left and right sides. To assess the functional status, 15-foot and 6-meter timed walk speed (6MTW) was conducted to get the walking speed. Bioelectrical impedance analysis (BIA) was applied with the InBody 720 bioimpedance body composition analyzer (Biospace Co., Ltd., Korea). Appendicular skeletal muscle mass index (ASMI) was calculated, which was the sum of the lean muscle mass of the upper and lower extremities adjusted with height. Also, the fat-free mass index (FFMI) was

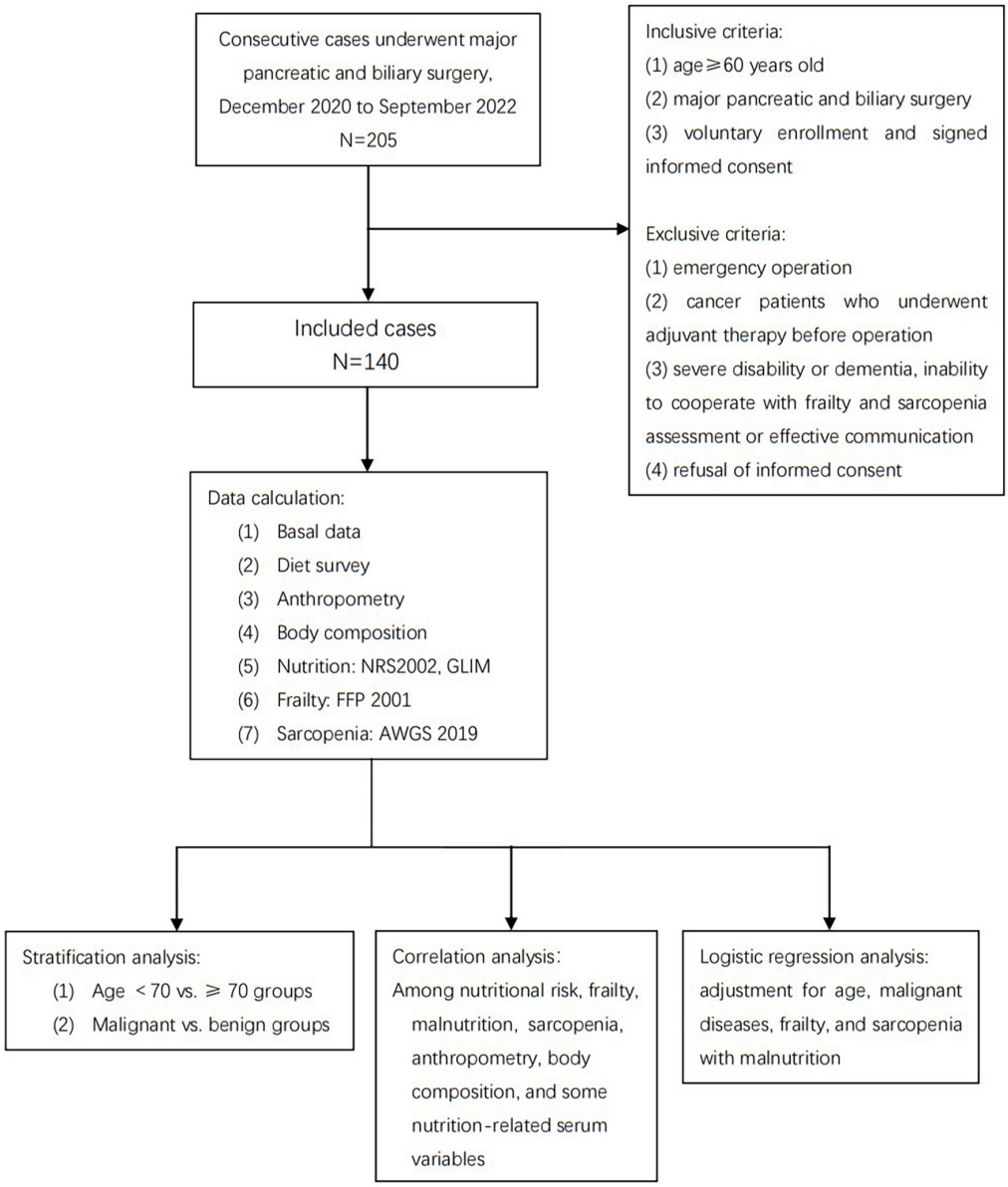

FIGURE 1
Flowchart of the study.

recorded. Visceral fat area (VFA), waist-hip ratio (WHR), and body fat percentage (BTP) were included to reflect fat metabolism.

2.3. Nutritional risk screening

We used Nutritional Risk Screening 2002 (NRS 2002) for nutritional screening for each patient within 24 h after admission, which was recommended by the European Society of Parenteral Enteral Nutrition (ESPEN) (15). NRS2002 contains three aspects: nutritional impairment: weight loss, intake reduction, and lower BMI (score 0–3), the severity of disease (score 0–3), and age [(score 0–1) (< 70 years: 0 scores and ≥ 70 years: 1 score)]. Scores for the final screening take into account all these three sections range from 0 to 7 and classify patients into one of two nutritional risk stages (or groups): at low nutritional risk group (NRS 2002 score < 3), and (moderate/high) risk of malnutrition group (NRS 2002 score ≥ 3). In pancreatic surgery, an NRS2002 score of more and equal to 5 was considered at high nutritional risk with remarkable clinical meaning (16).

2.4. Malnutrition diagnosis and grading

The Global Leadership Initiative on Malnutrition (GLIM) criteria were implemented for malnutrition diagnosis and grading among patients with nutritional risk determined by NRS2002 (17). The framework of GLIM criteria includes three phenotypic criteria and two etiologic criteria, and the detailed items and cut-off values could be determined and modified in different centers

TABLE 1 Comparison of the four tools.

	NRS2002	GLIM	AWGS 2019	FFP 2001
Weight loss	> 5% within past 3 months(1 score) >5% within past 2 months(2 scores) >5% within past 1 months(3 scores)	WT > 5% within past 6 months WT > 10% beyond 6 months	Unintentional weight loss	Unintentional weight loss: of 10 pounds in prior year, or of 5% of body weight in prior year at follow-up
BMI	BMI < 18.5 kg/m^2 (3 scores)	BMI < 18.5 kg/m^2 if age < 70 years BMI < 20 kg/m^2 if age ≥ 70 years	–	–
Muscle mass reduction	–	Reduced by validated body composition measuring techniques: FFMI by DXA or BIA, CT or MRI Anthropometric measures: calf circumferences Functional assessment: hand-grip strength	ASMI by DXA or BIA CC, SARC-F, or SARC-CalF Handgrip strength	Grip strength
Intake reduction	50–75% of normal requirement in preceding week (1 score) 25–50% of normal requirement in preceding week (2 scores) 0–25% of normal requirement in preceding week (3 scores)	≤ 50% of needs from 1 to 2 weeks any reduction for >2 weeks	–	–
Disease and inflammation burden	Patient with chronic disease, admitted to hospital due to complications. Protein requirement can be covered by oral diet or supplements (1 score) Patient confined to bed due to illness. Protein requirement can be covered by artificial feeding (2 scores) Patient in intensive care. Protein requirement is increased and cannot be covered even by artificial feeding (3 scores)	Acute disease/injury-related: Severe inflammation and mild-to-moderate inflammation Chronic disease-related: Chronic or recurrent mild-to-moderate inflammation Transient inflammation of a mild degree is excluded	Malnutrition Chronic conditions	——
Physical performance	–	–	6-meter walk time 5-time chair stand test SPPB	15-feet walk time Low physical activity level
Other	–	–	Depressive mood Cognitive impairment Repeated falls	Self-reported exhaustion

BMI, body mass index; WT, weight; FFMI, fat free mass index; DXA, Dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; CT, computed tomography; MRI, magnetic resonance imaging; ASMI, appendicular skeleton muscle index; CC, calf circumference; SPPB, Short Physical Performance Battery; SARC-F, Strength, Assistance walking, Rising from a chair, Climbing stairs, Falls; SARC-CalF, Strength, Assistance walking, Rising from a chair, Climbing stairs, Calf circumference, Falls.

and populations (18). In this study, we used GLIM criteria in a traditional way with the original criteria. Phenotypic criteria include (1) unintentional weight loss (WT): WT > 5% within the past 6 months, or WT > 10% beyond 6 months; (2) low BMI: BMI < 18.5 kg/m^2 if age < 70 years, BMI < 20 kg/m^2 if age ≥ 70 years; (3) reduced muscle mass: in our study, we used AMMI and FFMI assessed by BIA. AMMI < 7 kg/m^2 or FFMI < 17 kg/m^2 in men were considered patients with reduced muscle mass, and AMMI < 5.7 kg/m^2 or FFMI < 15 kg/m^2 in women were considered positive. Etiologic criteria include: (1) Reduced food intake: ≤50% of needs from 1 to 2 weeks, or any reduction for >2 weeks; (2) Disease burden or inflammation: in this study, most of the patients were suffering from malignancies and the co-morbidities were also taken into account. If at least one criterion was fulfilled in each section, malnutrition can be diagnosed.

The grading of malnutrition also followed the GLIM criteria. Unintentional weight loss (WT) > 10% within the past 6 months or WT > 20% beyond 6 months or low BMI (BMI < 17.0 kg/m^2 if age < 70 years or BMI < 17.8 kg/m^2 if age ≥ 70 years) or severe muscle deficit were defined as severe malnutrition. 5–10% Unintentional weight loss (WT) within the past 6 months or 10–20% WT beyond 6 months or low BMI (17.0 ≤ BMI < 20.0 kg/m^2 if age < 70 years or 17.8 ≤ BMI < 22.0 kg/m^2 if age ≥ 70 years) or Mild-to-Moderate muscle deficit were the grading criteria for moderate malnutrition.

2.5. Diagnosis of sarcopenia

In this study, we used the criteria for sarcopenia diagnosis recommended by the Asian Working Group for Sarcopenia (AWGS) (19). For patients in acute to chronic health care or clinical research settings, a two-step protocol was used: finding cases and diagnosis. In the first step, we tended to use objective criterion, so calf circumference (CC) (<34 cm in male, <33 cm in female) was facilitated to find cases at risk of sarcopenia, based on which, in the second step, sarcopenia can be diagnosed as

follows: (1) Muscle strength: men with grip strength (GS) < 28 kg, women with GS < 18 kg; (2) Physical performance: 6-meter walk < 1 m/s; (3) AMMI: men with AMMI < 7 kg/m^2, women with AMMI < 5.7 kg/m^2. The result containing low ASMI and low muscle strength or low physical performance was sarcopenia, and the result containing all three criteria was severe sarcopenia.

2.6. Diagnosis of frailty

The Fried Frailty Phenotype (FFP) is a recommended assessment tool for frailty in geriatric patients by Chinese expert group consensus (20). FFP criteria include five physical items: (1) Shrinking: Unintentional weight loss: ≥5% of body weight in the prior year; (2) Poor endurance and energy: self-reported exhaustion; (3) Weakness: poorer GS; (4) Slowness: lower walk speed; (5) Low physical activity. Patients who fulfilled none of these five criteria were classified as the non-frailty group, who fulfilled 1 or 2 criteria were classified as the pre-frailty group, and who fulfilled ≥3 criteria were considered as the frailty group. The thresholds of GS and gait speed were referred to the AWGS criteria. Table 1 shows the comparison of all the above diagnostic tools we used in this study.

TABLE 2 Baseline characteristics.

Variables	Basal data, *n* = 140
Sociodemographics	
Age, mean (SD), years	70.0 (7.3)
60–69, *n* (%)	76 (54.3)
≥ 70, *n* (%)	64 (45.7)
Male sex, *n* (%)	82 (58.6)
Admission diagnosis	
Malignancies, *n* (%)	105 (75.0)
Pancreatic cancer, *n* (%)	71 (50.7)
Bile duct cancer, *n* (%)	18 (12.9)
Duodenal cancer, *n* (%)	3 (2.1)
Ampulla cancer, *n* (%)	9 (6.4)
Other malignancies, *n* (%)	4 (2.9)
Benign diseases, *n* (%)	35 (25.0)
History	
Diabetes, *n* (%)	47 (33.6)
Chronic obstructive pulmonary disease, *n* (%)	4 (2.9)
Cardia-cerebral disease, *n* (%)	88 (62.9)
Smoking, *n* (%)	53 (37.9)
Drinking, *n* (%)	32 (22.9)
Blood test at admission	
White blood cell, mean (SD) × 10^9/L	6.0 (1.7)
Hemoglobin. mean (SD) g/L	122.6 (17.3)
Platelet, mean (SD) × 10^9/L	210.3 (61.7)
Fasting glucose, mean (SD) g/L	6.6 (2.9)
Total protein, mean (SD) g/L	64.3 (5.3)
Albumin, mean (SD) g/L	37.3 (4.3)
Pre-albumin, mean (SD) g/L	18.0 (7.7)
Alanine aminotransferase, median (IQR) U/L	21.0 (89.5)2
Creatine, mean (SD) μmol/L	64.7 (16.5)
Triglyceride, mean (SD) mmol/L	1.5 (1.0)
Total cholesterol, mean (SD) mmol/L	4.5 (1.3)

SD, standard deviation; BMI, body mass index; IQR, interquartile range.

2.7. Statistical analysis

The sample size was calculated by PASS software 11.0 (NCSS LLC., Kaysville, UT, USA). The confidence level was set at 0.8. According to our former study, the prevalence of malnutrition was 56.6% and we set the proportion at 60% (7). The tolerance error was set at 10%, so the two-sided confidential interval width was 0.12. The final sample size was 125. All statistical analysis was performed by IBM SPSS Statistics for Windows, version 27.0 (IBMCorp., Armonk, NY, USA). Measurement data that correspond to normal distribution were presented as mean with standard deviation (SD) and analyzed by Student's *t*-test. Measurement data that did not correspond to normal distribution were presented as median with interquartile range (IQR) and analyzed by Mann–Whitney U test. Categorical data were presented as counts and percentages, and compared by chi-square (χ^2) test. Correlations were analyzed by Spearman's correlation coefficient analysis according to the classification of variables. Multivariate analysis was performed by binary logistic regression to identify potential associated factors of malnutrition. A p-value < 0.05 were declared as statistically significant. All figures including flowchart, overlap bubble chart, and correlation heatmap were designed and drawn by Microsoft Office (Version 2016), and the regression analysis figure was drawn by GraphPad Prism version 7.0.0 for Windows (GraphPad Software, San Diego, CA, USA).

3. Results

3.1. Basal characteristics and nutrition status

A total of 140 participants were included with a mean age of 70.0 ± 7.3 years. 58.6% (82/140) were male. 75% (105/140) of cases were malignancies, of which, 71 cases were pancreatic duct adenocarcinoma. The details of the history and blood test at admission are shown in Table 2.

Table 3 shows the data for nutrition assessment. The mean BMI was 23.5 ± 3.6 kg/m^2. 83 cases (59.3%) experienced weight loss to varying degrees, in which, 66 cases exceeded 5%. According to NRS 2002, 70.0% (n = 98) of cases were at risk of nutrition. 94 cases (67.1%) were malnutrition and 49 cases (35.0%) were severe malnutrition according to GLIM criteria. Based on FFP criteria, 53.6% (n = 75) participants were pre-frailty, and 20.7% (n = 29) were frailty. According to the AWGS 2019 consensus, at the step of finding cases, 52.9% (n = 74) cases were at risk of sarcopenia determined by reduced calf circumference, among

10.3389/fnut.2023.1135854

TABLE 3 Data of nutrition measurement.

Variables	Nutrition data, *n* = 140
Nutrition assessment	
BMI, mean (SD) kg/m^2	23.5 (3.6)
BMI < 18.5 kg/m^2, *n* (%)	8 (5.7)
18.5 ≤ BMI < 24 kg/m^2, *n* (%)	74 (52.9)
24 ≤ BMI < 28 kg/m^{2,} *n* (%)	46 (32.9)
BMI ≥ 28 kg/m^{2,} *n* (%)	12 (8.6)
Weight at admission, mean (SD) kg	63.4 (11.0)
Weight loss, *n* (%)	83 (59.3)
Weight loss ≥ 5%, *n* (%)	66 (47.1)
Weight loss amount at admission, median (IQR) kg	3.0 (6.4)
Weight loss percentage at admission, median (IQR)%	4.3 (9.1)
NRS 2002–nutritional risk (score ≥ 3), *n* (%)	98 (70.0)
Low risk (score 3–4), *n* (%)	44 (31.4)
High risk (score 5–7), *n* (%)	54 (38.6)
Nutrition impairment	
Weight loss score 0/1/2/3, *n* (%)	58 (41.4)/12 (8.6)/10 (7.1)/60 (42.9)
Intake reduction score 0/1/2/3, *n* (%)	71 (50.7)/23 (16.4)/36 (25.7)/10 (7.1)
BMI score 0/3, *n* (%)	132 (94.3)/8 (5.7)
Disease burden score 0/1/2/3, *n* (%)	0 (0.0)/0 (0.0)/140 (100.0)/0 (0.0)
Age score 0/1, *n* (%)	76 (54.3)/64 (45.7)
GLIM – malnutrition, *n* (%)	94 (67.1)
Moderate-mid Malnutrition, *n* (%)	45 (32.1)
Severe malnutrition, *n* (%)	49 (35.0)
Phenotype criteria	
Weight loss meeting diagnostic criteria, *n* (%)	66 (47.1)
BMI meeting diagnostic criteria, *n* (%)	11 (7.9)
FFMI meeting diagnostic criteria, *n* (%)	62 (44.3)
Etiologic criteria	
Intake reduction meeting diagnostic criteria, *n* (%)	67 (47.9)
Disease burden meeting diagnostic criteria, *n* (%)	140 (100.0)
FFP 2001	
Pre-frailty, *n* (%)	75 (53.6)
Frailty, *n* (%)	29 (20.7)
Unintentional weight loss, *n* (%)	73 (52.1)
Self-reported exhaustion, *n* (%)	30 (21.4)
Low grip strengthen, *n* (%)	68 (48.6)
Low walking speed, *n* (%)	108 (77.1) [0.2pt]
Low physical activity, *n* (%)	14 (10.0)
AWGS 2019	
At risk of sarcopenia, *n* (%)	74 (52.9)
Low calf circumference, *n* (%)	74 (52.9)
Sarcopenia, *n* (%)	31 (36.4)
Severe sarcopenia, *n* (%)	31 (22.1)
Low grip strengthen, *n* (%)	68 (48.6)
Low walking speed, *n* (%)	108 (77.1)
Low ASMI, *n* (%)	53 (37.9)
Diet survey	
Energy reduction after diagnosis, median (IQR) kcal/d	76 (640.5)
Energy reduction percentage after diagnosis, median (IQR)%	5.3 (34.8)
Protein reduction after diagnosis, median (IQR) g/day	1.0 (25.2)
Protein reduction percentage after diagnosis, median (IQR)%	1.6 (46.8)
Fat reduction after diagnosis, median (IQR) g/day	0.0 (24.2)
Fat reduction after percentage after diagnosis, median (IQR)%	0.0 (49.3)
Anthropometry	
Calf circumference, mean (SD) cm	33.2 (3.5)
< 34 cm in male, *n* (%), *N* = 82	42 (51.2)
< 33 cm in female, *n* (%), *N* = 58	32 (55.2)
Grip strength, mean (SD) kg	24.9 (8.5)
< 28 kg in male, *n* (%), *N* = 82	50 (61.0)
< 18 kg in female, *n* (%), *N* = 58	18 (31.0)
6-meter timed walking speed, mean (SD) m/s	0.85 (0.21)
< 1 m/s, *n* (%)	108 (77.1)
Body composition	
Harris-Benedict equation, mean (SD) kcal/d	1279.8 (173.5)
ASMI, mean (SD) kg/m^2	6.7 (0.9)
< 7.0 kg/m^2 in male, *n* (%), *N* = 82	39 (47.6)
< 5.7 kg/m^2 in female, *n* (%), *N* = 58	14 (24.1)
FFMI, mean (SD) kg/m^2	16.5 (1.6)
< 17.0 kg/m^2 in male, *n* (%), *N* = 82	41 (50.0)
< 15.0 kg/m^2 in female, *n* (%), *N* = 58	21 (36.2)
Body fat percentage, mean (SD)%	27.8 (8.3)
Waist hip ratio, mean (SD)	0.92 (0.07)
Visceral fat area, mean (SD) cm^2	83.6 (27.6)

SD, standard deviation; BMI, body mass index; IQR, interquartile range; NRS, nutritional risk screening; GLIM, global leadership initiative malnutrition; FFP, Fried frailty phenotype; AWGS, Asian Working Group for Sarcopenia; ASMI, appendicular skeleton muscle index; FFMI, fat free mass index.

which, in the second step, 36.4% (*n* = 31) participants were diagnosed as sarcopenia, 24.2% (*n* = 34) fulfilled the criteria of severe sarcopenia. We also reported every diagnostic criterion in each tool in Table 3 to reflect the composition of every diagnosis.

Figure 2 displays the overlap of these three conditions, besides which, 21 (15.0%) cases fulfilled all three criteria, and 26 (18.6%) cases were considered normal by all three criteria. Furthermore,

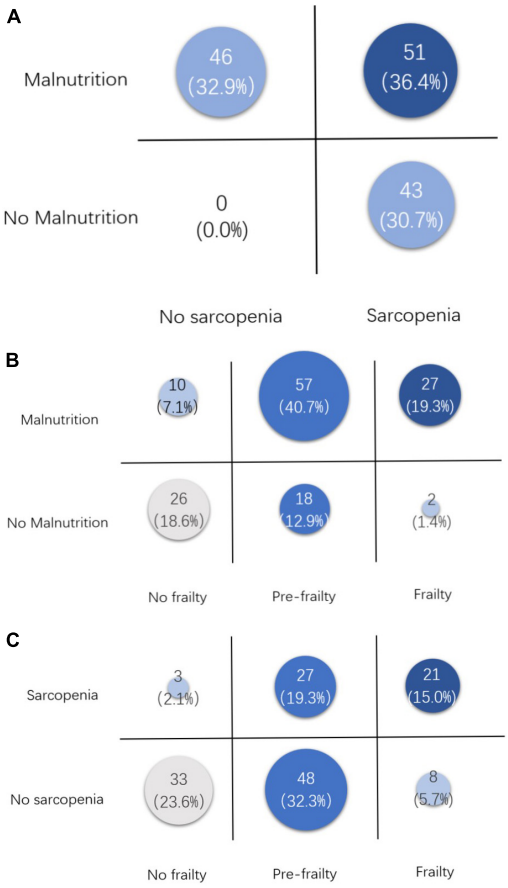

FIGURE 2
Overlaps between malnutrition, frailty, and sarcopenia. **(A)** Overlap between malnutrition and sarcopenia. **(B)** Overlap between malnutrition and frailty. **(C)** Overlap between sarcopenia and frailty.

we did a stratification analysis between the patients who fulfilled three criteria and healthy patients. The results showed that there were more patients with malignant diseases (54.3% vs. 16.7%, p = 0,024) and older age (70.8% vs. 17.4%, $p < 0.001$) in the fulfill-three-criteria group.

A diet survey showed 71 cases had a decline in the intake of total energy, protein, and fat before and after the diagnosis of the disease. In Table 3, the amounts and percentages of reduction of energy, protein, and fat were shown in detail. Results of anthropometry and body composition analysis are also recorded in Table 3 and more men than women suffered from a decline in muscle mass and muscle-related function variables such as CC, GS, ASMI, and FFMI.

3.2. Stratification analysis

3.2.1. Stratified by age

The patients were stratified by age and divided into the <70 years group and ≥70 years group. In Table 4, results show that the prevalence of nutritional risk, severe malnutrition, frailty, and sarcopenia were all significantly higher in the older group. Though there was no difference in the change in daily diet and weight, an obvious decline was found in both body composition and function. The changes in body composition appeared not only on the protein-related blood tests like hemoglobin, total protein, albumin, and pre-albumin, but also on the reduction of muscle mass (CC, ASMI, and FFMI), which logically affected the muscle function (e.g., GS and 6MTW).

3.2.2. Stratified by malignant and benign disease

When the patients were divided into malignant and benign groups, the results were completely different from the results in the groups stratified by age as above (Table 4). The main differences between malignant and benign groups were the changes in daily diet and weight, and no difference was found in body composition and function. Only prealbumin showed a significant decline in malignant disease in the benign disease group (16.6 ± 6.0 vs. 21.3 ± 10.2, p = 008), which was a sensitive variable to indicate recent nutrition changes. Both nutritional risk and severe nutritional risk were significantly higher in the malignant group, but no difference was found in the prevalence of GLIM-defined malnutrition. The malignant group possessed higher rates of frailty and sarcopenia.

3.3. Correlation between variables

Figure 3 is a heatmap showing the correlation between variables. From the perspective of overall color composition, the blue area shows a negative correlation between variables of serum test, body composition, and anthropometry with the four diagnostic tools. The red area could be divided into two parts: the part on the upper left of the blue area shows a positive correlation between every two of the four tools, and all six p-values were below 0.05; the part on the lower right of the blue area shows a positive correlation between variables of serum test, body composition, and anthropometry. In serum tests, hemoglobin, albumin, and prealbumin show a significant correlation with body composition and anthropometry. Body composition (BMI, ASMI, and FFMI) are well correlated with anthropometry (CC, GS, and 6MTW) with statistical significance.

The first column shows the correlation between age and other variables. The prevalence of nutritional risk, malnutrition, frailty, and sarcopenia were all positively correlated with age with significance, and all body composition and anthropometry variables were negatively correlated with age. Meanwhile, in the second column, nutritional risk, malnutrition, and frailty were proved to positively correlate with malignant diseases with statistical significance. However, a significant negative correlation was only found in prealbumin in all body composition and anthropometry variables ($r = -0.248$, $p = 0.018$).

3.4. Multivariate logistic regression analysis

After adjustment for age, malignant diseases, frailty, and sarcopenia with malnutrition as the dependent variables, multivariate logistic regression analysis showed that participants with frailty or sarcopenia were significantly more likely to suffer from malnutrition than their control groups with a 5.037 and 3.267

10.3389/fnut.2023.1135854

TABLE 4 Stratification analysis.

Variables, *n* = 140	< 70 years	≥ 70 years	*P*	Malignant	Benign	*P*
N	76	64		105	35	
Nutrition related blood test						
Hemoglobin, mean (SD) g/L	126.1 (16.1)	118.3 (18.1)	0.001	122.2 (18.0)	124.0 (15.6)	0.629
Fasting glucose, mean (SD) g/L	6.9 (3.5)	6.2 (1.9)	0.140	6.8 (3.2)	5.7 (1.2)	0.059
Total protein, mean (SD) g/L	65.44 (4.9)	62.8 (5.5)	0.004	64.1 (5.5)	64.7 (4.7)	0.542
Albumin, mean (SD) g/L	38.6 (3.9)	35.5 (4.3)	<0.001	37.0 (4.2)	38.0 (4.6)	0.208
Pre-albumin, mean (SD) g/L	21.1 (8.0)	14.3 (5.4)	<0.001	16.6 (6.0)	21.3 (10.2)	0.008
Triglyceride, mean (SD) mmol/L	1.3 (0.7)	1.7 (1.3)	0.050	1.6 (1.0)	1.3 (1.0)	0.157
Total cholesterol, mean (SD) mmol/L	4.4 (1.1)	4.5 (1.6)	0.826	4.6 (1.4)	4.1 (0.8)	0.108
Nutrition assessment						
BMI, mean (SD) kg/m^2	24.1 (3.7)	22.7 (3.4)	0.016	23.2 (3.6)	24.3 (3.6)	0.109
Weight loss, *n* (%)	42 (55.3)	41 (64.1)	0.291	70 (66.7)	13 (37.1)	0.002
Weight loss ≥ 5%, *n* (%)	35 (46.1)	31 (48.4)	0.778	56 (53.3)	10 (28.6)	0.011
Weight loss amount at admission, median (IQR) kg	3.0 (7.0)	3.0 (6.0)	0.709	3.8 (7.0)	0.0 (4.0)	0.017
Weight loss percentage at admission, median (IQR)%	4.0 (9.2)	4.7 (9.2)	0.521	5.3 (9.5)	0.0 (5.8)	0.012
NRS 2002–nutritional risk, *n* (%)	42 (55.3)	56 (87.5)	<0.001	85 (81.0)	13 (37.1)	<0.001
High risk, *n* (%)	20 (26.3)	34 (53.1)	0.001	47 (44.8)	7 (20.0)	0.009
GLIM–malnutrition, *n* (%)	47 (61.8)	47 (73.4)	0.146	75 (71.4)	19 (54.3)	0.061
Severe malnutrition, *n* (%)	18 (23.7)	31 (48.4)	0.002	41 (39.0)	8 (22.9)	0.082
FFP 2001			<0.001			0.029
Pre-frailty, *n* (%)	44 (57.9)	31 (48.4)		57 (54.3)	18 (51.4)	
Frailty, *n* (%)	6 (7.9)	23 (35.9)		26 (24.8)	3 (8.6)	
Self-reported exhaustion, *n* (%)	19 (29.7)	11 (14.5)	0.029	27 (25.7)	3 (8.6)	0.032
Low physical activity, *n* (%)	12 (18.8)	2 (2.6)	0.002	11 (10.5)	3 (8.6)	0.745
AWGS 2019						
At risk of sarcopenia, *n* (%)	31 (40.8)	43 (67.2)	0.002	55 (52.4)	19 (54.3)	0.845
Sarcopenia, *n* (%)	18 (23.7)	33 (51.6)	0.001	40 (38.1)	11 (31.4)	0.478
Severe sarcopenia, *n* (%)	8 (10.5)	26 (40.6)	<0.001	30 (28.6)	4 (11.4)	0.041
Diet survey						
Energy reduction after diagnosis, median (IQR) kcal/day	0.0 (523.0)	263.0 (817.0)	0.116	299.0 (817.0)	0.0 (0.0)	<0.001
Energy reduction percentage after diagnosis, median (IQR)%	0.0 (27.9)	14.5 (49.3)	0.074	18.7 (47.6)	0.0 (0.0)	<0.001
Protein reduction after diagnosis, median (IQR) g/d	0.0 (22.0)	10.0 (32.0)	0.105	13.0 (34.0)	0.0 (0.0)	<0.001
Protein reduction percentage after diagnosis, median (IQR)%	0.0 (32.8)	17.2 (54.1)	0.085	19.7 (51.9)	0.0 (0.0)	<0.001
Fat reduction after diagnosis, median (IQR) g/d	0.0 (12.0)	4.0 (33.0)	0.087	4.0 (28.0)	0.0 (0.0)	0.001
Fat reduction after percentage after diagnosis, median (IQR)%	0.0 (23.1)	8.9 (66.7)	0.070	8.9 (55.1)	0.0 (0.0)	0.001
Anthropometry						
Calf circumference, mean (SD) cm	34.3 (3.6)	32.0 (2.9)	<0.001	33.1 (3.6)	33.6 (3.3)	0.513
Grip strength, mean (SD) kg	28.0 (8.8)	21.3 (6.5)	<0.001	24.6 (8.5)	25.9 (8.5)	0.426
6-meter timed walk speed, <1 m/s, *n* (%)	0.92 (0.17)	0.74 (0.21)	<0.001	79 (75.2)	29 (82.9)	0.353
Body composition						
Harris-Benedict equation, mean (SD) kcal/day	1346.5 (167.4)	1199.0 (145.0)	<0.001	1273.1 (168.8)	1300.7 (188.3)	0.429
ASMI, mean (SD) kg/m^2	6.9 (0.9)	6.4 (0.8)	0.001	6.6 (0.9)	6.8 (0.9)	0.238
FFMI, mean (SD) kg/m^2	16.9 (1.7)	16.1 (1.3)	0.003	16.4 (1.7)	16.7 (1.5)	0.172
Body fat percentage, mean (SD)%	28.0 (8.4)	27.5 (8.2)	0.742	27.6 (8.6)	28.2 (7.6)	0.710
Waist hip ratio, mean (SD)	0.92 (0.06)	0.91 (0.07)	0.572	0.92 (0.06)	0.91 (0.07)	0.690
Visceral fat area, mean (SD) cm^2	84.4 (28.7)	82.8 (26.5)	0.739	83.0 (27.8)	85.6 (27.5)	0.636

SD, standard deviation; BMI, body mass index; IQR, interquartile range; NRS, nutritional risk screening; GLIM, global leadership initiative malnutrition; FFP, Fried frailty phenotype; AWGS, Asian Working Group for Sarcopenia; ASMI, appendicular skeleton muscle index; FFMI, fat free mass index.

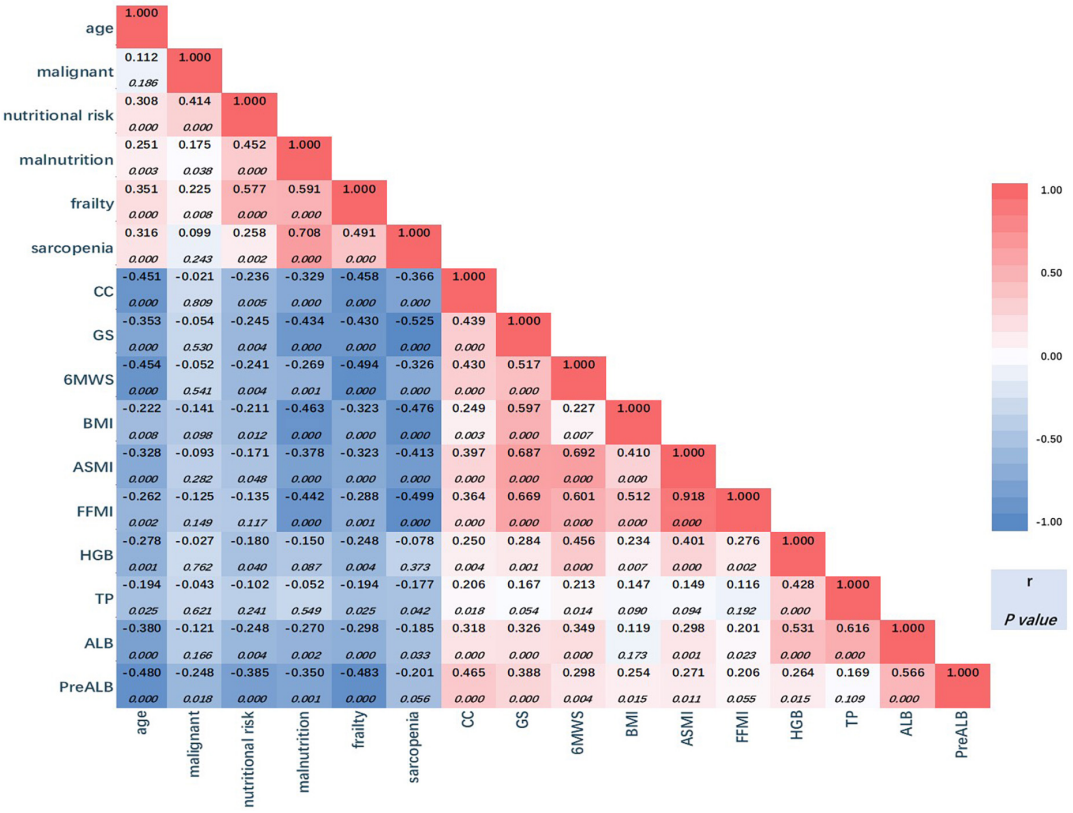

FIGURE 3
Correlation heatmap. The correlation coefficient numbers (r) are presented in the triangle, red for positive association, and blue for negative association. Darker colors indicate stronger associations (larger coefficient numbers). The significance levels for coefficients are presented below the r. CC, calf circumference; GS, grip strength; 6MWS, 6-meter walking speed; BMI, body mass index; ASMI, appendicular skeleton muscle index; FFMI, fat free mass index; HGB, hemoglobin; TP, total protein; ALB, albumin; PreALB, prealbumin.

times higher risk, respectively (for frailty, 95% CI: 1.715–14.794, $p = 0.003$ and for sarcopenia, 95% CI: 2.151–4.963, $p < 0.001$) (Figure 4).

4. Discussion

With increasing global aging problems, aging-related debilitating disorders, so-called geriatric syndrome, are becoming the hotspots of geriatric research. All frailty, sarcopenia, and malnutrition are components of geriatric syndrome and are closely interrelated and interdependent. Surgical patients suffer from a double attack of disease and aging. In our study, the prevalence of nutritional risk, and malnutrition are 70.0 and 67.1%, respectively, which are higher than in elderly patients with other gastrointestinal diseases (21). The prevalence of frailty is 20.7%, which is familiar to former articles and at a relatively higher proportion (9). The prevalence of sarcopenia is 36.4%, which is nearly the same as our data collected in pancreatic surgery diagnosed by a CT scan (7).

Diagnosis of malnutrition, frailty, and sarcopenia depend on the diagnostic tools, different tools might lead to different prevalence (22). In a recent systemic review, 18 tools of frailty diagnosis were reported, in which, FFP was the most commonly used one. Meanwhile, EWGSOP (European Working Group on Sarcopenia in Older People) criteria was the most commonly used in all and AWGS was the most commonly implemented in Asia. And for malnutrition, about thirteen tools were mentioned, besides which, BMI only and BMI with albumin were considered to be diagnostic criteria in three articles (12). However, it is difficult to avoid bias when calculating overlap data between different tools and it is still a controversy in this field. So in our study, we chose FFP, WGS, NRS2002, and GLIM to avoid selection bias.

Table 1 displays the comparison of FFP, WGS, NRS2002, and GLIM, which reflect the commonality and individuality of the tools. Weight loss was the only criterion shared by the four tools, which is not only for nutrition assessment but also a sensitive precursor for tumor diagnosis, especially for pancreatic cancer (23). Besides weight loss, NRS2002 and GLIM contain age, BMI, intake reduction, and assessment of disease (inflammation burden), which are relatively more comprehensive to assess the nutrition status. But no muscle assessment was contained in NRS2002, and GLIM contains the evaluation of muscle, but with a large range of measuring techniques. AWGS2019 and FFP2001 criteria are based on muscle assessment. The overlaps between frailty or sarcopenia and malnutrition were 19.3 and 36.4%, which are higher than was reported before (12). AWFS2019 criteria focus on both muscle mass and muscle function to diagnose sarcopenia, meanwhile, FFP2001 criteria only focus on muscle function and function-related symptoms like cognitive and behavioral impairment. So the overlap of sarcopenia and frailty (15.0%) was not as large as

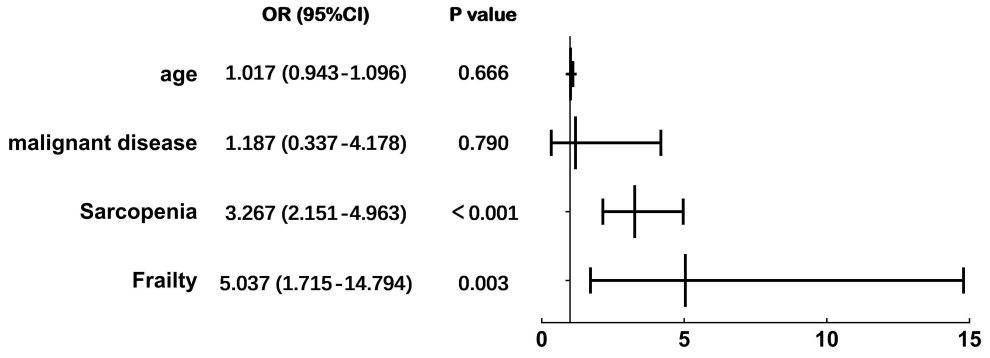

FIGURE 4
Multivariate regression analysis for malnutrition.

expected. Moreover, in this study, 21 (15.0%) cases fulfilled all three criteria, and 26 (18.6%) cases were considered normal or no risk by all three criteria. Therefore, due to different clinical values and low overlap rates, these diagnostic criteria would still coexist, and more comprehensive tools may be created and validated in the future.

According to the guidelines of ESPEN, malnutrition, sarcopenia, and frailty were treated as parallel definitions (24). The links between malnutrition and sarcopenia or frailty have already been explored in several cross-sectional studies, especially in older patients with chronic disease (25–27). In our study, in surgical patients, the correlations between these conditions were proved to be statistically significant, which were shown in **Figure 3**. However, it is difficult to judge the causal relationship between any two of these three statuses. Theoretically speaking, in this population, original surgical diseases lead to intake reduction and weight loss, which affected nutrients digestion and absorption, and then gave rise to the change in body composition, especially the change of muscle mass, sequentially muscular dysfunction. Nutrition risk or malnutrition seems to be the initiating factor (28, 29). Our results indicated that sarcopenia and frailty seemed to be risk factors for malnutrition, however, longitudinal studies are needed.

From the perspective of body composition in the criteria, BMI may not be sensitive enough to be used in the surgical population, only 5.7% of cases were lower than 18.5 kg/m^2, and nearly 40% of patients suffered from overweight and obesity, in which, nearly 20% were sarcopenia (7). Even in pancreatic surgery, higher BMI was treated as a risk factor for a fatty pancreas and postoperative pancreatic fistula rather than a nutrition parameter (30). FFMI and ASMI, which reflect the real change in muscle mass, had become the focus of diagnostic criteria. In this study, FFMI accounted for 44.3% of phenotype criteria in GLIM, second only to weight loss. And it was proved to be well consistent in GLIM-defined malnutrition in this study and other reports (31). ASMI was the sum of the lean muscle mass of the upper and lower extremities adjusted with height, which was reported to be used in GLIM and well related to sarcopenia and frailty (32, 33). So with the improvement of availability and simplification of the examination method, ASMI and FFMI will become more popular in clinical practice.

In this study, we did stratification analyses by age and malignancy. Like reports from other centers, it was no doubt that nutritional status became worse with aging and malignant diagnosis (34). However, from **Table 4**, by comparing the data from the two stratifications, an interesting phenomenon was notable. In the age stratification, the significant differences were mainly in the changes in body composition and its related parameters, including basic metabolic rate (Harris-Benedict equation), muscle mass (CC, ASMI, and FFMI), muscle function (GS and 6MWS), BMI, and serum test (hemoglobin, total protein, albumin, and prealbumin), all of which reflected the long-term changes of the body due to aging rather than disease. Meanwhile, in the stratification of malignant diseases, the significant differences between malignant and benign groups were only weight loss and intake reduction, which were short-term changes due to the pathophysiologic characteristics of cancer, but no change in body composition existed. In the serum test, only pre-albumin was significantly lower in the malignant group, which has been proposed to be a useful nutritional biomarker due to its shorter half-life than albumin and correlated with different nutritional markers and higher mortality risk (35). So when referring to preoperative therapy, for patients with advanced age, we must pay attention to both nutrition support and function exercise, to improve long-term nutrition and function problems caused by aging, and increase preoperative reservation, which was defined as "prehabilitation" and needed a relatively longer period (36). And for cancer patients with nutritional risk or malnutrition, we should commit to increasing intake and improving nutrition status by different support routes even for a short period (16, 37). Prealbumin might be a biomarker to monitor the effectiveness of preoperative nutrition support but needs further study.

As we know, few researchers have been reported to study the effect of two of the three conditions in older adults, but the three conditions are rarely studied together (38). This study is the first one to study the overlap of these three conditions in pancreatic and biliary surgery. Since this is a cross-sectional study, we tried our best to follow the STROBE statement, but there must be some limitations that are difficult to avoid. First, we used a relatively lower confidence level (0.8) and prevalence of malnutrition to determine the sample size, which may underestimate the sample size, especially when we did the stratification analysis; second, a cross-sectional study could not verify the causal relationship. Although we used multivariate regression analysis, the aim was to

explore the possible relevance and provide the necessary direction for future cohort studies. Third, the sample population is elderly, so whether the tangent point value can represent other populations should be a deeper study field and need more work.

5. Conclusion

Elderly inpatients undergoing major pancreatic and biliary surgery had a high prevalence and overlap rates of malnutrition, frailty, and sarcopenia. Body composition and function deteriorated obviously with aging. Patients with malignant diseases often suffer from short-term nutrition changes like intake reduction. Simple and effective biomarker needs to be explored and validated. Rational preoperative prehabilitation containing nutrition support and exercise should be considered in this population to reduce postoperative complications and mortality.

Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request. Requests to access the datasets should be directed to JX, xujingyong@bjhmoh.cn.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JX and JW: conception, design, and administrative support. JX, LL, JS, and JW: provision of study materials or patients. JX, YH, PL, LW, LD, and BC: collection, assembly of data, data analysis, and interpretation. LW, YH, and JX: manuscript writing. LW, PL, YH, BC, LD, LL, JS, JW, and JX: final approval of manuscript. All authors contributed to the article and approved the submitted version.

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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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The correlation of muscle quantity and quality between all vertebra levels and level L3, measured with CT: An exploratory study

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Introduction: In patients with cancer, low muscle mass has been associated with a higher risk of fatigue, poorer treatment outcomes, and mortality. To determine body composition with computed tomography (CT), measuring the muscle quantity at the level of lumbar 3 (L3) is suggested. However, in patients with cancer, CT imaging of the L3 level is not always available. Thus far, little is known about the extent to which other vertebra levels could be useful for measuring muscle status. In this study, we aimed to assess the correlation of the muscle quantity and quality between any vertebra level and L3 level in patients with various tumor localizations.

Methods: Two hundred-twenty Positron Emission Tomography (PET)-CT images of patients with four different tumor localizations were included: 1. head and neck (n = 34), 2. esophagus (n = 45), 3. lung (n = 54), and 4. melanoma (n = 87). From the whole body scan, 24 slices were used, i.e., one for each vertebra level. Two examiners contoured the muscles independently. After contouring, muscle quantity was estimated by calculating skeletal muscle area (SMA) and skeletal muscle index (SMI). Muscle quality was assessed by calculating muscle radiation attenuation (MRA). Pearson correlation coefficient was used to determine whether the other vertebra levels correlate with L3 level.

Results: For SMA, strong correlations were found between C1–C3 and L3, and C7–L5 and L3 (r = 0.72–0.95). For SMI, strong correlations were found between the levels C1–C2, C7–T5, T7–L5, and L3 (r = 0.70–0.93), respectively. For MRA, strong correlations were found between T1–L5 and L3 (r = 0.71–0.95).

Discussion: For muscle quantity, the correlations between the cervical, thoracic, and lumbar levels are good, except for the cervical levels in patients with esophageal cancer. For muscle quality, the correlations between the other levels and L3 are good, except for the cervical levels in patients with melanoma. If visualization of L3 on the CT scan is absent, the other thoracic and lumbar

vertebra levels could serve as a proxy to measure muscle quantity and quality in patients with head and neck, esophageal, lung cancer, and melanoma, whereas the cervical levels may be less reliable as a proxy in some patient groups.

KEYWORDS

correlation, muscle quantity, muscle quality, cancer, computed tomography, SMA, SMI, MRA

1. Introduction

Malnutrition and sarcopenia are highly prevalent in patients with cancer (1, 2). These nutrition (-related) disorders are linked to a combination of reduced food intake, loss of muscle quantity and quality, with or without the loss of fat mass, and poor physical performance (3–5). Previous studies show that low muscle quantity and quality are firmly associated with poorer clinical outcomes in patients with cancer (2, 6, 7). Patients with cancer with low muscle quantity and quality also have a higher risk of cancer-induced fatigue, lower quality of life, and mortality (1, 8, 9). When chemotherapy treatment is given to patients with cancer, it is often based on the body surface area (BSA). However, the BSA does not sufficiently take into account the interpersonal variations of body composition in patients with cancer, which could result in a higher risk of toxicity and incomplete treatment (7, 10–12). Therefore, in patients with cancer, it is important to measure muscle quantity (6). In addition, measuring muscle quantity is also an important part of evaluation of the nutritional status of the patient (5, 13).

To define muscle quantity, skeletal muscle cross-sectional area (SMA) and skeletal muscle index (SMI) can be measured with computed tomography (CT), a gold standard for body composition measurement (1). The SMI shows the relative muscle quantity, as it is corrected for height (SMI = SMA/height^2) (2). For this purpose, the third lumbar vertebra level (L3) is used, as the SMA correlates strongly with the muscle mass of the whole body (13, 14). It has also been shown that the levels above and below (±10 cm) L3 correlate well with the muscle mass of the entire body (14). However, a whole body CT scan is not always available in patients with cancer (7, 15). When the lumbar levels are not included in the CT scan image, for example in patients with head and neck cancer (7), it is unclear which vertebra levels can be used to estimate whole body muscle mass. In earlier studies in patients with head and neck cancer, the cervical level 3 (C3) and thoracic level 4 (T4) were used to measure muscles, and these levels showed a good correlation with L3 (7).

According to the European Working Group on Sarcopenia in Older People, muscle quality can be measured by muscle radiation attenuation (MRA), using CT images (5). Muscle quality is defined as muscle strength or power per unit of muscle mass and is closely intertwined with muscle strength (16). Intermuscular adipose tissue is an important factor underpinning muscle quality and also predicts muscle function (17). The intermuscular adipose tissue is located within the muscle, under the fascia, and encompasses intramuscular fat and low-density lean tissue (18). Muscle radiation attenuation closely correlates with direct measurements of muscle lipid content and therefore determines infiltration of fat into the muscle (19–21).

In addition, limited evidence regarding the correlation of muscle quantity and quality between vertebra levels other than L3 and the L3 level is available (22). As a first step in the search for which other vertebra levels, other than L3, could be used to determine whole body muscle mass, we aimed to examine the correlations between all vertebra levels with L3 for muscle quantity and quality in a sample of patients with various tumor localizations.

2. Materials and methods

2.1. Participants

Positron Emission Tomography CT (PET-CT) images of the participants were retrospectively extracted from medical records of the Radiology department of the University Hospital Brussels from December 2019 until February 2021. Patients aged ≥18 years

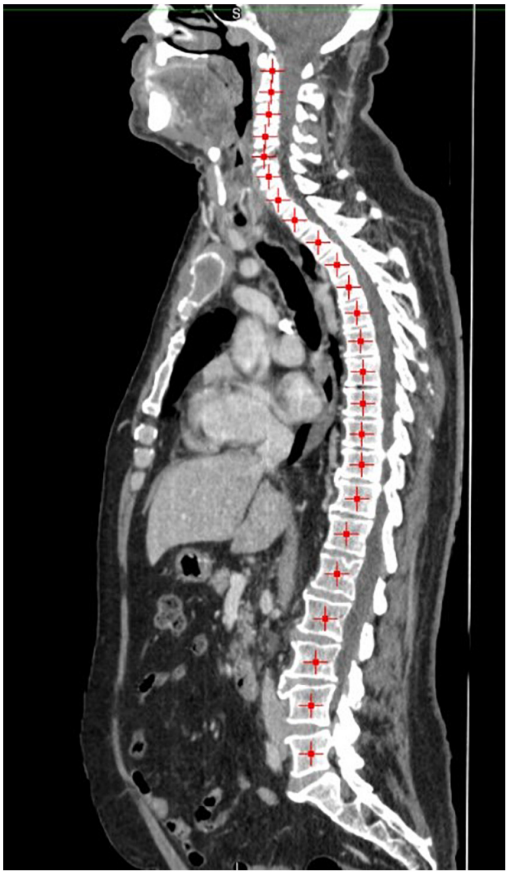

FIGURE 1
Twenty-four manually selected points on the vertebral column.

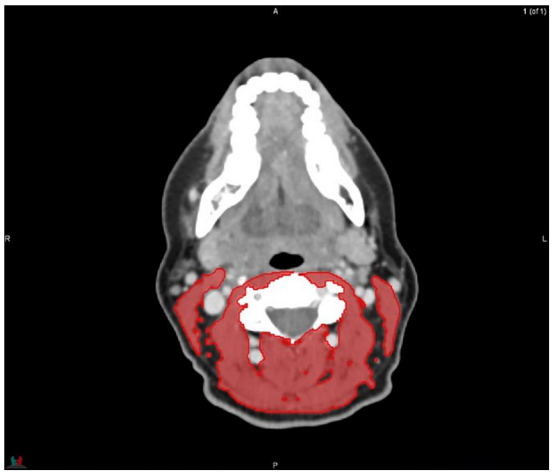

FIGURE 2
Contouring of the muscles at cervical level 3.

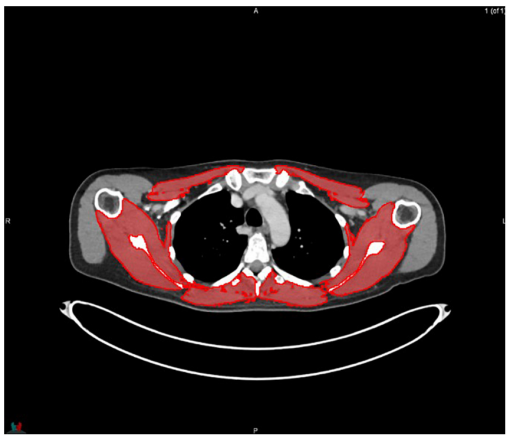

FIGURE 3
Contouring of the muscles at thoracic level 4.

with any of the following four localizations of newly diagnosed tumors were included: 1. head and neck cancer, 2. esophageal cancer, 3. lung cancer, and 4. melanoma. We excluded participants receiving treatment for current cancer at the time of the PET-CT scan and who had a previous diagnosis of cancer at another tumor localization. PET-CT images were included if they were performed between 2014 and February 2021. Sex, age (years), body weight (kg), body height (m), body mass index (BMI; kg/m^2), cancer stage, and Charlson Comorbidity Index (CCI) (23) were retrieved from the patients' medical chart.

2.2. Scanning procedure

The PET-CT images were performed with three different CT devices: Philips GEMINI TF TOF 64, SIEMENS Biograph20, and SIEMENS Biograph128. The patients were scanned helically with a slice thickness of 2 mm and 120 kilovoltage peak (kVp). An intravenous iodinated contrast agent was used in all patients, except

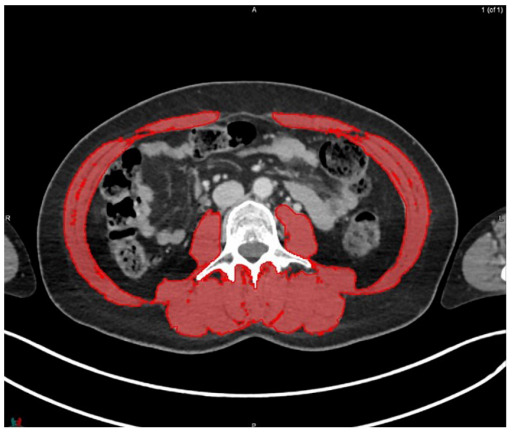

FIGURE 4
Contouring of the muscles at lumbar level 3.

TABLE 1 Characteristics of included patients.

		Total (n = 220)	Women (n = 64)	Men (n = 156)
Cancer type	Head and neck	34 (15%)	18 (28%)	16 (10%)
	Esophageal	45 (20%)	6 (10%)	39 (25%)
	Lung	54 (25%)	18 (28%)	36 (23%)
	Melanoma	87 (40%)	22 (34%)	65 (42%)
Age (years)		65.1 ± 10.9	63.8 ± 11.72	65.6 ± 10.6
Weight (kg)		74.5 [63.0–85.8]	62.0 [55.3–77.3]	78.0 [68.0–90.0]
Height (m)		1.71 ± 0.10	1.62 ± 0.06	1.74 ± 0.08
BMI (kg/m^2)		25.4 [22.4–29.0]	23.8 [20.4–29.2]	25.7 [23.2–29.0]
Cancer stage	Grade 1	25 (11%)	6 (9%)	19 (12%)
	Grade 2	41 (19%)	13 (20%)	28 (18%)
	Grade 3	70 (32%)	24 (38%)	46 (29%)
	Grade 4	59 (27%)	8 (13%)	51 (33%)
	Unknown	25 (11%)	13 (20%)	12 (8%)
CCI		3 [2–6]	3 [2–6]	3 [2–6]

Data are presented as mean ± SD or as median [interquartile range].
CCI, Charlsons' Comorbidity Index.

for 15% of the patients with a contra-indication for this contrast: i.e., the contrast was recently applied for another CT procedure in the short term or the patients had problems with their kidneys.

2.3. Image analysis

MIM software (Version 7.0.1) was used to process the images. The whole-body scan was uploaded, after which 24 points were selected manually in the sagittal plane by a researcher (JV), as shown in Figure 1. The researcher selected images based on the center of each vertebral body. With the Launch Workflow procedure, 24 transverse slices were taken at the chosen points. This procedure allows a consistent and precise image selection. The slices were used to contour the muscles, as shown in Figures 2–4. Trunk muscles included in the contouring were the

TABLE 2 Results for muscle quantity and quality at all vertebra levels.

	Total (n = 220)		
	SMA (cm^2)	SMI (cm^2/m^2)	MRA (HU)
C1	38.3 [32.3–45.1]	13.3 [11.4–14.9]	43.2 [37.9–49.0]
C2	38.1 [31.6–43.6]	12.9 [11.1–14.9]	42.7 ± 8.6
C3	42.7 [35.1–48.9]	14.4 [12.4–16.5]	45.7 ± 12.9
C4	50.9 [41.5–62.5]	17.1 [14.7–20.9]	44.9 ± 10.6
C5	69.9 [54.1–102.2]	22.9 [18.2–34.9]	40.0 ± 12.3
C6	105.7 [74.0–147.2]	36.8 [25.8–51.3]	34.4 ± 9.1
C7	142.3 [115.5–181.0]	49.6 ± 14.7	35.8 [30.0–40.9]
T1	168.1 ± 46.7	56.1 [47.3–65.1]	36.8 ± 7.3
T2	178.4 [145.6–217.4]	61.3 [51.4–71.0]	38.7 ± 7.7
T3	186.7 ± 45.9	62.4 [53.6–72.6]	38.5 ± 7.3
T4	176.6 [147.3–212.4]	59.6 [52.1–70.0]	38.1 [32.7–42.1]
T5	158.1 [131.9–192.5]	54.5 [47.1–64.2]	36.2 [31.2–40.9]
T6	132.1 [111.5–160.2]	45.5 [39.5–53.3]	32.8 ± 8.2
T7	111.8 [90.1–140.4]	37.3 [32.7–44.4]	30.6 [25.4–35.9]
T8	93.3 [74.9–116.9]	32.3 [26.4–38.5]	28.7 [23.9–34.8]
T9	80.3 [65.3–98.0]	27.1 [22.7–32.1]	27.3 ± 8.9
T10	73.3 [59.6–88.4]	24.5 [20.5–29.0]	27.3 ± 8.7
T11	73.4 [60.7–90.6]	24.8 [21.4–29.6]	29.1 ± 8.6
T12	82.7 [66.4–102.0]	28.1 [23.9–33.3]	29.8 ± 9.2
L1	97.7 [78.9–115.6]	32.7 [28.0–38.5]	30.0 ± 9.4
L2	124.3 [98.5–145.1]	41.5 [34.8–48.3]	29.5 ± 9.1
L3	141.5 [116.8–170.7]	48.5 [41.9–54.8]	30.3 ± 8.8
L4	138.0 [115.5–166.1]	48.0 [41.9–53.6]	30.6 ± 8.8
L5	135.2 [106.6–158.1]	44.8 [38.4–53.5]	34.0 ± 8.5

Data are presented as mean ± SD or as median [interquartile range].
SMA, skeletal muscle area; SMI, skeletal muscle index; MRA, muscle radiation attenuation; HU, Hounsfield units.

TABLE 3 Intraclass correlation coefficient for interrater reliability.

	SMA		MRA	
	Pearson correlation	Bootstrap [95% interval]	Pearson correlation	Bootstrap [95% interval]
C1	0.96	0.94–0.97	0.98	0.98–0.99
C2	0.98	0.98–0.99	0.99	NA
C3	0.99	0.99–1.00	1.00	NA
C4	1.00	0.99–1.00	1.00	NA
C5	1.00	0.99–1.00	1.00	NA
C6	0.99	0.99–1.00	0.99	NA
C7	0.97	NA	0.98	0.97–0.99
T1	0.97	NA	0.99	NA
T2	0.95	0.93–0.97	0.98	NA
T3	0.95	NA	0.99	NA
T4	0.96	0.92–0.97	0.99	0.98–0.99
T5	0.98	0.96–0.99	0.98	0.96–0.99
T6	0.98	0.97–0.99	1.00	NA
T7	0.99	0.99–1.00	1.00	1.00–1.00
T8	0.99	0.99–1.00	1.00	0.99–1.00
T9	0.99	0.99–0.99	1.00	NA
T10	0.99	0.99–0.99	1.00	NA
T11	0.98	0.98–0.99	0.99	NA
T12	0.98	0.98–0.99	0.99	NA
L1	0.98	0.98–0.99	1.00	NA
L2	0.99	0.98–0.99	1.00	NA
L3	1.00	1.00–1.00	1.00	NA
L4	0.99	0.99–1.00	0.99	NA
L5	0.99	0.99–1.00	1.00	NA

SMA, skeletal muscle area; MRA, muscle radiation attenuation; NA, not appropriate, bootstrap only in case of skewed data.

psoas, paraspinal, and abdominal wall muscles (2). In total, 12 examiners participated in this study to contour the muscles. In each slice, the muscles were measured twice. The two measurements were each performed by a different examiner, i.e., students from the Medical Imaging and Radiotherapeutic Techniques training program of Hanze University of Applied Sciences, Groningen, Netherlands, who were trained in muscle anatomy by an expert. During the process, the contouring by the examiners was regularly checked by this expert. Examiners were blinded to each other's measurements and the characteristics of the patient. To contour the muscles, the Hounsfield units (HU) were set at a range lock between −29 and 150 HU (24). After contouring, SMA and MRA were calculated with the MIM software program. To calculate SMI, SMA was corrected for squared height in meters (cm^2/m^2). SMA was recorded in cm^2, SMI in cm^2/m^2, and MRA in HU.

2.4. Statistical analysis

IBM SPSS statistics 26 was used to perform the statistical analyses. A Shapiro–Wilk test was performed to examine the normality of the distribution of the data. Normally distributed data are presented as mean and standard deviation (SD). Not normally distributed data are presented as median and interquartile range. An intraclass correlation coefficient (ICC) was calculated to analyze interrater reliability. When the data were not normally distributed, bootstrapping was applied to indicate whether the ICC was likely to be affected by the distribution of the data. With a high bootstrapping value (≥0.90), the ICC was not likely to be effected by the distribution of the data and the ICC value was accepted. When ICC values ranged between 0.0 and 0.20, the reliability was considered as slight, between 0.21 and 0.50 as poor, between 0.51 and 0.75 as moderate, between 0.76 and 0.90 as good, and 0.91 or above as excellent (25).

Next, Pearson correlation coefficients were calculated to assess whether the other levels of the spine correlated with the L3 level. Therefore, we took the average value of both examiners for each vertebra level. Finally, Pearson correlation coefficients were determined to analyze the correlation between all other levels with the L3 level, to study whether the tumor localization influenced the reliability. A Pearson correlation coefficient ≥0.70 is considered a

TABLE 4 Pearson correlation and bootstrap results between other vertebra levels and L3.

L3									
	SMA			SMI			MRA		
	Pearson correlation	*p*-Value	Bootstrap [95% interval]	Pearson correlation	*p*-Value	Bootstrap [95% interval]	Pearson correlation	*p*-Value	Bootstrap [95% interval]
C1	0.77	<0.001	0.70–0.82	0.71	<0.001	0.61–0.78	0.61	<0.001	0.53–0.71
C2	0.77	<0.001	0.71–0.82	0.71	<0.001	0.61–0.79	0.63	<0.001	NA
C3	0.72	<0.001	0.62–0.80	0.67	<0.001	0.53–0.78	0.59	<0.001	NA
C4	0.49	<0.001	0.33–0.65	0.49	<0.001	0.27–0.67	0.58	<0.001	NA
C5	0.53	<0.001	0.42–0.63	0.51	<0.001	0.63–0.64	0.56	<0.001	NA
C6	0.62	<0.001	0.52–0.70	0.57	<0.001	0.45–0.68	0.48	<0.001	NA
C7	0.73	<0.001	NA	0.68	<0.001	NA	0.59	<0.001	0.50–0.70
T1	0.76	<0.001	NA	0.70	<0.001	0.62–0.77	0.71	<0.001	NA
T2	0.77	<0.001	0.70–0.82	0.70	<0.001	0.61–0.77	0.75	<0.001	NA
T3	0.82	<0.001	NA	0.77	<0.001	0.68–0.83	0.79	<0.001	NA
T4	0.86	<0.001	0.82–0.89	0.81	<0.001	0.75–0.86	0.81	<0.001	0.76–0.85
T5	0.79	<0.001	0.74–0.83	0.72	<0.001	0.65–0.78	0.82	<0.001	0.77–0.86
T6	0.74	<0.001	0.69–0.79	0.65	<0.001	0.58–0.72	0.83	<0.001	NA
T7	0.79	<0.001	0.72–0.84	0.71	<0.001	0.62–0.78	0.85	<0.001	0.81–0.89
T8	0.80	<0.001	0.75–0.84	0.73	<0.001	0.70–0.79	0.86	<0.001	0.83–0.90
T9	0.80	<0.001	0.75–0.85	0.74	<0.001	0.67–0.81	0.87	<0.001	NA
T10	0.85	<0.001	0.80–0.89	0.81	<0.001	0.74–0.87	0.87	<0.001	NA
T11	0.91	<0.001	0.88–0.93	0.89	<0.001	0.84–0.92	0.90	<0.001	NA
T12	0.92	<0.001	0.89–0.94	0.90	<0.001	0.85–0.93	0.92	<0.001	NA
L1	0.92	<0.001	0.90–0.94	0.91	<0.001	0.87–0.93	0.93	<0.001	NA
L2	0.95	<0.001	0.93–0.96	0.93	<0.001	0.90–0.95	0.95	<0.001	NA
L4	0.92	<0.001	0.89–0.94	0.89	<0.001	0.84–0.93	0.94	<0.001	NA
L5	0.92	<0.001	0.89–0.93	0.89	<0.001	0.85–091	0.88	<0.001	NA

SMA, skeletal muscle area; SMI, skeletal muscle index; MRA, muscle radiation attenuation; NA, not appropriate, bootstrap only in case of skewed data.

strong correlation (25). *Post hoc* power analyses, using G*Power, were performed to analyze the power for each correlation. Power of 0.80 or higher was considered sufficient. For all analyses, the level of significance was set at $p < 0.05$.

3. Results

In total, 220 patients, including 34 patients with head and neck cancer, 45 with esophageal cancer, 54 with lung cancer, and 87 with melanoma, were included. Characteristics of the included patients are shown in Table 1. The descriptive data for SMA, SMI, and MRA at all vertebral levels are shown in Table 2.

The ICC values for the interrater reliability of the SMA and MRA for all vertebra levels ranged from 0.95 to 1.00. All interrater reliability values are shown in Table 3. The power was 1.00.

The Pearson correlation coefficients between the other vertebra levels and L3 are shown in Table 4. All correlations for SMA, SMI, and MRA were statistically significant. For SMA, correlations ranged from $r = 0.49$ to $r = 0.95$. Strong correlations were found between C1–C3 and L3, and C7–L5 and L3 ($r = 0.72$–0.95). For SMI, Pearson correlation coefficients ranged from $r = 0.49$ to $r = 0.93$. Strong correlations were found between the levels C1–C2, C7–T5, T7–L5, and L3 ($r = 0.70$–0.93), respectively. For MRA, the correlation ranged from $r = 0.48$ to $r = 0.95$. Strong correlations were found between T1–L5 and L3 ($r = 0.71$–0.95). The power was 1.00.

The correlations between the other levels and L3 per tumor localization are shown in Table 5. All *p*-values were significant ($p \leq 0.001$) and the bootstraps confirmed the correlation values, except for the SMA and SMI at the level of C4–C6 in the patients with esophageal cancer. Level T4 is the uppermost level in the vertebral column that reached a strong correlation with L3 for SMA, SMI, and MRA in all tumor localizations. The power analysis shows that for the smallest group (patients with head and neck cancer, $n = 34$) the power was 0.80 for correlations of $r = 0.60$ and higher. For the largest group (patients with melanoma, $n = 87$) the power was 0.80 for all correlations.

4. Discussion

This is the first study to assess the correlation of muscle quantity and quality between all other vertebra levels and L3. For muscle

TABLE 5 Pearson correlation values according to different tumor localizations.

	Head and neck cancer L3 (n = 34)			Esophageal cancer L3 (n = 45)			Lung cancer L3 (n = 54)			Melanoma L3 (n = 87)		
	SMA	SMI	MRA	SMA	SMI	MRA	SMA	SMI	MRA	SMA	SMI	MRA
C1	0.60	0.47	0.87	0.69	0.62	0.64	0.76	0.73	0.76	0.78	0.74	0.35
C2	0.71	0.62	0.86	0.57	0.48	0.80	0.76	0.70	0.74	0.78	0.74	0.39
C3	0.78	0.72	0.89	0.63	0.51	0.70	0.81	0.74	0.77	0.65	0.64	0.30
C4	0.64	0.61	0.74	X	X	0.79	0.70	0.64	0.66	0.44	0.50	0.43
C5	0.47	0.46	0.76	X	X	0.62	0.52	0.45	0.64	0.54	0.57	0.45
C6	0.70	0.63	0.70	X	X	0.49	0.59	0.67	0.46	0.62	0.59	0.42
C7	0.72	0.57	0.71	0.49	0.52	0.61	0.64	0.59	0.53	0.77	0.75	0.56
T1	0.74	0.60	0.82	0.58	0.58	0.74	0.69	0.61	0.81	0.79	0.74	0.60
T2	0.61	0.43	0.85	0.63	0.62	0.74	0.83	0.76	0.84	0.86	0.82	0.66
T3	0.68	0.54	0.83	0.76	0.73	0.80	0.88	0.81	0.87	0.86	0.84	0.74
T4	0.82	0.73	0.85	0.79	0.74	0.80	0.87	0.80	0.87	0.85	0.83	0.77
T5	0.76	0.66	0.88	0.71	0.64	0.84	0.82	0.77	0.86	0.76	0.70	0.76
T6	0.71	0.58	0.88	0.73	0.67	0.88	0.81	0.76	0.87	0.67	0.56	0.78
T7	0.77	0.67	0.91	0.76	0.71	0.89	0.80	0.74	0.88	0.74	0.64	0.79
T8	0.75	0.64	0.91	0.72	0.66	0.85	0.83	0.80	0.88	0.78	0.71	0.84
T9	0.74	0.62	0.91	0.75	0.70	0.87	0.86	0.83	0.90	0.76	0.71	0.82
T10	0.81	0.71	0.90	0.78	0.76	0.92	0.91	0.88	0.90	0.82	0.78	0.83
T11	0.88	0.81	0.93	0.84	0.83	0.91	0.93	0.91	0.92	0.91	0.90	0.86
T12	0.86	0.79	0.94	0.88	0.87	0.93	0.93	0.91	0.95	0.92	0.91	0.89
L1	0.90	0.86	0.95	0.91	0.90	0.92	0.90	0.89	0.96	0.93	0.92	0.91
L2	0.92	0.87	0.97	0.93	0.92	0.93	0.90	0.85	0.97	0.97	0.96	0.92
L4	0.90	0.88	0.98	0.87	0.84	0.93	0.88	0.79	0.95	0.93	0.92	0.92
L5	0.87	0.84	0.94	0.86	0.83	0.88	0.90	0.85	0.85	0.92	0.91	0.87

SMA, skeletal muscle area; SMI, skeletal muscle index; MRA, muscle radiation attenuation; X, bootstrap does not confirm this correlation.

quantity, i.e., SMA and SMI, most cervical, thoracic, and lumbar levels show a strong correlation with L3. Notably, in the group of patients with esophageal cancer, none of the cervical levels correlate strongly with L3 for SMA and SMI. For muscle quality, i.e., MRA, all thoracic and lumbar levels show a strong correlation with the muscle quality of L3, whereas the cervical levels do not. However, in patients with head and neck cancer, all levels, including the cervical, show a strong correlation with muscle quality at the L3 level. Also, in the patients with esophageal and lung cancer, some cervical levels show a strong correlation.

Our findings are in line with previous studies that determined the correlation between other vertebra levels and L3. For example, in patients with head and neck cancer, a strong correlation between the other lumbar levels and L3 was previously found (14, 26, 27). In patients with various types of advanced cancer, only thoracic levels, T5, T8, T10, and T12, have been studied, and moderate correlations for SMI and MRA between T5, T8, T10, and L3 were found (14, 26, 27). In patients with oral squamous cell carcinoma, the correlation between T12 and L3, was strong which is in agreement with the results of our study (28). However, for level C3, results are ambiguous in head and neck cancer patients and C3 was reported to not correlate well with L3 in patients with low muscle mass (29). In contrast, a strong correlation between the muscles at C3 and L3 in patients with head and neck cancer was found in our study. In patients with head and neck cancer, it is more difficult to measure the cervical muscles, because the tumor is located in the cervical region (26). For example, when contouring the sternocleidomastoid muscle, the SMA may be overestimated because the lymph node stations are located around this muscle (30). Doubling the SMA of the healthy sternocleidomastoid muscle to compensate for the lack of the SMA of the affected muscle can be considered, to avoid the muscle quantity being influenced by the tumor at the level of the affected sternocleidomastoid muscle (26). Moreover, a study in patients with head and neck cancer showed no significant difference in the correlation between C3 and L3 when comparing a group of patients with head and neck cancer with healthy participants (26). Unfortunately, we cannot explain why the cervical levels of the patients with esophageal cancer lacked correlation with L3 for muscle quantity. Further research is needed to identify determinants for the this correlation. Cervical MRA values in this study were more homogeneous for patients with melanoma compared to values for patients with other cancer types. This could explain the correlation between cervical levels and L3 being lower in the patients with melanoma compared to the other patients.

Our results confirm excellent interrater reliability of measuring SMA and MRA by CT scan analysis as found in previous research (31–33). Previous research demonstrated that longer time between measurements limits reliability. For example, when participants walk around for a while between the two measurements, the reliability for contouring the SMA was only acceptable (31). In our study, muscle contouring was performed twice on the same CT image. Moreover, the HU values were set and the segmentation was performed semi-automatically. A factor that may influence reliability of MRA is the accuracy of the contouring of the muscles. If intramuscular fat is incorporated in the SMA due to incorrect contouring, this could negatively affect reliability of MRA. In our study, the HU values corrected the contouring of the muscles, to ensure that only muscle tissue was contoured.

The current study has some limitations. Firstly, in 85% of our participants, intravenous contrast was used while taking the PET-CT. Previous research has demonstrated that the use of contrast fluid influences the SMI and MRA (32). More research is needed to determine whether contrast fluid influences the correlation between different vertebral levels (32). Secondly, while we have included a diverse group of patients with cancer with high incidence rates in the Belgian population (33), the sample size for each tumor localization group was small. Moreover, the proportion of women in our study was not large, due to using a convenience sample that reflects the distribution of sex in the patient populations. Therefore, more research with larger sample sizes and equal sex distribution is needed to confirm our conclusions. Thirdly, we were not able to correlate the vertebra levels to whole body muscle mass. Evaluation of whole body muscle mass requires complete inclusion of the arms in the scan, and unfortunately the diameter of the CT scan was set too small, based on the trunk, and therefore did not include the arms.

In the current study, we found that other levels are strongly correlated with L3. However, if a CT scan at the L3 level is not available the other thoracic and lumbar vertebra levels could serve as a proxy to measure muscle quantity in patients with head and neck-, lung-, esophageal cancer, and melanoma, whereas the cervical levels may be less reliable as a proxy in some patient groups. Future research is needed to develop prediction equations to estimate whole body muscle mass from the vertebra levels correlating well with the L3 level.

5. Conclusion

In patients with head and neck cancer, lung cancer, and melanoma, muscle quantity is strongly correlated between some cervical, and all thoracic and lumbar levels and L3. In esophageal patients, only the thoracic and lumbar levels are strongly correlated. For muscle quality, the cervical, thoracic, and lumbar levels and L3 are well correlated in the head and neck, esophageal, and lung patients, but in patients with melanoma the cervical levels do not correlate well with L3. If visualization of L3 on the CT scan is absent, we suggest that the other thoracic and lumbar vertebra levels could serve as a proxy to measure muscle quantity in patients with head and neck-, lung-, esophageal cancer, and melanoma, whereas the cervical levels may be less reliable as a proxy in some patient groups. Further research should determine whether our conclusions can be confirmed and that these levels can also be used to estimate whole body muscle mass by examining the correlation of these levels with whole body muscle mass.

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 human participants were reviewed and approved by the Commissie Medische Ethiek Brussel. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JV: acquisition, analysis, and interpretation of data, drafting the work, provide approval for publication, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MS, HJ-W, and AS: design of the work, interpretation of data, revising the work, and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CB: acquisition of data and revising the work. JK: analysis of data and revising the work. All authors contributed to the article and approved the submitted version.

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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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Intravenous dexamethasone administration during anesthesia induction can improve postoperative nutritional tolerance of patients following elective gastrointestinal surgery: A *post-hoc* analysis

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Aim: To investigate the effect of intravenous dexamethasone administration on postoperative enteral nutrition tolerance in patients following gastrointestinal surgery.

Methods: Based on the previous results of a randomized controlled study to explore whether intravenous administration of dexamethasone recovered gastrointestinal function after gastrointestinal surgery, we used the existing research data from 1 to 5 days post operation in patients with enteral nutrition tolerance and nutrition-related analyses of the changes in serum indices, and further analyzed the factors affecting resistance to enteral nutrition.

Result: The average daily enteral caloric intake was significantly higher in patients receiving intravenous administration of dexamethasone during anesthesia induction than in controls (8.80 ± 0.92 kcal/kg/d vs. 8.23 ± 1.13 kcal/kg/d, $P = 0.002$). Additionally, intravenous administration of 8 mg dexamethasone during anesthesia induction can reduce the changes in postoperative day (POD) 3, POD5, and preoperative values of serological indices, including ΔPA, ΔALB, and ΔRBP ($P < 0.05$). In the subgroup analysis, dexamethasone significantly increased the average daily enteral nutrition caloric intake in patients undergoing enterotomy (8.98 ± 0.87 vs. 8.37 ± 1.17 kcal/kg/d, $P = 0.010$) or in female patients (8.94 ± 0.98 vs. 8.10 ± 1.24 kcal/kg/d, $P = 0.019$). The changes of serological indexes (ΔPA, ΔALB, and ΔRBP) in the dexamethasone group were also significantly different on POD3 and POD5 ($P < 0.05$). In addition, multivariate analysis showed that dexamethasone use, surgical site, and age might influence enteral nutrition caloric tolerance.

Conclusion: Postoperative enteral nutrition tolerance was significantly improved in patients receiving intravenous administration of dexamethasone during anesthesia induction, especially in patients following enterotomy surgery, with significant improvements in average daily enteral caloric intake, PA levels, ALB levels, and RBP levels.

Clinical trial registration: http://www.chictr.org.cn, identifier: ChiCTR19000 24000.

KEYWORDS

gastrointestinal cancer, gastrointestinal surgery, enteral nutrition, dexamethasone, nutritional indicators

1. Introduction

Trauma and stress caused by surgery can lead to a catabolic state. Studies have shown that patients can lose ∼2 kg of body weight during recovery, even after uncomplicated elective surgery (1, 2). Postoperative malnutrition is more common in approximately 40% of patients undergoing gastrointestinal surgery due to inflammatory reactions, gastrointestinal dysfunction, and loss of gastrointestinal reserve function (3, 4).

Nutritional deficiency after gastrointestinal surgery is considered to be one of the important risk factors for postoperative complications and morbidity (5, 6), which may not only increase the length of hospital stay (LOS) and treatment cost but also affect the survival of cancer patients due to delayed adjuvant therapy after operation (7–10).

For decades, clinicians have been trying to improve the prognosis of surgical patients by reducing complications caused by nutritional deficiencies. Although enhanced recovery after surgery (ERAS) protocols and preoperative administration of oral nutritional supplements (ONSs) can improve the nutritional status of patients, some patients undergoing abdominal surgery suffer from malnutrition (11–14). Therefore, improving nutritional status as soon as possible after gastrointestinal surgery is particularly important. Postoperative stress in some patients leads to gastrointestinal motility dysfunction and intolerance to enteral nutrition, which limits the recovery of early gastrointestinal function. Data from one of our previous studies, the effect of dexamethasone on postoperative gastrointestinal motility (DOPGM) trial (15) concluded that a single intravenous dose of 8 mg dexamethasone at anesthesia induction significantly decreased the time to return of flatus improved abdominal distension at 72 h, and promoted tolerance of a liquid diet. However, our study did not calculate the average daily enteral nutritional energy tolerance during the intervention period. In addition, it also raised an important new problem that was not adequately addressed in the preplanned analysis: since there is no difference in LOS and quality of life (QoL), will this secondary outcome affect its application in real life? Different indicators reflect the clinical significance of various aspects. LOS and QoL might not be the only indicators for evaluating the applicability of dexamethasone in real-life clinical settings. Moreover, although the LOS and QoL did not improve significantly, the patient's time to first flatus and tolerance of a liquid diet was shortened. Abdominal distension was reduced at 72 h after surgery, which may improve the postoperative nutritional intake and nutritional status such as pre-albumin (PA), albumin (ALB), and retinol-binding protein (RBP), among others.

In this *post-hoc* analysis of the DOPGM trial, we analyzed the changes in postoperative indicators related to nutritional status between the two groups with random intervention to verify the hypothesis of whether a single intravenous dose of 8 mg dexamethasone at induction of anesthesia can improve postoperative enteral nutrition tolerance and nutritional status in the patients undergoing elective gastrointestinal surgery.

2. Methods

2.1. Patients and methods

This is a *post hoc* analysis of DOPGM, a prospective, double-blind, single-center, and randomized controlled trial carried out in the Department of Gastroenterology, Shandong Provincial Hospital, China. The study design, ethical approval, inclusion criteria, and procedures have been previously reported (15).

After obtaining informed consent, the 126 patients were randomized into two groups. One group received 8 mg of intravenous dexamethasone during the induction of anesthesia, and the other group received normal saline. All patients underwent standardized general anesthesia and elective gastrointestinal surgery. Our main aim was to assess the effects of preoperative dexamethasone administration on patient outcomes in terms of postoperative enteral nutrition tolerance. All 126 patients were included, whose PA, ALB, hemoglobin (Hb), lymphocyte count (LC), RBP, and fasting blood glucose (FBG) levels were measured preoperatively and on postoperative days (PODs) 1, 3, and 5 were recorded as part of the clinical routine. Postoperative energy and protein requirements were estimated according to the European Society of Clinical Nutrition and Metabolism (ESPAN) guidelines (16). The energy requirement was calculated according to 30 kcal/kg of body weight, while the protein requirement was 1.5 g/kg of body weight after the operation. On the first postoperative day, all patients started consuming clear liquids *via* oral or tube feeding. We considered the patient to be tolerant of the liquid diet if there were no reports of nausea, vomiting, or significant abdominal distention after an intake of 200 ml of clear liquid. The clear liquid diet was gradually adjusted to enteral nutrition (Abbott, Ensure, 1.06 kcal/ml) on the second postoperative day. According to our department's routine management process for enteral nutrition supplements after gastrointestinal surgery, we set that enteral nutrition provided 20% of the total target caloric intake from the second postoperative day and increased it by 10% daily. The rest of the caloric intake was supplied by parenteral nutrition. When enteral nutrition met 60% of the total caloric requirement, parenteral nutrition was stopped. Researchers have previously recorded the actual amount of daily enteral nutrition. The patients recorded the type and amount of the diet. The caloric and protein contents of the food were recorded according to the China Food Composition Tables [Yang (17)] so that the actual caloric and protein intakes on PODs 1–5 were recorded.

2.2. Outcome measures

The average daily enteral nutrition caloric intake and serum indices PA, ALB, RBP, LC, FBG, and the changes between preoperative and postoperative serum index values (including ΔPA, ΔALB, ΔRBP, ΔLC, ΔFBG, etc.) were compared between the two groups to evaluate the enteral nutrition tolerance and nutritional status of the patients.

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TABLE 1 Baseline characteristics of participants enrolled in the study.

	Dexamethasone ($n = 64$)	Control ($n = 62$)	*P*-value
Age (mean ± SD)	60.77 ± 12.63	61.06 ± 11.13	0.888
Gender			0.489
Female	20 (31.3%)	23 (37.1%)	
Male	44 (68.8%)	39 (62.9%)	
BMI	24.74 ± 3.45	24.12 ± 3.34	0.341
Site of surgery			0.808
Enterotomy	41 (64.1%)	41 (66.1%)	
Gastrectomy	23 (35.9%)	21 (33.9%)	
Serum indices			
Hb (g/L)	126.44 ± 20.93	129.08 ± 20.02	0.475
RBP (μg/L)	32.20 ± 10.13	37.02 ± 12.96	0.022
FBG (mmol/L)	5.48 ± 1.02	5.28 ± 1.048	0.310
ALB (g/L)	38.85 ± 4.02	40.19 ± 4.60	0.084
PA (mg/L)	212.41 ± 63.32	231.28 ± 65.49	0.103
LC (10^9/L)	1.79 ± 0.67	1.83 ± 0.74	0.798
nrs 2002 score			0.827
<3	55 (85.9%)	55 (88.7%)	
≥3	9 (14.1%)	7 (11.3%)	

SD, standard deviation; BMI, body mass index; Hb, hemoglobin; RBP, retinal-binding-protein; FBG, fasting blood glucose; PA, pre-albumin; ALB, albumin; LC, lymphocyte count.

2.3. Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 26.0. Normally distributed continuous variables are reported as mean and standard deviation, and an independent sample *t*-test was used to compare the differences between the treatment and control groups. Categorical variables are presented as numbers and analyzed using the χ^2 or Fisher's exact test, as appropriate. Linear regression analysis was used for univariate and multivariate analyses. Two-sided *P*-values were reported where necessary, with the significance level set at $P < 0.05$. A 95% confidence interval was used for all statistical analyses. Bar graphs and forest graphs were generated using GraphPad Prism 7.0.4.

3. Results

3.1. There was no difference in preoperative baseline among the 126 patients

In total, 126 participants completed the initial intervention. There were no significant demographic differences between the two groups. Compared with the control group, the preoperative RBP value was slightly lower in the dexamethasone group. There were no significant differences in the other indices. The baseline characteristics of the 126 participants included in the analysis are shown in Table 1.

TABLE 2 Postoperative caloric tolerance of enteral nutrition.

	Dexamethasone ($n = 64$)	Control ($n = 62$)	*P*-value
Average daily calorie intake by EN (kcal/kg/d)	8.80 ± 0.92	8.23 ± 1.13	0.002
Daily calorie intake by EN (kcal/kg/d)			
POD1	0.60 ± 0.99	0.62 ± 0.11	0.338
POD2	5.55 ± 1.02	4.97 ± 1.09	0.003
POD3	7.56 ± 1.27	7.10 ± 1.04	0.026
POD4	10.19 ± 1.18	9.40 ± 1.38	0.001
POD5	11.89 ± 1.27	11.45 ± 1.57	0.086

EN, enteral nutrition; POD, postoperative day.

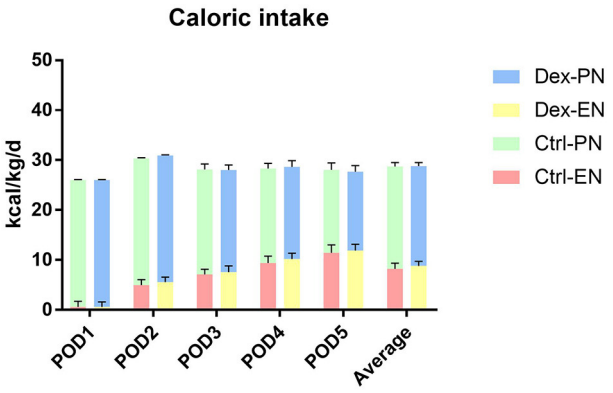

FIGURE 1
Postoperative nutritional caloric intake. Dex-PN, dexamethasone group parenteral nutrition; Dex-EN, dexamethasone group enteral nutrition; Ctrl-PN, control group parenteral nutrition; Ctrl-EN, control group enteral nutrition.

3.2. Patients in the dexamethasone group had better tolerance to enteral nutrition after surgery

Postoperative average daily caloric intake through enteral nutrition was significantly higher in the dexamethasone group than in the control group (8.80 ± 0.92 vs. 8.23 ± 1.13 kcal/kg/d, $P = 0.002$; Table 2 and Figure 1). With regard to caloric intake through enteral nutrition for each postoperative day, the dexamethasone group was higher than the control group on POD 2–4 ($P < 0.05$), and there was no difference in POD 5 ($P = 0.086$). The results of subgroup analysis showed that dexamethasone significantly increased the average daily enteral nutrition caloric intake in patients undergoing enterotomy (8.98 ± 0.87 vs. 8.37 ± 1.17 kcal/kg/d, $P = 0.010$; Table 3) or in female patients (8.94 ± 0.98 vs. 8.10 ± 1.24 kcal/kg/d, $P = 0.019$; Table 4). However, no significant differences were found between the subgroup of gastrostomy surgery patients (8.48 ± 0.94 vs. 7.95 ± 1.02 kcal/kg/d, $P = 0.083$; Figure 2). Enteral nutrition intake with dexamethasone was significantly higher in male patients than in controls, but this did not reach statistical significance (8.73 ± 0.90

10.3389/fnut.2023.1093662

TABLE 3 Enteral nutrition caloric intake in enterotomy surgery group.

	Dexamethasone ($n = 41$)	Control ($n = 41$)	*P*-value
Average daily calorie intake by EN (kcal/kg/d)	8.98 ± 0.87	8.37 ± 1.17	0.010
Daily calorie intake by EN (kcal/kg/d)			
POD1	0.60 ± 0.095	0.60 ± 0.096	0.927
POD2	5.83 ± 0.86	5.15 ± 106	0.002
POD3	7.71 ± 1.44	7.24 ± 1.11	0.106
POD4	10.34 ± 1.13	9.54 ± 1.42	0.006
POD5	12.02 ± 1.33	11.56 ± 1.61	0.160

EN, enteral nutrition; POD, postoperative day.

TABLE 4 Enteral nutrition caloric intake in the female patient group.

	Dexamethasone ($n = 20$)	Control ($n = 23$)	*P*-value
Average daily calorie intake by EN (kcal/kg/d)	8.94 ± 0.98	8.10 ± 1.24	0.019
Daily calorie intake by EN (kcal/kg/d)			
POD1	0.66 ± 0.10	0.67 ± 0.11	0.674
POD2	5.60 ± 1.05	4.96 ± 0.98	0.043
POD3	7.95 ± 1.10	7.00 ± 1.09	0.007
POD4	11.30 ± 1.33	10.30 ± 1.22	0.012
POD5	11.90 ± 1.33	11.30 ± 1.77	0.225

EN, enteral nutrition; POD, postoperative day.

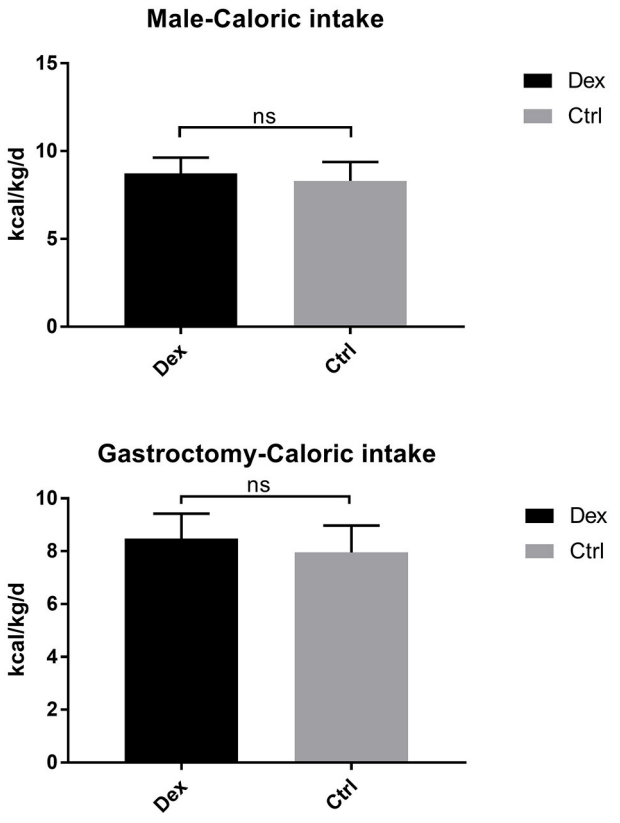

FIGURE 2
Avervage daily enteral nutrition caloric intake in the male and gastrosurgery groups. ns $P > 0.05$.

vs. 8.31 ± 1.07 kcal/kg/d, $P = 0.052$; Figure 2). Subgroup analysis revealed that dexamethasone significantly improved tolerance to enteral nutrition in female patients and undergoing enterotomy (Figure 3).

3.3. The decline in nutrition-related indices after surgery was smaller in the dexamethasone group

Compared with the control group, the dexamethasone group showed fewer changes in nutrition-related indices, such as ΔPA, ΔALB, and ΔRBP, on POD 3 and POD 5 [Figure 4; ΔPA: POD 3, 60.36 mg/L vs. 86.01, 95% CI (−45.28, −6.02), $P = 0.11$; POD 5, 48.64 vs. 74.42 mg/L, 95% CI (−47.72, −3.84), $P = 0.022$; ΔALB:POD 3, 3.00 vs. 4.52 g/L, 95% CI (−2.99, −0.05), $P = 0.043$; POD 5, 1.57 vs. 3.43 g/L, 95% CI (−3.51, −0.22), $P = 0.027$; ΔRBP: POD 3, 9.78 vs. 13.58 μg/L, 95% CI (−7.18, −0.41), $P = 0.028$; POD 5, 6.02 vs. 11.02 μg/L, 95% CI (−8.85, −1.15), $P = 0.011$]. Moreover, the results of the subgroup analysis showed that in patients undergoing enterotomy surgery, dexamethasone can reduce the declining level of PA and ALB values on the POD 3 [ΔPA: 61.08 vs. 85.01 mg/L, 95% CI (−47.00, −0.86), $P = 0.042$; ΔALB:2.65 vs. 4.33g/L, 95% CI (−3.31, −0.05), $P = 0.044$] and the declining level of RBP values both on the POD3 and POD 5 [ΔRBP: POD3, 9.50 vs. 14.29 μg/L, 95% CI (−9.08, −0.51), $P = 0.029$; POD 5, 6.54 vs. 12.02 μg/L, 95% CI (−10.25, −0.72), $P = 0.025$; Figure 5]. Similarly, in a subgroup analysis of female patients, the dexamethasone group had reduced changes in PA value on the POD 3 [ΔPA: 42.78 vs. 74.99 mg/L, 95% CI (−63.78, −0.65), $P = 0.046$; Figure 6]. However, such changes did not reach statistical significance in male patients or patients undergoing gastrectomy surgery.

3.4. Influencing factors of average daily enteral nutrition caloric intake

Univariate linear regression analysis of factors affecting the average daily caloric intake through enteral nutrition showed that surgical site, age, and intravenous dexamethasone might affect the average daily enteral nutrition caloric intake (Table 5). Multivariate linear regression analysis showed that surgical site, age, and intravenous dexamethasone use might be significant predictors of daily average enteral nutrition energy intake. With increasing age, the degree of enteral nutrition tolerance decreased (Table 6).

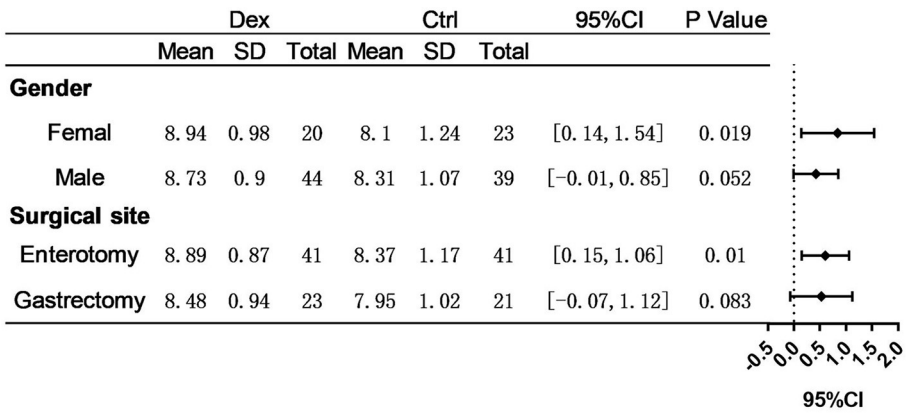

FIGURE 3
Assessment of differences in avervage daily enteral nutrition caloric intake. *P*-value represent intra-group significance.

4. Discussion

In our study, PA, ALB, RBP, FBG, and LC were used to evaluate nutrition-related indicators, which was consistent with previous studies. These indicators have been used to evaluate the nutritional status of patients in previous studies (18–21). In this *post-hoc* analysis of prospectively collected data from the DOPGM trial, we observed that the average daily caloric intake through enteral nutrition was significantly higher in the dexamethasone group than in the control group. This may be related to the faster recovery of intestinal function and faster tolerance of a liquid diet in the dexamethasone group. However, differences in daily enteral nutrient caloric intake are shown on POD 2–4. As time goes on, this difference between the two groups will no longer be statistically significant on POD 5. In terms of nutrition-related serological indices, there was no statistical difference between the two groups. Still, we found that the decline in nutrition-related indices after surgery, such as ΔPA, ΔALB, and ΔRBP, reached statistical significance on POD 3 and POD 5. These results suggest that 8 mg single-dose intravenous dexamethasone can improve postoperative nutritional status in patients with short-term nutritional status. Subgroup analysis showed that the average daily caloric intake through enteral nutrition was higher in patients undergoing enterotomy surgery than in the control group. However, in patients undergoing gastrectomy, the average daily caloric intake through enteral nutrition in the dexamethasone group did not show obvious advantages, which may be related to the longer duration of gastric surgery, greater surgical traumatic stress, longer time to a liquid diet, longer time to gastrointestinal function and motility recovery, and poor enteral nutrition tolerance. This may also be the reason for the lower decline in nutrition-related indices after enterotomy. Interestingly, female patients in the dexamethasone group also showed a similar change. However, we have not found in previous studies that after being given dexamethasone, females haves a better recovery of intestinal function after surgery than males. This may be due to intestinal flora differences between male and female patients with enteral nutrition absorption. Thus, further research is still needed to determine the reasons for the difference in caloric absorption caused by sex differences.

With the change in treatment mode and the popularization of the ERAS concept, the perioperative fasting time and surgical stress have been reduced in recent years. Although these measures improve the nutritional status of patients after major surgery, there are some still suffer from postoperative malnutrition, which is associated with poor postoperative outcomes. These include an increased incidence of infections, depression of the immune system, impaired wound healing, and increased mortality (22). Gastrointestinal dysfunction is an important factor that affects nutritional absorption after surgery. Early enteral feeding is particularly important to reduce surgical stress and the risk of postoperative complications caused by malnutrition and insufficient feeding, especially for patients who have nutritional risks before surgery or require gastrointestinal surgery (23, 24). Our previous studies have shown that preoperative intravenous dexamethasone can promote faster recovery of gastrointestinal function and better tolerance to a liquid diet. Meanwhile, this *post-hoc* analysis study showed that treatment with dexamethasone could improve short-term postoperative nutritional status. These findings strongly support the idea that preoperative dexamethasone administration can improve patients' postoperative recovery.

Meanwhile, inflammation could be another key factor in explaining these outcomes (25). Surgery is a type of trauma that can cause a series of reactions, including releasing stress hormones and inflammatory mediators. In severe cases, it can even cause the so-called "systemic inflammatory response syndrome," which significantly impacts metabolism (26, 27). In addition, previous studies have shown that inflammation can affect the nutritional support of patients in different ways (28, 29), such as affecting appetite and gastrointestinal function, reducing food intake, and increasing insulin resistance (30). At the cellular level, cytokines such as IL-6 interfere with the satiety center, leading to anorexia, delayed gastric emptying, and skeletal muscle protein catabolism (31). In contrast, previous studies have shown that dexamethasone significantly reduces IL-6 levels (32). Prevention of nausea and vomiting and reduction of pain may have been another reason for the increased food intake in the dexamethasone group (33). Whether additional administration could promote the recovery

10.3389/fnut.2023.1093662

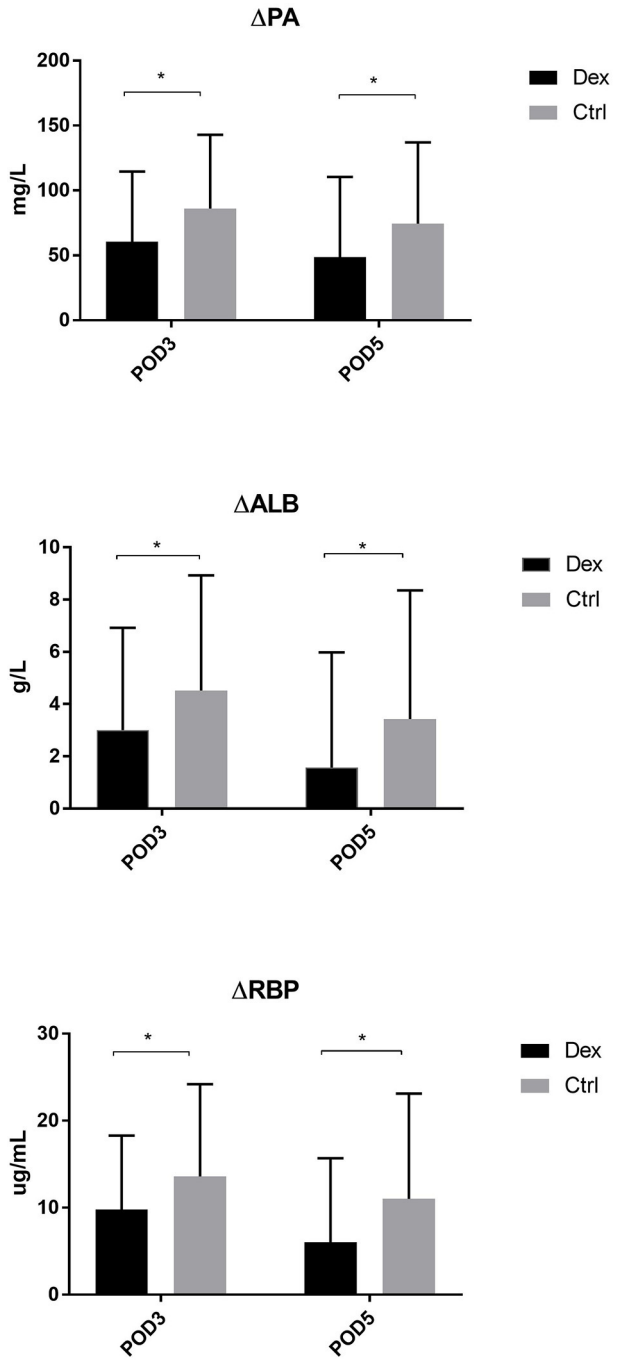

FIGURE 4
The decrease of PA, ALB, RBP in POD3 and POD5. Δ represents the difference between preoperative value and postoperative value. *$P < 0.05$.

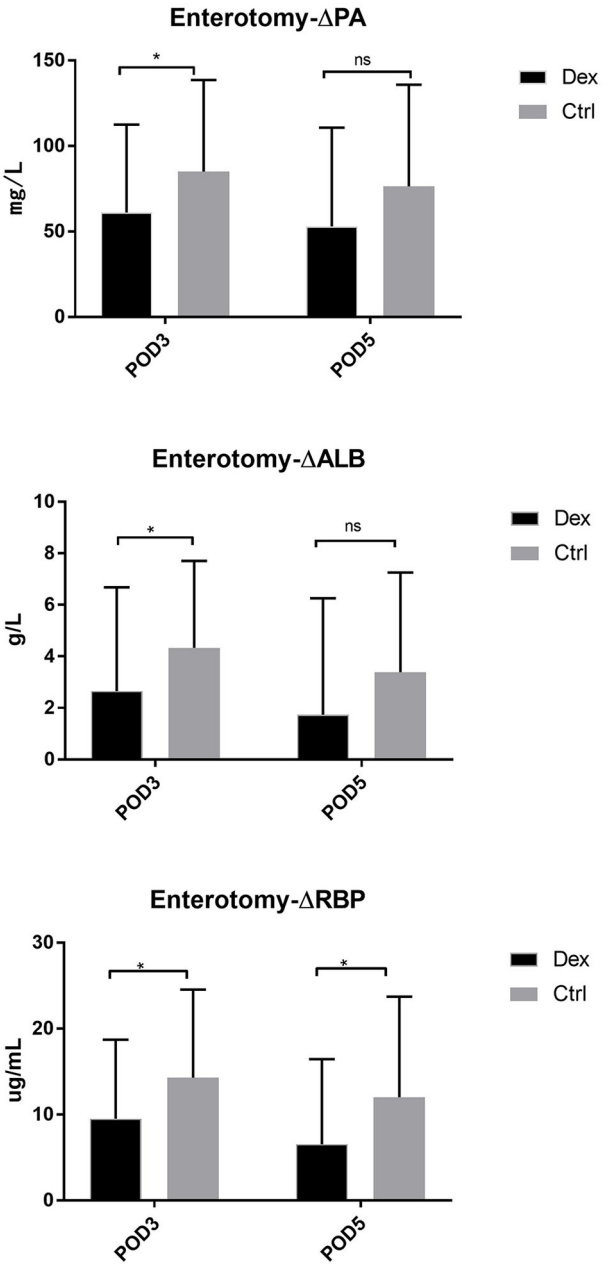

FIGURE 5
The decrease of PA, ALB, RBP in POD3 and POD5 in enterotomy surgery group. Δ represents the difference between preoperative value and postoperative value. ns $P > 0.05$, *$P < 0.05$.

of gastrointestinal function to improve nutritional status after gastrectomy still requires further prospective trials.

Correlation analysis showed that dexamethasone administration was an important predictor of the average daily enteral nutrition intake. This may be related to the reduction of intestinal stress and the promotion of gastrointestinal peristalsis. In addition, it was reported that a patient with esophageal cancer cachexia was treated with dexamethasone combined with nutritional drugs, and his nutritional status was significantly improved and he could tolerate chemotherapy (34). This may be due to the fact that corticosteroids such as dexamethasone can inhibit brain edema and improve appetite on the one hand, and stimulate the expression of neuropeptide y and prevent the synthesis of promelanocortin on the other hand, leading to increased appetite and hunger, thereby reducing the application of parenteral nutrition and improving the tolerance of enteral nutrition (35). This finding is consistent with our previous

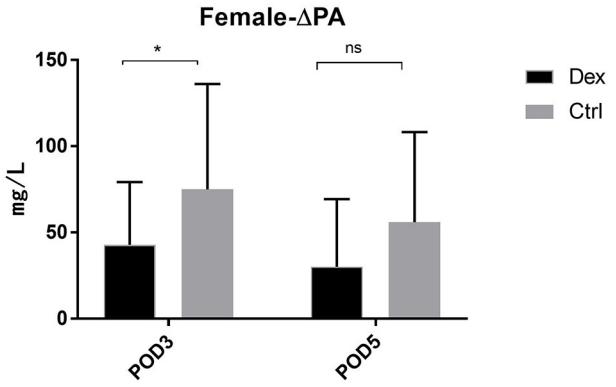

FIGURE 6
The decrease of PA in POD3 and POD5 in female patients. Δrepresents the difference between preoperative value and postoperative value. ns $P > 0.05$, *$P < 0.05$.

TABLE 5 Factors that may influence caloric intake from enteral nutrition.

	B	*t*	*P*-value	95% confidence interval	
Age	−0.036	−4.876	0.000	−0.051	−0.021
Dexamethasone	0.567	3.090	0.002	0.204	0.930
BMI	0.147	1.877	0.063	−0.003	0.096
Gender (femal/male)	−0.045	−0.223	0.824	−0.442	0.353
Site of surgery (enterotomy/ gastrectomy)	0.447	2.282	0.024	0.059	0.834

BMI, body mass index.

TABLE 6 Independent influencing factors of enteral nutrition caloric intake.

	B	*t*	*P*-value	95% confidence interval	
Age	−0.423	−5.458	0.000	−0.053	−0.025
Dexamethasone	0.552	3.339	0.001	0.225	0.879
Site of surgery (enterotomy/ gastrectomy)	0.196	2.525	0.013	0.095	0.788

findings. The increase in age, the increase in basic diseases, the decline in various body functions, and the use of anesthetics and antibiotics significantly impact the recovery of gastrointestinal peristalsis in the elderly, and the tolerance of enteral nutrition in the elderly decreases. Jang and Jeong (36) concluded in an analysis of early nutritional tolerance after gastrectomy: age (≥70 years), gender, tumor obstruction and operation time are related to poor tolerance of enteral nutrition, and male and tumor obstruction are independent influencing factors of poor tolerance. Therefore, age negatively correlates with the average daily tolerance to enteral nutrition.

5. Strengths and limitations

This *post hoc* analysis was based on the random nature of previous clinical trials, which ensured the balance of data between the two groups. However, this study has some limitations. First, we did not monitor cytokines such as IL-6, which may provide more detailed information. Second, the sample size of this experiment may be too small to find significant interactions in some research results. Finally, because this is a *post-hoc* analysis, our results are based on the study hypothesis of the first trial; therefore, further randomized controlled trials with independent samples are needed to verify the tolerance of enteral nutrition.

6. Conclusion

In a *post hoc* analysis of a previous clinical trial involving dexamethasone, we found that dexamethasone improved postoperative enteral nutrition tolerance, particularly in a subgroup of patients following enterotomy surgery, as well as significantly improved postoperative average daily enteral nutritional caloric intake and changes in nutrition-related serological indicators.

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 human participants were reviewed and approved by Shandong Provincial Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FT, XZ, and JW: analysis and interpretation, literature search, and writing manuscript. MW and ZS: materials, data collection, and processing. LL: design. YC and CJ: supervision, critical review, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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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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Postoperative parenteral glutamine supplementation improves the short-term outcomes in patients undergoing colorectal cancer surgery: A propensity score matching study

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Introduction: The clinical utility of glutamine in patients undergoing colorectal cancer (CRC) surgery remains unclear. Therefore, we aimed to investigate the impact of postoperative treatment with glutamine on postoperative outcomes in patients undergoing CRC surgery.

Methods: We included patients with CRC undergoing elective surgery between January 2014 and January 2021. Patients were divided into the glutamine and control groups. We retrospectively analyzed postoperative infections complications within 30days and other outcomes using propensity score matching and performed between-group comparisons.

Results: We included 1,004 patients who underwent CRC surgeries; among them, 660 received parenteral glutamine supplementation. After matching, there were 342 patients in each group. The overall incidence of postoperative complications was 14.9 and 36.8% in the glutamine and control groups, respectively, indicating that glutamine significantly reduced the incidence of postoperative complications [$p<0.001$; risk ratio (RR) 0.41 [95% CI 0.30–0.54]]. Compared with the control group, the glutamine group had a significantly lower postoperative infection complications rate (10.5 vs. 28.9%; $p<0.001$; RR 0.36 [95% CI 0.26–0.52]). Although there was no significant between-group difference in the time to first fluid diet ($p=0.052$), the time to first defecation ($p<0.001$), first exhaust ($p<0.001$), and first solid diet ($p<0.001$), as well as hospital stay ($p<0.001$) were significantly shorter in the glutamine group than in the control group. Furthermore, glutamine supplementation significantly reduced the incidence of postoperative intestinal obstruction ($p=0.046$). Moreover, glutamine supplementation alleviated the decrease in albumin ($p<0.001$), total protein ($p<0.001$), and prealbumin levels ($p<0.001$).

Conclusions: Taken together, postoperative parenteral glutamine supplementation can effectively reduce the incidence of postoperative complications, promote the recovery of intestinal function, and improve albumin levels in patients undergoing CRC surgery.

KEYWORDS

glutamine, colorectal cancer, postoperative complications, intestinal function, albumin, propensity score

1. Introduction

Worldwide, colorectal cancer (CRC) is the third most common cancer and among the most common mortality causes due to gastrointestinal cancer. In 2021, there were more than 1,800,000 new cases of CRC worldwide (1). Changes in diet and lifestyle have contributed to the incidence of CRC (2). Surgery has become the main treatment for CRC (3). Although there has been a gradual reduction in postoperative complications with the progress of perioperative nursing and technology, the incidence of complications after CRC surgery remains as high as 35% (4). Mechanical bowel preparation before CRC surgery can disrupt intestinal barrier function; further, potential intraoperative bacterial contamination may increase the risk of postoperative infectious complications (5, 6). Postoperative complications prolong hospital stay, increase hospitalization costs, and negatively affect the long-term prognosis of patients (7, 8). A recent meta-analysis reported that postoperative complications increased the risk of recurrence and decreased overall survival among patients with non-metastatic CRC (9). Therefore, reducing postoperative complications is crucial for improving the prognosis of patients.

Recent studies have demonstrated that immunonutritional therapy can reduce postoperative complications by regulating immune function in patients with CRC (8). Glutamine, which is crucially involved in immunonutrition, can regulate inflammatory response and immune balance, maintain the intestinal mucosal barrier, reduce intestinal damage, and reduce intestinal microbiota translocation (5, 8, 10). Accordingly, glutamine may provide a potential strategy for preventing postoperative complications. Additionally, a few studies have demonstrated that glutamine supplementation can reduce the length of hospital stay (5, 11).

However, there remains insufficient evidence for supporting the routine perioperative use of glutamine in patients with CRC. A recent meta-analysis recommended large-scale studies to evaluate the effect of perioperative glutamine supplementation in patients undergoing CRC surgery (8). Accordingly, we used propensity score matching (PSM) to investigate the effect of postoperative glutamine supplementation on postoperative complications and recovery in patients undergoing CRC surgery.

2. Methods

2.1. Study population

This retrospective cohort study was conducted between January 2014 and January 2021. This study was ethically approved by the Institutional Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. All the patients provided informed consent.

We included patients who underwent elective surgery for primary CRC with and without glutamine supplementation (20% alanyl-glutamine 50–100 mL daily) for ≥5 days from the day of surgery. We excluded cases without primary anastomosis; cases with multiple primary cancers, a history of treatment for other abdominal or pelvic malignancy, or multi-visceral resections; patients with hepatic or renal failures; and emergency cases.

Standardized laparoscopic colorectal cancer and robotic surgery were adopted in our hospital, all of which were performed by four surgeons with an experience of more than 100 laparoscopic colorectal cancer operations. We collected information regarding baseline characteristics, intraoperative details, and postoperative recovery from the electronic medical record system. Tumor staging was determined based on American Joint Committee on Cancer, 8th edition (12). Serum prealbumin, total protein, and albumin levels on the day before surgery and 5 days after surgery were collected.

2.2. Primary and secondary endpoints

The primary endpoints were postoperative infection complications within 30 postoperative days, including anastomotic leakage, intra-abdominal infection (excluding anastomotic leakage), wound infection, pneumonia, and urinary infection. The secondary endpoints included serum total protein and albumin levels; time to first exhaust, defecation, fluid diet, and solid diet; rate of postoperative complications, rate of reoperation within 30 postoperative days, postoperative length of hospital stay, and mortality.

2.3. Statistical analysis

The sample size was calculated based on the primary endpoint. A previous study (5) reports that the incidence of infectious complications is 42%; accordingly, assuming an incidence rate of 11% in the glutamine group, ≥31 patients were expected to be required in each group to achieve 80% power with a two-tailed p value <0.05. Eligible participants were divided into the glutamine and control groups based on whether they received intravenous glutamine supplementation. Between-group comparisons of categorical and continuous variables were performed using the chi-square test and Mann–Whitney U test (Kolmogorov–Smirnov tests showed that the data in this study were non-normally distributed), respectively. Dichotomous variables were described using percentages, while continuous variables by median (interquartile range: 25–75 percentile). To reduce potential confounders resulting from between-group differences in baseline characteristics, we performed PSM analysis using patient demographics (male, age, BMI, tumor stage, and neoadjuvant therapy), comorbidities (chronic obstructive pulmonary disease, liver disorder, hypertension, diabetes mellitus, coronary artery disease, and American Society of Anesthesiologists Physical Status classification), malnutrition (preoperative prealbumin, preoperative total protein, and albumin), and surgical data (surgical approach, diverting stoma, duration of surgery, intraoperative blood loss, intraoperative transfusion, and conversion). Using the nearest neighbor matching algorithm, the matching ratio was 1:1. Calipers were set to 0.2 times the standard deviation of the logarithm of the estimated propensity score. All statistical analyses were performed using IBM SPSS version 26. Statistical significance was set at a two-sided p value <0.05.

3. Results

3.1. Baseline characteristics before and after propensity score matching

We included 1,004 consecutive patients undergoing elective surgery for CRC (38.6%, female; median age, 62 years). There were 660 and 344

patients in the glutamine and control groups, respectively. Before matching, there were a significant between-group difference in neoadjuvant therapy, duration of surgery, intraoperative blood loss, and intraoperative transfusion, but not in patient demographics (male, age, BMI, and tumor stage), comorbidities (chronic obstructive pulmonary disease, liver disorder, hypertension, diabetes mellitus, coronary artery disease, and American Society of Anesthesiologists physical status classification), malnutrition (preoperative prealbumin, preoperative total protein, and preoperative albumin), and surgical data (surgical approach, diverting stoma, and conversion; Table 1). After PSM, there were no significant differences in all covariates between the glutamine ($n = 342$) and control ($n = 342$) groups (Table 1).

3.2. Postoperative short-term outcomes before and after propensity score matching

Before matching, the rate of postoperative complications was significantly lower in the glutamine group than in the control group [15.9 vs. 36.6%, respectively; $p < 0.001$; risk ratio (RR) 0.43 [95% CI 0.35–0.54]; Table 2]. After PSM, the overall incidence of postoperative complications in the glutamine and control groups was 14.9 and 36.8%, respectively ($p < 0.001$; RR 0.41 [95% CI 0.30–0.54]). The glutamine group had a significantly lower rate of postoperative infections than the control group (10.5 vs. 28.9%, respectively; $p < 0.001$; RR 0.36 [95% CI 0.26–0.52]). There was no significant between-group difference in the rate of wound infection ($p = 0.105$), urinary infection ($p = 0.101$), and bleeding at anastomotic site ($p = 0.412$); however, the glutamine group had a significantly lower rate of anastomotic leakage ($p = 0.043$), pulmonary tract infection ($p = 0.007$), and intraabdominal infection ($p < 0.001$) than the control group (Table 2).

Regarding postoperative intestinal function recovery, although there was no significant between-group difference in the time to first fluid diet ($p = 0.052$), the glutamine group showed a significantly shorter time to first exhaust ($p < 0.001$), first defecation ($p < 0.001$), and first solid diet ($p < 0.001$) than the control group. Additionally, glutamine supplementation significantly reduced the incidence of postoperative intestinal obstruction ($p = 0.046$). The median length of hospital stay was 8 and 9 days in the glutamine and control groups, respectively ($p < 0.001$). Moreover, the median hospitalization cost in the glutamine group (75871.5RMB) was comparable to that in the control group (84059.7RMB; $p = 0.950$). There was two death in the glutamine group and two deaths in the control group (Table 2).

The median postoperative total protein levels were 61 and 59 g/L in the glutamine and control groups, respectively ($p < 0.001$). Glutamine alleviated the decrease in perioperative albumin ($p < 0.001$) and prealbumin ($p < 0.001$) levels (Table 2). Details of Clavien-Dindo classification of postoperative complications are in Table 3.

4. Discussion

To our knowledge, this is the first large-scale study to explore the effects of glutamine on postoperative complications and recovery after CRC surgery. We found that glutamine supplementation could effectively reduce the incidence of postoperative complications; shorten the time to first exhaust, first defecation, and first solid diet; reduce the length of hospital stay; and improve serum prealbumin, total protein, and albumin levels. Postoperative complications negatively affect the short-term and long-term prognosis of patients with CRC. Colorectal surgery research has recently focused on the prevention of postoperative complications. Our findings provide current evidence regarding the prevention of postoperative complications and improvement of postoperative recovery in CRC surgery through glutamine supplementation.

Radical resection is the standard treatment for CRC (13). Immunonutrition therapy can effectively reduce the incidence and severity of postoperative complications in patients undergoing radical surgery for CRC (8). Glutamine is the preferred fuel for intestinal mucosal cells and immune cells; accordingly, it is crucially involved in regulating the body's immune function and maintaining the integrity of the intestinal mucosal barrier (8, 14). Surgical trauma reduces plasma and intracellular glutamine pool levels, which impairs the normal immune function of T cells, the bactericidal function of neutrophils, the phagocytic activity of macrophages, and interleukin-1 production (15–17). The depletion of stored glutamine may cause postoperative complications, including infectious complications, abnormal immune function, increased intestinal permeability, poor wound healing, and even multiple organ failure (5). Low serum glutamine levels are associated with shortened survival of patients with CRC (18). Therefore, glutamine supplementation may be crucial for preventing postoperative complications. In our study, glutamine supplementation effectively reduced the incidence of postoperative complications. Several studies have demonstrated that glutamine supplementation can reduce postoperative complications. O'Riordain et al. (17) found that glutamine supplementation enhanced postoperative T lymphocyte immune function in patients undergoing colorectal surgery. In a study conducted by Cui et al. (11), patients with colon cancer received 0.5 g/kg glutamine 24 h before and 1 h after surgery and found that glutamine supplementation reduced the incidence of postoperative complications. Similarly, Oguz et al. reported that intravenous glutamine supplementation reduced postoperative complications (5). Additionally, the incidence of anastomotic leakage is as high as 3–20% and is related to increased postoperative morbidity, mortality, permanent stoma rate, and recurrence rate (13, 19–21). Accordingly, we focused on the important complication of an anastomotic leak. We found that glutamine supplementation effectively reduced the incidence of anastomotic leaks. Consistent with this finding, Yang et al. reported a significantly lower incidence of anastomotic leak in the glutamine group than in the control group (RR = 0.23, 95% CI: 0.09–0.61) (8). This could be attributed to several factors. On the one hand, glutamine can increase collagen synthesis, and thus accelerate intestinal mucosal healing and regeneration (13, 22). On the other hand, inflammation severity is among the important factors affecting the healing of intestinal anastomosis. Accordingly, glutamine can reduce inflammatory injury and oxidative stress as well as protect the healing of anastomosis (13).

In addition to reducing postoperative complications, glutamine may also promote postoperative recovery of gastrointestinal function. Glutamine can prevent intestinal mucosal atrophy and protect the intestinal mucosal barrier (17). Glutamine supplementation has been shown to prevent chemotherapy-induced diarrhea (23). Using animal experiments with dogs, Ohno et al. reported that glutamine improved intestinal obstruction after abdominal surgery (24). Additionally, Ohno et al. (25) reported that glutamine supplementation improved the decrease in plasma glutamine levels and gastrointestinal motility after gastrectomy. Our findings demonstrated that glutamine supplementation promoted intestinal function recovery, including

TABLE 1 Baseline characteristics before and after propensity score matching.

	Group glutamine before PSM (*n*=660)	Group Non-glutamine before PSM (*n*=344)	*p* value [b]	χ^2	Group glutamine after PSM (*n*=342)	Group non-glutamine after PSM (*n*=342)	*p* value [b]	χ^2
Age (years)[a]	62 (54–69)	63 (53–69)	0.962	-	62 (54–69)	62.5 (53–69)	0.982	-
Gender (%)			0.278	1.176			0.430	0.622
Male	397 (60.2)	219 (63.7)			208 (60.8)	218 (63.7)		
Female	263 (39.8)	125 (36.3)			134 (39.2)	124 (36.3)		
BMI[a]	22.8 (20.7–24.6)	22.7 (20.6–24.5)	0.832	-	22.8 (20.8–24.4)	22.8 (20.7–24.5)	0.929	-
COPD (%)	38 (5.8)	23 (6.7)	0.559	0.342	19 (5.6)	23 (6.7)	0.524	0.406
Liver disorder (%)	20 (3)	9 (2.6)	0.710	0.138	10 (2.9)	9 (2.6)	0.816	0.054
Hypertension (%)	145 (22)	78 (22.7)	0.799	0.065	74 (21.6)	78 (22.8)	0.713	0.135
Diabetes mellitus (%)	76 (11.5)	37 (10.8)	0.718	0.131	42 (12.3)	37 (10.8)	0.550	0.358
Coronary artery disease (%)	56 (8.5)	22 (6.4)	0.240	1.378	28 (8.2)	22 (6.4)	0.378	0.777
ASA grade (%)			0.436	1.662			0.485	1.445
1	9 (1.4)	8 (2.3)			5 (1.5)	8 (2.3)		
2	485 (73.5)	244 (70.9)			254 (74.3)	242 (70.8)		
3	166 (25.2)	92 (26.7)			83 (24.3)	92 (26.9)		
Neoadjuvant therapy received (%)	29 (4.4)	26 (7.6)	0.037	4.373	15 (4.4)	26 (7.6)	0.076	3.139
Treatment modality (%)			0.951	0.004			0.533	0.389
Robotic/ Laparoscopy	621 (94.1)	324 (94.2)			318 (93)	322 (94.2)		
Conventional open	39 (5.9)	20 (5.8)			24 (7)	20 (5.8)		
Diverting stoma (%)	35 (5.3)	24 (7)	0.285	1.145	20 (5.8)	24 (7)	0.533	0.389
Duration of surgery (min)[a]	194.5 (150–240)	200 (160–250)	0.036	-	190 (150.8–245)	200 (160–250)	0.071	-
Intraoperative blood loss (ml)[a]	50 (20–100)	50 (20–100)	0.047	-	50 (20–100)	50 (20–100)	0.171	-
Transfusion (%)	7 (1.1)	12 (3.5)	0.007	7.179	4 (1.2)	10 (2.9)	0.105	2.625
Conversion (%)	5 (0.8)	3 (0.9)	0.846	0.038	2 (0.6)	3 (0.9)	0.654	0.201
Type of operation			0.131	7.093			0.546	3.072
Right hemicolectomy (%)	160 (24.2)	73 (21.2)			81 (23.7)	73 (21.3)		
Transverse colectomy	9 (1.4)	4 (1.2)			5 (1.5)	4 (1.2)		
Left hemicolectomy	36 (5.5)	13 (3.8)			16 (4.7)	13 (3.8)		
Sigmoid colectomy	110 (16.7)	45 (13.1)			55 (16.1)	45 (13.2)		
Anterior resection	345 (52.3)	209 (60.8)			185 (54.1)	207 (60.5)		
Year			0.192	8.683			0.279	7.472
2014	59 (8.9)	39 (11.3)			30 (8.8)	39 (11.4)		
2015	87 (13.2)	32 (9.3)			44 (12.9)	32 (9.4)		
2016	74 (11.2)	45 (13.1)			39 (11.4)	45 (13.2)		
2017	111 (16.8)	51 (14.8)			48 (14.0)	51 (14.9)		
2018	96 (14.5)	65 (18.9)			50 (14.6)	65 (19.0)		
2019	131 (19.8)	61 (17.7)			70 (20.5)	61 (17.8)		
2020[c]	102 (15.5)	51 (14.8)			61 (17.8)	49 (14.3)		
Preoperative prealbumin (mg/L)[a]	213.5 (188–234)	214 (188–237)	0.803	-	215 (186–237)	214 (188–238)	0.915	-
Preoperative total protein (g/L)[a]	68 (63–72)	68 (64–73)	0.125	-	69 (63–72)	68 (64–73)	0.438	-
Preoperative albumin (g/L)[a]	41 (38–44)	41 (37–44)	0.661	-	41 (37.8–45)	41 (37–44)	0.825	-
UICC stage (%)			0.288	2.487			0.731	0.627

(Continued)

TABLE 1 (Continued)

	Group glutamine before PSM (n=660)	Group Non-glutamine before PSM (n=344)	p value [b]	χ^2	Group glutamine after PSM (n=342)	Group non-glutamine after PSM (n=342)	p value [b]	χ^2
I	128 (19.4)	71 (20.6)			72 (21.1)	70 (20.5)		
II	286 (43.3)	162 (47.1)			151 (44.2)	161 (47.1)		
III	246 (37.3)	111 (32.3)			119 (34.8)	111 (32.5)		

Values in parentheses are percentages unless indicated otherwise.
[a]Values are median (interquartile range: 25–75th percentile).
[b]Statistical analyses were performed using the chi-square test or Mann–Whitney U test;
[c]Including January 2021.
ASA, American Society of anesthesiologists physical status classification; BMI, body mass index; COPD, chronic obstructive pulmonary disease; and PSM, propensity score matching.

TABLE 2 Operative outcomes before and after propensity score matching.

	Group glutamine before PSM (n=660)	Group non-glutamine before PSM (n=344)	p value[b]	χ^2	Group glutamine after PSM (n=342)	Group non-glutamine after PSM (n=342)	p value[b]	χ^2
Days to first flatus[a]	2 (1–3)	2 (2–3)	< 0.001	-	2 (1–3)	2 (2–3)	< 0.001	-
Days to first defecation[a]	3 (3–4)	4 (3–5)	< 0.001	-	3 (3–5)	4 (3–5)	< 0.001	-
Days to first fluid diet[a]	3 (2–3)	3 (2–3)	0.176	-	3 (2–3)	3 (2–3)	0.052	-
Days to first solid diet[a]	6 (5–7)	6 (5–7)	< 0.001	-	5 (4–7)	6 (5–7)	< 0.001	-
Reoperation (%)	3 (0.5)	2 (0.6)	0.786	0.073	2 (0.6)	2 (0.6)	1.00	0.000
Mortality (%)	2 (0.3)	2 (0.6)	0.506	0.442	2 (0.6)	2 (0.6)	1.00	0.000
Postoperative prealbumin (mg/L) [a]	181 (156–198)	138 (107–164)	< 0.001	-	184 (159.8–199)	138 (107–164)	< 0.001	-
Postoperative total protein (g/L)[a]	61 (58–66)	59 (55–63)	< 0.001	-	61 (58–66)	59 (55–63)	< 0.001	-
Postoperative albumin (g/L)[a]	35 (32–38)	34 (31–37)	< 0.001	-	35 (32–38)	34 (31–37)	< 0.001	-
Hospital stay (days)[a]	8 (7–10)	9 (7–11)	< 0.001	-	8 (7–10)	9 (7–11)	< 0.001	-
Postoperative complications (%)	105 (15.9)	126 (36.6)	< 0.001	54.799	51 (14.9)	126 (36.8)	< 0.001	42.874
Urinary infection (%)	2 (0.3)	5 (1.5)	0.038	4.323	1 (0.3)	5 (1.5)	0.101	2.690
Pneumonia (%)	20 (3)	24 (7)	0.004	8.405	9 (2.6)	24 (7)	0.007	7.164
Ileus (%)	11 (1.7)	18 (5.2)	0.001	10.251	8 (2.3)	18 (5.3)	0.046	3.998
Wound infection (%)	13 (2.0)	10 (2.9)	0.346	0.888	4 (1.2)	10 (2.9)	0.105	2.625
Intraabdominal infection (%)	37 (5.6)	48 (14)	< 0.001	20.333	18 (5.3)	48 (14)	< 0.001	15.093
Anastomotic leakage (%)	8 (1.2)	12 (3.5)	0.014	6.001	4 (1.2)	12 (3.5)	0.043	4.096
Bleeding at anastomotic site (%)	4 (0.6)	4 (1.2)	0.346	0.887	2 (0.6)	4 (1.2)	0.412	0.673
Others (%)	10 (1.5)	5 (1.5)	0.939	0.006	5 (1.5)	5 (1.5)	1.000	0.000

Values in parentheses are percentages, unless indicated otherwise.
[a]Values are median (interquartile range: 25–75th percentile).
[b]Statistical analyses were performed using the chi-square test or Mann–Whitney U test.
PSM, propensity score matching.

shortening the time to first exhaust, first defecation, and first solid diet as well as reducing the incidence of postoperative ileus. Additionally, we found that glutamine reduced postoperative hospital stay, which is consistent with previous reports (5, 11, 26) and could be attributed to decreased complications and improved recovery of intestinal function. This in turn could have contributed to reduced hospitalization costs. Thus we observed that additional glutamine supplementation did not increase total hospitalization costs.

Hypoproteinemia is related to increased postoperative morbidity and prolonged hospital stay (27, 28). Major gastrointestinal surgery is

TABLE 3 Clavien-Dindo classification of postoperative complication after propensity score matching.

	Group glutamine (n=342)	Group non-glutamine (n=342)	p value[a]	χ^2
Clavien-Dindo classification			0.679	2.311
I	8 (2.3)	13 (3.8)		
II	31 (9.1)	87 (25.4)		
III	7 (2)	15 (4.4)		
IV	3 (0.9)	9 (2.6)		
V	2 (0.6)	2 (0.6)		-

Values in parentheses are percentages.
[a]Statistical analyses were performed using the chi-square test or Mann–Whitney U test.

often accompanied by a high inflammatory response, which impairs liver protein metabolism. Glutamine can increase hepatocyte synthesis and improve hepatic metabolism (29). Wu et al. reported that glutamine supplementation increased serum albumin levels in patients with gastric cancer undergoing radical surgery (29), which is consistent with our findings. However, while the differences in these indicators (total protein levels, albumin levels, and prealbumin levels) were statistically significant, whether these differences are of significant clinical value remains to be determined.

Our study has two strengths. On the one hand, it is the study with the largest sample size to examine the effects of glutamine on patients undergoing colorectal cancer surgery. On the other hand, we used PSM to balance potential confounding factors between the groups.

This study has several limitations. First, this was a single-center retrospective study and there may be potential confounding factors. Second, we retrospectively collected information regarding the time to first exhaust, defecation, fluid diet, and first solid diet from the electronic medical records, which could lead to potential bias. Prospective studies are warranted to confirm the benefits of glutamine supplementation on the recovery of bowel function after surgery for CRC. Then, we did not measure plasma glutamine levels before and after the intervention. Future studies should consider plasma glutamine levels. Finally, as the current guidelines do not clarify whether or not to supplement glutamine in patients undergoing colorectal cancer surgery, in this study, this decision was not based on clear criteria. This could have led to some selection bias. Given these limitations, prospective randomized controlled studies are needed to validate the benefit of glutamine supplements in patients undergoing colorectal cancer surgery.

In conclusion, we found that postoperative intravenous glutamine supplementation could effectively reduce the incidence of postoperative complications, promote the recovery of intestinal function, and improve albumin levels in patients undergoing CRC surgery.

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.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Z-QW, FP, and GT: conceptualization. FP, GT, and Y-HQ: data collection and analyses. GT and FP: writing—original draft preparation. Z-QW, FP, GT, and Y-HQ: writing—review and editing and had primary responsibility for the final content. All authors contributed to the article and approved the submitted version.

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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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ERAS with or without supplemental artificial nutrition in open pancreatoduodenectomy for cancer. A multicenter, randomized, open labeled trial (RASTA study protocol)

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Purpose: The role of supplemental artificial nutrition in patients perioperatively treated according to enhanced recovery programs (ERAS) on surgery-related morbidity is not known. Therefore, there is a need of a clinical trials specifically designed to explore whether given a full nutritional requirement by parenteral feeding after surgery coupled with oral food "at will" compared to oral food "at will" alone, within an established ERAS program, could achieve a reduction of the morbidity burden.

Materials and analysis: RASTA will be a multicenter, randomized, parallel-arm, open labeled, superiority trial. The trial will be conducted in five Italian Institutions with proven experience in pancreatic surgery and already applying an established ERAS program. Adult patients (age≥18 and<90years of age) candidate to elective open pancreatoduodenectomy (PD) for any periampullary or pancreatic cancer will be randomized to receive a full ERAS protocol that establishes oral food "at will" plus parenteral nutrition (PN) from postoperative day 1 to day 5 (treatment arm), or to ERAS protocol without PN (control arm). The primary endpoint of the trial is the complication burden within 90days after the day of surgery. The complication burden will be assessed by the Comprehensive Complication Index, that incorporates all complications and their severity as defined by the Clavien-Dindo classification, and summarizes postoperative morbidity with a numerical scale ranging from 0 to 100. The H0 hypothesis tested is that he administration of a parenteral nutrition added to the ERAS protocol will not affect the CCI as compared to standard of care (ERAS). The H1 hypothesis is that the administration of a parenteral nutrition added to the ERAS protocol will positively affect the CCI as compared to standard of care (ERAS). The trial has been registered at ClinicalTrials.gov (number: NCT04438447; date: 18/05/2020).

Conclusion: This upcoming trial will permit to establish if early postoperative artificial nutritional support after PD may improve postoperative outcomes compared to oral nutrition alone within an established ERAS program.

KEYWORDS

ERAS, artificial nutrition, outcome, pancreatoduodenectomy, complication, randomized controlled trial

Introduction

The enhanced recovery after surgery (ERAS) program is currently considered the gold-standard pathway for perioperative care in many types of operations (1) including pancreatoduodenectomy (PD) (2). The protocol is a bundle of interventions derived from the best evidence-based perioperative treatments aimed to accelerate patient functional recovery through the reduction of dysmetabolism and dyshomeostasis caused by surgery- and anesthesiology-related injury. In general, the implementation of ERAS generates a reduction of surgery-related complication, duration of hospitalization, and health care-related costs (1).

The intake of adequate qualitative and quantitative nutritional substrates is needed for appropriate tissue healing and recovery/maintenance of organ function after major surgery. To recover gut function and tolerate early postoperative oral feeding, many ERAS elements need to be implemented as they act in synergy (3).

PD is one of the most complex and challenging abdominal operations with a high rate of morbidity (4) and significant catabolic consequences. Moreover, the proportion of patients undergoing PD for cancer are at high nutritional risk or suffer some nutritional derangements at baseline in up to 80% of the cases (5). In addition, delayed gastric emptying (DGE) after PD is frequent (up to 50%) (6) compromising the regular resumption of oral food with the risk of developing postoperative malnutrition.

According to expert opinions (7), artificial nutritional support should be implemented early postoperatively in malnourished patients, in those patients at high risk of developing malnutrition, in those who develop complications affecting oral feeding tolerance, and in well-nourished patients who do not tolerate at least 50% of their caloric and protein requirement by postoperative day 7 for any reason. Accordingly, most of the patients bearing pancreatic cancer and undergoing PD should receive some form of artificial nutritional support after the operation. Conversely, ERAS pathways promote oral food "at will" early after surgery and consider an artificial nutritional support only in selected cases (8). Furthermore, there are no convincing data on whether attaining adequate nutritional needs can be accomplished only by progressive increase of oral food intake. A study reported (9) that, the mean daily calorie and protein intake in the first 2 weeks were similar between the ERAS group and the patients managed conventionally. Anyhow, the results revealed that the total energy goal through oral feeding was not reached in both groups. Other studies did not analyze or reported incomplete data on tolerance to early postoperative oral feeding (EOF) after PD (10, 11). Robertson et al. (12) described compliance rates of 82% for resumption of oral fluids and 86% for tolerance of solid diet. Conversely, in another large study (13), postoperative oral liquids were tolerated by 55% of the patients and solid food in 53%, but compliance dropped substantially in patients with a complicated postoperative course. Thus, the available evidence suggests that using only oral feeding (food "at will") within an ERAS protocol may be only partially adequate to achieve the nutritional needs after PD.

Given the lack of strong evidence, there is a need for a randomized clinical trial specifically designed to explore the extent to which reaching full nutritional requirements by adding parenteral feeding in the first days after surgery within an established ERAS program impacts on postoperative morbidity compared to oral food "at will" alone.

Study design and management

RASTA will be a multicenter, randomized, parallel-arm, open labeled, superiority trial.

The trial will be conducted in five Italian Institutions with proven experience in pancreatic surgery and an established ERAS program.

THE RASTA trial will be managed and coordinated by the School of Medicine and Surgery of the Milano-Bicocca University and the HPB Unit of the IRCCS San Gerardo Hospital, Monza, Italy. The coordinating center will also be responsible for treatment allocation and monitoring, and statistical analysis with the support of the Centre of Biostatistics for Clinical Epidemiology of the Milano-Bicocca University.

The trial has been registered at ClinicalTrials.gov (ID: NCT04438447; date: June 16, 2020) and approved by the Italian Drug Agency (AIFA; number: EudraCT 2020–005483-66; date: September 13, 2021).

Pre-trial training

Before starting patient enrolment, multiple meetings will be organized to accomplish:

- Correct definition of eligibility, inclusion and exclusion criteria.
- Agreement on definition of postoperative complications.
- Training on randomization process and patient instruction on treatment arms.
- Accordance on ERAS elements (described in Table 1).
- Training of outcome assessors to record the occurrence of the primary and secondary endpoints. Each participating center will nominate two independent outcome assessors. The assessors will be trained by the single center principal investigator on the definition of complications during a dedicated pre-trial face-to-face meeting according to a modified Delphi method. In case of

TABLE 1 ERAS items implemented in both groups.

Item	Yes	No
Preoperative counseling	X	
Prehabilitation		X
Preoperative biliary drainage		X
Preoperative stop of smoking and alcohol consumption	X	
Preoperative nutrition		X
Perioperative oral immunonutrition		X
Preoperative fasting		X
Preoperative carbohydrate loading	X	
Pre-anesthetic medication		X
Anti-thrombotic prophylaxis	X	
Antimicrobial prophylaxis and skin preparation	X	
Epidural analgesia	X	
Opioid-sparing analgesia	X	
Wound catheter and transversus abdominis plane block	X	
Minimal invasive surgery		X
Nausea and vomiting prophylaxis	X	
Avoiding hypothermia	X	
Nasogastric intubation		X
Goal-directed fluid therapy	X	
Perianastomotic drainage	X	
Somatostatin analogues		X
Postoperative multimodal analgesia	X	
Postoperative glycemic control	X	
Urinary drainage early removal	X	
Stimulation of bowel movement		X
Early and scheduled mobilization	X	
Audit	X	

discordance on the assignment of the endpoint, a third expert will intervene to solve the dispute and classify the patients as complicated or not. Outcome assessors will be blinded to treatments.

- Training on how to fill out correctly the case report form.

Patient eligibility

Adult patients (age $\geq$ 18 and $<$ 90 years of age) scheduled for elective open pancreatoduodenectomy for any periampullary or pancreatic cancer.

Inclusion criteria

- Patients must be willing to participate in the study and able to provide written informed consent form prior to any study activity.
- Preoperative normal renal function, blood electrolytes (sodium, potassium, chlorite) and coagulation tests (PT, PTT).

Exclusion criteria

- American Society of Anesthesiologists (ASA) physical status classification >3
- Preoperative severe malnutrition (Weight loss >15% with respect to usual weight in the last 6 months, according to the new GLIM criteria) (14).
- Ascites
- Any proven hypersensitivity reaction to parenteral nutrition (PN) components
- Palliative surgery
- Early postoperative administration of enteral nutrition *via* a naso-enteric or jejunostomy feeding tube placed during surgery.

Screening and randomization processes

After being screened for inclusion and exclusion criteria, patients or their legal representative will be asked to sign a written informed consent. After enrolment in the study, patients will be randomly allocated into two arms. All reasons for exclusion after screening will be recorded.

Patients will be randomly allocated to ERAS or ERAS plus PN at 8:00 PM of the day of surgery, or at 8 AM in the morning of postoperative day one if the operation was concluded after 8 PM. Randomization will be performed by a computed-generated permuted-block sequence. A specific code will be generated for each center to achieve equivalent grouping. The allocation ratio will be 1:1 with a block size of 4. Randomization will be stratified by neoadjuvant chemo- or chemoradiation therapy and center. Randomization will be competitive among centers.

Surgeons and patients will not be blinded to treatment arm. Masking to allocation will be impossible to achieve for the study nature and design.

Patient chart evaluation and data entry for outcome recording will be done by trained assessors (selected in each center) and not directly involved in patient care and thus masked to patient allocation. Clear information on patient allocation will not be released to any hospital personnel with exception of ethical committee members under specific request.

Study duration and definition of termination

The expected duration of enrolment is approximately 2 years.

The study will be considered as terminated when the last enrolled patient will have completed the 90-day follow-up after the date of surgery.

Study intervention

Patients randomized in the treatment arm will be treated with a full ERAS protocol that establishes oral food "at will" plus parenteral nutrition (PN) from postoperative day 1. A ready-to-use, all-in-one, 3-bag compartment peripheral parenteral solution (mOsm <800) (Olimel N4E®, Baxter Italia, SpA) containing carbohydrate, lipids and proteins will be infused to deliver 20/25 total Kcal/kg/day for a total of 5 days after the operation with the addition of I.V. supplementation of vitamins (one vial/day) (Cernevit®, Baxter Italia SpA).

In case of occurrence of any complication impairing the full or partial recovery of oral food, the treatment will be continued or switched to tube enteral feeding until clinically indicated.

Administration of parenteral nutrition will be through a peripheral vein with a rate of delivery that is calculated based on patient body weight. The total volume of parenteral nutrition will be the result of the calculation of the amount of prescribed calories, multiplied for the patient body weight.

Control arm

Patients randomized in the control arm will be treated with a full ERAS protocol that establishes oral food "at will" after the operation. In case of occurrence of any complication impairing the full recovery of oral food within postoperative day 5, patients may receive parenteral or enteral nutrition as clinically indicated.

Procedures common to both arms

Patients of both groups will be treated according to the ERAS Society guidelines for perioperative care for PD (Table 1) (8). Blood glucose ≥180 mg/dl will be treated with insulin injection (either subcutaneous or by continuous IV infusion). Open PD technique will be chosen by the participating centers according to their standards.

Study plan

Study plan and schedule of assessment are summarized in Table 2.

Ethical aspects

The study has been approved by the Competent Authority (AIFA) the Ethical Committee of all participating centers. The local Ethical Committee, as coordinating center, provided the "not emendable judgement" according to the Italian legislation (approval number: 3467; date: February 11, 2022).

Outcomes

The primary endpoint of the trial is the complication burden within 90 days after surgery. The complication burden will be assessed by the Comprehensive Complication Index (CCI) (15), that incorporates all complications and their severity as defined by the Clavien-Dindo classification, and summarizes postoperative morbidity with a numerical scale ranging from 0 (no complication) to 100 (death).

Hypothesis tested

H0 hypothesis

The administration of a parenteral nutrition added to the ERAS protocol will not affect the CCI as compared to standard of care (ERAS).

H1 hypothesis

The administration of a parenteral nutrition added to the ERAS protocol will positively affect the CCI as compared to standard of care (ERAS).

Secondary outcome measures will be:

- Actual daily calories delivered by PN.
- Rate of unplanned artificial nutrition (for control group).
- Rate and severity of complications at 90 days after discharge.
- Rate of surgical site infections (16)
- The rate and severity of postoperative pancreatic fistula (17)
- Rate and severity of DGE (18)
- Rate and severity of hemorrhage (19)
- Length of stay (LOS) based on predefined criteria
- Actual LOS
- Rate of reoperation.
- Rate and duration of intensive care treatment.
- Rate of hyperglycemia (blood glucose >180 mg/dl)
- Use of insulin (subcutaneous bolus or continuous infusion)
- Δ plasma prealbumin levels (baseline, postoperative day 1 and 6)
- Use of morphine
- Readmission rate
- Body weight (90 days)
- 90-day mortality

Any attending surgeon will decide the day of discharge according to his individual clinical judgement. However, LOS will be also calculated by the achievement of pre-specified discharge criteria (full patient mobilization, pain controlled by oral therapy, full tolerance to oral feeding). In particular, a visual analog pain scale ≤2 must be achieved for safety discharge.

Post-discharge follow-up will be accomplished by weekly outpatient visits. Also telephone interviews will be allowed to monitor patient health state, but in case of warning signs or symptoms of a complication, patients will be asked to refer to the hospital where the operation was performed for further clinical evaluation.

Safety issue

Adverse events:

- the number of patients not reaching tolerance to oral feeding within 7 days after surgery
- the number of patients needing insulin therapy.
- the number of patients requiring electrolyte corrections.

TABLE 2 Study plan and schedule of assessment.

Visit	V pre	V1	V2		V3	V4	In hosp FU	Dis	FU
Time interval	Pre random	Basal at random	Intraoperative	Day 1	Day 3	Day 5	Once a day during index hospitalization	Discharge	3-mo. follow-up (from the day of surgery)
Informed consent	X								
Demographics	X								
Height	X								
Weight	X							X	X
Body mass index	X								
Physical examination (every day until discharge)	X			X	X	X	X	X	X
Patient history	X								
Inclusion criteria		X							
Exclusion criteria		X							
Blood pressure		X	X		X	X	X		
Heart rate		X	X		X	X	X		
ECG		X							
ICU admission							X		
Lab tests*		X		X	X	X	X	X	
Need of insulin			X	X	X	X	X	X	X
NRS-2002		X							
Death			X	X	X	X	X	X	X
Safety endpoints				X	X	X	X	X	X
Blood loss			X						
Duration of surgery			X						
Surgical details			X						
Fluid balance			X	X	X	X	X		
Histology			X					X	
Analgesia			X	X	X	X		X	
Discharge criteria						X	X		
Complications (CCI)				X	X	X	X	X	X
Drug administration (DAY 1-5)				X	X	X			

*Urea, Creatinine, Complete blood count, PT, PTT, Glucose, Na, K, Cl, prealbumin, albumin, glycate haemoglobin, bilirubin, CRP.

Statistical planning

The sample size of 120 patients per group is necessary to provide an 80% power to detect at least a 30% reduction in the CCI, which is expected to be around 23 (median) (IQR 21–31) or mean 27 (±20 SD) in complicated patients of the control group. The hypothesized reduction of 30% is based on sound clinical relevance meaning that such reduction will have a consistent and significant impact of the postoperative course with advantages on well-being, quality of life, shorter length of hospitalization and a relevant reduction of heath care burden and resources. The median CCI of 23 is retrieved from a previous publication (20). The rate of complication in this type of surgery is expected to be approximately of 60%.

A Mann–Whitney test is considered, type I error rate is fixed at 5% (two tails) and an expected drop-out of 10% is taken into account.

For the binary end-points, the relative risk (RR) with the corresponding 95% confidence interval, comparing the two groups, will be estimated. For the primary end-point, also the risk difference (RD) will be computed. For the numerical end-points

the difference in the location parameter (i.e., median pairwise difference) between the two groups with the corresponding 95% confidence interval will be computed. Fisher test and Mann–Whitney test will be adopted to evaluate univariate associations. Incidence of complications over time in the two groups will be described according to the Nelson-Aalen cumulative hazard estimator also accounting for multiple events per patient. The incidence in the two groups will also be compared by computing the incidence rate ratio (with 95% confidence interval). This analysis will be performed both considering all complications and only major complications.

A multivariate quantile regression model (focused on median, 25th and 75th percentiles) will be used to identify factors associated with the primary endpoint and to evaluate the effect of treatment adjusting for possible residual confounding. Logistic regression will also be used to model the probability of CCI >23. Using these regression models, the effect of PN over controls on the CCI will be also investigated within pre-specified subgroups to account for possible effect modification. The pre-specified risk factors for this analysis will be:

- Nutritional risk screeing-2002 (≥3)
- Body mass index (> 30)
- Sex (male)
- Age (>70 years)
- Charlson comorbidity index (>4)
- ASA score (=3)
- Blood loss (≥500 mL)
- Duration of surgery (>360 min)
- Biliary stenting
- Diabetes
- Pylorus-preserving PD (vs. Whipple)
- Pancreatic ductal carcinoma (vs. others)
- Fistula risk score (≥7)
- ERAS overall compliance (>70%)

All analyses will be done based on the principles of "intention-to-treat" and "per-protocol" and performed with the R software.

Study stopping rules

An ad interim analysis will be done at the achievement of 50% of the study power (120 patients in total). The study will be stopped only in case of an increase over 30% of the median CCI in either groups. Study will be stopped immediately in case death or, a life-threatening experience (that is, immediate risk of dying) related to the use of PN, or a persistent or significant disability/incapacity will exceed 5% of the enrolled population. A Data and Safety Monitoring Board will oversee and monitor the trial to ensure participant safety and the validity and integrity of the data.

Data collection and management

All data will be collected into an electronic database with a double entry to assure consistency of records. In case of missing or implausible data, queries will be mailed to the participating centers to obtain integrations or corrections. Data collectors will be blinded to allocation.

The patient first and last name and date of birth will be omitted according to the Italian legislation on privacy. Subject identification will be carried out only by the randomization code.

All data will be collected into a dedicated excel spreadsheet. This electronic registry will be identical for all centers and each center will have their own dataset. The excel spreadsheet will be protected by a password possessed by the assessor.

Case report form

The following baseline patient-related parameters will be recorded:

- Age (years)
- Sex
- Weight (kg)
- Height (m)
- Body mass index (kg/m^2)
- Nutritional risk score-2002
- Percent of weight loss in the 6 months prior to surgery
- Charlson comorbidity index
- Diabetes
- Jaundice
- Biliary stenting
- Routine laboratory test (albumin, preabumin, bilirubin, hemoglobin, creatinine, HbA1c, CRP)
- Primary disease with indication to surgical resection
- ASA score
- Neoadjuvant treatments

The following intraoperative parameters and events will be recorded:

- The day of operation
- Type of surgical procedure (PPPD, Whipple)
- Type of pancreatic anastomosis (gastric, jejunal)
- The level of intraoperative contamination (clean; clean-contaminated; contaminated; dirty)
- Use of epidural analgesia, TAP block, subfascial catheter
- Intraoperative hypothermia (defined as body temperature < 35.5°C for more than 30 min)
- Estimated blood loss (mL)
- Volume of IV fluid infusion
- Intraoperative blood transfusion
- Fluid balance (in and out difference)
- Duration of operation (minute)
- Main pancreatic duct diameter
- Pancreas texture (soft, intermediate, hard)
- Fistula risk score

After the operation the following parameters and events will be recorded:

- Capillary blood glucose levels (every 6 h for 5 consecutive days)
- Any administration of insulin (for blood glucose ≥180 mg/dL)

- Occurrence of a complication (90-days)
- Type of complication
- The complication burden according to CCI (90-day)
- The severity of complication according to Clavien-Dindo classification
- The need of reoperation, reason and postoperative day
- The need of unplanned intensive care treatment and the duration (days)
- The day of canalization to gas and stools
- The day of resumption of oral feeding
- The need and duration of artificial nutrition (for the control arm)
- Potential hospital discharge according to predefined criteria
- The actual day of hospital discharge
- Disease staging
- Readmission rate (30-day)
- Mortality rate (90-day)

Discussion

The use, timing of initiation, and route of delivery of artificial nutrition after PD is still a matter of debate for the conflicting evidence and the difference in study design. One randomized trial, showed that in patients submitted to PD and kept "nil by mouth" for 10 days after the operation, immediate parenteral feeding was associated with less complications when compared to progressive tube enteral nutrition (21) suggesting that the achievement of an immediate and full nutritional goal may be protective on the risk of morbidity. One systematic review (22) compared the outcomes of 5 feeding routes after PD and reported no difference in terms of safety and efficacy. A recent meta-analysis by Tanaka et al. (23) advocated that routine enteral nutrition after PD was associated with a lower incidence of infectious complications and a shorter length of hospital stay than non-enteral nutrition. Percutaneous tube feeding had a lower incidence of infectious complications and a shorter hospital stay than parenteral nutrition whereas naso-jejunal tube feeding was not associated with better postoperative outcomes. Thus, the authors concluded that as a supplement to regular oral diet, routine enteral nutrition, especially *via* a percutaneous enteral tube, may improve postoperative outcomes after PD.

The results of another randomized controlled trial (RCT) (24) on patients who underwent pylorus-preserving PD suggested additional early tube enteral nutrition did not affect the frequency of DGE and did not offer any further clinical advantages over early oral feeding. However, in persisting DGE, better outcomes were achieved when artificial nutrition, either parenteral or enteral, was started within 10 days of operation (25).

After the development of a clinically relevant pancreatic fistula, the use of enteral tube feeding was not superior to oral nutrition in terms of 30-day fistula closure rate. Compared with enteral feeding, oral feeding significantly reduced hospital costs and duration of stay (26).

Despite not specifically designed for patients undergoing PD, two recent large RCTs provided conflicting results on the need of early artificial nutritional support after major abdominal surgery. Zhang et al. (27) randomized patients at high nutritional risk, to immediate vs. gradual advancement to goal of enteral tube nutrition. The first group received 100% of the caloric requirement on postoperative day 3, while the other received 40% progressing to 80% of target on day 7. The results showed that immediate enteral feeding was non-inferior to gradual advancement in regards to infectious complications. However, immediate feeding was associated with more gastrointestinal intolerance events. The other trial (28) randomized 230 patients at high nutritional risk and poor tolerance to tube enteral nutrition, to receive supplemental PN early (on day 3) or late (on day 8) after surgery. The early group had significantly fewer nosocomial infections compared with the late group (8.7% vs. 18.4%; $p = 0.04$). No significant differences were found between the early and late group in the number of noninfectious complications. The authors concluded that early supplemental PN appeared a favorable strategy for patients with high nutritional risk and poor tolerance to EN.

In 2022, Joliat et al. (29) published the protocol of a multicenter, open-label, RCT for patients undergoing PD with a nutritional risk screening ≥ 3 in a setting of full ERAS strategy. Patients will be randomized to receive either early enteral nutrition (intervention group) or oral nutrition (control group) after the operation. Patients in the intervention group will receive tube enteral nutrition since the first night of the operation and the infusion will be increased daily if tolerated. The primary outcome will be the CCI at 90 days after surgery.

Differently from the above study design, we opted for parenteral nutrition instead of enteral tube feeding. The rational of giving parenteral feeding has been based on the ability of this therapy to provide the exact amount of calories and protein since the very beginning of administration. As opposite, tube enteral nutrition needs at least 4/5 days to reach the caloric target or even more depending on tolerance (30).

These two upcoming trials will allow to establish if early postoperative artificial nutritional support after PD may improve postoperative outcomes compared to oral nutrition alone within an established ERAS program. Moreover, the results might be useful for a potential updated version of the International Study Group on Pancreatic Surgery recommendations (7) on nutritional therapy in pancreatic surgery.

Ethics statement

The studies involving human participants were reviewed and approved by Monza e Brianza ethical committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent will be obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

LG, SP, MS, IF, NP, GC, and DPB contributed to conception, design of the study, and wrote sections of the manuscript. LG, SP, and

MS organized the database. DPB will perform the statistical analysis. LG wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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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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Neutrophil-to-high-density-lipoprotein-cholesterol ratio and mortality among patients with hepatocellular carcinoma

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Background: Inflammatory responses and lipid metabolism disorders contribute to the development and prognosis of hepatocellular carcinoma (HCC). This study aimed to investigate the prognostic value of lipid-related inflammatory parameters in patients with HCC.

Methods: From January 2010 to June 2017, we enrolled 1,639 patients with HCC at Beijing Ditan Hospital. Multivariate Cox regression analysis and area under the receiver operating characteristic (AUC) analysis were used to evaluate and compare the predictability and reliability of high-density lipoprotein cholesterol (HDL-C), neutrophil-to-HDL-C ratio (NHR), monocyte-to-HDL-C ratio (MHR), and lymphocyte-to-HDL-C ratio (LHR) values. A restricted cubic spline was used to explore the association between the NHR and 3-year mortality in patients with HCC. Differences in survival rates were estimated using the Kaplan–Meier method and compared using the log-rank test. The results were validated in an internal cohort between July 2017 and October 2019 (n=373).

Results: After adjusting for confounding variables, NHR was independently associated with 3-year mortality, both as a continuous and categorical variable (both p<0.05). The correlation between the mortality and the MHR and LHR was not statistically significant. The NHR showed a suitable prognostic value (AUC at 3 years: 0.740), similar to that of the Model for End-stage Liver Disease (MELD) (AUC at 3 years: 0.761). In the validation cohort, the AUC of the NHR was 0.734 at 3 years. The optimal cut-off values of NHR and MELD were 3.5 and 9, respectively. The 3-year survival rates in the low- (NHR<3.5 and MELD <9) and high-risk (NHR≥3.5 and MELD ≥9) groups were 81.8 and 19.4%, respectively, in the training cohort, and 84.6 and 27.5%, respectively, in the validation cohort.

Conclusion: Baseline NHR is a promising prognostic parameter for mortality in patients with HCC and patients with NHR≥3.5 and MELD ≥9 have a high mortality rate.

KEYWORDS

hepatocellular carcinoma, dyslipidemia, high-density lipoprotein cholesterol, inflammation, prognosis

Introduction

Hepatitis B virus (HBV) is a global public health problem and a major cause of hepatocellular carcinoma (HCC), causing approximately 200 million infected (1, 2). HCC is one of the most commonly occurring cancer and a common cause of cancer-associated mortality, accounting for 782,000 deaths worldwide every year (3). Despite substantial improvements in the treatment of HCC, the prognosis of HCC remains poor owing to a high recurrence rate (4). Given the increasing incidence and high mortality rate of HCC, early identification of the mortality risk of HCC is important to improve therapeutic intervention and long-term prognosis.

The inflammatory response plays an important role in the development and progression of HCC (5). Previous studies have shown that the neutrophil-to-lymphocyte ratio has a good prognostic value for HCC (6, 7). Recent studies have suggested that high-density lipoprotein cholesterol (HDL-C) exerts anti-inflammatory, anti-oxidation, and anti-apoptotic functions (8, 9). Decreased HDL-C levels were proven to be correlated with poor prognosis in several diseases (10–12). The neutrophil-to-HDL-C ratio (NHR), monocyte-to-HDL-C ratio (MHR), and lymphocyte-to-HDL-C ratio (LHR) have emerged as prognostic markers in cardiovascular events, diabetes, nerve diseases, and metabolic syndrome (13–17). However, research on the prognostic potential of these markers for mortality in patients with HCC is limited. Therefore, clarification on the reliability of these markers as prognostic biomarkers of HCC is necessary. In addition, the lack of consistent cutoff points for prognostic markers makes it difficult to distinguish between low-and high-risk mortality.

Patients with type 2 diabetes mellitus have an increased mortality risk due to HCC, in which inflammation and lipid metabolism disorders play important roles (18). Previous reports suggested that patients with diabetes have impaired HDL function and decreased HDL levels (19, 20). Therefore, the utility of lipid-related inflammatory markers in patients with diabetes is worth exploring.

Accordingly, we aimed to evaluate the association between the NHR, MHR, and LHR and mortality in patients with HCC using Cox regression analyses, identify high-risk populations using the Kaplan–Meier method, and conduct an early intervention to reduce mortality.

Materials and methods

Study population

We screened 2,490 patients diagnosed with HCC between January 2010 and June 2017 at Beijing Ditan Hospital, Capital Medical University. Patients aged between 18 and 75 years diagnosed with HBV-related HCC were recruited for this study. The exclusion criteria were as follows: (1) age <18 or >75 years, (2) presence of other types of tumors or liver transplantation, (3) other viral infections or human immunodeficiency virus infection, (4) incomplete clinical data, and (5) lost of follow-up within 1 year. As per these criteria, 1,639 patients were finally enrolled in the study. We also included 373 patients as an internal validation cohort between July 2017 and October 2019 (Figure 1). This study followed the ethical principles of the Declaration of Helsinki and approval was obtained from the Ethical Review Committee of the Beijing Ditan Hospital.

Clinical definition and follow-up

Chronic hepatitis B was defined as HBsAg positivity for >6 months (21). The diagnosis of cirrhosis was based on evidence from liver biopsy, endoscopy, ultrasound, or elastography, and/or signs of complications associated with portal hypertension (22). HCC diagnosis was as per the criteria of the Asia-Pacific clinical guidelines (23). Every 3 months, routine laboratory tests [including routine blood examination, liver, renal, coagulation function tests, HBV DNA, and alpha-fetoprotein (AFP)] and radiological examination, such as computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound were performed. The outcome was the occurrence of mortality within 3 years or at the end of the 3 years follow-up period.

Data collection

Baseline demographic characteristics and laboratory data, including age, sex, hypertension, diabetes, smoking history, alcohol consumption history, complications, liver function, renal function, coagulation function, serum lipid level, and AFP level, were collected from electronic medical records at enrollment. In addition, tumor characteristics, such as tumor number, size, vascular invasion, and tumor metastasis, were recorded based on the imaging data at baseline. NHR was calculated as the neutrophil count divided by the HDL-C value, while MHR as the monocyte count divided by the HDL-C value, and LHR as the lymphocyte count divided by the HDL-C value. The model for end-stage liver disease (MELD) was used to estimate the severity of the liver disease (24).

Statistical analysis

SPSS (version 25.0; SPSS, Inc., Chicago, IL, United States) and R (version 3.6.3; The R Foundation, Vienna, Austria) software were used for the statistical analyses. Continuous variables were reported as mean ± standard deviation or median with interquartile range (IQR), while categorical variables were reported as frequency (percentage). Continuous variables were compared using Student's *t*-test or the Mann–Whitney test; the chi–squared test or Fisher's exact test was used for two groups, as appropriate. Univariate and multivariate Cox regression analyses were used to assess the association between the HDL-C, NHR, MHR, LHR (continuous and tertile), and mortality. Results were considered statistically significant at p-value <0.05.

The predictive value of lipid-related inflammatory markers was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The prognostic power of these indicators was compared with that of the MELD score at 1, 2, and 3 years using the Delong test (25). The association between the NHR and 3-year mortality were evaluated on a continuous scale using a restricted cubic spline (RCS) with four knots at the 5th, 35th, 65th, and 95th percentiles and to test for nonlinearity (26). The optimal cut-off values were determined for the NHR and MELD scores for mortality using the X-tile software (Yale University School of Medicine, New

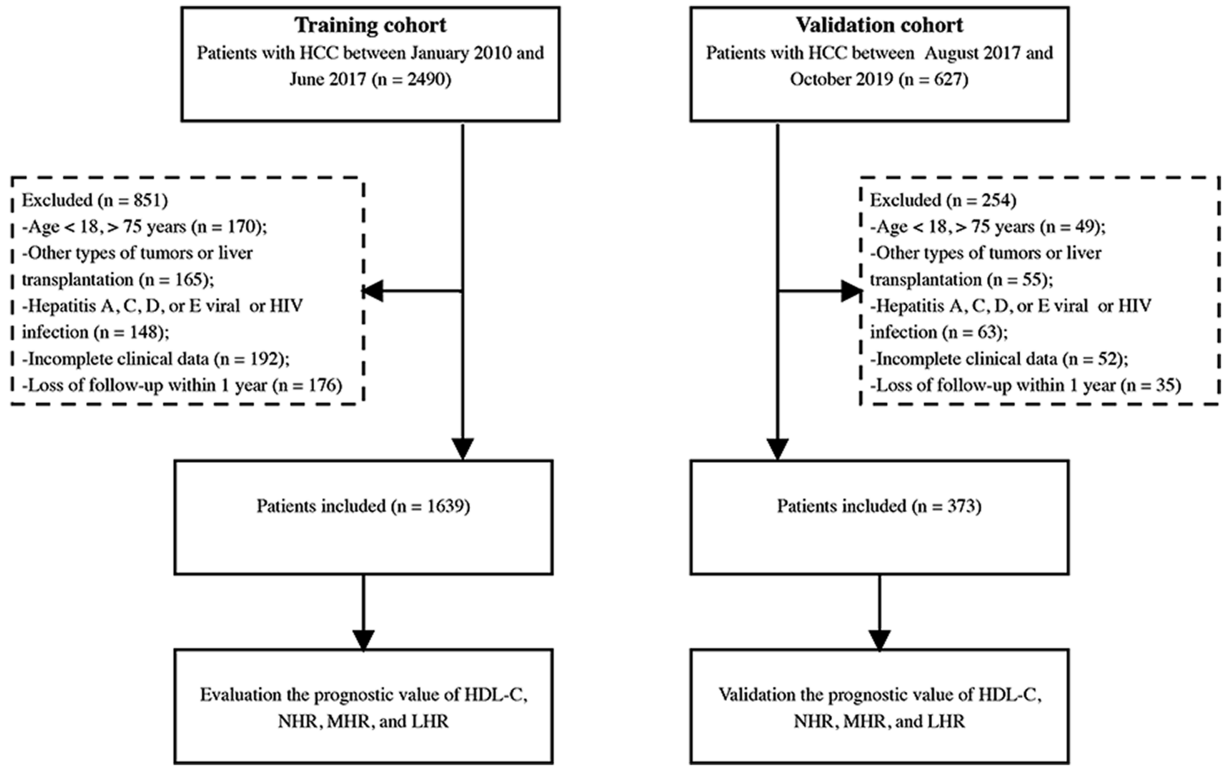

FIGURE 1
Study flow diagram. HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; HDL-C, high-density lipoprotein cholesterol; NHR, neutrophil to HDL-C ratio; MHR, monocyte to HDL-C ratio; LHR, lymphocyte to HDL-C ratio.

Haven, CT, United States). Differences in survival rates among the groups were analyzed using Kaplan–Meier curves and compared using log-rank tests.

Results

Baseline characteristics

A total of 1,639 and 373 patients in the training and validation cohorts, respectively, were included in the analysis. Baseline characteristics and laboratory data of the patients are shown in Table 1. The median age of the training cohort was 57.0 years (IQR, 50.0–63.0), with male predominance ($n = 1{,}563$, 77.6%). Of those patients, 181 (9.0%) patients underwent liver resection, 1,358 (67.5%) underwent minimally invasive therapy, whereas 473 (23.5%) received palliative therapy. Of the 1,639 patients in the training cohort, 1,563 patients (77.6%) were male and 1,306 patients (79.6%) were diagnosed with cirrhosis. During the 3-year follow-up period, 666 patients (40.6%) and 138 patients (37.0%) died in the training and validation cohorts, respectively. Overall, the patients in the two cohorts were similar when their baseline characteristics were considered.

Furthermore, we compared the survival and death characteristics of patients in the training cohort (Table 2). Patients who died were older, had a higher proportion of diabetes, tumor size ≥5 cm, AFP ≥ 400 ng/mL, higher total bilirubin (TBIL), γ-glutamyl transferase (GGT), creatinine (Cr), and international prothrombin ratio (INR), and lower albumin levels (all $p < 0.001$) than those who survived. Regarding inflammation and lipid-related markers, dead patients had higher levels of neutrophils, monocytes, NHR, MHR, and LHR, and lower levels of lymphocytes, total cholesterol (TC), and HDL-C compared with the patients who survived.

Associations of biomarkers with prognosis in patients

Univariate analysis showed that low HDL-C, high NHR, MHR, and LHR levels significantly increased the risk of 3-year mortality as both continuous and categorical variables (all $p < 0.001$; Table 3). In addition, univariate analysis indicated that age, sex, diabetes, alcohol consumption, alanine aminotransferase, aspartate aminotransferase, platelet count, alpha-fetoprotein, total cholesterol, Child-Pugh class, MELD score, Barcelona Clinic Liver Cancer (BCLC) stage, tumor size, and type of treatment were significantly associated with the 3-year mortality (all $p < 0.05$). These significant factors were included in the multivariate Cox regression analysis. After adjustment for confounding variables, these significant associations were found with low HDL-C (aHR, 0.31; 95% CI: 0.23–0.41, $p < 0.001$) and high NHR levels (aHR, 1.02; 95% CI: 1.01–1.03, $p < 0.001$) as continuous variables. However, the association of 3-year mortality with LHR and MHR was attenuated.

TABLE 1 Baseline demographics and clinical characteristics of patients with HCC in the training and validation cohorts.

	Total (*n* =2012)	Training cohort (*n* =1,639)	Validation cohort (*n* =373)	*p*-value
Patients background				
Age (year)	57.0 (50.0, 63.0)	56.0 (50.0, 63.0)	57.0 (50.0, 62.0)	0.402
Sex (male)	1,563 (77.6)	1,289 (78.6)	274 (73.4)	0.292
Family history of HCC	198 (9.8)	165 (10.1)	33 (8.8)	0.511
Cirrhosis	1,661 (82.6)	1,306 (79.6)	301 (80.6)	0.659
Smoking	895 (44.5)	747 (45.6)	148 (39.7)	0.054
Alcohol consumption	876 (43.5)	735 (44.8)	141 (37.8)	0.052
Hypertension	532 (26.4)	435 (26.5)	97 (26.0)	0.895
Diabetes	455 (22.6)	374 (22.8)	81 (21.7)	0.719
Laboratory parameters				
HBeAg (positive)	620 (30.8)	504 (30.7)	116 (31.1)	0.369
MELD score	8.8 (7.0, 11.9)	8.8 (7.0, 11.9)	8.7 (7.0, 10.9)	0.135
ALT (U/L)	32.4 (21.6, 53.8)	32.0 (21.2, 52.4)	34.7 (22.7, 58.6)	0.091
AST (U/L)	39.1 (26.6, 71.1)	39.1 (26.5, 70.4)	38.9 (27.7, 75.7)	0.098
TBIL (μmol/L)	19.5 (12.8, 33.1)	19.8 (12.8, 34.3)	18.7 (13.0, 32.4)	0.697
ALB (g/L)	36.1 ± 6.8	35.6 ± 6.7	36.8 ± 6.9	0.136
γ-GGT (U/L)	58.4 (27.0, 129.6)	58.3 (27.6, 129.1)	61.3 (28.4, 132.4)	0.486
PLT ($\times10^9$/L)	97.9 (63.3, 148.0)	96.2 (62.4, 147.3)	104.7 (64.5, 151.3)	0.169
INR	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)	1.1 (1.0, 1.2)	0.190
Cr (μmol/L)	67.0 (58.0, 78.2)	67.0 (58.0, 78.0)	66.6 (57.5, 78.6)	0.647
AFP (ng/mL) (≥400)	498 (24.7)	396 (24.1)	102 (27.3)	0.198
Neutrophils ($\times10^9$/L)	2.7 (1.8, 4.0)	2.6 (1.8, 4.0)	2.8 (1.8, 4.1)	0.741
Lymphocytes ($\times10^9$/L)	1.1 (0.8, 1.6)	1.1 (0.8, 1.6)	1.1 (0.7, 1.6)	0.645
Monocytes ($\times10^9$/L)	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.292
TC (mmol/L)	3.7 (3.1, 4.3)	3.6 (3.0, 4.3)	3.7 (3.2, 4.4)	0.798
TG (mmol/L)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.9 (0.6, 1.1)	0.536
HDL-C (mmol/L)	1.0 (0.7, 1.2)	1.0 (0.6, 1.2)	1.0 (0.8, 1.3)	0.526
LDL-C (mmol/L)	2.0 (1.7, 2.6)	2.0 (1.6, 2.6)	1.9 (1.6, 2.7)	0.199
NHR	2.7 (1.6, 4.8)	2.8 (1.6, 5.0)	2.5 (1.6, 4.4)	0.276
MHR	0.4 (0.2, 0.6)	0.4 (0.3, 0.6)	0.3 (0.2, 0.5)	0.301
LHR	1.2 (0.8, 1.8)	1.2 (0.8, 1.6)	1.1 (0.7, 1.8)	0.321
Child Pugh class				0.426
A	1,077 (53.5)	882 (53.8)	195 (52.3)	
B	558 (27.7)	456 (27.8)	102 (27.3)	
C	377 (18.8)	301 (18.4)	76 (20.4)	
Tumor–related indicators				
Tumor multiplicity (multiple)	937 (46.5)	753 (45.9)	184 (49.3)	0.237
Tumor size, cm (≥5)	670 (33.3)	555 (33.9)	115 (30.8)	0.291
BCLC stage				0.517
0–A	687 (34.1)	564 (34.4)	123 (33.0)	
B	669 (33.3)	539 (32.9)	130 (34.8)	
C	364 (18.1)	292 (17.8)	72 (19.3)	
D	292 (14.5)	244 (14.9)	48 (12.9)	

(Continued)

TABLE 1 (Continued)

	Total (*n* =2012)	Training cohort (*n* =1,639)	Validation cohort (*n* =373)	*p*-value
Types of treatment				0.108
Resection	181 (9.0)	151 (9.2)	30 (8.0)	
Minimally invasive	1,358 (67.5)	1,125 (68.7)	233 (62.5)	
Palliative	473 (23.5)	363 (22.1)	110 (29.5)	

TABLE 2 Baseline characteristics of survival and death patients in the training cohort.

	Survived (*n* =973)	Death (*n* =666)	*p*-value
Patients background			
Age (year)	56.0 (50.0, 62.0)	57.0 (50.0, 64.0)	0.054
Sex (male)	754 (77.5)	535 (80.3)	0.169
Family history of HCC	106 (10.9)	55 (8.8)	0.236
Cirrhosis	775 (79.6)	531 (79.7)	0.182
Smoking	432 (44.4)	315 (47.3)	0.251
Alcohol consumption	415 (42.6)	320 (48.0)	0.027
Hypertension	244 (25.1)	191 (28.7)	0.104
Diabetes	195 (20.0)	179 (26.9)	0.001
Laboratory parameters			
HBeAg (positive)	308 (31.6)	196 (29.4)	0.241
MELD score	7.7 (6.7, 9.7)	11.3 (8.6, 15.7)	<0.001
ALT (U/L)	28.9 (19.9, 44.3)	38.6 (23.8, 64.0)	0.002
AST (U/L)	30.7 (23.1, 48.1)	62.2 (38.4, 121.1)	<0.001
TBIL (μmol/L)	16.2 (11.3, 24.4)	30.4 (17.3, 56.8)	<0.001
ALB (g/L)	37.7 ± 6.3	32.6 ± 6.3	<0.001
γ-GGT (U/L)	40.8 (23.4, 81.2)	121.0 (51.5, 231.9)	<0.001
PLT ($\times10^9$/L)	92.2 (60.3, 142.0)	101.4 (64.0, 157.8)	<0.001
INR	1.1 (1.0, 1.2)	1.2 (1.1, 1.4)	<0.001
Cr (μmol/L)	67.0 (58.0, 76.7)	68.0 (58.0, 81.8)	<0.001
AFP (ng/mL) (≥400)	124 (12.7)	272 (40.8)	<0.001
Neutrophils ($\times10^9$/L)	2.3 (1.6, 3.2)	3.4 (2.2,5.2)	<0.001
Lymphocytes ($\times10^9$/L)	1.2 (0.8, 1.7)	0.9 (0.7, 1.3)	<0.001
Monocytes ($\times10^9$/L)	0.4 (0.3, 0.5)	0.5 (0.3, 0.7)	0.011
TC (mmol/L)	3.7 (3.2, 4.3)	3.4 (2.8, 4.2)	0.029
TG (mmol/L)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	0.376
HDL-C (mmol/L)	1.0 (0.9, 1.3)	0.8 (0.5, 1.1)	0.004
LDL-C (mmol/L)	2.0 (1.6, 2.6)	2.0 (1.5, 2.7)	0.140
NHR	2.2 (1.4, 3.5)	4.3 (2.3, 9.5)	<0.001
MHR	0.3 (0.2, 0.5)	0.5 (0.3,1.0)	0.011
LHR	1.2 (0.7, 1.7)	1.3 (0.8, 2.2)	<0.001
Child Pugh class			<0.001
A	712 (73.2)	170 (25.5)	
B	203 (20.9)	253 (38.0)	
C	58 (5.9)	243 (36.5)	

(Continued)

TABLE 2 (Continued)

	Survived (*n* =973)	Death (*n* =666)	*p*-value
Tumor–related indicators			
Tumor multiplicity (multiple)	303 (31.1)	450 (67.5)	<0.001
Tumor size, cm (≥ 5)	212 (21.8)	323 (48.4)	<0.001
BCLC stage			<0.001
0–A	498 (51.2)	66 (9.9)	
B	404 (41.5)	135 (20.3)	
C	34 (3.5)	258 (38.7)	
D	37 (3.8)	207 (31.1)	
Types of treatment			<0.001
Resection	138 (14.2)	13 (1.9)	
Minimally invasive	817 (84.0)	308 (46.2)	
Palliative	18 (1.8)	345 (51.8)	

HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALB, albumin; GGT, γ-glutamyl transferase; PLT, platelet count; Cr, creatinine; INR, international normalized ratio; AFP, alpha-fetoprotein; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NHR, neutrophil to HDL-C ratio; MHR, monocyte to HDL-C ratio; LHR, lymphocyte to HDL-C ratio; BCLC, Barcelona Clinic Liver Cancer.

TABLE 3 Univariate and multivariate Cox hazards analysis for 3-year mortality among patients with HCC.

Variable	Univariate HR (95%CI)	*p*-value	Adjusted HR* (95%CI)	*p*-value
HDL-C	0.13 (0.10–0.17)	<0.001	0.31 (0.23–0.41)	<0.001
Q1	Reference		Reference	
Q2	0.21 (0.18–0.25)	<0.001	0.46 (0.37–0.57)	<0.001
Q3	0.21 (0.16–0.26)	<0.001	0.38 (0.28–0.51)	<0.001
NHR	1.04 (1.03–1.05)	<0.001	1.02 (1.01–1.03)	<0.001
Q1	Reference		Reference	
Q2	2.33 (2.05–2.65)	0.014	1.75 (1.25–2.31)	0.001
Q3	5.08 (4.07–6.35)	<0.001	3.08 (2.25–4.22)	<0.001
LHR	1.08 (1.06–1.10)	<0.001	1.00 (0.96–1.04)	0.966
Q1	Reference		Reference	
Q2	1.11 (0.89–1.40)	0.337	1.24 (0.98–1.56)	0.067
Q3	2.13 (1.68–2.70)	<0.001	1.45 (1.13–1.86)	0.003
MHR	1.01 (1.00–1.02)	<0.001	1.00 (0.99–1.01)	0.277
Q1	Reference		Reference	
Q2	0.90 (0.74–1.09)	0.288	0.92 (0.75–1.18)	0.551
Q3	1.58 (1.28–1.93)	<0.001	1.43 (1.19–1.98)	0.001

*Adjusted for age, sex, diabetes, alcohol consumption, ALT, AST, PLT, AFP, TC, Child-Pugh class, MELD score, BCLC stage, tumor size, and type of treatment. HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PLT, platelet count; AFP, alpha-fetoprotein; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; NHR, neutrophil to HDL-C ratio; MHR, monocyte to HDL-C ratio; LHR, lymphocyte to HDL-C ratio; MELD, Model for End-Stage Liver Disease; HR, Hazard ratio; CI, confidence interval.

Prognosis value of lipid-related biomarkers in patients

Figures 2A–C show the 1-, 2-, and 3-year prognostic values of HDL-C, NHR, MHR, and LHR. Moreover, the performance of these markers was compared with that of the MELD score, a well-established prognosis score. In the training cohort, the AUCs of the NHR for mortality were 0.777 (95% CI 0.752–0.802), 0.760 (95% CI 0.722–0.784), and 0.740 (95% CI 0.715–0.767) at 1, 2, and 3 years, respectively. The NHR showed a similar predictive ability, compared to the MELD score (AUCs 1, 2, and 3 years: 0.786, 0.770, and 0.761, respectively). In addition, we compared the NHR with

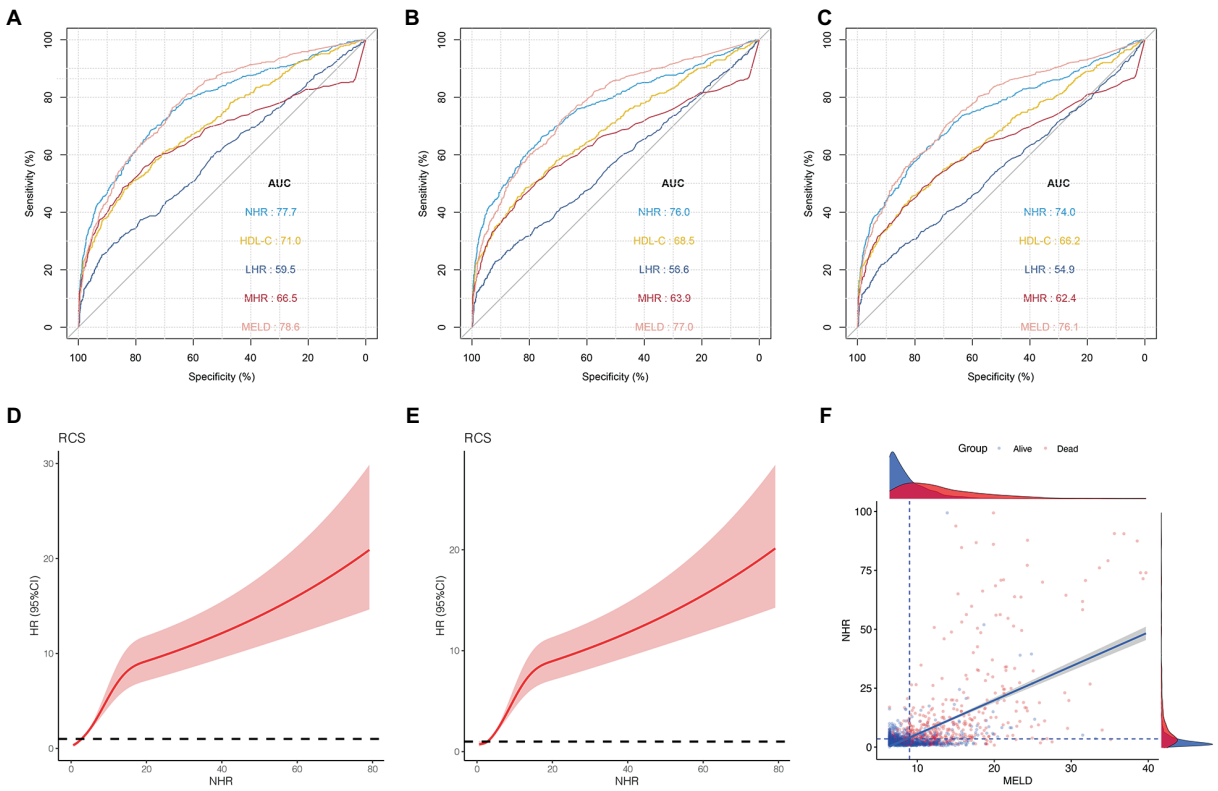

FIGURE 2
Predictive ability of different indicators for mortality and the association between NHR and outcome in the training cohort. ROC curves of NHR, HDL-C, MHR, LHR, and MELD score predicting 1 **(A)**, 2 **(B)**, and 3 years mortality **(C)**. **(D)** The association between NHR and 1-year mortality in all patients (unadjusted). **(E)** The association between NHR and 3-year mortality in all patients (unadjusted). **(F)** The distribution of survival and death patients in patients with HCC. Scatterplots using axis cut-points of ≥3.5 for NLR and ≥9 for the MELD score. ROC, receiver operating characteristic; HDL-C, high-density lipoprotein cholesterol; NHR, neutrophil to HDL-C ratio; MHR, monocyte to HDL-C ratio; LHR, lymphocyte to HDL-C ratio; MELD, Model for End-stage Liver Disease; BCLC, Barcelona Clinic Liver Cancer.

other lipid-related indicators, including HDL-C, MHR, and LHR. The results indicated that the AUC of the NHR was significantly higher than those of the HDL-C, MHR, and LHR at 1, 2, and 3 years (all $p < 0.05$).

As shown in Figures 2D,E, the risk was relatively low in the low NHR range and then increased in patients with HCC. These results indicate that the NHR was associated with the 1-and 3-year mortality risk and the test for nonlinearity was statistically significant ($p < 0.001$).

Optimal cut-off points for the NHR and MELD score

The optimal cut-off points for the NHR and MELD scores were determined using the X-tile software. When NHR ≥ 3.5 and MELD ≥ 9, the difference was the most statistically significant. The sensitivity and specificity of the NHR ≥ 3.5 were 70.1 and 74.7%, respectively, and those of the MELD ≥ 9 were 76.3 and 67.4%, respectively. Scatterplots were used to visualize the relationship between NHR, MELD score, and mortality in patients with HCC (Figure 2F). The scatterplots revealed that patients with NHR ≥ 3.5 and MELD ≥ 9 had poor outcomes in patients with HCC.

Risk stratification for patients with HCC

The Kaplan–Meier survival curves based on the NHR and MELD optimal cut-off values are shown in Figure 3. We observed a statistical difference between cut-off values of these two biomarkers and survival probability. The 3-year survival probability was 73.7% in patients with NHR < 3.5, whereas those with NHR ≥ 3.5 were 37.0% ($p < 0.0001$; Figure 3A). Furthermore, patients with MELD score < 9 had a significantly higher survival probability than those with MELD score ≥ 9 (77.3 vs. 39.0%, $p < 0.0001$; Figure 3B). Next, all patients were divided into three groups: low- (NHR < 3.5 and MELD <9, $n = 628$), medium- (NHR ≥ 3.5 or MELD ≥9, $n = 615$), and high-risk groups (NHR ≥ 3.5 and MELD ≥9, $n = 396$). The 3-year survival probabilities were 81.8, 62.1, and 19.4% in the low-, medium-, and high-risk groups, respectively ($p < 0.0001$; Figure 3C).

To examine the risk stratification for different ages, we divided patients into the following three subgroups: <40, 40–60, and >60 years. The Kaplan–Meier curve analysis showed that the 3-year survival probability in patients with a NHR < 3.5 and a MELD score < 9 was significantly higher than in patients with a NHR ≥ 3.5 and a MELD score ≥ 9, regardless of patient's ages (all $p < 0.0001$; Figures 3D–F).

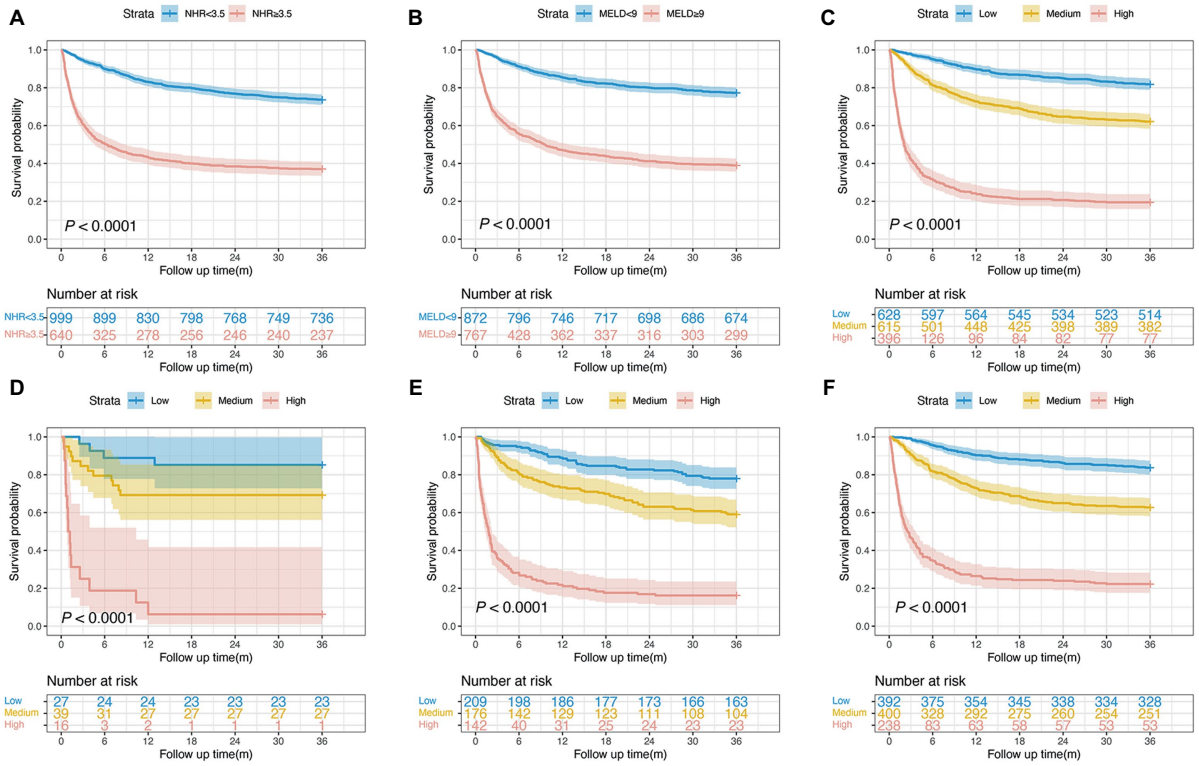

FIGURE 3
Survival curves of patients with HCC in the training cohort. **(A)** Survival probability in patients with NHR<3.5 and ≥3.5 (n=1,639, 73.7 vs. 37.0%, p<0.0001). **(B)** Survival probability in patients with MELD <9 and ≥9 (n=1,639, 77.3 vs. 39.0%, p<0.0001). **(C)** Survival probability in the low-, medium-, and high-risk group (n=1,639, 81.8 vs. 62.1 vs. 19.4%, p<0.0001). **(D)** Survival probability of patients aged <40 years in the low-, medium-, and high-risk group (n=82, 85.2 vs. 69.2 vs. 6.2%, p<0.0001). **(E)** Survival probability of patients aged 40–60 years in the low-, medium-, and high-risk group (n=527, 78.0 vs. 59.0 vs. 16.2%, p<0.0001). **(F)** Survival probability of patients aged >60 years in the low-, medium-, and high-risk group (n=1,030, 83.7 vs. 62.7 vs. 22.3%, p<0.0001). HCC, hepatocellular carcinoma; MELD, Model for end-stage liver disease; NHR, neutrophil to high-density lipoprotein cholesterol ratio.

Prognostic value of NHR in the diabetic subgroup

For the diabetic subgroup, the NHR had the highest AUC at 3-year (0.735; 95% CI: 0.681–0.779). The AUCs of the HDL-C, MHR, LHR, and MELD scores were 0.631 (95% CI: 0.573–0.688), 0.617 (95% CI: 0.558–0.675), 0.538 (95% CI: 0.474–0.592), and 0.753 (95% CI: 0.704–0.805), respectively. The NHR showed better performance than HDL-C, MHR, and LHR (all $p < 0.05$, Figure 4A). The 3-year survival probabilities of patients in the low-, medium-, and high-risk groups were 74.2, 54.8, and 18.4%, respectively ($p < 0.0001$; Figure 4B).

Validation of prognostic values of the NHR and the MELD score

In the validation cohort, baseline NHR offered good prognostic value for mortality with the AUC at 1, 2, and 3 years: 0.751 (95% CI: 0.696–0.807), 0.739 (95% CI: 0.695–0.785), and 0.734 (95% CI: 0.684–0.777), respectively. In addition, the NHR showed a performance similar to that of the MELD score (0.756; 95% CI 0.706–0.807) and was noted to have the highest AUC (0.734), which was followed by AUCs of the HDL-C (0.606; 95% CI 0.517–0.640), MHR (0.605; 95% CI 0.542–0.667), and LHR (0.500; 95% CI 0.438–0.561) at 3 years (all $p < 0.05$; Figures 5A–C).

Furthermore, patients with a NHR < 3.5 had a significantly higher survival probability than those with a NHR ≥ 3.5 (72.5 vs. 44.4%, $p < 0.0001$; Figure 5D). Patients with a MELD score ≥ 9 were associated with an increased risk of death compared with those with a MELD score < 9 ($p < 0.0001$; Figure 5E). The 3-year survival probabilities in patients in the low- (NHR < 3.5 and MELD <9, $n = 143$), medium- (NHR ≥ 3.5 or MELD ≥9, $n = 161$), and high-risk groups (NHR ≥ 3.5 and MELD ≥9, $n = 69$) were 84.6, 59.0, and 27.5%, respectively ($p < 0.001$; Figure 5F).

Discussion

HCC is the most common fatal malignant tumor with rapid progression and poor prognosis (27). Therefore, identifying high-risk patients and developing individualized therapies is essential. There exists an emerging interest in the relationship between lipid-related inflammatory parameters and the prognosis of liver disease. NHR, MHR, and LHR are novel parameters that can be readily acquired from routine blood examinations. However, there is little evidence regarding their prognostic value for mortality in patients with HCC.

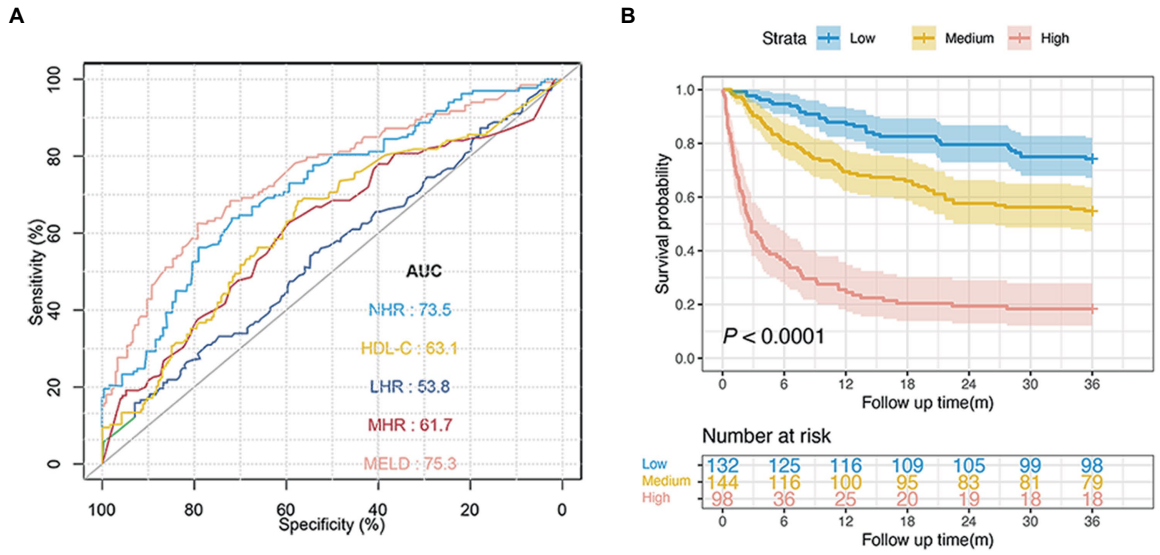

FIGURE 4
Predictive ability of different indicators for 3-year mortality and risk stratification in patients with diabetes. **(A)** ROC curves of NHR, HDL-C, MHR, LHR, and MELD score predicting 3-year mortality in diabetic patients. **(B)** Survival probability of diabetic patients in the low-, medium-, and high-risk group (n=374, 74.2 vs. 54.9 vs. 18.4%, p<0.0001). NHR, neutrophil to high-density lipoprotein cholesterol ratio; HDL-C, high-density lipoprotein cholesterol; MHR, monocyte to HDL-C ratio; LHR, lymphocyte to HDL-C ratio; MELD, Model for End-stage Liver Disease.

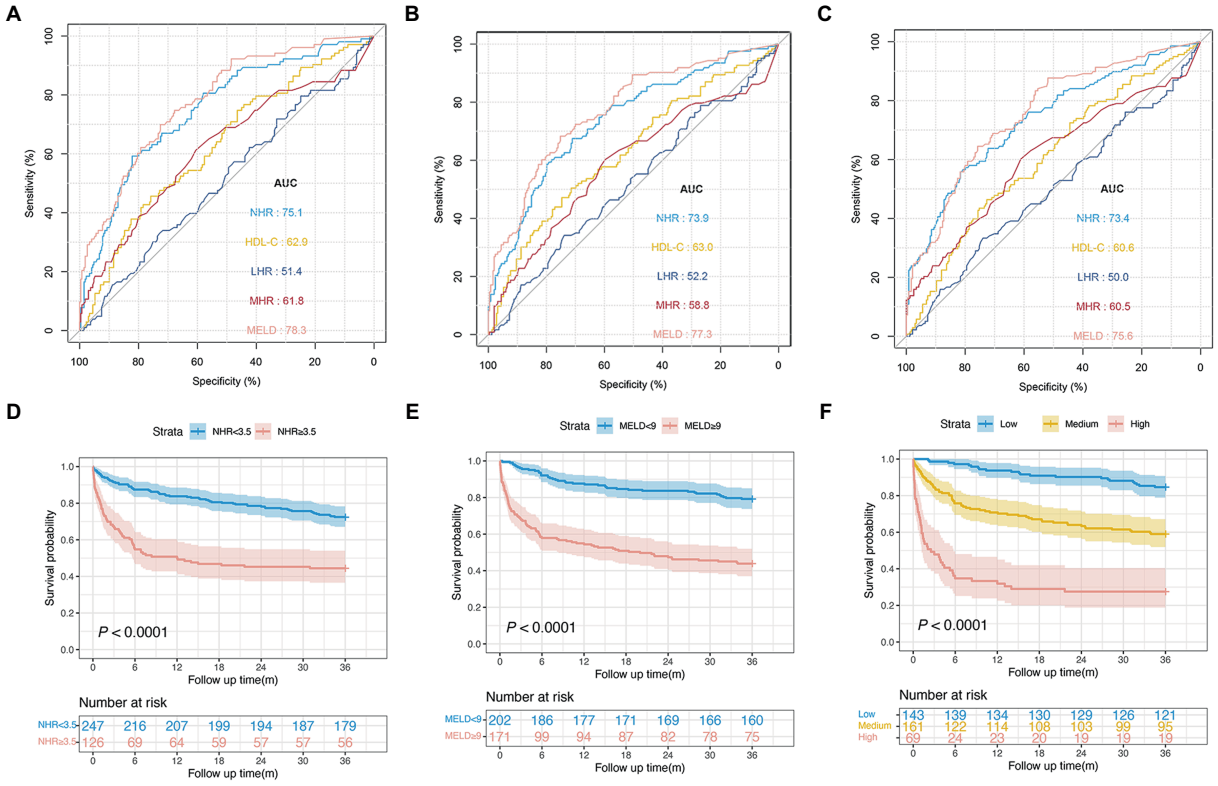

FIGURE 5
Performance of different indicators and risk stratification in the validation cohort. ROC curves of NHR, HDL-C, MHR, LHR, and MELD score predicting 1 **(A)**, 2 **(B)**, and 3years mortality **(C). (D)** Survival probability in patients with NHR<3.5 and ≥3.5 (n=373, 72.5 vs. 44.4%, p<0.0001). **(E)** Survival probability in patients with MELD <9 and ≥9 (n=373, 79.2 vs. 43.8%, p<0.0001). **(F)** Survival probability in the low-, medium-, and high-risk group (n=373, 84.6 vs. 59.0 vs. 27.5%, p<0.0001).

To our knowledge, this study with a large sample size is the first to clarify the relationship between lipid-related inflammatory biomarkers and 3-year mortality in patients with HCC. Multivariate analyses revealed that the NHR was a significant independent factor for 3-year mortality in patients with HCC, regardless of continuous or categorical variables (all $p < 0.05$). Additionally, compared with the HDL-C, MHR, LHR, and MELD scores, the NHR exhibited a better or comparable performance in predicting prognosis. The results indicate that the NHR can effectively predict mortality in patients with HCC. Moreover, we observed that NHR had a nonlinear association with 1-and 3-year mortality (p for nonlinearity <0.001). The morbidity and mortality rates of HCC are higher in patients with diabetes than in the general population (28). In the current study, we found that the 3-year mortality rate was significantly higher in diabetic patients than in nondiabetic patients ($p < 0.001$, Table 2). The NHR and MELD score had excellent discrimination in assessing the 3-year prognosis in patients with diabetes.

The pathogenesis of HCC is closely related to immune status and inflammatory response (29). When immune cells, including lymphocytes and neutrophils, are activated, proinflammatory and anti-inflammatory mediators are released (30). Neutrophils are the first line of the inflammatory response and produce cytokines that affect lymphocytes and monocytes (31), which may explain why the predictive ability of NHR is better than that of single markers (HDL-C) and other ratios (MHR and LHR) in the current study. The NHR is an effective biomarker of systemic inflammation and oxidative stress, and its prognostic power has been investigated (14, 32). Furthermore, as critical oxidative mediators, monocytes reveal the response capacity of the innate immune system (33). A decrease in circulating lipoprotein levels reflects the severity of the dysfunction of liver synthesis. Reduced HDL levels and function may play important roles in the pathophysiology of systemic inflammation (34). Previous studies indicated that HDL-C and apolipoprotein A-I are negatively associated with inflammatory markers (34, 35). HDL-C inhibits the activation and transformation of monocytes, thereby inhibiting the inflammatory response (36). In this study, most patients presented with cirrhosis at the time of diagnosis. Trieb et al. (37) reported that patients with cirrhosis showed reduced levels of HDL-C, which impaired the ability of HDL-C to inhibit monocyte production of proinflammatory factors. In addition, the anti-inflammatory and antioxidant activities of HDLs are impaired in patients with diabetes (38). Proinflammatory cytokines directly inhibit the activity of apolipoprotein synthesis enzymes, leading to reduced production of HDL-C (8, 39). Abnormal activation of neutrophils results in changes in the composition and function of HDL-C and increases neutrophil production (40), thereby, increasing the risk of mortality.

The MELD score is composed of three available biochemical indicators: TBIL, Cr, and INR. The MELD score is an accurate mortality risk assessment tool in chronic liver disease (41, 42). This score has predicted mortality in patients with HCC (43, 44). In the current population-based cohort study, we found that NHR and MELD scores had similar prognostic values. According to the scatter plot distribution and Kaplan–Meier curves, patients with higher NHR and MELD scores had poorer prognoses. In training cohort, patients in the low-risk group (NHR < 3.5 and MELD <9) had a 3-year survival rate of 81.8%, and patients in the high-risk group (NHR ≥ 3.5 and MELD ≥9) had a 3-year survival rate of 19.4%. Since HCC mortality rates remain considerable despite advanced treatments, the NHR and MELD scores are critical for clinicians to identify high-risk patients and facilitate appropriate and timely patient management.

Our study has some limitations. First, this study was a single-institution one with retrospective data collection. However, the result was validated using an internal cohort and NHR showed good discrimination. Second, in the training and validation cohorts, 151 (9.2%) and 30 (8.0%) patients with HCC underwent liver resection, respectively. Most patients receive local treatment, such as TACE or palliative treatment. In the future, a prospective multicenter large-sample study is required to confirm its prognostic value in patients with HCC underwent liver resection. Third, since hepatitis B virus infection is a common cause of HCC in China, whether NHR may be valuable in patients with other etiologies remains unclear.

In conclusion, a high NHR is a powerful independent risk factor for mortality and can be used to evaluate the prognosis of HCC. The association of patients having MELD ≥9 and NHR ≥ 3.5 with poor prognosis can aid clinicians in identifying high-risk patients.

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 human participants were reviewed and approved by The Ethics Committee of Beijing Ditan Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

XW and KS conceived and designed the project. KS, JH, QZ, and YB collected the data. KS and JH analyzed and interpreted the data. KS drafted the manuscript. QZ, YB, and XZ was responsible for manuscript modification. All authors contributed to the article and approved the submitted version.

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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/articless/10.3389/fnut.2023.1127913/full#supplementary-material

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Independent effect of fat-to-muscle mass ratio at bioimpedance analysis on long-term survival in patients receiving surgery for pancreatic cancer

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Introduction: Malnutrition and alteration of body composition are early features in pancreatic cancer and appear to be predictors of advanced stages and dismal overall survival. Whether specific patient characteristics measured at the preoperative bioimpedance analysis (BIA) could be associated with long-term outcomes following curative resection has not been yet described.

Methods: In a prospective multicenter study, all histologically proven resected pancreatic cancer patients were included in the analysis. BIA was measured for all patients on the day before surgery. Demographics, perioperative data, and postoperative outcomes were prospectively collected. Patients who experienced 90-day mortality were excluded from the analysis. Survival data were obtained through follow-up visits and phone interviews. Bioimpedance variables were analyzed according to the overall survival using the Kaplan–Meier curves and the univariate and multivariate Cox regression model.

Results: Overall, 161 pancreatic cancer patients were included. The median age was 66 (60–74) years, and 27.3% received systemic neoadjuvant treatment. There were 23 (14.3%) patients malnourished in the preoperative evaluation. Median OS was 34.0 (25.7–42.3) months. Several bioimpedance variables were associated with OS at the univariate analysis, namely the phase angle [HR 0.85, 95% CI 0.74–0.98)], standardized phase angle [HR 0.91, 95% CI 0.82–0.99)], and an increased ratio between the fat and lean mass (FM/FFM) [HR 4.27, 95% CI 1.10–16.64)]. At the multivariate analysis, the FM/FFM ratio was a confirmed independent predictor of OS following radical resection, together with a positive lymph nodal status.

Conclusion: Alteration of body composition at the preoperative bioimpedance vector analysis (BIVA) can predict dismal oncologic outcomes following pancreatic resection for cancer.

KEYWORDS

bioimpedance analysis, body composition, pancreatic cancer, outcomes, surgical oncology

Introduction

Pancreatic cancer (PC) has the poorest prognosis of any common solid malignancy, with a 5-year overall survival of approximately 20%. Pancreatic ductal adenocarcinoma now represents the third leading cause of overall cancer death (1), and both incidence and mortality rates increased by an average of 0.3% per year during the past decade (2). Underlying these trends is a combination of an aging population, a longer expected lifespan, and the public health pandemics of obesity and diabetes.

PC has aggressive biological characteristics. More than 50% of patients have distant metastases at presentation, and the majority of patients undergoing resection will develop local or distant recurrence within a few years after surgery, suggesting *de facto* the presence of systemic disease in patients with apparently localized tumors (3–5). The physiologic effects of PC can weaken patients, limiting their ability to withstand aggressive treatments. Some sort of nutritional derangement is present in up to 80% of PC (6). Patients with compromised nutritional status and alteration of body composition exhibit poor treatment tolerance, increased surgical morbidity, and dismal oncologic outcomes (7, 8). Preoperative alteration of different anthropometric indexes has been repeatedly associated with worsened survival after several types of major surgery (9, 10), including pancreatic resections (8). In particular, muscle mass wasting alone, or associated with obesity—the so-called sarcopenic obesity—has been reported as an independent factor for poor oncologic outcomes and increased mortality within a few years after radical pancreatic surgery (11). A systematic review and meta-analysis on this topic included 42 retrospective studies (12). Body composition assessment was carried out mainly at CT scan analysis (35 of 42), while seven studies used bioelectric impedance analysis (BIA). Even though most studies focused on patients receiving chemoradiation alone, BIA indexes were appraised to weigh the risk of short-term morbidity. To the best of our knowledge, no evidence on the association of preoperative BIA parameters in patients undergoing pancreatic surgery for PC and long-term overall survival has been provided. Despite CT remaining the reference imaging tool to estimate body compartments and their relative ratio (13), BIA has been repeatedly shown as a reliable method to assess both body composition and nutritional status (14). Therefore, we designed a prospective cohort study with the aim of assessing whether preoperative anthropometric indexes at BIA were independent predictors of long-term overall survival after pancreatic surgery for PC.

Materials and methods

Study overview and patient selection

Adult patients scheduled for elective pancreatic resection for PC between January 2016 and December 2018 at three Italian academic medical centers—San Gerardo Hospital, Monza, the Pancreas Institute, Verona, and Humanitas Research Hospital, Rozzano, Milan—were prospectively assessed for inclusion and asked to provide written consent. Exclusion criteria were as follows: kidney diseases with a glomerular filtration rate of < 60 mL/min and the presence of compartmentalized fluid collections (pleural effusion and peripheral edema). These conditions may interfere with the electrical properties of human tissues, resulting in unreliable body composition estimation such as fat or muscle mass. Further exclusion criteria were as follows: American Society of Anesthesiologists (ASA) score > 3; New York Heart Association > 2; presence of any infection in the previous 90 days; palliative surgery; and refusal to sign informed consent. The results are reported according to Strengthening the Reporting of Observational Studies in Epidemiology (15).

An identical electronic case report form was filled out by the three centers. Demographic data, medical history, comorbidity, malnutrition [ESPEN criteria (16)], and results from routine blood tests were collected at admission. The study protocol was approved by the ethics committees of all the institutions (Nr. 0005228).

Bioelectrical impedance assessment

A single-frequency phase-sensitive impedance analyzer (Nutrilab®, Akern SRL—Pisa, Italy) was used for the BIVA. BIVA was conducted 2 h before the induction of anesthesia. The BIVA method utilizes a phase-sensitive impedance instrument that introduces a constant, low-level alternating current with a tetrapolar surface electrode placement on the hands and feet for whole-body determinations (14, 17). Impedance (Z) and the delay of current, caused by the lag of current penetrating cell membranes and tissue interfaces, are measured by low Z electrodes and expressed as phase shift or phase angle (PA). Impedance is a complex number that comprises the resistance (R) or purely resistive component (water and electrolytes in fluids and tissues) and the reactance (Xc) or capacitive component in tissues (cells and tissue interfaces). Complex electronic circuitry permits the determination of the time delay between voltage and current at the cell membrane and tissue level and thus determines the phase

angle. The complex Z of an organism can be differentiated into R and Xc components with simple mathematics, Z (sin phase angle) and Z (cos phase angle), respectively, of an R–Xc series circuit for the body. Routinely, a 50-kHz phase-sensitive BIA instrument measures PA and Z and calculates R and Xc.

The standardized PA (SPA) is the observed PA—mean phase angle/standard deviation (SD), where the mean and SD are from sex-stratified, age-stratified, and BMI-stratified phase angle reference values. Hydration assessment of patients was conducted through the software Bodygram® (Akern SRL—Pisa, Italy). Details of BIVA principles, measurement methods, and definitions have been previously described (18).

Perioperative care

Pylorus-preserving pancreatoduodenectomy, classic Child operation, and distal and total pancreatectomy procedures were performed or supervised by experienced surgeons.

Perioperative care was provided *per* the Enhanced Recovery After Surgery recommendations (19). Intraoperative fluid administration was tailored to each patient according to either the variation of the cardiac output or the pulse pressure variation, through continuous radial arterial monitoring according to a goal-directed fluid therapy approach.

All postoperative complications were collected and graded according to the Clavien–Dindo classification (CDC) (20). For each complicated patient, the overall burden of postoperative morbidity was calculated *per* the comprehensive complication index (CCI) (21).

Follow-up and long-term outcome

All patients were followed using measurement of serum carbohydrate antigen 19-9, abdominal ultrasound, contrast computed tomography or magnetic resonance imaging, and office visits. In brief, each patient was followed up every 3 months for the first 2 years and then every 6 months or on clinical demand. OS was defined as the time interval in months from surgery to death; if alive, patient data were censored at the last available visit. Patient surveillance was closed at the end of April 2022. We used the eighth edition of the American Joint Committee on Cancer staging system for PC.

Study endpoints

The primary endpoint was to study the potential association between preoperative parameters of body composition at BIA and overall long-term survival (OS).

Statistical analysis

The normal distribution of continuous variables was evaluated at the Kolmogorov–Smirnov test. Data are expressed as median and interquartile range (IQR). The Mann–Whitney *U*-test was used for continuous variables. Non-random association for categorical variables was tested using Fisher's exact test.

Survival analysis for cancer patients

The Kaplan–Meier log-rank (Mantel–Cox) test and the univariate Cox proportional hazard method were used to analyze potential differences in overall survival according to the variables at the BIVA. If death was not reported during the follow-up period, patients were censored at the last available contact date.

A Cox proportional hazard model was built to assess factors independently associated with OS. The following variables were included in the model: age, the phase angle (PA), the standardized phase angle (SPA), the ratio between the fat mass and the fat-free mass (FM/FFM), the occurrence of major complications, the comprehensive complication index (CCI), and the nodal status. As the presence of disease at the specimen margins is a major determinant of OS in PC, a subgroup analysis according to the status of resection margins at the final pathology was conducted. Hazard rates (HRs) are reported with a 95% confidence interval (CI).

For each test, a two-sided *p*-value of 0.05 was considered significant. All computations were made with the IBM Corp. Released 2021. IBM SPSS Statistics, version 28.0. Armonk, NY.

Results

Overall, 161 patients were included and analyzed. Table 1 summarizes the perioperative characteristics of the included patients. The median age at diagnosis was 66 (IQR 60–74) years, 71 (44.1%) were female, and 44 out of 161 (27.3%) had undergone neoadjuvant treatment before the operation. The median BMI was 23.7 (IQR 21.7–26.6), and 23 (14.3%) were malnourished at the time of operation. The median PA and SPA were in the normal range according to the multicenter international series (22) with 5.3° (IQR 4.6°-5.9°) and 0.20 (IQR −0.70–1.40), respectively. Most patients underwent a proximal resection (69.6%). The median follow-up time was 27 (IQR 17–43) months. The estimated overall survival (OS) for the entire cohort was 34 (95% CI 25.7–42.3) months.

Univariate and multivariate analyses for overall survival

Several variables measured ad BIVA were associated with overall survival, which was significantly improved together with each unitary increase in the value of the PA ($p = 0.023$) and the SPA ($p = 0.045$). On the other side, increased values of extracellular water (ECW, $p = 0.037$), adipose tissue (fat mass – FM, $p = 0.013$), and the ratio between fat mass and fat-free mass (FM/FFM, $p = 0.037$) were associated with dismal survival rates (Table 2).

We ran an age-adjusted multivariate Cox proportional regression model including those BIVA variables, which showed an association with OS at the univariate analysis, together with

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TABLE 1 Perioperative characteristics of included patients.

Variable	Median (IQR) or number (%) Overall N=161
Age	66 (60-74)
Sex F/M	71/90 (44.1/55.9)
BMI	23.7 (21.7-26.6)
Malnutrition	23 (14.3)
Albumin (preoperative) (g/L)	41.2 (38.1-42.9)
PA (degrees)	5.3 (4.6-5.9)
SPA	0.20 (-0.70-1.40)
FFM	53.2 (44.9-60.1)
FM	13.7 (9.5-18.4)
TBW	39.3 (33.7-44.7)
Neoadjuvant treatment	44 (27.3)
Postoperative pancreatic fistula	
- Biochemical leakage - Grade B/C fistula	5 (3.1) 14 (8.7)
Biliary fistula	3 (3.7)
Major complications	17 (10.6)
Comprehensive complication index	8.7 (0.0-20.9)
Type of operation	
- PD	112 (69.6)
- DP	28 (17.4)
- TP	21 (13.0)
T	
- 0-2 - 3-4	131 (81.4) 30 (18.6)
N	
- 0 - 1 - 2	37 (23.0) 49 (30.4) 75 (46.6)
R	
- 0 - 1	94 (58.4) 67 (41.6)
Perineural infiltration	30 (18.6)
Lymphatic infiltration	21 (13.0)
Vascular infiltration	18 (11.2)
AJCC 18th	
- IA	17 (10.6)
- IB	17 (10.6)
- IIA	4 (2.5)
- IIB	49 (30.4)
- III	74 (46.0)

clinical and pathology variables generally associated with OS in resected PC, namely, the occurrence of major complications, the comprehensive complication index, and a positive lymph nodal status. As the status of resection margins at pathology remains a major predictor of long-term prognosis in PC, we analyzed separately two subgroups of patients, according to the R status (R0 vs. R+). To produce a more conservative model and minimize the number of covariates, the ECW was excluded from the multivariate analysis, as this variable can directly be calculated from the PA. As shown in Table 3, a positive nodal status and the ratio between FM/FFM remained independently associated with OS after radical resection, with HR 2.29 95% CI (1.12–4.69) and HR 24.05 95% CI (3.11–186.07), respectively.

TABLE 2 Univariate analysis of BIVA parameters for overall survival.

Variable	HR (95% CI)	*p*-value
PA	0.85 (0.74-0.98)	0.023
SPA	0.91 (0.82-0.99)	0.045
TBW	1.01 (0.99-1.04)	0.451
HI	1.04 (0.99-1.09)	0.121
ECW	1.05 (1.01-1.09)	0.037
FFM	1.0 (0.98-1.03)	0.676
FM	1.04 (1.01-1.06)	0.013
FM/FFM	4.27 (1.10-16.64)	0.037

We finally modeled a Kaplan–Meier curve to compare the OS according to the ratio FM/FFM, dichotomized at the median value observed in our study cohort (FM/FFM = 27). As presented in Figure 1, a high ratio FM/FFM was associated with significantly worse OS, with an estimated median survival rate of 44 months for FM/FFM<27 versus 26 months for FM/FFM $\geq$ 27, p = 0.040 at log-rank (Mantel–Cox) test.

Discussion

This prospective analysis shows that the preoperative appraisal of body composition at BIVA can be predictive of overall survival after surgical resection for pancreatic cancer. Specifically, decreased values of PA and SPA are related to unfavorable long-term prognosis following resection, while an increased ratio between FM/FFM is an independent determinant of poor overall survival (OS), with a hazard ratio (HR) of 16 (95% CI 2–139). This effect—observed in the subgroup of radical resection margins—was independent of the presence of positive lymph nodes at the final pathology.

In gastrointestinal solid cancer, the prognostic value of PA and its z-score SPA has been broadly demonstrated (23). Bioelectrical impedance is a non-invasive method of measuring body composition through the delivery of a low-frequency alternating current and works on the principle that different cellular structures have different levels of resistance to the passage of the current. The provided measures of resistance and reactance are representative of tissue hydration and cellular integrity, respectively (24). The arctangent between these latter—the phase angle—is a useful indicator of cellular health, and its clinical applications range from the evaluation of hydration status up to the stratification of long-term prognosis in oncologic settings (25). High values of PA

TABLE 3 Multivariate analysis for overall survival according to the pathological status at resection margins.

Variable	R0 (N=94)		R1 (N=67)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.02 (0.98-1.06)	0.380	0.99 (0.95-1.04)	0.752
PA	1.24 (0.75-2.05)	0.401	0.85 (0.51-1.41)	0.520
SPA	0.93 (0.69-1.24)	0.622	0.86 (0.57-1.28)	0.447
FM/FFM	24.05 (3.11-186.07)	0.002	1.57 (0.14-17.30)	0.715
CCI	1.00 (0.99-1.02)	0.645	1.02 (0.99-1.04)	0.164
Positive N status	2.29 (1.12-4.69)	0.023	0.59 (0.24-1.45)	0.254

R, resection margin status; HR, hazard ratio; PA, phase angle; FM, fat mass; FFM, fat-free mass; CCI, comprehensive complication index.

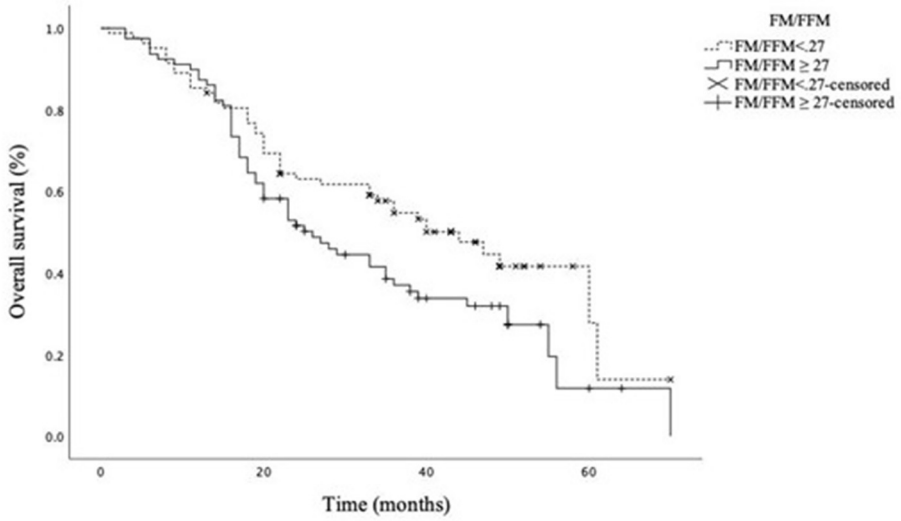

FIGURE 1
Overall survival according to the FM/FFM ratio dichotomized at the median value. Estimated median (95% CI) OS 44.0 (32.3–55.7) and 26.0 (18.7–33.3) months for FM/FFM<27 and FM/FFM ≥ 27, respectively. Log-rank (Mantel–Cox) test $p = 0.040$.

reflect high cellularity, cell membrane integrity, and preserved cell function. In solid tumors of the head and neck and in gynecologic patients, a low PA has been associated with a more advanced stage of the disease (25). Bioimpedance data on patients suffering from pancreatic cancer are limited. Gupta et al. showed that PA with a cutoff of 5° may be predictive of survival in advanced pancreatic cancer patients (26). Nonetheless, in their study, only non-surgical advanced pancreatic cancer patients were included. Consequently, much lower PA values could have been expected in comparison with our cohort of resectable patients. Additionally, in a large study by Yasui-Yamada et al. (27) including resected gastrointestinal and hepatobiliary-pancreatic cancer patients, an association between preoperative PA and long-term outcomes was observed (27). In that cohort, the subgroup of patients suffering from PC, although resectable, showed a median PA of 4.6°, again lower than that measured in our cohort (5.3°). Higher PA values may partially explain why we observed a limited prognostic ability of PA on overall survival, which was not confirmed after adjusting for other confounders in the multivariate analysis. Despite in contrast with published data showing a high prognostic value of the PA in cancer patients, some speculative explanation can be hypothesized. Most studies analyzing the prognostic significance of PA in cancer include patients with advanced stages of the disease, who showed PA values generally lower than that in our population. The extreme observation was found in a cohort of end-stage disease admitted to an acute palliative care unit, where a PA value of lower than 3° had an accuracy of 86% for 3-day survival (28). The PA is a comprehensive parameter for assessing cellular health and function. We can postulate that such general deterioration may represent a final event in the natural history of cancer and, consequently, was not yet detectable at the time of measurement in our resectable patients.

However, in our study other parameters of body composition at BIVA were associated with long-term oncologic outcomes. An increased fat mass was predictive of reduced OS, and furthermore, the combination of high FM together with low muscularity—intended as reduced fat-free mass (FFM)—was associated with a more than 4-fold increased risk of death. This effect was also confirmed in the multivariate analysis, where a high ratio between FM/FFM was predictive of a 24-fold increase in death, following radical resection for PC. The presence of positive nodal status was also an independent predictor of OS, with an HR of 2.3 (95% QI 1.1–4.7). Muscular and adipose compartment deviations in predicting survival in both advanced and resected pancreatic cancer

have been widely described. In a retrospective study including 301 resectable PC patients, Okumura et al. observed an association between visceral adiposity, sarcopenic visceral obesity, low muscle mass index, muscle attenuation, and overall survival (29). Gruber et al. observed that the preoperative presence of sarcopenia and sarcopenic obesity correlated with shorter OS, following resection for PC (30). In addition, in advanced PC, changes in body composition during the receipt of neoadjuvant treatment were associated with the likelihood of resection after neoadjuvant CT (31). The depletion of the muscular compartment alone and even more in combination with a high amount of visceral adiposity has been associated with impaired survival following resection for advanced PC patients undergoing chemoradiation, and the presence of cachectic weight loss thawed the effect of resection on OS (32). Accordingly, non-resected advanced PC showing a high visceral to subcutaneous adipose tissue ratio and low skeletal muscle index at diagnosis experienced unfavorable OS (33).

To the best of our knowledge, this is the first study to find an association between body composition and overall survival in resected PC patients by BIVA. Indeed, all published literature showed a correlation between radiologic features and prognosis. Even though a contrast-enhanced CT scan is required for clinical staging and restaging in PC, clinical aftermaths of body composition assessment at CT scan can be limited by the invasiveness of the examination. Moreover, dedicated software to process the images and interpretation from a trained radiologist are required. BIVA is a non-invasive, inexpensive, easy-to-use bedside technique and does not need any specific training to assess the body compartments. Certain body conditions provoking extreme hyperhydration or dehydration may bias the assessment of muscle mass (28); however, the use of BIVA for the determination of body compartments has been extensively validated in many healthy populations and several diseases (22, 27, 34), and the clinical feasibility of BIVA in the pancreatic surgical setting has already been confirmed in a previous trial from our research group (18).

It is well known that subclinical changes in body compartments are early manifestations of pancreatic cancer, which can occur even months before confirming the diagnosis (35). In a murine model of PC, Danai et al. observed an early activation of genes involved in autophagy and ubiquitin–proteasome degradation, suggesting the promotion of proteolysis and muscle volume depletion. In the clinical setting, a recent meta-analysis including 33 studies and more than 5,000 resectable and borderline resectable PC patients showed that the pooled prevalence of sarcopenia at diagnosis reached almost 40% (36).

Finally, the relatively small sample size and heterogeneity of our cohort in terms of pathology stage may justify why we observed the effect of BIVA on OS exclusively in the subgroup of radical resection margins. It has been broadly shown that the presence of a positive resection margin is one of the strongest determinants of OS following surgery in localized PC (37, 38). One more limitation of our study is that despite being prospective, it was not hypothesis-driven. Hence, further studies are needed to confirm the present findings. Moreover, despite widely used and validated, the accuracy of BIVA can be hampered by some medical conditions, such as severe edema, compartmentalized fluid collections, and renal failure. Even though surgical oncologic patients are not supposed to experience those conditions, this element could represent a limitation to the application of BIVA in a subgroup of patients. Finally, the measurement of FM and FFM is derived from the impedance and reactance and is not directly measured (39). As these latter can vary according to the type of impedance analyzer, the cut point of our study needs further validation according to the machine used.

Conclusion

In conclusion, the preoperative evaluation of body composition at BIVA and in particular, the combination between increased FM and reduced FFM helps stratify post-resection long-term outcomes in localized pancreatic cancer. The technical and cost feasibility of BIVA in comparison with the CT scan should promote the implementation of BIVA in clinical practice to improve the estimation of oncologic prognosis in patients undergoing pancreatic surgery for cancer. Further studies are needed to define specific cutoffs for groups at risk of dismal post-resection survival.

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 human participants were reviewed and approved by the Ethics Committee of IRCCS San Matteo Hospital, Pavia, Italy. Protocol number Nr. 0005228. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study conception and design: MS, SP, and LG. Data collection and drafted manuscript preparation: MC, MA, AG, SF, LR, and AF. Analysis and interpretation of results: MS, GC, GM, RS, FR, AZ, CB, and LG. All authors reviewed the results and approved the final 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.

Publisher's note

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Influence of body composition assessment with bioelectrical impedance vector analysis in cancer patients undergoing surgery

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Background: Malnutrition is common in patients undergoing surgery for cancers and is a risk factor for postoperative outcomes. Body composition provides information for precise nutrition intervention in perioperative period for improving patients' postoperative outcomes.

Objection: The aim was to determine changes in parameters of body composition and nutritional status of cancer patients during perioperative period.

Methods: A total of 92 patients diagnosed with cancer were divided into gastrointestinal and non-gastrointestinal cancer group according to different cancer types. The patients body composition assessed by bioelectrical impedance vector analysis (BIVA) on the day before surgery, postoperative day 1 and 1 day before discharge. The changes between two groups were compared and the correlation between body composition and preoperative serum nutritional indexes was analyzed.

Results: The nutritional status of all patients become worse after surgery, and phase angle (PA) continued to decrease in the perioperative period. Fat-free mass (FFM), fat-free mass index (FFMI), skeletal muscle mass (SMM), extracellular water (ECW), total body water (TBW), hydration, and body cell mass (BCM) rise slightly and then fall in the postoperative period in patients with gastrointestinal cancer, and had a sustained increase in non-gastrointestinal patients, respectively ($P<0.05$). Postoperative body composition changes in patients with gastrointestinal cancer are related to preoperative albumin, pre-albumin, hemoglobin, and C-reactive protein ($P<0.05$), whereas postoperative body composition changes in patients with non-gastrointestinal cancer are related to age ($P<0.05$).

Conclusions: Significant changes in body composition both in patients with gastrointestinal cancer and non-gastrointestinal cancer during perioperative period are observed. Changes in body composition for the cancer patients who undergoing surgery are related to age and preoperative serum nutrition index.

KEYWORDS

body composition, bioelectrical impedance vector analysis, gastrointestinal cancer, nutritional status, malnutrition

1 Introduction

Cancer is the second leading cause of death in the world and an important barrier to increasing life expectancy in China, placing a heavy burden on economic and public health systems (1). Over the past 35 years, the incidence and mortality rate of liver and stomach cancers have remained high, while that of lung, breast, colorectal, and prostate cancers has been growing rapidly in China (2).

The utilization of bioelectrical impedance analysis (BIA) for measuring body composition has generated significant interest in using various indicators, including skeletal muscle index (SMI), phase angle (PA), fat mass (FM), fat-free mass (FFM), fat-free mass index (FFMI), cellular water, to predict outcomes in patients with lung cancer (3, 4), breast cancer (5), prostate cancer (6), gastric cancer (7) and colorectal cancer (8). In contrast to traditional BIA methods, bioelectrical impedance vector analysis BIVA can provide more objective information about hy and BCM (9). Such equipment is faster, more portable, and provides more information for diagnosing malnutrition compared to cross-sectional imaging and has been proven good agreement with body composition data provided by the computed tomography (CT) (10) and dual-energy X-ray absorptiometry (DXA) (11) methods. Malnutrition is associated with disease progression and cancer treatments, with negative impacts on quality of life, high grade state of inflammation (12), poor tolerance to antineoplastic treatment and decreased survival, in addition to increasing postoperative complications (13), hospital stay and costs (14). Tumor subsite is one of the major risks of malnutrition, with cancers that affect gastrointestinal function having the highest prevalence (75% for gastroesophageal and 70.6% for pancreatic tumors). And the risk of malnutrition in patients with non-gastrointestinal tumors is significantly reduced (26.6–42.9% for lung tumors and 28.6% for prostate/testicle neoplasms), especially since prevalence is lower in patients with breast cancers (15, 16).

It is important to note that cancer treatments, including surgery, may further change body composition, and increase the risk of malnutrition. Patients with operable colorectal cancer showed a significant decrease in current body weight, FM, and visceral fat score and increased the average percentage of SMI and total water content at 3 months after surgery (17). Fredrix et al. were documented that after surgical removal of the tumor 1 year in non-small cell lung carcinoma patients with FM and FFM increased (18). For patients with gastric cancer, FFM and SMI were significantly decreased at 18 to 24 months after operative treatment (19), moreover, lean body mass after gastrectomy had a greater decrease in elderly (≥80 years old) than in non-elderly patients (<80 years old) (20). The above literature describes body composition changes 3-12 months or even more after malignant tumor surgery, and few literatures reported short-term body composition changes during hospitalization. Previous studies had reported that post-operation 1 week loss of lean body mass was significantly greater than the loss of fat mass in gastric cancer patients (21). Moreover, the changes in water distribution, PA, initial reduced muscle function, and altered biochemical values during the first 9 postoperative days were observed in patients after pancreatic surgery (22). However, few studies have reported a comparative analysis of body composition changes during surgical treatment in patients with gastrointestinal cancer and non-gastrointestinal cancer, which provide useful information for cancer prognosis and more precise nutritional support.

In this study, we performed serial evaluations of the body composition changes during surgical treatment using a bioelectrical impedance vector analyzer and compared the changes and contributing factors in body composition between patients with gastrointestinal cancer and non-gastrointestinal cancer.

2 Materials and methods

2.1 Study design and patients

Patients inclusion criteria were as follows (1): age 18 years or older, conscious and able to cooperate with relevant inspection; (2) a histologic or clinical diagnosis of lung cancer, breast cancer, prostatic cancer, stomach cancer, and colorectal cancer; (3) complete medical history records are available; (4) patients without severe and vital organ failure (heart, lung, liver, kidney, etc.) or Acquired Immune Deficiency Syndrome AIDS; (5) patients without a cardiac pacemaker or implanted medical device; (6) patients who did not require dialysis or received intravenous fluids within 1 hour before measurement intravenous line; (7) patients without severe pleural effusion and ascites. The prospective observational cohort study according to the above inclusion criteria finally included 92 patients with diagnoses of

lung cancer (N=18), breast cancer (N=16), prostatic cancer (N=20), stomach cancer ((N=19), and colorectal cancer (N=19), who were scheduled to receive surgery from September 2022 to December 2022 at Shaoxing People's Hospital (Shaoxing Hospital Zhejiang University School of Medicine).

General information including age, sex, grip strength, weight, and height was collected. Biochemical profiles and medical information were collected from electronic medical laboratory records. Body composition measurement was performed on preoperative day 1, postoperative day 1, and 1 day before discharge. And nutritional state assessment was performed within 24 hours of admission and before discharge (day -1). All the measurements and information collection were performed by well-trained researchers.

2.3 Anthropometry and body composition measurement

Height and body weight was measured using a calibrated stand-up scale and body mass index (BMI) was calculated according to the formula weight (kg)/height (m^2). Patients were in a standing position with the elbow fully extended and dominant hand-grip strength was measured 3 times by CAMRY EH101 dynamometer, with a maximum squeeze of at least 5s, and with a 30s gap between 3 trials, the maximum value was taken. Regard Jamar dynamometer as the reference device, Camry Digital Handgrip Dynamometer is a valid tool for assessing grip strength in hospitalized adult patients (23).

Body composition analysis was performed using the bioelectrical impedance vector analysis method with BIA 101 BIVA® PRO instrument (Akern/RJL) which applies alternating sinusoidal electric currents of 250 μA at an operating frequency of 50 kHz. The measurement was performed on preoperative day 1, postoperative day 1, and 1 day before discharge in the morning (8:30-10:00 a.m.).

Patients removed all metal objects and other items that might interfere with the scan and were lying supine on a bed for at least 5 minutes with their legs separated and arms abducted from the body. This method requires only the placement of two single use electrodes on the dorsal surface of the right hand/wrist and the other two on the right foot/ankle attaching leads according to the manufacturer's instructions. Specific data of sex, age, height, and current weight were added to the machine before starting the impedance. The following parameters were obtained: FM, FFM, PA, FFMI, skeletal muscle mass (SMM), extracellular water (ECW), total body water (TBW), hydration, and BCM.

2.4 Nutritional statuses assessment scale

All patients had malnutrition screening by the nutritional risk screening 2002 (NRS2002). NRS2002 with a total score ranging from 0 to 7 points, which has been proven to be a reliable tool for assessing malnutrition risk according to patients' nutritional status and disease severity. A score of ≥3 points is considered to be at risk of malnutrition (24).

Patient-generated subjective global assessment (PG-SGA) has been shown to be a strong predictor of malnutrition in cancer patients, based on objective indicators such as medical and dietary history (weight change, food intake, two or more weeks of continued gastrointestinal abnormality, and physical function) provided by the patient and combined with clinical examination (body fat loss, muscle mass loss, existence of edema, and hydrops abdominis) to assess the nutritional status of cancer patients. Higher scores (≥9) reflect higher risks of malnutrition (25).

Global Leadership Initiative on Malnutrition (GLIM) criteria (26), which include three phenotypic criteria (weight loss, low BMI, and reduced muscle mass) and two etiologic criteria (reduced food intake and disease burden/inflammation). As one of the GLIM diagnostic criteria for malnutrition, body composition shows its importance in the assessment of nutritional status. Patients are diagnosed with malnutrition at least present one of the phenotypic criteria and one of the etiological criteria. Higher scores (2 points) indicate that the patient has a primary diagnosis of malnutrition.

2.5 Biochemical profile and medical information

Biochemical values including serum levels of albumin (Alb), prealbumin (pre-Alb), hemoglobin (Hb), and C-reactive protein (CRP), as well as diagnosis, clinical tumor stage, length of stay, and hospital cost were collected from electronic medical laboratory records on admission.

2.6 Statistical analysis

Categorical variables were represented as numbers (percentage). Normally distributed continuous variables were reported as mean ± standard deviation (SD) and non-normally distributed continuous variables were reported as median (interquartile range, IQR). The Student's *t* test and Wilcoxon test were performed to compare the baseline characteristics between the gastrointestinal cancer group and the non-gastrointestinal cancer group, respectively, for normally and non-normally distributed continuous data. Additionally, the Chi-square test was used for the comparison of categorical variables.

Analysis of covariance (ANCOVA) was performed to detect postoperative differences compared to the preoperative values. Changing Trends of 3 times body composition were analyzed by repeated measures of variance (RMANOVA). The results of ANCOVA and RMANOVA were adjusted for baseline age, sex, BMI, grip, GLIM score, Alb, pre-Alb, Hb, and CRP.

Spearman test was used to explore relationships between body composition changes and baseline variables, and the correlation coefficients (r) were presented. *P* values of less than 0.05 were considered statistically significant. BIVA 2002 software was used for the construction of the vectorial plot (9). All results were analyzed using the Statistical Analysis Software (SAS) 9.4 (SAS Institute Inc., Cary, North Carolina, U.S.).

2.7 Ethical approval

All patients volunteered to participate in this study and received oral and written information about the project, before asking for their written informed consent. This study did not interfere with the clinical practice in the hospital and was approved by Shaoxing People's Hospital (Shaoxing Hospital Zhejiang University School of Medicine).

3 Results

3.1 Baseline characteristics of patients

As shown in Table 1, the study included 92 patients (53 males and 39 females) with an average age of 66.76 years old, an average BMI of 23.31 kg/$m^{2,}$ and an average grip of 27.72 kg. The gastrointestinal cancer group included 26 males and 12 females with an average age of 69.24 years old, an average BMI of 22.98 kg/$m^{2,}$ and an average grip of 28.58 kg. For the non-gastrointestinal cancer group, 27 males and 27 females were included and with an average age of 65.02 years old, an average BMI of 23.55 kg/$m^{2,}$and an average grip of 27.11 kg. No significant difference in age, sex, BMI, and grip between the gastrointestinal cancer group and non-gastrointestinal cancer group (P>0.05). A majority of patients (68.48%) were diagnosed with an early (1 or 2) cancer stage. A total of 4 patients with TNM (tumor, node, and metastasis) stage IV were included, all of them from the gastrointestinal cancer group. From a preoperative assessment, 17 patients (18.68%) had a malnutrition diagnosis (GLIM=2 points). The blood biochemical index including Alb, pre-Alb, and Hb in patients with gastrointestinal cancer was significantly lower than that of patients with non-gastrointestinal cancer (P<0.05), whereas the CRP was significantly higher in the gastrointestinal cancer group (P=0.0002). Additionally, longer stays (median=16, IQR=14-19 vs. median=9, IQR=7-12) and more cost (median=44927.8, IQR=37825.6-51565.80 vs. median=22366.94, IQR=19661.52-

TABLE 1 Basic characteristics of patients.

Baseline demographics	Total	Gastrointestinal Cancer group	Non-gastrointestinal Cancer group	*P* value
Patients (N)	92	38	54	
Age (year) (Mean ± SD)	66.76±11.21	69.24±9.84	65.02±11.86	0.1465
Sex, N (%)				0.0783
Male	53 (57.61)	26 (68.42)	27 (50.00)	
Female	39 (42.39)	12 (31.58)	27 (50.00)	
BMI (kg/m^2) (Mean ± SD)	23.31±3.43	22.98±3.80	23.55±3.17	0.1948
Grip (Kg) (Mean ± SD)	27.72±9.17	28.58±10.13	27.11±8.48	0.5388
TNM stage, N (%)				**<.0001**
I	42 (45.65)	11 (28.95)	31 (57.41)	
II	21 (22.83)	5 (13.16)	16 (29.63)	
III	25 (27.17)	18 (47.37)	7 (12.96)	
IV	4 (4.35)	4 (10.53)	0 (0)	
GLIM, N (%)				**0.0075**
1 point	74 (81.32)	26 (68.42)	48 (90.57)	
2 points	17 (18.68)	12 (31.58)	5 (9.43)	
Biochemical values (Mean ± SD)				
Albumin (g/l)	40.52±5.78	36.79±4.99	43.23±4.74	**<.0001**
Prealbumin (mg/l)	231.44±68.27	195.73±66.38	256.17±58.34	**<.0001**
C-reactive protein (mg/l)	9.74±29.69	15.75±27.96	5.47±30.4	**0.0002**
Hemoglobin (g/l)	131.87±23.26	126.7±21.90	135.36±23.72	**0.0117**
Length of hospital stay (day), Median (IQR)	12 (8 to 16)	16 (14 to 19)	9 (7 to 12)	**<.0001**
Hospitalization cost (yuan), Median (IQR)	31123.90 (22037.14 to 42922.85)	44927.8 (37825.6 to 51565.80)	22366.94 (19661.52 to 29072.42)	**<.0001**

BMI, body mass index; TNM, tumor, node, and metastasis; GLIM, the Global Leadership Initiative on Malnutrition. Bold values indicate that the difference is statistically significant, significance level P<0.05.

29072.42) for the patients with gastrointestinal cancer compared to the non-gastrointestinal cancer group (P<0.0001).

3.2 Changes in body composition, NRS2002, and PA-SGA during the perioperative period

The absolute values for body composition and nutrition statement during the perioperative period are shown in Table 2. Overall, after adjusted age, sex, grip, BMI, TNM stages, Alb, pre-Alb, CRP, and Hb by ANCOVA, significant perioperative changes were found in all patients. For the gastrointestinal cancer group, FFM, FFMI, and SMM increased modestly after surgery (FFM +1.39, SD=2.60; FFMI+0.47, SD=0.83; SMM+1.33, SD=2.37) (P<0.05) but declined significantly on 1 day before discharge (FFM-0.27, SD=2.32; FFMI-0.05, SD=0.81; SMM-0.12, SD=2.24) (P<0.05). FM decreased on postoperative day 1 (-1.39, SD=2.60) (P=0.0011) and increased on 1 day before discharge (+0.27, SD=2.32) (P<0.0001). PA value reduced significantly on 1 day

TABLE 2 Body composition, NRS2002 and PA-SGA values during the perioperative period.

	preoperative day 1	postoperative day 1	1 day before discharged	P^a value	P^b value	P^c value
Gastrointestinal Cancer						
BIVA parameter						
FFM (kg)	49.94 ± 9.37	51.33±9.49	49.67±9.02	**<.0001**	**<.0001**	**0.0174**
FM (kg)	12.80±7.40	11.41±7.48	13.07±6.88	**0.0011**	**<.0001**	**0.0164**
PA (°)	5.68±0.85	5.53±0.92	5.46±1.12	**0.0029**	**0.0007**	0.9366
FFMI (kg/m^2)	9.02±1.69	9.48±1.76	8.97±1.51	**0.0002**	**0.0003**	0.0515
SMM (kg)	24.86±6.27	26.19±6.60	24.74±5.86	**<.0001**	**<.0001**	**0.0465**
TBW (L)	36.91±7.09	38.22±7.37	36.77±6.71	**<.0001**	**<.0001**	0.0559
ECW (L)	17.52±3.51	18.48±3.92	17.92±3.55	**<.0001**	**<.0001**	0.1012
Hydration	73.75±2.88	74.31±3.39	74.06±3.45	**<.0001**	**<.0001**	0.2260
BCM	25.97±6.15	26.26±6.41	25.19±6.73	**<.0001**	**<.0001**	0.2707
Nutrition statement						
NRS2002	2.18±1.23	–	3.89±1.48	–	**<.0001**	–
PG-SGA	3.92±3.47	–	9.56±2.43	–	**<.0001**	–
Non-gastrointestinal cancer						
BIVA parameter						
FFM (kg)	49.45±8.84	50.82±9.40	50.81±9.74	**<.0001**	**<.0001**	**0.0174**
FM (kg)	13.42±5.54	12.05±5.70	12.04±6.19	**<.0001**	**0.0002**	**0.0164**
PA (°)	5.91±0.77	5.85±0.65	5.72±0.89	0.2442	0.4769	0.9366
FFMI (kg/m^2)	8.80±1.60	9.21±1.78	9.43±2.30	**<.0001**	0.9162	0.0515
SMM (kg)	23.78±5.87	24.85±6.33	25.49±7.70	**<.0001**	0.1053	**0.0465**
TBW (L)	36.28±6.56	37.34±7.08	37.89±7.86	**<.0001**	**0.0031**	0.0559
ECW (L)	16.73±2.73	17.31±3.01	17.80±3.04	**<.0001**	**0.0095**	0.1012
Hydration	73.16±0.92	73.34±0.65	73.77±1.90	0.0961	0.5611	0.2260
BCM	26.38±5.92	26.96±5.90	26.60±6.57	**<.0001**	**0.0007**	0.2707
Nutrition statement						
NRS2002	1.46±0.50	–	1.45±0.50	–	0.8997	–
PG-SGA	1.66±0.61	–	4.79±2.40	–	**0.0003**	–

Values expressed as Mean±SD. BIVA, bioelectric impedance vector analysis; FFM, fat free mass; FFMI, fat free mass index; FM, fat mass; PA, phase angle; SMM, skeletal muscle mass; TBW, total body water; ECW, extracellular water; BCM, body cell mass; NRS2002, the nutritional risk screening 2002; PG-SGA, the patient generated subjective global assessment.
P^a: ANCOVA for postoperative day vs. 1 preoperative day 1;
P^b: ANCOVA for 1 day before discharged vs. 1 preoperative day 1;
P^c: RMANOVA for the changes of body composition during perioperative period between gastrointestinal cancer group and non-gastrointestinal cancer group.
The results of ANCOVA and RMANOVA were adjusted for baseline age, sex, body mass index, grip, GLIM, albumin, prealbumin, hemoglobin and C-reactive protein. Bold values indicate that the difference is statistically significant, significance level P<0.05.

after surgery (-0.15, SD=0.75) (P=0.0029) and remained low on 1 day before discharge (-0.22, SD=0.82) (P=0.0007). Body water compartment changes were observed. In particular, ECW and hydration increased significantly on postoperative day 1 (ECW +0.97, SD=2.35; hydration+0.56, SD=2.05) (P<0.05) and, despite a small reduction, remained higher than the preoperative value before discharge (ECW+0.41, SD=2.17; hydration+0.30, SD=2.11) (P<0.05). Whereas TBW and BCM increased slightly after surgery (TBW+1.32, SD=2.41; BCM+0.29, SD=2.21) (P<0.05) but fell significantly on 1 day before discharge (TBW-0.14, SD=2.25; BCM-0.77, SD=2.23) (P<0.05). For the non-gastrointestinal cancer group, FFM, FM, TBW, ECW, and BCM increased on postoperative day 1, and 1 day before discharge (postoperative day 1:FFM+1.37, SD=3.03; FM-1.37, SD=3.03; TBW+1.06, SD=2.41; ECW+0.59, SD=1.65; BCM+0.58, SD=2.81; 1 day before discharge: FFM+1.36, SD=3.42; FM-1.38, SD=3.42; TBW+1.61, SD=4.79; ECW+1.07, SD=2.09; BCM+0.22, SD=3.67) (P<0.05). FFMI and SMM increased significantly on postoperative day 1 (FFMI+0.41, SD=0.87; SMM+1.07, SD=2.38) (P<0.05) and recovered before discharge (FFMI+0.63, SD=1.92; SMM+1.70, SD=5.37) (P>0.05).

With regard to the nutrition statement, all of the patients' PG-SGA scores increased significantly on 1 day before discharge compared to preoperative (gastrointestinal cancer group+5.64, SD=2.14; non-gastrointestinal cancer group+3.13, SD=2.03) (P<0.001), and the NRS2002 score was elevated only observed in patients with gastrointestinal cancer (+1.71, SD=1.20) (P<0.0001).

In addition, RMANOVA showed that the changes in FFM, FM, and SMM during the perioperative period between the gastrointestinal cancer group and non-gastrointestinal cancer group were significant differences (P<0.05). As shown in Figure 1, FFM, FM, and SMM increased slightly in the gastrointestinal cancer group on 1 day after surgery and decreased below the preoperative level before discharge, while SMM kept increasing in the non-gastrointestinal cancer group. Changes in body composition lead to alterations in electrical resistance (R) and reactance (Xc) within the body, which ultimately impact PA, considering that it is the angular transformation of the ratio between Xc and R (27). RXc mean graph with the 95% confidence ellipses during the perioperative period of the gastrointestinal cancer group and non-gastrointestinal cancer group are shown in Figure 2. With respect to the non-gastrointestinal cancer group vector, a shorter impedance vector was demonstrated in gastrointestinal cancer group patients both on preoperative day 1 and postoperative day 1, and a longer impedance vector was demonstrated on 1 day before discharge. The 95% confidence ellipses of the two groups were overlapping, which means no significant vector displacement.

3.3 Correlations between changes in body composition and baseline characteristics of patients

The correlation coefficient between changes in body composition and baseline characteristics of patients is shown in Table 3. For the gastrointestinal cancer group, on postoperative day 1, the changes in PA and BCM were positively correlated with preoperative Alb and pre-Alb level (P<0.05), and the changes in BCM were positively correlated with preoperative hemoglobin level (P<0.05). A significant negative correlation was found between the changes in hydration and preoperative pre-Alb level (P<0.05). No association was observed between CRP and changes in body composition on postoperative day 1 (P>0.05). On 1 day before discharge, the changes in PA and BCM were positively correlated with preoperative Alb and pre-Alb levels (P<0.05), and a significant positive correlation between BCM and preoperative Hb level was found(P<0.05), whereas the changes in ECW was negatively correlated with preoperative Alb and pre-Alb level (P<0.05). Preoperative CRP level was positively correlated with changes in FM, FFMI, SMM, TBW, ECW, and hydration (P<0.05), and negatively correlated with changes in FM, PA, and BCM (P<0.05). No association was observed between age, grip, BMI, TNM stage, and changes in body composition during the period of postoperative to pre-discharge (P>0.05).

For the non-gastrointestinal cancer group, on postoperative day 1, we found changes in ECW and hydration had a slight, negative, and significant correlation with age (P<0.05), and a significant positive correlation was found between the changes in PA and

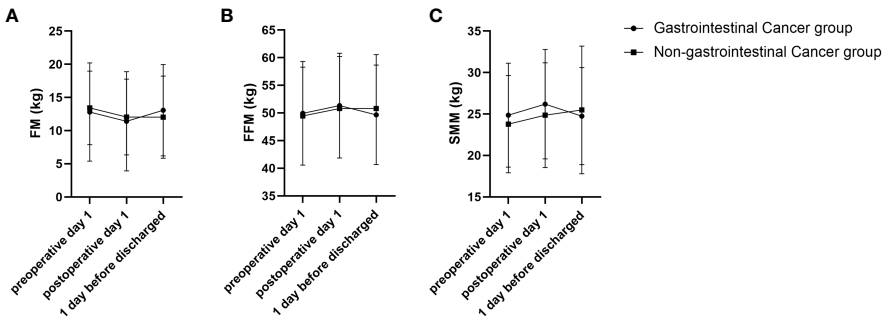

FIGURE 1
FM, FFM and SMM trajectories of changes during perioperative period of gastrointestinal cancer group and non-gastrointestinal cancer group. **(A)** FM trajectory of changes during perioperative of gastrointestinal cancer group and non-gastrointestinal cancer group; **(B)** FFM trajectory of changes during perioperative period of gastrointestinal cancer group and non-gastrointestinal cancer group; **(C)** SMM trajectory of changes during perioperative period of gastrointestinal cancer group and non-gastrointestinal cancer group.

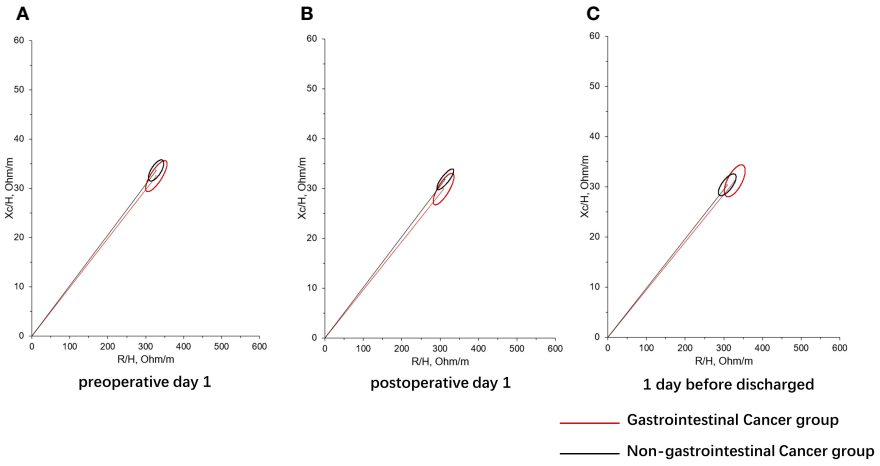

FIGURE 2
RXc mean graph with the 95% confidence ellipses during perioperative period of gastrointestinal cancer group and non-gastrointestinal cancer group. **(A)** RXc mean graph with the 95% confidence ellipses on preoperative day 1 of gastrointestinal cancer group and non-gastrointestinal cancer group; **(B)** RXc mean graph with the 95% confidence ellipses on postoperative day 1 of gastrointestinal cancer group and non-gastrointestinal cancer group; **(C)** RXc mean graph with the 95% confidence ellipses on 1 day before discharge of gastrointestinal cancer group and non-gastrointestinal cancer group. R is the resistance, Xc is the reactance, and H is the height.

TABLE 3 Correlations between changes in body composition and baseline characteristics of patients.

	Age	Grip	BMI	Alb	pre-Alb	CRP	Hemoglobin	TNM stage
Gastrointestinal cancer								
Changes are calculated as "measurement on postoperative day 1 - measurement on preoperative day 1".								
Changes in FFM (kg)	0.05905	0.04443	-0.07004	0.15914	0.03038	0.06924	0.17686	-0.17434
Changes in FM (kg)	-0.05905	-0.04443	0.07004	-0.15914	-0.03038	-0.06924	-0.17686	0.17434
Changes in PA (°)	0.03328	0.19038	-0.13892	**0.36270***	**0.43468***	-0.12316	0.25422	0.17610
Changes in FFMI (kg/m^2)	0.20171	-0.12598	-0.04962	0.00380	-0.11044	0.06955	-0.03004	-0.18746
Changes in SMM (kg)	0.18475	-0.11297	-0.01412	0.02823	-0.07919	0.05432	-0.00308	-0.17227
Changes in TBW (L)	0.18091	-0.08670	-0.02354	0.03897	-0.07043	0.03819	0.01732	-0.18456
Changes in ECW (L)	0.14972	-0.17990	-0.00471	-0.21783	-0.26275	0.05765	-0.19553	-0.22624
Changes in Hydration	0.13623	-0.24024	0.02053	-0.24356	**-0.35362***	0.02118	-0.25857	-0.19933
Changes in BCM	0.00428	0.27147	-0.18489	**0.49712***	**0.46701***	-0.20776	**0.34476***	-0.03473
Changes are calculated as "measurement on 1 day before discharged - measurement on preoperative day 1".								
Changes in FFM (kg)	0.04931	-0.09962	0.00996	-0.14524	-0.24271	**0.33264***	0.13205	-0.06814
Changes in FM (kg)	-0.04931	0.09962	-0.00996	0.14524	0.24271	**-0.33264***	-0.13205	0.06814
Changes in PA (°)	-0.23118	0.27990	0.13189	**0.32169***	**0.44811***	**-0.59432***	0.27745	0.01531
Changes in FFMI (kg/m^2)	0.13310	-0.16465	0.03464	-0.12014	-0.23624	**0.40625***	0.18463	0.00077
Changes in SMM (kg)	0.12229	-0.18369	0.00985	-0.13563	-0.26859	**0.40368***	0.15792	-0.01846
Changes in TBW (L)	0.11468	-0.17156	-0.00460	-0.13150	-0.26877	**0.41181***	0.15533	-0.02299
Changes in ECW (L)	0.27862	-0.28514	-0.10567	**-0.32266***	**-0.44144***	**0.64721***	-0.17559	-0.07199
Changes in Hydration	0.17930	-0.19369	-0.28010	-0.14339	-0.28688	**0.40898***	-0.12813	-0.12741
Changes in BCM	-0.24307	0.28338	0.07356	**0.33019***	**0.39204***	**-0.46555***	**0.34393***	-0.12375

(Continued)

TABLE 3 Continued

	Age	Grip	BMI	Alb	pre-Alb	CRP	Hemoglobin	TNM stage
Non-gastrointestinal cancer								
Changes are calculated as "measurement on postoperative day 1 - measurement on preoperative day 1".								
Changes in FFM (kg)	-0.14618	0.03440	0.10206	0.04815	0.19374	0.00141	0.03483	0.04404
Changes in FM (kg)	0.14618	-0.03440	-0.10206	-0.04815	-0.19374	-0.00141	-0.03483	-0.04404
Changes in PA (°)	**0.28773***	-0.09232	0.06146	-0.05289	-0.05248	0.09274	0.04754	-0.07639
Changes in FFMI (kg/m^2)	-0.18468	0.01453	0.11472	0.05455	0.18475	-0.02863	-0.01844	-0.00127
Changes in SMM (kg)	-0.17193	0.03586	0.11369	0.06130	0.18479	-0.00980	0.01010	0.01342
Changes in TBW (L)	-0.16821	0.04986	0.11146	0.04985	0.18525	0.00653	0.02099	0.01689
Changes in ECW (L)	**-0.36911***	0.04186	0.03578	0.02525	0.16034	-0.00970	-0.04845	-0.02942
Changes in Hydration	**-0.33026***	-0.09618	0.03747	0.03890	0.06627	-0.06383	-0.12733	-0.02815
Changes in BCM	0.07399	-0.00664	0.15451	0.03138	0.13022	0.06900	0.05766	-0.01991
Changes are calculated as "measurement on 1 day before discharged - measurement on preoperative day 1".								
Changes in FFM (kg)	-0.13099	0.15318	-0.01615	-0.01583	0.14786	-0.01346	-0.02531	0.08910
Changes in FM (kg)	0.13273	-0.13223	0.03177	0.02568	-0.13013	0.02247	0.02291	-0.07797
Changes in PA (°)	0.20948	-0.01805	-0.01474	-0.09527	-0.01009	-0.00934	0.01508	0.16397
Changes in FFMI (kg/m^2)	-0.15552	0.08645	-0.12107	-0.06395	0.05294	0.01165	-0.16758	0.01142
Changes in SMM (kg)	-0.15404	0.12532	-0.10539	-0.06647	0.07057	0.03959	-0.11158	0.04275
Changes in TBW (L)	-0.15087	0.13073	-0.09360	-0.06402	0.07634	0.03791	-0.10839	0.04163
Changes in ECW (L)	-0.22461	0.00574	-0.05673	-0.02606	0.02044	0.10237	-0.12981	-0.12020
Changes in Hydration	**-0.26398***	-0.10102	-0.09558	0.00518	0.00609	0.06882	-0.21382	-0.14554
Changes in BCM	0.02861	0.05901	0.00608	-0.05091	0.11440	-0.04125	-0.02498	0.08054

Values expressed as correlation coefficients (r). TNM, tumor, node, and metastasis; FFM, fat free mass; FFMI, fat free mass index; FM, fat mass; PA, phase angle; SMM, skeletal muscle mass; TBW, total body water; ECW, extracellular water; BCM, body cell mass; bold values indicate that the difference is statistically significant, significance level P<0.05.

age (P<0.05). On 1 day before discharge, the changes in hydration were negatively associated with age(P<0.05). No association was observed between grip, BMI, Alb, pre-Alb, CRP, Hb, TNM stage, and changes in body composition during the period of postoperative to pre-discharge (P>0.05).

4 Discussion

In the present study, we prospectively analyzed the changes in body composition during the perioperative period with operable patients who were diagnosed with lung, breast, prostate, gastric and colorectal cancers, and divided them into a gastrointestinal cancer group (gastric cancer and colorectal cancer) and non-gastrointestinal cancer group (lung cancer, breast cancer and prostate cancer) to compare differences. The results showed all patients in the study had changes in body composition throughout the hospitalization, the trajectories of FM, FFM, and SMM were significantly different between groups. And the changes in body composition of the gastrointestinal cancer group and non-gastrointestinal cancer group were related to preoperative serum markers of nutrition and age, respectively. To the best of our knowledge, our study is the first to use BIVA to find changes in body composition in patients operated for gastrointestinal and non-gastrointestinal cancer among the Chinese.

Our results indicate that the trajectories of FM, FFM, and SMM were minor increased after surgery and then decreased to below the preoperative level, while the non-gastrointestinal cancer group consistently increased before hospital discharge. This means that the nutritional status of patients with non-gastrointestinal cancer is less affected by surgery, while patients with gastrointestinal cancers have worse nutritional status after surgery. Moreover, patients with longer postoperative stays in bed and lack of exercise had more muscle atrophy and lost significant FFM at the time of discharge for gastrointestinal cancer patients. In addition, the short-term decrease in FM may be related to the accelerated rate of protein catabolism and metabolism caused by the stressful trauma of surgery, the postoperative fasting of patients, the slow recovery of digestive tract function, and the relative lack of nutrition supplemented by food intake (28). In contrast, patients with non-gastrointestinal cancer are less affected by postoperative food intake and activity limited.

Skeletal muscle contributes to systemic effects by secreting cytokines and other myokines (including IL-6, IL-8, IL-15, and

leukemia inhibitory factors) through local autocrine, paracrine, and endocrine actions (29). Therefore, lower levels of muscle associated with longer length of stay, higher risk of postsurgical complications and mortality (30), as well as lead to local and systemic inflammation (31), which may enhance catabolism, lead to ongoing muscle loss in cancer patients and associations with cancer survival (32, 33). Supplementation with whey protein, branched-chain amino acid, and vitamin D is not only beneficial for maintaining muscle mass (34), in conjunction with age-appropriate exercise, but also boosts FFM and strength that contribute to well-being in patients (35).

Researchers have considered that cellular hydration plays a protective role against weakness, frailty status and functional decline (36). We observed that the hydration status of the gastrointestinal cancer group temporarily increases after surgery, then declines and remains below preoperative levels. The non-gastrointestinal group had increases in TBW, ECW, and hydration, and this state occurred after surgery and persisted for the remainder of the study period. There is evidence that the cellular hydration state is an important factor controlling cellular protein turnover, protein synthesis and protein degradation are affected in opposite directions by cell swelling and shrinking (37). An increase in cellular hydration (swelling) acts as an anabolic proliferative signal, and loss of plasma fluid and small proteins leads to a decreased plasma capillary oncotic pressure, with ongoing interstitial leakage of fluid and electrolytes resulting in localized edema, which is increased as inflammation impedes the reabsorption and return of fluid to the circulation *via* the lymphatics (38). Our results showed that the higher the preoperative CRP, the less the decrease in FFM, FFMI, and SMM and the more the increase in ECW before discharge, suggesting that the preoperative inflammatory status of patients with gastrointestinal cancer may influence the distribution of hydration after operation. FFM contains virtually all the water and conducting electrolytes in the body, and its hydration is constant (39). Thus, high preoperative CRP levels and a smaller postoperative decrease in FFM may be associated with an increase in postoperative ECW. The shift in water distribution reflects the depletion of BCM (40), which indicates the impairment of organ function in patients with malignant tumors and affects patient prognosis (41). Moreover, we observed an increase in changes in hydration declines with age in the non-gastrointestinal tumor group. Risks of dehydration increase with advancing age (42), mechanistically, dehydration yields stable metabolism remodeling, an elevation of markers of inflammation and coagulation, and renal glomerular injury (43). Improving hydration throughout life may greatly decrease the prevalence of degenerative diseases relate to age.

PA is a sign of cell membrane health and integrity, hydration, and nutritional status. Previous studies have demonstrated that PA is a predictor of mortality or postoperative complications in different clinical settings (27). Although the vector did not shift significantly in either group of subjects, we observed a shorter impedance vector in the gastrointestinal cancer group with respect to the non-gastrointestinal cancer group on preoperative day 1 and postoperative day 1 (Figure 2). The present findings indicate a significant decrease of PA after surgery both in two groups, suggesting decreased cellular integrity and poorer nutritional status in them. Consistent with previous studies (44, 45), the changes of PA with serum Alb and pre-Alb were observed a remarkable positive correction on postoperative day 1 and before discharge in patients with gastrointestinal cancer. In addition, BCM showed similar postoperative changes to PA. It is suggested that postoperative PA and BCM loss decreases with the increase of preoperative serum nutrient parameters in patients with gastrointestinal cancer. Previously, Barrea et al. (46) documented that PA represents a valid predictor of CRP levels in both sexes regardless of body weight, and is possible to predict nutrition-related inflammation. On 1 day before discharge, we also observed a negative association between the changes of PA and CRP in the gastroenteric cancer group. High CRP before surgery may result in a significant decrease in PA. Therefore, preoperative nutritional supplementation should be encouraged in routine practice in patients undergoing operations for gastrointestinal cancer, which is helpful to suppress perioperative inflammation, improve the postoperative nutritional status, and reduce postoperative infection complications (47, 48). Additionally, body composition can inform the formulation of preoperative nutritional therapy for patients. Although no relationship was found between changes in body composition and baseline characteristics of patients with non-gastroenteric cancer in the present study, preoperative nutrition is also important for them (49).

PG-SGA is a tool to effectively assess the nutritional status of oncology patients (25). Compared to preoperative, the patients in this study all had higher PG-SGA scores and showed significant changes in body composition after surgical treatment. It is evident that body composition is an important component of the comprehensive nutritional evaluation of oncology patients, and this result is consistent with other studies (50, 51). Body composition measures can be a more effective predictor of the malnutrition than BMI or body weight and should be considered as part of preoperative risk management and when designing nutritional interventions for undergoing surgery cancer patients. The above findings indicated that the postoperative body composition of patients with malignant tumors is not only related to tumor type, but also significantly correlated with preoperative nutritional status and age.

Although the BIVA method is not considered the "gold standard" for assessing body composition, it has been shown to provide information on hydration and BCM, which allows for the evaluation of patients in whom we are unable to accurately extrapolated body composition due to altered hydration (52). This body composition measurement is useful in guiding the development of nutritional treatment.

This is the first study to use BIVA to identify early postoperative changes of body composition in Chinese patients undergoing surgery for gastrointestinal and non-gastrointestinal cancers, as a way to provide a foundation for personalized nutritional support during hospitalization. Understanding changes in body composition benefits personalized nutritional support and fluid rehydration programs for perioperative patients. For patients undergoing surgery for gastrointestinal, there is a significant loss and a slow recovery in FFM. Hence, it is important to focus on protein supplementation to prevent hypoproteinemia and excessive consumption of FFM during the perioperative period. For patients undergoing surgery for non-

gastrointestinal cancer, it is crucial to prioritize correct fluid rehydration during the perioperative period. This study has several limitations. Although we included multiple cancer patients, the sample size for each cancer was small. A larger sample will be needed to collect more accurate data and make more precise conclusions. We only excluded patients who were diagnosed with abdominal fluid and did not define abnormal hydration status by changes in skinfold thickness, heart rate, blood pressure, and hematological and urine parameters, which can be due to the change in TBW. In addition, there was no data on body composition in patients with non-malignant tumors, so we cannot compare the difference in body composition between cancer patients and patients with non-malignant tumors. It would be helpful for subsequent comparisons if data of body composition closer to normal were available.

5 Conclusions

We observed significant changes in the early postoperative body composition both in patients with gastrointestinal cancer and non-gastrointestinal cancer after radical resection tumor surgery. Postoperative body composition changes in patients with gastrointestinal cancer are related to preoperative Alb, pre-Alb, CRP, and Hb, whereas postoperative body composition changes in patients with non-gastrointestinal cancer are related to age.

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 Shaoxing People's Hospital (Shaoxing Hospital Zhejiang University School of Medicine). 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

BC: data collection, formal analysis and writing original draft. LL: data collection, conceptualization, validation, and writing review and editing. CZ: conceptualization, validation, and writing review and editing. LM: supervision and writing review and editing. QS: data collection, writing review and editing. YF: data collection. MW: conceptualization, supervision, methodology and writing review and editing. SC: project administration, conceptualization, methodology, supervision and data visualization. All authors contributed to the article and approved the submitted version.

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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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Impact of home-based training and nutritional behavior on body composition and metabolic markers in cancer patients: data from the CRBP-TS study

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Introduction: Obesity and physical inactivity are known to affect cancer's development and prognosis. In this context, physical aerobic and resistance training as well as a Mediterranean nutrition have been proven to have many positive health effects. The aim of this study was therefore to investigate the effect of home-based training on body composition and certain metabolic laboratory parameters.

Methods: Patients with breast, colorectal and prostate cancer who underwent curative surgery at stages T1N0M0–T3N3M0 were eligible for this trial and randomized to an intervention and control group. In the intervention group the patients carried out online-based strength-endurance home training during the 6-month study period. Body composition was assessed via bioelectrical impedance analysis (baseline, 3 months and 6 months). Metabolic blood parameters were also analyzed and nutrition behavior determined using the Mediterranean Diet Adherence Screener (MEDAS).

Results: The intervention group's fat mass decreased while their lean body mass increased (time effect $p = 0.001$ and $p = 0.001$, respectively). We found no interaction effect in body weight ($p = 0.19$), fat mass [$p = 0.06$, 6-months estimates −0.9 (95% CI −1.8 to −0.1)] and lean body mass ($p = 0.92$). Blood samples also failed to show a statistically significant interaction effect between time × group for HbA1c% ($p = 0.64$), Insulin ($p = 0.33$), Adiponectin ($p = 0.87$), Leptin ($p = 0.52$) and Triglycerides ($p = 0.43$). Only Adiponectin revealed significance in the time effect ($p < 0.001$) and Leptin in the group effect ($p = 0.03$). Dietary behavior during the study period was similar in patients in the intervention and control groups (interaction $p = 0.81$; group $p = 0.09$ and time $p = 0.03$).

Discussion: Individualized online-based home training in postoperative cancer patients revealed only minor changes, with no group differences in body composition or metabolic laboratory parameters, which were predominantly in the reference range at baseline. More studies investigating effects of online-based home training on body composition and nutrition behavior are needed.

Trial registration: https://drks.de/search/en/trial/DRKS00020499, DRKS-ID: DRKS00020499.

KEYWORDS

cancer, body composition, online-based home training, metabolic markers, Adiponectin, Leptin

1. Introduction

Among women worldwide, most develop breast cancer (24.5%), colorectal cancer (9.4%) and lung cancer (8.4%), whereas men develop lung cancer ranked first (14.3%), followed by prostate cancer (14.1%) and colorectal cancer (10.6%) (1).

Compelling evidence indicates that physical activity improves cancer-related health outcomes, and that physical exercise is generally safe during cancer therapy (2). Exercise and physical activity are beneficial for cancer patients at all stages (3–5) for helping to prevent various types of cancer and for surviving cancer overall (6–12), as it alleviates fatigue, loss of strength, diabetes mellitus, and metabolic syndrome while enhancing endurance performance and quality of life (13–15). Moreover, regular exercise reduces the risks of recurrence (16), recurrence mortality, and overall mortality in breast cancer and prostate patients (12, 17, 18). Individualized training, namely its frequency, intensity, and the patient's pre-and postoperative physical condition are important here (19, 20). The current physical activity guidelines recommend 150–300 min per week of moderate (3–5.9 METs) or an equivalent amount of vigorous intensity aerobic activity of 75–150 min per week (<6 METs). Online-based home training has thus become increasingly popular in recent years. The first studies have shown that home-based training also lowers body weight, body fat mass, and fasting insulin levels, and raises adiponectin levels (21, 22). However, the effects of distance-based exercise interventions on physical capacity and body composition reported so far have been small (23). Essential factors that help patients maintain their adherence to a training program include considering their individual capacity, giving them motivation-enhancing activity feedback, and bidirectional communication (24). Telemedicine-based exercise interventions in cancer patients enable measured activity tracking, but actual physical activity is usually self-reported (23).

Being overweight is one of the main factors contributing to cancer's development (25–27). Excess weight also triggers deviations in metabolic laboratory markers such as Adiponectin, Leptin, Triglycerides, and fasting Insulin (27).

A well-studied way to counteract obesity is the Mediterranean diet (MD) with its proven positive health effects (28). An MD effectively reduces body weight as well as risk factors for metabolic syndrome (29, 30). Cancer-positive impacts of MD have also been observed (31–33). A protective effect for gastric (34), colorectal (35), and bladder cancer (36) is particularly evident. A valid tool for assessing the MD is the Mediterranean Diet Adherence Screener (MEDAS) questionnaire, which asks about its implementation via 14 questions (37, 38).

Considering the insufficient evidence on the effects of home-based training and nutrition on body composition and metabolic markers, this paper's aim was to test whether online training and Mediterranean nutritional behavior would result in changes in body composition and certain metabolic laboratory markers in breast, prostate, and colorectal cancer patients.

2. Materials and methods

2.1. Study design and study population

ColoRectal, Breast, and Prostate Cancer-Telemonitoring and Self-management (CRBP-TS) was a prospective, multicenter randomized, controlled parallel-group trial done as a collaborative project conducted by Leipzig University (Institute of Sport Medicine and Prevention and Department of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital of Leipzig), the Hannover Medical School, and University Hospital Dresden (Germany). The study was approved by the Ethics Committee of the Medical Faculty, University of Leipzig (reference number 056/20-ek) and at all participating sites. The present analysis focuses on the body composition and metabolic data from the "CRBP-TS" study. Our primary and secondary study endpoints (cardiopulmonary exercise testing, physical activity data and, safety assessment) are described in Falz et al. (39).

Written informed consent was obtained from all participants. Eligible subjects were female and male cancer patients with International Classification of Diseases codes C18/19/20 (colorectal cancer), C50 (breast cancer), and C61 (prostate cancer) who underwent curative (R0) surgery at stages T1N0M0 to T3N3M0. Further inclusion criteria were an age between 18 and 75, Eastern Co-operative Oncology Group (ECOG) <1 without acute cardiac, renal, hepatic, endocrine, bone marrow or cerebral disorder and the cognitive ability to understand the postoperative program and participate actively. Of our screened patients, 148 were included in the study at three study sites in Germany.

2.2. Study plan, measurements and data collection

After recruitment, all patients were randomly assigned (1:1 allocation; stratified by study site and cancer entity; Clinical Trial Center Leipzig) to the intervention group (IG) or control group (CG). The study and data collection period lasted 6 months. Data collection occurred at baseline (T1), at 3 months (T2) and at 6 months (T3). All participants underwent an incremental exertion test at T1, T2, and T3, and further testing. A detailed description

of the study design has been published (39, 40). Additional end points of changes in flow-mediated dilatation, blood parameters (inflammation panel, tumor makers, miRNAs) and questionnaires (Patient Health Questionnaire-2, Depression Anxiety Stress Scale, Fatigue Severity Scale and Oral Health Impact Profile) from baseline to 6 months are not reported here.

2.2.1. Online-based home training and CRBP-TS application

The IG participated in individual online-based home training involving strength and endurance exercises with the instruction to train accordance with exercise guidelines (2, 41) for two (at least) or preferably three times or more, with counseling as needed. The strength endurance exercises mainly done with the patient's own body weight included for example stepping exercises, squats, rowing, upper body push and pull exercises, jumps and core exercises. The target training intensity was determined by the perceived exertion (target 5–8; CR10 scale) and by relying on an individual maximum heart rate (75% heart rate max or symptom-limited heart rate) defined during the cardiopulmonary exercise test at baseline.

All study participants were given a tablet (Lenovo Tab M10 TB-X606X; Lenovo, Hongkong, China) and an activity device (Vivoactive 4; Garmin, Olathe, Kansas, US) for activity tracking. The CRBP-TS application (Diavention GmbH, Leipzig, Germany) was installed on the tablet and the activity device was connected to the tablet via Bluetooth. The CRBP-TS app was used to visualize training videos and transfer the heartrate data via chest belt from the device throughout the training, to receive activity feedback (steps per day, activity time), and to fill in different questionnaires. The app of the CG was not equipped with training videos. The CG received standard care and basic information on lifestyle changes and physical activity according to the guidelines, as well as the wearable to get information on their activity (steps per day, activity time).

2.2.2. Clinical assessments

Body height and weight were measured to calculate the body mass index. Segmental bioimpedance served to analyze fat mass and lean body mass (*Lean body mass* is defined as the difference between total body weight and fat mass) (Leipzig & Dresden: BIACORPUS RX 4004M, MEDI CAL HealthCare GmbH, Germany; Hannover: InBody720; Biospace, Seoul, Republic of Korea). Thereby, a low-level electric current flows through the body tissue. Varying resistance to the current flow is shown depending on the type of tissue. Fatty tissue triggers strong impedance and structures, whereas tissue with aqueous content reveals low impedance (42).

Blood samples were collected at T1, T2, and T3 to assess potentially predictive outcome factors. The adipose and metabolic markers used in this study included HbA1c, Leptin, Adiponectin, Insulin, and Triglycerides. Ethylenediaminetetraacetic acid plasma was analyzed at each study center and serum was collected, centrifuged, and stored at −80°C until analysis. All serum samples were analyzed in a central core laboratory (Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University Hospital Leipzig).

TABLE 1 MEDAS questionnaire (38).

Questions	Criteria for 1 point
1. Do you use olive oil as main culinary fat?	Yes
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥4 tbsp
3. How many vegetable servings do you consume per day? [1 serving: 200 g (consider side dishes as half a serving)]	≥2 (≥1 portion raw o raw a salad)
4. How many fruit units (including natural fruit juices) do you consume per day?	≥3
5. How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving: 100–150 g)	<1
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving: 12 g)	<1
7. How many sweet or carbonated beverages do you drink per day?	<1
8. How much wine do you drink per week?	≥7 glasses
9. How many servings of legumes do you consume per week? (1 serving: 150 g)	≥3
10. How many servings of fish or shellfish do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	<3
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving: 30 g)	≥3
13. Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes
14. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek, or garlic and simmered with olive oil)?	≥2

The Mediterranean Diet Adherence Screener (MEDAS) was used to determine patients' adherence to the Mediterranean diet. It includes 14 questions in all, 12 questions on food consumption and frequencies, and 2 questions on eating habits considered to characterize MD (43). The evaluation is done by earning 0 or 1 point (Table 1). If a criterion is not met, 0 points are recorded.

2.3. Statistical analyses

All values are expressed as the means and standard deviation unless otherwise stated, and the significance level was defined as $p < 0.05$. Data were analyzed via IBM SPSS Statistics (Version 29; IBM, Armonk, New York, USA) and displayed using GraphPad Prism (Version 9; GraphPad Software Inc., California, USA). For distribution analysis, the D'Agostino-Pearson normality test was used. The evaluation was conducted on an intention-to-treat basis, and all randomized participants were included. Per-protocol analyses were conducted including only IG participants

10.3389/fnut.2023.1152218

who completed all study visits and who had engaged in at least 1.5 training sessions per week. All analyses were two-sided, and the level of significance was $p = 0.05$. To evaluate the endpoints, we applied mixed-effects models with a repeated-measurements structure (estimated using restricted maximum likelihood). In this model, the measured values (baseline, 3-month and 6-month follow-ups) were treated as the dependent variable. As fixed effects we have included the randomization arm and categorical time covariate in the model. Interactions were modeled for group and time. As random effect(s), an intercept for subjects was used. Within the mixed models, we calculated 95% confidence intervals and *p*-values for contrasts between groups for the 3- and 6-month periods. In a sensitivity analysis, only those patients were included who had complete paired baseline and 6-month follow-ups for time difference within groups (paired *t* test for dependent samples).

3. Results

Table 2 illustrates the entire sample's baseline clinical characteristics ($N = 148$) by randomized group assignment. The groups showed baseline imbalances.

All results of the mixed model for body composition, laboratory markers, MEDAS, physical activity parameters are in Table 3 (intent-to-treat analysis). Sixty-two patients completed the 6 months study period in IG (14 dropouts). Fourty-six (74%) of those patients performed at least 1.5 training sessions per week. Results of the per-protocol analysis were similar to the main results of the trial (Supplementary Table S1) and three-month visit data are presented in Supplementary Table S2.

3.1. Body composition

After 6 months of intervention, we observed no statistically significant interaction between time and group in body weight [$F_{(2,247)} = 1.655$, $p = 0.19$], fat mass [$F_{(2,246)} = 2.796$, $p = 0.063$] and lean body mass [$F_{(2,196)} = 0.082$, $p = 0.92$] parameters (Table 3). However, body fat mass [$F_{(2,252)} = 8.44$, $p < 0.001$] revealed a significant time effect and group effect [$F_{(1,85)} = 3.966$, $p = 0.05$]. Lean body mass also showed a significant time effect [$F_{(2,202)} = 13.0$, $p < 0.001$; Table 3].

3.2. Laboratory parameters

Blood samples failed to reveal a statistically significant interaction effect between time × group for HbA1c% [$F_{(2,248)} = 0.450$, $p = 0.64$], Insulin [$F_{(2,241)} = 1.127$, $p = 0.33$], Adiponectin [$F_{(2,245)} = 0.144$, $p = 0.87$], Leptin [$F_{(2,243)} = 0.653$, $p = 0.52$] and Triglycerides [$F_{(2,254)} = 0.844$, $p = 0.43$; Table 3]. Only Adiponectin showed significance in the time effect [$F_{(2,245)} = 11.78$, $p < 0.001$], and Leptin in the group effect [$F_{(1,141)} = 4.85$, $p = 0.03$; Table 3].

TABLE 2 Baseline characteristics in the intervention vs. control group.

	Mean (SD) Intervention group ($n = 76$)	Mean (SD) Control group ($n = 72$)
Age (years)	54.4 ± 1	54.6 ± 1
Sex		
Female (%)	45 (59)	43 (60)
Male (%)	31 (41)	29 (40)
Height (cm)	172 ± 8.2	171 ± 11.0
Body composition		
Weight (kg)	78.8 ± 15.3	74.9 ± 15.3
Fat mass (kg)	24.6 ± 10.3	21.3 ± 8.4
Lean body mass (kg)	54.2 ± 11.1	53.6 ± 10.6
Body mass index (kg/m^2)	26.9 ± 4.5	25.1 ± 4.7
Waist to hip ratio	0.90 ± 0.2	0.88 ± 0.1
Cancer entity no. (%)		
Colorectal cancer	10 (13)	9 (12)
Breast cancer	43 (57)	41 (57)
Prostate cancer	23 (30)	22 (31)
Dropouts no. (%)	14 (18)	12 (17)
SAE's no. (hospitalizations)	11	7
Comorbidities no (%)		
Diabetes type 2	4 (5)	2 (3)
Hypertension	23 (30)	17 (24)
Adipositas	4 (5)	0 (0)
Cardiovascular diseases	2 (3)	3 (4)
Hypothyroidism	13 (17)	15 (21)
Asthma	2 (3)	2 (3)

Values are presented as the means and standard deviation.

3.3. MEDAS

Statistical analysis of the Mediterranean Diet Adherence Screener (MEDAS) showed no significance in the interaction effect [$F_{(1,112)} = 0.056$, $p = 0.81$] or in the group effect [$F_{(1,131)} = 2.870$, $p = 0.09$; Table 3]. We detected a significant increase in mediterranean dietary habit across the groups [$F_{(1,113)} = 4.995$, $p = 0.03$] during study period (Table 3).

4. Discussion

The main findings of this randomized controlled trial involving individualized home-based training and activity feedback information were a reduction in fat mass and an increase in lean body mass, with no differences between patients in IG and CG. The intervention group tended to demonstrate a more reduced fat mass than the control group. Dietary behavior and steps per day did not differ between intervention and control patients. The metabolic

TABLE 3 Laboratory parameters, body composition, nutrition questionnaire and activity score at baseline and after 6 months (intent to treat analysis; mixed model with repeated measurements; T1–T3).

	Mean (SD) [sample size]						Difference[b] 6 months IG vs. CG (95% CI)	Time effect[c]	Group effect[c]	Inter-action effect[c]
	Intervention group			Control group				*p*-value	*p*-value	Group × time *p*-value
	T1	T3	Diff[a]	T1	T3	Diff[a]				
Laboratory										
HbA1c%	5.4 (0.4) [76]	5.5 (0.3) [62]	0.04 (0.4) [62]	5.4 (0.6) [71]	5.4 (0.3) [59]	0.05 (0.3) [59]	−0.017 (−0.15 to 0.09)	0.18	0.71	0.64
Insulin (pmol/L)	68.8 (53.2) [76]	62.9 (32.4) [61]	−2.3 (34.9) [61]	63.9 (53.5) [71]	61.8 (38.9) [59]	−1.1 (49.5) [59]	7.2 (−18 to 33)	0.81	0.71	0.33
Adiponectin (mg/L)	8.4 (5.6) [76]	9.5 (7.6) [62]	**1.4*** (3.9) [62]	9.1 (5.5) [71]	10.1 (5.8) [59]	**1.3*** (3.3) [59]	0.2 (−0.8 to 1.3)	**<0.001**	0.49	0.87
Leptin (ng/mL)	17.0 (20.3) [75]	14.8 (15.8) [62]	−2.2 (10.8) [62]	12.0 (13.7) [71]	10.2 (9.0) [59]	−0.01 (8.4) [59]	−1.1 (−4.7 to 2.3)	0.16	**0.03**	0.52
Triglycerides (mmol/L)	1.5 (0.6) [76]	1.5 (1.1) [62]	−0.1 (0.7) [62]	1.3 (0.8) [71]	1.4 (0.5) [59]	−0.03 (0.6) [59]	0.1 (−0.1 to 0.3)	0.58	0.28	0.43
Body-composition										
Weight (kg)	78.8 (15.3) [74]	79.7 (15.6) [63]	−0.28 (3.5) [63]	74.8 (15.3) [71]	74.2 (14.7) [60]	0.57 (2.5) [60]	−0.8 (−1.7 to 0.1)	0.75	0.15	0.19
Fat mass (kg)	24.6 (10.4) [74]	23.7 (10.1) [63]	**−1.2*** (3.2) [63]	21.3 (8.4) [71]	20.3 (7.3) [60]	−0.2 (2.4) [60]	**−0.9#** (−1.8 to −0.1)	**<0.001**	0.05	0.06
Lean body mass (kg)	54.2 (11.1) [74]	55.9 (12.3) [63]	**0.9*** (3.3) [63]	53.6 (10.6) [71]	54.0 (11.4) [60]	**0.8*** (1.9) [60]	0.05 (−0.8 to 0.9)	**<0.001**	0.74	0.92
Nutrition										
MEDAS	5.7 (2.2) [72]	6.1 (2.3) [52]	0.40 (2.2) [52]	6.2 (2.2) [63]	6.9 (2.5) [50]	0.5 (2.5) [50]	0.7 (−0.2 to 1.6)	**0.03**	0.09	0.81
Activity										
Steps per day[d]	8,069 (3,026) [74]	8,226 (2,687) [68]	−40 (1,680) [67]	8,625 (2,878) [69]	8,121 (2,712) [60]	−475 (2,655) [58]	500 (−175 to 1,176)	0.18	0.48	0.34

mo, months; diff, difference; HbA_{1c}, glycosylated hemoglobin.

[a]Sensitive analysis: results of the complete case analysis considering all available data.

[b]Estimates of differences between group changes.

[c]Main effects of mixed-effects models.

[d]Pre = week 1 to week 8 and 6 mo = week 17–week 25.

*Significant difference ($p < 0.05$; within groups).

#Significant difference ($p < 0.05$; between groups); reference ranges: Hba1c% <5.7; Insulin 20–144 pmol/L; Triglyceride <1.7 mmol/L; Adiponectin & Leptin depends on age and BMI. Significant results are highlighted in bold.

10.3389/fnut.2023.1152218

laboratory parameters also indicated no group differences, although they were already within the reference range (non-pathological) before the intervention.

4.1. Body composition

A reduction in fat mass and increase in lean body mass were evident throughout the entire study group without group differences. We noted a tendency for a greater loss of fat mass in the IG than in the CG [−1.2 vs. −0.2 kg; $p = 0.06$; estimates of differences of group changes after 6 months: −0.9 (−1.8 to −0.1)]. In line with this, we identified no time or group changes in weight. Christensen et al. (21) and Leclerc et al. (44) were unable to demonstrate significant changes in body composition via home- or group-based exercise programs either. However, Christensen's intervention was only 12 weeks and purely home-based interval walking training. Leclerc's intervention period was 12 weeks, during which 1.5 h of cardiovascular and muscular endurance training was done three times per week by supervised groups (21).

Note that the decrease in fat mass and increase in lean body mass should be positively stressed, as sarcopenia promotes the development of cancer and raises the mortality rate of cancer patients (45, 46). The inverse change in fat mass and lean body mass results in an unchanged body weight (Table 3).

A published study showed that the extent of body fat mass-loss depends on the training intensity (47). Courneya et al. (48) came to a similar conclusion when they investigated the influence of different exercise intensities and types in breast cancer patients in different weight categories. The different types of intervention were only aerobic exercise at low or high volume, and a low volume aerobic exercise together with resistance training. Their results showed that normal-weight to slightly overweight patients benefited most from higher-dose exercise, whereas overweight patients benefited most from combined exercise. Our study subjects had a mean BMI of 26.9 (IG) and 25.1 (CG) and the training intensity was the individual heart frequency adapted to each patient's capacity according to their baseline exercise test. Had we taken additional weight-based measurements of exercise intensity, we might have observed a stronger effect on the change in body composition in our study. This assumption is supported by Courneya's results (13), where a recommended increase in physical activity of 10 MET- hours/week among colon cancer patients failed to result in significant weight change. Furthermore, our analysis of the activity data (steps per day) showed no group difference or interaction effect between IG and CG patients. The CG, like the IG, received feedback information on their physical activity, suggesting a relevant effect on activity behavior. In our opinion, this may also be a reason for the lack of group difference in body composition. In addition, the fact that CRBP-TS training was exclusively home-based exercising may be behind the lack of significance. Telemedicine-based exercise interventions in cancer patients have revealed improvements in functional capacity and can maintain such improvement long-term (49), nevertheless, the effects on physical activity have been small (23). Studies involving supervised training in groups have proven to lead to a significant decrease in BMI, body weight, or fat mass (32, 39).

4.2. Laboratory parameters

Adiponectin revealed significance in the time effect ($p < 0.001$). We noted an increase in the IG of +1.4 mg/L and in the CG of +1.3 mg/L (estimates of difference between IG vs. CG = 0.2 mg/L) on average. This result is supported by the study by Lee (22), who observed a significant rise in Adiponectin levels after a 12-week exercise intervention entailing increased physical activity of 18 MET/week. The systematic review by Simpson and Singh (50) detected a significant change in Adiponectin levels only in one third of randomized controlled trails.

The Leptin concentrations differed significantly between IG and CG ($p = 0.03$), which is attributable to the IG's higher weight. The change in Leptin concentration did not differ in IG and CG (difference between IG vs. CG = −1.1 ng/mL). The review by Bouassida et al. (51) and studies by Fatouros et al. (52) and Dieli-Conwright et al. (53) also demonstrated such an increase in Adiponectin, and a slight change in Leptin due to aerobic and/or resistance training. However, most of their study subjects presented a higher BMI than ours, and were overweight or obese (52, 53). As mentioned above, our study subjects tended to be of normal weight. Furthermore, their nonsignificant decrease in Leptin could be related to consistent body weight and an only slightly reduced body fat mass (51–54). An intervention's intensity also affects changes in metabolic blood parameters. Thus, a subthreshold training intensity may be responsible for the nonsignificant change in Adiponectin and Leptin levels (47). Sturgeon et al. (47) also failed to demonstrate a drop in Leptin after an exercise intervention, suspecting a correlation with the subthreshold protocol.

As fasting Insulin levels were constant in our IG and CG (−2.3 pmol/L vs. −1.1 pmol/L; $p = 0.91$), we cannot confirm study findings that proved training's positive effect on fasting Insulin in cancer patients (22, 53, 55). All three studies investigated shorter intervention periods than our CRBP study, but more extensive training interventions (i.e., 190 or 210 min/week). A stable body weight or slight change in body composition may also counteract a more marked change in Insulin.

We detected no effect on Triglycerides (difference IG vs. CG = +0.1). Lee et al. (22) reported no significant decrease in Triglyceride levels either after 12 weeks of exercise intervention involving 18–27 MET/week. In contrast, de Jesus Leite et al. (56) reported a significant drop in Triglyceride levels after 12 weeks of resistance training entailing 150 min of exercise per week. Since none of the aforementioned studies also investigated a nutritional intervention, why a significant decrease in Triglyceride levels seems to be documented so seldom is difficult to explain.

4.3. MEDAS

Our evaluation of the Mediterranean Diet Adherence Screener (MEDAS) revealed a significant time effect ($p = 0.03$). However, interaction effects and any difference between IG and CG were not evident. The mean of both groups rose by just half a score point, +0.4 in IG and +0.5 in CG. The MD's final adherence can be classified as medium with a score of 6.1 (IG) and 6.9 (CG) (38).

Huo's meta-analysis (30) confirmed the positive impact of MD on body weight and blood parameters. We can thus assume that our CRBP-TS study's missing effects on body weight and laboratory parameters are related to the unchanging MEDAS scores. Note that none of our patients received nutritional instructions, or were encouraged to follow the Mediterranean Diet.

4.4. Limitations

Our study obviously has strengths and limitations that need to be understood. One limitation of our multicenter study is that the technologies applied to measure body composition were not the same at all study centers. Furthermore, the training implementation was not monitored on a daily basis—rather, that was sometimes done retrospectively, or after subjects reported having had problems. According to our per-protocol analyses, 74% of the IG fulfilled the recommended 75% of the number of workouts of at least 2.0 per week. To achieve more meaningful results in the future, we will need to monitor home-based training more closely. Thirdly, we can assume that mostly exercise-enthusiastic cancer patients participated in this study revealed by their normal body weight and lean body mass values. This is another potential explanation for their minor improvement in body composition. Fourth, the CG also got activity feedback from their fitness tracker. We therefore assume that there was a motivational influence. Our CG participants may have increased their activity after study entry and thereby limited our ability to detect a difference between groups. We did not conduct complete blinding in our study because that could have triggered a high drop-out rate among CG patients for negative motivational reasons. As another limitation, we must mention the low number of training sessions and low intensity due to the patients' postoperative condition, especially compared to other studies (53, 55, 56).

4.5. Conclusion

Individualized home-based training in postoperative cancer patients revealed only small changes, and no group differences in body composition and metabolic laboratory parameters. Activity feedback information given to IG and CG seems to contribute significantly to positive lifestyle management. To the best of our knowledge, the present results are the first describing the effect of home-based training (aerobic and resistance) on the blood parameters Adiponectin, Leptin, fasting Insulin, and Triglyceride concentrations in female and male patients with breast cancer, prostate cancer, or colorectal cancer in conjunction with the acquisition of Mediterranean nutrition. Our study cohort's body composition and laboratory parameters were predominantly in the reference range (non-pathological) at baseline, which may explain the minor change without group differences attributable to the training intervention.

More high-quality studies are needed to explore and demonstrate more accurately the physiological and metabolic changes triggered by exercise in breast, prostate and colorectal cancer patients, and before a true dose–response relationship can be identified.

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.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Medical Faculty, University of Leipzig. 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. Protocol No.: Leipzig 056/20-ek; Dresden BO-EK-581122020; Hannover 9195_BO_K_2020.

Author contributions

RF and MB conceived and designed the study. RT organized and planned the blood sample analysis. CB, IG, UT, PH, and JV gave advice on the implementation of the study design at the study sites and are involved in recruitment and data acquisition. RF, CB, SD, and JV analyzed and interpreted the data. SD and RF wrote the original draft. All authors substantively revised the work for important intellectual content and have read and approved the submitted manuscript.

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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.2023.1152218/full#supplementary-material

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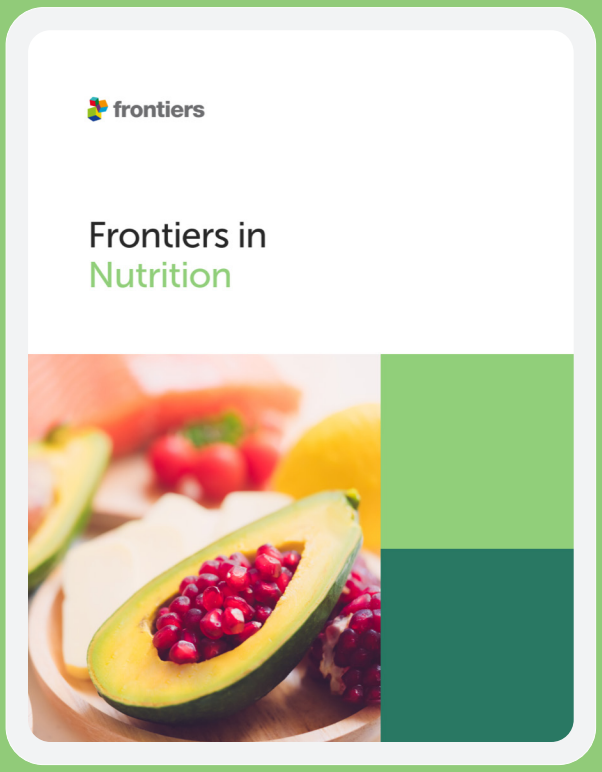

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