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RESEARCH ARTICLE

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Effect of adipose-related parameters on mortality in patients with liver cirrhosis: a meta-analysis

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ABSTRACT

Background: Some adipose-related parameters exhibit distinct prognostic value in patients with cirrhosis. However, the magnitude and direction of the association between individual adipose parameter and mortality in patients with cirrhosis are unclear.

Aim: This study aimed to evaluate the association between individual adipose parameter and mortality in patients with cirrhosis using the meta-analysis method.

Methods: The PubMed, Embase, Web of Science, China Biological Medicine, WanFang, and China National Knowledge Infrastructure databases were searched from inception through December 15, 2023, to identify eligible studies. The impact of each adipose parameter on mortality was assessed by the pooled unadjusted or adjusted hazard ratio (HR) with 95% confidence intervals (CIs) using the random effects model.

Results: A total of 33 studies involving 9626 patients were included in our analysis, with 11 adipose parameters evaluated. The pooled prevalence of sarcopenic obesity (SO) and myosteatosis in patients with cirrhosis was 15.5% and 34.4%, respectively. In adjusted analysis, each unit increase in subcutaneous adipose tissue index (SATI) (HR: 0.99, 95% CI: 0.98–1.00) or muscle attenuation (MA) (HR: 0.94, 95% CI: 0.90–0.98) and each unit decrease in visceral-to-subcutaneous adipose tissue ratio (VSR) (HR: 1.92, 95% CI: 1.45–2.54) showed an independent association with a decreased risk of mortality. However, concurrent myosteatosis (HR: 1.88, 95% CI: 1.48–2.40) or SO (HR: 2.77, 95% CI: 1.95–3.93) significantly increased the risk of mortality in patients with cirrhosis.

Conclusion: Decreased SATI or MA, increased VSR, and concurrent myosteatosis or SO were independently associated with a higher risk of mortality in patients with cirrhosis.

CORE TIP

The associations between various adipose parameters and mortality in patients with cirrhosis remain to be determined. Therefore, we performed the first meta-analysis to determine the effect of adipose parameters on survival in patients with cirrhosis. A total of 33 studies involving 11 adipose parameters were assessed in our analysis. We found that different adipose parameters exhibited varying prognostic value: decreased subcutaneous adipose tissue index or muscle radiodensity, increased visceral-to-subcutaneous ratio, and concurrent myosteatosis or sarcopenic obesity were independently associated with a higher risk of mortality in patients with cirrhosis. Prognostic models based on these adipose parameters will contribute to the individualized management of patients with liver cirrhosis.

Abbreviations: BMI: body mass index; CT: computed tomography; SO: sarcopenic obesity; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; MOOSE: Meta-analysis of Observational Studies in Epidemiology; CBM: China Biological Medicine; CNKI: China National Knowledge Infrastructure; HR: hazard ratio; CI: confidence interval; VFA: visceral fat area; VATI: visceral adipose tissue index; SFA: subcutaneous fat area; SATI: subcutaneous adipose

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tissue index; VSR: visceral-to-subcutaneous adipose tissue ratio; MA: muscle attenuation; VFD: visceral fat density; SFD: subcutaneous fat density; HSC: hepatic stellate cell; NAFLD: non-alcoholic fatty liver disease; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue

Introduction

Liver cirrhosis is an advanced stage of liver diseases and is responsible for a heavy global burden on medical and financial resources [1]. Recent epidemiological studies have documented an increasing prevalence of cirrhosis and a 47.15% increase in cirrhosis-related mortality from 1990 to 2017 [2]. In 2019, deaths attributed to cirrhosis reached 1.48 million [3]. Cirrhosis is classified as compensated or decompensated based on the presence of ascites, hepatic encephalopathy, variceal bleeding, and jaundice [4]. The occurrence of decompensation events indicates a significant reduction in the patient's life expectancy. The median survival time of patients with compensated cirrhosis is about 12 years, whereas the life expectancy in patients with decompensated cirrhosis is less than 2 years [5]. Therefore, prognostic assessment of patients with cirrhosis is essential but remains challenging.

The Child-Turcotte-Pugh score and the model for end-stage liver disease are the most widely applied prognostic scores in clinical practice [6]. However, they have several limitations, such as the inclusion of subjective components and limited predictive accuracy [7]. Most notably, they fail to consider the assessment of body composition parameters. Previous studies have shown a significant association between body composition and prognosis in patients with cirrhosis [8]. In particular, the association between sarcopenia and mortality has been recently documented [9]. In addition to muscle, body fat is also a body composition parameter associated with the prognosis of patients with cirrhosis [10,11]. Although body mass index (BMI) is commonly used to assess obesity, it is not a reliable indicator of body fat due to its susceptibility to be influenced by factors such as lean muscle mass, bone mass, and the presence of ascites.

Body composition can be assessed by various methods, such as bioelectrical impedance analysis, dual-energy X-ray absorptiometry, and computed tomography (CT) scan [12]. CT can differentiate body composition and the location of various adipose tissues (i.e. visceral, subcutaneous, intermuscular), and it avoids the influence of ascites [13]. A previous study demonstrated that CT cross-sectional areas of adipose tissue at the lumbar vertebra 3 were representative of whole body adipose tissue [14]. Although some adipose parameters, such as visceral adipose, subcutaneous adipose, myosteatosis, and sarcopenic obesity (SO) have been shown to be associated with the prognosis of patients with cirrhosis, the conclusions are undetermined [10,11,15]. To date, no meta-analysis has been performed to evaluate the association between adipose parameters and the risk of mortality in patients with cirrhosis. Therefore, we conducted a systematic review and meta-analysis to determine the effect of adipose parameters on survival in patients with cirrhosis.

Methods

Search strategy and literature selection

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement [16] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist [17], and the study protocol was preregistered on PROSPERO (CRD42022307253). Two researchers independently conducted a literature search across multiple databases, including PubMed, Embase, Web of Science, China Biological Medicine (CBM), WanFang, and China National Knowledge Infrastructure (CNKI), to identify relevant studies that examined the association between adipose-related parameters and mortality in patients with cirrhosis. The search terms included cirrhosis, adipose-related keywords, prognosis, and study type. The literature search covered the period from inception to May 19, 2022, and was updated on December 15, 2023. There were no language restrictions, and the search was confined to human studies. Detailed search strategies are provided in Supplementary Table 1. In addition, the references of included studies and relevant reviews were manually checked for potential studies. In studies with overlapping cohorts, preference was given to those with more recent or comprehensive data. Any discrepancies were resolved through consultation with a third reviewer.

Eligibility criteria

Inclusion criteria included: 1) Participants: Adult patients with biopsy-confirmed or clinically-confirmed

liver cirrhosis; 2) Exposures: BMI was defined as weight (kg) divided by the square of height (m). Other adipose parameters, such as subcutaneous adipose, visceral adipose, myosteatosis, and SO, were objectively measured, with no restrictions on the measurement methods or definitions. A minimum of two original studies was required for each parameter; 3) Outcomes: Studies reporting the association between adipose parameters and risk of all-cause mortality in the form of hazard ratios (HRs) and corresponding 95% confidence intervals (CIs); and 4) Study design: Prospective or retrospective cohort study. Studies were excluded if they included post-liver transplantation patients, had insufficient follow-up duration (less than 6 months), or had overlapping cohorts. Non-original studies or conference abstracts and studies with incomplete/unavailable data were also excluded.

Data extraction and quality assessment

Using a standardized data extraction form, two researchers independently extracted relevant information from each included study. The first author's name, the year of publication, study region and design, adipose parameter measurement method, adipose parameters, total sample size, male proportion, mean age, etiology of cirrhosis, severity of liver dysfunction, presence of hepatocellular carcinoma, adjusted variables, and duration of follow-up. Two researchers independently assessed the quality of the included studies using the Newcastle-Ottawa Scale with a maximum total score of 9 points [18]. The score is comprised of three main categories: Cohort selection (up to 4 points); intergroup comparability (up to 2 points); and outcome measurement (up to 3 points). Studies with a cumulative score of ≥ 7 were considered high quality (low risk of bias), those with scores between 4 and 6 were categorized as moderate quality (moderate risk of bias), and those with scores of 0 to 3 were deemed low quality (high risk of bias).

Statistical analysis

The prevalence of dichotomous adipose parameters and their corresponding 95% CIs were pooled using the random effects model and the logit transformation method. The primary outcome of this meta-analysis was the mortality risk associated with various adipose parameters in patients with cirrhosis. The effect of each adipose parameter on mortality was assessed by the pooled unadjusted or adjusted HR with 95% CIs using the random effects model (DerSimonian-Laird method). Heterogeneity across studies was evaluated using the I^2 and Cochran's Q statistic. A p value of ≤ 0.1 for the Q statistic or an $I^2 \geq 50\%$ was considered indicative of significant heterogeneity. Funnel plots and Egger's test were used to assess potential publication bias. If publication bias was detected, the trim-and-fill method was applied to evaluate the impact of potentially unpublished articles on pooled estimates. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant. The statistical analyses were performed using the "meta" package of R software (version 4.0.2).

Results

Literature search

The initial literature search yielded a total of 15235 potentially eligible records: 3474 from PubMed; 6001 from Embase; 5258 from Web of Science; 293 from CBM; 102 from WanFang; and 107 from CNKI. After excluding 5822 duplicate records and screening 9413 records by the titles and abstracts, 226 articles remained for a full-text review. Among these, 193 articles were excluded. Finally, 33 cohort studies [10,11,15,19–48] involving 9626 patients were included in this meta-analysis. The literature screening process is shown in Figure 1.

Study characteristics and quality assessment

The baseline characteristics of the included studies are presented in Table 1. Among the 33 studies [10,11,15,19–48], 25 [11,15,20,22,23,25–29,31–35,37,39–46,48] were retrospective cohort studies, and 8 [10,19,21,24,30,36,38,47] were prospective cohort studies. All the studies were published between 2016 and 2023. Among them, 9 studies [15,19,27,32,37,39,41,45,48] were conducted in China, 7 [20,23,26,31,35,43,46] in Japan, 5 [24,28,30,38,42] in the United States, 4 [10,11,34,40] in Canada, 2 in South Korea [21,47], 2 [25,36] in Greece, and one each in Italy [22], Germany [33], the United Kingdom [44], and France [29]. The sample sizes varied from 76 to 786 patients, and the mean age of patients ranged from 50 to 71 years. The proportion of male patients ranged from 46.2% to 88.1%. The mean follow-up period across studies ranged from 6.0 to 92.3 months. The majority of studies used CT scans to assess adipose tissue at the lumbar 3 level. Among the 33 cohort studies, 30 [10,11,15,19–24,26,28–38,40–48] were high-quality, while 3 [25,27,39] were moderate quality (Supplementary Table 2).

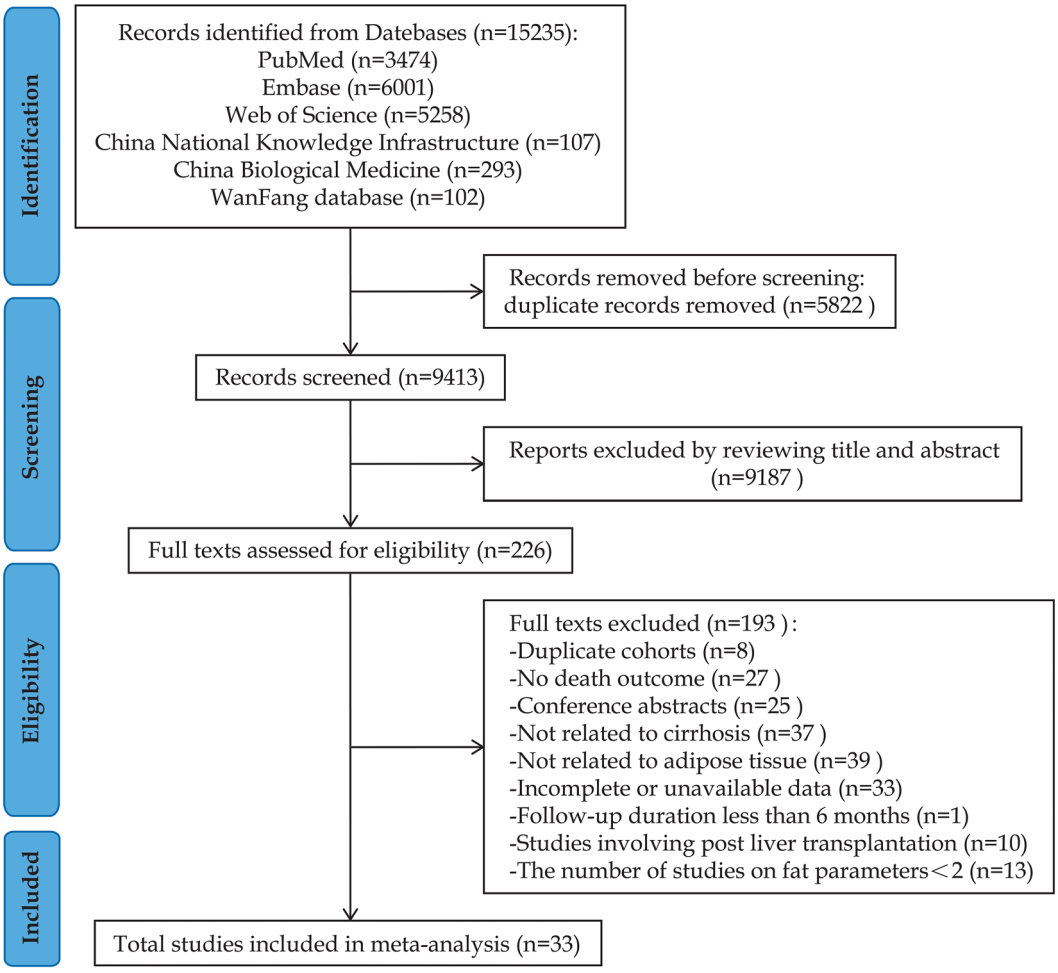


Figure 1. Flow diagram for literature search and selection.

Adipose parameters included in this meta-analysis

A total of 16 adipose parameters were initially identified from the included studies. Five parameters, including fat mass index, total adipose tissue index, triceps skinfold thickness, upper mid-arm fat area, and the subscapular-to-triceps skinfold thickness ratio, were excluded due to the insufficient number of studies (less than 2). In total, 11 adipose-related parameters were included in the mortality risk analysis. They included BMI, visceral fat area (VFA), visceral adipose tissue index (VATI), subcutaneous fat area (SFA), subcutaneous adipose tissue index (SATI), visceral-to-subcutaneous adipose tissue ratio (VSR), myosteatosis, SO, muscle attenuation (MA), visceral fat density (VFD), and subcutaneous fat density (SFD) (Supplementary Figure 1).

Adipose parameters and mortality

BMI and mortality

Eleven studies ($n=3274$) provided unadjusted data regarding the association between BMI and mortality. The pooled crude HR was 0.98 (95% CI: 0.95–1.01), and there was significant heterogeneity (I^2 = 47%, $p=0.04$). The data from multivariate analysis were lacking because almost all the univariate analyses did not achieve statistical significance (Figure 2; Supplementary Figure 2).

Visceral fat and mortality

VFA showed no significant association with a higher mortality risk in both unadjusted (4 studies, $n=891$) and adjusted analyses (3 studies, $n=714$). The pooled crude HR was 1.00 (95% CI: 0.99–1.01), and the adjusted HR was 1.17 (95% CI: 0.90–1.53), with low heterogeneity (I^2 = 37%, $p=0.20$) (Figure 2; Supplementary Figure 3).

Five studies analyzed VATI and mortality ($n=1875$). There was no association with mortality in the unadjusted analysis, showing a pooled unadjusted HR of 1.00 (95% CI: 1.00–1.00, I^2 = 0%, $p=0.90$). Similarly, in multivariate analysis only 2 studies ($n=661$) were included, and the pooled adjusted HR was not

Table 1. Main characteristics of included studies.

Author (year)	Country	Study design	Measuring methods of adipose parameters	Adipose parameters	Total sample size	Male %	Age (years)	Etiology of cirrhosis	Severity of liver dysfunction	HCC %	Adjustment variables	Follow-up time
Ebadi et al. [10] (2018)	Canada	prospective cohort	CT scans at L3	VATI, SATI	677	67.4	57	virus, 46% alcohol, 23% others, 31%	MELD score: 14	43	age, etiology, albumin, MELD score	21.0 months
Hou et al. [19] (2020)	China	prospective cohort	CT scans at L3	VSR, Myosteatosis	274	52.6	62	virus, 24% alcohol, 21% others, 55%	MELD score: 12	no	age, MELD score, CTP score, SMI	36.0 months
Kimura et al. [20] (2021)	Japan	retrospective cohort	CT scans at the umbilical level	VATI	87	67.8	66	virus, 40% alcohol, 37% others, 23%	CTP score: 7	32	WC	28.1 months
Cho et al. [21] (2021)	South Korea	prospective cohort	CT scans at L3	VATI, SATI	166	70.5	54	virus, 26% alcohol, 61% others, 13%	MELD score: 11	no	NA	60.0 months
Montano-Loza et al. [11] (2016)	Canada	retrospective cohort	CT scans at L3	Myosteatosis, BMI SO, MA	678	67.4	NA	virus, 46% alcohol, 23% others, 31%	MELD score: 15	43	INR, albumin, bilirubin, sodium, sarcopenia, MELD score, CTP score, NASH-cryptogenic cirrhosis	21.0 months
Lattanzi et al. [22] (2019)	Italy	retrospective cohort	CT scans at L3	Myosteatosis	249	76.3	60	virus, 57% alcohol, 24% others, 19%	MELD score: 14	45	MELD score, ascites, previous HE, sarcopenia	92.3 months
Feng et al. [15] (2020)	China	retrospective cohort	CT scans at L3	SO	200	53.0	62	virus, 25% alcohol/NAFLD, 24% others, 51%	MELD score: 12	no	age, NLR, MELD score	24.0 months
Ishizu et al. [23] (2021)	Japan	retrospective cohort	CT scans at L3	SO, VFA	335	52.2	64	virus, 44% alcohol, 21% others, 35%	CP score: 6	no	age, etiology, CTP score	44.7 months
Tapper et al. [24] (2019)	USA	prospective cohort	CT scans at T12	VFA, SFA, VFD, SFD, MA	274	57.3	58	virus, 29% alcohol, 21% others, 50%	MELD score: 11	no	NA	61.5 months
Kalafateli et al. [25] (2018)	Greece	retrospective cohort	CT scans at L4/L5	Myosteatosis, BMI, MA	98	72.4	63	virus, 24% alcohol, 46% others, 30%	MELD score: 11	14	age, sex, HCC, CTP score	45.0 months
Hamaguchi et al. [26] (2020)	Japan	retrospective cohort	CT scans at L3	Myosteatosis, VSR	173	56.1	50	virus, 36% others, 64%	MELD score: 15	8	neutrophil-lymphocyte ratio, MELD score, SMI	24.3 months
Yu et al. [27] (2020)	China	retrospective cohort	CT scans at L3	Myosteatosis, BMI	480	61.7	52/58	virus, 44% alcohol, 13% others, 43%	MELD score: 11.8	no	NA	24.0 months
Ronald et al. [28] (2020)	USA	retrospective cohort	CT scans at L3	SO	141	64.5	56	virus, 30% alcohol, 28% others, 42%	MELD score: 15	no	age, sex, emergent TIPS for refractory variceal bleeding, MELD score	16.7 months
Artru et al. [29] (2020)	France	retrospective cohort	CT scans at L3/L4	VFA, SFA	179	71.5	NA	virus, 4% alcohol, 86% others, 10%	MELD score: 12	no	MELD score, TPMT	overall: 6.0 months
Zou et al. [30] (2021)	USA	prospective cohort	CT scans at L3	VFA, SFA, VFD, SFD, MA	238	56.7	58	virus, 29% alcoholic, 21% others, 50%	MELD score: 10	no	NA	63.0 months
Okubo et al. [31] (2021)	Japan	retrospective cohort	CT scans at L3	VSR	181	68.0	67	virus, 77% others, 23%	NA	100	AJCC stage, CONUT grade, ASA score + 1, major hepatectomy	53.2 months

(*Continued*)

Table 1. Continued.

Author (year)	Country	Study design	Measuring methods of adipose parameters	Adipose parameters	Total sample size	Male %	Age (years)	Etiology of cirrhosis	Severity of liver dysfunction	HCC %	Adjustment variables	Follow-up time
Liu et al. [32] (2022)	China	retrospective cohort	CT scans at L3	Myosteatosis	224	71.0	54	virus, 78% alcohol, 8% others, 14%	MELD score: 12	no	NA	24.0 months
Engelmann et al. [33] (2022)	Germany	retrospective cohort	CT scans at L3/L4	VATI, SATI	612	66.7	52	virus, 8% alcohol, 64% others, 28%	MELD score: 17	no	age, BMI, MELD score, sex	12.0 months
Ebadi et al. [34] (2022)	Canada	retrospective cohort	CT scans at L3	SFA, VFD, SFD	786	66.7	56	virus, 48% alcohol, 24% others, 28%	MELD score: 15	43	NA	24.0 months
Ishizu et al. [35] (2022)	Japan	retrospective cohort	CT scans at L3	Myosteatosis	178	51.7	64	virus, 52% alcohol, 17% others, 31%	MELD score: 9	no	etiology, MELD score, albumin	61.0 months
Geladari et al. [36] (2023)	Greece	prospective cohort	CT scans at L3	SATI, VATI, Myosteatosis, BMI	197	67.0	61	viral, 23% alcohol, 43% others, 34%	MELD score: 11	no	age, BMI, MELD score, SMI	12.0 months
Zeng et al. [37] (2023)	China	retrospective cohort	CT scans at L3	Myosteatosis	480	61.7	NA	virus, 44% alcohol, 13% other, 43%	MELD score: 12	no	NA	24.0 months
Ha et al. [38] (2023)	USA	prospective cohort	CT scans at L3	SO	326	69.0	61	virus, 56% alcohol, 19% others, 25%	MELD score: 13	62	diabetes, ascites, HE, MELD-Na, liver frailty index	12.0 months
Chen et al. [39] (2022)	China	retrospective cohort	CT scans at L3	SATI, VATI, VSR, MA	223	64.6	53	virus, 57% alcohol, 16% others, 27%	MELD score: 12	no	age, MELD score, bilirubin, INR, albumin, HE, infection	65.1 months
Ebadi et al. [40] (2020)	Canada	retrospective cohort	CT scans at L3	VFD, SFD, MA, BMI	101	88.1	62	virus, 51% alcohol, 26% others, 23%	CTP class: B/C 31.7%	100	ALBI score, CTP score, number of tumors, BCLC stage, previous treatment, markers of portal hypertension	14.0 months
Zhang et al. [41] (2022)	China	retrospective cohort	CT scans at L3	MA	273	72.2	54	virus, 55% alcohol, 19% others, 26%	MELD score: 11	no	albumin, total bilirubin	12.0 months
Jahangiri et al. [42] (2019)	USA	retrospective cohort	CT scans at L4	MA	76	55.3	54	virus, 41% alcohol, 43% others, 44%	MELD score: 16	17	age, sex, hepatitis C virus infection, hepatocellular carcinoma, diabetes, baseline MELD score	13.5 months
Hanai et al. [43] (2019)	Japan	retrospective cohort	NA	BMI	563	66.6	71	virus, 60% alcohol, 15% others, 25%	CTP score: 6	71	NA	26.0 months
Benmassaoud et al. [44] (2022)	UK	retrospective cohort	NA	BMI	107	60.7	55	virus, 11% alcohol, 65% others, 44%	MELD score: 11	no	NA	14.2 months
Guo et al. [45] (2022)	China	retrospective cohort	NA	BMI	221	46.2	63	virus, 26% alcohol, 26% others, 48%	MELD score: 9	no	NA	24 months
Saeki et al. [46] (2023)	Japan	retrospective cohort	NA	BMI	126	61.1	71	virus, 39% alcohol, 37% others, 24%	MELD score: 9	no	NA	57.1 months

(*Continued*)

Table 1. Continued.

Author (year)	Country	Study design	Measuring methods of adipose parameters	Adipose parameters	Total sample size	Male %	Age (years)	Etiology of cirrhosis	Severity of liver dysfunction	HCC %	Adjustment variables	Follow-up time
Kim et al. [47] (2022)	South Korea	prospective cohort	NA	BMI	595	64.0	55	virus, 67% alcohol, 24% others, 9%	CTP score: 5	no	NA	30.1 month
Yin et al. [48] (2023)	China	retrospective cohort	NA	BMI	108	77.8	53	virus, 68% others, 32%	MELD score: 11	no	NA	24.0 month

HCC, hepatocellular carcinoma; CT, computed tomography; L3, 3rd lumbar vertebra; BMI, body mass index; VFA, visceral fat area; VATI, visceral adipose tissue index; SFA, subcutaneous fat area; SATI, subcutaneous adipose tissue index; VSR, the visceral-to-subcutaneous adipose tissue ratio; SO, sarcopenic obesity; MA, muscle attenuation; VFD, visceral fat density; SFD, subcutaneous fat density; MELD, the model for end-stage liver disease; CTP, the Child-Turcotte-Pugh; SMI, skeletal muscle index; WC, waist circumference; INR; international normalized ratio; NASH, non-alcoholic steatohepatitis; HE, hepatic encephalopathy; NLR, neutrophil-to-lymphocyte ratio; TIPS, transjugular intrahepatic portosystemic shunt; TPMT, transverse psoas muscle thickness; AJCC, American Joint Committee on Cancer; CONUT, Controlling Nutrition Status; ASA, American Society of Anesthesiologists; ALBI, the albumin–bilirubin; BCLC, the Barcelona Clinic Liver Cancer.

significant (adjusted HR: 1.03, 95% CI: 0.97–1.09, I^2 = 94%, $p < 0.01$) (Figure 2; Supplementary Figure 4).

Subcutaneous fat and mortality

Only the SFA and mortality data from the univariate analysis could be pooled. Four studies ($n = 1477$) showed no significant association between SFA and mortality. The pooled crude HR was 1.00 (95% CI: 0.99–1.00), with low heterogeneity (I^2 = 28%, $p = 0.24$) (Figure 2; Supplementary Figure 5).

We found that an increase of one unit in SATI was significantly associated with a decreased risk of mortality in both the unadjusted (5 studies, $n = 1875$) and the adjusted analyses (2 studies, $n = 1289$). The pooled crude HR was 0.99 (95% CI: 0.99–0.99), and the adjusted HR was 0.99 (95% CI: 0.98–1.00). No heterogeneity was observed in either analysis (I^2 = 0%) (Figure 2; Supplementary Figure 6).

VSR and mortality

A meta-analysis of three studies ($n = 670$) that analyzed VSR and mortality revealed a pooled HR of 2.46 (95% CI: 1.84–3.28), with no observed heterogeneity (I^2 = 0%, $p = 0.42$). Similarly, in the multivariate analysis (3 studies, $n = 628$), the pooled adjusted HR was 1.92 (95% CI: 1.45–2.54), and no heterogeneity was detected (I^2 = 0%, $p = 0.50$). Therefore, a one-unit increase in VSR was significantly associated with a 92% increased risk of mortality (Figure 2; Supplementary Figure 7).

Myosteatosis and mortality

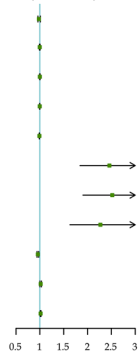
Ten studies ($n = 3031$) reported the prevalence data of myosteatosis in patients with cirrhosis, yielding a pooled prevalence of 34.4% (95% CI: 22.3–48.9%) (Figure 3A). In the univariate analysis, myosteatosis was associated with an increased risk of mortality, showing a pooled unadjusted HR of 2.52 (95% CI: 1.90–3.33). The heterogeneity between studies was high (I^2 = 62%, $p < 0.01$). In the multivariate analysis (6 studies, $n = 1749$), myosteatosis remained significantly associated with increased mortality, with a pooled adjusted HR of 1.88 (95% CI: 1.48–2.40), and a low likelihood of heterogeneity between studies (I^2 = 15%, $p = 0.32$) (Figure 2; Supplementary Figure 8).

So and mortality

Pooled data from 5 studies ($n = 1680$) revealed a pooled prevalence of 15.5% (95% CI: 12.3–19.5%) of SO in patients with cirrhosis (Figure 3B). In the univariate analysis (4 studies, $n = 1345$), SO was associated with an increased risk of mortality, as indicated by a

A

Adipose parameters	NO. of studies	NO. of patients	Unadjusted HR (95% CI)	P value	HR (95% CI)	I^2 value	$P_{heterogeneity}$
BMI, per one kg/m² increase	11	3274	0.98(0.95–1.01)	0.11		47%	0.04
VFA, per one cm² increase	4	891	1.00(0.99–1.01)	0.59		54%	0.09
VATI, per one cm²/m² increase	5	1875	1.00(1.00–1.00)	0.89		0%	0.90
SFA, per one cm² increase	4	1477	1.00(0.99–1.00)	0.21		36%	0.20
SATI, per one cm²/m² increase	5	1875	0.99(0.99–0.99)	<0.01		0%	0.89
VSR, per one unit increase	3	670	2.46(1.84–3.28)	<0.01		0%	0.42
Myosteatosis, (yes vs. no)	10	3031	2.52(1.90–3.33)	<0.01		62%	<0.01
SO, (yes vs. no)	4	1345	2.27(1.63–3.16)	<0.01		36%	0.20
MA, per one HU increase	8	1961	0.96(0.94–0.98)	<0.01		85%	<0.01
VFD, per one HU increase	4	1399	1.02(1.00–1.03)	0.03		88%	<0.01
SFD, per one HU increase	4	1399	1.02(1.01–1.02)	<0.01		67%	0.03



B

Adipose parameters	NO. of studies	NO. of patients	Adjusted HR (95% CI)	P value	HR (95% CI)	I^2 value	$P_{heterogeneity}$
VFA, per one cm² increase	3	714	1.17(0.90–1.53)	0.24		37%	0.20
VATI, per one cm²/m² increase	2	699	1.03(0.97–1.09)	0.39		94%	<0.01
SATI, per one cm²/m² increase	2	1289	0.99(0.98–1.00)	<0.01		0%	0.47
VSR, per one unit increase	3	628	1.92(1.45–2.54)	<0.01		0%	0.50
Myosteatosis, (yes vs. no)	6	1749	1.88(1.48–2.40)	<0.01		15%	0.32
SO, (yes vs. no)	4	1002	2.77(1.95–3.93)	<0.01		0%	0.89
MA, per one HU increase	4	670	0.94(0.90–0.98)	<0.01		75%	<0.01

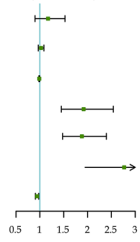


Figure 2. Pooled unadjusted and adjusted hazard ratios of the association between adipose-related parameters and mortality in patients with cirrhosis. A: Pooled unadjusted hazard ratios of the association between adipose-related parameters and mortality in patients with cirrhosis; B: Pooled adjusted hazard ratios of the association between adipose-related parameters and mortality in patients with cirrhosis. BMI, body mass index; CI, confidence interval; HR, hazard ratio; HU, Hounsfield units; SFD, subcutaneous fat density; SATI, subcutaneous adipose tissue index; SFA, subcutaneous fat area; so, sarcopenic obesity; MA, muscle attenuation; VFD, visceral fat density; VATI, visceral adipose tissue index; VFA, visceral fat area; VSR, visceral-to-subcutaneous adipose tissue ratio.

pooled unadjusted HR of 2.27 (95% CI: 1.63–3.16) with low observed heterogeneity (I^2 = 36%, p = 0.20). In the multivariate analysis (4 studies, n = 1002), the pooled adjusted HR was 2.77 (95% CI: 1.95–3.93), and no heterogeneity was observed between studies (I^2 = 0%, p = 0.89). The presence of SO was significantly associated with a 177% increased risk of mortality (Figure 2; Supplementary Figure 9).

Tissue radiodensity and mortality

Nine studies evaluated the association between tissue radiodensity and mortality. The association between MA and mortality was assessed in both unadjusted (8 studies, n = 1961) and adjusted analyses (4 studies, n = 670). The pooled crude HR was 0.96 (95% CI: 0.94–0.98), and the adjusted HR was 0.94 (95% CI: 0.90–0.98). Heterogeneity between studies was significant in both analyses (I^2 = 85%, p < 0.01 and I^2 = 75%, p < 0.01, respectively) (Figure 2; Supplementary Figure 10). A one-unit increase in MR was significantly associated with a 6% decreased risk of mortality.

Four studies (n = 1399) analyzed the association between VFD and mortality, which showed a pooled HR of 1.02 (95% CI: 1.00–1.03), with high heterogeneity (I^2 = 88%, p < 0.01) (Figure 2; Supplementary Figure 11). The association between SFD and mortality was assessed only in the unadjusted analysis (4 studies, n = 1399), and the pooled crude HR was 1.02 (95% CI: 1.01–1.02), with high heterogeneity (I^2 = 67%, p = 0.03) (Figure 2; Supplementary Figure 12).

Publication bias

Publication bias was assessed if at least three studies from the multivariate analysis were included [49]. Funnel plots and Egger's test showed potential publication bias for the pooled adjusted HRs of VFA (Supplementary Figure 13A). No publication bias was detected for the other adipose parameters (Supplementary Figures 14–17). Using the trim-and-fill method, two estimated HRs of VFA were added to achieve symmetry in the funnel plot (Supplementary Figure 13B). The resulting pooled adjusted HR was 1.04 (95% CI: 0.82–1.32) (I^2 = 38.2%, p = 0.17), which was similar to the results before using the trim-and-fill method (adjusted HR: 1.17, 95% CI: 0.90–1.53).

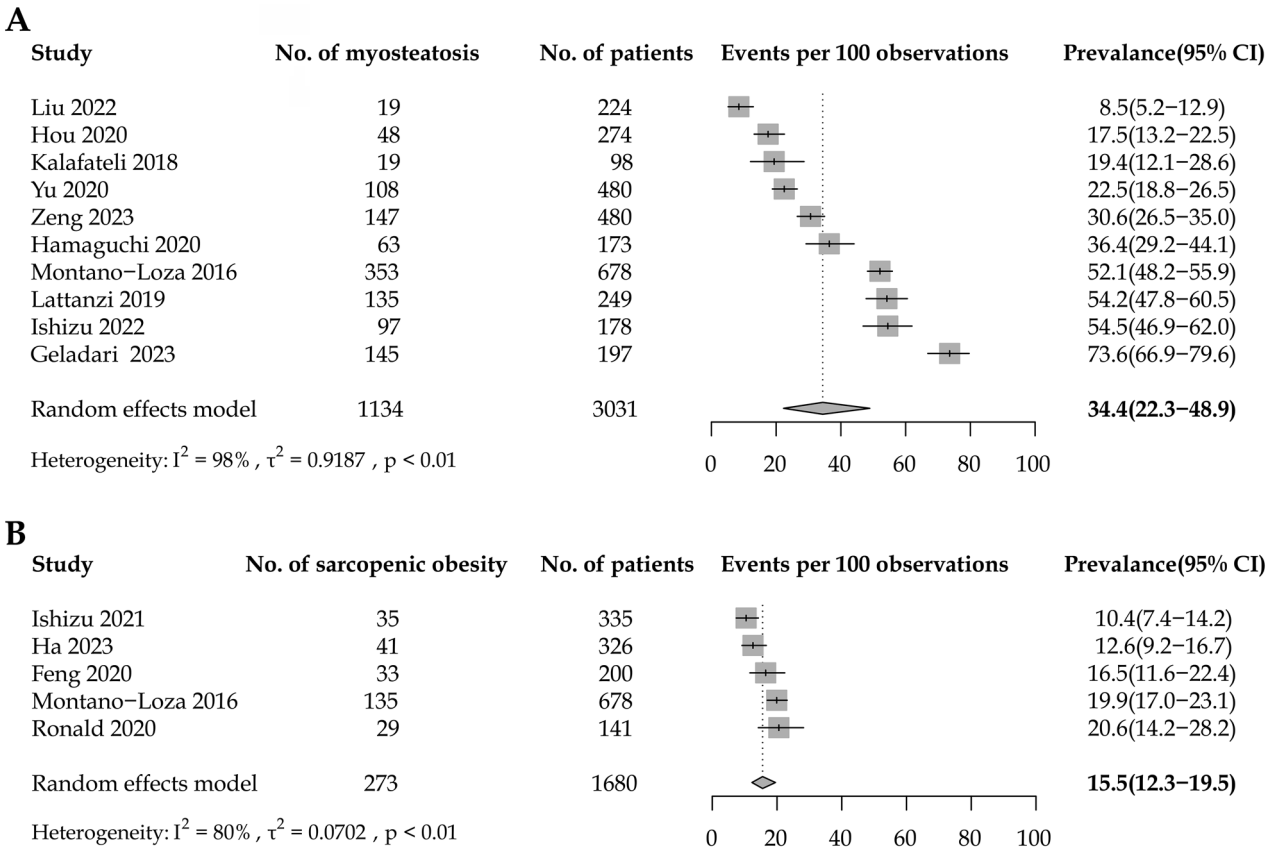


Figure 3. Pooled prevalence of myosteatosis and sarcopenic obesity in patients with cirrhosis. A: the prevalence of myosteatosis in patients with cirrhosis; B: the prevalence of sarcopenic obesity in patients with cirrhosis. CI, confidence interval.

Discussion

The aim of this meta-analysis was to assess the association between adipose-related parameters and mortality in patients with cirrhosis. In this systematic review and meta-analysis of 33 studies involving 9626 patients, we found that SATI and MA were associated with a decreased risk of mortality, while SFA, VSR, myosteatosis, SO, VFD, and SFD were associated with an increased risk of mortality in the univariate analysis. The association between mortality and SATI, VSR, myosteatosis, SO, and MA was similar in the multivariate analysis. Due to an insufficient number of studies, the multivariate analysis of VFD and SFD could not be conducted. Additionally, we observed a high prevalence of SO (16%) and myosteatosis (34%) in patients with liver cirrhosis.

According to our analysis, BMI has limited prognostic value despite being a conventional indicator for assessing obesity and body fat content. Patients with cirrhosis often have edema and ascites, which can affect the BMI value. The prognostic value of bone and muscle tissue is often different from that of adipose tissue [23], making BMI an inappropriate prognostic indicator in patients with cirrhosis. In recent years, adipose tissue has gained recognition as an endocrine organ capable of secreting both proinflammatory and anti-inflammatory cytokines and adipokines to regulate organ function [50]. Adipokines are bioactive proteins secreted by adipose tissue that play a crucial role in modulating hepatic fibrogenesis. These proteins influence a variety of biological processes critical to liver function, including inflammation, angiogenesis, vasodilation, and extracellular matrix deposition. Among the most extensively studied adipokines are adiponectin and leptin [51]. Adiponectin protects against hepatic inflammation and fibrogenesis, whereas leptin serves as a profibrogenic factor, promoting the development of liver fibrosis. Adiponectin inhibits the proliferation and migration of hepatic stellate cells (HSCs) stimulated by platelet-derived growth factor-BB and attenuates the effect of transforming growth factor-β1 on fibrogenic gene expression by inhibiting the nuclear translocation of Smad2. Leptin enhances cytokine secretion by Kupffer cells, stimulates endothelial cell proliferation, and promotes the production of reactive oxygen species. Additionally, leptin exerts direct effects on HSCs, which express functionally active leptin receptors [52]. A study involving obese individuals with biopsy-proven non-alcoholic fatty liver

disease (NAFLD) found that as the severity of liver steatosis increased, leptin levels progressively elevated, while adiponectin levels significantly decreased. Low adiponectin levels were associated with an increased risk of non-alcoholic steatohepatitis, while elevated leptin levels were linked to more severe fibrosis [53]. Furthermore, adiponectin is negatively correlated with insulin resistance, hypertension, and metabolic syndrome, while leptin is positively correlated with these metabolic abnormalities [53,54]. Interestingly, previous studies have found that visceral adipose tissue (VAT) is positively associated with leptin but not adiponectin, whereas higher subcutaneous adipose tissue (SAT) is indicative of higher circulating adiponectin levels [55,56]. The distinct adipokines determined by different adipose tissues may be the source of prognostic differences due to the varying distribution of adipose tissue.

VAT is located deep within the abdominal cavity and can release inflammatory cytokines, including resistin, tumor necrosis factor-α, interleukin-6, and C-reactive protein, suggesting a detrimental influence on the metabolic profile [57]. This process is frequently associated with adverse outcomes, including insulin resistance, hypertension, atherosclerosis, and NAFLD, among others [57,58]. Unlike VAT, SAT is less associated with the majority of metabolic risk factors [59]. SAT has a direct and beneficial capacity to modulate body weight and energy metabolism. Enhancing or restoring the functionality of SAT is an effective target for decreasing obesity-related complications [58]. Interestingly, a previous study in mice showed that the transplantation of SAT into the VAT area reduced body weight and enhanced insulin sensitivity [60]. The accumulation of VAT has been demonstrated to be associated with an increased risk of mortality [61] and obesity-related morbidities, including chronic liver diseases, metabolic diseases, cardiovascular diseases, and cancers [62–65]. In contrast, SAT exhibits a protective effect against these chronic diseases [10,63,66,67]. Previous studies showed that VATI and SATI (VFA and SFA corrected for height) exhibited better prognostic value compared to VFA and SFA alone [20,66,68]. Our study also revealed distinct prognostic value for VATI and SATI in patients with liver cirrhosis. The association between VATI and mortality did not reach statistical significance, which may be due to the limited sample size included in the adjusted analysis. Because VAT and SAT have distinct metabolic and inflammatory impacts on clinical outcomes, the relative distribution of body adiposity may be an important prognosis biomarker. The relative distribution of body adiposity is expressed as VSR, which was independently associated with an increased risk of incident NAFLD and diabetes mellitus [69,70]. Furthermore, elevated VSR was independently associated with poor prognosis of other acute and chronic diseases [71,72], which was consistent with our findings in cirrhosis.

While sarcopenia and obesity are distinct entities, they share common pathophysiological features and risk factors, including aging, physical activity, caloric intake, disrupted inflammation and oxidative stress response, and endocrine alterations [73]. Moreover, these conditions act synergistically, mutually reinforcing each other and contributing to a detrimental cycle [73]. A meta-analysis of 50 studies involving 86285 individuals revealed that 11% of older adults had SO globally [74], and another meta-analysis reported an SO prevalence of 20% in patients with various cancers [75]. Our study found that the prevalence of SO in patients with cirrhosis was 16%. Our finding that SO and mortality are independently associated has been validated in elderly populations and patients with cancer [73,75]. Myosteatosis in cirrhosis is commonly defined by mean muscle radiodensity, where low mean muscle radiodensity indicates poor-quality muscle with areas containing intramuscular or intermuscular adipose tissue [76]. Previous research revealed that 33.3% of patients with early nonalcoholic steatohepatitis [77] and 38.1% of older adults with cancer [78] had myosteatosis, which aligns with our finding in patients with cirrhosis (34.4%).

MA showed a negative association with mortality in both univariate and multivariate analyses. Specifically, for every one Hounsfield unit increase in MA, there was a 5% decrease in the mortality risk. Furthermore, when patients were categorized into those with myosteatosis and those without, the presence of myosteatosis was significantly associated with a higher risk of mortality. These findings have been validated in patients with other liver diseases [79]. Visceral and subcutaneous fat radiodensity have recently been shown to have significant prognostic value [34,80]. Fat radiodensity based on CT images reflects the output of various cellular and tissue-level characteristics of adipose tissue. Essentially, the low attenuation in CT images is indicative of more lipid-dense fat tissue and large adipocytes with high lipid droplet content. Our univariate analysis revealed an association between high fat radiodensity and an increased risk of mortality in patients with cirrhosis. This association may be attributed to adipose tissue remodeling and fibrosis [34,80]. However, due to the lack of multivariate data, further research is needed to confirm these results.

We provided a comprehensive list of all adipose-related parameters associated with mortality

in patients with cirrhosis. These adipose parameters exhibited distinct prognostic value. Integrating these parameters in clinical practice could identify patients with cirrhosis who are at a high risk of poor prognosis. However, this meta-analysis had some limitations. First, many adipose parameters were analyzed in a limited number of studies, especially for multivariate analysis. Additionally, the retrospective design of most studies increases the susceptibility of results to selection bias or residual confounding. Second, high heterogeneity among the studies was observed for some analyses. Heterogeneities arises from differences in clinical features such as method of definition, duration of follow-up, adjusted variables, and severity of liver disease. Due to the limited number of included studies for each adipose parameter, conducting sensitivity analyses, subgroup analyses, or meta-regressions to explore heterogeneity was not feasible. Third, some quantitative parameters, such as SATI and MA, exhibited relatively small effect sizes in relation to mortality. Future studies should further explore corresponding cutoff values to enhance their clinical utility. Fourth, this study only provided an overview of existing research on adipose parameters associated with mortality, including effect sizes and directions. Future studies are needed for unanalyzed adipose parameters and the impact of these parameters on mortality. Finally, the associations between adipose parameters and mortality in patients with cirrhosis may be complex or nonlinear, and quantitative indices might not fully capture the prognostic value of these parameters. Due to the limited number of available studies, more precise analyses were not feasible. Future research should further explore the potential nonlinear relationships between adipose parameters and mortality.

Conclusion

In conclusion, this systematic review and meta-analysis demonstrated adipose-related parameters with varying independent associations with mortality in patients with cirrhosis. Increased SATI or MA and decreased VSR were independently associated with a decreased risk of mortality. Concurrent myosteatosis or SO increased the risk of mortality in patients with cirrhosis. Future research should focus on establishing efficient risk prediction models based on these adipose parameters and explore potential interventions to improve prognosis in patients with cirrhosis. Multicenter, prospective, large-sample studies and mechanistic investigations are still needed to confirm our findings.

Author contributions

Z.W., S.T. and Q.R. were responsible for the literature search; Z.W. and X.T. participated in the data extraction process; J.Y. and Y.L. were responsible for the assessment of study quality; X.T. and Z.W. were involved in the study design and data analysis; X.T. and Z.W. drafted the manuscript; X.T., Y.Z., D.C., C.L., S.D., and J.W. participated in critical review of the manuscript; X.T. and Z.W. performed critical revision of the manuscript; X.T. and J.W. conceived the study and performed study supervision. All authors read the manuscript and approved it.

Special statement

Parts of this study's abstract were presented as a poster at the 2024 European Association for the Study of the Liver (EASL) Congress [81], held in Milan from June 5 to 8, 2024.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Some or all data, models, or code that support the findings of this study are available from the corresponding author upon reasonable request.

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