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Subcutaneous adipose tissue radiodensity as a predictor of poor prognosis in advanced biliary tract cancer

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The study protocol was approved by the Institutional Review Board of Hokkaido University Hospital (approval no: 024-0148) and conducted in accordance with the Declaration of Helsinki revised in 2013. Written informed consent was waived because of the retrospective observational study design. Informed consent was obtained using an optout form.

Abstract

Background: High subcutaneous adipose tissue radiodensity (SATr), an indirect surrogate marker of adipose tissue quality, was associated with poor prognosis in various cancers. The present study aimed to assess the association of SATr with survival outcomes in patients with advanced biliary tract cancer (BTC).

Methods: This retrospective, single-center study included patients with unresectable or recurrent BTC who underwent chemotherapy/chemoradiotherapy. Overall survival (OS) and progression-free survival (PFS) were assessed using the log-rank test and the Cox proportional hazards model according to the SATr status.

Results: The study cohort included 234 patients, including 38 and 196 patients with high and non-high SATr, respectively. The median OS durations were 10.5 and 17.4 months (HR = 1.72, 95% CI 1.19–2.49, $P < 0.01$) and the median PFS durations were 4.9 and 8.0 months (HR = 1.52, 95% CI 1.05–2.20, $P = 0.03$) in patients with high and non-high SATr, respectively. By multivariate analysis, high SATr, neutrophil/lymphocyte ratio > 5 , modified Glasgow prognostic score 1–2, and serum carcinoembryonic antigen > 5.0 ng/mL were predictors for OS (HR, 1.66, 2.42, 2.00, and 1.56, respectively; $P < 0.05$). By multivariable analysis, presence of metastasis, high SATr, neutrophil/lymphocyte ratio > 5 , and modified Glasgow prognostic score 1–2 were independent risk factors for worse PFS (HR, 1.56, 1.56, 1.81, and 1.57, respectively; $P < 0.05$).

Conclusions: High SATr was associated with risk of tumor progression and poor prognosis in patients

with advanced BTC treated by palliative chemotherapy/chemoradiotherapy.

Keywords: biliary tract cancer; subcutaneous adipose tissue; sarcopenia; prognosis; chemotherapy

Introduction

Most patients with biliary tract cancer (BTC) are diagnosed at an advanced stage, and recurrence rate is high, with a 5-year survival rate of < 40% despite surgical resection, which is the only potentially curative treatment approach.^{1,2} Palliative chemotherapy and chemoradiotherapy are widely performed in patients with advanced, metastatic, or recurrent BTC status. Surgical curability, nodal status, and histologic grade, important prognostic factors in patients undergoing resection, cannot be assessed or accurately predicted in patients not undergoing resection. Conversely, the modified Glasgow prognostic score (mGPS) and neutrophil/lymphocyte ratio (NLR), widely used prognostic scores based on systemic inflammation that are in several malignancies including BTC, can be assessed with blood tests. The mGPS is calculated using serum albumin and C-reactive protein levels.³ Based on several studies, mGPS of 1–2, NLR of > 5, serum carcinoembryonic antigen (CEA) level of > 5 ng/mL, and serum carbohydrate antigen 19-9 (CA19-9) level of > 300 U/mL are considered significant prognostic factors for advanced BTC.^{4,5}

Several recent studies reported the association of altered body composition with survival in several malignancies.⁶ Skeletal muscle is the most widely evaluated body composition component in clinical studies, followed by subcutaneous adipose tissue (SAT) and visceral adipose tissue. Of these, SAT radiodensity (SATr) can be objectively measured and quantified using computed tomography (CT), which is widely available in most hospital settings. Average SATr has been introduced as an indirect surrogate marker of adipose tissue quality.⁷ Previous studies demonstrated the association of high SATr

with poor prognosis in several malignancies,⁸ whereas only one study investigated the relationship of SAT with recurrence-free survival and overall survival (OS) after surgical resection in patients with BTC.⁹ However, the relationship between SAT and prognosis in patients with advanced BTC receiving palliative treatment is unclear. The present study aimed to evaluate the impact of SATr on prognosis in patients with advanced BTC undergoing palliative chemotherapy or chemoradiotherapy.

Methods

Study design

This retrospective observational cohort study included consecutive patients diagnosed with unresectable or recurrent BTC between January 1, 2010 and November 30, 2022 in Hokkaido University Hospital in Sapporo, Japan. Electronic medical records were used to identify patients who fulfilled the following inclusion criteria: 1) patients who underwent palliative chemotherapy or chemoradiotherapy for BTC, and 2) available consent from the patient or their family for study enrollment using the optout form. The exclusion criteria were as follows: 1) absence of plain CT imaging during the two-month period before the initiation of chemotherapy or chemoradiotherapy, 2) inability to measure SATr due to emaciation hindering the identification of regions of interest, 3) no medical records of physical findings or laboratory data, 4) observational period of shorter than one month, and 5) other concurrent advanced cancer. Eligible patients were followed until death or the end of the follow-up period (April 30, 2024), whichever came first.

The study protocol was approved by the Institutional Review Board of Hokkaido University Hospital (approval no: 024-0148) and conducted in accordance with the Declaration of Helsinki revised in 2013. Written informed consent was waived because of the retrospective observational study design. Informed consent was obtained using an optout form.

Evaluation of SATr and skeletal muscle mass

SATr was assessed at the level of the third lumbar vertebra (L3) using plain CT, based on the slight impact of contrast medium on SATr measurements. Briefly, intravenous administration of contrast increases the mean SATr by about 0.8%.¹⁰ SATr was calculated by taking the average of four circular areas (each diameter, 5 mm) in regions of interest within the subcutaneous fat away from major vessels (Fig. 1), as previously reported.^{11,12} No study to date has reported reference SATr cutoff values for patients with BTC. Therefore, high SATr was defined as an SATr of $>$ mean plus standard deviation (> -76.4 Hounsfield units [HU] for men and > -81.6 HU for women) referring to previous reports that examined differences in prognosis by SATr classification in other diseases.^{13,14} Whereas, non-high SATr was defined as $\leq$ mean plus standard deviation (≤ -76.4 HU for men and ≤ -81.6 HU for women). Plain CT images within two months before the start of treatment and closest to the start of treatment were used as SATr evaluation.

Skeletal muscle mass was determined using the psoas muscle mass index (PMI), as previously reported.^{15,16} The PMI was calculated by dividing the sum of the cross-sectional area of the right and

left psoas muscles at the level of the third lumbar vertebra by height squared, based on measurements obtained by manual tracing of target areas on CT images. Muscle atrophy was defined as a PMI of $< 3.74 \text{ cm}^2/\text{m}^2$ for men and $< 2.29 \text{ cm}^2/\text{m}^2$ for women, according to a previous study of healthy adults in Hokkaido, Japan.¹⁵

Assessment of chemotherapy outcomes

Chemotherapy/chemoradiotherapy efficacy was assessed using OS, defined as the duration from the start of first chemotherapy/chemoradiotherapy administration to death, and progression-free survival (PFS), defined as the duration from the first chemotherapy/chemoradiotherapy session to disease progression at the time of survival investigation. In OS analysis, patients who were still alive and those who were transferred to other hospitals and had no further clinical information were censored on the date of last follow-up registered in the medical records. In PFS analysis, patients whose treatment regimens were changed without evidence of disease progression were censored. Response to treatment was evaluated according to the Response Evaluation Criteria in Solid Tumors (ver. 1.1).¹⁷

Outcome measures

The primary study outcome was the difference in OS in patients categorized according to SATr. The secondary study outcomes were the difference in PFS in patients categorized according to SATr and prognostic factors for OS and PFS. Correlation coefficient between SATr values at the L3 and forth

lumbar vertebra (L4) was also evaluated.

Statistical analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan),¹⁸ a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Data were presented as means with SD for parametric variables, medians with interquartile ranges for nonparametric variables, and percentages for categorical variables. Parametric, nonparametric, and categorical variables were compared using Student's *t* test, the Wilcoxon signed-rank sum test, and the chi-squared or Fisher's exact test, respectively. Overall response rate and disease control rate were examined only in patients where target lesions were measurable. Survival analyses were performed using the Kaplan–Meier method, and the log-rank test was used to compare OS and PFS between the patients with high and non-high SATr. The Cox proportional hazards model was used to evaluate prognostic factors for OS and PFS, and variables with a *P* value of <0.05 in the univariate analysis were included in the multivariate analysis. mGPS 1–2 and NLR > 5 were significant prognostic factors for advanced BTC in previous reports^{4,5} and were used as respective cutoffs in this study. Cutoffs for CEA and CA19-9 were selected on the basis of the maximum significant differences for OS. Spearman's rank correlation coefficient was used to examine the association of specific explanatory variables with SATr. Explanatory variables with a correlation coefficient (*r*) of ≥ 0.7 , indicating their strong association, were excluded from the multivariate analysis of risk factors for OS

and PFS. Correlation coefficient (r) between SATr values at the L3 and L4 was also calculated using Spearman's rank correlation coefficient. A P value of < 0.05 was considered statistically significant.

Results

Among a total of 299 patients with BTC identified during the study period, 234 patients who fulfilled the inclusion and exclusion criteria were included in the final analysis (Fig. 2). The median duration from assessed plain CT to treatment initiation was 22.5 (interquartile range, 14–34) days. Mean SATr values were -94.1 (SD, ± 17.7) HU in men and -96.5 (SD, ± 14.9) HU in women. Therefore, high SATr was defined as an SATr of > -76.4 HU for men and > -81.6 HU for women, whereas non-high SATr was defined as an SATr of ≤ -76.4 HU for men and ≤ -81.6 HU for women. Based on the analysis of CT images, the final study cohort included 38 and 196 patients with high and non-high SATr, respectively.

Baseline cohort characteristics

The study cohort included 142 men and 92 women, with a mean age of 67.2 ± 9.8 years. Table 1 shows the baseline patient characteristics. Briefly, high SATr was associated with lower body mass index, worse Eastern Cooperative Oncology Group (ECOG) performance status score, and higher mGPS and serum CEA levels. Regarding first-line treatment regimens, the patients with non-high SATr were more likely to receive triple combination chemotherapy with gemcitabine, cisplatin, and S-1 compared to

those with high SATr. The PMI values were not significantly different between the patients with high and non-high SATr.

Overall response rate and disease control rate according to the SATr status

Of the 234 patients, 217 patients were measurable. There was no significant difference in overall response rate between the two groups. The disease control rates in patients high and non-high SATr groups were 57.6% and 89.1%, respectively. The disease control rate in patients with high SATr was significantly lower than that in patients with non-high SATr ($P < 0.01$). The details of treatment response are summarized in Table 2.

Comparison of OS and PFS between the patients with high and non-high SATr

During a median follow-up of 15.9 (interquartile range, 9.3–23.1) months, 199 patients (85.0%) experienced tumor progression and 205 patients (87.6%) died. The median OS was 10.5 months in patients with high SATr and 17.4 months in those with non-high SATr (hazard ratio [HR] 1.72, 95% confidence interval [CI] 1.19–2.49, $P < 0.01$) (Fig. 3a). The median PFS was 4.9 months in patients with high SATr and 8.0 months in those with non-high SATr (HR 1.52, 95% CI 1.05–2.20, $P = 0.03$) (Fig. 3b).

Risk factors for OS and PFS

In univariate analysis for OS, ECOG performance status score of 1–2, metastatic as disease status, high SATr, NLR of > 5 , mGPS of 1–2, serum CEA level of > 5.0 ng/mL, and serum CA19-9 level of > 700.0 U/mL were significant prognostic factors for survival ($P < 0.05$) (Table 3). In multivariate analysis, high SATr, NLR of > 5 , mGPS of 1–2, and serum CEA level of > 5.0 ng/mL were independent predictive factors for OS (HR, 1.66, 2.42, 2.00, and 1.56, respectively; P values < 0.05).

In univariate analysis for PFS, ECOG performance status score of 1–2, metastatic as disease status, high SATr, NLR of > 5 , mGPS of 1–2, and serum CA19-9 level of > 700.0 U/mL were significant risk factors for tumor progression ($P < 0.05$) (Table 4). In multivariate analysis, metastatic as disease status, high SATr, NLR of > 5 , and mGPS of 1–2 were independent risk factors for tumor progression (HR, 1.56, 1.56, 1.81, and 1.57, respectively; P values < 0.05). We found no explanatory variables that were strongly associated with SATr in multivariate analysis for OS and PFS, based on an r of ≥ 0.7 . Muscle atrophy was not an independent factor associated with poor OS and PFS in univariate and multivariate analyses.

Correlation analysis between SATr values between at L3 and L4

Since the evaluation only from the SATr at the L3 level might be biased, we also checked the correlation between the SATr values at the L3 and the other lumbar spine level (L4). The correlation between these SATr values were strong ($r = 0.93$, $P < 0.01$) (Supplemental Fig. 1).

Discussion

This is the first study to report that high SATr was associated with risk factor for poor prognosis and tumor progression in patients with advanced BTC undergoing chemotherapy or chemoradiotherapy. SATr plays a pivotal role in lipid storage and energy homeostasis and is currently recognized for its multifaceted endocrine functions, given the role of adipokines in the regulation of diverse metabolic and inflammatory processes.¹⁹ A elevated SATr not only indicates a reduced SAT volume but also implies adipose tissue remodeling, which is characterized by morphologic changes such as atrophy, based on the observation of smaller and shrunken adipocytes, expanded interstitial space, and mononuclear cell infiltration.¹⁹ Therefore, in patients with advanced BTC, high SATr reflects energy depletion leading to unfavorable clinical outcomes. Importantly, measuring SATr using four circular regions of interest of identical size within subcutaneous fat is simple and easy;^{11,12} it can be widely implemented without the need for special equipment or software, highlighting its potential utility as a novel prognostic marker in patients with advanced BTC undergoing treatment.

One study investigating the relationship of SATr with recurrence-free survival and OS in patients with BTC after surgical resection reported that SATr was not associated with poor prognosis.⁹ However, the study included a relatively small cohort of 94 patients with various BTC types who were treated with a variety of surgical methods and the cutoff SATr was not specified, unlike the present study, which might have affected the study findings. SATr after surgical resection has not

been fully characterized in patients with BTC, and further investigation is warranted to evaluate the relationship between SATr and prognosis in patients with BTC undergoing curative resection.

In patients with advanced BTC, whether aggressive nutritional therapy can improve SATr and long-term clinical outcomes is a critical question. However, to the best of our knowledge, no study to date have evaluated their association of aggressive nutritional therapy and long-term clinical outcomes in patients with any type of cancer. Prospective studies are necessary to evaluate whether nutritional therapy improves SATr and prognosis in patients with advanced BTC.

From the perspective of clinical researches, the L3 is the most commonly used vertebral landmark for body composition studies, including the SATr studies.⁸ Thus, our findings are clinically meaningful for clinicians and researchers to identify advanced BTC patients with unfavorable SAT quality who have a poor prognosis. Additionally, the SATr was also obtained from the single CT slice at the L4 in this study referring to other reports,⁸ and a strong correlation between the SATr values at the L3 and L4 was confirmed. However, SATr values between these slices were not completely consistent, and SATr might vary across abdominal slices. Further studies are needed to explore which slice or multiple slices are best and to investigate other methods of SATr assessment.

CT serves as a valuable indicator of fat quality, including SAT quality, and its clinical utility is commonly assessed by CT.²⁰ Furthermore, advantage of SAT assessment using CT is the ease of assessing SATr in conjunction with routine diagnosis and treatment assessment of advanced BTC and the use of CT for treatment-related adverse events. Most recently, it has been reported that magnetic

resonance imaging (MRI) can be used to assess fat quality,²¹ although studies of MRI fat quality have not been sufficient. The advantage of MRI is that there is no radiation exposure, and it also assesses other parameters than CT; therefore, future studies on fat quality using MRI, especially SAT quality, and its association with clinical outcomes of advanced BTC are warranted.

The potential relationship of skeletal muscle mass with survival outcomes has not been fully investigated in patients with advanced BTC. In patients with advanced BTC, several studies reported that muscle atrophy was associated with poor survival,^{22,23} whereas others reported no association,^{24,25} in agreement with the current study findings. In the present study, we assessed skeletal muscle mass using only the PMI but other methods, which might have impacted our findings. Several studies demonstrated that skeletal muscle quality based on skeletal muscle density measured by CT, and not skeletal muscle mass, was associated with prognosis in patients with advanced BTC.^{24,25} Future studies should include the comprehensive evaluation of the quantity and quality of skeletal muscle in patients with advanced BTC to determine best measurement methods for prognostic prediction in patients with advanced BTC.

The present study has several limitations. First, this was a retrospective study conducted in a single center. Second, only 16% of the patients in the study cohort had high SATr based on the specific SATr cutoff used, although previous studies using the cutoffs derived using the same method reported comparable rates of patients with high SATr (11.1%–13.4%).^{13,14} Third, we did not investigate changes in SATr during treatment. In many cases, contrast-enhanced CT was the only

routine examination after starting treatment, and plain CT was not routinely performed (date not shown). Contrast medium has a small but definite effect on SATr,¹⁰ and it is expected that SATr will also vary depending on the timing after contrast injection even in the same patient. In the future, the relationship between the change in SATr on plain CT and the clinical outcome should be examined in a large cohort. Fourth, due to the retrospective study design, certain clinical parameters, including markers of nutritional status, details of nutritional therapy and activities of daily life, and muscular strength, were not evaluated. Future prospective studies should evaluate the relationship between body structural components, including SAT and nutritional status, and should further explore whether nutritional therapy improves SATr and prognosis. Finally, the study cohort did not include patients treated with immune checkpoint inhibitors, and the relationship of SATr with the effects of these increasingly common therapeutics should be explored in future studies.

In conclusion, in this retrospective, single-center study, we found that high SATr was associated with increased risk of tumor progression and poor prognosis in patients with advanced BTC undergoing palliative chemotherapy or chemoradiotherapy, implicating that nutritional interventions might improve clinical outcomes in patients with high SATr.

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Tables

Table 1. Baseline characteristics

	High SATr (n = 38)	Non-high SATr (n = 196)	<i>P</i> value
Age, mean (SD), year	68.0 (± 10.8)	67.0 (± 9.6)	0.59
Male sex, n (%)	22 (57.9)	120 (61.2)	0.72
Body mass index, mean (SD), kg/m ²	18.7 (± 2.1)	22.8 (± 3.6)	< 0.01
ECOG PS, n (%)			< 0.01
0	16 (42.1)	122 (62.2)	
1	20 (52.6)	74 (37.8)	
2	2 (5.3)	0	
Primary tumor site, n (%)			0.81
Extrahepatic cholangiocarcinoma	15 (39.5)	79 (40.3)	
Intrahepatic cholangiocarcinoma	13 (34.2)	54 (27.6)	
Gallbladder cancer	10 (26.3)	58 (29.6)	
Ampullary cancer	0	5 (2.6)	
Disease status, n (%)			0.26
Localized	7 (18.4)	62 (31.6)	
Metastatic	17 (44.7)	75 (38.3)	
Recurrent	14 (36.8)	59 (30.1)	
PMI, mean (SD), cm ² /m ²			
Male	4.65 (1.24)	4.98 (1.49)	0.33
Female	2.90 (0.94)	3.36 (0.82)	0.05
Muscle atrophy, n (%)	8 (21.1)	36 (18.4)	0.66
NLR, median (IQR)	3.2 (2.2–5.1)	2.5 (1.8–3.7)	0.10
mGPS, n (%)			< 0.01

0	10 (26.3)	90 (45.9)	
1	10 (26.3)	61 (31.1)	
2	18 (47.4)	45 (23.0)	
CEA, median (IQR), ng/mL	6.0 (3.0–16.1)	3.8 (2.4–6.2)	0.04
CA19-9, median (IQR), U/mL	131.8 (25.9–590.3)	104.9 (32.1–465.1)	0.54
First line treatment, n (%)			0.03
GEM/CDDP/S-1	4 (10.5)	45 (23.0)	
GEM/CDDP	22 (57.9)	114 (58.2)	
GEM/S-1	3 (7.9)	3 (1.5)	
GEM	7 (18.4)	26 (13.3)	
S-1	0	6 (3.1)	
S-1+radiation	2 (5.3)	2 (1.0)	

CA19-9, carbohydrate antigen 19-9; CDDP, cisplatin; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; IQR, interquartile range; NLR, Neutrophil-lymphocyte-ratio; mGPS, modified Glasgow Prognostic Score; PMI, psoas muscle mass index; PS, performance status; SD, standard deviation

Table 2. Details of treatment response

	High SATr (n = 33)	Non-high SATr (n = 184)	<i>P</i> value
Treatment response, n (%)			< 0.01
Complete response	0	0	
Partial response	3 (9.1)	28 (15.2)	
Stable disease	16 (48.5)	136 (73.9)	
Progressive disease	14 (42.4)	20 (10.9)	
Overall response rate, %	9.1	14.3	0.43
Disease control rate, %	57.6	89.1	< 0.01

Table 3. Univariate and multivariate analyses of prognostic factors for survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age, > 75 vs. ≤ 75 years	1.20 (0.82–1.74)	0.34		
Sex, male vs. female	1.08 (0.82–1.44)	0.58		
BMI, > 22 vs. ≤ 22 kg/m ²	0.83 (0.63–1.09)	0.17		
ECOG PS 1–2 vs. 0	1.49 (1.13–1.97)	< 0.01	1.10 (0.81–1.49)	0.54
Extrahepatic Cholangiocarcinoma vs. others	0.85 (0.64–1.13)	0.26		
Metastatic vs. other status	1.55 (1.17–2.06)	< 0.01	1.34 (0.99–1.80)	0.05
Muscle atrophy, presence vs. absence	0.91 (0.65–1.28)	0.58		
SATr, high vs. non-high	1.74 (1.21–2.50)	< 0.01	1.66 (1.12–2.40)	< 0.01
NLR, > 5 vs. ≤ 5	2.98 (2.02–4.40)	< 0.01	2.42 (1.60–3.69)	< 0.01
mGPS, 1–2 vs. 0	2.35 (1.77–3.14)	< 0.01	2.00 (1.46–2.74)	< 0.01
CEA, > 5.0 vs. ≤ 5.0 ng/mL	1.61 (1.21–2.14)	< 0.01	1.56 (1.17–2.10)	< 0.01
CA19-9, > 700.0 vs. ≤ 700.0 U/mL	1.53 (1.14–2.04)	< 0.01	1.38 (0.95–2.01)	0.09
First treatment, combined chemotherapy vs. other				
	1.13 (0.79–1.60)	0.51		

BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CDDP, cisplatin; CEA, carcinoembryonic antigen; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; HR, hazard ratio; IQR, interquartile range; NLR, Neutrophil-lymphocyte-ratio; mGPS, modified Glasgow Prognostic Score; PMI, psoas muscle mass index; PS, performance status; SATr, subcutaneous adipose tissue radiodensity; SD, standard deviation

Table 4. Univariate and multivariate analyses of risk factors for tumor progression

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age, > 75 vs. ≤ 75 years	0.94 (0.65–1.38)	0.77		
Sex, male vs. female	0.93 (0.70–1.24)	0.64		
BMI, > 22 vs. ≤ 22 kg/m ²	0.81 (0.61–1.07)	0.14		
ECOG PS 1–2 vs. 0	1.39 (1.05–1.86)	0.02	1.18 (0.88–1.59)	0.28
Extrahepatic Cholangiocarcinoma vs. others	0.82 (0.62–1.09)	0.18		
Metastatic vs. other status	1.60 (1.20–2.13)	< 0.01	1.56 (1.16–2.10)	< 0.01
Muscle atrophy, presence vs. absence	0.93 (0.65–1.32)	0.68		
SATr, high vs. non-high	1.78 (1.21–2.60)	< 0.01	1.56 (1.07–2.27)	0.02
NLR, > 5 vs. ≤ 5	2.21 (1.50–3.25)	< 0.01	1.81 (1.19–2.75)	< 0.01
mGPS, 1–2 vs. 0	1.89 (1.42–2.52)	< 0.01	1.57 (1.16–2.15)	< 0.01
CEA, > 5.0 vs. ≤ 5.0 ng/mL	1.28 (0.95–1.72)	0.10		
CA19-9, > 700.0 vs. ≤ 700.0 U/mL	1.52 (1.13–2.03)	< 0.01	1.42 (0.98–2.07)	0.07
First treatment, combined chemotherapy vs. other				
	0.98 (0.69–1.39)	0.90		

BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CDDP, cisplatin; CEA,

carcinoembryonic antigen; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group;

GEM, gemcitabine; HR, hazard ratio; IQR, interquartile range; NLR, Neutrophil-lymphocyte-ratio;
mGPS, modified Glasgow Prognostic Score; PMI, psoas muscle mass index; PS, performance status;
SATr, subcutaneous adipose tissue radiodensity; SD, standard deviation

Figure legends

Figure 1. Measurement of subcutaneous adipose tissue radiodensity (SATr)

SATr was assessed at the level of the third lumbar vertebra in plain computed tomography images.

SATr was calculated by taking the average of four circles of interest with identical size in subcutaneous fat away from major vessels.

Figure 2. Study flow chart

CT, computed tomography; SATr, subcutaneous adipose tissue radiodensity

Figure 3. Kaplan–Meier survival curves

(a) Overall survival rates in patients categorized according to SATr.

(b) Progression-free survival rates in patients categorized according to SATr.

CI, confidence interval; HR, hazard ratio; SATr, subcutaneous adipose tissue radiodensity



Search of the database
between January 1, 2010 and November 30, 2022

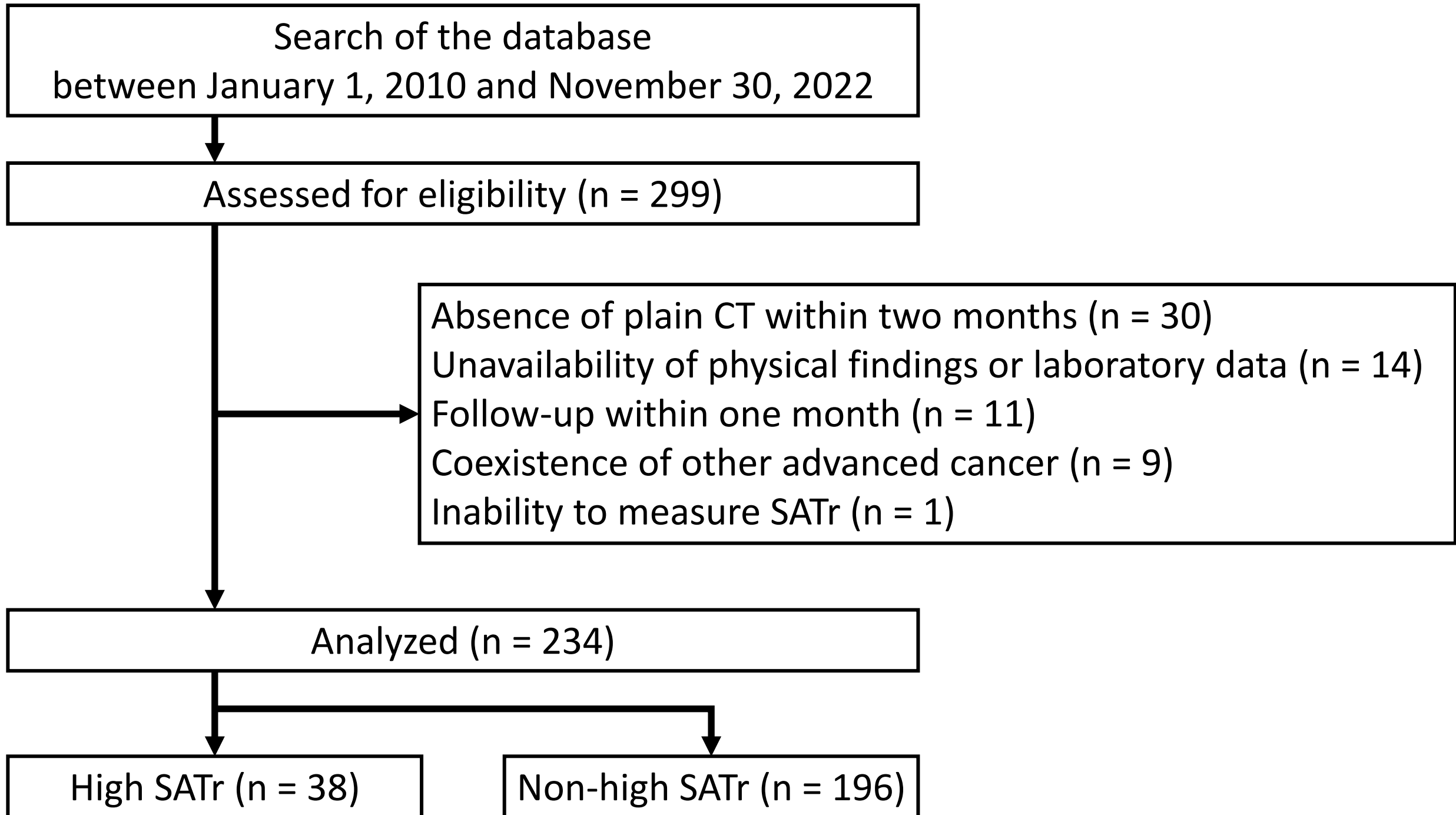
Assessed for eligibility (n = 299)

Absence of plain CT within two months (n = 30)
Unavailability of physical findings or laboratory data (n = 14)
Follow-up within one month (n = 11)
Coexistence of other advanced cancer (n = 9)
Inability to measure SATr (n = 1)

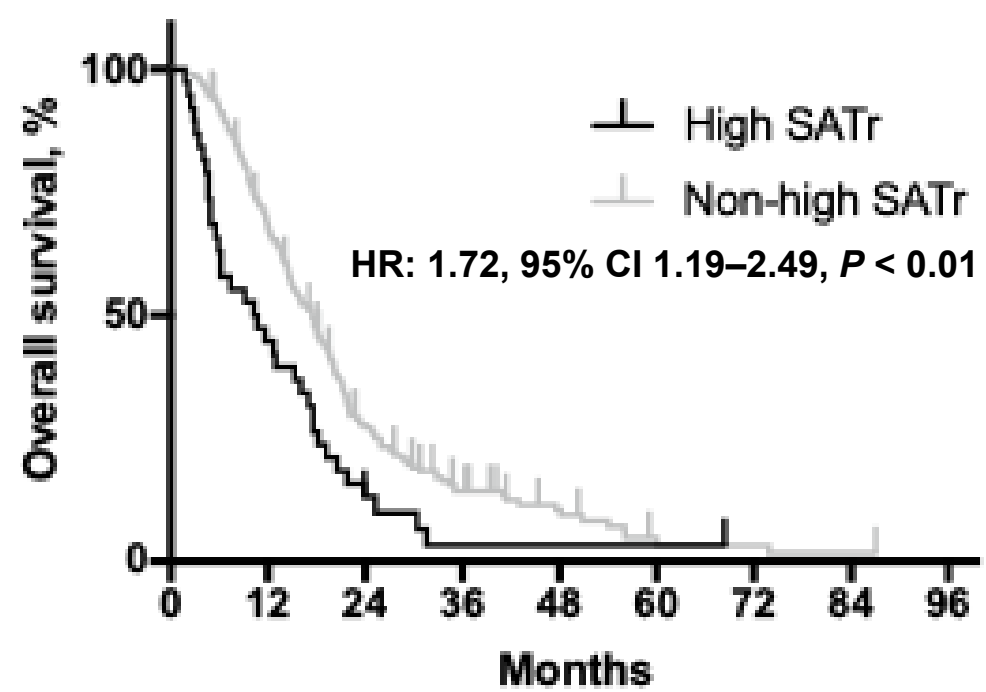
Analyzed (n = 234)

High SATr (n = 38)

Non-high SATr (n = 196)



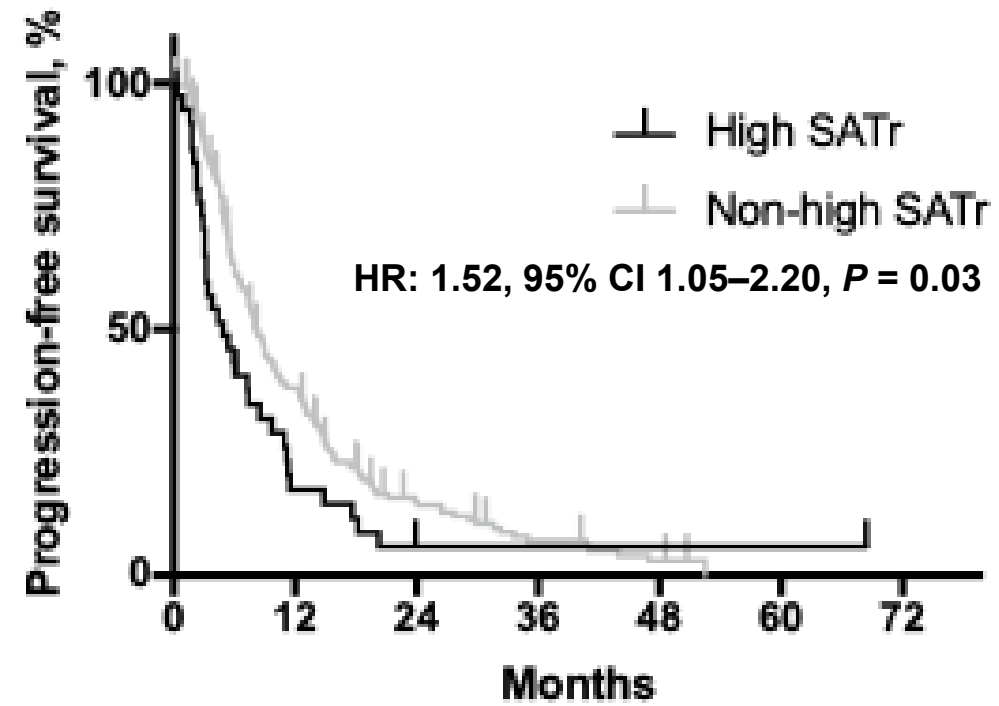
(a)



Number at risk

High SATr							
38	17	4	1	1	1	0	0
Non-high SATr							
196	130	47	20	10	2	2	1

(b)



Number at risk

High SATr					
38	6	1	1	1	1
Non-high SATr					
196	67	20	8	3	0