Preoperative Sarcopenia is Associated with Poorer Compliance Rate of Adjuvant Chemotherapy and Worse Disease-free Survival of Patients with Stage Ⅲ Colon Cancer

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Abstract

Purpose: Preoperative sarcopenia has been proved to be associated with worse postoperative outcomes in cancer patients. This study aimed to evaluate whether preoperative sarcopenia affects the perioperative outcomes, adjuvant chemotherapy, and long-term outcomes of patients with stage Ⅲ colon cancer.

Methods: Total 218 patients who underwent curative resection for stage Ⅲ colon cancer in our department from January, 2015 and December, 2018 were retrospectively analyzed. Sarcopenia was assessed by total psoas index, which measured the total area the level of L3 vertebral body and normalized according to patients' height. Perioperative complications, postoperative adjuvant chemotherapy, and long-term prognosis were retrospectively analyzed.

Results: Of 218 patients, 100(45.9%) patients were diagnosed with sarcopenia. Sarcopenia did not add the risk of perioperative complications (20.0% vs 15.3%, P=0.357), but it increased hospital stays (7.6±3.9 vs 6.7±2.2 days, P=0.042). Patients with sarcopenia had a lower rate of receiving adjuvant chemotherapy (70.0% vs 82.2%, p=0.033) and less likely to receive adequate adjuvant chemotherapy (58.6% vs 70.1, P=0.08). Patients with adequate adjuvant chemotherapy had significantly better 3-year OS (89.8% vs 79.5, P=0.005) and a tendency of better 3-year DFS (76.4% vs 63.6%, P=0.055) than those with inadequate adjuvant chemotherapy and Non-adjuvant chemotherapy. Compared with the patients without sarcopenia, patients with sarcopenia had significantly worse 3-year DFS (76.9% vs 62.8%, P=0.026).

Conclusion: Preoperative sarcopenia was an important indicator to predict the compliance of AC in stage Ⅲ colon cancer patients, and it is also a significant prognostic factor of worse 3-year DFS.

Introduction

Sarcopenia is defined as a progressive and generalized skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality by the European Working Group on Sarcopenia in Older People (EWGSOP) in its latest guideline.[1] Sarcopenia can be exacerbated by the hypercatabolic state and inflammatory response caused by malignancy.[2] Therefore, Sarcopenia has been proposed to be an alternative marker of frailty for cancer patients in some study groups,[3-5] and preoperative sarcopenia is associated with poor postoperative outcomes, such as wound infection, anastomotic leakage, length of hospital stays, in patients with gastrointestinal surgery.[4, 6] There also were some studies finding sarcopenia was a negative prognostic factor for disease-free survival (DFS) and overall survival (OS) in colorectal cancer patients[7, 8].

Sarcopenia is commonly diagnosed by measuring cross-sectional skeletal muscle area at the level of the third lumbar(L3) on the preoperative CT scan in most studies.[4, 5, 9, 10] However, this method is often time-consuming and complicated, and is not suitable for clinical application. Some studies tried to use the

total psoas index (TPI), which measured the total area at the level of L3 vertebral body and normalized according to patients' height, to assess sarcopenia and satisfactory results were obtained[8, 11, 12]. The TPI is easy to measure and reproduced in clinical practice.

The association between TPI and surgical outcomes has been explored in recent years, and the results indicated it was a poor prognostic predictor in colorectal cancer[11]. However, whether low TPI (sarcopenia) affected the compliance of patients to receive the recommended standard adjuvant chemotherapy (AC) has not been well explored. According to the guideline of the National Comprehensive Cancer Network (NCCN), patients with stage Ⅲ colon cancer were recommended to receive AC because the results of multiple studies that demonstrated a clear benefits of AC,[13-16] and the 6 months of oxaliplatin combined with either infusional 5-fluorouacil plus folinic acid (FOLFOX) or capecitabine (CAPOX) became standard adjuvant regimen because of a consistent, albeit moderate, disease-free survival benefit compared with that of fluorouracil plus folinic acid alone.[15, 17] However, the compliance rate of AC for patients with stage Ⅲ colon cancer was unsatisfactory due to the complications, frailty after surgery, or economic reasons. Even in MOSAIC trial, only 74.7% patients completed the standard.[13] Sarcopenia was associated with weakness and delayed recovery after surgery, which may be one important risk factor of the compliance of AC. The present study aimed to evaluate whether sarcopenia affected the compliance of patients to receive the recommended standard AC and its impact on the long-term prognosis of stage Ⅲ colon cancer.

Materials And Methods

Study population

We retrospectively analyzed 1352 consecutive patients with localized colon cancer who underwent radical resection in the Department of Colorectal Surgery of Fujian Medical University Union Hospital (FMUUH) from January 2015 to December 2018. Patients who met the following criteria were included in the final analysis: (1) pathologically confirmed as stage Ⅲ colon cancer according to the AJCC TNM staging system; (2) received abdominal CT scan within 30 days before surgery; (3) received operation without neoadjuvant chemotherapy. Patients were excluded from the present study if they met any of the following criteria: (1) synchronous malignancy or a history of other malignant tumors; (2) distant metastatic diseases; (3) incomplete clinicopathological data. The flow chart was shown in Fig 1. This retrospective study was approved by the institutional review board of FMUUH.

Treatment and follow-up

All the included patients underwent radical resection and were recommended to receive AC according to the guideline of the National Comprehensive Cancer Network (NCCN)[18] and the Ministry of Health of the People's Republic of China[19]. For p-Stage III colon cancer patients in our institute, the CAPOX (capecitabine and oxaliplatin) was a regular regime for AC. Adequate AC was defined as receiving CAPOX

for more than 3 months. Inadequate AC included patients that received CAPOX less than 3 months and that only received oral capecitabine. The follow-up evaluations were performed every 3 months for the first 2 years, then every 6 months for the next 3 years, and annually thereafter. The postoperative follow-up included a physical examination, serum carcinoembryonic antigen (CEA) test, chest-to-pelvic CT, and colonoscopy. The baseline clinicopathological characteristics, postoperative complications (such as intestinal obstruction, anastomotic leak, abdominal infection, wound infection, pneumonia), recurrence status, and metastasis information of patients were collected from their medical records or through a telephone follow-up.

Image analysis

Total psoas area (TPA, mm^2) was retrospectively measured on the preoperative CT scan at the level of the third lumbar vertebral (L3). The exact level of measurement was defined as the axial plane CT slice in which both L3 transverse processes were maximally in the view according to the earlier study. TPA was measured by manual outlining of both the left and right psoas muscle borders at the L3 level, and the area was automatically calculated on Picture Archiving and Communication System (PACS) software (Fig 2). The area was then normalized by the square of the height (m^2) to obtain the total psoas index (TPI, mm^2/m^2). The TPA was measured by two trained investigators (LY and GC) separately and the average was taken to final analysis, both were blinded to the patient outcomes at the time of quantification. Sarcopenia was defined using sex-specific thresholds of <524 mm^2/m^2 for male patients and <385 mm^2/m^2 for female patients according to earlier studies[8]. Sarcopenia was defined as an absolute variable and patients were classified as sarcopenia or non-sarcopenia in this study.

Statistical analysis

Categorical variables were present as frequencies and percentages, and Continuous variables were described as mean with standard deviation (SD) or interquartile range (IQR). Chi-square or Fisher's exact test was used to analyze categorical variables and a two-sample t-test or the Wilcoxon signed-rank test was performed to analyze continuous variables. The Kaplan-Meier method and the log-rank test were used for survival analysis. Multivariate analysis was conducted using a Cox proportional hazards model. All analyses were performed with SPSS 23.0 for MAC (SPSS Inc., Chicago, IL, USA). A two-tailed P value <0.05 was considered statistically significant.

Results

Baseline demographic and clinicopathological characteristics

A total of 218 eligible patients with stage □ colon cancer were finally enrolled in this study between January 2015 and December 2018, including 135(61.9%) males and 83(38.1%) females, and the median age was 62 years (IQR 54-68 years). The median follow-up time was 34.3 months (IQR 26.6-51.3 months). The median TPI for all patients was 472.1 mm^2/m^2 (IQR 364.5-581.6 mm^2/m^2) and 549.0 mm^2/m^2 (IQR 454.2-640.2 mm^2/m^2), 357.8 mm^2/m^2 (IQR 285.9-443.0 mm^2/m^2). Baseline demographic and clinicopathological characteristics are shown in Table 1.

Table 1

Baseline demographics, clinicopathological characteristics of the patients with stage □ colon cancer.

Characteristic	All patients n=218(%)	Patients with sarcopenia n=100(%)	Patients without sarcopenia n=118(%)	P value
Age (mean±SD)	60.9±12	63.2±12.2	58.9±11.5	**0.01**
Gender				**0.005**
Male	135 (61.9)	52(52.0)	83(70.3)	
Female	83 (38.1)	48(48.0)	35(29.7)	
BMI(kg/m^2), mean±SD	22.9±3.6	21.6±3.3	23.9±3.6	**<0.001**
Location of tumor				0.435
Left	129(59.2)	62(62.0)	67（56.8）	
Right	89(40.8)	38(38.0）	51（43.2）	
pT				0.624
T1	2(0.9)	1(1.0)	1(0.8)	
T2	2(0.9)	0(0.0)	2(1.7)	
T3	172(78.9)	79(79.0)	93(78.8)	
T4	42(19.3)	20(20.0)	22(18.6)	
pN				0.403
N1	153(70.2)	73(73.0)	80(67.8)	
N2	65(29.8)	27(27.0)	38(32.2)	
pTNM				0.595
IIIA	12(5.5)	4(4.0)	8(6.8)	
IIIB	160(73.4)	76(76.0)	84(71.2)	
IIIC	46(21.1)	20(20.2)	26(22.0)	
Perineural invasion				**0.037**
Yes	77(35.3)	28(28.0)	49(41.5)	
No	141(64.7)	72(72.0)	69(58.5)	
Vascular invasion				**0.035**
Yes	68(31.2)	24(24.0)	44(37.3)	
No	150(68.8)	76(76.0)	74(62.7)	
ASA grade				0.811

1	32(14.7)	13(13.0)	19(16.1)	
2	167(76.6)	78(78.0)	89(75.4)	
3	19(8.7)	9(9.0)	10(8.5)	
In-hospital complication				0.357
Yes	38(17.4)	20(20.0)	18(15.3)	
No	180(82.6)	80(80.0)	100(84.7)	
Hospitalization days	7.1±3.1	7.6±3.9	6.7±2.2	**0.042**
Completion of AC				**0.033**
Adequate	109(50.0)	41(41.0)	68(57.6)	
Inadequate	58(26.6)	29(29.0)	29(24.6)	
Non-AC	51(23.4)	30(30.0)	21(17.8)	
TPA(mean±SD, mm^2)	1330.0±499.9	980.7±310.5	1626.0±435.0	**<0.001**
TPI(mean±SD,mm^2/m^2)	472.1±165.8	359.1±90.5	597.4±133.2	**<0.001**
Abbreviation: BMI, body mass index; AC: adjuvant chemotherapy; TPA: Total psoas area; TPI: total psoas index.				

The median interval between CT scan and operation was 9 days (IQR 6.0-14.0 days). Of these 218 patients, one hundred (45.9%) patients were classified as sarcopenia by TPI cutoff values of male and female, including 52 (57.8%) males and 48 (38.5%) females. The ratio of sarcopenia in the female was higher than that in the male (P=0.008). The average BMI was 22.9 kg/m^2(3.6), and patients with sarcopenia were more likely to have lower BMI than patients without sarcopenia (21.6±3.3 vs 23.9±3.6 kg/m^2, P<0.001).

Postoperative outcome

38 (17.4%) patients experienced postoperative complications after surgery. There was no significant difference in postoperative complications between sarcopenia and non-sarcopenia patients (20.0% vs 15.3%, P=0.357). The mean length of postoperative hospital stay was 7.1 days (4-26 days), and patients with sarcopenia had significantly longer postoperative hospital stays than those without sarcopenia (average 7.6±3.9 vs 6.7±2.2 days, P=0.042). Each group had one mortality during the hospital stay, one died of severe pneumonia and the other died of aspiration in the sarcopenia and non-sarcopenia group respectively.

Adjuvant chemotherapy and survival analysis

There were 76.6% of total patients receiving AC, and 58.1% of them were non-sarcopenia. The rate of receiving AC in the non-sarcopenia group was significantly better than the sarcopenia group (82.2% vs 70%, p=0.033, Figure 3A). Patients without sarcopenia had more likely to receive adequate AC (more than 3 months) than patients with sarcopenia (70.1% vs 58.6, P=0.084, Figure 3B), though the difference did not reach significance. It should be noticed that patients who received AC had significantly better 3-year OS (87.6% vs 76.8%, P=0.007, Figure 4A) and DFS (73.6% vs 59.5%, P=0.034, Figure 4B) than patients without AC. In the subgroup analysis, when compared with patients who did not receive AC or received inadequate AC, patients who received adequate AC had significantly better 3-year OS (89.8% vs 79.5, P=0.005, Figure 4C) and a tendency of better 3-year DFS (76.4% vs 63.6%, P=0.055, Figure 4D).

The 3-year overall survival (OS) rate and disease-free survival (DFS) rate of total patients were 85.2% and 70.5%, respectively. Patients with sarcopenia had significant worse 3-year DFS than that of patients without sarcopenia (76.9% vs 62.8%, P=0.026, Figure 5A), although the 3-year overall survival rate (OS) of two teams had no significant difference (90.0% vs 79.6%, P=0.092, Figure 5B).

Univariate and multivariate analysis indicated the AC (HR 0.57, 95%CI 0.32-0.99, P=0.049) and sarcopenia (HR 1.77, 95%CI 1.05-2.98, P=0.033) were significantly associated with 3-year DFS (Table 2).

Table 2

univariate and multivariate analysis of prognostic factor of 3-year DFS

characteristics	Univariate analysis			Multivariate analysis		
	3-year DFS	95%CI	P value	Adjusted HR	95%CI	P value
Age			0.181			
<65	74.3%	53.1-63.5				
≤65	65.1%	45.9-59.2				
Gender			0.216			
Male	73.3%	53.1-63.3				
Female	65.9%	43.6-56.6				
BMI			0.903			
≥25	72.8%	48.2-63.7				
<25	69.6%	49.7-59.3				
Location of tumor			0.528			
Left colon	70.0%	49.4-60.2				
Right colon	71.3%	51.1-63.9				
Pathological N stage			**0.002**			
N1	78.2%	55.8-65.1		Ref		
N2	54.9%	38.1-53.2		1.78	0.98-3.21	0.057
Pathological TNM stage			**0.020**			
IIIA	90.9%	54.8-76.7		Ref		
IIIB	74.7%	53.4-62.7		0.27	0.03-2.17	0.217
IIIC	53.2%	36.0-54.4		0.63	0.33-1.19	0.150
Perineural invasion			0.204			
Yes	73.8%	52.8-62.9				
No	65.0%	45.4-59.6				
Vascular invasion			0.175			
Yes	67.5%	48.9-59.1				
No	76.7%	52.5-66.7				
ASA stage			0.636			
□	62.0%	40.9-63.1				

□	71.9%	51.7-61.0				
□	73.7%	39.9-63.6				
In-hospital complication			0.967			
Yes	69.6%	44.0-62.9				
No	70.7%	51.3-60.4				
Hospitalization days			0.827			
≥7 days	70.2%	51.4-60.8				
<7 days	68.3%	45.5-62.6				
Adjuvant chemotherapy			**0.034**			
No	59.5%	36.8-54.0		Ref		
Yes	73.6%	53.7-62.8		0.57	0.32-0.99	**0.049**
Sarcopenia			**0.026**			
No	76.9%	54.7-65.4		Ref		
Yes	62.8%	42.6-54.5		1.77	1.05-2.98	**0.033**

P value were calculated using the log-rank test for univariate analysis and COX proportional hazards model for multivariate analysis.

Ref: reference

Discussion

This study showed that sarcopenia, which was defined by TPI, was significantly associated with a longer postoperative hospital stay in patients with stage □ colon cancer who underwent laparoscopic radical resection, and patients with sarcopenia had a poorer completion rate of adequate AC. Sarcopenia was also a significant prognostic predictor for 3-year DFS.

Nowadays, there are two main methods to quantify sarcopenia, including measuring cross-sectional skeletal muscle area or cross-sectional area of psoas muscles at the level of the L3.[20] In this study, we defined sarcopenia by measuring a sectional area of psoas muscles due to its operability and clinical practicality.

Sarcopenia was diagnosed in 19.6% to 32.9% of colorectal cancer patients in early studies.[8, 11] There were 45.9% of patients being classified as sarcopenia in our study. This may because we only included patients with stage □ colon cancer, which was more likely to cause frailty. We found patients with sarcopenia had longer postoperative hospital stay than those without sarcopenia, though the overall rate

of postoperative morbidity was not significantly different between the two groups. A longer postoperative hospital stay may be due to the frailty caused by sarcopenia, which made the patients need more time to recover from the surgical trauma.

In the past 30 years, AC has been the standard treatment for patients with stage Ⅲ colon cancer since the previous studies have shown the benefits in relapse-free survival and overall survival by using AC.[21, 22] Consistent with early studies, our study showed AC significantly improved 3-year OS and DFS. However, due to economic, physical, or psychological factors, not all patients with stage Ⅲ colon cancer can finish the formal AC in clinical practice.[23] Roger H et al found that up to 40% of patients with stage Ⅲ or high-risk stage Ⅱ colon cancer did not receive recommended AC in their study.[24]

According to the final results of a prospective, pooled analysis of six randomized, phase 3 trials (IDEA collaboration), the 5-year overall survival between 3 months and 6months of AC was similar (82.1% versus 81.2%, HR 0.96 [0.85-1.08]), which supported the use of 3 months of adjuvant CAPOX for most patients with stage III colon cancer.[21] In our study, we define that receiving AC more than 3 months of CAPOX as an adequate AC. For the first time, we found sarcopenia was a significant factor to influence the compliance of receiving both AC and adequate AC for patients with stage Ⅲ colon cancer. Patients with sarcopenia had significantly lower compliance than those without sarcopenia. In addition, among patients who received AC, the rate of receiving adequate AC in the non-sarcopenia group was higher than in the sarcopenia group.

The reason for a lower rate of adequate AC in the sarcopenia group may be that the surgery trauma aggravated the frailty of patients who had sarcopenia, which makes them unable to withstand the toxicity and complications of AC. Nowadays, some studies explored the feasibility and efficacy of neoadjuvant chemotherapy for locally advanced colon cancer and demonstrated the potential benefit when compared to AC[25-27]. Considering the low compliance of AC in patients with sarcopenia, neoadjuvant chemotherapy may be an option, and better nutrition support for the malnourished sarcopenia patients before the operation may benefit the short-term and long-term outcome,[28] which need further study to confirm.

The prognostic significance of sarcopenia in patients with colorectal cancer (CRC) is controversial. A retrospective study of 220 stage Ⅱ-Ⅲ CRC found that sarcopenia was an independent risk factor for both recurrence-free survival (RFS) and OS.[6] However, another study including 494 patients with CRC showed sarcopenia did not significantly correlate with OS or RFS.[29] The reason for the different results between the two studies may be that they used different diagnostic criteria. In this study, when using the TPI as the diagnostic criteria for sarcopenia, we found sarcopenia was a significantly negative prognosis factor of 3-year DFS in patients with stage Ⅲ colon cancer. There was a tendency that patients with sarcopenia had poorer 3-year OS than those without sarcopenia (79.6% vs 90.0%, P=0.092), though the P-value did not reach the significance, the possible reason for these results is the relatively small sample size and inadequate follow up.

There were some limitations of this study that should be addressed. First, this was a single-institution, retrospective study with relatively small sample size. Second, we used the predefined cutoff for sarcopenia in the previous study, which may be not appropriated for the population included in this study. The optimal cut-off values for TPI that define sarcopenia in Asian patients with colon cancer, still require further investigation. Third, limited by data, the dose intensity of chemotherapy drugs was not analyzed in this study, and whether the dose intensity influenced the completion rate of AC was not discussed.

Conclusion

To the best of our knowledge, this is the first study to explore whether sarcopenia affects the compliance of patients to receive the recommended AC. Sarcopenia was an important indicator to predict the compliance of postoperative AC of stage □ colon cancer patients, and patients without sarcopenia had better compliance to the adjuvant chemotherapy. Sarcopenia was also a significant prognostic factor, which was associated with a worse 3-year DFS. To improve the compliance of AC and prognosis, it may be helpful to provide nutrition support and relieve sarcopenia before surgery, and further study on this topic is warranted. If possible, the more appropriate AC regimen should be administered according to the individual condition, and it can also further explore the feasibility of neoadjuvant chemotherapy in patients with sarcopenia.

Declarations

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Conflicts of interest

No author has any conflicts of interest related to this study.

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Figures

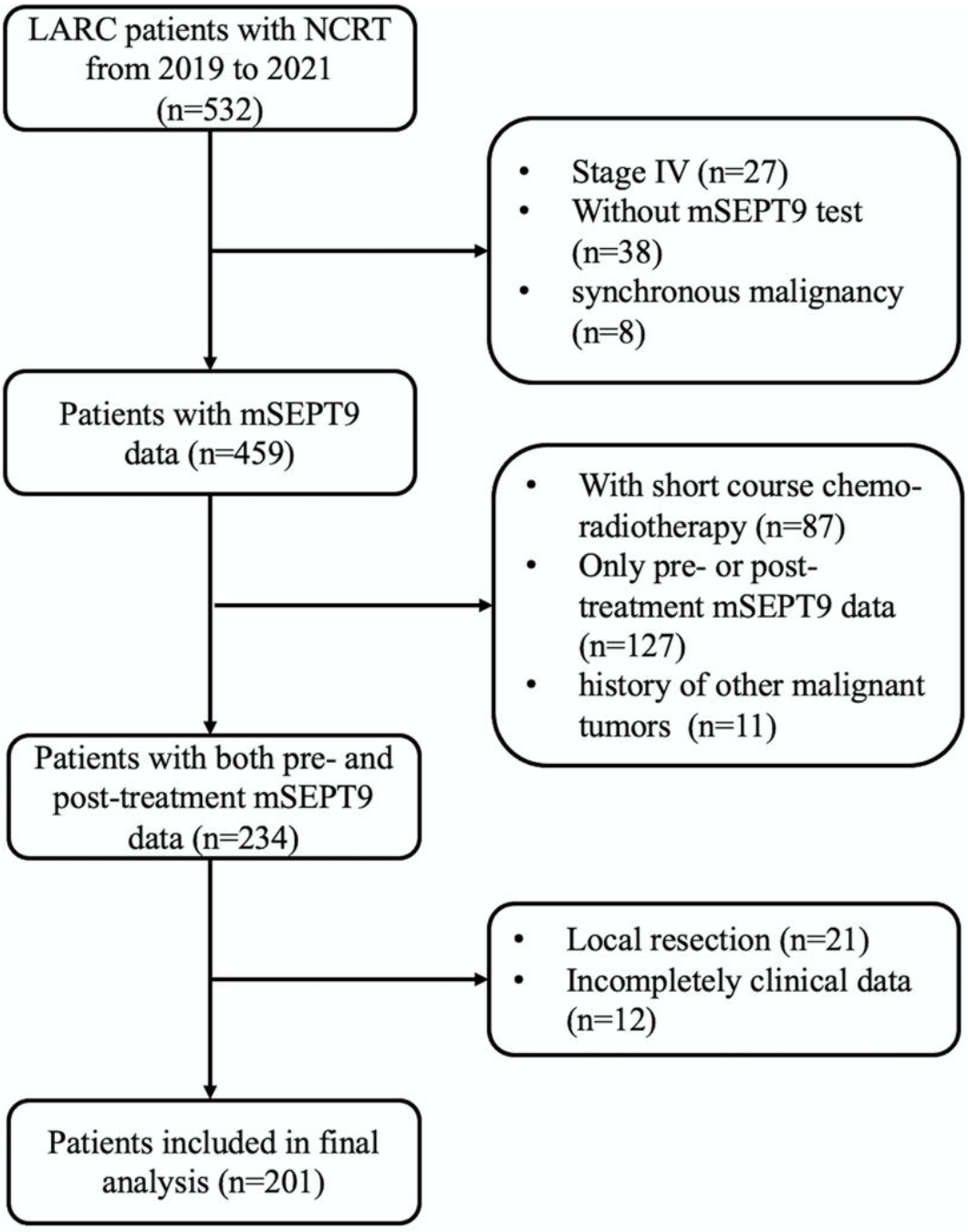

Figure 1

Flow chart.

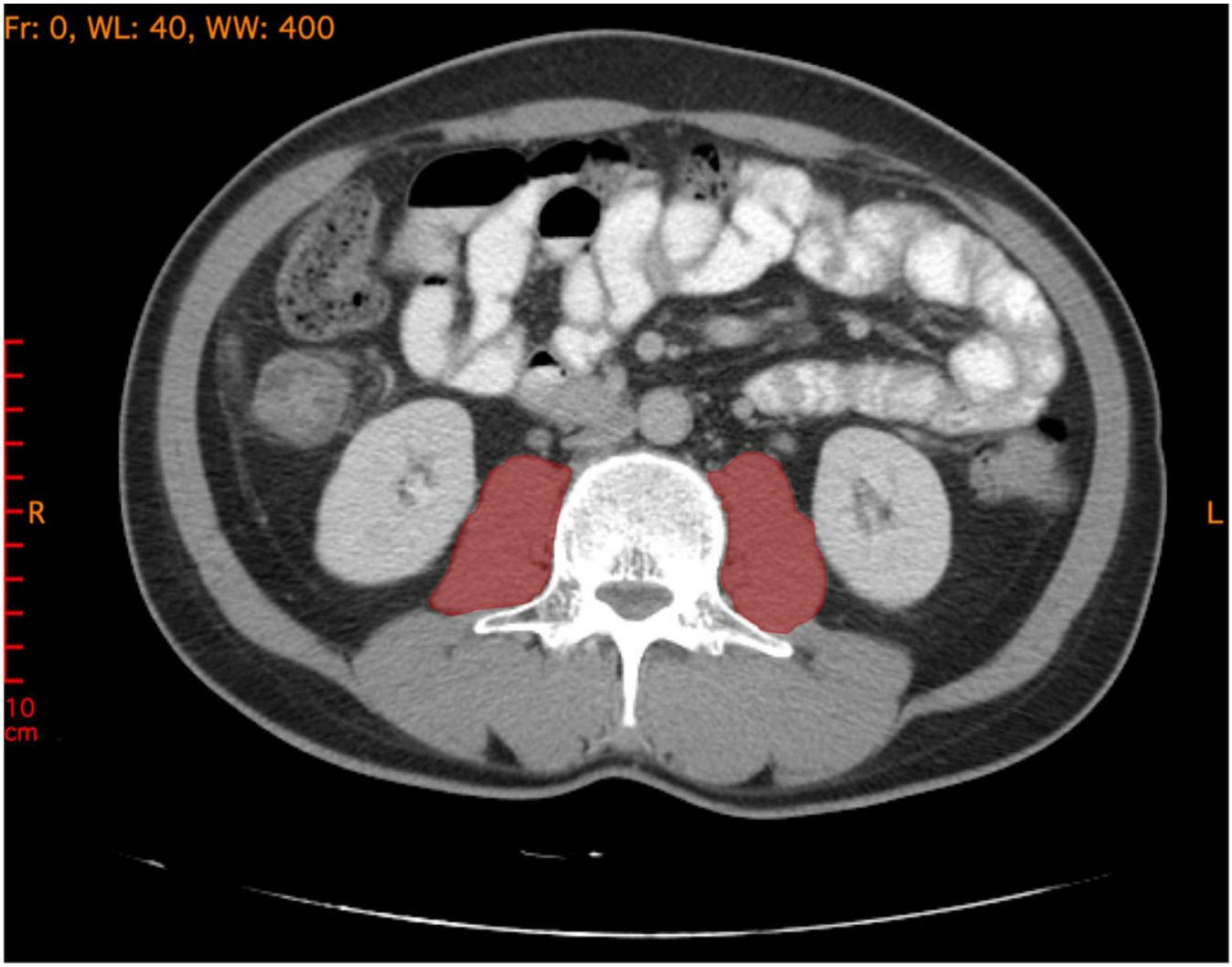

Figure 2

Psoas muscle (red area) at the level of L3 vertebral body.

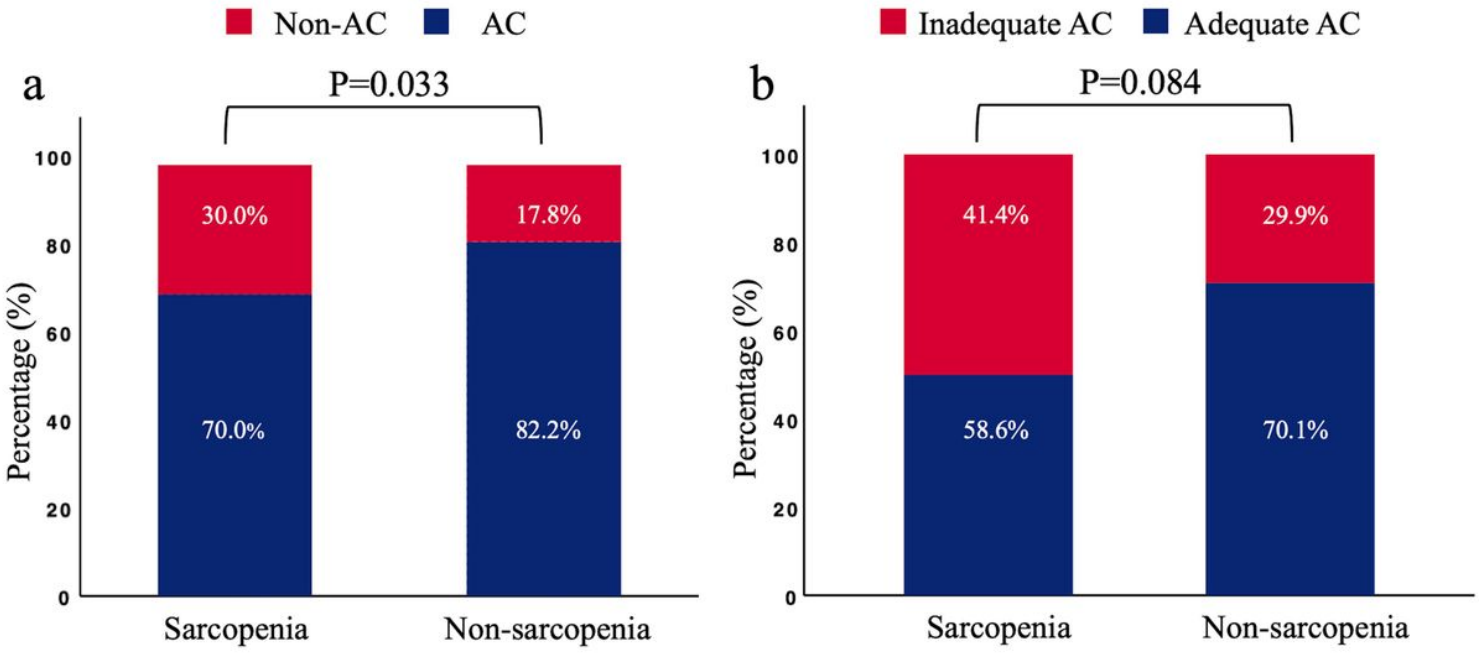

Figure 3

(A). The ratio of patients received adjuvant chemotherapy (AC) in sarcopenia group and non-sarcopenia group. (B). For all patients who received AC, the ratio of patients received adequate AC and inadequate AC in two groups.

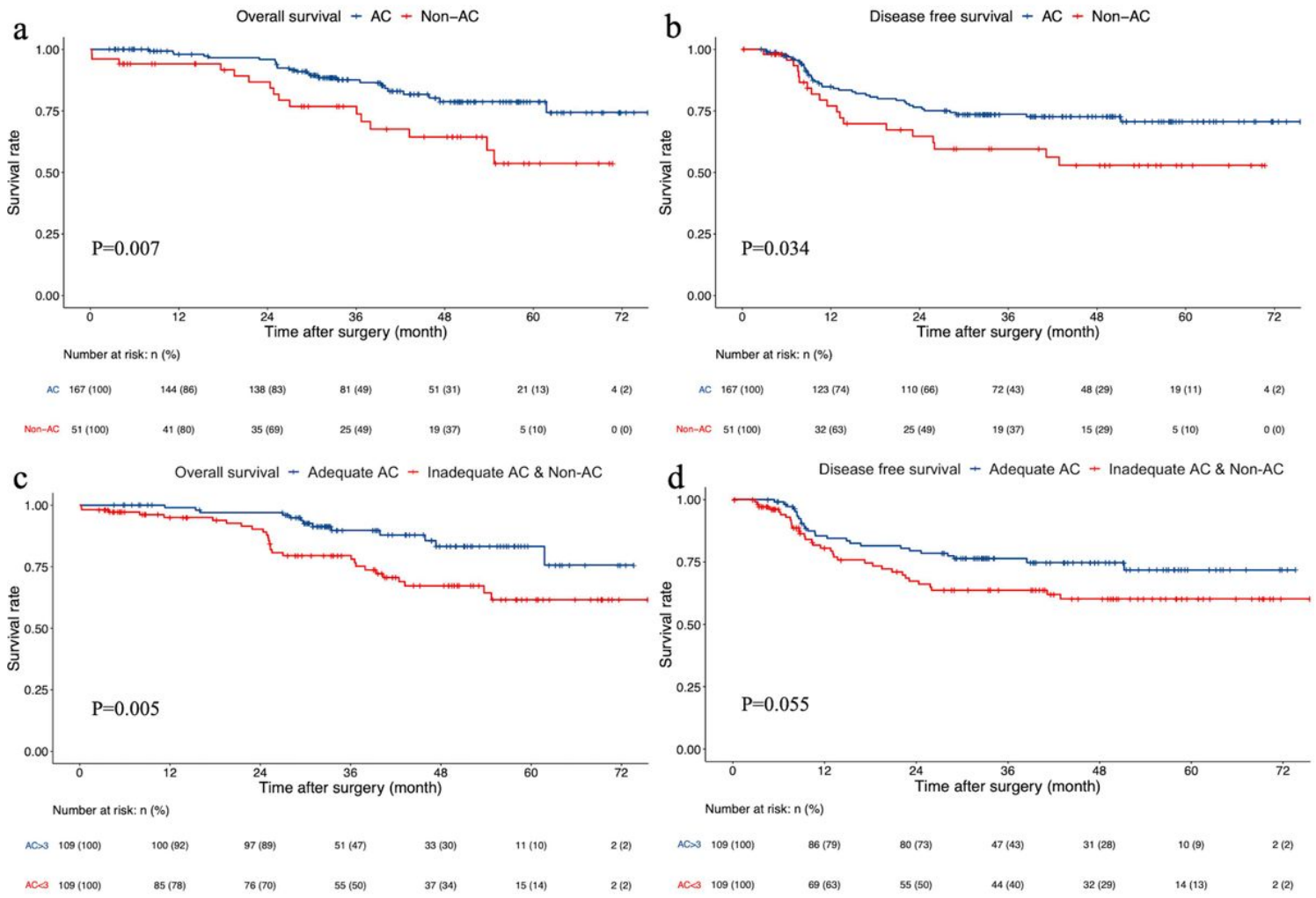

Figure 4

(A). Analysis of overall survival according to whether patients received AC. (B). Analysis of disease-free survival according to whether patients received AC. (C). Patients who received adequate AC had significantly better 3-year OS than that received inadequate AC. (D) There was a tendency that Patients who received adequate AC had better 3-year DFS than that received inadequate AC.

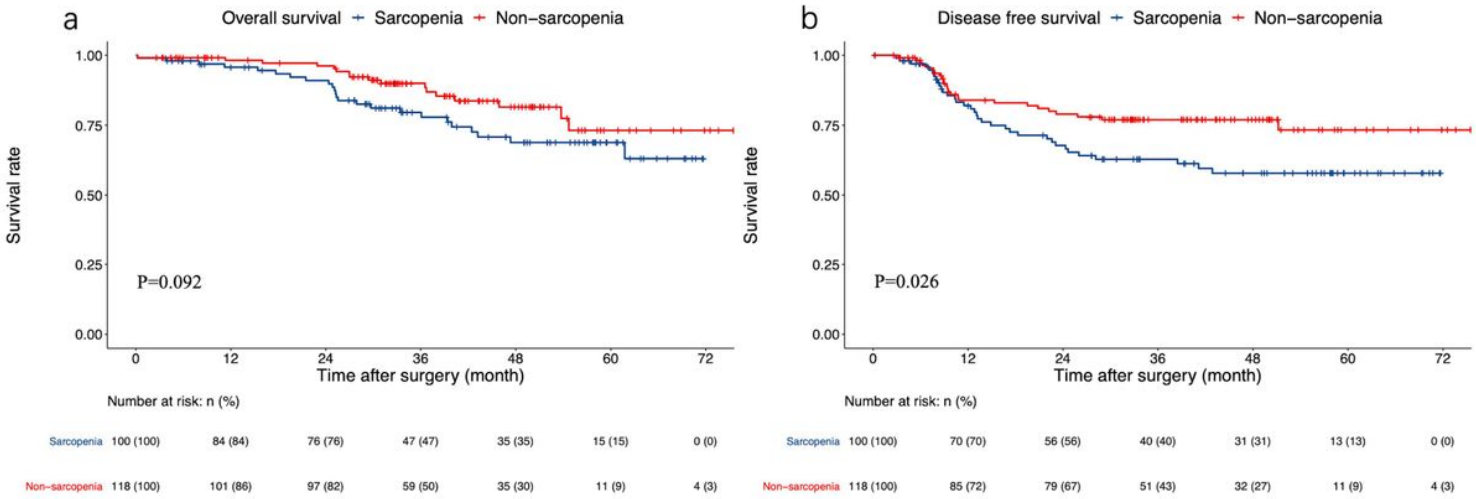

Figure 5

Analysis of overall survival (A) and disease-free survival (B) between patients with Sarcopenia and that without sarcopenia.