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Highlights

- Effects of deceased donor liver transplantation (DDLT) on sarcopenia were examined
- L3SMI and IMAC were measured at admission, discharge, and 1-year post-DDLT
- DDLT contributed to improved muscle quality
- Skeletal muscle mass and quality on admission do not affect post-DDLT survival

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Abstract:
Background: In Japan, there are very few cases of deceased donor liver transplantation (DDLT) and even fewer studies on the effects of DDLT on sarcopenia. This study examined the changes in skeletal muscle mass and quality in DDLT, the factors related to these changes, and survival rates.
Methods: Using computed tomography (CT), we retrospectively measured L3 skeletal muscle index (L3SMI) and intramuscular adipose tissue content (IMAC) at admission, discharge, and 1-year post-DDLT in 23 patients with DDLT from our hospital between 2011 and 2020. We investigated the relationships between changes in L3SMI and IMAC associated with DDLT as well as between various admission factors and survival.
Results: Patients with DDLT showed significant decreases in L3SMI during hospitalization ($p<0.05$). Although L3SMI tended to increase post-discharge, in 11 (73%) cases, it was lower at 1-year post-DDLT than that on admission. Moreover, decreases in L3SMI during hospitalization were correlated to L3SMI on admission ($r=-0.475$, $p<0.05$). IMAC tended to increase from admission to discharge and decreased 1-year post-DDLT. Admission L3SMI and IMAC were not significantly correlated with survival.
Conclusions: This study suggests that skeletal muscle mass of DDLT patients decreased during hospitalization and showed a slight tendency to improve after discharge, but the decrease tended to be prolonged. In addition, patients with higher skeletal muscle mass at admission tended to lose more skeletal muscle mass during hospitalization. DDLT was identified as a potential contributor to improved muscle quality, while skeletal muscle mass and quality on admission do not affect post-DDLT survival.

Keywords: deceased donor liver transplantation; sarcopenia; skeletal muscle mass; skeletal muscle quality.

1. Introduction

Liver transplantation is a treatment option for patients with end-stage liver disease. The first liver transplantation was performed by Starzl in the United States in 1963 [1,2], and liver transplantation has since developed through advances in various technologies, such as immunosuppressants and organ preservation technology. By 2017, 8795 cases of living donor liver transplantation (LDLT) and 447 cases of deceased donor liver transplantation (DDLT) had been performed in Japan [3]. From 2011 to 2020, 23 cases of DDLT (3.8% of the total) were performed at our hospital.

Since Rosenberg reported on the importance of skeletal muscle mass loss with aging and proposed the coined word “sarcopenia” in 1989, sarcopenia has attracted much attention in developed countries with an increase in the aged population. Sarcopenia is defined as the loss of mass, quality, and strength of the skeletal muscles and was first regarded as an age-related disorder in older people (primary sarcopenia) [4]. Subsequently, sarcopenia was found to also occur at a young age due to a range of chronic disorders such as cancer, chronic liver disease, anorexia, or malnutrition (secondary sarcopenia) [4]. As almost all liver transplant recipients have end-stage liver disease, most of them have decompensated cirrhosis. Because decompensated cirrhosis causes poor intake, decreased appetite, decreased activity, protein energy undernutrition, and increased muscle protein catabolism [5–7], secondary sarcopenia is likely to coexist with liver disease. The Japanese Society of Hepatology has published diagnostic criteria regarding secondary sarcopenia in liver disease (Figure 1). Many studies have reported that sarcopenia is an independent predictor of poor survival in liver disease [8,9]. Although the significance of sarcopenia in liver transplantation has been reported in Europe and the United States, where many DDLTs are performed [10–12], the relationship between DDLT and sarcopenia in Japan has not been reported.

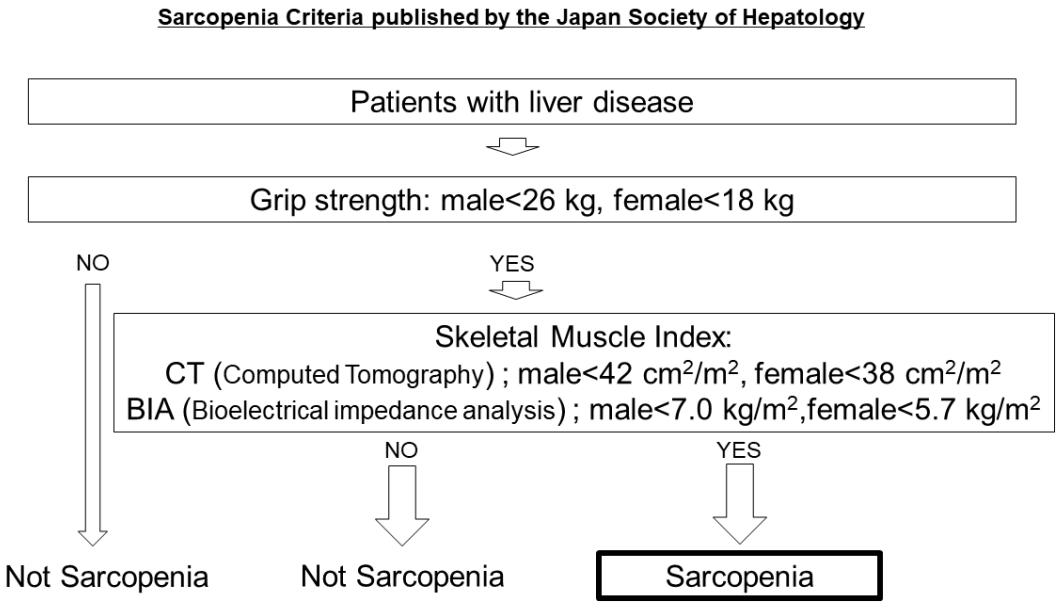


Figure 1. Flowchart for the diagnosis of sarcopenia. The diagnostic criteria regarding secondary sarcopenia in liver disease published by the Japanese Society of Hepatology shows the steps for diagnosis.

Furthermore, in recent years, the importance of muscle quality in cancer and liver transplant patients has been clarified, and intramuscular fattening has been reported to be correlated with muscle weakness and functional decline [13]. In Japan, it has also been reported that intramuscular adipose tissue content (IMAC), which is a parameter of intramuscular fattening and an index of muscle quality, is a prognostic factor in LDLT patients [14]. Although IMAC may also be of importance for DDLT, there are no reports investigating the significance of IMAC for DDLT.

In this study, we aimed to examine the significance of skeletal muscle mass and quality in DDLT and to investigate the changes in skeletal muscle mass and quality and factors related to these changes for the first time in Japan.

2. Materials and Methods

2.1. Patients

Twenty-three adults underwent DDLT between June 2011 and June 2020 at Kobe University Hospital (Kobe, Japan) and were all included in the study. This study was approved by the ethics committee and the institutional review board of our affiliated institutions (IRB number B210257). The study was in accordance with the Declaration of Helsinki for human research.

2.2. Clinical and Laboratory Assessments

Variables of interest were obtained from the electronic medical records, including age, sex, height, disease status for DDLT, date of admission, date of surgery, date of discharge, date of discharge from the postoperative intensive care unit (ICU), date of last confirmed survival, a model for end-stage liver disease (MELD) score, albumin-bilirubin (ALBI) score, and serum ammonia. Clinical and laboratory data were acquired within 7 days of admission.

2.3. Image Analyses (Figure 2 [15])

2.3.1. Computed tomography (CT) scans

Abdominal CT scans performed on admission, at discharge, and at 1-year post-DDLT were used for analysis. If no CT scans were taken at any of the three time-points, L3SMI and IMAC at the corresponding time points were treated as missing values.

2.3.2. L3 skeletal muscle index (L3SMI) [16,17]

The muscles in the cross-sectional CT at the third lumbar vertebra (L3) level, including the lumbar muscles, erector spinae, quadratus lumborum, transversus abdominis, external oblique abdominis, internal oblique abdominis, and rectus abdominis, were analyzed using Ziostation2® (Ziosoft Corporation, Minato-ku, Tokyo). Reports indicate that the assessment of abdominal CT images at L3 can yield reliable results for the measurement of whole-body skeletal muscle mass. Muscles were quantified in the range of -29 to 150 HU, and tissue boundaries were manually modified as needed. The L3 skeletal muscle area calculated from each image was divided by height squared (m^2) to derive L3SMI (cm^2/m^2).

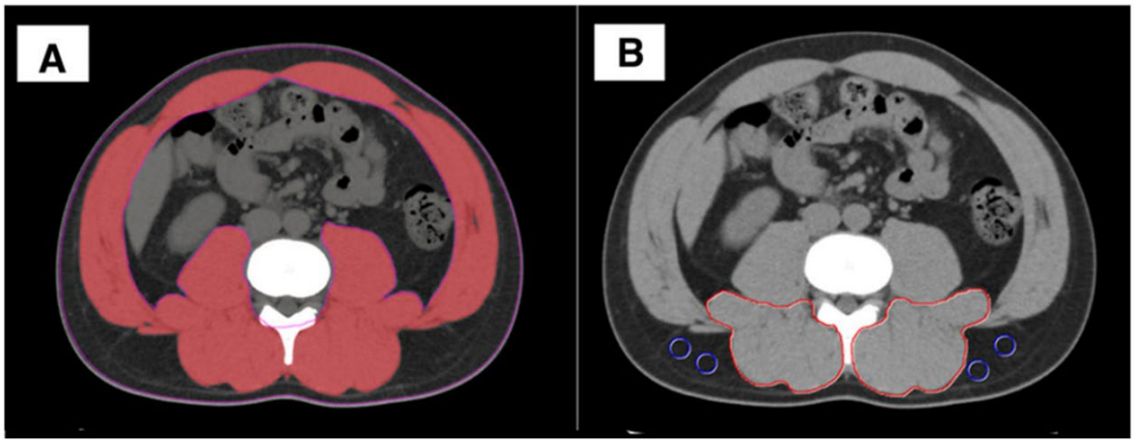
2.3.3. Sarcopenia and non-sarcopenia

According to the criteria for sarcopenia indicated by the Japanese Society of Hepatology, male and female patients with admission L3SMI of < 42 cm^2/m^2 and < 38 cm^2/m^2, respectively, were defined as the sarcopenia group, and the others were defined as the non-sarcopenia group. The statistical differences between the two groups were investigated.

2.3.4. IMAC [15]

IMAC is a parameter of intramuscular adipose tissue calculated from the CT value of the multifidus muscle and the CT value of the back subcutaneous fat. A large IMAC indicates a large amount of intramuscular adipose tissue, that is, low muscle quality. IMAC was calculated as previously described by Kitajima et al.: [IMAC = average CT values (HU) of the multifidus muscle at the umbilical level divided by average CT values (HU) of subcutaneous fat at the umbilical level]. Subfascial muscular tissue in the multifidus muscle was precisely traced on the plain CT cross-sectional image before surgery at the umbilical level and CT values (HU) were measured. CT values were measured for regions of interest (ROIs) of the four circles on

the subcutaneous fat away from major vessels. The mean values of these four ROIs were used as the ROI for the subcutaneous fat.



(A)L3SMI (B)IMAC

Figure 2. Measurement method for L3SMI and IMAC. (A)The red colored area of shows the L3 skeletal muscle area . The L3 skeletal muscle area calculated from each image was divided by height squared to derive L3SMI. (B)The multifidus muscle is covered with a red line and a round ROI is set in the subcutaneous fat on the back.

2.4. Investigation of L3SMI

By measuring the L3SMI at three-time points: on admission, at discharge, and at 1-year post-DDLT, we investigated the changes in L3SMI after DDLT in the sarcopenia and non-sarcopenia groups. We also examined whether these changes were statistically significant.

In addition, we analyzed the correlation between L3SMI and various parameters. The parameters were age, overall survival rate, L3SMI, and IMAC at the three-time points, change in L3SMI and IMAC during hospitalization, duration of hospital stay, waiting time for surgery, postoperative ICU stay, MELD score, ALBI score, and serum NH_3. We also analyzed the factors involved in the change in L3SMI during hospitalization.

2.5. Investigation of IMAC

By measuring IMAC at the three time-points: on admission, at discharge, and at 1-year post-DDLT, we investigated the changes in IMAC associated with DDLT in the sarcopenia group and non-sarcopenia groups. Furthermore, we examined whether the changes were statistically significant.

In addition, we analyzed the correlation between IMAC and various parameters. The parameters were age, overall survival rate, L3SMI and IMAC at the three time-points, changes in L3SMI and IMAC during hospitalization, duration of hospital stay, waiting time for surgery, postoperative ICU stay, MELD score, ALBI score, and serum NH_3.

2.6. Evaluation of Overall Survival Time and Overall Survival Rates

The overall survival time was calculated from the date of transplantation to the date of death due to disease-related causes. For patients confirmed to be alive at the last assessment, the overall survival time was calculated from the date of transplantation to the date of the last visit to our hospital.

We analyzed the correlation between the overall survival rate and various parameters. The parameters were the same as for the IMAC investigation in the subsection above.

In addition, we examined the impact of the background status for DDLT (fulminant or non-fulminant hepatitis) and sarcopenia on overall survival time.

2.7. Statistical Analysis

Statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY, USA). The significance level was set at $p < 0.05$. The Mann–Whitney–U test was used to compare various parameters between the sarcopenia and non-sarcopenia groups. For L3SMI and IMAC, Friedman's test was used to analyze the within-subject effect of the parameters at admission, discharge, and 1-year post-DDLT. Spearman's rank correlation coefficient was used to investigate the correlation between the parameters. The relationship between overall survival rates and the background status for DDLT (fulminant or non-fulminant hepatitis) was examined using the log-rank test and Kaplan–Meier curve. The relationship between overall survival rates and sarcopenia was also examined using the log-rank test and Kaplan–Meier curve.

3. Results

3.1. Patient Characteristics

A summary of the clinical and biochemical characteristics of the patients is presented in Table 1. The average duration of hospital stay was approximately 122 days and the average postoperative ICU stay was 15 days. At the time of evaluation, four patients had died.

Table 1. Baseline Characteristics of the 23 patients

Characteristics	Average±SD or Number of Patients (% of total)
Age(years)	43.8±13.35
Sex	
Male	9 (39%)
Female	14 (61%)
Height(m)	1.59±0.11
MELD score	21.22±12.02
ALBI score	-0.98±0.74
NH_3(μg/dl)	172.64±62.19
Sarcopenia	
Sarcopenia on admission	5

Non-sarcopenia on admission	15
Waiting time for operation (days)	29.96±39.27
Duration of hospital Stay (days)	122.48±65.90
Postoperative Hospital Stay (days)	92.52±52.23
Postoperative ICU Stay (days)	15.00±16.649
Death	4 (17%)
Background status for liver transplantation	
Fluminant hepatitis	10
Others	13

n = 23 in total. MELD score: Model for End-Stage Liver Disease score, ALBI score: Albumin-Bilirubin score

The background status for liver transplantation were fulminant hepatitis in 10 patients, liver failure after LDLT in two patients, primary biliary cholangitis in two patients, and primary sclerosing cholangitis, hepatitis C virus infection, biliary atresia, alcoholic liver failure, autoimmune hepatitis, intravascular lymphoma, hereditary hemorrhagic telangiectasia, familial hypolipoproteinemia, and glycogenosis in one patient each.

3.2. Sarcopenia and non-Sarcopenia

There were five patients with sarcopenia and 15 patients without sarcopenia. L3SMI on admission was missing for three patients. There were no significant differences in the background or characteristics between the sarcopenia and non-sarcopenia groups (data not shown).

3.3. L3SMI

L3SMI decreased significantly during hospitalization. Although L3SMI showed a trend toward improvement after discharge, many cases showed a lower L3SMI at 1-year post-DDLT compared to that at the time of admission (Figure 3A). L3SMI of the sarcopenia group showed gradual improvement during hospitalization. L3SMI at discharge in the non-sarcopenia group was significantly lower than that on admission and did not increase after discharge (Figure 3A).

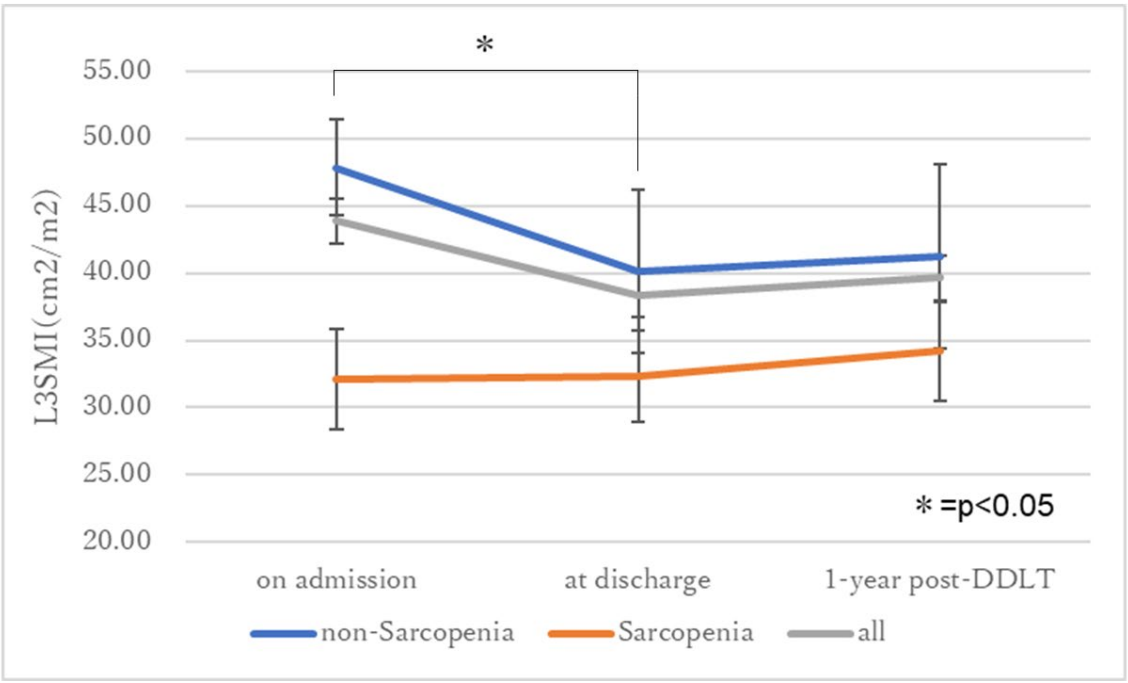


Figure 3A. Changes in L3SMI at three points (admission, discharge, and 1-year post-DDLT) in the sarcopenia, non-sarcopenia group, and total groups. In the all group, L3SMI at discharge was lower compared to that at admission. L3SMI did not improve at 1-year post-DDLT in any group. In the sarcopenia group, L3SMI did not show a clear decrease at discharge or 1-year post-DDLT. * indicates $p<0.05$, it shows a statistically significant change between L3SMI on admission and L3SMI at discharge.

The correlation coefficients of L3SMI on admission, at discharge, and 1-year post-DDLT and the change in L3SMI during hospitalization are shown in Table 2. L3SMI on admission showed a significant positive correlation with L3SMI at discharge ($r=0.702$, $p=0.001$) and 1-year post-DDLT ($r=0.525$, $p=0.044$) (Table 2). L3SMI on admission was not significantly correlated with the duration of hospital stay, age, or overall survival rate. In contrast, there was a significant negative correlation between L3SMI on admission and change in L3SMI during hospitalization ($r=-0.475$, $p=0.04$) (Table 2). We did not find any significant correlation between skeletal muscle loss during hospitalization and L3SMI on admission.

Table 2. Correlation coefficients of L3SMI

L3SMI	On admission		At discharge		1-year post DDLT		Change during hospitalization	
Factors	r	p	r	p	r	p	r	p
Age	-0.366	0.112	-0.207	0.356	-0.44	0.068	0.207	0.396
Overall survival rate	0.36	0.879	-0.056	0.805	-0.244	0.329	-0.132	0.591

L3SMI on admission			0.702	0.001*	0.525	0.044*	-0.475	0.04*
L3SMI at discharge	0.702	0.001*			0.775	<0.001*	0.105	0.668
L3SMI 1-year post DDLT	0.525	0.044*	0.775	<0.001*			0.253	0.383
Change in L3SMI during hospitalization	-0.475	0.04*	0.105	0.668	0.253	0.383		
IMAC on admission	-0.077	0.753	-0.177	0.468	-0.209	0.438	0.247	0.324
IMAC at discharge	-0.126	0.606	-0.054	0.813	-0.137	0.599	0.228	0.348
IMAC 1-year post-DDLT	0	1	-0.24	0.353	-0.247	0.324	-0.13	0.659
Change of IMAC during hospitalization	-0.032	0.898	0.104	0.673	0.209	0.474	-0.07	0.775
Duration of hospital stay	-0.053	0.823	-0.186	0.406	-0.39	0.11	0.012	0.96
Waiting time for operation	0.02	0.932	0.143	0.525	-0.011	0.964	0.062	0.802
Post-operative ICU stay	-0.481	0.032*	-0.156	0.488	-0.251	0.315	-0.001	0.997
MELD score	0.112	0.637	0.011	0.96	0.018	0.945	-0.296	0.218
ALBI score	-0.266	0.258	0.199	0.374	0.24	0.338	0.232	0.34
Serum NH_3	-0.168	0.478	0.077	0.741	0.105	0.687	0.065	0.792

L3SMI: L3 skeletal muscle index, IMAC: Intramuscular adipose tissue content, DDLT: deceased donor liver transplantation, MELD score: Model for End-Stage Liver Disease score, ALBI score: Albumin-Bilirubin score, OS: overall survival rate

3.4. IMAC

There was a tendency for IMAC to increase from admission to discharge and to decrease 1-year post-DDLT (Figure 3B) considering the entire population. In the non-sarcopenia group, IMAC showed changes similar to those in the entire population. However, in the sarcopenia group, IMAC decreased consistently. The correlation coefficients of IMAC on admission, at discharge, and 1-year post-DDLT and the change in IMAC during hospitalization are shown in Table 3. IMAC at discharge was positively correlated with age (r=0.498, p=0.018) and the duration of hospital stay (r=0.507, p=0.016) (Table 3). In addition, the change in IMAC during hospitalization was positively correlated with the NH_3 level on admission (r=0.539, p=0.017) (Table 3). No other significant correlations were found.

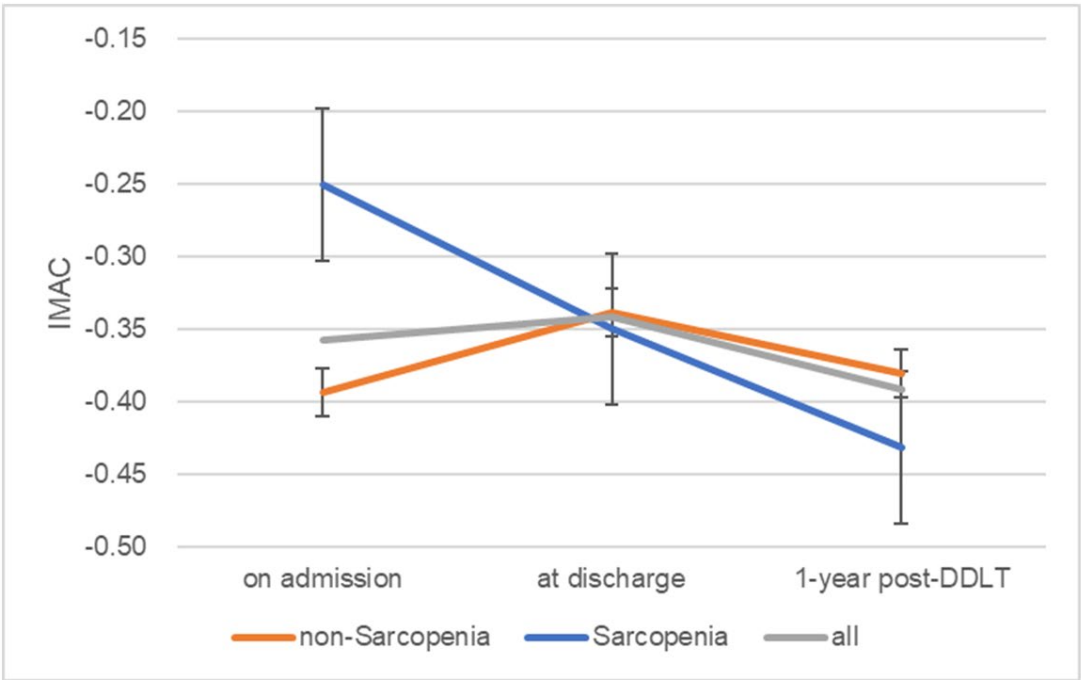


Figure 3B. Changes in IMAC at three points (admission, discharge, and 1-year post-DDLT) in the sarcopenia group, non-sarcopenia, and all groups. In all groups, IMAC increases from admission to discharge and declines from discharge to 1-year post-DDLT. In the non-sarcopenia group, IMAC changed similarly to the all group. However, in the sarcopenia group, IMAC consistently decreased from admission through 1-year post-DDLT.

Table 3. Correlation coefficients of IMAC

IMAC	On admission		At discharge		1-year post DDLT		Change during hospitalization	
Factors	r	p	r	p	r	p	r	p
Age	0.327	0.16	0.498	0.018*	0.547	0.019*	0.164	0.504
Overall survival rate	0	1	0.167	0.457	0.417	0.085	0.158	0.518
L3SMI on admission	-0.077	0.753	-0.126	0.606	0	1	-0.032	0.898
L3SMI at discharge	-0.177	0.468	-0.054	0.813	-0.24	0.353	0.104	0.673
L3SMI 1-year post DDLT	-0.209	0.438	-0.137	0.599	-0.247	0.324	0.209	0.474
Change in L3SMI during hospitalization	0.247	0.324	0.228	0.348	-0.13	0.659	-0.07	0.775
IMAC on admission			0.67	0.002*	0.712	0.002*	-0.044	0.861
IMAC at discharge	0.67	0.002*			0.561	0.019*	0.605	0.006*

IMAC 1-year post-DDLT	0.712	0.002	0.561	0.019			-0.037	0.899
Change of IMAC during hospitalization	-0.044	0.861	0.605	0.006*	-0.037	0.899		
Duration of hospital stay	0.315	0.177	0.507	0.016*	0.338	0.17	0.136	0.579
Waiting time for operation	0.035	0.884	0.114	0.612	0.085	0.737	-0.129	0.598
Post-operative ICU stay	-0.176	0.458	0.116	0.606	0.029	0.908	0.178	0.466
MELD score	-0.251	0.285	-0.211	0.347	0.124	0.624	0.027	0.912
ALBI score	-0.034	0.887	-0.229	0.306	0.165	0.512	-0.293	0.223
Serum NH_3	0.161	0.498	0.254	0.267	0.164	0.529	0.539	0.017*

L3SMI: L3 skeletal muscle index, IMAC: Intramuscular adipose tissue content, DDLT: deceased donor liver transplantation, MELD score: Model for End-Stage Liver Disease score, ALBI score: Albumin-Bilirubin score, OS: overall survival rate

3.5. Evaluation of Overall Survival Time and Overall Survival Rates

One of the patients in the sarcopenia group died, while three patients in the non-sarcopenia group died. There was no significant correlation between the overall survival rate and L3SMI or IMAC at any time point (Table 4). In addition, no significant correlation was found with indicators of liver function, such as the MELD and ALBI scores on admission (Table 4). Regarding the log-rank test, the relationship between the overall survival time and the background status for liver transplantation (fulminant vs. non-fulminant hepatitis) showed a significant difference (p=0.019, Figure 4A) and the relationship between the overall survival time and sarcopenia showed no significant difference (p=0.600, Figure 4B).

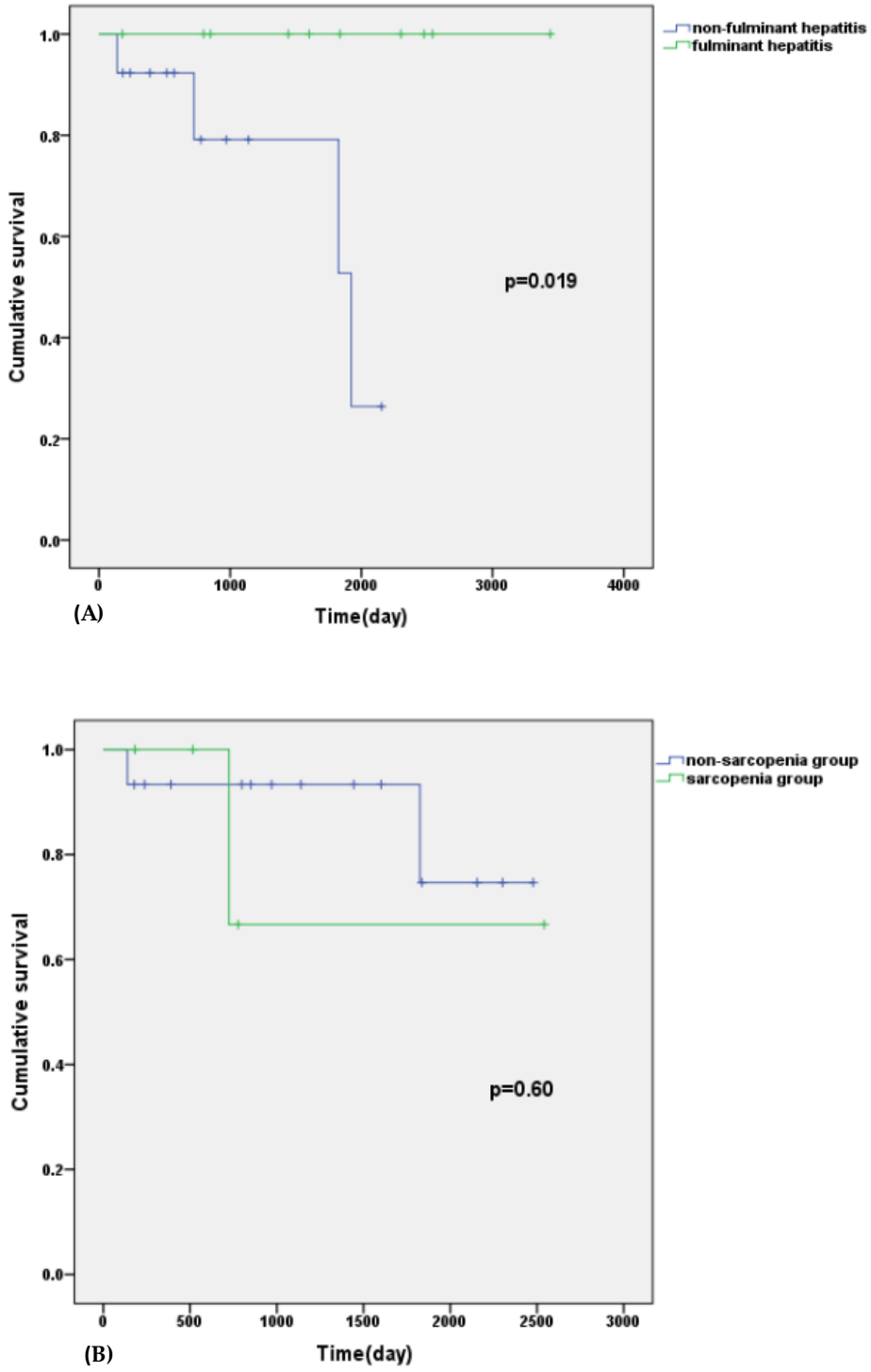


Figure 4. (A) Kaplan–Meier survival curves of patients with fulminant hepatitis and without. None of the patients with fulminant hepatitis died, while four of the patients without fulminant hepatitis died. There was a statistically significant difference in survival between the two groups (p=0.019). (B) **Figure 4B.** Kaplan–Meier survival curves of sarcopenia group and non-sarcopenia group. One of the patients in the sarcopenia group died, while three patients in the non-sarcopenia group died. There was no statistically significant difference in survival between

the two groups (p=0.60).

Table 4. Correlation coefficients of overall survival rate

	OS	
Factors	r	p
Age	0.572	0.004*
Overall survival rate		
L3SMI on admission	0.036	0.879
L3SMI at discharge	-0.056	0.805
L3SMI 1-year post DDLT	-0.244	0.329
Change in L3SMI during hospitalization	-0.132	0.591
IMAC on admission	0	1
IMAC at discharge	0.167	0.457
IMAC 1-year post-DDLT	0.417	0.085
Change of IMAC during hospitalization	0.158	0.518
Duration of hospital stay	0.104	0.637
Waiting time for operation	-0.26	0.23
Postoperative ICU stay	0.026	0.906
MELD score	0.251	0.247
ALBI score	0.069	0.754
Serum NH_3	0.149	0.509

L3SMI: L3 skeletal muscle index, IMAC: Intramuscular adipose tissue content, DDLT: deceased donor liver transplantation, MELD score: Model for End-Stage Liver Disease score, ALBI score: Albumin-Bilirubin score, OS: overall survival rate

4. Discussion

In this study, we investigated the significance of skeletal muscle mass and muscle quality in DDLT and the changes in skeletal muscle mass and muscle quality in patients with DDLT for the first time in Japan. We found that the skeletal muscle mass of patients who underwent DDLT significantly decreased during hospitalization. Furthermore, the non-sarcopenia group tended to have more L3SMI loss than the sarcopenia group during hospitalization and did not show sufficient improvement after discharge. However, the sarcopenia group had persistently low L3SMI after discharge compared to the non-sarcopenia group. Although patients with liver dysfunction are prone to sarcopenia due to various factors, our study suggests that skeletal muscle mass loss tends to persist even after DDLT. This is a new finding, and we consider the possibility that post discharge nutritional status and exercise intensity may be related to muscle mass recovery. This study did not evaluate post-discharge parameters, which we believe is an avenue for future research.

Although we examined the factors related to skeletal muscle loss during hospitalization, no significant correlations were found other than L3SMI on admission. In 2019, Hartley et al. conducted a systematic review and meta-analysis of skeletal muscle changes during unplanned hospital admission in adult patients [18]. The report suggested that unplanned hospitalization may cause a small reduction in skeletal muscle mass and muscle strength, and that inflammation is associated with a higher loss of muscle strength. The authors also mentioned the possibility that patients with high skeletal muscle mass may be more prone to decline, and that the loss of skeletal muscle mass during hospitalization may be defined only by the initial skeletal muscle mass. This finding is consistent with the results of the present study.

With regard to muscle quality, we observed a worsening of muscle quality at the time of discharge compared to that at the time of admission but noted an improvement in muscle quality after 1-year. To the best of our knowledge, this is the first study to suggest that DDLT may contribute to improved muscle quality. Furthermore, the duration of hospitalization was positively correlated with IMAC at discharge, suggesting that prolonged hospitalization may be associated with lower muscle quality. In addition, changes in muscle quality during hospitalization were positively correlated with serum NH_3 levels at admission. A report on the relationship between hyperammonemia and sarcopenia [19] also revealed the possibility that NH_3 may affect skeletal muscle mass and muscle quality.

Of the 23 patients that underwent DDLT at our hospital, four died and 19 survived, with an overall survival rate of approximately 83%. In this study, the background status for liver transplantation (fulminant or non-fulminant hepatitis) and age were significantly correlated with the overall survival rate. However, there was no association between low skeletal muscle mass or quality and overall survival, and the preoperative sarcopenia status did not affect DDLT survival in this study. Sarcopenia and low muscle quality have been reported as prognostic factors for liver transplantation in studies on liver transplantation in Western countries and LDLT in Japan. In this study, fulminant hepatitis accounted for the majority (44%) of the background status for liver transplantation. However, alcoholic cirrhosis and hepatitis C are the main background status for liver transplantation (30-40%) in Western studies, with fulminant hepatitis accounting for less than 10% [20–22]. Because the background status for DDLT differ between Japan and other countries, it can be assumed that the prognostic factors also differ.

This study has some limitations. First, we could not compare DDLT with LDLT performed at our institution. We could not clarify the usefulness of DDLT or the differences between DDLT and LDLT. Furthermore, because the study was conducted at a single facility, we were unable to compare with DDLT at other facilities. Second, the number of cases was very small because of the rarity of the cases. Third, because this was a retrospective observational study, the amount of data obtained was limited. Finally, skeletal muscle mass and quality were only evaluated on imaging, and actual muscle strength was not measured.

5. Conclusion

In this study, we examined, for the first time in Japan, the significance of skeletal muscle mass and quality and their changes over time in patients with DDLT. Skeletal muscle mass decreased during hospitalization and showed a slight tendency to improve after discharge, but the decrease tended to be prolonged. In addition, patients with higher skeletal muscle mass at admission tended to lose more skeletal muscle mass during hospitalization. Furthermore, DDLT was identified as a potential contributor to improved muscle quality. Sarcopenia status did not affect DDLT prognosis, suggesting an association between the background status for DDLT and overall survival. It is possible that prognostic factors may differ between Western countries and Japan due to the differences in background status for DDLT. Further investigation of DDLT seems needed to increase the number of procedures in Japan.

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Informed Consent Statement: Informed consent was obtained in the form of opt-out on the web-site.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, RY, upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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