ORIGINAL ARTICLE

Low skeletal muscle mass is associated with increased hospital costs in patients with cirrhosis listed for liver transplantation–a retrospective study

Jeroen L. A. van Vugt[1], Stefan Buettner[1], Louise J. M. Alferink[2], Niek Bossche[3], Ron W. F. de Bruin[1], Sarwa Darwish Murad[2], Wojciech G. Polak[1], Herold J. Metselaar[2] & Jan N. M. IJzermans[1]

1 Department of Surgery, Division of HPB and Transplant Surgery, Erasmus MC University Medical Centre, Rotterdam, the Netherlands
2 Department of Gastroenterology and Hepatology, Erasmus MC University Medical Centre, Rotterdam, the Netherlands
3 Department of Control and Compliance, Erasmus MC University Medical Centre, Rotterdam, the Netherlands

*Correspondence
Jeroen L. A. van Vugt, MD, Department of Surgery, Erasmus MC University Medical Centre, Wytemaweg 80, 3015 CE Rotterdam, The Netherlands.
Tel.: +31 10 704 36 83;
fax: +31 10 7032396;
e-mail: j.l.a.vanvugt@erasmusmc.nl

SUMMARY

Low skeletal muscle mass (sarcopenia) is associated with increased morbidity and mortality in liver transplant candidates. We investigated the association between sarcopenia and hospital costs in patients listed for liver transplantation. Consecutive patients with cirrhosis listed for liver transplantation between 2007 and 2014 in a Eurotransplant centre were identified. The skeletal muscle index (SMI, cm^2/m^2) was measured on CT performed within 90 days from waiting list placement. The lowest sex-specific quartile represented patients with sarcopenia. In total, 224 patients were included. Median time on the waiting list was 170 (IQR 47–306) days, and median MELD score was 16 (IQR 11–20). The median total hospital costs in patients with sarcopenia were €11 294 (IQR 3570–46 469) compared with €6878 (IQR 1305–20 683) in patients without sarcopenia ($P = 0.008$). In multivariable regression analysis, an incremental increase in SMI was significantly associated with a decrease in total costs (€455 per incremental SMI, 95% CI 11–900, $P = 0.045$), independent of the total time on the waiting list. In conclusion, sarcopenia is independently associated with increased health-related costs for patients on the waiting list for liver transplantation. Optimizing skeletal muscle mass may therefore lead to a decrease in hospital expenditure, in addition to greater health benefit for the transplant candidate.

Transplant International 2018; 31: 165–174

Key words
cirrhosis, hospital costs, liver transplantation, sarcopenia, skeletal muscle mass, waiting list

Received: 25 May 2017; Revision requested: 24 July 2017; Accepted: 26 August 2017

Introduction

Liver transplantation is the only curative treatment for patients with end-stage liver disease [1]. The 1-year and 3-year survival rates of patients who undergo orthotopic liver transplantation in Europe and the United States are around 85% and 80%, respectively [1]. While allocation of donor organs is based on the Model for End-stage Liver Disease (MELD) score [2,3], which measures liver function, patients on the waiting list are at increased risk for major morbidity and mortality, particularly due to infections [1,4–6]. Indeed, hospital admissions in patients with end-stage liver disease occur frequently and are costly [7–9].

One of the factors related to hospital admissions is frailty, which is defined as the increased vulnerability to stressors due to reduced physiological reserves. Frailty is a known risk factor for adverse outcome in cirrhosis and

doi:10.1111/tri.13048

liver transplant patients [10–13]. Sarcopenia, defined as the involuntary loss of skeletal muscle mass and function, is part of the frailty syndrome and highly prevalent among patients with end-stage liver disease [14]. In patients with cirrhosis, low skeletal muscle mass is associated with increased mortality on the liver transplantation waiting list and post-transplant morbidity and mortality, independently of well-established predictors such as the MELD score [14,15]. Sarcopenia has also been associated with higher healthcare costs in abdominal cancer patients undergoing surgery [16–18]. To date, only one study from the United States described the association between gait speed, as a measure of frailty, and increased hospital costs in patients with cirrhosis [11]. However, generalizability of these data is limited because, as a consequence of income inequality, great differences exist between the United States and Western Europe regarding healthcare accessibility [19–21].

The primary objective of this study, therefore, was to investigate the association between skeletal muscle mass and hospital costs in patients with cirrhosis listed for liver transplantation in a European transplant centre. A secondary objective was to assess the association between skeletal muscle mass and total hospital costs during admission for liver transplantation in the subgroup of patients who eventually underwent liver transplantation.

Methods

Patients and data acquisition

All consecutive patients who were listed for liver transplantation from January 2007 to December 2014 at Erasmus MC University Medical Centre were identified using the Eurotransplant registry [22]. Patients listed for reasons other than cirrhosis ($n = 30$), patients with acute liver failure/listed with high urgency ($n = 58$), patients undergoing retransplantation ($n = 58$), and those removed because of clinical improvement ($n = 9$) or other reasons such as patient preferences or substance abuse ($n = 5$) were excluded. The following parameters were collected at the moment of liver transplantation screening: sex, age, body height and weight, aetiology of liver disease, blood group, MELD score, and the occurrence of complications (i.e. ascites, spontaneous bacterial peritonitis, hepatic encephalopathy or variceal bleeding) before listing. All hospital admissions (including 1-day admissions) with corresponding indication were recorded, and the cumulative days of hospital stay were calculated. The indication for hospital admission was scored as follows: decompensated cirrhosis, infection, scheduled intervention (e.g. transarterial chemoembolization (TACE), radiofrequency ablation (RFA), endoscopic retrograde cholangiopancreatography (ERCP), colonoscopy, biopsy), other, or unknown.

The endpoint of the study was reached when patients underwent liver transplantation, were removed from the waiting list (due to clinical deterioration), or died on the waiting list. Patients who were removed from the waiting list because of clinical improvement or who were still on the waiting list at 31 December 2016, were excluded. All patients with hepatocellular carcinoma (HCC) were transplanted within the Milan criteria [23]. Patients with HCC with disease progression beyond the Milan criteria were removed from the waiting list and considered as clinically deteriorated. In the study period, no prehabilitation programme was conducted.

In patients who underwent liver transplantation, the cumulative length of hospital stay (LOS) was calculated as the sum of the index admission and all readmissions within 30 days of discharge. The Institutional Review Board approved the study and a waiver for informed consent was granted.

Skeletal muscle mass measurements

The cross-sectional skeletal muscle area (cm^2) was measured on contrast-enhanced (portal-venous phase) abdominal computed tomography (CT) at the level of the third lumbar vertebra (L3) and adjusted for patients' height squared, as previously described (Fig. 1) [24]. This resulted in the skeletal muscle index (cm^2/m^2), a measure strongly correlated with total body skeletal muscle mass [25]. Established cut-off values take body mass index (BMI) into account [26], which is known to be inaccurate in patients with liver failure due to ascites and peripheral oedema. Consequently, sex-specific skeletal muscle mass quartiles were created. Patients in the lowest sex-specific quartile were considered to have sarcopenia. CT scans closest to the date of listing, but within 90 days from the listing date, were used for analyses.

Cost analyses

All hospital costs (i.e. both clinical and outpatient department costs) that were made during the period that patients were listed for liver transplantation (i.e. from the date of listing to the endpoint, excluding hospitalization for liver transplantation) were included, as previously described. Costs for medication were not included. In patients who underwent liver transplantation, total hospital costs during index admission (including the day of

Transplant International 2018; 31: 165–174

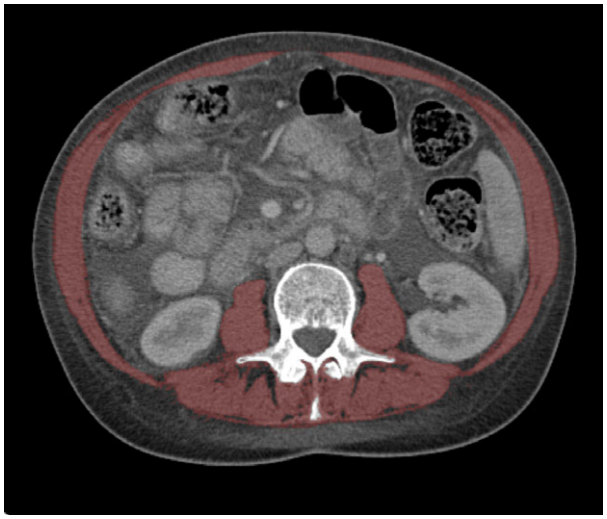

Figure 1 Cross-sectional skeletal muscle mass measurement. Example of a measurement of skeletal muscle mass on CT. The cross-sectional skeletal muscle area (129.74 cm^2) is depicted of a 60-year-old female with a body mass index of 22.1 kg/m^2. With a body height of 1.74 m this resulted in a skeletal muscle index of 42.9 cm^2/m^2. Consequently, this patient was considered not to have sarcopenia.

liver transplantation) for the liver transplantation and during readmission(s) within 30 days after discharge from the index admission were also collected. In these transplanted patients, the grand total was calculated by adding the total hospital costs during waiting list placement and total hospital costs during hospital admission for liver transplantation.

Costs were extracted from the hospital's electronic accounting system. Total costs were calculated by the sum of all unit cost prices. Financial data were limited to hospital expenditure and did not include costs made outside our centre. Adjustment for inflation was performed by indexing all cost prices to the year 2015 according to data of the Dutch Healthcare Authority. All financial data are reported in Euros (€).

Statistical analyses

Categorical data are reported as counts with percentages. Continuous data are reported as median with interquartile range (IQR) or mean with standard deviation (SD), depending on their distribution. The Chi-square test was used to compare categorical data, whereas the Mann–Whitney *U*-test was used to compare hospital costs between patients with and without sarcopenia. A multivariable linear regression analysis was performed to investigate the association of an incremental skeletal muscle index with total hospital costs after correction for possible confounding and clinically relevant factors. Sex was added to the model to adjust for differences in skeletal muscle mass per gender. Sex-specific skeletal muscle mass quartiles were compared using the Kruskal–Wallis test. Subgroup analyses were performed for the presence of HCC. Two-sided *P*-values <0.05 were considered statistically significant. All analyses were performed using SPSS for Windows (IBM Corp., Armonk, NY, USA), version 22.

Results

Patients

In total, 362 patients with cirrhosis were listed for liver transplantation, of whom 224 (61.9%) patients were eligible for the study (Fig. 2). Baseline characteristics are shown in Table 1. Of these patients, 149 (66.5%) were male, and 75 (33.5%) had concomitant HCC. Baseline characteristics and total hospital costs did not significantly differ between the included and excluded patients (data not shown). Baseline characteristics and outcome (i.e. total costs) did not significantly differ between in- and excluded patients.

In total, 165 (73.7%) patients eventually underwent liver transplantation. The remaining patients were removed from the waiting list due to infections (12.9%), rapid clinical deterioration with decompensated cirrhosis (2.7%), progression of HCC beyond the Milan criteria (8.5%), diagnosis of other malignancies (1.3%) or cardiopulmonary decompensation (0.9%).

Hospital costs

The median total hospital costs across the entire study cohort were €7761 (IQR 1630-23 954), corresponding to €44 (IQR 12–164) per day on the waiting list. The median total hospital costs were significantly lower in patients who eventually underwent liver transplantation compared with patients who were removed from the waiting list (i.e. due to mortality, clinical deterioration, progression of HCC beyond the Milan criteria, or other malignancies). Furthermore, costs were significantly higher in patients without HCC compared with patients with HCC (Table 2).

Skeletal muscle mass and total hospital costs during the waiting list period

The median time between CT and waiting list placement was 30 (IQR 17–51) days. The median skeletal

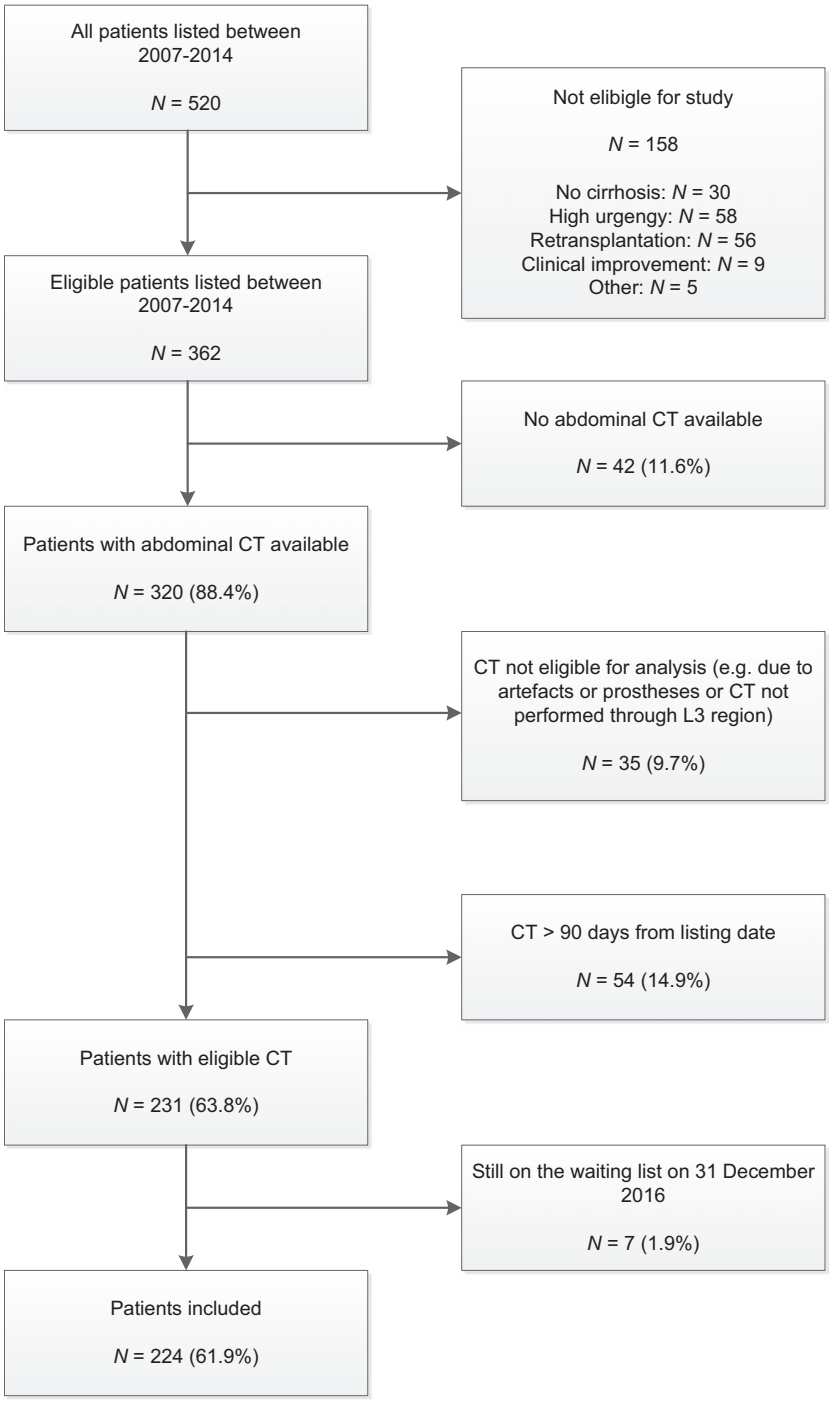

Figure 2 Inclusion flow chart.

muscle index was 50.4 cm^2/m^2 (IQR 44.1–55.0) for males and 41.8 cm^2/m^2 (IQR 37.9–46.5) for females ($P < 0.001$).

Total hospital costs decreased per incremental increase in SMI sex-specific quartile (Fig. 3a and b). The median total hospital costs in patients with sarcopenia were €11 294 (IQR 3570–46 469) compared with €6878 (IQR 1305–20 683) in patients without sarcopenia ($P = 0.008$, Table 2). This corresponds to €68 (IQR 16–503) per day on the waiting list in patients with sarcopenia compared with €40 (IQR 10–108) in patients without sarcopenia ($P = 0.013$).

Table 1. Baseline characteristics (Total cohort, n = 224).

	Sarcopenia (n = 55)	No sarcopenia (n = 169)	P-value
Sex (male)	37 (67.3)	112 (66.3)	0.891
Age (years)	56 (48–62)	56 (49–61)	0.954
BMI (kg/m²)	23.1 (21.6–25.1)	26.3 (23.6–29.4)	<0.001
Primary aetiology of cirrhosis			
Alcoholic	9 (16.4)	19 (11.2)	0.012
Hepatitis B virus	3 (5.5)	4 (2.4)	
Hepatitis C virus	3 (5.5)	13 (7.7)	
PSC/PBC	21 (38.2)	44 (26.0)	
HCC	8 (14.5)	67 (39.6)	
Cholangiocarcinoma	0 (0.0)	1 (0.6)	
NASH	5 (9.1)	2 (1.2)	
Cryptogenic	2 (3.6)	7 (4.1)	
Auto-immune hepatitis	1 (1.8)	4 (2.4)	
Other	3 (5.5)	8 (4.7)	
Blood type			
O	29 (52.7)	67 (39.6)	0.264
A	19 (34.5)	67 (39.6)	
B	6 (10.9)	24 (14.2)	
AB	1 (1.8)	11 (6.5)	
MELD score	18 (15–21)	15 (11–20)	0.012
Complications before waiting list placement			
Any	45 (81.8)	112 (66.3)	0.029
Ascites	43 (78.2)	99 (58.6)	0.009
Spontaneous bacterial peritonitis	12 (21.8)	24 (14.2)	0.182
Hepatic encephalopathy	20 (36.4)	41 (24.3)	0.080
Oesophageal variceal bleeding	16 (29.1)	42 (24.9)	0.533
Median days on the waiting list	165 (32–374)	170 (51–304)	0.755

BMI, body mass index; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; HCC, hepatocellular carcinoma; NASH, nonalcoholic steatohepatitis; MELD, model for end-stage liver disease.

Table 2. Median total hospital costs for the entire cohort and for several subgroups.

	Median total hospital costs in Euros (IQR)	P-value
Total cohort	7761 (1630–23 954)	n/a
Patients who underwent LT	5413 (1345–17 801)	<0.001
Patients removed	19 951 (5184–36 565)	
Patients with HCC	5007 (1254–11 426)	0.002
Patients without HCC	10 615 (1951–29 868)	
Patients with sarcopenia	11 294 (3570–46 469)	0.008
Patients without sarcopenia	6878 (1305–20 683)	

IQR, interquartile range; LT, liver transplantation; HCC, hepatocellular carcinoma.

Multivariable linear regression analysis on costs during the waiting list period

Adjusted for age at the moment of listing, sex, MELD score at the moment of listing, complications before listing, presence of malignancy (i.e. HCC or cholangiocarcinoma), and total time on the waiting list, an incremental increase in SMI was significantly associated with a decrease in total hospital costs (€455 per incremental increase in SMI, 95% CI 11–900, P = 0.045), independent of the total time on the waiting list (Table 3).

Subgroup analyses in patients with and without HCC

Because patients without HCC had significantly higher total hospital costs compared with patients with HCC and a significantly higher number of HCC was observed in patients without sarcopenia compared with patients with sarcopenia (39.6% vs. 14.5%, P < 0.001), subgroup analyses in patients with and without HCC were performed. Significantly more males then females presented with HCC (77.6% vs. 22.4%, P = 0.012). The median MELD score was significantly lower in patients with HCC compared with

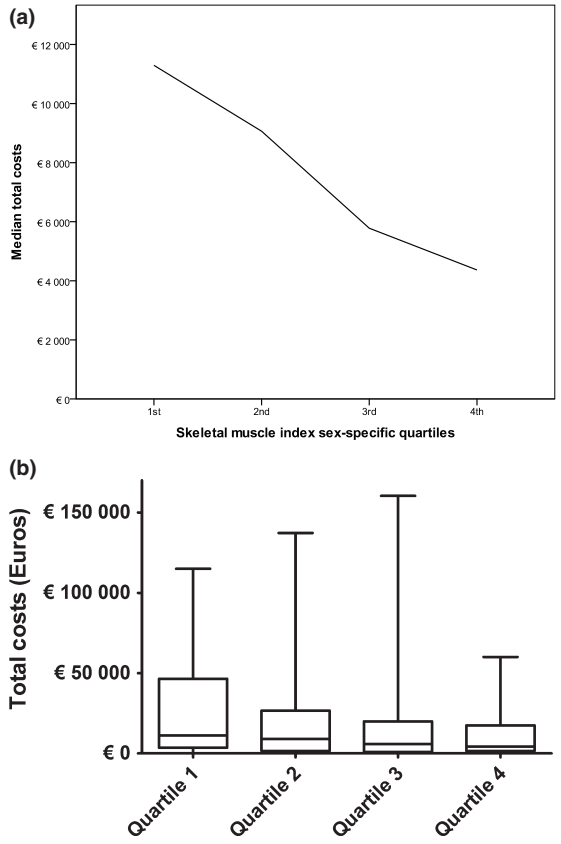

Figure 3 Total hospital costs by skeletal muscle mass in sex-specific quartiles. (a) The total hospital costs significantly decreased per sex-specific skeletal muscle mass quartile from a median of €11 294 (IQR 3570–46 469) in the first quartile, €9066 (IQR 1515–26 648) in the second quartile, €5781 (IQR 910–19 928) in the third quartile, to €4366 (IQR 1550–17 490) in the fourth quartile ($P = 0.026$). (b) The total hospital costs presented in a boxplot.

patients without HCC [10 (IQR 8–12) vs. 19 (IQR 16–22), $P < 0.001$].

Patients without HCC and sarcopenia had significantly higher total costs compared with patients without HCC without sarcopenia [€19 586 (IQR 3573–52 406) vs. €7644 (IQR 1462-28 074), $P = 0.023$], whereas no difference was found between HCC patients with and without sarcopenia [€4610 (IQR 1792–10 243) vs. €5001 (IQR 1112–12 209), $P = 0.933$]. In a multivariable linear regression model in patients without HCC, an incremental increase in SMI was associated with decreased total hospital costs (€692 per incremental increase in SMI, 95% CI 77–1306, $P = 0.028$), independently of total time on the waiting list (€29 per day, 95% CI 12–46, $P = 0.001$; Table S1).

Table 3. Multivariable linear regression analysis for the total hospital costs per patient during waiting list placement ($n = 224$).

	Per Euros per unit	Standard Error, Euros	*P*-value
Skeletal muscle index (per cm²/m²)	−455	226	0.045
Sex (female versus male)	−3146	3890	0.420
Age at moment of listing (per year)	18	163	0.911
MELD score at moment of listing (per point)	507	380	0.184
Complications before listing (yes versus no)	2134	4036	0.598
Malignancy (HCC/Cholangiocarcinoma versus other indication)	−4305	4741	0.365
Time on the waiting list (per day)	30	7	<0.001

MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma.

Skeletal muscle mass and total hospital costs in transplanted patients

The median time on the waiting list for the 165 patients (73.7%) who eventually underwent liver transplantation was 176 (IQR 51–306) days. The median time between CT and liver transplantation was 213 (IQR 90–343) days. Waiting time did not significantly differ between patients with and without sarcopenia [168 (IQR 39–301) vs. 205 (IQR 52–311) days, $P = 0.597$], although patients with sarcopenia had a significantly higher MELD score on the moment of waiting list placement [18 (IQR 13–21) vs. 15 (IQR 10–19), $P = 0.044$], and fewer patients had HCC (18.2% vs. 39.7%, $P = 0.010$) compared with patients without sarcopenia. The cumulative post-transplant LOS did not significantly differ between patients with and without sarcopenia [26 (IQR 15–36) vs. 20 (IQR 15–32) days, $P = 0.124$].

The median total hospital costs during the admission for liver transplantation of the entire cohort were €77 074 (IQR 54 410–98 505). These did not significantly differ between patients with and without sarcopenia [€81 569 (IQR 59 233–108 190) vs. €74 612 (IQR 52 899–93 632), $P = 0.202$]. The grand total was €86 412 (IQR 62 478–113 791). This was significantly higher in patients with sarcopenia [€98 703 (IQR

75 909–121 071)] compared with patients without sarcopenia [€81 173 (IQR 58 961–110 258)], $P = 0.030$.

Hospitalization and hospital costs

In total, 52 (23.2%) patients were admitted to the hospital during the waiting list period minimal once, accounting for 194 hospital admissions. In these patients, the median number of hospitalizations was 2 (IQR 1–3) with a median stay of 6 (IQR 2–14) days. The most frequent indication for hospitalization was a scheduled intervention ($n = 47$, 24.2%), followed by infection ($n = 42$, 21.6%; Table 4). Twenty-six (50.0%) patients were hospitalized because of decompensated disease at least once, with a median of 2 (IQR 1–3) hospital admissions for decompensated disease. Patients who were admitted during the waiting list period had significantly higher hospital costs [€16 799 (IQR 9 046-29 064) vs. €4396 (IQR 1049–20 043), $P < 0.001$]. Although a precise estimation could not be made, this would mean that an average day in the hospital costs a total of €1034. Number of admissions ($P = 0.640$) and cumulative length of hospitalization ($P = 0.609$), however, did not differ between patients with and without sarcopenia. A not statistically significant higher proportion of patients with sarcopenia was admitted because of liver decompensation ($n = 9$, 64.3%) compared with patients without sarcopenia ($n = 17$, 44.7%), $P = 0.211$. These patients also showed a higher number of hospital admissions for decompensated disease [3 (IQR 0–2) vs. 1 (IQR 0–4), $P = 0.150$].

In patients without sarcopenia, those who were admitted had significantly higher hospital costs compared with those not admitted [€17 529 (IQR 10 088–27 989) vs. €3503 (IQR 979–16 267), $P < 0.001$]. However, in patients with sarcopenia, those who were admitted had comparable hospital costs compared with those not admitted [€16 087 (IQR 7878–53 319) vs. €10 746 (IQR 2227–45 602), $P = 0.324$].

Table 4. Indications for hospitalization during the waiting list period ($n = 194$).

	n	%
Decompensation of cirrhosis		
Clinical deterioration of liver function	3	1.5
Ascites	26	13.4
Hepatic encephalopathy (+ infection)	10 (5)	5.2 (2.6)
Infection	31	16.0
SBP (with hepatic encephalopathy)	5 (1)	2.6 (0.5)
Scheduled intervention	47	24.2
Other	62	32.0
Unknown	4	2.1

SBP, spontaneous bacterial peritonitis.

Discussion

To the best of our knowledge, this is the first study to describe that healthcare costs in patients with cirrhosis and sarcopenia listed for liver transplantation are higher, and in our case involve almost €4500 more, than patients without sarcopenia. In patients who eventually underwent liver transplantation, the difference in total costs (i.e. the sum of the hospital costs during waiting list placement and during the admission for transplantation) was even higher, at over €17 000.

Frailty has previously been investigated in cirrhosis patients by Dunn *et al.* and Sinclair *et al.*, and their conclusion is in line with our findings on sarcopenia. Frailty, a measure for contractile function and balance, was found to be an independent risk factor for cirrhosis complications needing hospitalization [11,27] and increased hospital costs [11]. The waiting list period offers a window of opportunity to improve functional status and skeletal muscle mass. Suggested regimens in patients with cirrhosis may consist of the use of proteins with low ammoniagenic potential, leucine enriched amino acid supplementation, long-term ammonia lowering strategies and a combination of resistance and endurance exercise to increase muscle mass and function [28]. Reversing or halting skeletal muscle wasting may lead to decreased costs on the waiting list.

We found significantly lower hospital costs in patients with HCC compared with patients without HCC. The significantly lower MELD score in patients with HCC compared with patients without HCC may explain this difference. After all, the lower median MELD score indicates less severity of the liver disease in patients with HCC. In addition to cancer [29] and age [30], liver disease itself is an important cause of skeletal muscle depletion [28]. Not only alterations in food intake, hypermetabolism, amino acid profiles, endotoxemia, accelerated starvation and decreased mobility lead to liver disease induced skeletal muscle depletion, but recent findings also indicate hyperammonia as a mediator in the liver-muscle axis [28].

Although the association between sarcopenia and hospital expenditure is strong, we do not believe this to be a causal relationship. Instead, we believe that cirrhotic frail patients or those with sarcopenia are at increased risk for morbidity and mortality due to clinical and subclinical sequelae [12] and have increased (re)

admission rates [8,9,11] which eventually lead to increased hospital costs [11]. Although we did not find differences in hospital admissions in general between patients with and without sarcopenia, we found a not statistically significant difference in the proportion of hospital admissions due to liver decompensation in favour of patients without sarcopenia. The low number of patients may have led to a type II error.

The significantly lower prevalence of sarcopenia among patients with HCC seems to be in contrast with previous studies describing a high prevalence of sarcopenia among patients with HCC [29,31]. However, our study cohort consisted of patients within the Milan criteria only [23] and consequently the tumour load was limited. Furthermore, this difference may also be explained by the use of different cut-off values instead of continuous SMI in those studies [14]. Many previous studies of liver transplant patients used cut-off values based on body mass index (BMI) or body surface area (BSA). In our opinion, this is a suboptimal measurement, as both measures are calculated using body weight in patients with ascites [32–35]. In a large series of Japanese patients with HCC ($n = 1257$), using cut-off values to predict mortality using optimal stratification in their patient cohort, a prevalence of low skeletal muscle mass of only 11.1% was found [31].

A statistically non-significant difference of €6957 in hospital costs during the admission for liver transplantation, and a statistically significant difference of €17 530 in the grand total, favouring patients without sarcopenia was found. As this was not the primary objective of the study, skeletal muscle mass was not measured on the CT closest to transplantation. Consequently, the median time interval between CT and liver transplantation was 213 days and the subgroup was relatively small ($n = 166$). As patients may lose significant amounts of skeletal muscle mass during the waiting list period [13], these results should be interpreted with caution and should be validated in a future study with a smaller interval between CT and transplantation. The waiting list period may be used to halt or reverse skeletal muscle wasting. Currently, promising results have been shown in animal studies, and multiple human phase II trials are being performed [36,37].

There are no widely accepted cut-off values to classify patients as having sarcopenia yet. The most commonly used cut-off values are those of Martin and colleagues, established in a cohort of cancer patients [26]. Recently, cut-off values for patients with end-stage liver disease have been proposed in a North-American population, which have not been validated yet [38]. Due to differences between the American and European population, we chose to use our own cut-off values to exemplify cost differences between patients with low and high skeletal muscle mass. However, the independent association between skeletal muscle mass and hospital expenditure was shown using the skeletal muscle index (cm^2/m^2) as a continuous measure.

Although sarcopenia is a subject of interest in patients with liver disease, we are the first to show the actual costs involved alongside this comorbidity. However, there are some limitations in this study that need to be addressed. Firstly, we were not able to include healthcare costs made outside the hospital. However, the median hospital costs during the waiting list period (€7761) were comparable with a previous German study (€6294) [39]. Furthermore, we may have missed some costs and these results should, therefore, be considered as estimates. Although the current results may consequently be an underestimation of the real costs, one may expect that sarcopenia is associated with increased resource utilization after hospital discharge. We therefore believe that the difference between patients with and without sarcopenia might be underestimated rather than overestimated. Secondly, selection bias may have occurred due to the retrospective design of the study. However, all consecutive patients listed for liver transplantation were identified. Although a substantial part of patients listed for liver transplantation was excluded, significant differences were not found between baseline characteristics and outcome. Consequently, selection bias seems highly unlikeable. Thirdly, we only measured skeletal muscle mass and did not assess muscle function. Lastly, we were not able to monitor skeletal muscle wasting over time because consecutive CT examina tions were not routinely performed.

In conclusion, sarcopenia is independently associated with higher hospital costs during waiting list placement of liver transplant candidates, as well as with higher total hospital costs (i.e. during waiting list placement and the admission for transplantation) in patients undergoing liver transplantation. Optimizing patients' skeletal muscle mass may therefore lead to a decrease in hospital expenditure. The differences in costs justify the efforts and the use of resources to explore therapies and treatments to reduce or stop skeletal muscle wasting in patients with end-stage liver disease. Furthermore, it underlines that low skeletal muscle mass may be used as a parameter for case-mix comparisons and corrections.

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflict of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Multivariable linear regression analysis for the total hospital costs per patient in a subgroup of patients without hepatocellular carcinoma (n = 148).

REFERENCES

1. Cardenas A, Gines P. Management of patients with cirrhosis awaiting liver transplantation. *Gut* 2011; **60**: 412.
2. Freeman RB Jr, Wiesner RH, Harper A, *et al.* The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl* 2002; **8**: 851.
3. Kamath PS, Kim WR. Advanced Liver Disease Study G. The model for end-stage liver disease (MELD). *Hepatology* 2007; **45**: 797.
4. Jalan R, Fernandez J, Wiest R, *et al.* Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol* 2014; **60**: 1310.
5. Arvaniti V, D'Amico G, Fede G, *et al.* Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010; **139**: 1246, 56 e1-5.
6. Alferink LJ, Oey RC, Hansen BE, *et al.* The impact of infections on delisting patients from the liver transplantation waiting list. *Transpl Int* 2017; **30**: 807.
7. Volk ML, Tocco RS, Bazick J, Rakoski MO, Lok AS. Hospital readmissions among patients with decompensated cirrhosis. *Am J Gastroenterol* 2012; **107**: 247.
8. Bajaj JS, Reddy KR, Tandon P, *et al.* The 3-month readmission rate remains unacceptably high in a large North American cohort of patients with cirrhosis. *Hepatology* 2016; **64**: 200.
9. Berman K, Tandra S, Forssell K, *et al.* Incidence and predictors of 30-day readmission among patients hospitalized for advanced liver disease. *Clin Gastroenterol Hepatol* 2011; **9**: 254.
10. Makary MA, Segev DL, Pronovost PJ, *et al.* Frailty as a predictor of surgical outcomes in older patients. *J Am Coll Surg* 2010; **210**: 901.
11. Dunn MA, Josbeno DA, Tevar AD, *et al.* Frailty as tested by gait speed is an independent risk factor for cirrhosis complications that require hospita lization. *Am J Gastroenterol* 2016; **111**: 1768.
12. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant* 2014; **14**: 1870.
13. Lai JC, Dodge JL, Sen S, Covinsky K, Feng S. Functional decline in patients with cirrhosis awaiting liver transplantation: Results from the functional assessment in liver transplantation (FrAILT) study. *Hepatology* 2016; **63**: 574.
14. van Vugt JL, Levolger S, de Bruin RW, van Rosmalen J, Metselaar HJ, IJzermans JN. Systematic review and meta-analysis of the impact of computed tomography-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation. *Am J Transplant* 2016; **16**: 2277.
15. Durand F, Buyse S, Francoz C, *et al.* Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. *J Hepatol* 2014; **60**: 1151.
16. Gani F, Buettner S, Margonis GA, *et al.* Sarcopenia predicts costs among patients undergoing major abdominal operations. *Surgery* 2016; **160**: 1162.
17. Kirk PS, Friedman JF, Cron DC, *et al.* One-year postoperative resource utilization in sarcopenic patients. *J Surg Res* 2015; **199**: 51.
18. Sheetz KH, Waits SA, Terjimanian MN, *et al.* Cost of major surgery in the sarcopenic patient. *J Am Coll Surg* 2013; **217**: 813.
19. Gornick ME, Eggers PW, Reilly TW, *et al.* Effects of race and income on mortality and use of services among Medicare beneficiaries. *N Engl J Med* 1996; **335**: 791.
20. Kroneman M, Boerma W, van den Berg M, Groenewegen P, de Jong J, van Ginneken E. Netherlands: health system review. *Health Syst Transit* 2016; **18**: 1.
21. Obama B. United States health care reform: Progress to date and next steps. *JAMA* 2016; **316**: 525.
22. Eurotransplant. *Eurotransplant* 2000; Available from: www.eurotransplant.org [cited 29 December 2016].
23. Mazzaferro V, Regalia E, Doci R, *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693.
24. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg* 2012; **99**: 550.
25. Shen W, Punyanitya M, Wang Z, *et al.* Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol* 1985; **2004**: 2333.
26. Martin L, Birdsell L, Macdonald N, *et al.* Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013; **31**: 1539.
27. Sinclair M, Poltavskiy E, Dodge JL, Lai JC. Frailty is independently associated with increased hospitalisation days in patients on the liver transplant waitlist. *World J Gastroenterol* 2017; **23**: 899.
28. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol* 2016; **65**: 1232.
29. Levolger S, van Vugt JL, de Bruin RW, IJzermans JN. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. *Br J Surg* 2015; **102**: 1448.
30. Rolland Y, Abellan van Kan G, Gillette-Guyonnet S, Vellas B. Cachexia versus sarcopenia. *Curr Opin Clin Nutr Metab Care* 2011; **14**: 15.
31. Fujiwara N, Nakagawa H, Kudo Y, *et al.* Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol* 2015; **63**: 131.
32. Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, *et al.* Inclusion of

sarcopenia within MELD (MELD-Sarcopenia) and the prediction of mortality in patients with cirrhosis. *Clin Transl Gastroenterol* 2015; **6**: e102.
33. Yoshizumi T, Shirabe K, Nakagawara H, *et al.* Skeletal muscle area correlates with body surface area in healthy adults. *Hepatol Res* 2014; **44**: 313.
34. Meza-Junco J, Montano-Loza AJ, Baracos VE, *et al.* Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. *J Clin Gastroenterol* 2013; **47**: 861.
35. Montano-Loza AJ, Meza-Junco J, Baracos VE, *et al.* Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation. *Liver Transpl* 2014; **20**: 640.
36. Dingemans AM, de Vos-Geelen J, Langen R, Schols AM. Phase II drugs that are currently in development for the treatment of cachexia. *Expert Opin Investig Drugs* 2014; **23**: 1655.
37. Zhou X, Wang JL, Lu J, *et al.* Reversal of cancer cachexia and muscle wasting by ActRIIB antagonism leads to prolonged survival. *Cell* 2010; **142**: 531.
38. Carey EJ, Lai JC, Wang CW, *et al.* A multi-center study to define sarcopenia in patients with end-stage liver disease. *Liver Transpl* 2017; **23**: 625.
39. Harries L, Schrem H, Stahmeyer JT, Krauth C, Amelung VE. High resource utilization in liver transplantation-how strongly differ costs between the care sectors and what are the main cost drivers?: a retrospective study. *Transpl Int* 2017; **30**: 621.