The role of recipient myosteatosis in graft and patient survival after deceased donor liver transplantation

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Running title: Body composition and survival

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ABBREVIATIONS

AASLD  American Association for the Study of Liver Diseases
ALF   Acute liver failure
BAR   Balance of Risk
BC    Body Composition
BMI   Body Mass Index
CCI   Comprehensive Complication Index
CD    Clavien-Dindo classification
CI    Confidence Interval
CT    Computed Tomography
CVA   Cerebrovascular Accident
EAD   Early Allograft Dysfunction
EASL  European Association for the Study of the Liver
ECD   Extended Criteria Donor
FFP units  Fresh Frozen Plasma units
GCP   Good Clinical Practice
HU    Hounsfield unit
ICH   International Conference on Harmonisation
ICU   Intensive Care Unit
IMAC  Intramuscular Adipose Tissue Content index
KPS   Karnofsky Performance Score
POD   Postoperative day
MELD  Model of End-stage Liver Disease
OLT   Orthotopic Liver Transplantation
OR    Odds-ratio
PACS  Picture Archiving and Communication System
PBC   Primary Biliary Cirrhosis
PLT count  Platelet count
PSC   Primary Sclerosing Cholangitis
RBC units  Red Blood Cell units
ROC   Receiver Operating Characteristics
SE    Standard error
SM-RA  Skeletal muscle radiation attenuation
SMI   Skeletal muscle index
SMM   Skeletal muscle mass
SOFT  Survival outcomes following liver transplantation
UH-RWTH  University Hospital of the RWTH University
ABSTRACT

Background: Myosteatosis is associated with perioperative outcomes in orthotopic liver transplantation (OLT). Here we investigated the effects of body composition (BC) and myosteatosis on long-term graft and patient survival following OLT.

Methods: Clinical data from 225 consecutive OLT-recipients from a prospective database were retrospectively analyzed (05/2010-12/2017). Computed tomography-based lumbar skeletal muscle index/SMI (muscle mass) and mean skeletal muscle radiation attenuation/SM-RA (myosteatosis) were calculated using a segmentation tool (3DSlicer). Patients with low skeletal muscle mass (low SMI), and myosteatosis (low SM-RA) were identified using predefined and validated cutoff values.

Results: The mean donor and recipient age was 55±16 and 54±12 years, respectively. Some 67% of the recipients were male. The probability of graft and patient survival were significantly lower in patients with myosteatosis compared to patients with higher SM-RA values (p=0.011, p=0.001, respectively). Low skeletal muscle mass alone was not associated with graft and patient survival (p=0.273, p=0.278, respectively). Dividing the cohort into quartiles, based on the values of SMI and SM-RA, resulted in significant differences in patient but not in graft survival (p=0.011). Even though multivariable analysis identified low SM-RA as an important prognostic marker (Hazard ratio: 2.260, 95% Confidence interval: 1.177-4.340, p=0.014), myosteatosis lost its significance when early mortality (90 days) was excluded from the final multivariable model. Patients with myosteatosis showed significantly higher all-cause mortality, and in particular higher rates of deaths due to respiratory and septic complication (p=0.002, p=0.022, p=0.049, respectively).

Conclusion: Preoperative myosteatosis may be an important prognostic marker in patients undergoing deceased donor liver transplantation. The prognostic value of
myosteatosis seems to be particularly important in the early postoperative phase. Validation in prospective clinical trials is warranted.
INTRODUCTION

Pathological variations of body composition (BC) are frequently seen in critical illness and have been associated with inferior clinical outcomes in a variety of medical conditions [1, 2]. Accordingly, malnutrition and muscle wasting are characteristic for patients with chronic liver disease [1, 3], and as such, nutritional screening as well as the assessment of BC were recently implemented in the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) practice guidelines on nutrition in chronic liver disease [4, 5].

Even though numerous methods are used for clinical BC assessment [6], the direct quantification of muscle and fat tissue using cross-sectional computed-tomography (CT) imaging is considered the gold standard in transplant waiting list candidates and in patients with chronic liver disease [1, 4, 6]. While sarcopenia – the pure loss of muscle mass and strength – was linked to clinical outcomes in various diseases [3, 6-10], the long-term prognostic value of muscle quality (muscle density or myosteatosis) compared to muscle quantity (muscle mass or sarcopenia) remains to be determined [1, 3, 7-9].

Nowadays, an increasing number of extended criteria donor (ECD) allografts are utilized that were previously considered unsuitable for transplantation [11, 12]. Because of that, a careful selection and matching of donors and recipients is essential to improve allograft utilization and post-OLT outcomes [13]. Recent studies by our group and others demonstrated a high prevalence of BC alterations in patients with end-stage liver disease. In particular, myosteatosis was identified as an important prognostic factor in predicting adverse perioperative outcomes in patients undergoing OLT [9, 10, 14-17].

Since myosteatosis seems to be an accurate predictor for clinical outcomes, the goal of the present study was to assess the performance of CT-based recipient BC
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profiling in predicting long-term graft and patient survival in individuals undergoing deceased donor OLT.
PATIENTS and METHODS

Patients and ethics

Between May 2010 and December 2017, all consecutive patients undergoing OLT at the University Hospital RWTH Aachen (UH-RWTH), Aachen, Germany, were considered for inclusion. Exclusion criteria were defined as (i) CT scans older than 6 months and/or those not including images from the third lumbar vertebra (L3) level [14]; (ii) living related or split liver transplantation. Patients undergoing re-OLT have been assessed only for the primary transplantation and consecutive transplantations were included in the follow-up. The study was conducted at the UH-RWTH in accordance with the current version of the Declaration of Helsinki as well as the Declaration of Istanbul, and the good clinical practice (ICH-GCP) guidelines. The study was approved by the responsible Institutional Review Board of the RWTH-Aachen University (EK 047/18). Informed consent was waived due to the retrospective study design and collection of readily available clinical data.

Segmentation and body composition analysis

All CT-scans were performed by using a state-of-the-art multi-slice CT-scanner. The technical parameters for CT-imaging were described before [14].

Data of the most recent preoperative CT-imaging were retrieved from digital storage in the Picture Archiving and Communication System (PACS). Body composition analysis was performed as previously described by our group [14]. Briefly, a single cross-sectional CT image at the level of L3 was used and the segmentation of skeletal muscle and adipose tissue was performed using the 3D Slicer software platform version 4.1 and BC module (https://www.slicer.org/, [18]) in a semiautomatic fashion. Skeletal muscle area was identified and quantified by using attenuation values of -29 to 150 Hounsfield units (HU). Skeletal muscle index (SMI; the indicator of low
skeletal muscle mass-SMM or structural aspect of sarcopenia) has been calculated by normalizing the measured muscle area to the square height of the patient (cm²/m²) [14]. Skeletal muscle radiation attenuation (SM-RA) as an indicator of muscle density and myosteatosis has been recorded in HUs [14]. Visceral fat was quantified by using the attenuation values -150 to -50 HU. To identify subcutaneous adipose tissue, the attenuation values of -190 to -30 were used (Figure 1) [14]. All measurements were performed by the same researcher, experienced in complex BC analyses.

Based on the SMI and SM-RA, reduced skeletal muscle mass and myosteatosis were defined using cut-off values determined specifically for patients on OLT waiting list (SMI: female 39 cm²/m², male 50 cm²/m²; SM-RA <41 HU for patients with a BMI up to 24.9 kg/m² and <33 HU for patients with a BMI ≥25 kg/m²) [6, 14, 19]. Based on previous literature findings from patient cohorts with terminal liver disease, no adjustment for sex was made for SM-RA [6, 14].

**Perioperative management and data collection**

All OLT waiting-list indications were discussed and decided within a multidisciplinary liver transplantation board meeting in accordance to the German national and Eurotransplant guidelines (Eurotransplant Manual version 5.5, Eurotransplant Foundation, Leiden, The Netherlands). Organ allocation followed national and Eurotransplant regulations. The liver transplantation procedure was performed using a standardized approach of total cava replacement as previously described [14, 20]. The standard perioperative care and immunosuppression regimen consisted of basiliximab, tacrolimus, mycophenolate-mofetil and corticosteroids [14, 20].

Clinical data were obtained from a prospective institutional database and analyzed retrospectively. Various OLT risk-scores (Table 1) have been calculated as described
before [14, 21-23]. Extended criteria donor allografts (ECD) were defined according to the definitions of the German Medical Chamber [24]. To assess post-transplant early allograft dysfunction (EAD) the Olthoff criteria were adopted [25].

Postoperative morbidity was evaluated for all surgical complications observed during the first 90-days after OLT according to the Clavien-Dindo classification (CD) and quantified using the Comprehensive Complication Index (CCI®) [26, 27]. Recipient pre-OLT performance status has been assessed using the Karnofsky performance score (KPS) [28]. Postoperative transfusions were defined as any blood products given within the first 7-days following OLT. Blood products administered later in the postoperative period were categorized as postoperative complications according to the recommendations of the Clavien-Dindo classification [27]. Length of ICU-stay represents the initial stay after the OLT procedure until the transfer of the patient to our standard care transplantation unit. Hospital stay was defined by the date of admission for OLT and the day of discharge from the UH-RWTH. Readmission to the ICU was included in the total hospital stay. Our transplantation outpatient department as well as the responsible general practitioner and/or hepatologist provided all follow-up data used for the survival analyses in this study.

**Study endpoints and statistical analysis**

Probability of patient survival at 5-years was chosen as the primary endpoint for the survival analyses. Five-year graft survival was used as secondary endpoint.

Categorical data are presented in the form of numbers and percentages. Data derived from continuous variables were presented as mean and standard deviation. Categorical data were compared using the chi-squared test or Fisher's exact test according to scale and number counts. The associations of graft and patient survival with BC characteristics were assessed using univariate and multivariable Cox
proportional hazards regression models. Survival curves were generated by the Kaplan-Meier method and compared with the log-rank test. All p-values <0.05 were considered statistically significant. Statistical analysis has been performed using SPSS Statistics v24 (IBM Corp., Armonk, NY, USA).
RESULTS

Patient and graft characteristics

Out of all 357 consecutive OLTs performed, 225 patients met the predefined inclusion and exclusion criteria [14]. Among 132 excluded patients were recipients of living related (n=5) or split liver allografts (n=4), and cases without sufficient preoperative CT imaging (n=123). Patients’ characteristics and perioperative outcome data of the cohort were in part reported previously [14] and are also summarized in Table 1.

The median time between the CT-imaging used for segmentation and OLT was 5 weeks (range 0-24). The mean SMI was 57±39 cm²/m² for male and 47±11 cm²/m² for female patients. The mean SM-RA were 35±11 HU for males and 32±11 HU for females, respectively. Figure 2 depicts the distribution of the SMI and SM-RA values within the patient cohort.

Impact of low muscle mass and myosteatosis on long-term graft and patient survival

There were 19 patients (8%) who died within the first 90 days following OLT. A total of 59 patients died over the follow-up period (05/2010-05/2020, see Table 3). The probability of graft survival at 5-years was significantly worse for patients with myosteatosis compared to patients with higher muscle density (65% vs. 81%; p=0.011, Figure 3). When patients were divided into quartiles based on the SM-RA values, no significant difference was found in terms of graft survival (SM-RA Q4 70% vs. Q3 66% vs. Q2 72% vs. Q1 88%; p=0.083, Figure 3).

Similar to the graft survival rates, the probability of patient survival at 5-years were significantly worse for patients with myosteatosis compared to patients above the defined cutoffs of SM-RA (65% vs. 85%; p=0.001, Figure 4). When the SM-RA
quartiles were considered, there was also a significant difference in patient survival, (SM-RA Q4 71% vs. Q3 66% vs. Q2 80% vs. Q1 91%; p=0.011, Figure 4).

Alterations of muscle mass alone had no significant effects on graft and patient survival, neither as a single cutoff for low SMM nor as SMI quartiles (Figure 3 and 4). Probability of graft and patient survival for individuals with low SMM were 67% and 70% versus 78% and 80% for individuals without low SMM (p=0.273; p=0.278) (Figure 3 and 4).

Because most of the difference in survival occurred during the early post-OLT phase (Figure 3 and 4), emphasizing the significant effects of myosteatosis on perioperative outcomes [14], secondary survival analyses with exclusion of patients who have died within the first 90 days after OLT (n=19) were carried out (Figure 5). Interestingly, myosteatosis lost its prognostic value for graft and patient survival (p=0.011 vs. p=0.477 and p=0.001 vs. p=0.092, respectively, see Figure 3, 4, and 5). The significant difference of the log-rank test between the SM-RA quartiles for patient survival was also lost when individuals with early mortality were excluded from the analysis (p=0.011 vs. p=0.303, Figure 4 and 5).

We next performed uni- and multivariable Cox regression analyses to identify independent risk factors for graft loss and overall mortality. Although, our univariable Cox proportional hazards regression model showed a relevant association of recipient pre-transplant ICU stay (2.213 OR, 1.256-3.899 95%CI, p=0.006), KPS (1.773 OR, 1.018-3.088 95%CI, p=0.043), intraoperative transfusion of RBC units (2.252 OR, 1.232-4.116 95%CI, p=0.008), and the presence of myosteatosis (2.025 OR, 1.154-3.553 95%CI, p=0.014) with graft survival, none of these factors remained significant in the final multivariable model (Supplementary table 1 and Table 2).

The multivariable analysis has identified myosteatosis as an independent factor associated with impaired patient survival (2.260 OR, 1.177-4.340 95%CI, p=0.014,
Supplementary table 1 and Table 2). In contrast, although, labMELD (1.909 OR, 1.060-3.439 95%CI, p=0.031), pre-transplant ICU stay (2.798 OR, 1.553-4.041 95%CI, p=0.001), KPS (2.399 OR, 1.327-4.336 95%CI, p=0.004), intraoperative transfusion of RBC units (2.102 OR, 1.109-3.987 95%CI, p=0.023) showed significant hazard ratios (HRs) in the univariable analysis, they lost their significance in the multivariable model (Supplementary table 1 and Table 2).

In line with the observations made in the Kaplan-Meier analysis and log-rank tests, the significant association of myosteatosis with a decreased graft and patient survival was lost already in the univariable analysis when early mortality (90-day mortality, n=19) was excluded from the analysis resulting in a HR of 1.290 (0.636-2.617) and a p-value=0.481 for graft survival and a HR of 1.914 (0.885-4.141) and a p-value=0.099 for patient survival (Supplementary table 1 and Table 2).

Furthermore, patients with myosteatosis showed significantly higher all-cause mortality (37% vs. 18% p=0.002), and a higher incidence of deaths due to respiratory and septic complications (8% vs. 2% p=0.022 and 16% vs. 8% p=0.049, respectively; see Table 3).
DISCUSSION

This study explores the association of myosteatosis with long-term post-OLT graft and patient survival. While there was a high incidence of pathological BC alterations in our cohort with more than 40% of our patients suffering from myosteatosis and 37% presenting with low SMM, we here show a limited long-term prognostic role of myosteatosis and low SMM in deceased donor OLT. Interestingly, based on our data, the prognostic value of myosteatosis seems to be accentuated in the early postoperative phase, as BC loses its prognostic value on long-term outcomes when patients with early mortality are excluded.

Since the gap between allograft supply and demand continues to increase, the optimal risk-stratification and utilization of the available donor pool are based not only on conventional risk factors, but also on nutritional donor-recipient characteristics [13, 14, 29]. While a handful of reports have suggested a potential role of myosteatosis in clinical outcome following OLT, the majority of previous studies focused on sarcopenia and on Asian cohorts of living donor liver transplantation (LDLT) [1, 6, 9, 14, 30, 31]. In addition, recent data from our group and others suggest that myosteatosis, as characterized by the presence of inter- and intramyocellular fat depositions, may result in dysregulated pathophysiological responses and consequential inferior clinical outcomes even in patients with normal or slightly reduced muscle mass [6, 14]. In a recent report by Hamaguchi et al., the authors investigated CT-based BC in a single-center Japanese cohort of 657 living liver donors and identified SMI and intramuscular adipose tissue content (IMAC) as independent predictors of post-transplant recipient survival [31]. A further study by the same group evaluated IMAC and psoas muscle mass index (PMI) in 200 adult recipients undergoing LDLT and demonstrated a significant association of recipient mortality with high IMAC and low PMI [30]. Furthermore, Bhanji et al. reported a correlation of myosteatosis with hepatic
encephalopathy and waiting list mortality in a large cohort of 675 cirrhotic patients [3]. Although, myosteatosis was previously linked to inferior waiting list survival in end-stage liver disease and in patients undergoing LDLT, its specific effects on graft and patient survival in patients undergoing deceased donor OLT remained to be determined [1, 3, 9, 14, 32].

Recently, our group investigated the role of myosteatosis and low SMM in early perioperative outcomes [14]. Patients with myosteatosis experienced a higher number and more severe surgical complications over the first 3 months following OLT. Also, increased rates of EAD, higher CCI scores, longer ICU- and hospital stays, higher procedural costs, and an increased need for intraoperative blood transfusions were seen in patients with myosteatosis [14]. Of note, low SMM alone was not associated with any of the above-mentioned peri-operative outcome parameters. To further explore this observation, we investigated the prognostic role of muscle quality (myosteatosis) and low SMM in post-OLT graft and patient survival. Patients were divided into low and normal SM-RA and SMI cohorts and were also stratified into SM-RA and SMI quartiles (Figures 2, 3, 4, and 5). For this we used validated cut-off values from large cohorts of patients with chronic liver disease, adopting recent recommendations of the North-American expert group on fitness, life enhancement, and exercise in liver transplantation [6, 8, 19, 33].

In the present study, the probability of graft and patient survival at 5-years was significantly worse in the presence of myosteatosis. Our quartile-based analysis of patient survival also showed significant differences between the various SM-RA quartiles. Patients belonging to the first SM-RA quartile (thus having the highest muscle density) demonstrated an excellent 91% patient survival compared to 66% and 71% in Q3 and Q4, respectively (p=0.011).
Subsequently, BC parameters were fitted into a Cox proportional hazards regression model to further assess the association of low SMM and myosteatosis with graft and patient survival in our cohort. Here we identified the presence of myosteatosis as an independent predictor of inferior 5-year patient survival in the final multivariable model. Interestingly, the significant effect of myosteatosis on graft and patient survival was lost in our secondary uni- and multivariable analyses where patients who died within the first 90-days after OLT were excluded. Low SMM did not show any significant hazard ratios in the analysis for graft and patient survival.

Next, cause of mortality over the observation period was analyzed in detail to further explore the role myosteatosis in mortality. Patients with myosteatosis showed not only a significantly higher all-cause mortality, but death due to respiratory and septic complication were more frequent in the myosteatosis sub-cohort. This is in line with previous findings, showing that structural alteration of the skeletal muscle compartment and muscle wasting are associated with infectious and respiratory complications, not only in liver disease and OLT but also in various oncological entities [1, 16, 34, 35].

Although, myosteatosis can occur when lipid intake simply exceeds the disposal capacity of the human body [7, 14, 36], pathological fat deposition was also confirmed in non-obese or even in underweight patients [14, 37], highlighting that mechanisms other than exogenous lipid intake (e.g. liver-muscle cross-talk, alterations of lipoprotein metabolism in liver disease), may play an important role in the development of myosteatosis in patients with chronic liver disease [6, 7, 14]. These observations support previous findings on the potent short-term effects of myosteatosis and low muscle density [6, 14]. While inflammatory responses play a pivotal role in early ischemia-reperfusion injury of the liver allograft (ischemic complications, rejection)
[38], a pro-inflammatory tissue microenvironment as it is the case in the presence of myosteatosis, likely also impacts early graft and patient survival following OLT.

The findings of this study should be interpreted in the light of potential limitations. First, due to the inherent uncontrolled, retrospective, and single-center nature of our analysis, no preoperative functional assessment of fitness, muscle strength, and nutritional status was possible [9, 14]. Second, despite our observation and important conclusion on the effects of myosteatosis on clinical outcome (predominantly short-term), there was still a non-significant difference in the Kaplan-Meier curves for graft and patient survival even after exclusion of early mortality (Figure 4). It is therefore reasonable to assume that our analysis may have also been limited by the sample size and a relatively heterogeneous study population.

Notwithstanding the aforementioned limitations, we identified recipient myosteatosis as an important prognostic marker for clinical outcomes following deceased donor OLT. The prognostic value of myosteatosis seems to be particularly important in the early post-OLT phase. This observation is not only important for our understanding on how inter-individual alterations of BC influence clinical outcomes in these patients, but it may also represent an important therapeutic target for interventions during the perioperative phase. Validation in prospective interventional clinical trials is warranted.
FIGURE LEGENDS

**Figure 1:** Segmentation of cross-sectional computed tomography images at the level of the third lumbar vertebra
Representative axial images of the preoperative CT scan of a 55-year-old male patient underwent liver transplantation for hepatocellular carcinoma during the study period. (A and B) Skeletal muscle area (red) was determined by using computed tomography attenuation values of -29 to 150 HU. Subcutaneous fat area (light green) was defined as attenuation values of -190 to -30 HU. For visceral fat area (dark green) -150 to -50 HU attenuation values were used. In this patient with considerable structural alterations of the skeletal muscle, panel C shows the amount of intramuscular adipose tissue in dark green (-190 to -50 HU). While normal attenuation muscle has been marked red (+30 to 150 HU), myosteatotic, low attenuation muscle was delineated in violet (-29 to 29 HU). Note the large amount of low attenuation muscle (violet color) in panel C, indicating the presence of low quality myosteatotic muscle.

**Figure 2:** Distribution of SMI and SM-RA values within the patient cohort
(A) Quartile based distribution of lumbar 3 skeletal muscle index. (B) Quartile based distribution of lumbar 3 skeletal muscle radiation attenuation

**Figure 3:** Probability of graft survival stratified by body composition
(A) Normal SMM 78% vs. Low SMM 67% (B) SMI Q4 73% vs. Q3 75% vs. Q2 68% vs. Q1 80% (C) No Myosteatosis 81% vs. Myosteatosis 65% (D) SM-RA Q4 70% vs. Q3 66% vs. Q2 72% vs. Q1 88%

**Figure 4:** Probability of patient survival stratified by body composition
(A) Normal SMM 80% vs. Low SMM 70% (B) SMI Q4 73% vs. Q3 80% vs. Q2 73% vs. Q1 80% (C) No Myosteatosis 85% vs. Myosteatosis 65% (D) SM-RA Q4 71% vs. Q3 66% vs. Q2 80% vs. Q1 91%

**Figure 5:** Probability of graft and patient survival stratified by myosteatosis after excluding 90-day mortality
To show the long-term effects of myosteatosis, subgroup survival analyses were repeated, and patients who died within 90 days of transplantation (n=19) were excluded.
(A) Graft survival by No Myosteatosis 83% vs. Myosteatosis 77% (B) Graft survival by SM-RA Q4 81% vs. Q3 78% vs. Q2 77% vs. Q1 87% (C) Patient survival by No Myosteatosis 88% vs. Myosteatosis 77% (D) Patient survival by SM-RA Q4 81% vs. Q3 84% vs. Q2 82% vs. Q1 88%
## Table 1: Donor and recipient characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=225)</th>
<th>Patients without 90-day mortality (n=206)</th>
</tr>
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<tbody>
<tr>
<td><strong>Donor age (years)</strong></td>
<td>55±16</td>
<td>55±16</td>
</tr>
<tr>
<td><strong>Donor BMI</strong></td>
<td>30±8</td>
<td>30±8</td>
</tr>
<tr>
<td><strong>Donor sex ratio (F:M)</strong></td>
<td>108 (48%) : 117 (52%)</td>
<td>100 (48%) : 106 (52%)</td>
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<tr>
<td><strong>DRI</strong></td>
<td>1.77±0.35</td>
<td>1.76±0.35</td>
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<tr>
<td><strong>Donor cause of death</strong></td>
<td></td>
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<tr>
<td>CVA</td>
<td>138 (61%)</td>
<td>130 (63%)</td>
</tr>
<tr>
<td>Anoxia</td>
<td>51 (23%)</td>
<td>47 (23%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>25 (11%)</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (5%)</td>
<td>8 (4%)</td>
</tr>
<tr>
<td><strong>ECD</strong></td>
<td>154 (68%)</td>
<td>139 (68%)</td>
</tr>
<tr>
<td><strong>Recipient age (years)</strong></td>
<td>54±12</td>
<td>54±12</td>
</tr>
<tr>
<td><strong>Recipient BMI</strong></td>
<td>27±5</td>
<td>27±5</td>
</tr>
<tr>
<td><strong>Recipient sex ratio (F:M)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 (33%) : 150 (67%)</td>
<td>66 (32%) : 140 (68%)</td>
<td></td>
</tr>
<tr>
<td><strong>Etiology of liver disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALF</td>
<td>31 (14%)</td>
<td>29 (14%)</td>
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<tr>
<td>HCC</td>
<td>63 (28%)</td>
<td>57 (28%)</td>
</tr>
<tr>
<td>Alc. cirrhosis</td>
<td>45 (20%)</td>
<td>40 (19%)</td>
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<tr>
<td>Viral</td>
<td>15 (7%)</td>
<td>13 (6%)</td>
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<tr>
<td>PSC/PBC</td>
<td>21 (9%)</td>
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<td>Graft failure</td>
<td>4 (2%)</td>
<td>3 (2%)</td>
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<tr>
<td>Other</td>
<td>46 (20%)</td>
<td>44 (21%)</td>
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<tr>
<td><strong>Pre-transplant Child-Pugh Score</strong></td>
<td>7±2</td>
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<td><strong>Pre-transplant labMELD</strong></td>
<td>20±11</td>
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<td><strong>BAR Score</strong></td>
<td>9±6</td>
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<td><strong>SOFT Score</strong></td>
<td>15±10</td>
<td>14±9</td>
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<tr>
<td><strong>Recipient pre-transplant ICU</strong></td>
<td>56 (25%)</td>
<td>45 (22%)</td>
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<tr>
<td><strong>Recipient pre-transplant abdominal surgery</strong></td>
<td>82 (36%)</td>
<td>72 (35%)</td>
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<tr>
<td><strong>Recipient pre-transplant encephalopathy</strong></td>
<td>90 (40%)</td>
<td>82 (40%)</td>
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<tr>
<td><strong>Karnofsky Performance Score</strong></td>
<td>60±25</td>
<td>62±24</td>
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<tr>
<td><strong>Cold ischemic time (min)</strong></td>
<td>516±139</td>
<td>511±134</td>
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<td><strong>Warm ischemic time (min)</strong></td>
<td>46±7</td>
<td>46±7</td>
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<tr>
<td><strong>Intra-operative red blood cell transfusions (units)</strong></td>
<td>9±8</td>
<td>9±8</td>
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<td><strong>Intra-operative fresh frozen plasma transfusions (units)</strong></td>
<td>18±10</td>
<td>17±10</td>
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<tr>
<td><strong>Post-operative red blood cell transfusions (units)</strong></td>
<td>4±6</td>
<td>3±5</td>
</tr>
<tr>
<td><strong>Post-operative fresh frozen plasma transfusions (units)</strong></td>
<td>6±11</td>
<td>5±8</td>
</tr>
<tr>
<td><strong>90-day ≥CD3b complications</strong></td>
<td>114 (51%)</td>
<td>95 (46%)</td>
</tr>
<tr>
<td><strong>90-day mortality</strong></td>
<td>19 (8%)</td>
<td>not applicable</td>
</tr>
<tr>
<td><strong>Early allograft dysfunction n (%)</strong></td>
<td>60 (27%)</td>
<td>53 (26%)</td>
</tr>
<tr>
<td><strong>ICU stay (days)</strong></td>
<td>14±23</td>
<td>12±21</td>
</tr>
<tr>
<td><strong>Hospital stay (days)</strong></td>
<td>43±42</td>
<td>42±43</td>
</tr>
<tr>
<td><strong>90-day CCI</strong></td>
<td>54±33</td>
<td>50±31</td>
</tr>
</tbody>
</table>

Values were given as mean±standard deviation or numbers and (per cent).

1Refers to Feng et al.[39]; 2Refers to German Medical Chamber Guidelines [24]; 3Refers to Schlegel et al.[21]; 4Refers to Rana et al.[40]; 5Refers to Kelly et al.[28]; 6Refers to Olthoff et al.[25]; 7Refers to Slankamenac et al.[26]

Table 2: Multivariable Cox regression analysis of prognostic factors for graft- and patient survival

<table>
<thead>
<tr>
<th></th>
<th>Graft survival - Multivariable analysis</th>
<th>Patient survival - Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% Confidence Interval)</td>
<td>p value</td>
</tr>
<tr>
<td>Pre-transplant labMELD ≥25</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Recipient pre-transplant ICU Yes</td>
<td>1.969 (0.780-4.967)</td>
<td>0.151</td>
</tr>
<tr>
<td>Karnofsky Performance Score &lt;60</td>
<td>0.801 (0.317-2.020)</td>
<td>0.638</td>
</tr>
<tr>
<td>Intraoperative RBC Units ≥15</td>
<td>1.735 (0.908-3.316)</td>
<td>0.095</td>
</tr>
<tr>
<td>Myosteatosis (SM-RA) Yes</td>
<td>1.716 (0.937-3.143)</td>
<td>0.080*</td>
</tr>
</tbody>
</table>

Results from the Cox proportional hazards regression model were given as hazard ratios (HR) with 95% confidence intervals. Factors showing significant results in the univariable analysis (see Supplementary table 1) were included into the multivariable logistic regression model. Only significant results are shown. To avoid a multicollinearity effect, certain variables were not included into the Cox regression model.

*When removing patients with perioperative mortality (90-day mortality, n=19) myosteatosis loses its significant effect on graft survival, Hazard ratio: 1.290, 95% Confidence interval: 0.636-2.617, p=0.481 in univariable analysis. *When removing patients with perioperative mortality myosteatosis loses its significant effect on patient survival, Hazard ratio: 1.914, 95% Confidence interval: 0.895-4.141, p=0.039 in univariable analysis.

Abbreviations used: MELD: model for end-stage liver disease, ICU: intensive care, RBC: red blood cell units, SM-RA: lumbar 3 skeletal muscle radiation attenuation.
**Table 3:** Cause of death for all patients died until the time-point of last follow-up*

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>All patients (n=225)</th>
<th>Myosteatosis (n=98)</th>
<th>No myosteatosis (n=127)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>59 (26)</td>
<td>36 (37)</td>
<td>23 (18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Primary non-function</td>
<td>2 (1)</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>0.189</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1 (&lt;1)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>0.436</td>
</tr>
<tr>
<td>Respiratory</td>
<td>10 (4)</td>
<td>8 (8)</td>
<td>2 (2)</td>
<td>0.022</td>
</tr>
<tr>
<td>Recurrent liver disease</td>
<td>7 (3)</td>
<td>3 (3)</td>
<td>4 (3)</td>
<td>0.970</td>
</tr>
<tr>
<td>Septic</td>
<td>26 (12)</td>
<td>16 (16)</td>
<td>10 (8)</td>
<td>0.049</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6 (3)</td>
<td>2 (2)</td>
<td>4 (3)</td>
<td>0.699</td>
</tr>
<tr>
<td>Other</td>
<td>7 (3)</td>
<td>4 (4)</td>
<td>3 (2)</td>
<td>0.408</td>
</tr>
</tbody>
</table>

Total follow-up period reported: 05/2010-05/2020
AUTHORSHIP: The study was designed by the initiating study team (ZC, GL, UPN). Data collection and analysis were performed by ZC, WK, IL, JB, HM, PS, SAL, TFU, PB, UPN, GL. Manuscript was drafted by ZC, GL, MWVV, WK. Further authors (WK, IL, HM, JB, SAL, TFU, PB, PS, CT, MWVV, FT, UPN, GL) have substantially contributed to the final version of the manuscript. All authors have read and approved the final version of the manuscript.

DISCLOSURE: The authors of this manuscript have no conflict of interest to disclose.

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REFERENCES


Figure 3

A

Graph Survival (%) vs Time (Months)

- Normal SMM
- Low SMM

log rank p=0.273

Numbers at risk
Normal SMM 141
Low SMM 84

B

Graph Survival (%) vs Time (Months)

- SWI C4
- SWI C3
- SWI C2
- SWI C1

log rank p=0.553

Numbers at risk
SWI C4 48
SWI C3 67
SWI C2 63
SWI C1 57

C

Graph Survival (%) vs Time (Months)

- No Mycophenolate
- Mycophenolate

log rank p=0.011

Numbers at risk
No Mycophenolate 127
Mycophenolate 90

D

Graph Survival (%) vs Time (Months)

- SM-RA C4
- SM-RA C3
- SM-RA C2
- SM-RA C1

log rank p=0.083

Numbers at risk
SM-RA C4 54
SM-RA C3 58
SM-RA C2 57
SM-RA C1 56
Figure 4
Figure 5

A

B

C

D

[Graphs showing graft and patient survival rates over time with log rank p-values and numbers at risk for different conditions and subgroups.]

Numbers at risk

No Mycetohaptosis

Mycetohaptosis

Time (Months)

Graft Survival (%)

0 12 24 36 48 60

log rank p=0.477

Numbers at risk

No Mycetohaptosis

Mycetohaptosis

Time (Months)

Patient Survival (%)

0 12 24 36 48 60

log rank p=0.092

Numbers at risk

No Mycetohaptosis

Mycetohaptosis

Time (Months)

Graft Survival (%)

0 12 24 36 48 60

log rank p=0.533

Numbers at risk

SM-RA Q4

SM-RA Q3

SM-RA Q2

SM-RA Q1

Time (Months)

Patient Survival (%)

0 12 24 36 48 60

log rank p=0.303

Numbers at risk

SM-RA Q4

SM-RA Q3

SM-RA Q2

SM-RA Q1

Time (Months)