ORIGINAL ARTICLE

# New-onset obesity after liver transplantation—outcomes and risk factors: the Swiss Transplant Cohort Study

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## SUMMARY

Weight gain after liver transplantation (LTx) facilitates development of new-onset obesity; however, its risk factors and outcomes are poorly understood. We identified the impact of new-onset obesity on cardiovascular events (CVEs) and patient survival, and risk factors for new-onset obesity. Multiple Cox regression models examined risk factors for CVEs, patient survival, and new-onset obesity in 253 adults (mean age 52.2 ± 11.6 years, male gender 63.6%, mean follow up 5.7 ± 2.1 years). Cumulative incidence of post-LTx CVE was 28.1%; that of new-onset obesity was 21.3%. Regardless of CVE at LTx, post-LTx CVEs were predicted by new-onset obesity [Hazard Ratio (HR), 2.95; $P = 0.002$] and higher age at LTx (HR, 1.05; $P < 0.001$). In patients without known pre-LTx CVEs ($n = 214$), risk factors for post-LTx CVEs were new-onset obesity (HR, 2.59; $P = 0.014$) and higher age (HR, 1.04; $P = 0.001$). Survival was not associated with new-onset obesity ($P = 0.696$). Alcoholic liver disease predicted new-onset obesity (HR, 3.37; $P = 0.025$), female gender was protective (HR, 0.39; $P = 0.034$). In 114 patients with available genetic data, alcoholic liver disease (HR, 12.82; $P = 0.014$) and hepatocellular carcinoma (HR, 10.02; $P = 0.048$) predicted new-onset obesity, and genetics remained borderline significant (HR, 1.07; $P = 0.071$). Early introduction of post-LTx weight management programs may suggest a potential pathway to reduce CVE risk.

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## Introduction

Following liver transplantation (LTx), weight gain is common. Studies from diverse geographical regions describe mean weight gain of 2–9 kg within the first year after transplantation [1–4]. After 1 year post-LTx, weight gain slows, but typically continues, leading to a new-onset obesity incidence of 22% at 2 years [1,2] and up to 38% at 3 years post-LTx [3,4].

Long-term post-LTx survival is affected by metabolic and cardiovascular comorbidities [5–7], as they increase the risk of death due to cardiovascular events (CVE) [8,9]. However, evidence regarding the impact of post-LTx obesity on CVE is scarce [10]. Albeldawi *et al.* [11] found patients with obesity at 1 year post-LTx more likely to experience CVEs compared to their nonobese counterparts (49% vs. 35%, $P = 0.06$). However, as the authors did not differentiate between patients who were consistently obese over the course of LTx and those who became obese after LTx, the impact of new-onset obesity on CVE remains unclear. Additionally, their cross-sectional study design precluded causal inferences. As CVEs also develop over the long-term post-LTx trajectory [9,10,12,13], post-LTx body weight parameters should be considered as influencing factors.

The mechanisms leading to weight gain and subsequent obesity are driven by a complex interplay of genetic, physiological, behavioral, and environmental factors [14,15]. Still, despite frequent reports of weight gain and development of new-onset obesity after LTx, few studies have examined risk factors in this population. Multivariable analyses showed that higher recipient and donor BMI at LTx, being married, and absence of post-LTx rejection, predicted new-onset obesity at 2 years post-LTx. In univariate analyses, factors associated with new-onset obesity were older age, former smoking, family history of overweight, pre-LTx diabetes, dialysis in the week before LTx, and higher Model for End-Stage Liver Disease (MELD) scores at LTx [1,2,16]. Another study, not differentiating between new-onset and continuing obesity, found that age, pre-LTx BMI, and post-LTx diabetes predicted obesity at 1 year post-LTx [12]. Understanding factors contributing to new-onset obesity in LTx would provide a much-needed evidence base to identify intervention leverage points.

The prospective, nationwide Swiss Transplant Cohort Study (STCS) provides a research framework to assess new-onset obesity, its consequences, and risk factors. Its prospective pre- and post-transplant data collection allows the capture and examination of time-dependent events such as CVE. It also includes a set of sociodemographic, behavioral, biomedical, psychological, and genetic variables, allowing assessment of the broadest range of potential risk factors for new-onset obesity assessed to date. The aims of the current study were first to examine the impact of new-onset obesity on CVE (primary outcome) and patient survival (secondary outcome), and second, to determine risk factors for the development of new-onset obesity after LTx.

## Patients and methods

### Design, sample and setting

Since May 2008, the STCS has enrolled LTx patients from 3 Swiss transplant centers. Data are collected before LTx, 6- and 12-months post-LTx, then yearly thereafter. Inclusion criteria for this analysis were as follows: receiving a first and solitary LTx between May 5, 2008 and May 31, 2012, age ≥18 years, and available data about weight and height at time of LTx. Patients who were obese at LTx but lost weight after LTx - and were therefore categorized as nonobese in at least the first post-LTx measurement at 6 months—were included. The reason was that LTx patients with cirrhosis might have fluid overload (e.g., ascites), which reverses after LTx. Patients with obesity at LTx who remained continuously obese after LTx were excluded. Patients who did not have at least 1 post-LTx measurement at 6 months because of death or re-transplantation were also excluded.

### Variables and measurement

The STCS dataset includes clinical and genetic data as well as sociodemographic, psychosocial, behavioral, and quality of life variables. The latter factors are assessed via the STCS Psychosocial Questionnaire (PSQ). More information about the STCS methodology is provided elsewhere [17,18]. The STCS was approved by all relevant Swiss cantonal ethics committees.

#### *Body weight parameters*

*BMI* was calculated as weight in kg divided by the square of height in meters and categorized as follows: underweight <18.5 kg/m$^2$, normal weight 18.5–24.9 kg/m$^2$, overweight 25–29.9 kg/m$^2$, obesity ≥30 kg/m$^2$, obesity class I 30–34.9 kg/m$^2$, obesity class II 34.9–40 kg/m$^2$, and obesity class III ≥40 kg/m$^2$ [19]. *Weight changes* over time were examined in relation to the measurement at LTx. *New-onset obesity after LTx* was defined at

the first assessment of BMI ≥30 kg/m$^2$ in the post-LTx follow-up. Once categorized as new-onset obese, patients remained in this group for further analysis.

*Clinical outcomes*

The primary clinical outcome was any *CVE during post-LTx* follow-up. Consistent with the World Health Organization [20], the STCS defined CVE as coronary heart disease, cerebral vascular disease, peripheral vascular disease, left ventricular dysfunction, pulmonary embolism or venous thrombosis, and others (e.g., myocardial infarction, circulatory failure). The first occurrence of post-LTx CVE was considered for analysis. The secondary outcome was *patient survival* later than 6 months until end of follow-up after LTx. Patients without death were censored to the last known assessment date or the date of data extraction from the database (January 17, 2017).

*Risk factors for new-onset obesity*

We assessed sociodemographic, behavioral biomedical, psychological, and genetic variables as risk factors for new-onset obesity. Variables were assigned to the categories of our theoretical framework (Fig. 1), which was developed based on previous evidence [14,15].

The baseline PSQ is usually distributed at time of listing for LTx. Given that the median waiting list time in Switzerland ranged from 204 to 319 days across the previous 5 years [21], selected PSQ variables at 6 months post-LTx were considered to be more appropriate for examination compared to the measures before LTx.

*Sociodemographic factors* were as follows: age (years), gender (male/female), ethnicity (Caucasian/African/Asian/other), marital status (living alone/partnership), level of education (<9, 10–13, >14 years), and monthly income in Swiss Francs (<4500, 4501–6000, >6001). Working capacity was assessed at 6 months post-LTx (0%, 1–50%, >51%). The *behavioral factor* was smoking, evaluated with the question "Do you smoke?" with the answer options yes/no [22].

*Biomedical factors* were as follows: type of organ donor (deceased/living), etiology of liver disease (viral hepatitis/alcoholic liver disease/hepatocellular carcinoma/nonalcoholic steatohepatitis/other such as Wilson Disease, autoimmune diseases, cholangiocarcinoma), MELD score (calculated at LTx as raw laboratory MELD without exception points), presence of comorbidities (chronic kidney disease/diabetes mellitus) at LTx, and type of post-LTx immunosuppressive medication (most commonly used drugs and combined regimen). *Perceived health status* at 6 months post-LTx was assessed by the EQ-5D in view of mobility, self-care, usual activities, pain/discomfort, anxiety/depression [23]. We dichotomized each dimension's answer categories as: no problem/problems (i.e., some problems or extreme

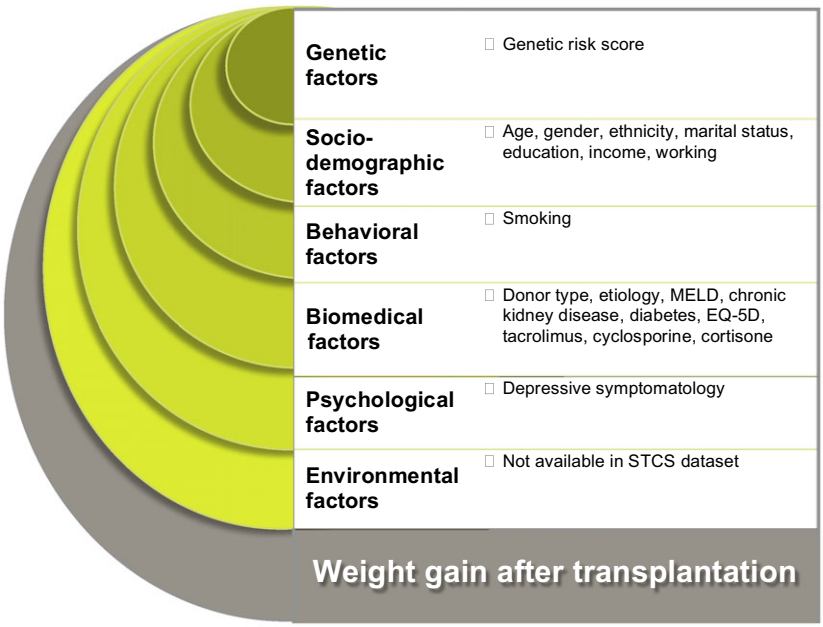


**Figure 1** Framework of factors influencing post-LTx weight gain included in this study. LTx, liver transplantation; MELD, Model for End-Stage Liver Disease; STCS, Swiss Transplant Cohort Study.



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problems). On the EQ–visual analogue scale (EQ–VAS), patients self-rated their health between 0 (worst imaginable health state) and 100 (best imaginable health state), which was treated as continuous variable.

The *psychological variable* was depressive symptomatology at 6 months post-LTx, measured via a 7-item subscale from the Hospital Anxiety and Depression Scale, a self-report nondiagnostic screening instrument integrated in the PSQ [24]. Each of the seven items was answered on a four-point Likert scale from 0 (not at all) to 3 (most of the time) and summed up (range 0–21). The presence of depressive symptomatology was noted if the calculated score was ≥8 [25].

*Genetic factor:* The generation of the genetic risk score (GRS) was based on 97 single nucleotide polymorphisms (SNPs), associated with BMI in a recent genome-wide association study in the general population [26]. For each SNP, genotypes in our Caucasian sample were coded as 0, 1 or 2, depending on the number of specific BMI risk alleles. But as the effect on BMI differs among SNPs, each SNP was weighted for its relative effect size by the β-coefficient as mentioned in the genome-wide association study [26]. For an easier interpretation (i.e., increase of one unit of the GRS corresponds to one additional risk allele), the GRS was rescaled. The weighted GRS has been used previously in an STCS sample; detailed information on the calculation and rescaling have been described elsewhere [27–29].

### Data analysis

Patient characteristics and weight changes were described using frequency and percentage, mean and standard deviation (SD) as appropriate for the data measurement level and distribution. The mean weight change over time in relation to LTx was shown graphically.

Multiple Cox Regression modeling was used to test new-onset obesity's relationships with CVE and patient survival. In the model examining CVE, new-onset obesity, cyclosporine, tacrolimus, and cortisone use were entered as time-dependent variables along with the following other covariates: age, gender, smoking, diabetes, etiology, income, and CVE at time of LTx. Missing values were not imputed. Manual backward elimination of variables with $P$ values <0.05 was used to purge the model to only its significant predictors. We also performed a subanalysis only considering patients without CVE at LTx. The model with patient survival included new-onset obesity as time-dependent predictor.

The same approach was used to examine risk factors for new-onset obesity in those who became obese and those who did not. Given the complex mechanisms of weight gain and subsequent new-onset obesity, the original intention was to include risk factors from each of the framework's categories in the analysis. As the number of new-onset obesity events required a reduction in factors, the final selection was based on evidence from the literature and availability of relevant data in the STCS dataset: GRS, age, gender, smoking, etiology, and income. The use of tacrolimus, cyclosporine, and cortisone was entered as time-dependent variables. Statistical analyses were conducted using IBM SPSS Version 23 and SAS version 9.4 software. A two-tailed $P$-value <0.05 was considered statistically significant.

## Results

### Patient characteristics

Of 3315 solid organ transplant recipients in the STCS dataset, 253 LTx patients met our inclusion criteria (Fig. 2). Sample characteristics are presented in Table 1.

### New-onset obesity after LTx

The cumulative incidence of new-onset obesity during post-LTx follow-up was 21.3% ($n$ = 54, Fig. 3a). With one exception, all patients were categorized as obesity class I (BMI 30–34.9 kg/m$^2$). Therefore, we did not distinguish between obesity classes. Overall, both groups, with and without new-onset obesity, lost weight from LTx to 6 months post-LTx and gained weight afterwards (Fig. 4). Those who became obese had their highest proportional weight gain between 6 months and 2 years post-LTx. Of the 54 patients who developed new-onset obesity after LTx, 15 met the obesity criteria at LTx, but lost weight early after LTx and had fallen below the obesity threshold, shifting to overweight ($n$ = 13) or normal weight ($n$ = 2). The evolution of their BMI over time is shown in Fig. 5.

### Impact of new-onset obesity on CVE

Seventy-one patients (28.1%) experienced CVE during follow-up, mostly within the first year post-LTx (Fig. 3b). The majority ($n$ = 44, 62%) had cardiovascular or peripheral vascular events, while $n$ = 27 (38%) had thrombotic events. Patients with new-onset obesity had a greater incidence of CVE after LTx than those

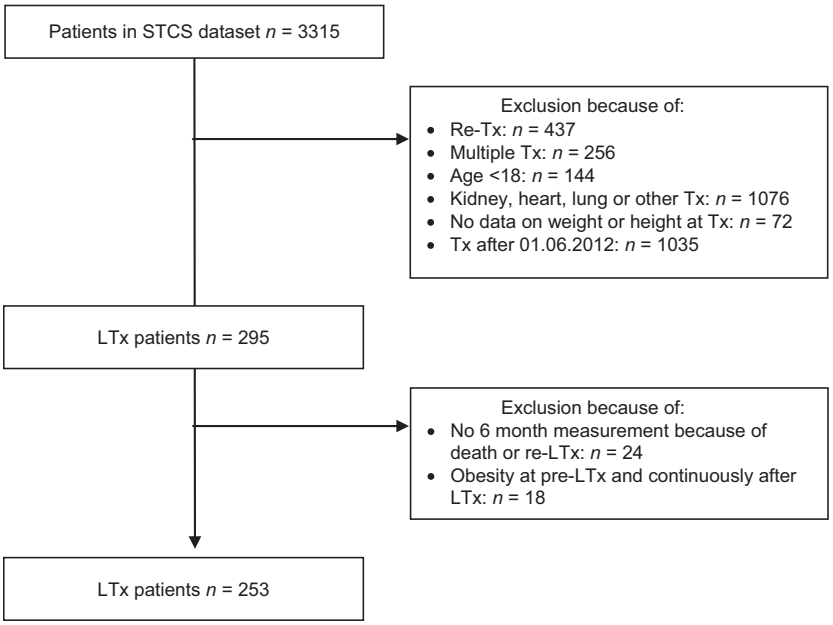


**Figure 2** Flowchart of the sample. LTx, liver transplantation; Tx, transplantation.

without (46.3% vs. 23.1%). The multivariable models of risk factors for CVE after LTx are shown in Table 2. Following independent risk factors for CVE were identified in the final models: new-onset obesity [Hazard Ratio (HR) 2.95; 95% confidence interval (CI) 1.47–5.95; $P = 0.002$] and higher age (HR 1.05; 95% CI 1.02–1.08; $P = 0.0003$). In the sensitivity analysis, using a sample of 214 patients without CVE at LTx, new-onset obesity (HR, 2.59; 95% CI, 1.21–5.53; $P = 0.014$) and higher age (HR, 1.04; 95% CI, 1.02–1.07; $P = 0.001$) remained predictors for CVE after LTx.

### Impact of new-onset obesity on mortality

Between 6 months and end of follow-up, 52 patients (20.6%) died. The group of patients who did not become obese had a higher mortality compared to those with new-onset obesity (23.1% vs. 11.1%). New-onset obesity was not associated with increased mortality (HR, 0.84; 95% CI, 0.34–2.04; $P = 0.69$).

### Risk factors for new-onset obesity after LTx

The multivariable models of risk factors for new-onset obesity after LTx are shown in Table 3. Alcoholic liver disease was an independent risk factor for new-onset obesity (HR, 3.37; 95% CI, 1.17–9.71; $P = 0.025$). Female gender was protective (HR, 0.39; 95% CI, 0.16–0.93; $P = 0.034$).

As the GRS was only available for a limited sample of 114 patients, we performed a separate analysis. The exploratory GRS model showed that alcoholic liver disease (HR, 12.82; 95% CI, 1.66–98.94; $P = 0.014$) and hepatocellular carcinoma (HR, 10.02; 95% CI, 1.03–97.94; $P = 0.048$) were independent predictors for new-onset obesity. We left the GRS in the purged exploratory model to show its borderline significance (HR, 1.07; 95% CI, 0.99–1.15; $P = 0.071$). To examine whether gender, which was not a predictor anymore in this model, was explained by the GRS, or dropped as a result of the reduced sample size, we performed a sensitivity analysis excluding the GRS in the sample of 114 patients. Alcoholic liver disease (HR, 12.99; 95% CI, 1.69–100.06; $P = 0.014$) and hepatocellular carcinoma (HR, 11.71; 95% CI, 1.22–112.68; $P = 0.033$) remained the only significant predictors for new-onset obesity.

## Discussion

Weight gain and obesity are well-known health issues after LTx [30]. This analysis of the nationwide STCS contributes to our understanding of the incidence of new-onset obesity, its impact on clinical outcomes and about risk factors for new-onset obesity. After nearly 6 years of follow-up, the cumulative incidence of new-onset obesity was 21.3%, which is comparable to studies with shorter follow-up from the United States (21.6% at 2 years) [2], Brazil (23.7% at 3 years) [1], and the

**Table 1.** Clinical patient characteristics and risk factor variables.

| Variables | Valid *n* | Total group | Valid *n* | New-onset obesity | Valid *n* | No new-onset obesity |
|---|---|---|---|---|---|---|
| Body weight parameters | | | | | | |
| New-onset obesity; *n* (%) | | | 54 | 21.3% | 199 | 78.7% |
| Weight at LTx | | | | | | |
| Mean ± SD | 253 | 75.5 ± 15 | 54 | 84.3 ± 13.4 | 199 | 70.6 ± 14 |
| Weight at 6 months | | | | | | |
| Mean ± SD | 225 | 68 ± 12.6 | 49 | 78 ± 11.1 | 176 | 65.4 ± 11.7 |
| BMI at LTx | | | | | | |
| Mean ± SD | 253 | 24.9 ± 3.9 | 54 | 28.1 ± 3.6 | 199 | 24 ± 3.5 |
| BMI at 6 months | | | | | | |
| Mean ± SD | 225 | 23.1 ± 3.2 | 49 | 26 ± 2.5 | 176 | 22.3 ± 2.9 |
| BMI category at LTx | | | | | | |
| Underweight; *n* (%) | 253 | 9 (3.6) | 54 | 0 (0) | 199 | 9 (4.5) |
| Normal weight; *n* (%) | 253 | 137 (54.2) | 54 | 9 (16.7) | 199 | 128 (64.3) |
| Overweight; *n* (%) | 253 | 77 (30.4) | 54 | 30 (55.6) | 199 | 47 (23.6) |
| Obesity; *n* (%) | 253 | 30 (11.9) | 54 | 15 (27.8) | 199 | 15 (7.5) |
| BMI category at 6 months | | | | | | |
| Underweight; *n* (%) | 225 | 18 (8.0) | 49 | 0 (0) | 176 | 18 (10.2) |
| Normal weight; *n* (%) | 225 | 138 (61.3) | 49 | 15 (30.6) | 176 | 123 (69.9) |
| Overweight; *n* (%) | 225 | 69 (30.7) | 49 | 34 (69.4) | 176 | 35 (19.9) |
| Clinical outcomes | | | | | | |
| CVE at LTx; *n* (%) | 253 | 39 (15.4) | 54 | 8 (14.8) | 199 | 31 (15.6) |
| CVE after LTx; *n* (%) | 253 | 71 (28.1) | 54 | 25 (46.3) | 199 | 46 (23.1) |
| Death later than 6 months until end of follow up; *n* (%) | 253 | 52 (20.6) | 54 | 6 (11.1) | 199 | 46 (23.1) |
| Re-LTx later than 6 months; *n* (%) | 253 | 9 (3.6) | 54 | 0 (0) | 199 | 9 (4.5) |
| Rejection episode after LTx; *n* (%) | 253 | 125 (49.4) | 54 | 18 (33.3) | 199 | 107 (53.8) |
| Follow up in years, mean ± SD | 253 | 5.7 ± 2.1 | 54 | 6.4 ± 1.5 | 199 | 5.5 ± 2.2 |
| Sociodemographic risk factors | | | | | | |
| Age in years at Tx | | | | | | |
| Mean ± SD | 253 | 52.2 ± 11.6 | 54 | 54.9 ± 9 | 199 | 51.5 ± 12.1 |
| Sex | | | | | | |
| Male; *n* (%) | 253 | 161 (63.6) | 54 | 44 (81.5) | 199 | 117 (58.8) |
| Ethnicity | | | | | | |
| Caucasian; *n* (%) | 253 | 240 (94.9) | 54 | 52 (96.3) | 199 | 188 (94.5) |
| African; *n* (%) | 253 | 7 (2.8) | 54 | 1 (1.9) | 199 | 6 (3) |
| Asian; *n* (%) | 253 | 6 (2.4) | 54 | 1 (1.9) | 199 | 5 (2.5) |
| Marital status before LTx | | | | | | |
| Living alone; *n* (%) | 218 | 68 (31.2) | 48 | 15 (31.3) | 170 | 53 (31.2) |
| Living in a partnership; *n* (%) | 218 | 150 (68.8) | 48 | 33 (68.8) | 170 | 117 (68.8) |
| Level of education before LTx | | | | | | |
| ≤9 years; *n* (%) | 243 | 66 (27.2) | 53 | 15 (28.3) | 190 | 51 (26.8) |
| 10–13 years; *n* (%) | 243 | 108 (44.4) | 53 | 26 (49.1) | 190 | 81 (43.2) |
| ≥14 years; *n* (%) | 243 | 69 (28.4) | 53 | 12 (22.6) | 190 | 57 (30) |
| Working capacity at 6 months | | | | | | |
| 0%; *n* (%) | 206 | 135 (65.5) | 44 | 35 (79.5) | 162 | 100 (61.7) |
| 1–50%; *n* (%) | 206 | 29 (14.1) | 44 | 4 (9.1) | 162 | 25 (15.4) |
| >51%; *n* (%) | 206 | 42 (20.4) | 44 | 5 (11.4) | 162 | 37 (22.8) |
| Income before LTx per month | | | | | | |
| <4500 CHF; *n* (%) | 184 | 85 (46.2) | 42 | 21 (50) | 142 | 64 (45.1) |
| 4501–6000 CHF; *n* (%) | 184 | 45 (24.5) | 42 | 14 (33.3) | 142 | 31 (21.8) |
| >6000 CHF; *n* (%) | 184 | 54 (29.3) | 42 | 7 (16.7) | 142 | 47 (33.1) |
| Behavioral risk factors | | | | | | |
| Smoking before LTx | | | | | | |
| Smoker; *n* (%) | 219 | 61 (27.9) | 48 | 13 (27.1) | 171 | 48 (28.1) |
| Nonsmoker; *n* (%) | 219 | 158 (72.1) | 48 | 35 (72.9) | 171 | 123 (71.9) |

**Table 1.** Continued.

| Variables | Valid *n* | Total group | Valid *n* | New-onset obesity | Valid *n* | No new-onset obesity |
|---|---|---|---|---|---|---|
| Biomedical risk factors | | | | | | |
| Donor type | | | | | | |
| Deceased donor; *n* (%) | 253 | 235 (92.9) | 54 | 53 (98.1) | 199 | 182 (91.5) |
| Etiology | | | | | | |
| Viral hepatitis; *n* (%) | 253 | 89 (35.2) | 54 | 15 (27.8) | 199 | 74 (37.2) |
| Alcoholic liver disease; *n* (%) | 253 | 57 (22.5) | 54 | 20 (37) | 199 | 37 (18.6) |
| Hepatocellular carcinoma; *n* (%) | 253 | 22 (8.7) | 54 | 8 (14.8) | 199 | 14 (7) |
| Nonalcoholic steatohepatitis; *n* (%) | 253 | 7 (2.8) | 54 | 3 (5.6) | 199 | 4 (2) |
| Other; *n* (%) | 253 | 78 (30.8) | 54 | 8 (14.8) | 199 | 70 (35.2) |
| Severity of disease—MELD | | | | | | |
| Mean ± SD | 253 | 18 ± 10.4 | 54 | 17.1 ± 8.8 | 199 | 18.4 ± 10.8 |
| Comorbidities | | | | | | |
| Chronic Kidney Disease at LTx; *n* (%) | 253 | 53 (20.9) | 54 | 9 (16.7) | 199 | 44 (22.1) |
| Diabetes Mellitus at LTx; *n* (%) | 253 | 52 (20.6) | 54 | 16 (29.6) | 199 | 36 (18.1) |
| Immunosuppressive drugs at 6 months | | | | | | |
| Cyclosporine; *n* (%) | 253 | 53 (20.9) | 54 | 14 (25.9) | 199 | 39 (19.6) |
| Tacrolimus; *n* (%) | 253 | 140 (55.3) | 54 | 29 (53.7) | 199 | 111 (55.8) |
| Cortisone; *n* (%) | 253 | 94 (37.2) | 54 | 14 (25.9) | 199 | 80 (40.2) |
| mTOR inhibitors; *n* (%) | 253 | 33 (13) | 54 | 8 (14.8) | 199 | 25 (12.6) |
| Cortisone and cyclosporine; *n* (%) | 253 | 21 (8.3) | 54 | 3 (5.6) | 199 | 18 (9.0) |
| Cortisone and tacrolimus; *n* (%) | 253 | 60 (23.7) | 54 | 10 (18.5) | 199 | 50 (25.1) |
| Perceived Health Status at 6 months | | | | | | |
| Mobility problems; *n* (%) | 211 | 71 (33.6) | 48 | 13 (27.1) | 163 | 58 (35.6) |
| Self-care problems; *n* (%) | 212 | 17 (8.0) | 48 | 5 (10.4) | 164 | 12 (7.3) |
| Activity problems; *n* (%) | 209 | 102 (48.8) | 47 | 18 (38.3) | 162 | 84 (51.9) |
| Pain problems; *n* (%) | 208 | 130 (62.5) | 47 | 29 (61.7) | 161 | 101 (62.7) |
| Anxiety problems; *n* (%) | 210 | 80 (38.1) | 46 | 13 (28.3) | 164 | 67 (40.9) |
| EQ-VAS; mean ± SD | 209 | 69.6 ± 19.2 | 48 | 72.6 ± 18 | 161 | 68.7 ± 19.5 |
| Psychological risk factors | | | | | | |
| Depression at 6 months; *n* (%) | 214 | 34 (15.9) | 48 | 5 (10.4) | 166 | 29 (17.5) |
| Genetic risk factor | | | | | | |
| GRS at LTx, mean ± SD | 114 | 2.15 ± 0.16 | 29 | 2.18 ± 0.14 | 85 | 2.14 ± 0.17 |

BMI, body mass index; CVE, cardiovascular event; EQ-VAS, visual analogue scale; GRS, genetic risk score; LTx, liver transplantation; MELD, Model for End-Stage Liver Disease; SD, standard deviation.

United Kingdom (26.3% at 3 years) [3]. Male gender, etiology of alcoholic liver disease, and hepatocellular carcinoma independently predicted new-onset obesity. From transplantation until end of follow-up, CVE occurred in nearly one-third of recipients. Independent of the presence of CVE at LTx, patients with new-onset obesity had a nearly threefold higher risk for CVE. New-onset obesity was not associated with increased mortality.

### Impact of new-onset obesity on outcomes

Our analyses revealed mixed results regarding the impact of new-onset obesity on patient outcomes. Our sample's CVE incidence was within the range of CVE later than 6 months after LTx reported by a systematic review (mean 11.8%; range 0–31.4%) [10]. To the best of our knowledge, our study was the first to show that new-onset obesity predicts CVE after LTx. Fussner *et al.* [12] also studied post-LTx body weight parameters in a single-center cohort of 455 LTx patients. Nearly 30% of recipients experienced CVE after 8–12 years of follow-up. Post-LTx BMI change, defined as a change of at least 1 BMI point in relation to the BMI at 4 months post-LTx, was not associated with CVE. A recent systematic literature review aimed to identify risk factors for CVE after LTx (e.g., individual cardiac events or combined outcomes) [10]. Only three of 29 studies examined post-LTx body weight parameters. None found any association



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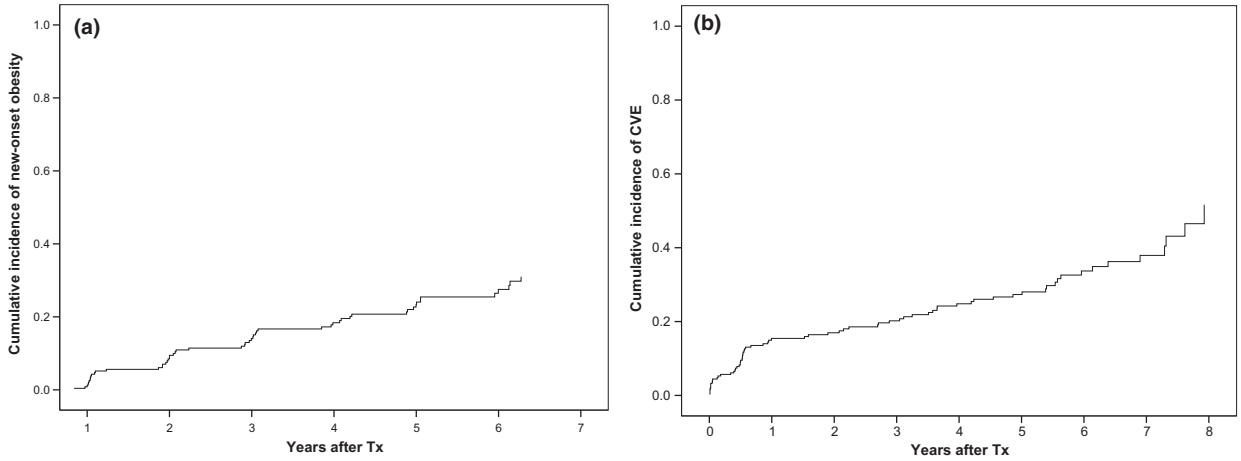



| Numbers at risk | 6 month | 1 year | 2 year | 3 year | 4 year | 5 year | 6 year | 7 year | 8 year |
|---|---|---|---|---|---|---|---|---|---|
| Patients, *n* | **225** | **221** | **193** | **170** | **178** | **149** | **102** | **61** | **24** |
| New-onset obesity, *n* (cumulative) | 0 | 12 | 25 | 35 | 42 | 49 | 54 | 54 | 54 |
| CVE after LTx, *n* (cumulative) | 23 | 36 | 39 | 45 | 53 | 57 | 64 | 67 | 71 |

**Figure 3** Cumulative incidence of (a) new-onset obesity and (b) CVE in LTx patients. CVE, cardiovascular event; LTx, liver transplantation; mo, months; y, year.

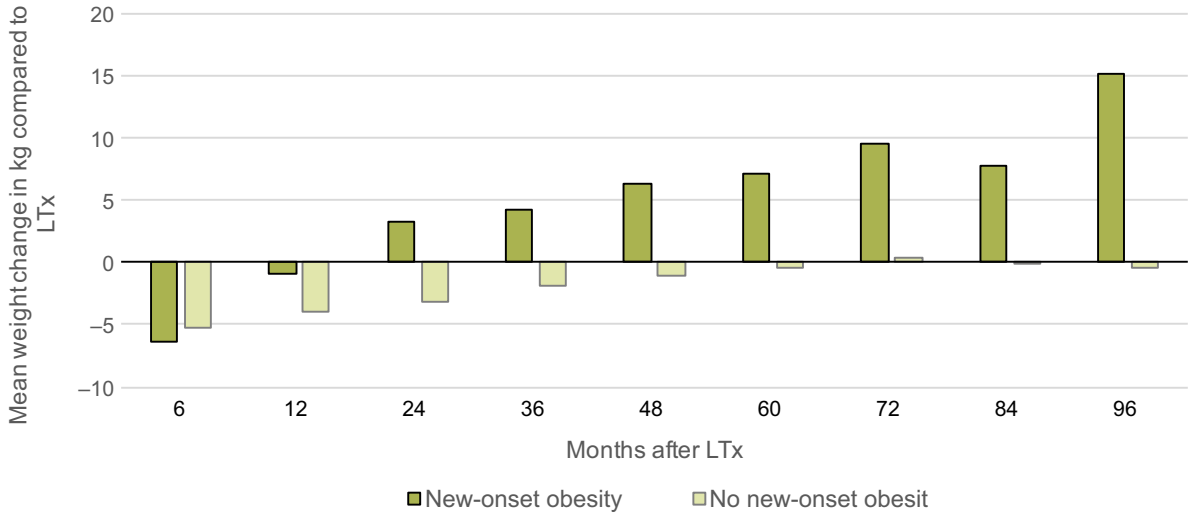
between BMI at 1 year post-LTx and CVE in multivariate analyses.

To date, very few studies have examined post-LTx body weight parameters (i.e., post-LTx BMI or BMI change) in relation to CVE after LTx. This is rather surprising: CVE is a common post-LTx complication, increasing the mortality risk [8,9]. In light of the existing literature, which has showed no relationship between post-LTx body weight parameters and CVE, our finding in a prospective cohort is novel. We excluded patients who continuously remained obese from pre- to post-LTx, meaning, at least between LTx and the first measurement at 6 months post-LTx, all patients were under-, normal-, or overweight. This operationalization of new-onset obesity and our results emphasizes the need of weight gain prevention to avoid new-onset obesity. However, it will require further investigation if the prevention of new-onset obesity might also have the potential to lower the risk of CVE.

New-onset obesity did not predict mortality. Moreover, the descriptive results actually showed lower mortality in those who became obese compared to those who did not (11% vs. 23%). Data published in 2016 show that weight gain and obesity may actually convey a survival benefit. Using data from 2968 patients with initial BMI values between 16 and 25 kg/m$^2$, Martinez-Camacho *et al.* [16] examined weight gain at 2 years post-LTx. Recipients who had gained weight (increase of >1 BMI point) showed significantly increased 5-year patient and graft survival compared to those whose weight decreased (decline of >1 BMI point) or remained stable. Additionally, patients who became obese by 2 years post-LTx (4.7%) had significantly longer patient and graft survival compared to those whose BMIs remained stable. Although the findings of this study support our observation, the methodology differed. First, in that study, new-onset obesity was examined at 1 year post-LTx, while we analyzed it as a time-dependent event; second, their sample was limited to patients with BMIs between 16 and 25 kg/m$^2$. This was probably why that study showed a lower incidence of new-onset obesity compared to ours (4.7% vs. 21.3%). However, this issue requires further examination, especially as the results in LTx contradict studies in kidney transplantation, where weight gain and obesity at 1 year after transplant are associated with increased risks of cardiovascular and all-cause mortality [31–33] as well as graft failure [31–34].

### Risk factors for new-onset obesity

Our finding that alcoholic liver disease and hepatocellular carcinoma predicted new-onset obesity is novel. Few




| | 6 month | 12 month | 24 month | 36 month | 48 month | 60 month | 72 month | 84 month | 96 month |
|---|---|---|---|---|---|---|---|---|---|
| **Total, *n*** | **225** | **221** | **193** | **170** | **178** | **149** | **102** | **61** | **24** |
| **New-onset obesity, valid *n*** | 49 | 51 | 50 | 43 | 43 | 39 | 29 | 16 | 7 |
| **weight change (kg), mean ± SD** | –6.3 ± 9.8 | –0.9 ± 10.7 | 3.2 ± 10.6 | 4.3 ± 13.3 | 6.3 ± 13.2 | 7.1 ± 11.0 | 9.6 ± 12.3 | 7.8 ± 15.6 | 15.1 ± 17.3 |
| **No new-onset obesity, valid *n*** | 176 | 170 | 143 | 127 | 135 | 110 | 73 | 45 | 17 |
| **weight change (kg), mean ± SD** | –5.2 ± 7.9 | –3.9 ± 8.9 | –3.1 ± 9.1 | –1.8 ± 9.8 | –1.0 ± 9.3 | –0.4 ± 9.6 | 0.4 ± 10.2 | –0.1 ± 10.3 | –0.4 ± 12.2 |

**Figure 4** Mean weight change compared to liver transplantation in patients with or without new-onset obesity. Mean weight changes in kg were calculated as difference between each measurement point and the weight at LTx. LTx, liver transplantation; mo, months.

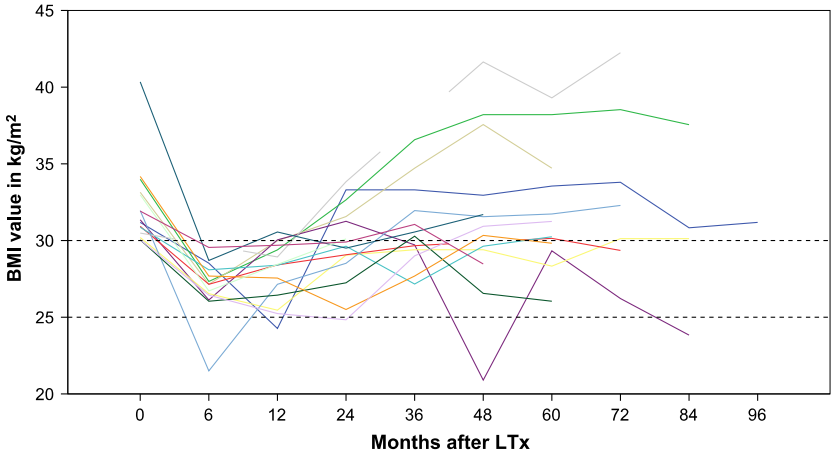



**Figure 5** Evolution of the Body Mass Index in 15 patients, who were obese at liver transplantation and developed new-onset obesity after a period of being overweight or normal weight. The dashed horizontal lines represent the cutoffs for overweight (BMI ≥25 kg/m$^2$) and obesity (≥30 kg/m$^2$). LTx, liver transplantation.

studies examined the indication for LTx as risk factor with new-onset obesity or weight gain after LTx, respectively. While Bianchi *et al.* [35] found no differences between becoming overweight/obese after LTx in relation to the etiology (i.e., alcoholic, hepatitis B/C and others), Anastacio *et al.* [1] identified alcoholic cirrhosis as risk

**Table 2.** Multiple cox regression models of risk factors for CVE after LTx.

| | Model1: Full HR [95% CI] *P*-values | Model 1: Final HR [95% CI] *P*-values | Model 2: Full without CVD at LTX HR [95% CI] *P*-values | Model 2: Final without CVD at LTX HR [95% CI] *P*-values |
|---|---|---|---|---|
| New-onset obesity | 2.47 [1.07–5.73] 0.035 | 2.95 [1.47–5.95] 0.002 | 2.44 [1.06–5.66] 0.037 | 2.59 [1.21–5.53] 0.014 |
| Age at LTx | 1.04 [0.99–1.08] 0.073 | 1.05 [1.02–1.08] 0.0003 | 1.04 [0.99–1.08] 0.069 | 1.04 [1.02–1.07] 0.001 |
| Female versus male gender | 0.61 [0.28–1.31] 0.206 | | 0.60 [0.28–1.29] 0.191 | |
| Smoking at LTx | 0.97 [0.47–1.99] 0.943 | | 0.99 [0.49–2.03] 0.984 | |
| Diabetes at LTx | 0.80 [0.39–1.66] 0.548 | | 0.76 [0.38–1.55] 0.456 | |
| Etiology | | | | |
| HCC versus others | 0.62 [0.13–2.99] 0.552 | | 0.55 [0.12–2.49] 0.439 | |
| Alcoholic versus others | 1.54 [0.54–4.37] 0.421 | | 1.48 [0.53–4.14] 0.455 | |
| NASH versus others | 1.19 [0.25–5.63] 0.831 | | 1.15 [0.24–5.39] 0.862 | |
| Viral hepatitis versus others | 0.83 [0.30–2.30] 0.723 | | 0.81 [0.29–2.22] 0.679 | |
| Income at LTx | 1.05 [0.73–1.50] 0.810 | | 1.03 [0.72–1.47] 0.874 | |
| Tacrolimus after LTx | 1.14 [0.53–2.45] 0.740 | | 1.13 [0.53–2.42] 0.755 | |
| Cyclosporine after LTx | 1.05 [0.44–2.53] 0.910 | | 1.05 [0.44–2.50] 0.92 | |
| Cortisone after LTx | 1.12 [0.55–2.28] 0.751 | | 1.11 [0.55–2.25] 0.768 | |
| CVE at LTx | 0.80 [0.32–1.96] 0.622 | | – | – |
| Sample size, *n* | 161 | 253 | 161 | 214 |
| Endpoint: CVE after LTx, *n* | 49 | 71 | 49 | 61 |

CVE, cardiovascular event; LTx, liver transplantation; HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.

factor for weight gain at 1-, 2-, and 3 years after LTx. Previous research also showed a nearly fourfold higher risk for post-LTx metabolic syndrome in patients with pre-LTx alcohol disorder [36]; however, the mechanism driving this remains unclear. Brunault *et al.* [37] hypothesized that LTx patients with previous alcohol use disorder switch from alcohol addiction to food addiction, leading to their higher post-Tx prevalence of obesity and metabolic syndrome. This issue, however, warrants further investigation. Given the wide confidence intervals in our analysis, these relationships should to be examined in bigger samples. It is especially important to study the impact of new-onset obesity on clinical outcomes in patients who underwent LTx for hepatocellular carcinoma, as previous research showed that post-LTx obesity almost doubled the risks for all-cause mortality and recurrence of the disease in this patient group [38].

Another predictor for new-onset obesity in our sample but not in previous research was male gender. Interestingly, in the general population, the global prevalence of obesity is higher in women than in men [39]. Despite the multitude of factors contributing to weight gain, gender-specific risk factors such as hormones, menopause, and pregnancy place women at higher obesity risk [40]. The reason why men were more likely than women to become obese following LTx remains unclear. However, the likelihood for men to gain weight has also been shown in a large database study comparing male and female recipients with BMI changes after LTx [16]. In that study, 65% of patients who gained weight by 2 years post-LTx were male.

It is well established that genes contribute to obesity in the general population [26]. The power of our exploratory GRS model was limited and only indicated a trend toward significance. However, another STCS study examined two samples of kidney, liver, heart, lung, and multi-organ transplant patients (total $n = 1151$), showing that the GRS predicted 10% of weight gain in the first year after transplant [29]. The authors also found that the multivariable models with genetic variables better predicted weight gain compared to those with none. To date, evidence on the impact of genes on body weight parameters in the transplant population is scarce. Of the few studies to examine

**Table 3.** Multiple Cox regression model of risk factors for new-onset obesity after LTx.

| Risk factor | Model 1: Full HR [95% CI] *P*-values | Model 1: Final HR [95% CI] *P*-values | Full exploratory GRS Model HR [95% CI] *P*-values | Final exploratory GRS Model HR [95% CI] *P*-values | Exploratory GRS Model: final sensitivity analysis |
|---|---|---|---|---|---|
| Age at LTx | 1.00 [0.96–1.05] 0.955 | | 0.91 [0.80–1.03] 0.127 | | |
| Female versus male gender | 0.43 [0.16–1.14] 0.091 | 0.39 [0.16–0.93] 0.034 | 0.28 [0.04–1.80] 0.178 | | |
| Smoking at LTx | 1.11 [0.45–2.75] 0.825 | | 3.82 [0.61–23.97] 0.153 | | |
| Etiology | | | | | |
| HCC versus others | 2.99 [0.57–15.62] 0.193 | 3.40 [0.98–11.77] 0.054 | 70.21 [0.97–5095.80] 0.052 | 10.02 [1.03–97.94] 0.048 | 11.71 [1.22–112.68] 0.033 |
| Alcoholic versus others | 1.46 [0.34–6.39] 0.612 | 3.37 [1.17–9.71] 0.025 | 3.07 [0.11–89.15] 0.515 | 12.82 [1.66–98.94] 0.014 | 12.99 [1.69–100.06] 0.014 |
| NASH versus others | 2.71 [0.33–22.34] 0.354 | 4.22 [0.82–21.88] 0.086 | 0.00 [–] 0.995* | 0.00 [–] 0.994* | 0.00 [–] 0.993* |
| Viral hepatitis versus others | 1.20 [0.32–4.45] 0.790 | 1.26 [0.41–3.83] 0.686 | 0.47 [0.02–9.18] 0.621 | 3.00 [0.34–26.83] 0.326 | 3.03 [0.34–27.14] 0.321 |
| Income at LTx | 0.69 [0.42–1.13] 0.140 | | 0.27 [0.07–0.99] 0.049 | | |
| Tacrolimus after LTx | 0.74 [0.34–1.63] 0.455 | | 0.45 [0.11–1.93] 0.281 | | |
| Cyclosporine after LTx | 1.49 [0.54–4.08] 0.438 | | 2.30 [0.61–8.67] 0.218 | | |
| Cortisone after LTx | 2.00 [0.82–4.86] 0.127 | | 7.75 [1.29–46.51] 0.025 | | |
| Genetic risk score | – | – | 1.28 [1.05–1.55] 0.014 | 1.07 [0.99–1.15] 0.071 | – |
| Sample size, *n* | 161 | 253 | 71 | 114 | 114 |
| Endpoint: New-onset obesity, *n* | 29 | 38 | 14 | 20 | 20 |

CI, confidence interval; GRS, genetic risk score; HCC, hepatocellular carcinoma; HR, hazard ratio; LTx, liver transplantation; NASH, nonalcoholic steatohepatitis.

*No variation because of small sample of NASH patients in GRS model.

candidate genes or SNPs, although all found significant associations between the genetic variables and increased risk for weight gain and obesity after liver [41,42] and kidney transplant [43]. Given that weight gain is driven by a complex interplay of factors, these results highlight the importance of incorporating genes in studies examining weight gain and obesity.

While the present study showed meaningful and partly novel results, some limitations should be mentioned. First, physical activity, relevant factor regarding weight gain and obesity, has only been measured in the STCS since 2012, and therefore, >80% of the data were missing. Therefore, two EQ-5D dimensions—mobility and usual activity—were considered as proxies for activity level at 6 months post-LTx, although these dimensions might not effectively reflect the behavior performed. Second, we could not correct the weight and BMI at time of LTx for potential fluid overload (e.g., ascites). Therefore, we included patients with obesity at LTx only if they lost enough weight afterwards to shift them into a lower BMI category for at least the first measurement at 6 months post-LTx. It is likely that some of those patients did not have fluid overload but were obese because of increased fat mass. Third, we had no data on body weight parameters before liver disease was diagnosed. Therefore, while an elevated BMI before liver disease has been shown to predict post-LTx weight gain [1], it could not be included as covariate in our multivariate model. Fourth, the risk factors included were measured at different time points. As some risk factors (e.g., income, perceived health status) might be subject to change over the post-LTx course, future studies might consider them time-dependent variables. Fifth, we were unable to consider detailed data on immunosuppressive drugs (e.g., amount, drug regimen in the LTx center) as this is not available in the STCS database. Finally, sample sizes of the exploratory GRS model were small and should be interpreted with caution.

Future research should focus on better understanding individual risk factors for weight gain and subsequent obesity, for example, gender, alcoholic liver disease, and hepatocellular carcinoma, but also to identify interrelationships and combined effects based on the interplay of those risk factors. Healthcare professionals in follow-up care should consider that new-onset obesity gradually increases over time. Therefore, to prevent the development of new-onset obesity, patients who are normal weight or overweight after LTx, males and those transplanted because of alcoholic liver disease or hepatocellular carcinoma should be subject to long-term weight gain monitoring after LTx. Although older patients and those who became obese were at higher risk for CVE, prevention of CVE should be considered in all LTx recipients as adherence to a healthy lifestyle (diet, physical activity, and nonsmoking) has the potential to prevent 80% of CVE [44].

In conclusion, post-LTx new-onset obesity had an incidence of 21.3% in our sample, and was predicted by alcoholic liver disease and hepatocellular carcinoma as reason for LTx. However, it was not associated with patient survival. Independent of a history of pre-LTx CVE, both new-onset obesity and older age predicted CVE after LTx. Therefore, prevention of weight gain and new-onset obesity via a weight management program early after LTx might reduce the risk for CVE.

## Authorship

SB and SDG: designed the study, performed the research, analyzed data, and wrote the manuscript. KD and SS: performed the research, analyzed data, and reviewed the manuscript. NSM, IB, EB and MK: participated in the research and reviewed the manuscript. All authors approved the final manuscript.

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## Conflict of interest

The authors have declared no conflicts of interest.

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## APPENDIX

The members of the Psychosocial Interest Group are: Sabina De Geest, Kris Denhaerynck, Remon Helmy, Lynn Leppla, Xhyljeta Luta, Oliver Mauthner, Marian Struker (University of Basel); Annette Boehler, Sabine Gerull, Michael Koller, Lut Berben (University Hospital Basel); Uyen Huynh-Do (University Hospital Inselspital Bern); Elsa Boely (University Hospital Geneva); Emmanuelle Catana (University Hospital Lausanne); Annina Seiler, Richard Klaghofer (University Hospital Zurich); Isabelle Binet (Cantonal Hospital St. Gallen); Patrizia Künzler-Heule (University of Basel, Cantonal Hospital St. Gallen); Hanna Burkhalter (Sleepmed Hirslanden), Sonja Beckmann (University of Basel, University Hospital Zurich).

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