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Morbid obesity increases death and dropout from the liver transplantation waiting list: A prospective cohort study

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Abstract

Liver transplant (LT) candidates with a body mass index (BMI) over 40 kg/m^2 have lower access to a liver graft without clear explanation. Thus, we studied the impact of obesity on the waiting list (WL) and aimed to explore graft proposals and refusal.

Method: Data between January 2007 and December 2017 were extracted from the French prospective national database: CRISTAL. Competing risk analyses were performed to evaluate predictors of receiving LT. Competitive events were (1) death/WL removal for disease aggravation or (2) improvement. The link between grade obesity, grafts propositions, and reason for refusal was studied.

Results: 15,184 patients were analysed: 10,813 transplant, 2847 death/dropout for aggravation, 748 redirected for improvement, and 776 censored. Mortality/dropout were higher in BMI over 35 (18% vs. 14% 1 year after listing) than in other candidates. In multivariate analysis, BMI>35, age, hepatic encephalopathy, and ascites were independent predictors of death/dropout. Candidates with a BMI $\geq$ 35 kg/m^2 had reduced access to LT, without differences in graft proposals. However, grafts refusal was more frequent especially for 'morphological incompatibility' (14.9% vs. 12.7% $p < 0.01$).

Conclusion: BMI over 35 kg/m^2 reduces access to LT with increased risk of dropout and mortality. Increased mortality and dropout could be due to a lower access to liver graft secondary to increased graft refusal for morphological incompatibility.

KEYWORDS
access to liver graft, body-mass index, dropout, graft refusal, liver transplantation, LT, morbid obesity, mortality, severe obesity, waitlist

INTRODUCTION

The liver graft shortage is an issue of concern responsible for reduced access to liver transplantation (LT) and increased mortality on the WL.[1] Thus, allocation graft policies evolved to prioritize the 'sickest' patients with the use of the Model for End-Stage Liver Disease (MELD) score (Model for End-Stage Liver Disease) to reduce mortality on the WL.[2,3] Although better than the Child-Pugh Turcotte score, the MELD score still underestimates several subgroups of patients with a higher risk of mortality on the WL as those with portal hypertension and hepatic encephalopathy, female gender, age, and severe obesity.[4–7]

The epidemiological evolution of obesity during the last 40 years, with a prevalence that almost tripled in the general population, influenced the profile of LT candidates. Non-Alcoholic Fatty Liver Disease (NAFLD) among LT recipients rose when the rate of Hepatitis C Virus (HCV)-related cirrhosis fell since the advent of new direct antiviral drugs therapy.[8] NAFLD now represents the second cause of LT for hepatocellular carcinoma (HCC) and the third for decompensated cirrhosis in the USA. In Europe, the proportion of

Non Alcoholic SteatoHepatitis (NASH) patient on the WL increased from 1.2% in 2002 to 8.4% in 2016.[9] Similar observations have been done in Nordic countries where NAFLD appears as the second most rapidly increasing indication of LT (from 2% to 6% between 1995 and 2015).[10] Besides NASH, obesity also affects other causes of cirrhosis and indication for LT. Indeed, obesity gradually increases the risk of clinical decompensation, independently of the aetiology of liver disease.[11–13] Therefore, obesity and diabetes became highly prevalent in LT candidates.[9] Regardless of liver disease aetiology, the prevalence of obesity on the WL is close to 40% with 15% of grade III obesity (BMI ≥ 40 kg/m^2)[1,14–16] in liver transplants candidates. Thus, obesity and especially grade II (40 > BMI ≥ 35 kg/m^2) and III obesity, associated with high risk of metabolic outcomes, appears as one of the future decades' challenges in LT.

More than the obese status, it is BMI ≥35 kg/m^2 (grade II and III obesity) which is recognized as clinically relevant with surgical challenges, higher postoperative infections,[17] and liver graft issues.[18–20] Despite, comparable early post-transplant (at 90 days) survival results between NASH and other etiologies, age and elevated BMI, especially,[21] grade II and III obesity in liver recipients seems to reduce the benefit from LT[19,20] with poor long-term survival[9,22,23] due to increased risk of cardiovascular events and the risk of recurrence of NASH on the graft.[24]

In addition, data have shown that access to a liver graft is reduced for candidates with grade III obesity due to an overall risk of mortality and dropout on the WL.[16,25] It appears that this higher risk of dropout and mortality on the WL is associated with a longer duration on the list which exposes the patient to a higher risk of liver related mortality. No explicative cause has been raised. Moreover, the data are still scares and debated on the risk and the impact of class II obesity (BMI between 35 and 40 kg/m^2).

This work aimed to study the impact of obesity on access to LT with a defined allocation system at a national scale. We explored liver graft allocation/refusal during the same period to understand the reasons for potential lower access to LT.

Key Summary

What is already known about this subject?

- In the USA, candidates with a body mass index (BMI) over 40 kg/m^2 have a higher risk of mortality on the waiting list (WL) before liver transplantation.
- Access to liver transplantation is reduced in morbid obese candidates.

What are the new findings in your manuscript?

- This study, outside the USA, confirms that BMI over 35 kg/m^2 increases the risk of death and dropout the WL.
- Patients with a BMI over 35 have the same rate of graft proposal but a significant higher risk of graft refusal than patient with a BMI under 35 kg/m^2.
- Graft refusal for morphological incompatibility between the donor and the recipient was significantly more frequent in patients with BMI over 35 kg/m^2.
- Donors for recipients with a BMI over 35 kg/m^2 were older and had a significant higher BMI than donors for recipients with a BMI under 35 kg/m^2.

How might your results change the direction of research or the focus of clinical practice?

- New strategies for weight management on the WL should be worked out, to reduce graft refusal for morphological incompatibility between donors and recipients.

PATIENTS AND METHODS

Study design and population

All adult patients (aged ≥ 18 years) registered for the first time on the LT WL in France from 1 January 2007, corresponding to the onset of the 'MELD era' in France, and 31 December 2017, were evaluated using data from the prospective national database (CRISTAL). Initiated in 1996, CRISTAL is a national database and administrated by the *Agence de la biomedicine* (*French transplant Agency*) that prospectively collects data on all organ transplantation candidates, recipients, and donors in France together with candidates and recipient outcomes. The 'MELD era' corresponds to an allocation graft system based on the MELD score. This allocation system supplanted the previous system, which was a state/region system. Since 2007, access to liver transplants is equivalent in all the French regions.

Covariables

Demographic information, laboratory data, and relevant dates were extracted from the French database CRISTAL. At the time of the inscription on the WL; sex, age, and comorbidities associated with liver disease, including the major cause of registration (HCC, cirrhosis, neither HCC nor cirrhosis), albumin level (g/L), presence of clinical ascites (yes/no), presence of hepatic encephalopathy (yes/no) and MELD score, BMI at listing and pretransplant diagnosis of diabetes were included. BMI was calculated using the standard formula: weight (kg)/ [height (m)]^2. Subjects were categorized according to listing BMI: non-severe obese (BMI < 35 kg/m^2) and severely obese (BMI ≥ 35 kg/m^2). MELD score was calculated using the standard formula: MELD = 3.78 × ln (bilirubin [mg/dL]) + 11.2 × ln (INR) + 9.57 × ln (creatinine [mg/dL]) + 6.43.

Statistical analysis

Clinical characteristics and laboratory data were summarized as follows: categorical variables were presented as proportions and

frequencies; continuous variables were presented as mean and standard deviation (sd). Comparisons between groups were performed using Chi-square and Student t-tests, as appropriate.

The study was conducted in two steps.

First, competing risk analyses were performed. These methods are relevant if the time to a specific event is of primary interest, but competing events may preclude its occurrence. In this study, the event of interest was receiving an LT. The outcomes of: 1/ death and WL removal due to liver disease aggravation; two/ WL dropout owing to improvement, were considered as competing events. Patients still on the WL on 31 December 2017, or dropped out due to the personal decision was censored. Patient observation time was measured from listing to the first event or last follow-up. The absolute risk of an event's occurrence up to a follow-up time point t is formalized by the cumulative incidence function (CIF), which is defined for each event type separately. The CIF at time t is defined as the probability that an event of that type occurs at any time point between inscription and time t. To explore the association between covariates and the absolute risk, we used the Fine and Grey approach,[26] as often in this context. It performs regression on the CIF. The effect measure for each covariate is a subdistribution hazard ratio (SHR). The numerical interpretation of SHR is not straightforward, but an SHR higher than one means that a considering event's cumulative incidence is higher in patients presenting a given characteristic than in patients who did not have this, whereas an SHR < 1 implies the opposite. Two sensitivity analyses were performed: (1) by presence and degree of ascites at inscription and (2) by cause of registration.

Second, we performed a descriptive analysis to evaluate the potential link between grade II and III obesity and graft propositions. We obtained the list of all offered grafts and the associated decision (accepted or not + refusal reason [one per proposition]). The number of graft propositions per patient was compared overall and, in each subgroup, defined by the patient's status on 31 December 2017 (LT, death or disease aggravation, disease improvement, still on the WL). Then in the subgroup of graft proposition that does not result in LT, we performed a pairwise comparison of proportions for graft refusal reasons according to the presence or not of BMI $\geq$ 35 kg/m^2. Graft refusal reasons could be graft quality, recipient state, morphological incompatibility between the donor and the recipient, logistic constraints, accepted graft but attributed to another LT team, Hbc antigens or HCV grafts, technical conditions, other local recipients chosen by the LT team, and graft to another international organization, other.

Moreover, additional information on donor was available in case of LT: age, BMI, graft quality (presence of steatosis evaluated by Abdominal CT scan, aspartate transferase (AST), alanine transferase (ALT), glutamine transferase [GGT]). When a graft, leading to a LT, was proposed to several patients, donor information had been merged to the effective recipient of LT and to recipients for whom graft was refused. In the subgroup of LT patients and for each cause of refusal, donor information had been compared according to the severe obesity criteria.

Analyses were performed using the software R version 3.4.3.

Data collection extracted for the CRISTAL database was declared the French *Commission Nationale de l'Informatique et des Libertés* (CNIL) (declaration number: DEC16-264) and approved by the scientific committee of Agence de la Biomedecine 23 July 2018.

RESULTS

Study design and population

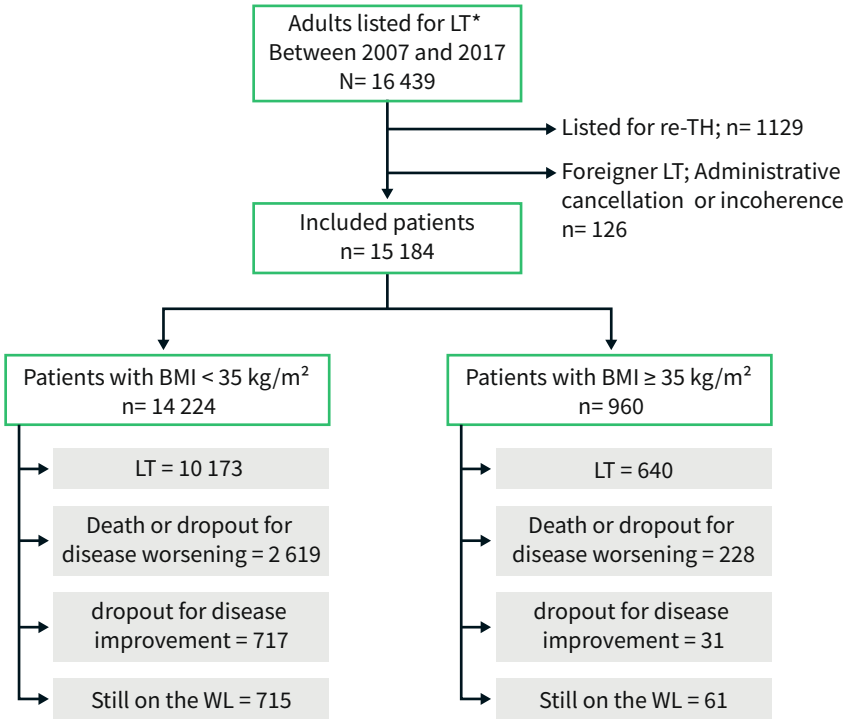
Between 2007 and 2017, 16,439 adult patients were listed for LT in France. Patients listed for multiple organ transplantation, simultaneous kidney-liver transplantation, or heart/lung liver transplantation were not extracted for analysis due to differences in the allocation system in comparison to other candidates. For the same reasons, 1129 patients listed for retransplantation were excluded patients. Finally, 15,184 patients were analysed (flow chart on Figure 1).

Characteristics of the population were summarized in Table 1. Compared to non-obese candidates, obese candidates with a BMI between 30 and 35 kg/m^2 (grade I obesity) were more frequently diabetic (19.8% vs. 33.8%), of male gender (72.9% vs. 80.3%) and listed for HCC (30.2% vs. 43%). There were no differences in terms of liver disease severity (MELD: 15.8 vs. 15.4). When comparing patients with grade I obesity and those with grade II and III, patients with BMI $\geq$ 35 kg/m^2 were more frequently diabetic (36.9% vs. 33.8%) and a more severe liver disease (MELD 15.4 vs. 16.6) (Table 1).

Between 2007 and 2017, obesity prevalence has increased from 19.6% to 29.0%, and BMI $\geq$ 35 kg/m^2 rose from 4.0% in 2007 to 8.7% in 2017. During the study period, the proportion of candidates with a BMI 35 kg/m^2 among obese patients rose from 20.4% to 30% ($p < 0.001$) (Figure 2).

Impact of obesity on access to liver transplantation

The overall median event-free WL time was 139 days (IQR: 28–321). LT occurred for 10,813 of the listed patients (71.2%). Cumulative probabilities to be transplanted at 1 month, 6 months, and 1 year were respectively 20.5% (CI: 19.9%–21.2%), 44.3% (CI: 43.5%–45.1%), and 60.6% (CI: 59.8%–61.4%) (Figure 3a). Compared to non-obese patients, the 1 year cumulative probability of being transplanted was significantly lower for candidates with a BMI $\geq$ 35 kg/m^2 (56.1% (CI:52.8%–59.2%) versus 61.1% (CI: 60.2%-62.0) (Figure 3b), whereas they had an increased 1 year cumulative probability of death and dropping out of the WL due to disease aggravation 18.4% (CI: 16.0%–20.9%) versus 14.5% (CI: 13.9%–15.2%), Figure 3c). At the opposite, non-obese patients had a slightly better 1 year cumulative probability to be removed from the list for disease improvement (2.8% (CI: 2.5%–3.1%) versus 1.6% (CI: 0.9%–2.6%), Figure 3d).



*: Patients listed for multiple organ transplantationwere non included

FIGURE 1 Flow chart

TABLE 1 Patient characteristics

	All patients	BMI < 30	30 ≤ BMI <35	BMI ≥ 35	*p*-Value
Number of patients	15,184	11,757	2467	960	
Male (%)	11 ,272 (74.2)	8576 (72.9)	1981 (80.3)	715 (74.5)	<0.001
Age at listing, mean (SD), years	56.0 (10.4)	53.6 (10.8)	57.3 (8.1)	55.8 (8.5)	<0.001
BMI, mean (SD), kg/m^2	26.2 (5.3)	24.1 (3.1)	31.6 (1.4)	38.5 (6.7)	–
Severe obesity (%)	960 (6.3)	0 (–)	0 (–)	960 (6.3)	
Main cause of listing (%)					<0.001
HCC	4988 (32.9)	3551 (30.2)	1061 (43.0)	376 (39.2)	
Cirrhosis	8093 (53.3)	6457 (54.9)	1179 (47.8)	457 (47.6)	
Nor HCC nor cirrhosis	210 (13.9)	1749 (14.9)	227 (9.2)	127 (13.2)	
Diabetes	3515 (23.1)	2327 (19.8)	834 (33.8)	354 (36.9)	<0.001
MELD score, mean (SD)	15.8 (10.7)	15.8 (10.7)	15.4 (10.6)	16.6 (11.3)	0.38
Albumin, mean (SD),	32.6 (29.7)	32.8 (33.4)	32.1 (10.7)	30.9 (6.9)	0.05
Ascites (%)	8065 (53.1)	6295 (53.5)	1275 (51.7)	495 (51.6)	0.12
Hepatic encephalopathy (%)	4844 (31.9)	3787 (32.2)	729 (29.6)	328 (34.2)	0.01
First occurred outcome					<0.001
Liver transplantation	10 ,813 (71.2)	8374 (71.2)	1799 (72.9)	640 (66.7)	
Death or aggravation	2847 (18.8)	2154 (18.3)	465 (18.8)	228 (23.8)	
Improvement	748 (4.9)	627 (5.3)	90 (3.6)	31 (3.2)	

Note: All variables were evaluated at inscription on the waiting list.

Abbreviations: BMI, body mass index; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease.

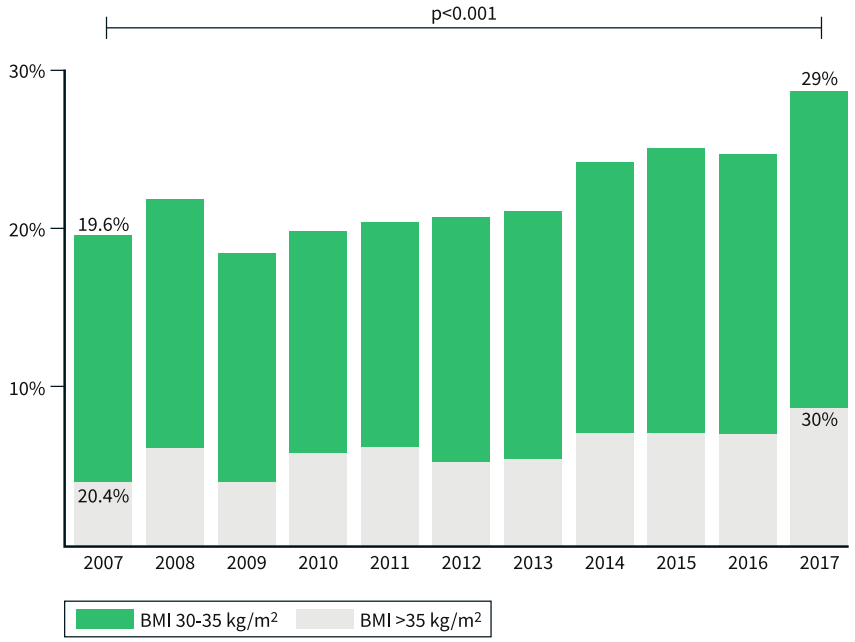


FIGURE 2 Annual prevalence of obesity in patients listed for liver transplantation in France between 2007 and 2017

Between grade I obesity patients and non-obese patients, no significant difference was found for the 1 year cumulative probability of LT 60.0% (CI: 58.0%–61.9%) versus 61.1% (CI: 60.2%–62.0%) and death/aggravation [14.2% (CI: 12.8%–15.6%) versus 14.5% (CI: 13.9%–15.2%)] but exists for improvement [1.5% (CI: 1.0%–2.0%) versus 2.8% (CI: 2.5%–3.1%)].

Predictors of Liver transplant and predictors of death/disease aggravation

In univariate models (Table 2), all considered covariates, except albumin level at the inscription, were predictors of LT and death/dropout due to disease aggravation. Albumin was only associated with death and dropout due to disease aggravation (Table 2). In multivariate analysis (Table 3), age, class II and III obesity, and being registered for HCC were deleterious for both outcomes. A higher MELD score increased access to LT as well as death or disease aggravation. Complications of cirrhosis (ascites and hepatic encephalopathy) increased the incidence of death and dropout due to a worsening state, whereas higher albumin levels decreased these incidences.

Improvement on the waiting list

Patients who were removed from the WL for improvement were initially listed for severe cirrhosis or acute liver failure (around 90% of cases). These patients were significantly younger (49 ± 12.6 years), less diabetic (12.3%) and less obese (4.0% of class II and III obesity).

Improvement of liver disease on the WL was better in younger candidates and non-diabetics in multivariate analysis but no influence of obesity was found (Table 3).

Sensitivity analysis

Thus, only patients with a BMI over 35 kg/m^2 had different outcomes after inscription on the WL for LT; grade I obesity patients had the same course that non obese patients. Our results were unchanged when class of obesity was dichotomized into BMI +/− 35 kg/m^2 (Tables S1 and S2) and legitimized that our next results will be presented as follows BMI < 35 kg/m^2, BMI ≥35 kg/m^2.

In presence of ascites, weight could be higher and could contribute to changing class of obesity. In absence of specific information on the CRISTAL database, we assumed the BMI was calculated from dry weight (i.e. without ascites) and we performed a sensitivity analysis, stratifying on the presence of ascites at inscription. Our results were unchanged suggesting that ascites did not negatively impact our results and that severe obesity impacts the LT course (Tables S3A–C).

Cause of registration did not influence our results concerning the impact of obesity since similar trends were found (Tables S4A–C).

Graft proposition

Twelve thousand five hundred and forty eight listed patients (82.6%) had a minimum of one graft proposition, and 67,167

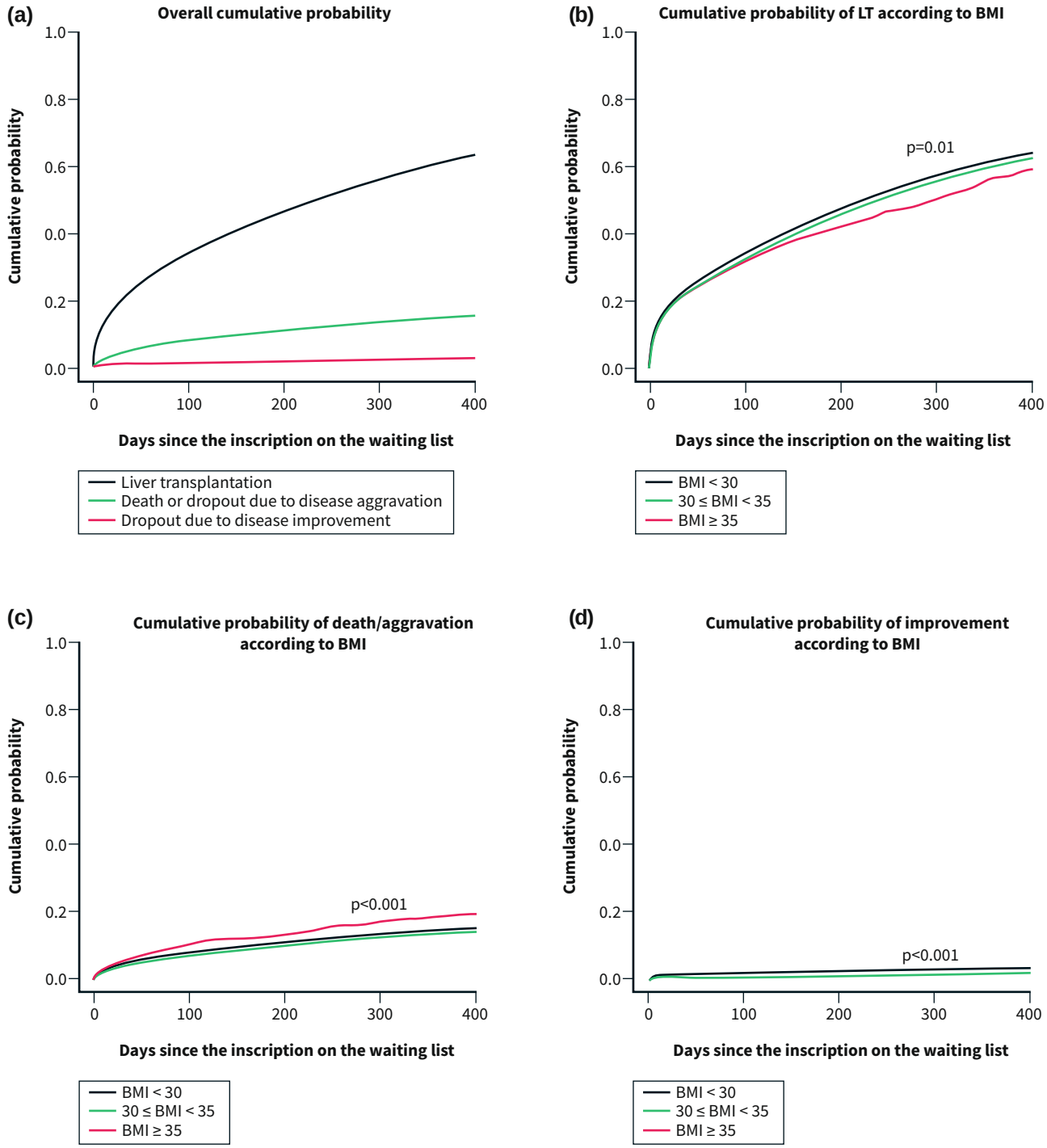


FIGURE 3 (a) Overall cumulative probabilities; cumulative probabilities of (b) Liver transplant (LT), (c) death or aggravation, (d) improvement according to the BMI

propositions were recorded during the study period (a graft is generally proposed for several recipients). Before the first event, the median number of propositions per patient was two (IQR: 1–5). The subgroup of LT patients had significantly more propositions than the other subgroups. Nevertheless, this number did not differ between candidates with a BMI ≥35 and the other candidates, overall and whatever the first outcome occurred (Table 4, Tables S5A–D).

Cause of graft refusal

Overall, 56,354 (83.9%) propositions did not result in an LT.

Considering the reason for graft refusal, the three leading causes of refusal were the same in class II and III obese patients and in the others: poor graft quality (steatotic and fibrotic liver), recipient state, and morphology (Table 5). However, pairwise comparisons of proportions showed the graft was significantly more refused for

TABLE 2 Predictors of access to liver transplantation, death/disease aggravation and improvement: subhazard ratio (SHR) and their 95% confidence interval (CI 95%) in univariate analysis

	Outcome: LT SHR (CI95%)	Outcome: Death/aggravation SHR (CI95%)	Outcome: Disease improvement SHR (CI95%)
Men (vs. women)	0.890 (0.840–0.940)	1.122 (1.042–1.196)	0.300 (0.020–0.530)
Age (1 year increment)	0.991 (0.989–0.993)	1.030 (1.020–1.030)	0.996 (0.953–0.964)
Class of obesity (vs. non obese)			
I (30≤BMI<35)	1.004 (0.956–1.055)	1.020 (0.923–1.130)	0.674 (0.541–0.840)
II or III (BMI≥35)	0.884 (0.816–0.958)	1.340 (1.166–1.530)	0.601 (0.419–0.862)
Cause or registration (vs. HCC)			
Cirrhosis	1.350 (1.300–1.400)	0.894 (0.827–0.967)	3.900 (3.050–4.990)
Nor HCC nor cirrhosis	1.540 (1.440–1.640)	0.713 (0.626–0.812)	7.680 (5.890–10.020)
Diabetes (vs. no diabetes)	0.898 (0.860–0.937)	1.200 (1.100–1.300)	0.475 (0.381–0.591)
MELD score (1 point increment)	1.031 (1.030–1.032)	1.000 (1.000–1.001)	1.000 (0.997–1.010)
Albumin level	0.996 (0.987–1.000)	0.989 (0.983–0.995)	1.000 (1.000–1.000)
Ascites (vs. no ascites)	1.300 (1.260–1.350)	1.190 (1.110–1.290)	0.723 (0.626–0.836)
Encephalopathy (vs..no encephalopathy)	1.330 (1.270–1.390)	1.290 (1.190–1.390)	1.010 (0.865–1.180)

TABLE 3 Predictors of access to liver transplantation, death/disease aggravation and improvement: subhazard ratio (SHR) and their 95% confidence interval (CI 95%) in multivariate analysis

	Outcome: LT SHR (CI95%)	Outcome: Death/aggravation SHR (CI95%)	Outcome: Disease improvement SHR (CI95%)
Men (vs. women)	0.980 (0.927–1.037)	1.030 (0.932–1.139)	0.877 (0.733–1.050)
Age (1 year increment)	0.996 (0.993–0.998)	1.025 (1.020–1.030)	0.978 (0.971–0.985)
Class of obesity (vs. non obese)			
I (30≤BMI<35)	1.049 (0.989–1.112)	0.913 (0.819–1.019)	0.986 (0.773–1.260)
II and III (BMI≥35)	0.888 (0.809–0.975)	1.205 (1.038–1.400)	0.754 (0.499–1.138)
Cause or registration (vs. HCC)			
Cirrhosis	1.021 (0.969–1.075)	0.796 (0.718–0.883)	3.915 (2.976–5.150)
Nor HCC nor cirrhosis	1.174 (1.070–1.289)	0.604 (0.500–0.729)	4.300 (3.121–5.922)
Diabetes (vs. no diabetes)	0.981 (0.933–1.032)	1.032 (0.940–1.133)	0.697 (0.549–0.886)
MELD score (1 point increment)	1.031 (1.028–1.035)	1.007 (1.002–1.012)	Non included
Albumin level	Non included	0.993 (0.987–1.000)	Non included
Ascites (vs. no ascites)	1.053 (1.000–1.108)	1.118 (1.013–1.234)	0.695 (0.586–0.823)
Encephalopathy (vs..no encephalopathy)	0.962 (0.906–1.022)	1.204 (1.091–1.329)	Non included

TABLE 4 Median number of graft proposition per patient, and the interquartile range, stratified by the patient's status at the end of the study (31 December 2017) and according to class of obesity

	Overall	BMI < 35	BMI ≥ 35
Overall	2 (1–5)	2 (1–5)	2 (1–5)
Liver transplantation	3 (1–6)	3 (1–6)	3 (2–6)
Death or drop out due to disease aggravation	0 (0–2)	0 (0–2)	0 (0–2)
Drop out due to disease improvement	0 (0–2)	0 (0–2)	0 (0–2)
Censored at 31 December 2017	0 (0–1)	0 (0–1)	0 (0–1)

morphological incompatibility in patients with grade II and III obesity (14.9% vs. 12.7%, $p < 0.01$). The rate of refusal, for this reason, increased significantly with the grade of obesity from 11.8% for grade 1 obesity to 14.1% for grade 2 obesity and 16.7% for grade 3 obesity. The rate of graft refusal for morphological incompatibility between the donor and the recipient increased in men with the severity of BMI for 10.6% for non-obese, 11.7% for grade I obesity, 14.7% for grade II obesity and 18% for grade III obesity. This effect was not observed in women.

Donor characteristics

Among the 10,813 LT patients, donor information was available for 10,591 (97.9%). The donors of severe obese recipients were significantly older (57.3 vs. 55.5) and had higher BMI: 7.0% were severe obese versus 3.4% in the subgroup of non-severe obese patients (Table 6). Interestingly, the difference between the BMI of the recipient and the donor was significantly higher in the subgroup of severe obese recipients than in recipients with a BMI <35 kg/m^2: 0.2 ± 5.7 versus 11.9 ± 8.8 kg/m^2 (Figure 4). On the contrary, there was no difference in terms of graft steatosis and biological donor characteristics (AST, ALT, GGT) (Table 6).

For patients who were not transplanted, donor characteristics were compared within each cause of graft refusal. Number of missing donor information varied across causes but were not different according to the BMI of the recipient. Of interest, the only subgroup in which donor BMI was significantly different according to the severe obesity of the recipient was the 'morphological incompatibility' subgroup. In this case, BMI of the donor was significantly lower in severe obese recipient than in recipient with a BMI <35 kg/m^2, illustrating

TABLE 5 Proportion of each reasons of the graft refusal for the 56 ,354 propositions which did not result on according to severe obesity

	Overall	BMI < 35	BMI ≥ 35	*p*-Value
Graft quality	40.8%	40.5%	38.2%	0.16
Recipient state	16.0%	16.2%	17.7%	0.59
Morphology	12.9%	12.7%	14.9%	0.01
Logistic constraints	12.2%	12.4%	12.7%	0.49
Accepted graft but attributed to another LT team	6.1%	6.2%	6.4%	1.00
Graft infected by virus	2.8%	2.8%	2.4%	1.00
Technical conditions	2.3%	2.0%	0.6%	0.00
Other local recipient chosen by LT team	1.8%	1.9%	2.3%	1.00
Graft given to another international organisation	0.0%	0.1%	0.0%	1.00
Other reason	5.1%	5.2%	4.8%	1.00

Abbreviation: LT, liver transplant.

TABLE 6 Donor characteristics for the 10,813 patients

	All patients	BMI < 35	BMI ≥ 35	*p*-Value
Number of proposition	10,813	10,173	640	
Missing donor information (%)	222 (2.1)	209 (2.1)	13 (2.0)	
Donor age, mean (SD), years	55.6 (18.5)	55.5 (18.6)	57.3 (17.3)	<0.05
Donor BMI, mean (SD), kg/m^2	25.4 (4.7)	25.3 (4.6)	26.6 (5.6)	<0.05
Normal (%)	5590 (52.8)	5317 (53.4)	273 (43.5)	<0.05
Overweight (%)	3519 (33.2)	3292 (33.0)	227 (36.2)	
Obesity I (%)	1103 (10.4)	1020 (10.2)	83 (13.2)	
Severe obesity (%)	379 (3.6)	335 (3.4)	44 (7.0)	
Donor steatosis liver[a] **(%)**	406 (3.9)	382 (3.9)	24 (3.9)	NS
Donor AST	96.8 (186.0)	96.7 (185.8)	99.7 (189.4)	NS
Donor ALT	74.2 (160.0)	73.8 (159.0)	81.0 (174.4)	NS
Donor GGT	54.0 (71.7)	53.7 (71.3)	59.3 (77.9)	0.05

Abbreviations: ALT, alanine transferase; AST, aspartate transferase; GGT, glutamine transferase; LT, liver transplant.

[a]Defined by presence Abdominal CT scan.

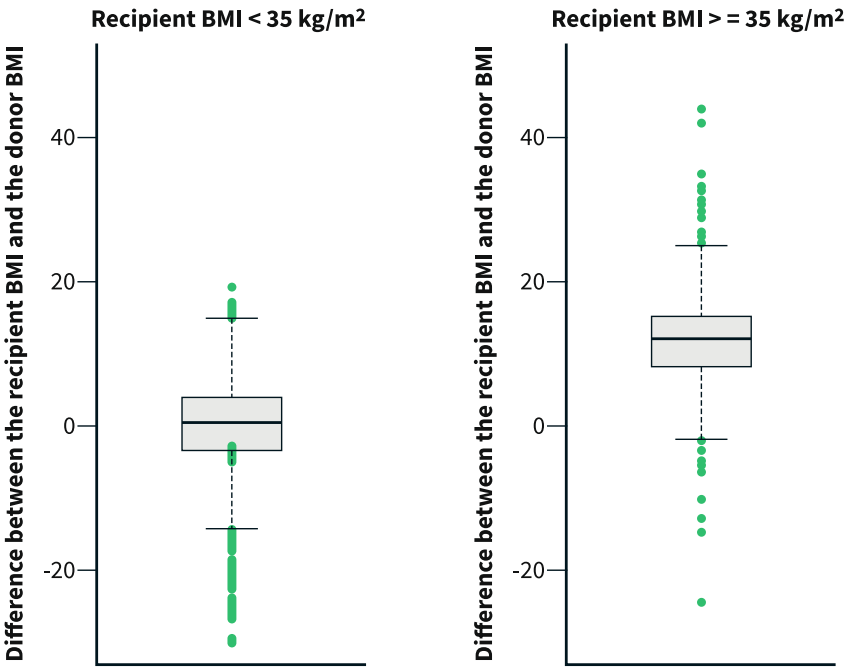


FIGURE 4 Difference between BMI of the recipient and the donor according to the severe obesity of the recipient

TABLE 7 Donor characteristics in the case of graft refusal for morphological incompatibility

	All patients	BMI <35	BMI ≥35	*p*-Value
Number of proposition	7248	6757	491	
Missing donor information (%)	2626 (36.2)	2459 (36.4)	167 (34.0)	
Donor age, mean (SD), years	58.4 (17.0)	58.1 (16.8)	62.2 (18.8)	<0.001
Donor BMI, mean (SD), kg/m^2	27.8 (6.2)	27.9 (6.2)	26.2 (6.6)	<0.001
Normal (%)	1665 (36.0)	1493 (34.7)	172 (35.0)	
Overweight (%)	1456 (31.5)	1375 (32.0)	81 (16.5)	
Obesity I (%)	956 (20.7)	914 (12.0)	42 (8.6)	
Severe obesity (%)	545 (11.8)	516 (7.6)	29 (5.9)	
Donor steatosis liver[a] **(%)**	208 (4.5)	197 (4.6)	11 (3.4)	0.39
Donor AST	93.6 (177.8)	94.3 (180.7)	84.1 (133.0)	0.32
Donor ALT	71.3 (141.8)	71.6 (143.6)	66.7 (114.7)	0.55
Donor GGT	55.5 (64.4)	55.6 (64.7)	54.3 (60.2)	0.73

Abbreviations: ALT, alanine transferase; AST, aspartate transferase.

[a]Defined by presence at Abdominal CT scan.

morphological incompatibility (27.9 ± 6.2 vs. 26.2 ± 6.6 kg/m^2). No differences in terms of graft quality were found (Table 7).

DISCUSSION

In the French cohort of candidates to LT (CRISTAL), LT candidates with BMI over 35 kg/m^2 had a reduced access to a liver graft, resulting in a longer duration on the WL with higher risk of mortality and dropout due to disease aggravation. One possible explanation is that candidates with BMI ≥ 35 kg/m^2 had more graft refusal for the morphological incompatibility between the donor and the recipient without differences in terms of number of graft proposal in comparison with candidates with lower BMI.

Our data corroborate previous studies showing the negative impact of BMI ≥ 35 kg/m^2 on the WL dropout and mortality since the MELD era.[16] However, these data are the first outside USA, in a country with a lower prevalence of severe obesity in the total

population and the transplant list.[27] This study suggests that BMI's negative impact is already quantifiable even if NASH prevalence seems less frequent in the transplant WL.[9] In France, NASH status is only recorded since 2019; therefore, we could not quantify its impact on access to LT during the study period and consist in a limitation of our work. Future studies should be performed to measure the progressive impact of obesity on the WL while the prevalence of NASH and obesity is increasing.

In the literature, several explicative hypotheses on the negative impact of severe obesity have been suggested: increased portal vein thrombosis, a higher rate of infection or risk of HCC progression; none have been confirmed.[6,11,28] However, very few corrective decisions or treatments can be set up for these situations. In our study, patients listed for HCC tended to have a higher risk of HCC progression (aggravation of the disease), but this point was not significant. This observation could be related to a longer duration on the WL, or lower access to HCC treatment before LT. Further studies are needed for this specific question. Our work suggests that severely obese patients have a higher rate of graft refusal due to morphological mismatch. The higher rate of graft refusal in men than in women suggests that the gynoid (define as hips fat excess distribution with a waist-hip-ratio (WHR) < 0.85) or the android obesity (excess of abdominal visceral fat defined by a waist circumference $\geq$ 102 cm in men and $\geq$ 88 cm in women with a WHR >1 in men and >0.85 in women)[29] may influenced graft acceptance. Further explorations on this morphological mismatch should be a workout. Unfortunately, the graft-to-recipient weight ratio was not recorded in the database, and additional investigations cannot be performed. In addition, reasons for graft refusal may be multiple. Many factors are involved in the decision and the database proposes only one single choice. We cannot exclude those other reasons as cold ischaemic time or previous abdominal surgery (or others) may have balanced in the choice of the graft.

Nevertheless, the recommended graft-to-recipient weight ratio of >0.8% to avoid '*small for size*' is quite a debate; mostly, it is unknown in severe and morbidly obese patients.[30] Indeed, the severe obese candidate requires a larger graft and a more prominent donor who may disclose more severe steatosis. No precise data are available to determine the ideal ratio for graft without steatosis. Moreover, liver machine perfusion with defatting procedures is emerging and could contribute to the graft's optimization in the following years.[31]

Different weight loss strategies before LT, including lifestyle interventions (diet and exercise) or bariatric surgery, have been tested but are limited in the presence of severe liver disease. Severe obese patients are frequently frail and undernourished, with increased mortality.[32,33] In this situation, diet to induce weight loss is inappropriate, while nutrition with high protein intake for muscle reinforcing and cardiorespiratory reconditioning seems more crucial.[34,35] From another perspective, bariatric surgery could be an exciting option, but the optimal time for intervention remains unclear. The pretransplant surgical management of obesity appears interesting for compensated cirrhosis. Among procedures, sleeve gastrectomy seems to be the most appropriate in highly selected patients. In these rare patients, the sleeve has acceptable risk, with significant and sustained weight loss comparable to bariatric patients without cirrhosis. Notably, some authors have reported that sleeve gastrectomy improves metabolic comorbidities post-LT. However, this approach is limited to selected patients and could delay LT. Alternatively, performing bariatric surgery after or simultaneously to LT is another option with encouraging results in carefully selected patients.[36] Although their results are impressive to reduce morbidity and potentially the risk of NASH recurrence after LT, it does not resolve the problem of reduced access and higher mortality on the WL list. Further studies on weight loss strategies before LT and their impact on the access to transplantation are warranted.

In conclusion, as in post-LT, the management of severe obesity on the WL is a concerning issue. It seems that further studies on graft-recipient matching in the setting of severe and morbid obesity should be warranted.

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CONFLICT OF INTEREST

Guillaume Lassailly guaranties the integrity of the work/and declares no conflict of interest.

AUTHOR CONTRIBUTIONS

Delacôte Claire, Favre Mathilde: analysed the data and wrote the paper. El Amrani Medhi, Bauvin Pierre; wrote the paper. Boleslawski Emmanuel; Millet Guillaume; Massih Ningarhari; Elise. Lemaitre, Truant Stephanie, Mathurin Philippe; Louvet alexandre, Canva Valérie, Lebuffe Gilles, Pruvot François René: contributed to the design of the study and worked on the submitted version. Dharancy Sébastien: designed the research study and wrote the paper. Lassailly Guillaume: performed the research, collected, analysed the data, designed the research study wrote the paper. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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