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# Recipient body mass index and infectious complications following liver transplantation


Authors

Rafael Diaz-Nieto, Panagis M. Lykoudis, Brian R. Davidson.

Affiliation

Department of Hepato-Pancreato-Biliary Surgery & Liver Transplantation, Royal Free Hospital, Pond street, NW3 2QG, Hampstead, London, UK

rafadiaznieto@hotmail.com, p.lykoudis@ucl.ac.uk, b.davidson@ucl.ac.uk

Corresponding author

Mr Panagis M Lykoudis, MD MSc MRCS

Senior Clinical Fellow in Hepato-Pancreato-Biliary Surgery & Liver Transplantation

Royal Free Hospital

Pond street

Hampstead

NW3 2QG

London

UK

Email: p.lykoudis@ucl.ac.uk

Additional information

a) Original article

b) Part of results was presented as a Poster during the annual congress of the British Transplant Society (2015, Bournemouth, UK)

Abstract

Background

Nutritional problems are common in patients requiring liver transplantation. Recipient obesity or malnutrition are thought to increase postoperative complications. Body mass index (BMI) is commonly used prior to major surgery but its value specifically in liver transplant assessment has not been established. This is a retrospective study assessing the correlation between the BMI of individuals undergoing liver transplant and the development of postoperative infectious complications.

Methods

Data were collected from a prospectively maintained database regarding all consecutive patients over a period of 23 years. Preoperative recipient BMI was correlated with the number, nature and outcome of postoperative infective complications.

Results

Of a total of 1156 consecutive patients, 13.2% developed infectious complications. Thirty-day mortality was 7.2% and 90-day mortality was 10%. Higher BMI was associated with higher risk of infections (p=0.002). Wound infections occurred predominantly in obese patients (p=0.001) while other types of infections were more common in malnourished patients (p<0.001).

Discussion

Extremes of BMI are associated with increased infectious complications following liver transplantation. Patients with lower BMI had a higher rate of overall infectious complications whereas those with a higher BMI had increased general and wound complications.

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## Introduction

According to recent data, worldwide obesity has increased three-fold since 1975[1]. In 2016, approximately 39% of adults were overweight and 650 million were obese[1]. Obesity can cause non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NASH) that can lead to cirrhosis[2, 3]. Frequency of liver transplantation (LT) due to NASH is increasing over recent years, and the latter is expected to be the most common indication for LT in United States of America in the coming years[4]. Both obesity and underweight can impact on surgical outcomes[5, 6] and are potentially reversible in those awaiting surgery for chronic disease, such as liver transplant. Malnutrition is frequently associated with chronic liver disease and its prevalence is considerably higher in those patients with more severe liver impairment (20–25% in Child A–B patients) compared with >50% in those with Child C cirrhosis[7]. Body mass index (BMI) is an objective measurement based on the weight and height of the patient and is the basis of the World Health Organization (WHO) classification of obesity and malnutrition[1]. Previous studies have analysed the association between recipient BMI and outcomes following liver transplant. Some studies report worse outcomes in obese recipients while others describe no differences between different BMI groups[8-12].

The aim of this study was to examine the association between the BMI of liver transplant recipients and early postoperative outcomes, focusing primarily on infectious complications.

## Methods

A prospectively maintained database was analysed, consisting of all consecutive patients who underwent liver transplantation in a single centre over a 23-year period from October 1988 to March 2012, to allow adequate follow up information on recorded outcomes. Data retrieved included preoperative BMI, length of hospital stay (in days), ITU stay (in days), number of days on ventilatory support, postoperative infections (chest, wound, abdominal, bacteraemia), type of infections (bacterial, viral, fungal) and mortality within 30 and 90 days postoperatively.

### Antimicrobial prophylaxis and diagnosis of sepsis

All patients received preoperative prophylaxis with antibiotics at the time of anaesthesia induction. Drugs were based on internal protocol and covered most common microorganisms. From 1988 till 1998, prophylaxis consisted of Ampicilin, Netilmicin and Metronidazole. From 1998 till 2004 only piperacillin and tazobactam were given, and since 2004, local protocol includes cefotaxime and metronidazole. The protocols were implemented for all patients, without any deviation for extreme BMI. Diagnosis of infection was always based on clinical evidence of sepsis and supported where possible by blood or other cultures. Presence of fever and elevated inflammatory markers (white blood cells and/or C-reactive protein) in the absence of other ongoing medical problems were considered adequate to establish the diagnosis of infection. Clinical suspicion of chest infection was supported by findings on chest X-ray or computerized tomography (CT) scan. Wound infection diagnosis was based on clinical findings including evidence of cellulitis, purulent discharge or positive cultures from samples. Intra-abdominal sources of sepsis were commonly reported based on CT findings confirmed following drainage. Bacteraemia was only diagnosed in the presence of a positive blood culture.

## Statistical analysis

Statistical processing of data was conducted using SPSS v20 software (IBM Corporation, USA). BMI was assessed in 5 different approaches: a) as a scale variable; b) according to WHO classification [13]; c) in two groups with a threshold of 30 (BMI<30 vs BMI≥30); d) in two groups with a threshold of 16 (BMI<16 vs BMI≥16); and e) in three groups using both aforementioned thresholds (BMI≤16 vs BMI between 16 and 30 vs BMI≥30). Postoperative infections were assessed in 3 different approaches: a) any infection vs no infection; b) wound infection vs all other; and c) wound infection vs non-wound Infection vs no infection. A further subgroup analysis was performed for the three subclasses of obesity (I: BMI 30-34.9, II: BMI 35-39.9 & III: BMI>40.

Bivariate correlations between scale independent variables (BMI) and binomial dependent variables was performed using Mann-Whitney U test, while in case of multinomial dependent variables, Independent Sample Median Test (ISMT) was performed. Correlations between scale dependent and independent variables was performed using Spearman's correlation. Correlations of categorical variables in 4-fold tables was performed using Fisher's exact test (2-sided) and in >4-fold tables using chi-square test (2-sided). A p value of less than 0.05 was considered significant.

Results

A total of 1156 consecutive patients were included in the analysis. Median age was 50 years (range 10-70 years) while 646 were female (49.9%). Median BMI was 23.3 (range 12.7 and 46.9). The BMI distribution is presented in Figure 1. Severely underweight patients (BMI<16) represented only 1.4% (16 patients) of the studied sample while obese patients (BMI>30) were 131 (11.3%). Hospital stay ranged from 7 to 394 days with a median of 23 days, ITU stay ranged from 0 to 140 days with a median of 3 days and ventilatory support duration ranged from 0 to 140 days with a median of 2 days. Eighty-three patients died within 30 days (30-day mortality of 7.2%) and 33 died between 30 and 90 days post transplantation (90-day mortality of 10%). Wound infection was developed in 101 patients (8.7%), while 52 (4.5%) developed infections of other sources. Fifty-five patients developed intra-abdominal infections, 1 of which had a jejunal perforation, 3 had a liver abscess, 5 were in the context of bile leak, 13 represented infected haematomas and 15 represented cholangiitis. The remaining 18 incidents were abdominal collections found on CT scans, drained, with a positive culture, in the context of symptoms of sepsis.

Total length of hospital stay, ITU stay, ventilatory support, 30- and 90-day mortality did not demonstrate a statistically significant correlation with pre-operative recipient BMI. BMI as a scale variable demonstrated a statistically significant positive correlation with development of infection of any source (Figure 2). The median BMI of patients that did not develop any infection was 23.8 (range: 12.7-46.1) while the respective BMI for those that developed infection of any source was 24.9 (range: 12.71-46.9) (p=0.002). BMI did not correlate with any other preoperative variable, including MELD and UKELD scores of the recipient. BMI categorized according to WHO classification also demonstrated a statistically significant correlation with development of infections (Figure 3). Recipients at the extremes of BMI were more prone to infections ($p<0.001$). The patient group with BMI < 16 (severely underweight) developed more frequent abdominal and chest infections compared to those with normal/high BMI (Figure 4). A subgroup analysis of the three obesity classes according to the WHO classification, demonstrated a borderline non-significant distribution of the three infection classifications (no infection versus wound infection versus non-wound infection, $p=0.054$), as well as a non-significant distribution of clustered infections (no infection versus any infection, $p=0.163$). When comparing obesity class I versus aggregated classes II & III, infection-related outcomes were significantly worse in the second group (Table 1), while length of ITU stay and number of days on ventilatory support were not statistically significantly different ($p=0.307$ and $p=0.311$ repsectively).

The studied period was divided in two groups, 1988 till 1999 and 2000 till 2012. The differences regarding BMI and infection related outcomes were assessed between these two periods to assess for discrepancies. The median BMI of patients transplanted in the early period was 23.8, ranging from 12.7 to 41.6, while the respective number for the later period was 24.3, ranging from 13.7 to 46.9. The difference was not statistically significant ($p=0.069$). The overall infection rate was 16.4% (80 out of 487 patients) for the first period and 12.4 (83 out of 669 patients) for the second period ($p=0.060$). Amongst patients that did develop some infectious complication, wound infection accounted for 76.3% of these in the earlier period, but only for 56.6% in the second period ($p=0.004$). This was the only statistically significant difference detected in this stratification analysis.

## Discussion

The present study, the largest so far in literature, demonstrated that obese patients (BMI>30) are more likely to develop infectious complications, particularly wound related, following liver transplantation. Malnourished patients were also prone to postoperative infections, but not wound infections. Infections in the underweight group included chest infections which could be predisposed to by muscle wasting and poor respiratory reserves. However, ITU stay and duration of ventilatory support was not significantly increased in those with a low BMI. The latter might have been a result of the small number of recipients in this BMI group. Low BMI may also have been expected to predispose to other sites of infection as malnutrition is likely to be a risk for all types and sites of infection[14]. However, as chest infections usually develop early following liver transplant, their treatment may have mitigated the development of other septic complications which occur later post-transplant.

Current literature is characterized by heterogeneity, particularly regarding BMI cut-off values, and most studies focus on obesity rather than both ends of the spectrum of malnutrition. Indicatively, a BMI below 18.5 is reported to convey a relative risk on survival of 1.55, a BMI of more than 40 is reported to convey a relative risk on survival of 1.44 – 1.5, and a relative risk on graft survival of 1.7[9-11].

Similar data correlating malnutrition with increased infectious complications have been reported with other organ transplants. Studies on renal and pancreas transplantation report an increased morbidity, especially due to infections, but no differences in terms of patients´ or grafts´ survival between groups with extreme BMI[15, 16]. The reason that BMI did not impact on mortality despite increasing infection rates may be related to the effectiveness of anti-microbial therapy. However, most studies have included small numbers of patients with very low or high BMI and could thus be considered under-powered to detect differences in survival. A few studies did include a large number of patients and reported that recipient BMI does not correlate with early postoperative complications[8, 17]. However, these studies were focused on analysing outcomes such as graft and patient survival, and due to the limitations of multi-centre data collections did not have detailed information on infective complications.

The influence of recipient BMI to long term outcomes following liver transplant is also unclear. Some studies have shown no influence of BMI on long-term survival[9], while others have shown worse survival in obese patients following liver transplant[8, 11, 12]. Once again, the discrepancy can be attributed to the small number of patients with very low or high BMI included in the studies. Conzen et al. reported no differences in outcomes 3 years after transplant , but a significantly reduced 5-year graft (49.0% versus 75.8%; $P < 0.02$) and patient (51.3% versus 78.8%; $P < 0.01$) survival for those patients with morbid obesity (BMI higher that 40 kg/m$^2$)[8] suggesting that the risks of poor long term outcomes may be related to the complications of obesity. Multivariate analysis confirmed that BMI was an independent adverse prognostic factor for 5-year patient and graft survival. Similarly, LaMattina et al, reported lower patient and graft survival for patients with BMI 35-40[11]. Whether the long-term outcome can be improved by dietary modification, exercise, improved diabetic management or indeed the addition of obesity surgery requires to be addressed in prospective trials.

Nutritional assessment is difficult in patients with advanced cirrhosis[8, 18] and modifications have been made to ensure relevance to cirrhotic patients. Modified BMI (mBMI) multiplies the classical BMI score by the serum albumin in order to compensate for the potential accumulation of fluid related to hypoalbuminaemia. However, the mBMI has not been shown to correlate with outcomes following liver transplant[19].

Malnutrition is now less common than obesity in advanced chronic liver disease. The definition of malnutrition in the cirrhotic patient remains unclear as it should include the loss of skeletal muscle and adipose tissue mass, as well as micronutrient deficiencies[20]. However, an optimal method for the nutritional assessment of patients with cirrhosis has not been established[18, 20]. In one of the largest reported cohorts, 2.5% of patients were underweight at the time of listing and 32.5% were obese[21]. Poor nutrition was associated with lower survival compared to normal weight patients but also compared to obese patients (hazard ratio of 1.24-1.42). This study addressed whether we can improve outcome by nutritional modification prior to transplant. Underweight patients had a median increase in BMI of 2.6 while on the waiting list, with each gained BMI unit leading to a 2% decrease in death related hazard ratio. As far as obese patients were concerned, the BMI changes were minimal, with no effect on postoperative outcome[19, 22]. Surgical interventions, have been carried out before, during or after liver transplantation with a view to decrease the adverse effects of obesity. The procedures have been considered safe and effective in terms of weight loss. However, the impact on outcomes is unproven. The weight loss has been associated with physiological decompensation and adverse events[21], but also with maintained lower weight and improved management of metabolic syndrome[22]. Most relevant studies though, were small, had a short follow-up and were under powered to assess the risk of surgical complications adding obesity surgery to the complex background of liver transplantation[19].

Identification of patients with higher risk of developing complications can be clinically important. Not only for the purposes of transplantation but also for the implementation of preoperative strategies that may improve the nutritional status and minimize the risk for these potential complications[21]. The use of steroids post-transplantation in obese patients seems to promote a higher weight gain, incidence of diabetes, dyslipidaemia and hypertension[23]. In this sense, weight control may result in major benefit post liver transplantation. However obese patients that had good weight reduction during transplant assessment often gain weight post-transplant and develop metabolic complications[22, 23].

The present study included a large number of transplanted patients, yet with a relatively small proportion of them belonging in the three lower BMI classes (8.3%) or the three higher ones (11.3%). However, this seems to be in lines with other published studies and is therefore representative of the population on transplant waiting lists. It was a review of prospectively collected data on patients who proceeded to transplant and hence the number of patients appropriate for transplant but turned down for nutritional reasons is not known. Thus, it is not possible to draw any conclusions regarding risk/benefit ratio of offering transplantation to these patients, although it can be argued that current selection system is producing satisfactory transplant outcomes. Data regarding BMI trend before and after transplantation were not recorded. Finally, other factors that could interact with BMI and outcomes, such as mobility, metabolic conditions, psychological aspects and nutritional immunomodulation were not assessed. Some of these, such as smoking, diabetes and perioperative mobility, had not been captured in the existing database. Moreover, the small number of patients that developed such complications would not allow for a full multifactorial analysis.

Several issues need to be addressed to better understand nutritional status and outcomes in liver transplant. Firstly, nutritional assessment tools need to be specifically adapted and validated for patients with liver cirrhosis and those undergoing liver transplant. These then need to be incorporated into large prospective trials to determine the true associated between nutrition and outcome. Once established, nutrition assessment tools can then form the basis for interventional trials of nutritional support in the malnourished and obesity patients, including bariatric surgery in those with morbid obesity requiring organ transplant for end stage liver disease. Long term studies are essential as the poor long-term outcomes may be related more to the underlying obesity than the transplantation. Finally, the benefit or risk of extending the BMI criteria for transplant urgently needs to be addressed in view of the obesity epidemic.

Tables

Table 1, distribution of infection-related complications, compared between Obesity class I versus Obesity classes II & III).

| | | Obesity class I (BMI from 30 to 34.9) n (%) | Obesity classes II & III (BMI>34.9) n (%) | p value |
|---|---|---|---|---|
| Overall infections | No infection | 82 (85.4) | 26 (66.7) | 0.018 |
| | Infection of any source | 14 (14.6) | 13 (33.3) | |
| Sub grouped infections | No infection | 82 (85.4) | 26 (66.7) | 0.025 |
| | Wound infection | 7 (7.3) | 9 (23.1) | |
| | Non-wound infection | 7 (7.3) | 4 (10.3) | |

Figures

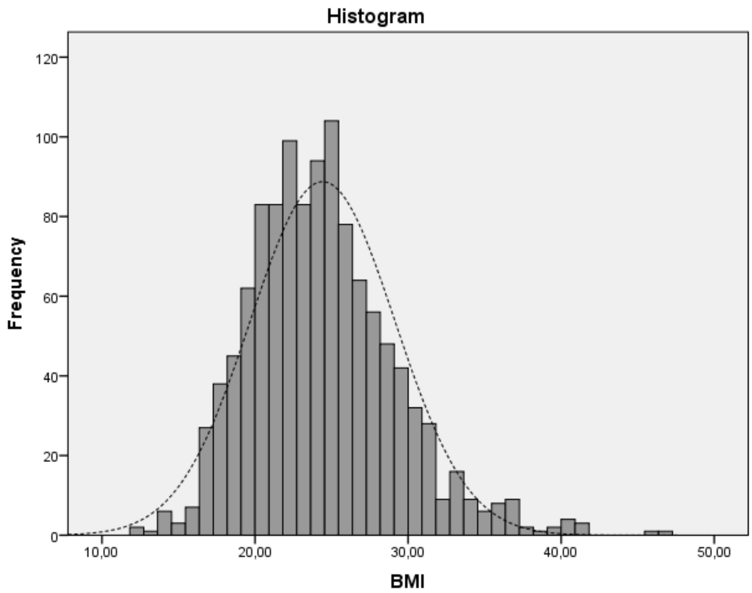


Figure 1. Histogram of frequencies for BMI of patients included in the study, depicting distribution with mild positive skewness and only a small number of patients at the extremes.

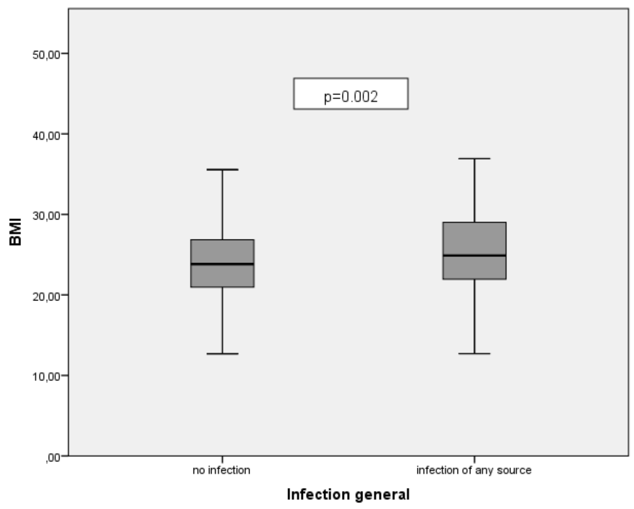


Figure 2. Comparison of median BMI across infection groups.

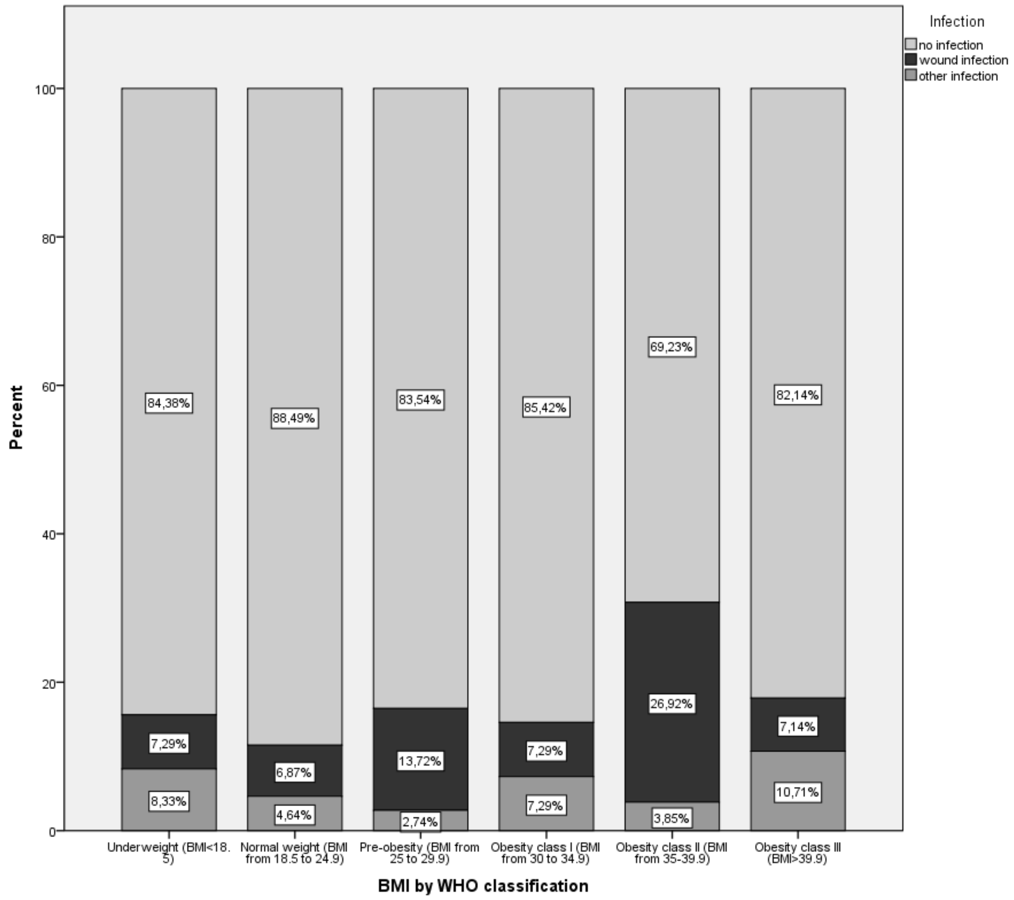


Figure 3. Distribution of infections across WHO BMI categorieswith statistically significant overall variation (p=0.001).

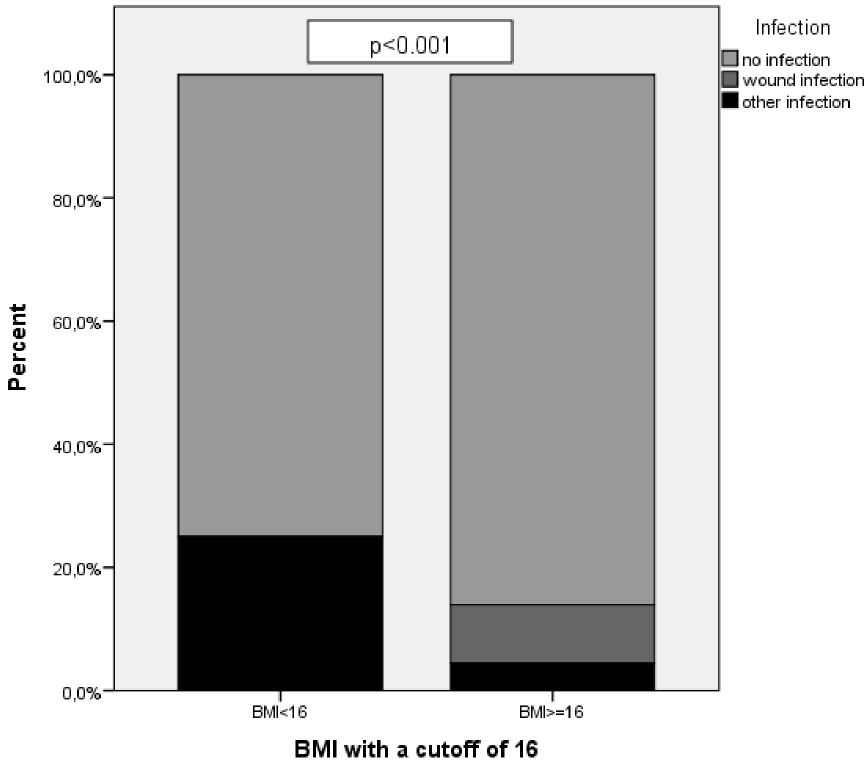


Figure 4. Infectious complications in the severely malnourished (BMI<16).

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