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Review Article

Obesity as predictor of postoperative outcomes in liver transplant candidates: Review of the literature and future perspectives

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ABSTRACT

Background: Current American and European guidelines consider a pre-transplant BMI ≥40 kg/m^2 as a relative contraindication for liver transplantation but this recommendation is graded as uncertain and requires further research. Moreover, conflicting results are reported on the predictive value of BMI 30–39.9 kg/m^2 on post-transplant complication and mortality risk.
Aim: This study analyzed the data of the literature on the effect of all three BMI classes of obesity on postoperative outcomes in liver transplantation.
Materials and methods: A PubMed and Cochrane Library search was conducted from inception to October 2015.
Results: Analysis of the literature demonstrates that discrepancies among studies are mainly either due to limitations of BMI *per se*, the different BMI cut-offs used to select patients with obesity or reference group and the different outcomes considered. Moreover, the evaluation of visceral adipose tissue and the detrimental effect of muscle mass reduction in presence of obesity are never considered.
Conclusions: BMI assessment should be used as a preliminary method to evaluate obesity. Subsequently, the assessment of visceral adipose tissue and muscle mass should complete the preoperative evaluation of liver transplant candidates. This innovative approach could represent a new field of research in liver transplantation.

1. Introduction

Patients with obesity suffer from a large number of medical comorbidities and are at higher risk of postoperative respiratory (pneumonia, atelectasis, pulmonary embolism), cardiac (atrial fibrillation), infectious (nosocomial infections, wound infections) and surgical (wound dehiscence) complications [1–3].

The continuous increase of obesity in the general population translates into an increase in the number of patients with obesity eligible for liver transplantation [4]. In fact, the percentage of liver transplant recipients with obesity increased from 21% to 32% in the periods 1988–1996 and 2001–2011, respectively [5–7]. On the other hand, the prevalence of malnutrition in two large cross sectional studies including 73,538 and 38,194 adult US liver transplant recipients, from 1987 to 2007 and from 2004 to 2011, was only 2.5% [7,8].

Obesity is identified by a body mass index (BMI) ≥30 kg/m^2 [8], but a lower cut-off value (BMI ≥25) has been set in Japan, China and Korea [9–11]. The calculation of BMI was first devised by Adolphe Quetelet in the eighteenth century [12]. Since then, it has been widely used as an anthropometric index because of its easy application. However, the BMI has several limitations. It does not take into account several factors: body composition, *i.e.* the percentage of fat free mass and fat mass of the subjects, gender, age, and consequently, the significantly different percentage of fat mass in men and women and the decrease of fat free mass, namely the muscle mass, in the elderly [13]. Moreover, it does not consider the increase in extracellular fluids, as it occurs in the case of edema or ascites, an aspect particularly important in the case of advanced liver disease.

Finally, it has been proposed that a specific measurement of visceral adipose tissue (VAT) would be more relevant than just BMI for the evaluation of adverse postoperative events related to obesity in patients undergoing general surgery [3,14]. Moreover, obesity might be associated with a decrease of muscle mass, a condition that increases the negative effects of obesity, giving rise

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to the scenario of sarcopenic obesity [15,16]. Sarcopenia is a well characterized syndrome in elderly (namely primary or age-related) defined by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes. A disease-related sarcopenia (secondary sarcopenia) is associated with advanced organ failure (heart, lung, kidney and brain), inflammatory disease, malignancy or endocrine diseases. Only recently, the concept of sarcopenia has been extended to the cirrhotic population, but some considerations including the underlying mechanisms, suggest the need to modify the definition of sarcopenia in this specific setting of patients [17–19].

All these considerations imply that most of the literature assessing obesity on the basis of the mere BMI to predict postoperative outcomes in liver transplant candidates suffers some limitations and does not offer either conclusive results or practical suggestions. In the present review we approached the data of the literature from a new prospective, revisiting the results obtained on the basis of BMI and trying to cover the aspects that were not adequately considered in previous reviews. Finally, new materials that offer more definite conclusions were incorporated.

To achieve the goal of this research, the effect of the three classes of BMI corresponding to the three obesity categories on postoperative outcomes in liver transplantation were analyzed. Then, the predictive value of sarcopenia and visceral adipose tissue, which is currently used to evaluate the postoperative risk related to obesity in general surgery was examined. Finally, the possibility of extending the use of these two parameters to evaluate the postoperative risk in liver transplant recipients with obesity was discussed.

A MEDLINE, PubMed and Cochrane Library search that included studies published up to March 2017 was conducted using the search terms 'body mass index', 'obesity', 'visceral adipose tissue', 'sarcopenia', 'liver transplant*', 'general surgery', 'complication', 'mortality', 'survival', with AND/OR as Boolean connectors. Moreover, further relevant articles were hand-searched using the references of the selected studies.

The novelty of this manuscript relies on the original approach used to compare the BMI studies and supports the evaluation of visceral fat and sarcopenia in the transplant setting (it is plausible that data concerning patients with obesity undergoing general surgery might also be applicable to liver transplant recipients). For the first time, we propose a combined assessment of visceral fat and sarcopenia as prognostic factors for postoperative complication and mortality risk in obese liver transplant candidates, which are two parameters easily derivable from the imaging studies expected for preoperative protocols.

2. BMI as prognostic factor

2.1. Post-transplant complication risks

The studies on the influence of pre-operative BMI on postoperative complications in liver transplant recipients are summarized in Table 1, with data from 1987 to 2012 taken into consideration. The first part of the table contains a list of studies that report an increased risk of postoperative complications, while the second part contains a list of studies with opposite results. Only in 4 of these 11 studies recipients with a BMI ≥ or > 40 are compared with recipients with lower BMI; 4 studies adopted a BMI ≥ or > 35 as cut-off but used recipients with BMI < 30 (3 studies) or BMI 18.5–24.9 (one study) as controls; 1 study used a different cut-off for male and female recipients (31.1 and 32.3, respectively) and 2 studies a cut-off >30. Sawyer et al. [20] found a significantly higher number of wound infections in 30 liver transplant recipients with BMI ≥35 (severe obesity) but, at the same time, in these patients they report a total number of complications similar to that found in the 217 patients with a BMI <30 used as reference group. Nair et al. [21] reported significantly higher postoperative complications (respiratory failure and systemic vascular events) in 21 liver transplant recipients with a BMI >32.3 for women and >31.1 for men (severe obesity) as compared to 100 controls with a lower BMI (≤27.8 for women and ≤27.3 for men). Dick et al. [22] analyzed 1447 patients with BMI ≥40 (severe obesity) as compared to 68,172 patients with a BMI 18.5–39.9. In this study, significantly longer periods of hospitalization and use of intensive care unit services following transplantation were observed. Schaeffer et al. [23] found a significantly higher rate of wound infections and dehiscences in 10 liver transplant recipients with a BMI >35 as compared to the 143 controls with a BMI <30. Analysing data retrieved from a prospectively maintained database, including liver transplant recipients, Hakeem et al. [24] observed a longer mean hospital and intensive care unit stay in patients with BMI ≥35 (73 pts.) as compared to patients with normal BMI (646 pts.). Dare et al. [25] described a higher risk of postoperative complications (cardiovascular and respiratory) in 72 liver transplant recipients with a BMI ≥30 as compared to 102 controls (BMI 18.5–29.9). In a recent paper including 12,445 liver transplant recipients, Singhal et al. [26] reported that 416 (3.3%) BMI ≥40 recipients had higher hospital length of stay and were less often discharged as compared to 12,029 BMI <40 controls. By contrast, a study of Braunfeld et al. [27] did not find an increase of intra- and postoperative complications when 40 liver transplant recipients with a BMI >35 were compared to a cohort of 61 time-matched controls (BMI <30). Fujikawa et al. [28] reported that, after liver transplantation, 167 (24%) patients with obesity (BMI range 30–42) had clinical outcomes similar to 533 patients with a BMI <30. Leonard et al. [29] analyzed length of hospital and intensive care unit stay, early and late complications in 704 patients by comparing 22 patients with a BMI >35 plus 10 patients with a BMI >40 versus 672 patients with a BMI ranging from <18.5 to 34.9 without finding any significant differences. However, this was the only study, together with the one from Hillingso et al. [30], which corrected the BMI based on the degree of ascites. Finally, in a single center study on 758 liver transplant recipients, Conzen et al. [31] found no difference among the different BMI categories, including 26 patients with BMI >40, when postoperative complications, hospital and intensive care unit stay were analyzed.

In none of the above-mentioned studies was a different BMI taken into consideration according to gender and ethnicity. Moreover, the presence of sarcopenia was not assessed.

2.2. Post-transplant mortality risk

In the first and second part of Table 1, studies that analyzed not only post-transplant mortality, but also postoperative complications are reported, while in the third part of the table the studies that exclusively analyzed post-transplant mortality are listed. As observed for postoperative complications, conflicting data are also reported on short- and long-term post-transplant mortality in patients with obesity, receiving liver transplantation from 1987 to 2012.

Among the 16 studies analyzed, 7 used a BMI ≥ or > 40 as cut-off for comparison with lower BMI, but in 2 of these studies BMI 19–22 and 20–24.9 were used as controls. Four studies assumed as cut-off a BMI ≥ or > 35 but used recipients with BMI < 30 (3 studies) or BMI 18.5 24.9 (one study) as controls; 1 study used a different cut-off for male and female recipients (31.1 and 32.3, respectively) and 4 studies a cut-off >30.

Five studies reported a significant increase of post-transplant mortality. Sawyer et al. [20] found a significantly higher number of deaths from multi organ failure but a similar overall mortality in the early post-transplant period, and a survival rate at 1 and 3 years, similar to recipients with BMI ≥35 and <30. Nair et al.

Table 1
Postoperative complication and mortality risk in liver transplant recipients with obesity assessed by BMI.

Studies (ref.)	LT period (years)	BMI categories (No. of pts.)	Postoperative complications (p value)	Postoperative mortality		
				30 days	1–3 years	5 years
1st part						
Sawyer et al. [20]	1989–1996	BMI >35 (30) vs. BMI <30 (217)	Wound infections (p = 0.0001); overall complications (n.s.)	p = 0.0001 for MOF[a] Overall mortality n.s.[2]		n.s.[b]
Nair et al. [21]	1994–1996	BMI >32.3 for women and >31.1 for men (21) vs. BMI <27.8 for women and <27.3 for men (64)	Respiratory failure (p = 0.009), cardiovascular complications, length of hospital stay (p = 0.04)	n.s.		
Dick et al. [22]	1987–2007	BMI ≥40 (1447) vs. BMI 18.5–39.9 (68,172)	Length of ICU and hospital stay (p < 0.02)	p < 0.02		
Schaeffer et al. [23]	1999–2003	BMI >35 (10) vs. BMI <30 (143)	Wound infections and dehiscence (p = 0.0001)	BMI >30 (24) vs BMI <30 (143) n.s.		n.d.[c]
Hakeem et al. [24]	1994–2009	BMI ≥35 (73) vs. BMI 18.5–24.9 (646)	Length of ICU (p = 0.03) and hospital (p = 0.047) stay	n.s.		
Dare et al. [25]	2000–2010	BMI ≥30 (72) vs. BMI 18.5–29.9 (102)	Cardiovascular (p < 0.001) and respiratory (p < 0.03) complications	n.s.		
Singhal et al. [26]	2007–2011	BMI ≥40 (416) vs. BMI <40 (12,029)	Length of ICU and hospital stay (p < 0.0001)	n.d.	n.s.	n.d.
2nd part						
Braunfeld et al. [27]	About 4 years before 1996	BMI >35 (40) vs. BMI <30 (61)	Pulmonary and cardiac complications, length of ICU and hospital stay (n.s.)	n.s.		n.d.
Fujikawa et al. [28]	1990–2005	BMI 30–42 (167) vs. BMI <30 (533)	Major vascular and biliary complicantions and length of hospital stay (n.s.)	n.d.	n.s.	
Leonard et al. [29]	1990–1994	BMI >40 (10) and BMI >35 (22) vs. lower BMI (672)	Early and late complications, length of ICU and hospital stay (n.s.)	BMI >40 (33) and BMI >35 (69) vs. lower BMI (1211) n.s.		
Conzen et al. [31]	2002–2012	BMI >40 (26) vs. BMI <18.0 (9), 18.0–24.9 (210), 25.0–29.9 (294), 30.0–35.0 (169), 35.1–40.0 (77)	Vascular and biliary complicantions, infection and length of ICU and hospital stay (n.s.)	n.s.		p < 0.009
3rd part						
Nair et al. [5]	1988–1996	BMI >40 (355) vs. BMI ≤25 (8,382), 25.1–30 (5,913), 30.1–35 (2,611), 35.1–40 (911)	n.d.	p < 0.01		BMI >35 vs. all other BMI p < 0.02
Rustgi et al. [32]	1992–2000	BMI ≥40 (738) vs. BMI 19–22 (3702)	n.d.	p < 0.05		
Hillingsø et al. [30]	1990–2003	BMI >30 (20) vs. BMI <30 (20)	n.d.	n.s.	p = 0.013	n.d.
Pelletier et al. [6]	2001–2004	BMI ≥40 (152), BMI >35 (402), BMI >30 (994), vs. BMI 20–24.9 (1,161)	n.d.	n.s.		
Wong et al. [33]	2003–2012	BMI >30 (18,815), vs. BMI 18-24.9 (38,440)	n.d.	n.d.	n.s.	

In addition to the specific postoperative complications reported in the table, Refs. [20,22,30,31] analyzed the risk for neoplasia, finding a higher risk of cancer in patient with higher BMI only in one report [8].

[a] MOF: multi organ failure.

[b] n.s.: not significant.

[c] n.d.: not determined.

[5] found a significantly lower survival at 30 days, 1 and 2 years after liver transplantation when comparing BMI ≥40 patients with the other BMI categories (normal, overweight, class I and II obesity). Interestingly, 5-year mortality was significantly higher both in the BMI 35.1–40 and >40, and in both cases this was related to cardiovascular events. Rustgi et al. [32], using data retrieved from a database including 32,515 liver transplant recipients found a significantly increased mortality risk in the BMI ≥40 category as compared to their unusual reference group (BMI 19.0–22.0). As reported by Dick et al. [22], liver transplant recipients with BMI ≥40 had a significantly lower survival rate than patients with a BMI 18.5–39.9. Conzen et al. [31], analysing the post-transplant outcomes in 785 patients, showed that patients with a BMI >40 had a significantly reduced patient survival only at 5 years after transplant, as compared with the other categories of BMI (18.0–24.9, 25.0–29.9, 30.0–35.0, 35.1–40.0).

On the other hand, 9 studies found opposite results. Braunfeld et al. [27] did not find an increase of postoperative mortality at 30 days and 1 year when 40 liver transplant recipients with a BMI >35 were compared to a cohort of 61 time-matched controls (BMI <30). Hillingsø et al. [30], using data from a medium-size European center, also did not find any significant difference in mortality between 20 liver transplant recipients with a BMI >30 and 20 liver transplant recipients with BMI <30, using a BMI calculated only after paracentesis (dry BMI). To study post-transplant patient survival Leonard et al. [29] summarized the data of two similar cohorts of patients undergoing liver transplantation in 1990–1994 and 1998–2006. The early and late post-transplant patient survival was similar across all BMI categories (561 normal and 405 overweight pts., 178 pts. grade I, 69 pts. grade II and 33 pts. grade III obesity). Pelletier et al. [6] analyzed 4488 patients and reported that early and late post-transplant mortality in liver transplant recipients with BMI 30–34.9, 35–39.9 and ≥40 (994, 402 and 152 pts. respectively) was similar to that found in 1161 patients with normal BMI (20–24.9). Schaeffer et al. [23] found no difference in early post-transplant mortality and 1-year survival when comparing liver transplant recipients with a BMI >30 (14 pts. with BMI >30 and 10 pts. with BMI >35) and 143 controls with a BMI <30. Hakeem et al. [24] also found no difference in death-censored patient survival between patients with normal BMI (646 pts.) and BMI ≥35 (73 pts.). Dare et al. [25] evaluated 202 patients who had undergone liver transplantation and did not find any difference in post-transplant survival at 30 days, 1 and 5 years in controls (BMI <30) and patients with obesity (27.6% grade I and 15.1% grade II and III obesity). Singhal et al. [26] divided 12,445 liver transplant recipients in two BMI categories (12,029 < 40 and 416 ≥ 40) and compared survival outcomes. With a median follow-up of 2 years, patient survivals were equivalent between the two groups. Finally, Wong et al. [33] reported that none of the three classes of obesity (18,937 pts.) was associated with lower post-transplant survival as compared to 18.0–24.9 BMI category (38,318 pts.). On the contrary, they found a better survival rate in patients with class I obesity as compared to patients with a BMI 18.0–24.9 [33]. This result was similar to that reported by Conzen et al. [31] when comparing patients with a BMI 25–34.9 to a reference group with a BMI 19.0–22.0. Unfortunately, in the study of Wong et al. [33], the comparison was performed between class I obesity and normal BMI (including also BMI 18–18.5), while in the study of Conzen et al. [31], overweight and class I obesity patients were compared with a reference group in the low range of normal BMI.

As discussed in the previous paragraph, in all studies a different BMI according to gender and ethnicity, and the presence of sarcopenia were not considered.

3. Evaluation of visceral obesity and sarcopenia

3.1. General aspects

Since obesity is characterized by an excessive accumulation of body fat, all methods that are able to evaluate the fat mass (FM) can be useful to recognize such a condition. The most common methods are: bioelectrical impedance analysis (BIA), dual energy X-ray absorptiometry (DXA) and anthropometry, while computed tomography (CT) and magnetic resonance imaging (MRI) are used in some specific settings. The water retention typical of the cirrhotic patient determines changes in tissue density and hydration fraction of the free fat mass (FFM). Since BIA is based on the assumption that these variables remain constant, this method is less reliable for the evaluation of the FM and FFM in this category of patients [34–37]. DXA is a good method for evaluating the FM and FFM in cirrhotic patients [37–41], offering comparable results to those obtained with more complex techniques such as the *in vivo* neutron activation analysis and D_2O dilution [37]. A comparison between anthropometry and DXA shows that the former technique is correlated with the DXA but only in cirrhotic patients without water retention [41,42]. Finally, CT and MRI are able to analyze fat and muscle distribution in the different body compartments, but their use has been limited by the cost, and in the case of CT, the exposure of the patient to a high radiation dose. However, since CT is part of the pre-transplant evaluation protocol for liver transplant recipients, it could represent the ideal method to assess both FM and FFM in this clinical setting.

3.2. Visceral adipose tissue (VAT) evaluation

The distribution of fat mass, particularly the distinction between peripheral and abdominal obesity, seems to more specifically identify the cardiometabolic risk [43]. In particular, in the context of abdominal obesity, visceral obesity is specifically associated with coronary artery disease, diabetes and metabolic syndrome [44,45]. This is due to the fact that visceral adipose tissue (VAT) is a source of hormones that influence body metabolism (adiponectin, leptin, resistin) and contains macrophages that produce more pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6. These cytokines induce insulin resistance and play a major role in the pathogenesis of endothelial dysfunction and subsequently atherosclerosis [44–46].

The "normal" amount of visceral adipose tissue varies according to ethnicity and gender, since in Caucasian subjects it is prevalent in men, among African-American subjects in women, and in Asian subjects in both sexes [44].

The identification of VAT requires imaging techniques such as computed tomography and magnetic resonance imaging. Recently, DXA has been applied not only to the study of body composition but also to the measurement of VAT [47]. The advantages of this technique are high precision, minimum X-ray exposure and rapid execution time.

3.3. Evaluation of sarcopenia

Although the prevalence of sarcopenia in patients with liver cirrhosis is estimated to be 40–70%, there is still a lack of established diagnostic criteria and consequently the absence of a standardized terminology for this specific clinical setting [20,48]. In fact, while the definition of sarcopenia in elderly patients and in case of inflammatory and oncologic diseases is well-established, based on the simultaneous assessment of muscle mass and functional muscle strength, all studies investigating the prognostic impact of sarcopenia in cirrhotic patients have been based on quantita-

tive methods (to measure muscle mass) or functional methods (to measure muscle strength) [48].

Imaging techniques represent the best methods to evaluate total muscle mass. To reduce the CT scan radiation exposure, a measurement of cross-sectional muscle area at the level of the third or fourth lumbar vertebrae is a widely accepted method since it well correlates with the total body muscle mass [49,50]. When it is adjusted for patient height, cross-sectional muscle area generates the skeletal muscle index [51,52].

An alternative method could be represented by DXA, but its inability to differentiate water from muscle, as evident in the presence of edema, can produce an overestimation of muscle mass [53], limiting the use of this technique in cirrhotics. However, given its lower cost and the low radiation exposure, DXA could be useful in monitoring sarcopenia in interventional studies or in the post liver transplant follow up. Skeletal muscle mass calculation by DXA is based on the sum of the bone-free/fat-free mass (lean mass) of the four limbs, namely appendicular skeletal muscle mass (ASM), adjusted for patient height as ASM/height^2 (kg/m^2) and defined a skeletal muscle mass index (SMI) [54]. Alternative methods to calculate cut-off points for the diagnosis of sarcopenia are more extensively discussed elsewhere [16,55].

4. Visceral adipose tissue as prognostic factor

4.1. Postoperative complications

It has been proposed that in patients undergoing general surgery, a specific measurement of VAT would be more relevant than just BMI for the evaluation of adverse postoperative events related to obesity [14,15]. However, in the liver transplant setting, only one study evaluated the predictive value of VAT on post-transplant risks focusing on the risk of diabetes development [56]. Nevertheless, it is plausible that the data concerning the predictive value of VAT on postoperative outcomes in patients with obesity undergoing general surgery might be also applicable to patients receiving a liver transplant.

In this setting, the measurement of VAT has been shown to be more predictive of cardiometabolic risk than BMI [57]. As shown in Table 2, VAT threshold values associated with an increased risk of cardio-metabolic complications ranged from 125 to 140 cm^2 (median 135) in Caucasian men, excluding the data of Carroll et al. [64] in only 13 subjects, and from 70 to 141 cm^2 in Caucasian women (median 120). Lower values have been found in Asiatic subjects (mean = 133 in men and 76 in women); whereas the data reported in the three studies analysing VAT in African-Americans were less consistent.

In particular, an increased risk of postoperative complications, operating time and hospital stay was observed only when patients were stratified by VAT and not by BMI [72–75]. In Table 3, the VAT threshold values that may be useful to identify the risk of post-operative complications are reported. In this case only 2 studies, including a small number of Caucasian patients, were reported [83,84] without a distinction of gender, while the majority of the studies were performed in Asian patients without taking into account sex-related differences, obtaining 100 cm^2 as univocal result. In all the studies that were considered, the assessment of VAT was performed using CT scan at umbilical level. Almost all studies used the multivariate regression analysis to demonstrate the role of VAT assessment as a predictor of postoperative complications using a VAT cut-off of 100 cm^2. The methods used to calculate VAT cut-off were unclear, apart from the study by Kozlow at al. [84] that used the ROC curve. The data shown in the table highlight that VAT threshold values differ according to ethnicity.

4.2. Postoperative mortality risk

There are no data concerning the predictive value of VAT on postoperative mortality in patients with obesity undergoing liver transplantation.

The prognostic value of VAT on postoperative mortality represents a rather new field of research that has been mostly evaluated in cancer patients undergoing general surgery [86–89] with conflicting results. Surgery for cancer should consider the risk of metastatic disease, chemotherapy and direct effects of the neoplasia on nutritional status and body composition, all aspects that are absent in a population with benign disease [89], thus not applicable to liver transplant recipients. The predictive value of VAT on postoperative mortality in patients undergoing liver transplantation is yet to be evaluated.

5. Sarcopenia as prognostic factor

5.1. Post-transplant complications

Sarcopenia has been demonstrated to represent a significant predictor of postoperative complications in candidates undergoing liver transplantation [90–93]. In these patients, a large majority of infections occurred within 60–90 days from transplant [90–92]. Only in one study was the number of infections evaluated in patients with similar BMI, including patients with obesity (28.0 ± 5.7 vs. 27.5 ± 6.7 BMI, $p = 0.56$) [90]. In this case the authors assessed the total psoas area by preoperative CT scans, observing a higher number of events in patients with lower vs. higher total psoas area ($p < 0.01$). In another large study, including 325 patients, Lee et al. [93] evaluated the dorsal muscle group area by CT scan (a parameter highly correlated to the total psoas area), demonstrating that this parameter was a significant predictor of 1-year sepsis, bacterial infection and other postoperative complications (OR = 0.67, $p = 0.007$). However, in this study, including also patients with BMI >30, liver transplant recipients were categorized/compared on the basis of dorsal muscle area and not on BMI. Finally, in the latter two studies, postoperative sepsis was evaluated in patients with a BMI <30, hence sarcopenia was evaluated as a single risk factor and not in combination with obesity.

5.2. Post-transplant mortality risk

Conflicting data are reported in the literature on the predictive value of sarcopenia in post-transplant mortality risk. However, only one study examined the post-transplant mortality risk in patients with similar BMI, including patients with obesity (28.0 ± 5.7 vs. 27.5 ± 6.7 $p = 0.56$), thus comparing sarcopenia in presence of obesity [90]. In this study, Krell et al. [90] demonstrated that patients developing postoperative infections had a worse 1-year survival as compared to those without infections (76% versus 92%, $p = 0.003$). The study of Masuda et al. [92] found an approximately 2-fold higher risk of post-transplant death in patients with sarcopenia vs. those without sarcopenia (HR = 2.06, P = 0.047), but they included patients with a BMI <30. Another study demonstrated that a lower dorsal muscle group area was a significant predictor of three- and five-year mortality (OR = 0.53, $p = 0.001$ and OR = 0.53, $p < 0.001$, respectively) [93]. However, even if the study also included patients with BMI >30, liver transplant recipients were categorized/compared on the basis of dorsal muscle area and not on BMI. Finally, only one study found no difference in the median postoperative survival between sarcopenic and non-sarcopenic patients ($p = 0.4$) [91], but in this case the population of transplanted patients had a BMI <30.

Table 2
Cardiometabolic risk associated to the visceral adipose tissue threshold, calculated on the basis of gender and ethnicity.

Studies (ref.)	No.	Population	End-point	Diagnostic approach	Statistical method used	Visceral adipose tissue threshold (cm^2)		
						Men	Women	Both genders
Caucasian								
Despres and Lamarche [58]	187	Canada	Diabetes risk & CV risk	CT scan	Quintiles stratification	135	128	–
Hunter et al. [59]	46	US	CV risk	CT scan & anthropometric measures	ROC curves & construction of criteria	131	–	–
Williams et al. [60]	220	US	Assessment of cardiovascular risk	CT scan, DXA	ROC curves & Risk factors analysis	–	110	–
Nicklas et al. [61]	184	US	Coronary heart disease risk	CT scan	Quintiles stratification & regression analysis	–	106	–
Onat et al. [62]	157	Turkey	Aterogenic risk factors & coronary heart disease risk	CT scan & anthropometric measures	Regression analysis	140	120	–
Von Eyben et al. [63]	46	Denmark	Metabolic syndr. risk	CT scan & anthropometric measures	ROC curves & construction of Venn diagrams	–	–	144
Carroll et al. [64]	47	US	Metabolic syndr. risk	CT scan	ANOVA & regression analysis	202	124	–
Pickhardt et al. [65]	474	US	Metabolic syndr. risk	CT scan	ROC curves & threshold analysis	125	70	–
Katzmarzyk et al. [57]	835	US	Cardiometabolic risk	CT scan	Quintiles analysis, ROC curves & Youden index	140	141	–
Asiatic								
Tanaka et al. [66]	279	Japan	Coronary Heart disease risk	CT scan	ROC curves	–	60	–
Han et al. [67]	816	Korea	CV disease risk	CT scan	ROC curves & regression analysis	100	70	–
Hyun et al. [68]	349	Korea	Metabolic syndr.	CT scan	ROC curves	–	87	–
Oka et al. [69]	1870	Japan	Metabolic syndr.	CT scan	ROC curves & Optimal cutoff identification	133	91	–
Ye et al. [70]	381	China	Diabetes	CT scan	ROC curves &Youden index	–	–	90
Misra et al. [71]	100	India	CV disease risk	MRI	Tertiles analysis & ROC curves	135	76	–
African American								
Nicklas et al. [61]	49	US	Coronary heart disease risk	CT scan	Quintiles stratification & regression analysis	–	163	–
Carroll et al. [64]	66	US	Metabolic syndrome risk	CT scan	ANOVA & regression analysis	146	102	–
Katzmarzyk et al. [57]	411	US	Cardiometabolic risk	CT scan	Quintiles analysis, ROC curves & Youden index	82	97	–

CV = cardiovascular, CT = computer tomography, MRI = magnetic resonance imaging.

Table 3
Visceral adipose tissue thresholds associated to postoperative complications.

Studies (ref.)	No.	Country	End-point	Diagnostic approach	Statistical method used	Visceral adipose tissue threshold (cm^2)		
						Men	Women	Both genders
Asiatic								
Tsukada et al. [73]	139	Japan	Complication risk in gastric and colorectal resection	CT scan at umbilicus	Uni/Multi-variate logistic regression analysis	160	120	
Ishii et al. [74]	46	Japan	Complication risk in laparoscopic rectal cancer	CT scan at umbilicus or 3rd-4th lumbar body	Mann–Whitney, X2, logistic regression analysis			100
Tsujinaka et al. [75]	133							130
Makino et al. [76]	100	Japan	Complication risk in open gastrectomy	CT scan at umbilicus	X2, *t*-test, logistic regressions			100
Sakai et al. [77]	79	Japan	Complication risk after colorectal resection	CT scan	Univariate analysis			100
Ueda et al. [78]	30	Japan	Complication risk in laparoscopic gastrectomy	CT scan	Univariate analysis			100
Hagiwara et al. [79]	121	Japan	Complication risk in laparoscopic nephrectomy	CT scan at umbelicus	Univariate and Multivariate analysis			100
Park et al. [80]	181	Korea	Complication risk in pancreatic resection	CT scan	Univariate and Multivariate analysis			100
Watanabe et al. [81]	338	Japan	Complication risk in laparoscopic colon surgery	CT scan	Logistic regression analysis			100
Yuge et al. [82]	167	Japan	Complication risk in laparoscopic nephrectomy	CT scan	Multivariate analysis			100
Caucasian								
Tranchart et al. [83]	103	France	Complication risk after pancreaticoduodenectomy	CT scan	Multivariate analysis			84
Kozlow et al. [84]	34	US	Complication risk after sternal reconstru-ction	CT scan at T9-through T12 levels	Univariate and multivariate logistic regression analysis, ROC curve			125
Aquina et al. [85]	103	US	Incision ernia risk after open or laparoscopic surgery	CT scanatumbelicus	Univariate analysis & Cox regression analysis	2250[a]	1560[a]	

[a]Values are expressed as cm^3.

None of the above mentioned studies reported a cut off value to identify sarcopenia in subjects with a BMI ≥30, and the only values reported in the literature on sarcopenia in presence of obesity have been described in a cohort of 250 patients with solid tumors (L3 skeletal muscle index: ≤38.5 cm^2/m^2 for women and ≤52.4 cm^2/m^2 for men) [94].

6. Discussion

The continuous increase in the prevalence of obesity in USA and Europe, involving 35.3% and 28–30% of the population, respectively [95,96] points out the importance of this issue and its relevant consequences in the field of transplantation.

It has been reported that liver transplantation provides a survival benefit to patients with end-stage liver disease regardless of BMI class [6,97]. However, both the British Transplant Society [98] as well as the more recent guidelines from the American Association for the Study of Liver Disease (AASLD) and the American Society of Transplantation considers morbid obesity (BMI ≥40) as a relative contraindication for liver transplantation [4]. In addition, current practice seems to indicate that surgeons are reluctant to transplant patients with a BMI ≥35 and morbidly obese patients appear to be relatively disadvantaged in their access to LT [99,100].

Until now, evaluations of postoperative complications and short- and long-term post-transplant survival in patients with a condition of obesity classified by BMI have generated conflicting results. Some authors have attributed the lack of consistent results to the amount of ascites/peripheral edema that has not been taken into account when calculating BMI [29,30,97], or to the misleading extrapolation of the results obtained in liver transplant recipients with obesity to all potential candidates with obesity [97].

Our review of the literature suggests that such a discrepancy could be due to several other factors: 1) gender and ethnicity were not taken in account; 2) different values of BMI were used to define "obesity" (BMI = 30 or 35 or 40 for both genders or >32.3 in women and >31.1 in men); 3) different BMI ranges were used to select the control population (BMI <30 including or not BMI <18.5, BMI 18.5–34.9 and 18.5–39.9, BMI ≤32.3 in women and ≤31.1 in men); 4) different outcomes were considered as postoperative complications; 5) period of liver transplant taken into consideration (older studies burdened by less surgical experience and knowledge on the use of immunosuppressive drugs, have a tendency to find worst outcomes); 6) an elevated BMI is often associated with comorbidities such as type 2 diabetes and other confounding factors (metabolic syndrome, cardiovascular risk, cancer risk, etc.) that are known to affect *per se* outcomes [25]. However, for theoretical reasons, a revision of the literature is based on raw data (a comparison among different studies would require an adjustment for the same parameters) and this represent a limitation shared by all systematic meta-analytic studies.

Moreover, two aspects were never considered in these studies on liver transplant recipients with obesity: the value of VAT and the prevalence of sarcopenia, although the latter condition has been observed in 56% of liver transplant candidates with a BMI >30 [99]. In particular, VAT was never evaluated as prognostic factor for postoperative complications and mortality in the setting of liver transplant patients. As far as the negative predictive value of sarcopenia in the setting of liver transplant patients is concerned, it was considered only as a single parameter whereas sarcopenic obesity, *i.e.* the coexistence of a BMI >30 associated to sarcopenia was never evaluated as a specific condition influencing postoperative outcomes. In our opinion, it is plausible that the data concerning the predictive value of VAT and sarcopenia on postoperative outcome in patients with obesity undergoing general surgery might also be applicable to liver transplant recipients.

Finally, the evaluation of post-transplant outcome is further complicated by additional peculiarities such as donor factors, donor-recipient match factors, and use of immunosuppressive drugs [101–104]. As a matter of fact, while earlier meta-analysis on post-transplant mortality risk conclude by stating that BMI does not specifically impact patient survival [105], our recent meta-analysis based on a larger number of studies support a higher risk of post-transplant mortality for patients with a BMI ≥40 at 30 days, 1 and 2 years after transplantation [106].

6.1. Research gaps and future directions

On the basis of the studies analyzed in the present review, it is evident that a research gap exists between transplantation surgery and other surgical settings as far as the identification of risk factors related to obesity. A possible new scenario for the preoperative evaluation of liver transplant candidates is suggested, by introducing the evaluation of VAT and muscle mass for the assessment of postoperative risks. In this case, obesity should be assessed using the same VAT cut-off associated with an increased risk of cardiometabolic and postoperative complications in the general surgery, and muscle mass should complete the assessment using the CT-scan evaluation with appropriate cut-off values.

6.2. Conclusions

Numerous factors could have accounted for misleading conclusions regarding postoperative complication and mortality risk in liver transplant recipients classified as obese by BMI. Since the simple BMI is not able to determine VAT and sarcopenia, of which both could influence postoperative outcomes, it is suggested that BMI should be used as a preliminary method to identify the condition of obesity. Successively, the assessment of VAT and sarcopenia should complete the pre-transplant evaluation. This new approach would be easy to perform and implement without additional costs or stress for the patients since CT scan is part of the standardized preoperative protocol.

Conflict of interest

None declared.

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