REVIEW ARTICLE



The Role of Bariatric Surgery in Abdominal Organ Transplantation—the Next Big Challenge?

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Abstract Obesity is linked to inferior transplant outcome. Bariatric surgery (BS) is an established treatment of morbid obesity. We provide an overview on BS in the field of kidney (KT) and liver transplantation (LT). In end-stage renal disease (ESRD) and KT patients, BS seems safe and feasible. Complication rates were slightly higher compared to the non-transplant population, whereas weight loss and improvement of comorbidities were comparable. Sleeve gastrectomy (SG) was the preferred procedure before KT and superior to gastric bypass (GB) in regard to mortality and morbidity. If conducted after KT, both procedures showed comparable results. BS before LT was associated with high complication rates, in particular after GB. Albeit distinct complications, SG conducted after LT showed the best results. Immunosuppression (IS) changes after BS were rare.

Keywords Obesity · Organ transplantation · Kidney transplantation · Liver transplantation · Bariatric surgery

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Introduction

Obesity is becoming a major challenge in developed countries and is likewise affecting the population of patients either awaiting or recipients of an organ transplantation (OT). In 2014, Ogden et al. reported 35% of the adult US population as obese, defined by a body mass index (BMI) \geq 30 kg/m² [1]. At the same time, the prevalence of obesity in KT recipients amounted 23% [2]. Obesity is associated with a multitude of concomitant health problems, such as metabolic syndrome and cardiovascular diseases (CVDs), therefore impairing transplant outcome [3, 4].

Obesity and metabolic syndrome manifest as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in the liver [5]. Rates of end-stage liver disease (ESLD) caused by NAFLD and NASH are increasing in developed countries [5, 6]. Further, recent data suggest a deep interaction between adipose tissue and the immune system [7].

Materials and Methods

We conducted a systematic review of PubMed, Embase, and Cochrane Library databases by using combinations of following search terms: "kidney transplantation," "liver transplantation," "obesity," "obesity surgery," "bariatric surgery," "gastric bypass," "sleeve gastrectomy," and "gastric banding." All original full-text studies submitted in English reporting BS in adults were included. Proof-of-concept publications and studies missing follow-up data were excluded.

Impact of Obesity on Immunological Function After Transplantation

Obesity as a chronic proinflammatory disease is very likely to alter the immune response after OT. The majority of studies underlined an increased incidence of acute rejection in high BMI patients, while an extensive review by Nicoletto et al. did not find a correlation between obesity and acute rejection rates [3, 8]. Interestingly, studies by Meier-Kriesche et al. and Chang et al. showed that the major cause for graft failure in obese patients was chronic rejection, implying an ongoing immunological activation beyond the short-term risk of acute rejection [9, 10]. None of the available studies did examine the potential of BS to decrease proinflammatory state and its consequences on alloimmune activation, cardiovascular status, or concomitant diseases after OT.

Effects of Obesity on Kidney Transplantation Outcome

Obesity-associated effects, such as glomerular hyperfiltration, proteinuria, and metabolic syndrome, play important roles in the development of ESRD. Albeit KT being associated with a survival advantage compared to dialysis patients, the benefits of KT in obese patients are subject to controversial discussion [11]. Increased rates of delayed graft function (DGF), primary non-function (PNF), and inferior graft outcomes are reported in morbidly obese KT recipients [12, 13]. Data suggest that a BMI of >36 kg/m² is associated with DGF rates up to 51%, while a BMI >40 kg/m² increases the odds of DGF threefold [8, 14]. Furthermore, a BMI of \geq 35 kg/m² was reported to significantly increase graft failure rates [11]. The effects of obesity on mortality in the setting of KT are less pronounced [4, 15]. Nevertheless, obesity remains an independent risk factor for death caused by CVD in KT recipients [16]. Additionally, an increase in surgical site infections (SSIs) from 8.5% in non-obese to 40% in morbidly obese KT recipients was reported [17]. As a consequence, many transplant centers tend to restrict access to the KT waiting list by establishing BMI-linked thresholds (range $35-45 \text{ kg/m}^2$). Considering the poor outcome of KT in morbidly obese patients, existing guidelines recommend a supervised weight loss regimen, targeting a BMI of less than 30 kg/m² prior to KT [18, 19]. In reality, the majority of patients gain weight on dialysis and the recommended weight goals are rarely achieved [20]. Furthermore, weight gain after KT is a pronounced side effect of most IS regimes, and was shown to propagate pre-existing metabolic malconditions and negatively affects graft and patient survival [21].

Effect of Obesity on Liver Transplantation Outcome

The prevalence of NAFLD has doubled in the last 20 years, while incidences of other chronic liver diseases have remained stable or decreased (e.g., hepatitis C) [22, 23]. The progression of NAFLD to NASH dramatically increases the risks of cirrhosis, liver failure, and hepatocellular carcinoma (HCC) [47]. In LT, obesity and concomitant diseases are associated with increased perioperative morbidity and SSIs, resulting in

higher resource utilization [24, 25]. However, data on the outcome of LT in obese patients is heterogeneous [26–29]. Older long-term series report an increased likelihood of death due to CVD in LT recipients with a BMI >35 kg/m² [28, 30], whereas in more recent mid- and short-term studies, these effects are less pronounced or non-existent [31, 32].

After transplantation, the impact of obesity on graft survival is still a matter of discussion. Singhal et al. recently observed comparable patient and graft survival rates of obese vs non-obese LT recipients, even though morbidly obese patients were sicker at time of LT [33]. However, obesity was observed to play a major role in recurrence of NAFLD and NASH in LT recipients with an increase of the risk of HCC after LT twofold higher than in non-obese LT recipients [34–36].

Bariatric Surgery and Kidney Transplantation

Bariatric Surgery in ESRD and Kidney Waiting List Patients Regarding BS prior to KT, eight retrospective studies were identified including 154 patients (102 SGs, 42 GBs, four adjustable gastric bandings [AGB], and six other procedures). Half of the retrieved studies (n = 4) were case reports/series, while the others were single-center series, reporting between 21 and 52 patients (Table 1). Seven authors reported a followup up to 12 months or longer. Weight loss was observed in all reported series (EWL range 21-68%). In these series, GB was the most effective procedure (EWL 64.3 vs 48.9% after SG), and AGB showed the least weight loss (EWL $35.3 \pm 3.5\%$). Three authors reported a total of eight complications (5.1%)[37-39]. Six major complications, including anastomotic leakage, strictures, and ulcers, occurred in GB patients (12%). One major (reversible organ insufficiency) and one minor complication (2%) were observed after SG. Overall mortality was 4.2% in GB patients and 3.9% in SG patients. Improvement of comorbid conditions like diabetes, hypertension, and renal function were reported by three authors [37, 40, 41]. Two studies reported adequate post-transplant kidney function in 42 of the 154 patients after BS [38, 42, 43]. One group from Innsbruck recently reported prospective data on SG in eight patients before KT. No surgical complications occurred and seven patients (87.5%) underwent KT after the procedure [44].

In conclusion, BS appears safe in the reported patient series and provided good weight loss before KT. GB was associated with a slightly higher mortality and distinct higher morbidity (12 vs 2%) compared to SG.

Bariatric Surgery After Kidney Transplantation Seven studies focused on BS after KT, including a total of 119 patients (88 GBs, 15 SGs, and 16 other procedures; Table 1). All but one study were small case series. The largest cohort up to date was published in 2009 [45] with GB performed in 70

| And the second of th | | Author | Year | Type | Surgery type | No. of natients | Follow-up | Percent of FWI | Improvement of comorbidities | Morbidity | Mortality | | | Graft survival | Graft function |
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| AGB adjustable gastric banding, EWL excess weight loss, DGF delayed graft function, GB gastric bypass, KT kidney transplantation, $n.R$. not reported, SG sleeve gastrectomy, SSI surgical site infection Patients proceeded to transplantation Mean (\pm SD) |) | Total | 0004 | | 3 | 119 | 11 | 2 | 2011 | 3 major (2.5%), 1 minor (0.8%) | 5 | 5 | arrest) arrest) 1 early (0.8%), 2 late (1.7%) | R | |
| | Pat Me | 3 adjustable gastric ients proceeded to :an (±SD) | banding transpla | <i>, EWL</i> excent | ss weight loss, <i>l</i> | DGF delay | ed graft funct | ion, GB gast | ic bypass, <i>KT</i> kidı | rey transplantation. | , <i>n.R.</i> not rel | ported, SG sl | eeve gastrectomy, SSI | surgical si | te infection |

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patients. The percent of EWL ranged from 31 to 61%. Thirtyday mortality was equal to patients on the waiting list with 3.5%. Overall, the %EWL in studies referring to BS after ranged from 30 to 87%, with SG showing the best weight loss and AGB being the least effective. All authors reported follow-up data up to 12 months or longer. Three major complications (2.5%) were reported [45-47]. Two patients needed a reoperation after SG (13.3%) and one acute reversible rejection (1.1%) occurred after GB. No mortality was observed after SG, whereas three patients died within 1 year after GB (3.3%) [40, 45]. Four authors observed improvement of comorbidities [46–49]. Furthermore, three out of four studies containing 20 patients observed improvement in graft function [46, 47, 49, 50]. One kidney graft loss after GB was reported [48]. After BS, no or only minor modifications in IS dosages were reported which were independent of the procedure [47, 50].

In summary, GB and SG showed comparable results with low mortality and complication rates.

Bariatric Surgery and Liver Transplantation

Bariatric Surgery Prior to or Simultaneously with Liver Transplantation Three publications with a total of 29 patients reported BS prior to LT, including one single-center series with 20 patients (Table 2). Sufficient weight loss was observed by all authors (EWL range 40-66%). Two studies reported follow-up data up to 2 years. The major complication rate after SG was 17.9%, including two bleedings, one leakage, and one liver insufficiency [37, 51]. Three patients died within 1 year after SG [37]. Improvements of obesity-associated comorbidities were observed in all patients after SG. Regarding GB prior to LT, only one case report was identified. The patient with a BMI of 50.9 kg/ m² underwent GB followed by LT due to cirrhosis [52]. Post-operative bleeding, requiring a reoperation, and renal failure requiring renal replacement therapy were documented. One year after LT, a stable graft and renal function and remission of DM were observed.

Three groups reported BS simultaneously with LT in 11 patients. Weight loss was satisfactory (EWL 28–45%). One group placed an AGB during LT and observed amelioration of hypertension and DM [53]. A similar approach with SG in seven patients with a mean MELD score of 32 at LT reported three early complications (42.9%), including one leakage from the gastric staple line causing severe early graft dysfunction [54]. Recently, another group presented similar results with good amelioration of concomitant diseases. However, two complications needed treatment (one biliary leakage and one transient kidney failure) [55]. No mortality and no metabolic complications were observed.

The available data suggest that BS prior to LT is associated with high morbidity and mortality.

Bariatric Surgery After Liver Transplantation Concerning BS after LT, six single-center reports including 25 patients were identified (15 SGs, 10 GBs) (Table 2). Weight loss was observed in all reported series (EWL range 21-75%). The highest weight loss was achieved in patients after SG (EWL 54.9 vs 37.9% after GB). Long-term follow-up was reported by one study containing seven patients after GB. Overall, a high complication rate (40%) was documented with substantial major complications (20%). Following SG, major complications (26.7%) included one bile leakage, one early reoperation due to dysphagia, and one bleeding [46, 56], whereas after GB, major complications occurred in 10% [57, 58]. No mortality was observed after SG, while two patients died within 1 year after GB (septic shock, esophageal carcinoma; 20%) [58]. All authors reported improvement of obesity-related comorbidities. Stable graft functions and unaltered IS regimes were observed. Two series reported improvement of graft function after GB (i.e., biopsy-proven regression of steatosis) [57, 58].

In summary, only case series were available. Complications occurred more often after SG, while mortality was higher after GB. Immunosuppression regimen was reported to be unaffected of the BS procedure.

Discussion

Only few data are available on surgical treatment of morbid obesity in the setting of OT. However, an increasing clinical interest is reflected by a growing number of publications on this subject. While 503 publications dealt with this topic between 2000 and 2010, the number of original publications and reviews has more than doubled within the last 5 years [59, 60].

In the field of KT, available data suggest that BS is a reasonable, feasible, and safe option in the treatment of morbidly obese ESRD patients and KT recipients, regardless of the timing related to the OT. Aside from the less effective AGB, all surveys demonstrated weight loss comparable to the non-transplant population [61, 62]. Unfortunately, medium- and long-term follow-ups were only reported by five studies. In contrast to KT waiting list patients (SG), GB was the preferred procedure after KT (79%). This may be explained by a better health condition of KT patients compared to the waiting list population and the willingness of surgeons of performing a more complex procedure in a stable patient setting. Patients undergoing GB showed markedly lower major complication rates after than before KT (1.1 vs 12%). The post-KT complication rates were comparable to a non-transplant population [63]. Albeit the reported overall 30-day mortality was low (0.8%), the 1-year mortality of BS of 3.9% before KT and 2.5%

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| | | | | score | iype | patients | up (montns) | 01 E W L | or comorbidities | | <30 days | <90 days | Overall at 1 year | survival (%) | IUNCHON |
| _ | Lin et al. | 2013 | Before LT | Π | SG | 20 6 ^a | 24 ^b | 66% | + | 5 (25%) early (2 SSIs, 1 organ insufficiency, | 0 | 0 | 3 (15%) | 85 | Stable |
| 7 | Takata et al. | 2008 | Before LT | n.R. | SG | × | 11.4 ^b | 40% | ‡ | 1 bleeding, 1 leakage) 2 (25%) early (cirrhotic patients: 1 bleeding, 1 heavie | 0 | 0 | 0 | 100 | n.R. |
| ŝ | Marszalek et al. | 2015 | Before LT | n.R. | GB | 1 1 ^a | >24 | 50% | n.R. | I nepauc encephalopathy) I (100%) early (bleeding, revision, | 0 | 0 | 0 | 100 | Stable |
| Total | | | | | | $29 7^{a}$ | | | | renal failure) $6 (20.7\%)$ major, $2 \frac{3}{2} \frac{1}{2} $ | | | 3 (10.3%) late | | |
| 4 | Campsen et al. | 2008 | With LT | n.R. | AGB | 1 | 9 | 45% | + | 2 IIIII0T (0.9%) | n.R. | n.R. | n.R. | 100 | Stable |
| 5 | Heimbach et al. | 2013 | With LT | 32 | SG | 7 | 17 ^b | 33% | n.R. | 3 (43%) early | 0 | 0 | 0 | 100 | Stable |
| 9 | Nesher et al. | 2017 | With LT | 24 | SG | ŝ | 13 | 27.9% | ++ | (1 leakage + revision, 1 bleeding, 1 rejection) 2 (67%) early (1 | 0 | 0 | 0 | 100 | Stable |
| | | | | | | | | | | biliary leakage + transient acute kidnev failure) | | | | | |
| Total | | | | | | 11 | | | | 5 (45.5%) early | | | 0 | | |
| 7 | Duchini et al. | 2001 | After LT | I | GB | 2 | 27 | 35.3% | + | 1 (50%) mild dumping | 0 | 0 | 0 | 100 | Improved |
| ~ | Lin et al. | 2013 | After LT | I | SG | 6 | 6 ^b | 56% | ++ | 3 (33.3%) early revisions (1 hernia, 1 bile leakage, 1 | 0 | 0 | 0 | 100 | Stable |
| 6 | Al-Nowaylati et al. | 2013 | After LT | I | GB | 7 | 59 ^b | 41% | + | 5 (71.4%) late (1 reversal, 2 SSIs, 2 herniae) | 0 | 0 | 2 (28.6%) (1 septic shock, 1 econhageal (A) | 74 | Improved |
| 10 | Pajecki et al. | 2014 | After LT | I | SG | 1 | 5 | 75% | ‡ | 0 | 0 | 0 | 0 | 100 | Stable |
| 11 | Tichansky et al. | 2015 | After LT | I | GB | 1 | 4 | 21% | + | 0 | 0 | 0 | 0 | 0 | n.R. |
| 12 Total | Khoraki et al. | 2015 | Post-Tx | I | SG | 5 25 | 18 ^b | 48% | ++ | 1 (25%) early (bleeding) 5 (20%) major, 5 (20%) minor | 0 | 0 | 0 2 (8%) late | 100 | Stable |

 Table 2
 Summary of bariatric surgeries performed in liver transplant recipients

^a Patients proceeded to transplantation

^b Mean

after KT was above the rates of the non-transplant setting (<1%) [64, 65]. In contrast, average 1-year mortality on the waiting list is 7% and falls to 3% after KT [11, 66]. After KT, the association between obesity and mortality is unclear; however, most authors report no apparent association [67]. Hence, taking into account the impaired health condition of the ESRD and KT patients, the reported rates seem acceptable. Nonetheless, two deaths in ESRD patients were directly BS-related and a total of five out of nine deaths were caused by cardiovascular events. In the general population, the long-term Swedish Obese Subjects trial reported a 33% reduction in cardiovascular events by BS, compared to patients without surgery [62]. Therefore, given the substantial time on the waiting list, the longterm effects of weight loss prior to KT may positively influence perioperative surgical and CVD risk profiles in these patients. Additionally, improvements of obesity-related comorbidities before and after KT were observed [46, 47, 49].

Regarding the timing, data suggest that BS is safest when conducted after KT. However, certain patients seem to benefit from an early access to BS before KT and it has been shown that complication rates of BS prior to KT are acceptable and BS does help to meet weight-based waiting list thresholds. Especially the recent prospective publication by Kienzl-Wagner and colleagues showed that SG can be performed with low complication rates before KT. In this publication, seven out of eight patients reached KT criteria and were transplanted successfully with good organ function in the follow-up period. Thus, the application of BS before KT may be justified. Here, SG may be the procedure of choice, being a shorter and less traumatic procedure with mid-term weight loss comparable to GB (Fig. 1).

Only few data on the effects of BS in the setting of LT were available and most of the publications were case reports. In contrast to ESRD and KT patients, the benefits of BS in the setting of LT seem less clear. Regardless of the procedure and strategy, all patients showed a sustainable weight reduction. Despite amelioration of comorbidities, substantial effects on graft function and posttransplant survival have not been reported so far. Most surgeons preferred SG in favor of GB due a shorter operative time and lower technical complexity, and the preservation of the access to the biliary tree, together with presumed unclear effects of GB on IS absorption. Hereby, only one patient received a GB ahead of LT, whereas 28 received a SG. The overall major complication rate of 27.6% was distinctly higher than in the general population. Three authors performed SG simultaneously with LT to reduce trauma. However, the procedures were associated with unfavorable complications and prolonged hospital stay, albeit no deaths were reported. Consequently, this concept should be seen critically.

In BS applied after LT, major adverse events, requiring reoperations or further interventions, were lower than before LT. No mortality was observed after SG, whereas two patients died within 1 year after GB (26%). Despite the low patient numbers and high complication rates, the results imply a slight trend in favor for SG. Nevertheless, due to short observation periods, long-term effects and late complications have not been analyzed, and thus, the role of this technique remains unclear.

Regarding GB, the situation in ESLD patients is further more difficult. While a potential liver transplantation is burdened by high complication rates, recent series however did not find an increase of perioperative mortality in morbidly adipose patients [32]. Any surgery under general anesthesia except of the liver transplant itself has a considerable risk of death in patients with decompensated cirrhosis, ranging from 8.3 to 25% [68]. Consequently, advanced liver diseases with the presence of portal hypertension are usually considered as contraindications for any elective surgery [69].

Therefore, any BS needs to be carefully balanced against its risks in liver cirrhosis patients. The few reports of concomitant BS at the time of transplantation showed high complication rates, and given the increasing paucity of good liver grafts with a therefore high potential of initial poor organ function, such a combined procedure cannot be recommended.

After successful liver transplantation, obese patients have a high potential to further gain weight. The very limited international experience with BS after LT shows good weight control after such a procedure. However, several concerns regarding especially GB after LT need to be considered. First, the GB excludes the possibility for easy retrograde access to the biliary system in a patient cohort, which eventually requires such an intervention in about 30% of all cases after LT [70]. Further, concerns have been raised regarding the kinetic of the enteral absorption of the immunosuppression after a malabsorptive procedure. Unlike this assumption, no relevant effects on IS uptake were observed and most reports refuted this strong argument [58]. Further, the extent of dissection after liver transplantation required for GB results is a higher surgical risk for the LT patients compared to a SG, which however does not seem to translate in higher complication rates in the reported selected patient cohorts.

Considering the available literature, we suggest that BS should be recommended only after exhaustion of all conservative therapies and recovery from LT. If performed in these patients, SG should be favored (Fig. 1).

At least, the perception of BS in the transplant community is changing. Albeit still being a maverick, BS is more often performed as most transplant centers are confronted

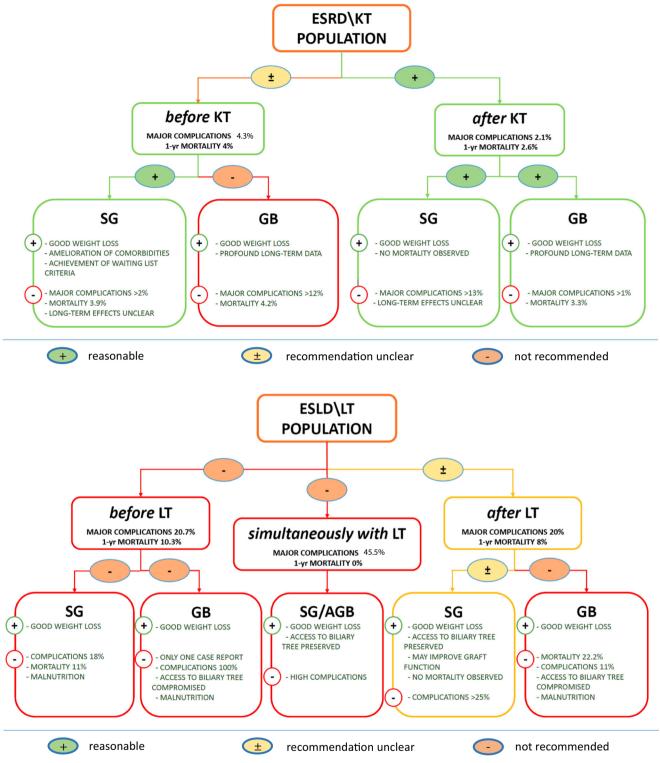


Fig. 1 Suggestions for bariatric surgery in organ transplantation

with the complex situations of morbidly obese patients. However, the variety of approaches and lack of prospective data reflect the current disunity in the transplant community and the lack of treatment guidelines in this growing complex inhomogeneous cohort. Since BS has been proven well effective in the nontransplant population, it is likely to have similar benefits in OT patients (Table 3).

Table 3 Highlights

- Obesity is strongly associated with inferior patient and graft survival after OT
- · Bariatric surgery is effective and safe in selected patients
- In the setting of KT, bariatric surgery is feasible showing good weight loss and may be applied
 - After KT, SG and GB seem safe
- In ESRD patients, to reach waiting list criteria, SG should be favored
- In LT, bariatric surgery is feasible with distinct morbidity and mortality
 - Bariatric surgery is notably safer after LT
 - GB is associated with high complication rates
 - SG seems to be the procedure of choice

Limitations

The main limitations of the study are the small sample sizes of the reported cohorts and the modest number of prospective data. All original full-text studies published in English reporting BS in adult abdominal transplantation were initially included. However, to achieve comparability throughout the manuscript, we had to exclude proof of concept publications, case studies, and studies missing follow-up data. Thus, not all publications dealing with the topic were discussed. We also excluded journals that publish primarily in a language other than English, especially if only an abstract was available. Further many manuscripts varied widely in methodology and homogeneity of the cohorts, which made a sound comparability difficult. However, we tried to pick out the most valid ones to make our conclusions comprehensive.

BMI body mass index, BS bariatric surgery, CKD chronic kidney disease, CNI calcineurin inhibitor, CsA cyclosporine A, CVD cardiovascular disease, DGF delayed graft function, DM diabetes mellitus, eGFR estimated glomerular filtration rate, ESLD end-stage liver disease, ESRD end-stage renal disease, GERD gastroesophageal reflux disease, GS gastric sleeve, HCC hepatocellular carcinoma, IDDM insulin-dependent diabetes mellitus, IS immunosuppression, LAGB laparoscopic gastric banding, LGB laparoscopic gastric bypass, LSG laparoscopic sleeve gastrectomy, MELD model for end-stage liver disease, NAFTLD non-alcoholic fatty liver disease, NASH nonalcoholic steatohepatitis, OT organ transplantation, SSI surgical site infection, WHO World Health Organization

Compliance with Ethical Standards

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Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval Statement For this type of study, formal consent is not required.

Informed Consent Statement Does not apply.

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