Original Article

Obesity and its influence on liver dysfunction, morbidity and mortality after liver resection

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Background: Obesity and associated steatosis is an increasing health problem worldwide. Its influence on post-hepatectomy liver failure (PHLF) and after liver resection (LR) is still unclear.

Methods: Patients who underwent LR were investigated and divided into three groups [normal weight: body mass index (BMI) 18.5–24.9 kg/m^2, overweight: BMI 25.0–29.9 kg/m^2, obese: BMI ≥30 kg/m^2] in this retrospective study. Primary aim of this study was to assess the influence of BMI and nonalcoholic steatohepatitis (NASH) on PHLF and morbidity.

Results: Of 888 included patients, 361 (40.7%) had normal weight, 360 (40.5%) were overweight, 167 (18.8%) were obese. Median age was 62.5 years (IQR, 54–69 years). The primary indication for LR was colorectal liver metastases (CLM) (n=366, 41.2%). NASH was present in 58 (16.1%) of normal weight, 84 (23.3%) of overweight and 69 (41.3%) of obese patients (P<0.001). PHLF occurred in 16.3% in normal weight, 15.3% in overweight and 11.4% in obese patients (P=0.32). NASH was not associated with PHLF. There was no association between patients' weight and the occurrence of postoperative complications (P=0.45). At multivariable analysis, solely major LR [odds ratio (OR): 2.7, 95% confidence interval (CI): 1.83–4.04; P<0.001] remained a significant predictor for PHLF.

Conclusions: Postoperative complications and PHLF are comparable in normal weight, overweight and obese patients and LRs using modern techniques can be safely performed in these patients.

Keywords: Obesity; liver resection (LR); post-hepatectomy liver failure (PHLF); morbidity

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Introduction

The rates of obese and morbidly obese patients are increasing worldwide (1). Obesity is associated with hyperlipidemia, arterial hypertension and diabetes, thus representing a significant risk factor for an increased all-cause mortality (2). In liver surgery, morbidly obese patients have been found to be at higher risk for a dismal outcome including surgical-site infections and major complications (3).

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Obesity was identified as one of the main causes of hepatic steatosis, which has become the most common chronic liver disease in the Western world (4). In line with that, the global prevalence of nonalcoholic fatty liver disease (NAFLD) is 25% with the highest prevalence in the Middle East and South America and the lowest in Africa (5). The presence of NAFLD is associated with an increased risk for developing liver-related complications and hepatocellular cancer (6).

In liver surgery, post-hepatectomy liver failure (PHLF) remains a major cause of mortality (7). Its rate ranges between 0% to 43.1%, depending on its definition (8). There is experimental and clinical data showing that hepatic regeneration is impaired in steatotic livers (9-11). However, the influence of obesity and NASH on PHLF and morbidity is unclear (3,12-14). This study investigated postoperative outcomes after liver resection (LR) in a large cohort of patients. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-291/rc).

Methods

This was a retrospective single-center study approved by the institutional review board of the Medical University of Vienna (IRB number: 1368/2021) and performed in accordance with the principles of the Declaration of Helsinki (as revised in 2013). Informed consent has not been achieved due to the retrospective character and anonymous data collection.

Consecutive patients ≥18 years who underwent elective LR at the Medical University of Vienna between December 2004 and May 2017 were included in this study. Relevant data was collected from the in-hospital database registry.

Patients divided into three BMI groups according to the World Health Organization definition of obesity (normal weight: BMI 18.5–24.9 kg/m^2, overweight: BMI 25.0–29.9 kg/m^2, obese: BMI ≥30 kg/m^2) (15). LRs were classified as minor (<3 liver segments) and major (≥3 liver segments) (16).

All patients were further divided into "healthy" without comorbidities and "unhealthy" with comorbidities, such as diabetes, arterial hypertension, coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD) (17).

To evaluate preoperative liver function, indocyanine green (ICG) clearance was used. ICG clearance testing [plasma disappearance rate (PDR) and ICG retention rate at 15 minutes (R15)] was performed on the day of administration. Patients received 0.25 mg/kg ICG intravenously. PDR and R15 were measured by pulse spectrometry.

Statistical analysis

SPSS® version 26.0 software (IBM Inc., Armonk, NY, USA) was used for statistical analyses. Figures were created with GraphPad Prism 9 (Graph Pad Software Inc., La Jolla, CA, USA) and with BioRender.com.

Normally distributed values were expressed as mean ± standard deviation (SD) or otherwise as median with interquartile range (IQR). Comparative analyses were performed by Kruskal-Wallis test or analysis of variance (ANOVA), as appropriate. Significant P values by the Kruskal-Wallis test were checked pairwise for significance by Mann Whitney *U*, according to the closed testing principle. To assess risk stratification for obesity, multivariable analysis using logistic regression was performed to determine unadjusted and risk-adjusted complication and mortality rates. A P value <0.05 was considered statistically significant.

For power analysis, a logistic regression for one normal covariate was conducted with nQuery (nQuery Sample Size Software, Graph Pad Software DBA Statistical Solutions, San Diego CA 92108), according to our historically PHLF rate of 15%. When sample size is 883, the logistic regression test of $\beta=0$ ($\alpha=0.05$ two-sided) will have 90% power to detect a β of 0.323 [an odds ratio (OR) of 1.381].

Endpoints

The primary study endpoint was PHLF as defined by the International Study Group of Liver Surgery (ISGLS) classification (abnormal bilirubin levels and prothrombin

Highlight box

Key findings
- No association of BMI or NASH with PHLF.
- No association of BMI and surgical complications.
- Major liver resection is a significant predictor for PHLF.

What is known and what is new?
- Obesity and associated steatosis are an increasing health problem worldwide.
- The influence of obesity on PHLF and liver resection is still unclear.

What is the implication and what should change now?
- Liver resections can safely be performed in obese patients.

time on or after postoperative day 5) (18).

The secondary endpoints were morbidity and mortality according to the Clavien-Dindo Classification (19) and grade of fibrosis and steatosis according to the nonalcoholic steatohepatitis (NASH) Clinical Research Network (CRN) scoring system (20). Specimens were rendered according to the scoring system into “no steatosis” (0 points), “not-NASH” (1–2 points), “borderline NASH” (3–4 points) or “NASH” (≥5 points). Fibrosis grading according to the NASH CRN was based on a 4-staged system. Stage 1 is perisinusoidal/periportal fibrosis. Stage 2 is stage 1 with additional portal/periportal fibrosis, stage 3 is bridging fibrosis and stage 4 is cirrhosis.

Results

The database consisted of 1,052 patients. Twenty-one patients with a BMI <18.5 kg/m^2 and 143 patients with singular atypical resections were excluded. A total of 888 patients were finally included in the study.

Patient characteristics

Median age was 62.5 years (IQR, 54–69 years). The main indications for LR were colorectal liver metastases (CLM) (n=366; 41.2%), cholangiocarcinoma (n=158; 17.8%) and hepatocellular carcinoma (HCC) (n=137; 15.4%). Median BMI was 26 (IQR, 23–29) kg/m^2. Normal body weight was found in 361 (40.7%) patients, 360 were overweight (40.5%) and 167 were obese (18.8%). According to the WHO subdivision of obesity, 126 patients could be classified for obese class I (BMI: 30–34.9 kg/m^2), 31 patients obese class II (BMI: 35–39.9 kg/m^2) and 10 patients obese class III (BMI: ≥40 kg/m^2). Patient characteristics, surgical indications and procedures are reported in *Table 1*. Overweight and obese patients were predominantly male [normal weight: n=175 (48.5%), overweight: n=240 (66.7%), obese: n=97 (58.1%); P<0.001], had a significantly higher rate of diabetes [normal weight: n=19 (5.3%), overweight: n=51 (14.2%), obese: n=38 (22.8%); P<0.001], and arterial hypertension [normal weight: n=95 (26.3%), overweight: n=105 (29.2%), obese: n=67 (40.1%); P=0.005]. One patient of the obese group underwent omega loop gastric bypass previous to liver surgery.

Preoperative evaluation of liver function and surgical technique

ICG clearance testing (PDR, R15) was performed in 633/888 patients. The median PDR in the normal weight group was 22%/min (18.0–26.2), median R15 was 3.7% (2.0–7.0%). For the overweight group median PDR was 20.2%/min (17.5–24.0), median R15 was 4.9% (2.5–7.0%). For the obese group median PDR was 21.0%/min (18.0–24.7), median R15 was 4.4% (2.5–7.0%) (PDR: P=0.079, R15: P=0.086).

Laparoscopic liver surgery was performed in 9/361 (2.5%) patients in the normal weight group, 3/360 (0.8%) patients of the overweight group and 9/167 (5.4%) of the obese group. Cavitron Ultrasonic Surgical Aspirator (CUSA Clarity, Integra Life Science Corp., USA) and Thunderbeat™ (Olympus Medical Systems Corp., Tokyo, Japan) are used as standard technique for LR at our department.

Intermittent Pringle maneuver was used in 54/361 (15.0%) patients of the normal weight group, 52/360 (14.4%) patients of the overweight group and 18/167 (10.8%) patients of the obese group. Portal vein embolization was used in 28/361 (7.8%) patients in the normal weight group, 34/360 (9.4%) patients of the overweight group and 10/167 (6.0%) patients in the obese group. Multi-Step approach [mini-associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)] was performed in 4/361 (1.1%) patients in the normal weight group, 3/360 (0.8%) patients of the overweight group and 1/167 (0.6%) patients of the obese group.

Steatosis and fibrosis

The rates of NASH and borderline NASH were significantly higher in the obese and overweight group compared to normal weight patients [NASH: normal weight: n=58 (16.1%), overweight: n=84 (23.3%), obese: n=69 (41.3%); P<0.001] (*Table 2*, *Figure 1A*), this was verified by pairwise testing [normal weight *vs.* overweight (P=0.001), normal weight *vs.* obese (P<0.001), overweight *vs.* obese (P=0.001)]. Furthermore, there was a significantly higher fibrosis grading in the overweight and obese cohort compared to normal weight patients (P=0.014) (*Table 2*, *Figure 1B*).

PHLF

PHLF occurred in 133 (15.0%) of all patients and was comparable between groups [normal weight: n=59 (16.3%), overweight: n=55 (15.3%), obese: n=19 (11.4%); P=0.32] (*Table 3* and *Figure 2*).

Table 1 Patient characteristics, surgical indications and procedures

Patient characteristics	Overall (n=888)	Normal weight (BMI 18.5–24.9 kg/m^2) (n=361)	Overweight (BMI 25.0–29.9 kg/m^2) (n=360)	Obese (BMI ≥30 kg/m^2) (n=167)	P value
Sex (male)	512 (57.6)	175 (48.5)	240 (66.7)	97 (58.1)	<0.001
Age (years)	62.5 [54–69]	62 [49–69]	63 [56–69]	62 [56–68]	0.06
BMI (kg/m^2)	26 [23–29]	23 [21–24]	27 [26–28]	33 [31–35]	
Comorbidities					
Coronary artery disease	54 (6.1)	16 (4.4)	28 (7.8)	10 (6.0)	0.17
COPD	34 (3.8)	13 (3.6)	17 (4.7)	4 (2.4)	0.42
Diabetes	108 (12.2)	19 (5.3)	51 (14.2)	38 (22.8)	<0.001
Hypertension	267 (30.0)	95 (26.3)	105 (29.2)	67 (40.1)	0.005
Neoadjuvant chemotherapy	94 (10.6)	41 (11.4)	43 (11.9)	10 (6.0)	0.098
Indications					0.38
Liver metastases	466 (52.5)	186 (51.5)	198 (55.0)	82 (49.1)	
Colorectal	366 (41.2)	147 (40.7)	154 (42.8)	65 (38.9)	
Non-colorectal	100 (11.3)	39 (10.8)	44 (12.2)	17 (10.2)	
Cholangiocarcinoma	158 (17.8)	67 (18.6)	62 (17.2)	29 (17.4)	0.88
Hepatocellular carcinoma	137 (15.4)	60 (16.6)	46 (12.8)	31 (18.6)	0.17
Echinococcosis	21 (2.4)	3 (0.8)	9 (2.5)	9 (5.4)	0.006
Adenoma	22 (2.5)	4 (1.1)	11 (3.1)	7 (4.2)	0.07
Hemangioma	33 (3.7)	11 (3.0)	17 (4.7)	5 (3.0)	0.42
FNH	23 (2.6)	14 (3.9)	8 (2.2)	1 (0.6)	0.07
Others	28 (3.2)	16 (0.04)	9 (0.02)	3 (0.01)	0.89
Type of liver resection					
Minor LR (<3 segments)	455 (51.2)	179 (49.6)	177 (49.2)	99 (59.3)	0.07
Major LR (≥3 segments)	433 (48.8)	182 (50.4)	183 (50.8)	68 (40.7)	

Data are presented as n (%) or median [IQR]. IQR, interquartile range; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FNH, focal nodular hyperplasia; LR, liver resection.

At univariate binary logistic regression analysis, BMI (kg/m^2) was no significant predictor of PHLF [OR: 0.99, 95% confidence interval (CI): 0.95–1.04; P=0.73] (*Table 4*). No relevant sensitivity or specificity could be shown with an AUC (area under the curve) 0.48 (95% CI: 0.42–0.53) (Figure S1).

At multivariable logistic regression analysis of age, gender, BMI, neoadjuvant chemotherapy, diabetes, hypertension, COPD, CAD, fibrosis, NAFLD activity score, Clavien-Dindo classification and resection group (major/minor), only major resections remained a significant predictor for PHLF (OR: 2.8, 95% CI: 1.87–4.27; P<0.001) (*Table 5*).

When PHLF was compared in "obese" patients *vs.* "rest", PHLF occurrence was not significantly different [normal weight + overweight patients: n=114/721 (15.8%) *vs.* obese patients n=19/167 (11.4%), P=0.15]. For the multivariable analysis, none of the tested factors (gender, age, comorbidities, Pringle maneuver, NASH activity score, fibrosis, neoadjuvant chemotherapy, type of LR) remained a significant predictor of PHLF.

In patients undergoing major LR, the occurrence of PHLF was also similar between groups [normal weight: n=8 (13.6%), overweight: n=14 (16.7%), obese: n=4 (5.8%); P=0.11].

Table 2 Histopathological features

Histopathological features	Overall (n=888)	Normal weight (BMI 18.5–24.9 kg/m^2) (n=361)	Overweight (BMI 25.0–29.9 kg/m^2) (n=360)	Obese (BMI ≥30 kg/m^2) (n=167)	P value
Fibrosis grading					0.014
0	430 (48.4)	192 (53.2)	168 (46.7)	70 (41.9)	
1	310 (34.9)	120 (33.2)	127 (35.3)	63 (37.7)	
2	74 (8.4)	31 (8.6)	29 (8.1)	14 (8.4)	
3	15 (1.7)	3 (0.8)	7 (1.9)	5 (3.0)	
4 (cirrhosis)	59 (6.6)	15 (4.2)	29 (8.1)	15 (9.0)	
NAFLD activity score					<0.001
No steatosis	427 (48.1)	225 (62.3)	161 (44.7)	41 (24.6)	
Not-NASH	110 (12.4)	35 (9.7)	52 (14.4)	23 (13.8)	
Borderline NASH	140 (15.8)	43 (11.9)	63 (17.5)	34 (20.4)	
NASH	211 (23.8)	58 (16.1)	84 (23.3)	69 (41.3)	

Data are presented as n (%). BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

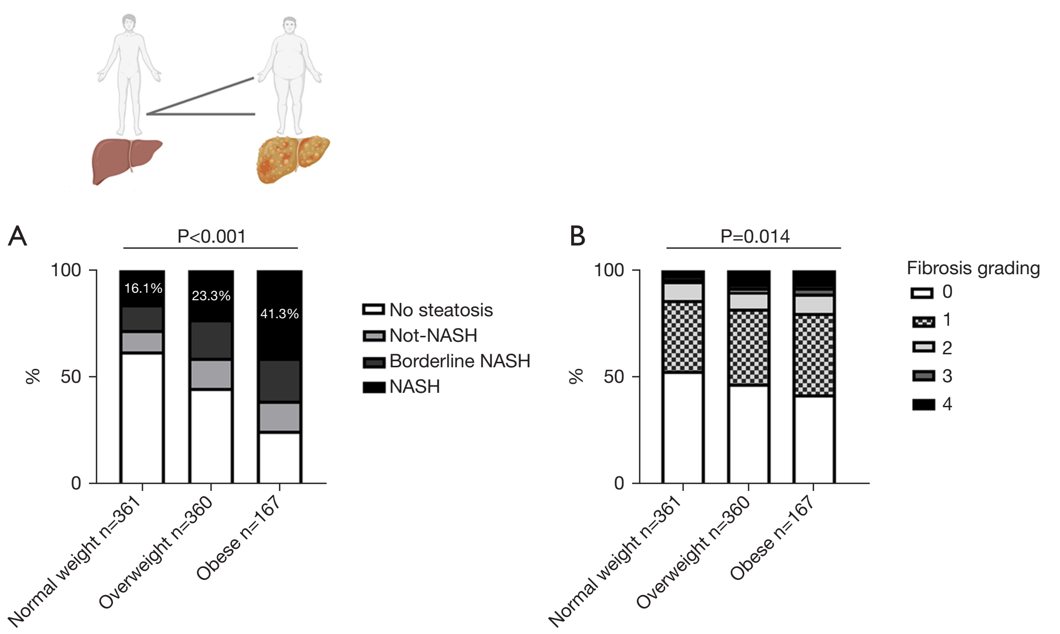

Figure 1 Histopathological features of the resected liver. (A) The rate of NASH was 16.1% in normal weight patients, 23.3% in the overweight cohort and 41.3% in obese patients (P<0.001). (B) In line with that, there was a significant increase in fibrosis grading in higher weight patients compared to normal weight patients (P=0.014). NASH, nonalcoholic steatohepatitis.

For the HCC only cohort (n=137), multivariable regression analysis showed no remaining significant predictors of PHLF, not even resection group (major/minor) remained a significant predictor. In regression analysis of the CCC only cohort (n=158), NAFLD activity score remained a significant predictor of PHLF (OR: 0.58, 95% CI: 0.363–0.953, P=0.03).

Patients with NASH did not show higher rates of

Table 3 Treatment and postoperative complications

Postoperative complications	Overall (n=888)	Normal weight (BMI 18.5–24.9 kg/m^2) (n=361)	Overweight (BMI 25.0–29.9 kg/m^2) (n=360)	Obese (BMI ≥30 kg/m^2) (n=167)	P value
PHLF					0.32
Yes	133 (15.0)	59 (16.3)	55 (15.3)	19 (11.4)	
No	755 (85.0)	302 (83.7)	305 (84.7)	148 (88.6)	
Clavien-Dindo Class					0.45
0	483 (54.4)	185 (51.2)	198 (55.0)	100 (59.9)	
I	80 (9.0)	38 (10.5)	32 (8.9)	10 (6.0)	
II	146 (16.4)	74 (20.5)	51 (14.2)	21 (12.6)	
IIIa	76 (8.6)	23 (6.4)	36 (10.0)	17 (10.2)	
IIIb	68 (7.6)	30 (8.3)	27 (7.5)	11 (6.6)	
IVa	5 (0.6)	3 (0.8)	2 (0.6)	0 (0.0)	
IVb	3 (0.4)	1 (0.3)	2 (0.6)	0 (0.0)	
V (= mortality)	27 (3.0)	7 (1.9)	12 (3.3)	8 (4.8)	
Intraoperative blood transfusions	59 (6.6)	26 (7.2)	21 (5.8)	12 (7.1)	0.69
Length of stay (days)	11 [8–15]	11 [8–15]	10.5 [8–16]	10 [8–14]	0.56

Data are presented as n (%) or median [IQR]. BMI, body mass index; PHLF, post-hepatectomy liver failure; IQR, interquartile range.

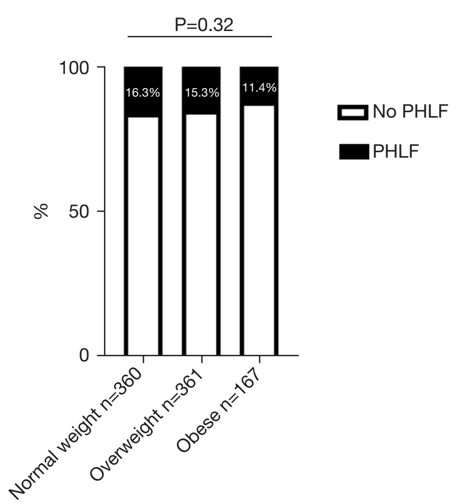

Figure 2 PHLF: the rate of PHLF did not show a statistically relevant difference in the analyzed weight groups (normal weight: 16.3%, overweight: 15.3% and obese: 11.4%) (P=0.32). PHLF, post-hepatectomy liver failure.

Table 4 Univariate binary logistic regression analysis for BMI (continuous variable) as predictor for PHLF

Model variables	B	SE(B)	Sig.	Exp(B)	95% CI
BMI (kg/m^2)	−0.007	0.021	0.734	0.993	0.953–1.035

BMI, body mass index; PHLF, post-hepatectomy liver failure; B, logistic regression coefficient; SE(B), standard error; Sig., significance probability; Exp(B), odds ratio; 95% CI, 95% confidence interval.

PHLF compared to patients without steatosis [NASH: n=26 (12.3%) *vs.* no steatosis: n=77 (18%), P=0.36]. These non-significant results were similar for the not NASH and borderline NASH group, compared to patients without steatosis [not NASH *vs.* no steatosis: n=13 (11.8%) *vs.* n=77 (18%), P=0.25; borderline NASH *vs.* no steatosis: n=17 (12.1%) *vs.* n=77 (18%), P=0.29]. In a subgroup analysis of major LRs in NASH patients, no significant difference in

Table 5 Multivariate binary logistic regression analysis for predictors of PHLF

Model variables	B	SE(B)	Sig.	Exp(B)	95% CI
Age	0.005	0.008	0.52	1.005	0.989–1.022
Gender	0.279	0.214	0.19	1.322	0.870–2.010
BMI (kg/m^2)	−0.002	0.024	0.92	0.998	0.951–1.046
Fibrosis	0.000	0.095	0.99	1.000	0.830–1.204
Neoadjuvant chemotherapy	−0.569	0.363	0.12	0.566	0.278–1.152
Diabetes	0.270	0.363	0.39	1.310	0.712–2.409
Hypertension	−0.221	0.234	0.35	0.802	0.507–1.268
COPD	0.833	0.436	0.06	2.301	0.979–5.408
Coronary artery disease	−0.139	0.344	0.69	0.870	0.443–1.703
NAFLD activity score	−0.113	0.086	0.19	0.893	0.754–1.057
Clavien-Dindo Class	0.017	0.040	0.996	1.000	0.939–1.101
Type of liver resection	1.036	0.210	<0.001	2.818	1.866–4.266

PHLF, post-hepatectomy liver failure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; NAFLD, nonalcoholic fatty liver disease; B, logistic regression coefficient; SE(B), standard error; Sig., significance probability; Exp(B), odds ratio; 95% CI, 95% confidence interval.

the occurrence of PHLF between the three weight groups could be observed [normal weight: n=6/29 (20.7%) *vs.* overweight: n=10/44 (22.7%) *vs.* obese: n=3/29 (10.3%); P=0.39]. These non-significant results were similar for the not NASH and borderline NASH group [not NASH: normal weight: n=4 (22.2%) *vs.* overweight: n=5 (19.2%) *vs.* obese: n=1 (11.1%); P=0.78); borderline NASH: normal weight: n=3 (18.8%) *vs.* overweight: n=3 (12%) *vs.* obese: n=2 (25%); P=0.66].

In logistic regression analysis, fibrosis was also no significant predictor of PHLF (OR: 1.2, 95% CI: 0.98–1.60, P=0.07), only major resection in fibrotic patients showed a significant prediction of PHLF (OR: 3.0, 95% CI: 1.69–5.42, P<0.001).

Binary logistic regression analysis of patients without fibrosis (fibrosis grading 0, n=430) did not show a significant correlation of BMI or morbidity and PHLF (morbidity, OR: 0.98, 95% CI: 0.865–1.120, P=0.81; BMI, OR: 0.82, 95% CI: 0.519–1.307, P=0.41).

Morbidity and mortality

No significant difference between BMI groups with respect to morbidity and mortality was observed (P=0.45). Severe complications (Clavien-Dindo ≥ IIIb) occurred in 101 (11.3%) of all patients and were similar between all groups [normal weight: n=41 (11.4%), overweight: n=43 (11.9%), obese: n=17 (10.2%); P=0.87].

At multivariable analysis of comorbidities, fibrosis, NAFLD activity score and resection group (major/minor), none of the factors remained statistically significant (comorbidities, OR: 0.87, 95% CI: −0.51 to 0.23, P=0.48; fibrosis, OR: 1.95, 95% CI: −0.96 to 0.22, P=0.42; NAFLD activity score, OR: 1.06, 95% CI: −0.13 to 0.15, P=0.93; resection group, OR: 0.84, 95% CI: −0.49 to 0.15, P=0.30).

Intraoperative administration of red blood cell transfusions was not associated with BMI group. In the normal weight group 26 patients (7.2%) received red blood cell transfusion *vs.* 21 patients in the overweight group (5.8%) and 12 patients in the obese group (7.1%) (P=0.56).

The median length of stay was 11 days (IQR, 8–15 days) and was comparable between groups [normal weight: 11 days (IQR, 8–15 days), overweight: 10.5 days (IQR, 8–16 days), obese: 10 days (IQR, 8–14 days), P=0.56]. Of note, patients undergoing major resection showed a longer length of stay compared to patients with minor resections [minor LR: 9 days (IQR, 7–13 days) *vs.* major LR: 12 days (IQR, 9–18 days); P<0.001].

Postoperative death occurred in 27 patients (3%) and was comparable between the three groups [normal weight: n=7 (1.9%), overweight: n=12 (3.3%), obese: n=8 (4.8%); P=0.19].

Comorbidities

Patients were divided into "healthy" or "unhealthy" patients. The number of "unhealthy" patients was 114 in the normal weight group (31.6%), 141 in the overweight cohort (39.2%), and 84 in the obese group (50.2%) (P<0.001). Complications were comparable between the two subgroups (OR: 0.85, CI: −0.49 to 0.167, P=0.33). Health status was also no predictor of PHLF (OR: 0.82, CI: 0.56–1.19, P=0.31). There was no difference in PHLF in "unhealthy" patients [normal weight: n=22 (19.3%), overweight n=25 (17.7%), obese n=14 (16.7%), P=0.89]. Furthermore, morbidity and mortality were also comparable between "unhealthy" patients of the distinct weight groups (Table S1).

Discussion

Obesity has substantially increased worldwide during the last decades (1). LR in overweight and obese patients is challenging due to an increased anesthesiologic risk and a technically more demanding surgical access (21,22). Obese patients have an increased risk for prolonged operation times, severe complications and extended length of stay in hospital after different types of major abdominal surgery (23,24). Additionally, these patients have a higher risk of postoperative infections and more need of intensive care (21,25). Reports on postoperative outcome after LR in obese patients are contradictory and (12,14,26-28) direct evidence of the influence of obesity on PHLF is still lacking. Historically PHLF had no universal definition, therefore variable rates of PHLF have been described and comparison of data is difficult (11,29,30). In our study the ISGLS criteria was used to determine PHLF, to detect smaller differences in the incidence of liver regeneration-related problems.

To our knowledge, this is the largest study investigating PHLF and postoperative outcome in overweight and obese patients. We found no significant differences in PHLF, complications, and mortality between normal weight, overweight and obese patients, independent of comorbidities. Only the extent of the LR was associated with complications at multivariable analysis. Major LRs are known to be associated with PHLF, morbidity, and mortality (31-33). We assume the almost significantly lower number of major resections of our obese patients to be a possible explanation for the non-significant results of PHLF, as major resections were the only predictor for PHLF.

In the present study, obesity was associated with NASH and liver fibrosis, respectively. In our cohort, the rate of NASH was higher than expected in the general population. NASH was diagnosed in 16% of the normal weight *vs.* 23% in the overweight *vs.* 41% in the obese group. According to the literature, NASH is strongly related to diabetes and obesity and increases annually, which goes in line with our results. The prevalence of NASH among NAFLD patients who underwent a random biopsy is declared around 7%. The prevalence of NASH among NAFLD patients with a clinical indication for a liver biopsy is stated around 59% (34). Steatosis seems to be a predictor for morbidity and mortality in patients undergoing LR (35-37). A higher incidence of postoperative infections, perihepatic abscesses and postoperative bowel dysmotility was found in previous studies, whereas the frequency of major complications or length of stay was not associated with steatosis (36,37). NASH is known to be associated with an increased risk of fibrosis and cirrhosis (38,39). Severe fibrosis has been reported be associated with poorer early postoperative and late oncologic outcome, respectively (40). In contrast to that, Yang *et al.* found severe fibrosis not to be associated with overall morbidity in 2011 (41). This is in keeping with our results showing that fibrosis and NASH were not associated with PHLF and morbidity, while only major resections were found to be a significant predictor of PHLF.

PHLF occurred in 15.0% of our patients, which is in line with the literature in normal weight patients (8,42,43). Notably, the rate of PHLF was comparable amongst the different weight groups. Our findings stand in contrast to some recent studies showing an influence of obesity on PHLF (12,29).

The Oklahoma University carried out a retrospective database analysis of the national surgical quality improvement program data set from 2005 to 2017 (12). In this study, 36,969 patients who underwent LR were divided into two groups (BMI <35 kg/m^2 and BMI ≥35 kg/m^2), which is different from the WHO-classification of obesity. Moreover, patients were subclassified into "healthy" (without comorbidities) and "unhealthy" patients (with comorbidities). Patients in the higher BMI group showed a 2.2 times higher risk of mortality. Although, no difference in mortality after adjustment of other covariates between "healthy" or "unhealthy" obese was reported, which goes in line with a comparison of "healthy" and "unhealthy" obese in our current analysis, where no differences of complications or mortality could be shown. This is despite of the different classification of weight groups in the Oklahoma University database (12). A recent large retrospective analysis with steatotic and normal livers of the American College of Surgeons National Surgical Quality Improvement Program database associated the metabolic syndrome with a worsened outcome after major LRs. Patients with a steatotic liver had an increased risk of overall and major complications, such as deep-surgical site infections with the need for invasive treatment (29). The observed difference to our study could be explained by the definition of liver steatosis. Whereas, in the previous study, steatosis was visually assessed by the surgeon during surgery, we performed a detailed histological grading according to NASH CRN scoring system (20). We assume that by macroscopical evaluation of the liver, lower grades of steatosis were not classified as steatotic in this analysis.

In our study obese patients had a significantly higher rate of minor LRs compared to the normal weight and overweight patients, which could be a potential bias. To address this issue, we performed a subgroup analysis studying only major LRs, which also did not show an influence of BMI on the occurrence of PHLF. Accordingly, NASH and NAFLD activity score gradings were not associated with PHLF in the overall cohort and in the major LR subgroup. Similar results to our findings were reported in 2011 showing that liver failure, biliary leakage and other severe complications occurred with equal frequency in normal weight and obese patients (44). Additionally, another study of obese patients undergoing LR in HCC also showed no difference in PHLF (13). In another study, super-obesity defined as a BMI >50 kg/m^2 was found to be one of the most relevant predictors for increased critical care complications such as pneumonia, septic shock and renal insufficiency in patients undergoing LR (3). According to the WHO subdivision of obesity, in our cohort, only 10 patients in our cohort had a BMI ≥40 kg/m^2 (obese class III), thus a subgroup analysis of this cohort would not be valuable.

One of the limitations of this study is the retrospective character and the assessment of obesity using the BMI, which does not represent the body composition (e.g., intraabdominal fat or waist-hip ratio). Also, the limited number of patients in our subgroup analysis of NASH and major resections could lead to false negative results due to the inadequate power.

However, this study states for the first time in a large cohort of patients with a detailed follow up that obesity is not associated with a higher risk for postoperative complications or PHLF in patients undergoing either minor or major LRs. We therefore conclude that LRs can be safely performed in obese patients. Future prospective studies with measurement of intraabdominal fat and the waist-hip ratio are required to identify patients, who might have an increased perioperative risk of PHLF and postoperative complications.

Conclusions

Postoperative complications and PHLF are comparable in normal weight, overweight and obese patients and LRs using modern techniques can be safely performed in these patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-291/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-291/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-291/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This was a retrospective single-center study approved by the institutional review board of the Medical University of Vienna (IRB number: 1368/2021) and performed in accordance with the principles of the Declaration of Helsinki (as revised in 2013). Informed consent has not been achieved due to the retrospective character and anonymous data collection.

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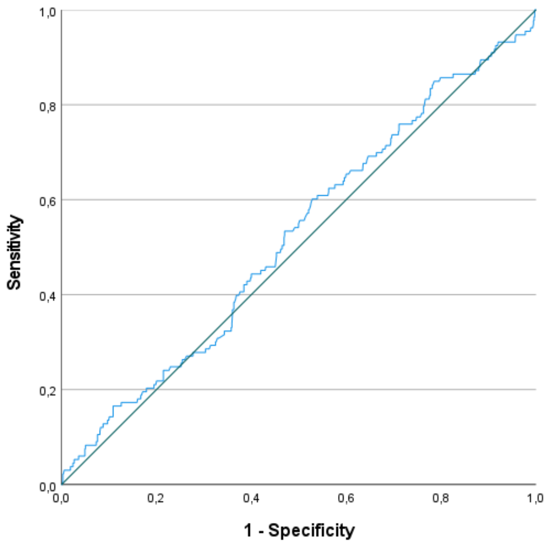

Figure S1 ROC curve analysis of BMI (kg/m^2) showing no significant predictive value for PHLF. No relevant sensitivity or specificity could be shown [AUC 0.48 (95% CI: 0.42–0.53)]. ROC, receiver operating characteristic;

Table S1 Morbidity in patients with comorbidities

Unhealthy group	Normal weight (BMI 18.5–24.9 kg/m^2) (n=114)	Overweight (BMI 25.0–29.9 kg/m^2) (n=141)	Obese (BMI ≥30 kg/m^2) (n=84)	P value
PHLF, n (%)				0.89
Yes	22 (19.3)	25 (17.7)	14 (16.7)	
No	92 (80.7)	116 (82.3)	70 (83.3)	
Clavien-Dindo Class, n (%)				0.86
0	55 (48.2)	71 (50.4)	41 (48.8)	
I	8 (7.0)	7 (5.0)	6 (7.1)	
II	24 (21.1)	25 (17.7)	12 (14.3)	
IIIa	7 (6.1)	16 (11.3)	8 (9.5)	
IIIb	9 (7.9)	10 (7.1)	4 (4.8)	
IVa	1 (0.9)	0 (0.0)	0 (0.0)	
IVb	1 (0.9)	1 (0.7)	0 (0.0)	
V (= mortality)	2 (1.8)	7 (5.0)	5 (6.0)	

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