Asian Journal of Surgery (2019) 42, 172–179

Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Revisiting donor risk over two decades of single-center experience: More attention on the impact of overweight

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Received 10 December 2017; received in revised form 14 January 2018; accepted 29 January 2018
Available online 14 February 2018

KEYWORDS
living liver donor;
morbidity;
liver transplantation;
overweight

Summary *Objective:* Morbidity rates after living donor hepatectomy vary greatly among centers. Donor morbidity in a tertiary center over the past two decades was revisited.
Methods: Clinical data and grading of complications were reviewed by a nontransplant surgeon based on Clavien 5 tier grading. Risk factors were analyzed.
Results: In total, 473 consecutive living liver donors from 1997 to 2016 were included for analysis; 305 were right liver donors and 168 left liver donors, and the corresponding morbidity rates were 27.2% and 9.5%. The majority (81/99, 81.2%) of complications were grade I and II. Donors with morbidity compared with those without were significantly younger, nonoverweight body figure (BMI $<$ 25), more as the right liver donors, and longer length of hospital stay. Right liver donation had significantly higher morbidity rates than did left liver donation in earlier periods (before 2011), but not thereafter. Multivariate modeling revealed that right lobe donation and overweight (BMI $\geq$ 25 kg/m^2) were significant factors associated with donor morbidity, with adjusted hazard ratios HR (95% confidence interval) of 3.401 (1.909–6.060) and 0.550 (0.304–0.996), respectively. Further, overweight was a paradoxical risk factor in right donor hepatectomy with HR 0.422 (0.209–0.851), but the effect was nonsignificant in left liver donors. Most complications in overweight donors were grade I and not specific to liver surgery.
Conclusions: The overall complication rate was 20.9%. Overweight might be protective against morbidity in right hepatectomy and warrants further deliberation.

Abbreviations: BMI, body mass index; CI, confidence interval; GDWR, graft donor weight ratio; HR, hazard ratio; IHD, intrahepatic duct; INR, international normalized ratio.

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https://doi.org/10.1016/j.asjsur.2018.01.002

1. Introduction

Living donor liver transplantation is a widely adopted strategy in countries with a shortage of deceased organ donation.[1] The ethical conflict between operating on healthy living donors and saving the lives of sick recipients has always been a concern.[2,3] Donor safety is of the utmost importance in this strategy, yet postoperative complications are sometimes unavoidable, even in expert centers worldwide.[4] Live liver donors are "supernormal" patients and are subjected to rigorous screening. However, they may encounter dangerous circumstances later in life because unlike liver surgery for space-occupying tumor resection, functional liver volume is definitely reduced in donor surgery. Experiences reported in different centers vary greatly.[4,5] This phenomenon indicates the importance of the topic, although the surgeons involved are naturally reluctant to be associated with surgery complications.

In a systematic review of literature published in 2016, which summarized 33 studies reporting the outcomes of 12,653 donors, the average complication rates of living liver donor surgery was 20.5%, with a biliary complication rate of 6.2%.[5] Some complications were surgery-related (liver specific or nonspecific). Donor death, reported to be 0.15%,[6,7] is an unacceptable outcome and it continues to occur despite recent technological advances.[8,9]

Right liver donation is at increased risk of complications compared to left liver donation.[10,11] There is a paucity of literature that describes other risk factors for complications of donor hepatectomy.[12,13] Therefore, we reviewed the morbidity rates of live liver donors over the last two decades in our center and systematically analyzed the associated risk factors through logistic regression.

2. Methods

2.1. Donor subjects

Between October 1989 and September 2016, 607 consecutive patients underwent liver transplantation in our institute. Among them, since 1997, 473 patients received livers from living related donors (Fig. 1). The medical records of 473 living liver donors who underwent donor hepatectomy were retrospectively reviewed. Before 2005, we performed less than 20 living donor liver transplants per year except in 2003 (period 1: 1997—2004). After then, we performed more than 20 living donor liver transplants per year (period 2: 2005—2010). In 2011, one additional surgeon (HCM) joined to perform donor operations (period 3: 2011—2016). All living donors voluntarily signed the informed consent form in accordance with the ethics group of the Vancouver Forum.[14] All candidates and procedures were approved by the national supervisory organization, the Taiwan registry and sharing center, or the institution's ethical committee. The Institutional Review Board of National Taiwan University Hospital, Taipei, Taiwan, approved this study (NTUH REC: 201701044RIND).

2.2. Donor evaluation, graft retrieval, postoperative care, and follow-up

Potential donors were screened in clinic and were free from hepatitis and systemic diseases such as diabetes mellitus, hypertension, and hyperlipidemia. The protocols of donor evaluation, operation procedures, and perioperative management were as described previously.[15] Donor hepatectomy was performed in the order of the following steps: mobilization of graft liver by releasing the attached ligaments, hilum dissection to isolate the relevant hepatic artery and the portal vein, intra-operative cholangiography for identification of the exact site of bile duct bifurcation or potential anomaly, dissection of the junction of hepatic vein and inferior vena cava, parenchymal transection until fully division of the graft lobe, bile duct division, and finally graft retrieval after ligation and division of the isolated hepatic artery, portal vein, and hepatic vein. In our center, computed tomography was performed to quantitatively evaluate the severity of liver steatosis, and candidates with a liver: spleen ratio less than 1 were not eligible to donate.[15] Furthermore, we adopted magnetic resonance spectroscopy in donor evaluation of hepatic steatosis since 2011.[16]

2.3. Demographic and clinical variables

Demographic information including sex, age, height, body weight, body mass index (BMI), date of surgery, surgical procedure, graft weight, graft volume, intraoperative blood loss, and length of hospital stay were collected. Overweight was defined as BMI $\geq$ 25 kg/m^2. Liver density was defined as graft weight/volume, and graft donor weight ratio (GDWR) as percentage of graft weight/donor body weight.

2.4. Morbidity as outcome

Postoperative complications were graded according to the Clavien—Dindo classification.[17] Posthepatectomy liver dysfunction was assessed using the reported criteria of the International Study Group for Liver Surgery (ISGLS), which is characterized by an increased international normalized ratio (INR) and concomitant hyperbilirubinemia on or after postoperative day 5.[18] The definitions of complications are detailed in Supplemental Table S1. A nontransplant surgeon (HYM) reviewed the medical records independently. All donors were followed for at least 6 months after operation. For donors with complications, the follow-up time was longer, lasting until the condition became stationary.

2.5. Statistical analysis

Data were expressed as mean $\pm$ standard deviation, and number (percentage) when appropriate. Student's t or χ^2 test was used to compare the variables where appropriate. Independent risk factors of morbidity were identified through logistic regression. Multivariate analysis was used to adjust for the potential confounding of risk factors.

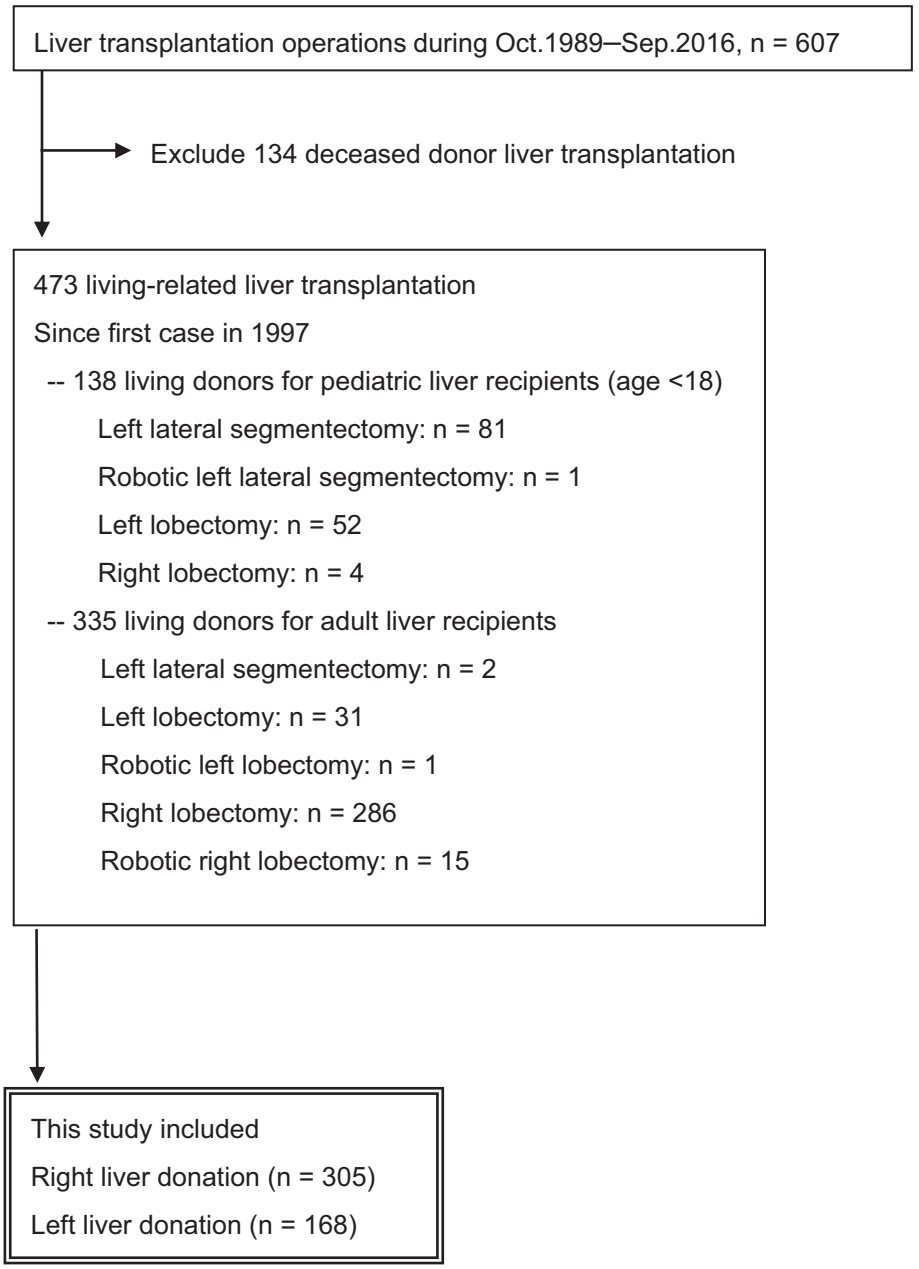

Figure 1 Living liver donor selection and surgical procedures.

Sensitivity analysis was performed by stratifying subgroups for potential significant risk factors of interest. Two-sided $P < 0.05$ was considered to indicate statistical significance. Analyses were performed using the Statistical Package for Social Sciences (SPSS)® version 21.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Series of living related liver donor surgery

Since 1997, 473 living related liver transplants were performed, with 138 being pediatric recipients and 335 being adult recipients. Detailed operation methods are shown in Fig. 1. In total, 305 and 168 donors who donated right and left livers, respectively, (including left lateral segment and left lobe) were included in this study.

3.2. Demographic characteristics of live liver donors

Table 1 shows the clinical and demographic characteristics of donors classified into right and left liver donation groups. The right group had higher male percentage, height, graft weight, graft volume, GDWR, length of hospital stay, and morbidity (overall, severity subgroups, and surgery-related complications), and less graft density ($P < 0.05$). No differences in age, body weight, BMI, overweight (BMI $\geq$ 25; borderline significant difference, $P = 0.057$), intraoperative blood loss, operation time, and nonsurgical morbidity between the two groups were observed.

Table 1 Clinical and demographic characteristics of live liver donors.

Variables	Right n = 305	Left n = 168	P
Sex (male, %)	164 (53.8)	67 (39.9)	0.004
Age (years, SD)	32.1 (9.7)	32.5 (6.7)	0.634
Body figures			
Height (cm, SD)	166.6 (8.9)	164.2 (8.6)	0.005
Weight (kg, SD)	64.1 (11.6)	62.8 (12.6)	0.277
BMI (m/kg^2, SD)	22.99 (3.19)	23.16 (3.44)	0.592
Overweight (BMI $\geq$ 25) (%)	70 (23.0)	45 (26.8)	0.057
Graft nature			
Mean weight (g, SD)	695.5 (131.3)	326.7 (90.6)	<0.001
Mean volume (ml, SD)	696.4 (131.7)	320.5 (102.5)	<0.001
Mean density (g/ml, SD)	1.002 (0.077)	1.030 (0.135)	0.005
Mean graft donor weight ratio (%, SD)	1.095 (0.160)	0.525 (0.117)	<0.001
Intraoperative blood loss (ml, SD)	180.4 (145.7) (n = 72)	225.0 (256.3) (n = 24)	0.290
Operative time (min, SD)	407.1 (110.6) (n = 69)	365.7 (124.7) (n = 23)	0.136
Hospital stay (days, SD)	11.4 (5.7)	9.7 (3.6)	0.001
Morbidity			
Overall	83	16	<0.001
1/2/3a/3b	44/22/12/5	11/4/0/1	<0.001
Nonspecific surgery related	41	12	0.034
Liver surgery related	38	4	<0.001
Non-surgical	4	0	0.302

3.3. Donor morbidity: profiles and description

Supplemental Table S2 presents the morbidity profiles according to the Clavien—Dindo classification. Overall, 99 donors (20.9%) had complications and 374 had uneventful postoperative courses. Most (55.6%) morbidities were grade I, and no grade IV or V complications were observed in our cohort. The most common grade I morbidities included self-limited fever and jaundice; II, discharge with drain tube; IIIa, biloma; and IIIb, ventral hernia. Donors with morbidity grade IIIa and IIIb received readmission for further management, except one case of postoperative bleeding, who received exploratory laparotomy to stop the postoperative bleeding during the same hospital stay as their liver donation surgery. Biloma or intra-abdominal abscesses were managed using conservative antibiotics (grade II), additional pigtail drainage (grade IIIa), or surgery (grade IIIb). Biliary complications were 3.2% (15/473) and higher for right liver donation (4.3%, 13/305) than left (1.2%, 2/168). One female donor who received robotic right lobectomy experienced morbidity of infected biloma three months after surgery and subsequent biliary hilar stenosis 11 months after surgery. Her liver function improved after percutaneous transhepatic biliary drainage and dilatation.

3.4. Donor morbidity evolution

We divided the series into three periods (period 1: 1997—2004; period 2: 2005—2010; period 3: 2011—2016), as shown in Supplemental Fig. S1. In period 1, only donors without anatomical variation of intrahepatic ducts (IHDs) were accepted for living donor hepatectomy. Since 2005 (period 2 and 3), donors with anatomical variation of IHDs were approved for liver donation in cases where the surgery of both donor and recipient were technically feasible. The three periods differed significantly in the distribution of donor morbidity for overall (P = 0.026, Table 2) and right liver donation (P = 0.048). For left liver donation, a borderline significance was observed (P = 0.052). Right liver donation had significantly higher morbidity rates than left liver donation in period 1 (11/51 vs. 1/43, P = 0.005) and period 2 (39/109 vs. 7/64, P < 0.001) but not period 3 (33/145 vs. 8/61, P = 0.113). Right liver donation had a significantly lower morbidity rate in period 3 than in period 2 (P = 0.025).

3.5. Comparison between donors with and without morbidity

Donors with morbidity compared with those without were significantly younger, taller, nonoverweight (BMI < 25), from the right liver donation group, higher graft weight, graft size, GDWR, and longer length of hospital stay. No differences were observed in sex, body weight, BMI, graft density, intraoperative blood loss, or operative time (Table 2).

3.6. Risk factor analysis of morbidity after live liver donor surgery

Hazard ratio (HR), determined through univariate analysis, for age was 0.964 [95% confidence interval (CI) 0.938—0.991], height 1.032 (1.006—1.058), overweight

Table 2 Comparison between live liver donors with and without morbidity.

Variables	Morbidity n = 99	Uneventful n = 374	P
Sex (male)	55	176	0.143
Age (years, SD)	30.2 (9.7)	32.7 (8.4)	0.009
Body figures			
Height (cm, SD)	167.7 (8.5)	165.2 (8.9)	0.014
Weight (kg, SD)	64.0 (10.4)	63.5 (12.3)	0.710
BMI (m/kg^2, SD)	22.68 (2.89)	23.15 (3.37)	0.201
Overweight (BMI $\geq$ 25) (%)	16 (16.2)	99 (26.5)	0.011
Graft nature			
Right liver lobe donation (%)	83 (83.8)	222 (59.4)	<0.001
Mean weight (g, SD)	634.2 (179.1)	546.6 (217.1)	<0.001
Mean volume (ml, SD)	639.5 (183.9)	543.2 (221.3)	<0.001
Mean density (g/ml, SD)	1.0019 (0.1018)	1.0143 (0.1025)	0.285
Mean graft donor weight ratio (%, SD)	0.9999 (0.2704)	0.8655 (0.3134)	<0.001
Intraoperative blood loss (ml, SD)	226.2 (195.3) (n = 21)	181.8 (173.9) (n = 77)	0.315
Operative time (min, SD)	417.2 (132.0) (n = 18)	391.7 (110.9) (n = 74)	0.402
Hospital stay (days, SD)	13.2 (9.5)	10.1 (2.8)	<0.001
Period			0.026
1997–2004	12	82	
2005–2010	46	127	
2011–2016	41	165	

0.535 (0.299–0.959), right lobe donation 3.552 (2.002–6.303), graft weight 1.002 (1.001–1.003), graft volume 1.002 (1.001–1.003), and GDWR 4.499 (2.060–9.830) (Table 3). Compared with period 1, HR for period 2 was 2.475 (1.237–4.951) and 1.698 (0.847–3.405) for period 3. When all significant univariate factors, except the period, were included in the multivariate analysis, no significant risk factors could be identified (Supplemental Table S3). For multivariate risk factors of overweight and right lobe donation, the adjusted HRs were 0.550 (0.304–0.996) and 3.512 (1.976–6.243) (Table 3). The effect of GDWR was confounded by right lobe donation as the HRs were <1 after stratification (Supplemental Table S4).

3.7. Sensitivity analysis of overweight as a paradoxical risk factor in donor morbidity

Distribution of donor BMI and grades of complication are shown in Fig. 2. Most complications occurred when BMI was less than 25 among all and right liver donors (Fig. 2A, B). Complications were most frequently seen in left liver donors with BMIs of 19–20 (Fig. 2C). Subgroup analysis was performed to show the impact of overweight on donor morbidity (Table S5). Age did not influence the effect size of the HR of overweight. The HR of overweight was approximately 0.4 for both left lobe and right liver donation, with the right exhibiting significance (HR 0.422 [0.209–0.851], P = 0.016). However, overweight had a

Table 3 Risk factor analysis of live liver donor morbidity.

Variables	Univariate model		Multivariate model	
	HR (95%CI)	P	HR (95%CI)	P
Age (years)	0.964 (0.938–0.991)	0.010	–	–
Height (cm)	1.032 (1.006–1.058)	0.014	–	–
Overweight (BMI $\geq$ 25)	0.535 (0.299–0.959)	0.036	0.550 (0.304–0.996)	0.048
Right lobe donation[b]	3.552 (2.002–6.303)	<0.001	3.512 (1.976–6.243)	<0.001
Graft weight	1.002 (1.001–1.003)	<0.001	–	–
Graft volume	1.002 (1.001–1.003)	<0.001	–	–
Graft donor weight ratio	4.499 (2.060–9.830)	<0.001	–	–
Period[a]		0.029		
2005–2010	2.475 (1.237–4.951)	0.010		
2011–2016	1.698 (0.847–3.405)	0.136		

HR: hazard ratio; CI: confidence interval; BMI: body mass index.
[a] 1997–2004 as reference.
[b] Left lobe donation as reference.

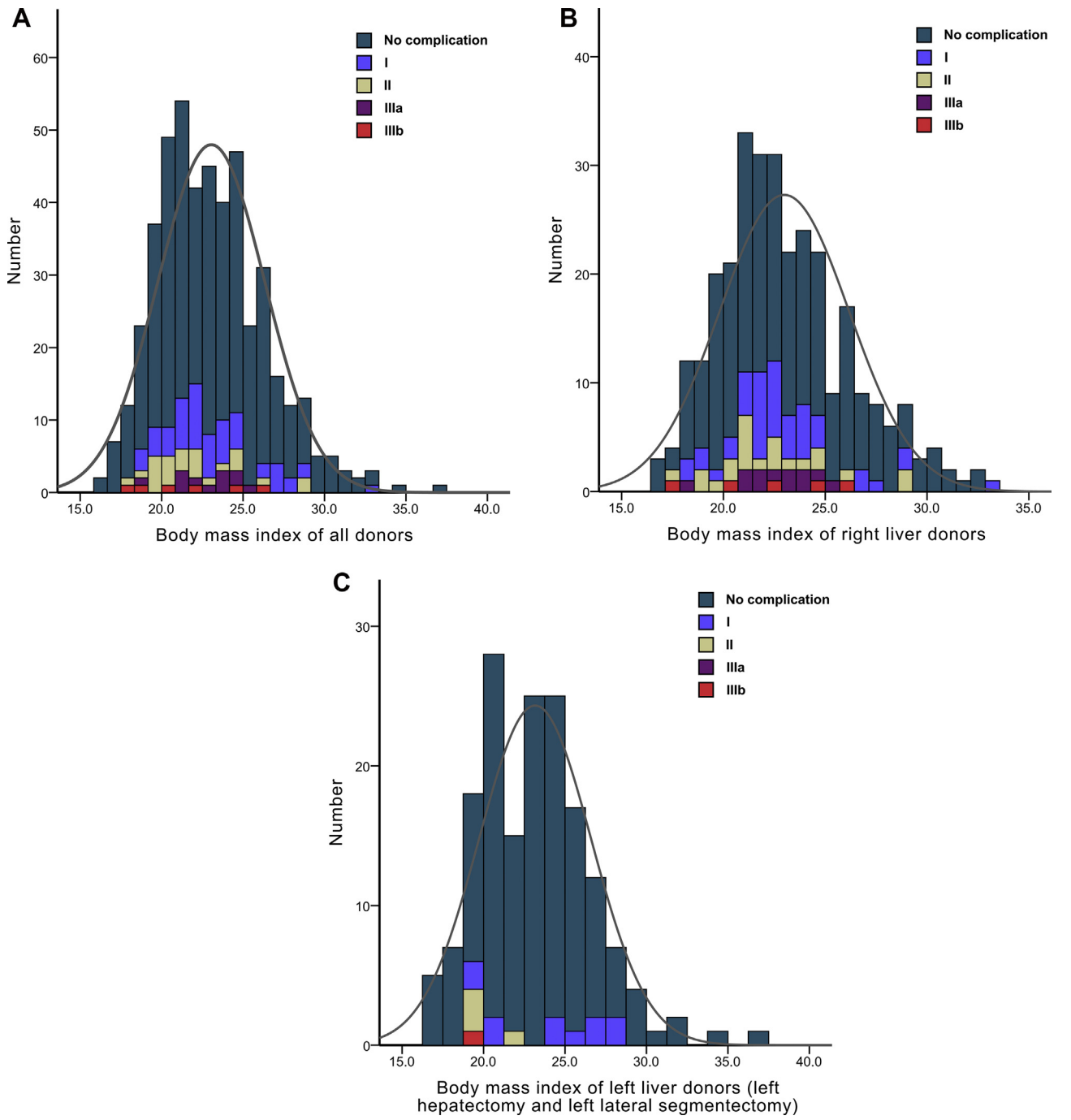

Figure 2 Distribution of donor BMI and grades of complication in all (2A), right liver (2B), and left liver (left hepatectomy and left lateral segmentectomy) (2C) donors.

hazard trend on left lateral donation, with an HR of 2.857 (0.710—11.500). Among the 115 overweight donors, 16 had complications and most were grade I (11/16, 68.8%) and non-liver surgery specific (11/16, 68.8%).

4. Discussion

The presents study analyzed a live liver donor cohort, and the main findings are as follows. First, the overall morbidity rate was 20.9%, with significantly higher morbidity for right liver donation (27.2%) than left liver (9.5%), but the trend became nonsignificant in period 3. Second, most common complications included self-limited fever (n = 26), self-limited jaundice (n = 18), bile leak or biloma (n = 15). Morbidity grades were I (55.6%), II (26.3%), IIIa (12.1%), and IIIb (6.1%), respectively. Third, multivariate analysis revealed the significant factors [HR (95%CI)] were right lobe donation [3.471 (1.951—6.173)] and overweight [0.550 (0.304—0.996)]. Lastly, overweight was identified as a significant protective factor for right liver donation but with a hazardous trend on the left lateral segment donation [2.857

(0.710—11.500)]. Most complications in overweight donors were grade I and non-liver surgery specific.

Our study showed that overweight was protective in right donor hepatectomy. Obesity (BMI $\geq$ 35 kg/m^2) and fatty liver are not in equal connection, although a reduction of fatty liver can be achieved through weight loss.[19] In our series, the overweight donors (most of them <35) had normal liver function test results and no other signs of metabolic syndrome. Limited data regarding the impact of overweight or obesity on liver donor surgery is available in literature derived from Asia, where the majority of living donor surgeries were performed.[5] The obesity paradox showed protection against morbidity in nonbariatric general surgery, but data of liver-related surgeries were limited.[20] Studies have suggested a trend toward hazard of obesity in liver surgeries,[21—23] including donor surgery.[24] However, Toronto group found no difference in postoperative complications between donors with BMI <30 versus ≥30.[25] While there are several explanations for the existence of obesity paradox,[26] the exact biologic mechanism underlying the observation is unclear. In our series, most overweight donors were not obese (BMI between 25 and 30), with normal tests of blood chemistry, and without underlying systemic disease which might pose risk in donor surgery. These highly selective "healthy" people (though overweight) may be attributed to less complications. As overweight and obesity have become epidemics worldwide,[27] it is more likely for transplant surgeons to operate on these live donors. The potential accumulated risk of morbidity cannot be overemphasized and is a problem in need of further study.

A hazard trend (although most are minor complications) was observed in left lateral segment liver donation of overweight donors. This observation suggested that the underlying biological mechanism might not be dominated by hepatic steatosis. The difference between left lateral segment donation and left lateral segmentectomy was that the resection line in donor surgery was actually made central to the falciform ligament. Part of segment 4 was removed and vascular supply was sometimes compromised. Whether this caused potentially higher morbidity in overweight donors needs further investigation.

Right lobe donation has higher morbidity rates than left liver donation.[10,11] Our study showed no exception, with an overall complication rate of 20.9%. The reported complication rates in selected well-known centers ranges widely from 3.5% to 62.5%.[4] In period 2, more complications occurred when more complex anatomical variations of donors were permitted for donor hepatectomy. One of the reasons for this is that surgeons strive to make the recipient operation simpler if possible. They usually maintain a short or nearly zero biliary or vascular stump to make a common channel or patch for anastomosis. This may cause stenosis of the bile duct or vascular structure on the donor side. Efforts to improve surgical precision have been shown to decrease the "complication-prone" nature of right hepatectomy.[28,29] At our institute during period 3, the complication rates between right and left liver donation became nonsignificant. Compared with period 2, the complication rate after donor right hepatectomy was significantly less in period 3, implying surgical improvement. Accumulation of experience, communication with experts, continuous team maturation, and surgical instrument improvement may all contribute toward a safer environment for living liver donors.

The limitation of this study is the retrospective nature of a single center cohort. However, our study provides evidence from Asia that overweight is protective against morbidity in donor right hepatectomy but might be hazardous in left lateral segment liver donation. Our experience may also encourage developing centers that attempt to expand their donor pools by utilizing living donors but have great concern for donor safety.

5. Conclusion

The overall complication rate over two decades of experience was 20.9% and 3.2% for biliary morbidity. Right liver donation carried significantly more hazard than left, but the trend is nonsignificant in period 3. Most common complications were less than grade III. Overweight might be protective against morbidity in right hepatectomy.

Authors' contributions

CMH drafted the manuscript. CMH, YMH, MCH, and RHH designed the study. CMH, YMH, YMW, and PHL processed the data. CMH and YMH performed statistical analysis. MCH was the director responsible for general organization and instruction.

Funding source

Nil.

Potential conflict of interest

Nothing to report.

Acknowledgments

We thank all our liver transplant team members at National Taiwan University Hospital for their incredible and unceasing love and passion for the living donor liver transplant program. We thank Dr. Chi-Ling Chen for kindly providing statistical consultation.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.01.002.

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