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Liver transplantation using grafts of living donors with isolated unconjugated hyperbilirubinemia: a matched case–control study

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Summary

Unconjugated bilirubin has shown both cytotoxic and cytoprotective effects, acting as either an oxidant or an antioxidant. Elevated unconjugated bilirubin with otherwise normal, so-called isolated unconjugated hyperbilirubinemia (IUHB), is encountered frequently in living liver donor evaluation. However, the significance of IUHB on transplantation-related outcomes has not been clarified in donors and recipients. Forty-six living donors with IUHB were matched 1:1 with the control donors and 43 recipients who received grafts from donors with IUHB were matched 1:1 with the control recipients. Matched variables included donor/recipient age, residual liver volume, steatosis, cold ischemic time, graft versus recipient weight ratio, the MELD score and others. Donors in the control and IUHB group were comparable regarding the maximum postoperative transaminase concentrations, postoperative complications, and hospital stay. Recipients in the control and IUHB group were comparable regarding primary graft dysfunction, major postoperative complications, long-term ICU/hospital stay, 1-year mortality, and rejection rate, as well as recipient/graft survival rates. Recipients' unconjugated bilirubin concentration at 3 years after transplantation was higher in IUHB group with otherwise comparable liver function. It was concluded that living donor liver transplantation is safe for donors with IUHB and their recipients.

Introduction

Living donor liver transplantation (LDLT) has partially relieved the wide discrepancy between the demand of transplantation and the deceased donor liver supply at the price of donor safety [1]. Despite advances in surgical technique and perioperative management strategies, donor morbidity following liver resection remains considerable with overall complication ranging from 40% to 77% and major complication arising in 5–15% of cases [2,3]. The high rate of donor morbidity and increase in the use of marginal liver to compensate the demand has added to the ongoing controversy regarding the indication of LDLT [4].

Serum bilirubin is an essential parameter in preoperative donor evaluation. In principle, bilirubin concentrations should be within the normal range in that hyperbilirubinemia indicates the possibility of various pathologies, including hepatobiliary diseases. In practice, physicians frequently encounter donor candidates with elevated unconjugated bilirubin (UCB) level, and with otherwise normal liver function tests and no evidence of hemolysis or structural liver disease (so-called isolated unconjugated hyperbilirubinemia). However, the clinical significance of isolated unconjugated hyperbilirubinemia on living donor safety and transplant-related outcomes has not been clarified, which causes hesitancy regarding the indication of LDLT [5].

For long, UCB, as a waste product of heme degradation, was thought of as merely a toxic metabolite to be scavenged, which induces cell apoptosis and necrosis [6]. Apart from this cytotoxic effect, during the past two decades, a large body of evidence has illuminated alternative function

of UCB as a potent cell protector mainly in the field of cardiovascular and cancer medicine [7–9]. Recent experimental research has suggested that the cytoprotective properties of UCB could also be indicated in the hepatobiliary system [10–13].

Considering that the incidence of isolated unconjugated hyperbilirubinemia is not rare among the living donor population and that graft shortage is an essential problem, it is necessary to clarify whether the UCB affects the donor and recipient outcome. To address this issue, we investigated the effects of UCB in donors and recipients.

Patients and methods

The approval of Institutional Review Board was obtained for this retrospective matched case–control study. Five hundred thirty-five consecutive donors and recipients who underwent adult-to-adult LDLT between February 2007 and August 2012 were the initial screened population. Computerized medical records and prospectively collected liver transplantation database were the source of demographic, biochemical, and clinical information. Conjugated and UCB concentrations were estimated from total and direct bilirubin, being measured using Jendrassik-Grof diazo procedure with caffeine/benzoate solution (a widely used bilirubin analysis).

Propensity score based donor matching

Of the 535 donors, 217 (40.6%) underwent intermittent inflow occlusion during parenchymal dissection, and were excluded from the study along with the paired 217 recipients. Of the remaining 318 donors, 51 (16.0%) showed isolated unconjugated hyperbilirubinemia on preoperative evaluation, which was defined when total bilirubin (TB) concentration ≥ 1.2 mg/dl and conjugated bilirubin concentration ≤ 0.5 mg/dl [14]. Donors with isolated unconjugated hyperbilirubinemia were matched 1:1 with control donors with the followings as contributors to the propensity score [15]: age, gender, body mass index (BMI), alcohol intake history (immoderate intake was defined when daily alcohol intake >40 g for male and 20 g for female) [16], residual liver volume, and the presence of macro-/microvesicular steatosis [16]. Five hyperbilirubinemic donors were not matched with control donors because of the lack of identical propensity scores and excluded from the study. Overall, 46 matched hyperbilirubinemic-control donors were enrolled into the study.

Propensity score based recipient matching

Matching for recipients was performed independently from donor matching. Prior to the matching, two hyperbilirubinemic donors who underwent LDLT in the year of 2012 were excluded to obtain minimum follow-up period of 1 year. Remaining 49 recipients who received grafts from hyperbilirubinemic donors were matched 1:1 with control recipients with the followings as contributors to the propensity score: donor age, donor gender, macro-/microvesicular steatosis, cold ischemia time, recipients age, recipients gender, recipients BMI, graft versus recipients weight ratio, the MELD score, acute/emergent characteristic of hepatic failure, and the year of transplantation. Six hyperbilirubinemic recipients did not find control recipients with identical propensity scores and excluded. Overall, 43 matched hyperbilirubinemic-control recipients were enrolled into the study. The indications for transplantation of 86 donors were cirrhosis secondary to viral etiology (35 patients), hepatocellular carcinoma with viral cirrhosis (40 patients), hepatocellular carcinoma with alcoholic cirrhosis (two patients), alcoholic cirrhosis (four patients), cirrhosis secondary to Wilson disease (one patient), toxic hepatitis (one patient), autoimmune hepatitis (one patient), and cryptogenic cirrhosis (two patients).

Donor evaluation and intraoperative management

All living donors completed the multidisciplinary evaluation process. Acceptance criteria for donors were adult ≤ 65 years, BMI < 35 kg/m^2, normal biochemical laboratory test values (with the exception of isolated hyperbilirubinemia), macrovesicular steatosis $\leq 30\%$, and residual liver volume $\geq 30\%$. Computed tomography and magnetic resonance imaging were routinely performed to assess the vascular and biliary anatomy as well as to estimate the volume of the whole liver and the remnant liver. Right lobe grafts consisted of segment 5–8 without the middle hepatic vein trunk. For right hepatectomy, a transection plane was drawn after temporary inflow occlusion via the hepatic artery and portal vein on the right side of the liver. A parenchymal resection was performed using an ultrasonic dissector (CUSA EX cel^{TM}, Valleylab^{TM}, CO, USA) and a bipolar coagulator. After grafts procurement from donors, the graft liver was perfused through the portal vein by gravity flow with 2.5–3.0 l of histidine tryptophan ketoglutarate solution until the perfusate was clear. A cryopreserved iliac artery/vein was interposed for the drainage of the middle hepatic vein territory (V5 and 8) for a middle hepatic vein tributary ≥ 5 mm in size. Bile duct ductoplasty was performed whenever feasible.

Immunologic regimens

Recipients were given Basiliximab for immunosuppression induction during the operative procedure. Maintenance immunosuppression regimen consisted of a calcineurin

inhibitor, mycophenolate mofetil. Methylprednisolone 500 mg was given during surgery prior to reperfusion and gradually tapered off at approximately 3 months after surgery.

Study outcomes

With respect to donor analysis, the primary outcome was the incidence of postoperative complications. The secondary outcome was the peak transaminases (AST and ALT) level within the first week after surgery. With respect to recipient analysis, the primary outcomes were the 1-year mortality, primary graft dysfunction, and graft survival rate. The secondary outcomes were the incidence of major complications, rejection free rate as well as bilirubin concentrations at 3 years after surgery. Any deviation from the normal postoperative course was counted as complication and graded according to the Clavien-Dindo classification [17,18]. Major complication was defined as the complication of the Clavien-Dindo grades 2b to 4 (those requiring radiological/surgical intervention, organ failure, or death). Primary graft dysfunction was defined when the peak AST level >1500 IU/l and a prothrombin time <50% coexisting within the first week after surgery.

Statistical analysis

All data were analyzed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as median with IQR and analyzed using Mann–Whitney *U*-test. The categorical variables were expressed as number (%) and analyzed using Chi-squared test or Fisher's exact test, as appropriate. Survival analysis was performed using the Kaplan–Meier method, and comparison in the survival rate between hyperbilirubinemic and control groups were performed using Gehan–Breslow–Wilcoxon test. The outcome event for patient survival was "death" and for graft survival "hepatic failure". Death that was not associated with hepatic dysfunction was not counted as an event for the graft survival. A *P*-value of <0.05 was considered statistically significant.

Results

Matched donors analysis

There were no adverse intraoperative events, including massive blood loss or significant hypotension requiring rapid fluid infusion, transfusion, or death during living donor right hepatectomy. Table 1 showed that the matched variables were comparable between the control and hyperbilirubinemic group. The two groups were also comparable in terms of preoperative values of liver function tests with the exception of bilirubin concentrations. Preoperative TB and UCB levels in hyperbilirubinemic group were higher by two times those in the control group [TB, 1.5 (IQR 1.3–1.6, range 1.2–2.5 mg/dl) vs. 0.7 (IQR 0.6–0.8, range 0.3–1.1 mg/dl); UCB, 1.0 (IQR 1.0–1.2, range 0.9–2.1 mg/dl) vs. 0.5 (IQR 0.4–0.6, range 0.2–0.9 mg/dl)]. Operative time and the amount of intraoperative blood loss/infused fluids were also comparable.

Table 1. Demographic and operative data of donors in the control and hyperbilirubinemic group.

	Control (n = 46)	Hyperbilirubinemic (n = 46)	P
Age (years)	27 (22–37)	31 (23–41)	0.128
Gender (M/F)	39/6	36/10	0.346
Immoderate alcohol intake	4 (8.7)	2 (4.3)	0.677
Body mass index (kg/m^2)	23.6 (21.2–25.6)	22.6 (20.8–25.1)	0.223
Macrovesicular steatosis	23 (50.0)	20 (43.5)	0.531
Microvesicular steatosis	25 (54.3)	24 (52.2)	0.834
Residual liver volume	34 (32–40)	33 (31–36)	0.224
Operative time (min)	369 (333–400)	368 (325–405)	0.791
Blood loss (ml)*	366 (209–494)	330 (235–487)	0.976
Crystalloid (ml/h)	315 (253–429)	311 (255–377)	0.517
Preoperative level			
AST (IU/l)	17 (15–22)	18 (14–22)	0.938
ALT (IU/l)	20 (15–25)	18 (12–26)	0.407
Total bilirubin (mg/dl)	0.7 (0.6–0.8)	1.5 (1.3–1.6)	<0.001
Unconjugated bilirubin (mg/dl)	0.5 (0.4–0.6)	1.0 (1.0–1.2)	<0.001

Data are presented as median (IQR) or number (%).
*Calculated from perioperative hematocrit change and estimated blood volume.

The minimum/mean/longest follow-up period for donors was 70 days/3 months/8 months, respectively. As shown in Table 2, the maximum postoperative values of transaminase concentrations were not significantly different between the control and hyperbilirubinemic group. The maximum TB concentrations were significantly higher in hyperbilirubinemic group than in the control group. There was a significant linear association between preoperative and postoperative TB concentrations (Fig. 1). The overall complication rate was comparable. Also, the two groups showed comparable incidences of biliary, infectious, pulmonary, and wound complications, as well as intra-abdominal fluid collection and ileus. Major complications occurred with comparable incidences in the two groups. Transfusion rate and postoperative hospital stay were also identical. There were no patients who underwent intensive care after surgery in both groups.

Table 2. Postoperative outcome of donors in the control and hyperbilirubinemic group.

	Control (n = 46)	Hyperbilirubinemic (n = 46)	P
Postoperative maximum level			
AST (IU/l)	208 (171–268)	189 (163–245)	0.314
ALT (IU/l)	207 (175–263)	195 (166–227)	0.314
Total bilirubin (mg/dl)	3.1 (2.6–5.0)	4.4 (3.5–5.4)	0.007
Overall complication	28 (60.9)	26 (56.5)	0.672
Biliary*	3 (6.5)	2 (4.3)	0.646
Infectious†	4 (8.7)	2 (4.3)	0.677
Pulmonary‡	10 (21.7)	6 (13.0)	0.271
Wound§	12 (26.1)	10 (21.7)	0.625
Fluid collection	5 (10.9)	4 (8.7)	0.726
Ileus	3 (6.5)	3 (6.5)	1
RBC transfusion	4 (8.7)	3 (6.5)	0.694
FFP transfusion	9 (19.6)	10 (21.7)	0.797
Clavien-Dindo grade¶			
IIa	9 (19.6)	5 (10.9)	0.246
IIb	4 (8.7)	3 (6.5)	0.694
III + IV	0	0	–
Postoperative hospital stay	11 (9–16)	11 (10–15)	0.968

Data are presented as median (IQR) or number (%). There were donors with multiple morbidities.
*Biliary fluid collection, bile leakage, biloma, bile duct stricture.
†Any situation requiring antibiotics management.
‡Pleural effusion, atelectasis, pulmonary edema.
§Wound problem requiring procedure at bedside or operating room.
¶Grade IIa, complications requiring specific drug therapy or postoperative bleeding requiring >3 units of blood; grade IIb, complications requiring surgical, endoscopic, or radiological intervention; grade III, any complication with residual or lasting functional disability; grade IV, complications that lead to death.

Table 3. Transplant-related characteristics of recipients in the control and hyperbilirubinemic group.

	Normal UCB (n = 43)	High UCB (n = 43)	P
Donor factors			
Age (years)	29 (23–40)	29 (23–39)	0.822
Female gender	7 (16.3)	7 (16.3)	1
Total bilirubin (mg/dl)	0.7 (0.6–0.9)	1.5 (1.4–1.7)	<0.001
Unconjugated bilirubin (mg/dl)	0.5 (0.4–0.7)	1.1 (1.0–1.3)	<0.001
Macrosteatosis	19 (44.2)	18 (41.9)	0.828
Microsteatosis	24 (55.8)	21 (48.8)	0.517
Recipient factors			
Age (years)	52 (47–59)	53 (48–56)	0.917
Female gender	10 (23.3)	12 (27.9)	0.621
BMI (kg/m^2)	25.1 (22.0–27.1)	23.6 (22.0–26.3)	0.362
Primary causes			
HBV related	32 (74.4)	37 (86.0)	0.419
HCV related	4 (9.3)	2 (4.7)	
Alcoholic	4 (9.3)	1 (2.3)	
Others	3 (7.0)	3 (7.0)	
Underlying HCC	21 (48.8)	22 (51.2)	0.829
MELD	17 (14–31)	17 (14–27)	0.959
Acute deterioration of hepatic failure	5 (11.6)	5 (11.6)	1
GRWR (%)	1.08 (0.92–1.27)	1.10 (0.88–1.23)	0.976
Cold ischemia time (min)	84 (71–101)	90 (70–105)	0.442
Warm ischemia time (min)	31 (26–37)	33 (24–39)	0.833
Middle hepatic vein reconstruction	36 (83.7)	35 (81.4)	0.776

UCB, unconjugated bilirubin; MELD, model for end-stage liver disease; GRWR, graft versus recipient weight ratio.

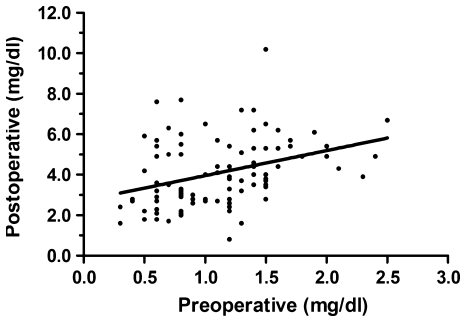

Figure 1 Linear relationship between preoperative bilirubin concentration and the maximum postoperative bilirubin concentration for 92 donors ($\beta = 1.23 \pm 0.34$, $P = 0.0006$).

Matched recipients analysis

Preoperative TB and UCB levels of paired donors in hyperbilirubinemic group were higher by more than two times those in the control group [TB, 1.5 (IQR 1.4–1.7, range 1.2–2.7 mg/dl) vs. 0.7 (IQR 0.6–0.9, range 0.3–1.0 mg/dl); UCB, 1.1 (IQR 1.0–1.3, range 0.7–2.3 mg/dl) vs. 0.5 (IQR 0.4–0.7, range 0.2–0.8 mg/dl)]. As expected, the control and hyperbilirubinemic group were comparable regarding the matched variables described above, including the MELD score, steatosis, cold ischemia time, graft versus recipients weight ratio, and acute/emergent deterioration of hepatic failure (Table 3). The two groups were also comparable in terms of the etiology for end-stage liver disease, warm ischemia time, and the rate of middle hepatic vein reconstruction.

The minimum follow-up period was 12 months for recipients. One recipient in control group and three in hyperbilirubinemic group developed primary graft dysfunction; among them, only one in the control group died with primary nonfunction (Table 4). The two groups showed a comparable vulnerability to the ischemia-reperfusion insult demonstrated by the median values of peak AST (225 vs. 351 IU/l) and ALT (263 vs. 300 IU/l). Overall major complication rate was comparable between the groups, as well

Table 4. Early and late outcome of recipients in the control and hyperbilirubinemic group.

	Normal UCB (n = 43)	High UCB (n = 43)	P
Peak AST (IU/l)*	225 (190–440)	351 (213–974)	0.055
Peak ALT (IU/l)*	263 (183–469)	300 (218–758)	0.153
Primary graft dysfunction	1 (2.3)	3 (7.0)	0.306
Overall major complication	31 (72.1)	23 (53.5)	0.074
Biliary stricture	19 (44.2)	18 (41.9)	0.828
Biliary leakage	4 (9.3)	1 (2.3)	0.167
ICU stay (days)	9 (7–15)	8 (7–11)	0.560
ICU stay >3 weeks	2 (4.7)	4 (9.3)	0.397
Hospital stay (days)	19 (12–22)	24 (19–36)	0.018
Hospital stay >6 weeks	16 (37.2)	13 (30.2)	0.494
3-month mortality	4 (9.3)	2 (4.7)	0.676
1-year mortality	6 (14.0)	7 (16.3)	0.763
3/5-year patient survival rate (%)	81.0/67.0	75.9/75.9	0.892
3/5-year graft survival rate (%)	85.1/80.4	86.7/86.7	0.577
1/3-year rejection free rate (%)	92.5/92.5	88.4/81.1	0.163
Biochemical tests at 3 years after surgery†			
Total bilirubin (mg/dl)	0.7 (0.5–1.4)	1.3 (0.7–1.6)	0.165
UCB bilirubin (mg/dl)	0.6 (0.4–1.1)	1.0 (0.6–1.2)	0.042
AST (IU/l)	29 (19–35)	29 (20–43)	0.615
ALT (IU/l)	19 (13–43)	28 (19–49)	0.357
PT (%)	100 (94–119)	96 (91–110)	0.777

Data are presented as median (IQR) or number (%).
*Peak serum transaminases within the first week after surgery.
†Data were obtained from 12 recipients in control group and 22 in hyperbilirubinemic group.

as the incidences of biliary stricture and biliary leakage requiring therapeutic interventions. The median ICU stay was comparable between the groups as well as was the proportion of recipients with long-term ICU stay (>3 weeks). Although the median hospital stay was longer in hyperbilirubinemic group than in the control group (24 vs. 19 days), the proportion of recipients with long-term hospital stay (>6 weeks) was comparable between the groups. The 3-month and 1-year mortality were comparable between the control and hyperbilirubinemic group (9.3% vs. 4.7% and 14% vs. 16.3%, respectively). The patients and graft survival rate were also comparable (Fig. 2). The event-free rate for pathologically diagnosed rejection was not significantly different, either.

The short-term postoperative course of UCB is shown in Fig. 3, which was comparable between the control and hyperbilirubinemic group. The values of biochemical liver function tests at 3 years after surgery were analyzed from 12 recipients in the control group and 22 in hyperbilirubinemic group who showed stable liver function with transaminase concentrations considered within normal range. The median UCB was significantly higher in hyperbilirubi-

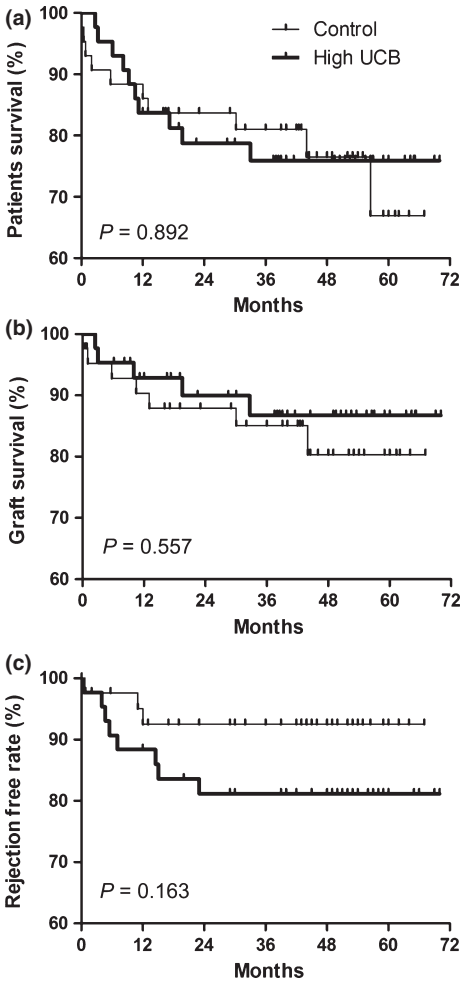

Figure 2 Recipient- (a) and graft (b) survival rates, as well as the rejection free rate (c), according to the donors' preoperative unconjugated bilirubin concentration.

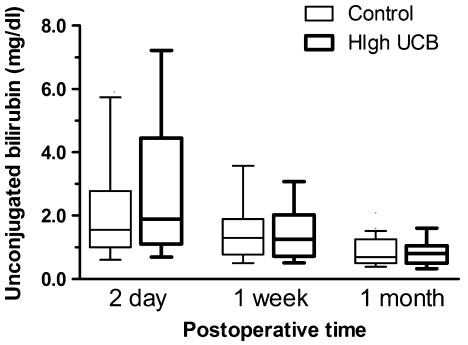

Figure 3 The postoperative course of unconjugated bilirubin of recipients according to donors' preoperative unconjugated bilirubin concentration. Box indicates the median value and IQR. Whiskers indicate 10 and 90 percentiles.

nemic group than in the control group (0.6 vs. 1.0 mg/dl, $P = 0.042$). The median TB did not reach statistical significance (control 0.7 vs. hyperbilirubinemic 1.3 mg/dl). Other tests showed comparable results (Table 4).

Discussion

As a potent antioxidant, UCB counteracts the oxidative stress and thus protect tissues from oxidant cell damage [7]. Accumulating evidence suggests that the cytoprotective action is mediated by anti-inflammatory, antiapoptotic, antiproliferative, and antioxidant mechanisms [19,20]. Recent experimental data have also identified that the protective role of UCB involves the inhibition of complement activity [21,22]. These molecular mechanisms were derived mainly from experimental studies and were tested in large epidemiologic studies initially in the field of cardiovascular diseases, cancer, and neuropathies [8,20,23]. More recent experimental studies have focused on the implications of the versatile effects of UCB on the liver [11–13,21,22].

However, the fact that UCB has shown cytotoxic effects along with cytoprotective effects depending on particular clinical scenarios has added to the hesitancy of physicians regarding the indication of liver harvesting [8,20,24]. The difficulty of this decision might increase with the existence of other risk factors. This study has determined that isolated unconjugated hyperbilirubinemia does not impair biochemical liver function and clinical outcomes after LDLT in both donors and recipients. Also, higher bilirubin concentrations shown in hyperbilirubinemic donors were considered as a benign finding as this finding did not translate into either impaired biochemical liver function or adverse clinical outcomes. Thus, preoperative isolated unconjugated hyperbilirubinemia should not limit the donor criteria or delay the operation until bilirubin concentration is within normal range, especially in the case of high emergency accompanied by acute deterioration of hepatic failure. In addition, considering the results of the study that isolated unconjugated hyperbilirubinemia has no harmful effect on postoperative outcomes, we recommend against liver biopsies or genomic test to confirm the exact etiology of high bilirubin with otherwise normal liver function tests and no evidence of hemolysis, e.g., Gilbert's syndrome, which exposes donors to unnecessary risk and cost. As the most common hereditary disease of hepatic bilirubin metabolism, Gilbert's syndrome is characterized by a mild, chronic, unconjugated hyperbilirubinemia. This condition is prevalent and thought to be benign because it does not result histological changes like chronic inflammation or progressive fibrosis. The syndrome tends to be detected during routine preoperative workup in relation to fasting state [9]. We believe that most of the hyperbilirubinemic donors in our study could be clinically diagnosed as Gilbert's syndrome.

Living liver donors have full evaluation with regard to physical/medical health status, as well as liver function and structural liver disease, by means of extended biochemical and imaging studies. Thus, the donors in hyperbilirubinemic group in the study could be diagnosed as isolated hyperbilirubinemia. Also, this study was carefully designed to minimize potential confounding effects. Propensity-based matching between the case and hyperbilirubinemic group in donors and recipients was performed independently; hyperbilirubinemic donors and their recipients who did not find donors and recipients with identical propensity scores were discarded. The data analysis determined that the control and hyperbilirubinemic groups were comparable for not only the matched variables but also other operative variables (donors in Table 1 and recipients in Table 3). Thus, despite the relatively small study population, the case–control pairs in donors and recipients in the study might be an appropriate model to assess the independent effect of UCB on the postoperative outcome.

The hyperbilirubinemic disposition of living donor liver graft seemed to transfer to recipient. The UCB level at 3 years after surgery was significantly higher in hyperbilirubinemic recipients than in nonhyperbilirubinemic recipients, being in consistent with previous clinical research [24–26]. Experimental studies in transplantation setting have demonstrated that UCB intervenes in whole courses of graft dysfunction and ameliorates ischemia reperfusion injuries, acute rejection, and chronic rejection *via* antioxidant and anti-inflammatory effects described elsewhere. A recent clinical study of patients undergoing kidney transplantation showed a protective effect of increased endogenous bilirubin against development of late graft failure [27]. Thus, it could be assumed that liver graft of donors with above-normal UCB level is associated with more favorable clinical courses in relation with ischemic reperfusion injury and rejections rather than be only considered as safe as the graft of donors with normal UCB [24,28]. In this study, however, the expected favorable effects of UCB on the biochemical hepatic injury demonstrated by transaminase concentrations during the early postoperative period, and graft rejection were not found. These results might be in part attributable to a delay required for the transfer and manifestation of the hyperbilirubinemic disposition of the transplanted graft [24]. All rejections in the study were pathologically diagnosed as acute rejections. Further research focusing on chronic graft rejection with longer follow-up period is warranted.

This retrospective study has limitations. First, donors in hyperbilirubinemic groups had a mild to moderately increased bilirubin concentrations with the maximum preoperative TB and UCB concentrations being 2.7 and

2.3 mg/dl, respectively. It is unclear whether greater UCB could result unfavorable/favorable effects [8,20,21]. Thus, the detailed dose-dependent effect of UCB needs to be determined. Secondly, postoperative UCB concentration was not analyzed in donors after hepatectomy because direct bilirubin was not measured routinely during the postoperative period in the institution of the study. Differential diagnosis of unconjugated/conjugated dominant hyperbilirubinemia after living donor hepatectomy might help the differential diagnosis between pathologic and physiologic hyperbilirubinemia.

The results of this study concluded that LDLT is safe for both donors who show isolated unconjugated hyperbilirubinemia with TB of ≤ 2.7 mg/dl and UCB of ≤ 2.3 mg/dl, as well as their recipients. Therefore, we recommend that mild to moderate isolated unconjugated hyperbilirubinemia shown in healthy donor candidates is not considered as an unfavorable factor limiting the donor criteria or delaying the LDLT.

Authorship

SBH: analyzed data and wrote the manuscript. GSK: designed study and gave critical revision of article. SJC: helped acquisition data and analyzed data. JSK: helped drafting article. MSG: gave critical revision of article. JWJ: helped acquisition data and gave critical revision of article.

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