Albumin-Bilirubin Score for Predicting Post-Transplant Complications Following Adult-to-Adult Living Donor Liver Transplantation

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Background: Albumin-Bilirubin (ALBI) grade has been evaluated as an objective method to assess liver function and predict postoperative complications, particularly after hepatectomy in patients with hepatocellular carcinoma (HCC). However, ALBI grade was rarely used in evaluation in living donor liver transplantation (LDLT).

Material/Methods: Between March 2005 and November 2015, 272 consecutive patients undergoing right-lobe LDLT were enrolled in this study. According to the ALBI score used to evaluate recipients preoperatively, those patients were divided into 3 grades (I, II, and III). Demographic findings and the post-operative complication rates were collected and compared among groups.

Results: The proportions of massive blood cell transfusions were different among those 3 grades (p<0.05). The patients in grade III had a higher risk of bacterial pneumonia and early allograft dysfunction (EAD) compared to grade I (p=0.029 and p=0.038, respectively) and grade II (p=0.006 and p=0.007, respectively). The area under the receiver operating characteristic curve of ALBI, Child-Pugh, and MELD for predicting 30-day mortality were 0.702 (95% CI: 0.644–0.756), 0.669 (95% CI: 0.580–0.697, p=0.510, versus ALBI grade), and 0.540 (95% CI: 0.580–0.697, p=0.144, versus ALBI grade), respectively.

Conclusions: ALBI grade was a good index for predicting post-operative complications and had a predictive ability similar to those of the Child-Pugh classification and MELD score.

MeSH Keywords: Liver Transplantation • Living Donors • Postoperative Complications

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Background

Since Starzl et al. performed the first liver transplantation (LT) successfully, LT has been regarded as the best choice for end-stage liver disease and selected malignant liver tumors [1–3]. However, due to scarcity of available grafts and the large number of patients awaiting LT, the mortality rate of patients on the waiting list remains high. As an important component of LT, living donor liver transplantation (LDLT) experienced a flourishing development in the past 2 decades, increasing the size of the donor pool, especially in most Asian countries [4]. As a partial graft, the liver graft size is a determinant of post-transplant outcome and survival of adult-to-adult LDLT (A-ALDLT) and was previously thought to be associated with high risk of early allograft dysfunction (EAD) and primary non-function (PNF) [5]. Aside from the donor status, the risk of post-operative complications was also associated with recipient characteristics, such as the etiology of diseases and preoperative liver function [6,7].

Preoperative assessment of the liver function is quite important because it is connected to the severity of liver disease, thereby predicting time on the waiting list and postoperative short- or long-term outcomes [8,9]. Various prognostic scores have been devised to predict the outcome of LT; the most commonly used systems are the Model for End-Stage Liver Disease (MELD) and Child-Pugh stage [10]. More recently, Johnson et al. developed a novel but simple model, named the Albumin-Bilirubin (ALBI) grade, to assess liver function in patients with HCC [11]. Studies have had demonstrated its effect in predicting the postoperative complication and survival after liver resection [12,13]. Moreover, it can be used in some other liver diseases, such as primary biliary cirrhosis and liver failure [14,15]. However, the ALBI score has not been evaluated for use in LT. Therefore, we designed the present study to evaluate the ALBI score in predicting post-transplant complications and to assess its predictive value compared to other systems in right-lobe A-ALDLT.

Material and Methods

This study was approved by the West China Hospital Ethics Committee and was performed in accordance with the ethics guidelines of the Declaration of Helsinki.

Patients

This was a retrospective study and all the clinical and demographic data were collected from the records of the Chinese Liver Transplant Registry (CLTR: *http://cltr.cotr.cn*). Between January 2001 and December 2015, 364 patients received LDLT at the Liver Transplantation Center of West China Hospital, Sichuan University, Chengdu, China. To avoid selection bias, left-lobe graft LDLT and pediatric liver transplantation were excluded. Finally, a total of 272 consecutive patients undergoing right-lobe A-ALDLT between March 2005 and November 2015 were involved in this study.

Patient age, sex, body mass index (BMI), and pre-transplant blood tests, including creatinine, total bilirubin (TB), and international normalized ratio (INR), were collected. The MELD score and Child-Pugh stage were calculated. Etiological factors and peri-operative complications were also analyzed. Moreover, cold ischemia and anhepatic phase, estimated blood loss, and blood transfusion was also assessed (Tables 1, 2).

Definition

The ALBI score was computed by a formula using only albumin and total bilirubin measurements [ALBI score=$\log_{10}$ bilirubin (µmol/L)×0.66) + (albumin (g/L)×−0.0852)], and the ALBI grades were stratified in 3 grades: grade I, ≤−2.60; grade II, <−2.60 to ≤−1.39; and grade III, >−1.39. For rapid assessment and calculated, an algorithm was designed based on a previous study [11].

The definition of EAD should include 1 or more of the following variables: (1) bilirubin ≥10 mg/dl on postoperative day 7; (2) INR ≥1.6 on postoperative day 7; and (3) aminotransferase level (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >2000 IU/ml within the first 7 post-operative days [6].

Small-for-size dysfunction (SFSD) was defined as the presence of 2 of the following on 3 consecutive days during the first postoperative week when a 'small' partial liver graft (GRWR <0.8%) was used and other causes were excluded: (1) bilirubin >100 umol/l, (2) INR > 2, and (3) encephalopathy grade 3 or 4 [16].

The Clavien-Dindo classification was used to assess the severity of post-operative complications. Grade III was defined as the course requiring surgical, endoscopic, or radiological intervention, grade IV was associated with life-threatening complications, and grade V was death of the patient [17]. In our study, massive blood transfusion was defined as receiving ≥5 red blood cell units within 24 h after transplantation.

Study design and statistical analysis

Statistical analysis was performed with IBM SPSS for Windows, version 19.0 (Armonk, NY, USA). Clinical data of the patients are expressed as counts, percentages, means and standard deviation, or median and range, as appropriate. The t test was used for continuous variables and the chi-square or Fisher's exact test was used in comparison of categorical variables. Based on the occurrence of some complications after LDLT, we assessed the predictive ability of ALBI, MELD, and Child-Pugh stages by

Table 1. Preoperative and surgical characteristics of recipients in different ALBI group.

	ALBI-I n=48		ALBI-II n=136		ALBI-III n=88		P value I vs. II	P value II vs. III	P value I vs. III
Recipient age (year)*	41.4	(±8.9)	42.9	(±8.8)	42.0	(±8.8)	0.311	0.451	0.708
Donor age (year)*	35.8	(±8.1)	36.7	(±10.4)	35.7	(±10.9)	0.561	0.507	0.947
Recipient Male (%)	41	(85.4)	114	(83.8)	75	(85.2)	0.795	0.777	0.976
Recipient BMI (kg/m²)*	22.9	(±2.5)	22.4	(±3.1)	22.54	(±3.40)	0.277	0.706	0.465
Pre-transplant creatinine (umol/L)*	80	(±25)	78	(±27)	99	(±64)	0.585	0.004	0.016
Pre-transplant bilirubin (umol/L)*	18	(±11)	61	(±107)	224	(±215)	<0.001	<0.001	<0.001
Pre-transplant INR*	1.11	(±0.21)	1.34	(±0.36)	2.32	(±1.97)	<0.001	<0.001	<0.001
MELD at Transplant*	7.5	(6.1–9.3)	11.5	(8.8–14.8)	17.6	(15.2–23.1)	<0.001	<0.001	<0.001
Child-Pugh stage									
A	18	(37.5)	40	(29.4)	4	(4.5)	0.300	<0.001	<0.001
B	29	(60.4)	83	(61.0)	28	(31.8)	0.940	<0.001	0.001
C	1	(2.1)	13	(9.6)	56	(63.7)	0.119	<0.001	<0.001
GRWR*	0.88	(±0.18)	0.96	(±0.22)	0.96	(±0.21)	0.009	0.968	0.014
Cold ischemia time (min)#	98	(20–201)	90	(20–191)	88	(21–188)	0.681	0.933	0.695
Duration of anhepatic phase (min)#	77	(63–95)	89	(67–110)	92	(64–109)	0.042	0.831	0.057
Estimated blood loss (mL)*	1183	(±1273)	1538	(±2045)	2045	(±2810)	0.165	0.146	0.015
Massive blood cell transfusion (%)	16	(33.3)	79	(58.1)	65	(73.9)	0.003	0.016	<0.001
Etiology of liver disease									
HBV infection (%)	39	(81.3)	105	(77.2)	60	(68.2)	0.559	0.134	0.102
HBV related cirrhosis without tumor (%)	4	(8.3)	32	(23.5)	31	(35.2)	0.021	0.057	0.001
HCC (%)	43	(89.6)	82	(60.3)	20	(22.7)	<0.001	<0.001	<0.001
Fulminant hepatic failure (%)	0	(0)	4	(2.9)	19	(21.6)	0.574	<0.001	<0.001

* Means (SD); # Median (IQR). BMI – body mass index; MELD – model for end-stage liver disease; GRWR – graft- to-recipient weight ratio; HCC – hepatocellular carcinoma.

the receiver operating characteristic (ROC) curve and corresponding area under the ROC (AUC) curve. The optimal cutoff value was set as the value of the Youden index, which was the maximizing sum of sensitivity and specificity. Comparison between different ROC was performed using MedCalc software (*https://www.medcalc.org*). Statistical differences were considered significant at p<0.05.

Results

Patients' characteristics

We enrolled 272 consecutive patients. The median age of recipients was 42.4±8.8 years old and 36.1±10.2 years old for

donors. Most patients (75.0%) had a history of HBV infection and 53.3% of all patients underwent LDLT due to hepatocellular carcinoma (HCC). Seventy-seven percent of patients had Child B and C stage of liver function. Seventy-two recipients (26.4%) received a small-for-size graft with GRWR less than 0.8%.

According to the definition of ALBI, we divided the patients into 3 ALBI grades and compared their characteristics (Table 1). Half of the patients were ALBI grade II when they underwent LDLT. There were no significant differences in age, sex, or BMI among the 3 groups. Pre-transplant TB, INR, and MELD were significantly different among the 3 grades (p <0.001). The percentage of patients in different Child stages were significantly different in ALBI grade III compared to ALBI I and II (p<0.001). The proportions of massive blood cell transfusions were different

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Table 2. Perioperative complications of recipients in different ALBI group.

	ALBI-I n=48		ALBI-II n=136		ALBI-III n=88		P value I *vs.* II	P value II *vs.* III	P value I *vs.* III
Pre-transplantation complications									
Encephalopathy (%)	0	(0)	3	(2.2)	17	(19.3)	0.569	<0.001	0.001
GI bleeding (%)	1	(2.1)	14	(10.3)	5	(5.7)	0.121	0.226	0.589
Peritonitis (%)	1	(2.1)	3	(2.2)	3	(3.4)	0.960	0.904	0.662
Renal insuffienciency (%)	1	(2.1)	1	(0.7)	4	(4.5)	0.455	0.155	0.801
Uncontrolled ascites (%)	1	(2.1)	12	(8.8)	18	(20.5)	0.189	0.013	0.007
Early post-operative complications (%)									
Post-operative bleeding (%)	2	(4.2)	3	(2.2)	9	(10.2)	0.840	0.021	0.363
Arterial thrombosis (%)	0	(0)	4	(2.9)	2	(2.3)	0.574	0.762	0.540
Portal vein thrombosis (%)	0	(0)	3	(2.2)	1	(1.1)	0.569	0.941	0.459
Biliary leakage (%)	0	(0)	4	(2.9)	3	(3.4)	0.574	0.844	0.552
Intra-abdominal collection (%)	8	(16.7)	23	(16.9)	18	(20.5)	0.969	0.503	0.591
Bacterial pneumonia (%)	1	(2.1)	5	(3.7)	12	(13.6)	0.951	0.006	0.029
Pleural effusion (%)	9	(18.8)	24	(17.6)	17	(19.3)	0.864	0.752	0.936
Renal failure (%)	0	(0)	3	(2.2)	4	(4.5)	0.569	0.555	0.297
EAD (%)	3	(6.3)	12	(8.8)	19	(21.6)	0.800	0.007	0.038
GRWR <0.8%	16	(33.3)	37	(27.2)	19	(21.6)	0.420	0.343	0.134
SFSD (/GRWR <0.8%), (%)	2	(12.5)	7	(18.9)	6	(31.6)	0.863	0.288	0.244
SFSD (%)	2	(4.2)	7	(5.1)	6	(6.8)	0.787	0.601	0.805
Late post-operative complications (%)									
Hepatic vein thrombosis (%)	1	(2.1)	2	(5.1)	3	(3.4)	0.773	0.620	0.662
Biliary leakage (%)	0	(0)	5	(3.7)	3	(3.4)	0.329	0.916	0.552
Biliary stenosis (%)	1	(2.1)	7	(5.1)	4	(4.5)	0.629	0.839	0.801
Dindo-Clavien IIIb, IV within 30d (%)	7	(14.6)	16	(11.8)	20	(22.7)	0.612	0.029	0.255
30-day mortality	1	(2.1)	5	(3.7)	13	(14.8)	0.593	0.003	0.042
6-month mortality	4	(8.3)	13	(9.5)	20	(22.7)	0.801	0.007	0.035

GI – gastrointestinal bleeding; EAD – early allograft dysfunction; SFSD – small-for-size dysfunction.

among the 3 grades (grade I versus grade II, p=0.003; grade II versus grade III, p=0.016; grade I versus grade III, p<0.001). The average GRWR was smaller in ALBI grade I (versus grade II, p=0.009; versus grade III, p=0.014). Most patients (89.6%) in ALBI grade I were diagnosed as HCC, compared to 60.3% in grade II (p<0.001) and 22.7% in grade III (p <0.001). Moreover, nearly 21.6% of the patients in ALBI grade III underwent LDLT due fulminant hepatic failure.

Perioperative complications of recipients in different ALBI groups

The perioperative complications of recipients are listed in Table 2. The proportion of pre-transplantation encephalopathy and uncontrolled ascites was significantly higher in ALBI grade III (encephalopathy: versus grade I, p=0.001, versus grade II, p<0.001; uncontrolled ascites: versus grade I, p=0.013, versus grade II, p=0.007). Similarly, the patients in grade III had a higher risk of bacterial pneumonia and EAD compared
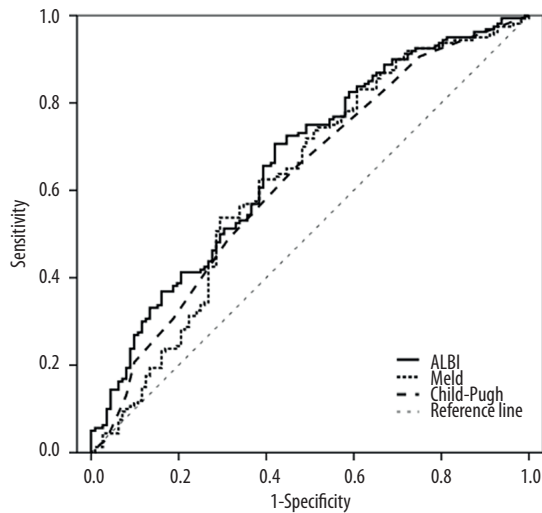
Figure 1. Receiver operating characteristics (ROC) curves for preoperative albumin-bilirubin (ALBI), MELD, and Child-Pugh in predicting intra-transplant probability of massive blood transfusion in the whole group of living donor liver transplantation patients.

to grade I (p=0.029 and p=0.038, respectively) and grade II (p=0.006 and p=0.007, respectively). Moreover, the 30-d mortality was significantly higher in grade III (14.8% versus 2.1% in grade I, p=0.042; versus 3.7% in grade II, p=0.003). The occurrence of post-operative bleeding and severe complication defined as Dindo-Clavien IIIb and above were different between grade II and grade III (p=0.021 and p=0.029, respectively). However, in the subgroup of HCC patients, there were

no significant differences in complication rates among different ALBI groups (all p>0.05).

Comparison of ability to predict complications among different systems

The diagnostic accuracies in predicting major complications of the 3 systems (ALBI, Child-Pugh classification, and MELD scores) were compared with the ROC method. The intra-transplant probability of massive blood transfusion is shown in Figure 1. The AUCs of ALBI, Child-Pugh, and MELD were 0.664 (95% CI: 0.604–0.720), 0.626 (95% CI: 0.565–0.684, p=0.179, versus ALBI grade), and 0.626 (95% CI: 0.566–0.684, p=0.152, versus ALBI grade), respectively.

As shown in Figure 2A, the AUCs of ALBI, Child-Pugh, and MELD in predicting postoperative bacterial pneumonia were 0.765 (95% CI: 0.710–0.814), 0.690 (95% CI: 0.632–0.745, p=0.153, versus ALBI grade), and 0.716 (95% CI: 0.658–0.768, p=0.439, versus ALBI grade), respectively. ALBI had a cutoff value of −1.180 with a sensitivity of 66.7% and a specificity of 80.7%. Child-Pugh had a cutoff value of 9.5 with a sensitivity of 61.1% and a specificity of 76.8%. MELD had a cutoff value of 13 with a sensitivity of 83.3% and a specificity of 56.7%. The predictive abilities of post-transplant EAD are shown in Figure 2B. The AUCs of ALBI, Child-Pugh, and MELD were 0.659 (95% CI: 0.599–0.715), 0.621 (95% CI: 0.560–0.679, p=0.348, versus ALBI grade), and 0.630 (95% CI: 0.570–0.688, p=0.490, versus ALBI grade), respectively.

Moreover, we compared the predictable ability of postoperative severe complication rates and 30-day mortality. The AUCs
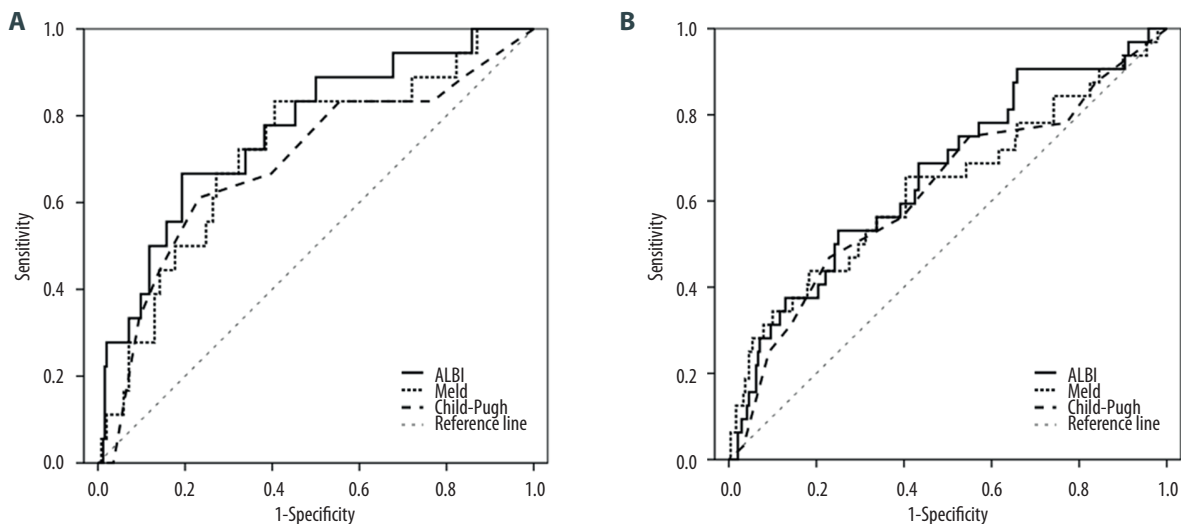

Figure 2. Receiver operating characteristics (ROC) curves for pre-operative albumin-bilirubin (ALBI), MELD, and Child-Pugh in predicting postoperative bacterial pneumonia (**A**) and early allograft dysfunction (**B**).
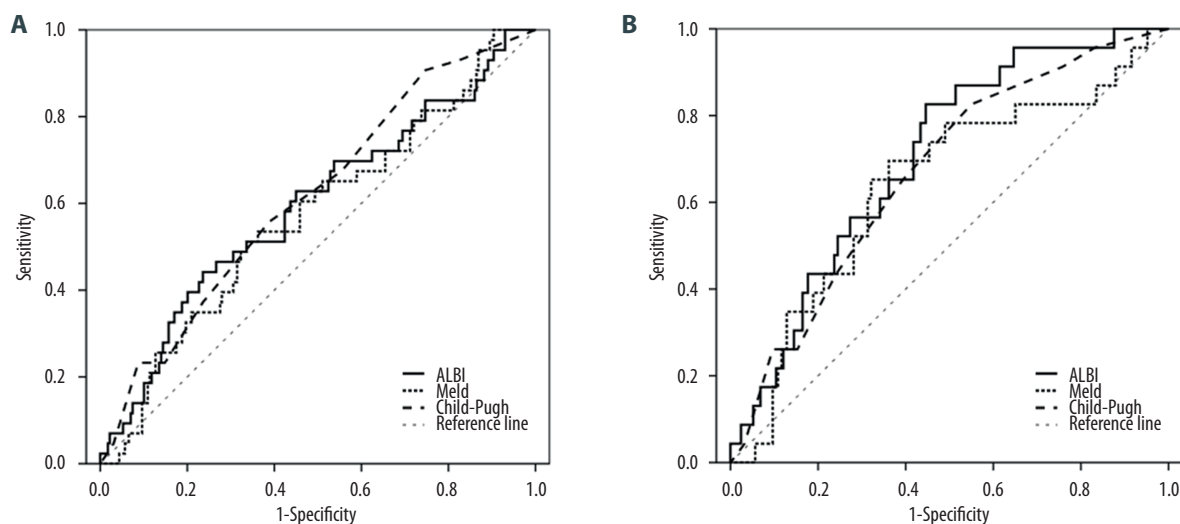
Figure 3. Receiver operating characteristics (ROC) curves for pre-operative albumin-bilirubin (ALBI), MELD, and Child-Pugh in predicting severe complication rate (**A**) and 30-day mortality (**B**).

of ALBI, Child-Pugh, and MELD for predicting severe complication rate were 0.594 (95% CI: 0.533–0.653), 0.615 (95% CI: 0.555–0.673, p=0.535, versus ALBI grade), and 0.573 (95% CI: 0.511–0.632, p=0.445, versus ALBI grade), respectively, which is shown in Figure 3A. Figure 3B shows that the AUCs of ALBI, Child-Pugh, and MELD for predicting 30-day mortality were 0.702 (95% CI: 0.644–0.756), 0.669 (95% CI: 0.580–0.697, p=0.510, versus ALBI grade), and 0.540 (95% CI: 0.580–0.697, p=0.144, versus ALBI grade), respectively. ALBI had a cutoff value of −1.775 with a sensitivity of 82.6% and a specificity of 55.4%.

Discussion

To increase the pool of available organs and alleviate the organ shortage problem, LDLT was first introduced by Raia in 1989 [18]. In some countries, the percentage of LDLT was more than 90% of the liver transplant activity [19]. Pre-operative evaluation of liver function is extremely important; it not only decides the severity of disease and the waiting time for liver sources, but is also closely related to intraoperative risks and postoperative complication rate and outcome. Recently, Johnson et al. created a new model, named ALBI grade, to assess liver function before hepatectomy in patients with HCC [11]. In that study, a training cohort of 1313 Japanese patients and a validation cohort of 5097 patients from other geographic regions were involved. Only 2 objective indexes, albumin and bilirubin, were used in the model. Thereafter, ALBI grade was widely applied in several aspects of liver disease to assess liver function and predict outcome of treatments compared with the Child-Pugh stage and MELD score [14,15,20–22]. The ALBI

score is the simplest score compared to other scores that need 4 or 5 parameters. Moreover, albumin and bilirubin are easily obtained and objectively evaluated, avoiding the subjective judgment involved in in clinical ascites and encephalopathy, although these 2 parameters are always important when different treatments are considered. According to the definition of ALBI, we divided the patients into 3 ALBI grade groups in our study. The occurrence of preoperative encephalopathy and ascites involved in Child-Pugh stage are higher in ALBI grade III group than in the lower ALBI group (grade I and II). Pre-transplant creatinine and INR, which are the main parameters in MELD and even the MELD score itself, were significantly different between ALBI grade III and the ALBI grade I and II. This suggests that the pre-transplant INR, creatinine, encephalopathy, and ascites may not be complementary due to their interrelationships with bilirubin and albumin. Moreover, we used the ROC method to compare the ALBI grade to Child-Pugh classification and MELD score in predicting intra-operate probability of massive blood transfusion, post-operative occurrence of EAD and bacterial pneumonia, postoperative severe complication rate, and 30-day mortality. The results show that ALBI is compatible with Child-Pugh classification and MELD score without significant differences. This suggests that the ALBI grade just using 2 indexes could probably be satisfactory in predicting postoperative complications compared the Child-Pugh classification and MELD score.

Massive blood transfusion in the perioperative period was usually considered to be associated with the preoperative coagulopathy of liver disease and the history of upper-abdominal surgery [23,24]. Donor condition, such as donor age and high level of serum sodium, was also related to the massive blood

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transfusion rate [25]. Pre-transplant INR, hemoglobin, platelet, and creatinine were also independent risk factors [23,26]. Although multiple studies have included the preoperative Child-Pugh classification to analyze its association in increased blood loss and massive blood transfusion during liver transplantation, the results were contradictory [23,24,26,27], and some studies also showed that the MELD score might not predict blood loss and blood product requirements [28]. Massive blood transfusion and massive blood loss can probably result in dysfunctional immunity and some other complications. As previous studies reported, due to the immunosuppression, massive blood transfusion, and prolonged period of mechanical ventilation during surgery, LDLT patients also had a high risk of postoperative bacterial pneumonia [29–31]. The incidence rate of early-onset pneumonia has reported to be 14.5% to 18.2%, with mortality rates of 21.7% to 25.5% [30–32]. In our study, we demonstrated that the preoperative ALBI grade could possibly predict the occurrence of massive blood transfusion and bacterial pneumonia, and thereby provide an approach to estimate the perioperative risk.

Donor characteristics, transplantation procedure, and recipient status all affect the initial graft function after LDLT. In a previous study, Pomposelli et al. [33] analyzed the risk factors associated with EAD in 631 LDLT recipients. They found that left-lobe grafts, smaller GRWR grafts, higher operative bilirubin, higher portal reperfusion pressure, older donor age, and higher donor BMI are risk factors for developing EAD after LDLT. In our study, the ALBI could also provide a good way to predict the occurrence of EAD, especially for patients between the higher ALBI group (grade III) and lower ALBI group (grade I and II). In the procedure of liver transplantation, transplant surgeons try to guarantee adequate liver volume for both recipients and donors. Even though an increasing number of successful transplantation cases with small size grafts have been reported in recent years, the sufficient function of undersized grafts was still a major concern [34,35]. When small partial grafts are unable to meet the demands, SFSS might occurred in recipients when the grafts are smaller than 0.8% GRWR [16]. In our study, 26% of recipients received small grafts. For ALBI grade I recipients, the percentage could reach 33.3%, but in the 16 ALBI grade I patients whose grafts were less than 0.8% GRWR, only 2 had SFSD. Although there was not significant difference in the results, a smaller graft could possibly be a safer choice for lower ALBI-grade patients and should be considered in future preoperative decision-making.

The ALBI grades are usually used as an alternative index of liver function in HCC patients [36,37]. Most studies focused on liver resection, radiofrequency ablation, and transarterial chemoembolization, but few studies specifically discussed the impact of ALBI in liver transplantation. Chen et al. demonstrated that ALBI grade could be integrated into the Cancer of the Liver Italian Program (CLIP) systems, the Barcelona Clinic Liver Cancer (BCLC) systems, and the Japan Integrated Staging (JIS) in certain patients, which provided a reasonable prognostic information for the HCC patients and was as useful as the Child-Pugh stage [20,36,38]. Moreover, Dong et al. suggested that the ALBI score was correlated to the serum gamma-glutamyl transpeptidase in solitary HCC within the Milan criteria and Child-Pugh A cirrhosis, which could be used to screen the postoperative intrahepatic recurrence in HCC populations [37]. However, due to the lack of samples in our study, we did not demonstrate a significant difference in complication rates among different ALBI grades in the subgroup of HCC and fulminant hepatic failure patients.

There are some limitations in our study. Firstly, it was a retrospective study and a single-center experience, and certain biases could not be avoided completely. Secondly, the total number of LDLT patients was small and the occurrence of some complications was low, so we did not use a validation group to judge the effect of ALBI in predicting the outcome. Thirdly, even though we compared the 30-day mortality rates of these patients, we did not compare the survival rates in different groups because the percentage of HCC patients was much more in the lower ALBI grades, which may have influenced the overall survival rate.

Conclusions

ALBI grade is a good index for predicting post-operative complications and had a predictive ability similar to those of the Child-Pugh classification and MELD score.

Conflict of interest

None.

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