TABLE 1 Comparisons of patients' background characteristics

Variables	B-HCC ($n = 110$)	C-HCC ($n = 474$)	NBNC-HCC ($n = 110$)	p value	
				Versus B-HCC	Versus C-HCC
Age (year)	55 ± 11	68 ± 8	66 ± 10	<0.0001	0.0882
Male/female	83/27	304/170	81/29	0.7569	0.0541
BMI	23.1 ± 2.8	23.0 ± 3.1	22.9 ± 3.3	0.7389	0.7334
DM (%)	19 (17 %)	133 (28 %)	42 (38 %)	0.0005	0.1014
Daily drinking (%)	28 (26 %)	104 (22 %)	41 (37 %)	0.0322	0.0018
Plt ($\times 10^4$ μl)	15.3 ± 17.4	17.6 ± 44.3	20.5 ± 24.3	0.0658	0.4977
T-bil (mg/dl)	0.9 ± 0.4	0.8 ± 0.3	0.8 ± 0.4	0.1263	0.2215
Alb (g/dl)	4.0 ± 0.4	3.8 ± 0.2	4.0 ± 0.4	0.8278	0.0011
AST (IU/L)	42 ± 24	57 ± 38	43 ± 29	0.8725	0.0003
ALT (IU/L)	43 ± 27	57 ± 39	41 ± 30	0.5280	<0.0001
PT (%)	86 ± 15	88 ± 16	90 ± 17	0.0549	0.1516
ICGR15 (%)	15.7 ± 12.1	19.7 ± 10.8	16.2 ± 10.1	0.7344	0.0025
Child A (%)	104 (95 %)	438 (92 %)	103 (94 %)	0.7748	0.7538
Liver damage A (%)	85 (77 %)	313 (66 %)	84 (76 %)	0.9869	0.1018

BMI body mass index, *DM* diabetis melitus, *Plt* platelet count, *T-bil* total bilirubi, *Alb* albumin, *AST* asparate aminotransferase, *ALT* alanine aminotransferase, *ICGR15* indocyaine green retention rate at 15 min

TABLE 2 Comparison of short-term outcomes

Variables	B-HCC ($n = 110$)	C-HCC ($n = 474$)	NBNC-HCC ($n = 110$)	p value	
				Versus B-HCC	Versus C-HCC
Surgical outcomes					
Operation time (min)	230 ± 106	214 ± 94	230 ± 93	0.9814	0.1038
Blood loss (g)	614 ± 663	637 ± 1172	700 ± 648	0.3317	0.5832
Transfusion (%)	33 (30 %)	166 (35 %)	37 (34 %)	0.3521	0.7591
Resected volume (g)	206 ± 260	116 ± 170	247 ± 314	0.2980	<0.0001
Anatomical resection (%)	57 (52 %)	157 (33 %)	55 (50 %)	0.7874	0.0011
Surgical margin (mm)	4 ± 6	5 ± 6	5 ± 6	0.4932	0.9408
Postoperative courses					
Mortality (%)	1 (1 %)	2 (0.4 %)	2 (2 %)	0.5573	0.5301
Morbidity (%)	28 (25 %)	162 (34 %)	30 (27 %)	0.7596	0.1870
Hospital stay (days)	21 ± 17	22 ± 18	21 ± 12	0.8423	0.5002

C-HCC group (33 %; $p = 0.0011$). There were no significant differences in mortality, morbidity, or the duration of hospital stay among the three groups.

Tumor-Related Factors

The tumor-related factors are summarized in Table 3. The mean tumor size in the NBNC-HCC group (4.5 ± 3.6 cm) was significantly larger than that in the C-HCC group (2.9 ± 1.8 cm; $p < 0.0001$). The ratio of a plural number of HCC in the NBNC-HCC group (13 %) was significantly lower than that in the C-HCC group (22 %; $p = 0.0314$). The ratio of poorly differentiated HCC in the NBNC-HCC group (36 %) was significantly higher than that in the C-HCC group (31 %; $p = 0.0019$). The serum level of α-fetoprotein (AFP) in the NBNC-HCC group (1,407 ± 4,410 ng/mL) was significantly higher than that in the C-HCC group (449 ± 2,051 ng/mL; $p = 0.0007$). The complication rate of histological cirrhosis (lc) in the NBNC-HCC group (37 %) was significantly lower than that in both the B-HCC group (67 %; $p < 0.0001$) and C-HCC group (53 %; $p = 0.0061$).

Survival After Hepatic Resections for HCC

The disease-free survival (DFS) and overall survival (OS) curves are provided in Fig. 1. There were no significant differences in DFS or OS among the three groups.

TABLE 3 Comparison of tumor-related factors

Variables	B-HCC (n = 110)	C-HCC (n = 474)	NBNC-HCC (n = 110)	p value	
				Versus B-HCC	Versus C-HCC
Tumor diameter (cm)	3.7 ± 2.7	2.9 ± 1.8	4.5 ± 3.6	0.0588	<0.0001
Plural number	22 (20 %)	104 (22 %)	14 (13 %)	0.2188	0.0314
Poorly dif. (%)	27 (25 %)	148 (31 %)	40 (36 %)	0.0765	0.0019
fc (+) (%)	68 (62 %)	315 (66 %)	72 (65 %)	0.1294	0.7790
fc-inf (+) (%)	51 (46 %)	246 (52 %)	58 (53 %)	0.3345	0.8491
vp/im (+) (%)	70 (64 %)	259 (55 %)	60 (55 %)	0.0957	0.8864
Stage III or IVA (%)	61 (55 %)	227 (48 %)	57 (52 %)	0.8626	0.6499
AFP (ng/ml)	5024 ± 4323	449 ± 2051	1407 ± 4410	0.3848	0.0007
DCP (mAU/ml)	1599 ± 5333	1504 ± 4318	1450 ± 3843	0.8284	0.9130
lc (+) (%)	74 (67 %)	251 (53 %)	41 (37 %)	<0.0001	0.0061

Poorly dif. poorly differentiated HCC, *fc* fibrous capsule, *fi-inf* fibrous capsule infiltration, *vp* portal venous infiltration, *im* intrahepatic metastasis, *AFP* α-fetoprotein, *DCP* Des-γ-carboxy prothrombin, *lc* histrological liver cirrhosis

The 5-year DFS rates in the B-HCC, C-HCC, and NBNC-HCC groups were 36, 32, and 37 %, respectively. The 5-year OS rates in the B-HCC, C-HCC, and NBNC-HCC were 65, 68, and 67 %, respectively.

Recurrence After Hepatic Resection for HCC

Table 4 summarizes the pattern of recurrence, as no recurrence, liver recurrence ≤3 nodules, or liver recurrence >3 nodules and/or distant recurrence after curative resection of HCC. The rate of liver recurrence >3 nodules and/or distant recurrence (i.e., "multiple or distant recurrence") in the NBNC-HCC group (25 %) was significantly higher than that in the C-HCC group (17 %; $p = 0.0482$).

Table 5 summarizes the durations of HCC recurrence after curative resection of HCC, as no recurrence, within 2 years (i.e., "early recurrence"), over 2 years (i.e., "late recurrence"). The rate of late recurrence in the NBNC-HCC group (24 %) was significantly higher than that in the B-HCC group (12 %; $p = 0.0223$).

DISCUSSION

It is generally accepted that NBNC-HCC can be caused by alcoholic liver injury, autoimmune hepatitis, primary biliary cirrhosis, Budd-Chiari syndrome, occult HBV infection (anti-HBc-antibody positive), nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), aflatoxin B1 exposure, and other conditions.[19–25] In our patient series, the complication rate of daily drinking in the NBNC-HCC group (37 %) was significantly higher than those in both the B-HCC (26 %; $p = 0.0322$) and the C-HCC groups (22 %; $p = 0.0018$). Thirty-two patients (29 %) in the NBNC-HCC group were positive for anti-HBC-antibody. However, in our series, histological examination identified the possible cause of HCC in only

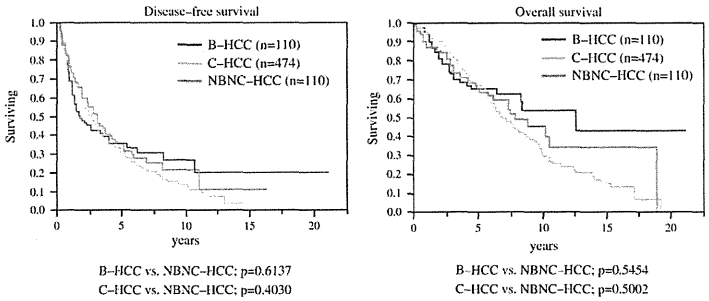
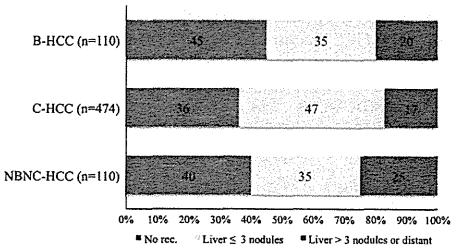


FIG. 1 Disease-free (DFS) and overall survival (OS) curves after curative resection in patients with HBs-Ag-positive HCC (B-HCC), HCVAb-positive HCC (C-HCC), or HBsAg-negative/HCVAb-negative HCC (NBNC-HCC)

TABLE 4 Recurrence patterns of HCC



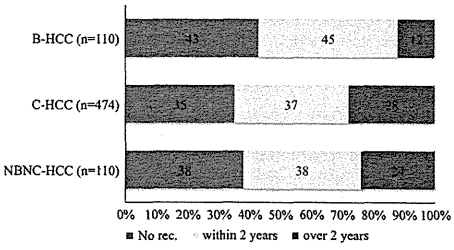
* Ratio of "Liver >3 nodules or distant" in the NBNC-HCC group is significantly higher than that in the C-HCC group ($p = 0.0482$)

17 patients, alcoholic liver injury in ten patients, autoimmune hepatitis in one patient, primary biliary cirrhosis in 1 patient, and NASH in five patients. Among almost remaining 103 patients in the NBNC-HCC group, histological examination revealed the mild inflammation and/or fatty changes of the liver; however, we could find out no possible causes of HCC in such patients.

Epidemiological studies showed that metabolic disorders such as diabetes mellitus and obesity were powerful risk factors for the development of HCC.[26,27] In our present series, however, there were no significant differences in body mass index (BMI) among the three groups. The complication rate of diabetes mellitus in the NBNC-HCC group (38 %) was significantly higher than that in the B-HCC group (17 %; $p = 0.0005$). Therefore, in our series, alcohol liver injury and diabetes mellitus should be one of the major causes related to NBNC-HCC.

According to previous reports, the liver function of patients with NBNC-HCC is more preserved and the values of AST/ALT are less than those of patients with C-HCC.[5,10,11,28] Also

TABLE 5 Duration of HCC recurrence after curative resection



* Ratio of "over 2 years" in the NBNC-HCC group is significantly higher than that in the B-HCC group ($p = 0.0223$)

in our series, the serum value of albumin in the NBNC-HCC group was significantly higher ($p = 0.0011$), ICGR-15 was significantly lower ($p = 0.0025$), and that of AST/ALT was significantly lower ($p = 0.0003, p < 0.0001$) than those in the C-HCC group. The indicators of liver function in the NBNC-HCC group were similar to those in the B-HCC group, but the complication rate of lc in the NBNC-HCC group (37 %) was significantly lower than those in the B-HCC (67 %; $p < 0.0001$) and in the C-HCC groups (53 %; $p = 0.0061$).[5] The complication rate of lc in the C-HCC group seems low, although consistent with previous Japanese reports (44 %).[10,11] From these results, we hypothesized that the mechanism of NBNC-HCC may be closely related not to the generally accepted concept of "stepwise progression" but rather to the alternative hypothesis of "de novo development.".[29,30]

Concerning the tumor-related factors, we found that in the present series, the mean HCC diameter was significantly larger (4.5 vs. 2.9 cm; $p < 0.0001$), the rate of poorly differentiated HCC was significantly higher (36 vs. 31 %; $p = 0.0019$), and the AFP values were significantly higher (1,407 vs. 449 ng/mL; $p = 0.0007$) in the NBNC-HCC group compared with those in the C-HCC group. In our series, the complication rate of a plural number of HCC was significantly lower in the NBNC-HCC group than in the C-HCC group (13 vs. 22 %; $p = 0.0314$); however, the tumor-grade itself of the NBNC-HCC patients was more advanced than that of the C-HCC patients at hepatic resection. We suspected that this was due to the lack of periodic checkup of the HCC in patients with NBNC-HCC compared with the patients with C-HCC.[5,10,11,28] Hatanaka et al. described that there were many similar factors in background liver and HCC characteristics between patients with B-HCC and NBNC-HCC.[5]

Kaibori et al. summarized the short-term surgical results of patients with NBNC-HCC, and they reported that there were no significant differences in morbidity, surgical time, or surgical blood loss compared with those of patients with B-HCC or C-HCC.[10] They also reported that the rate of limited hepatic resection was significantly higher (55 %) than that with C-HCC (83 %; $p = 0.0041$). Also in our series, the short-term surgical results, such as mortality, morbidity, and hospital stay, of the patients with NBNC-HCC were not significantly different from the corresponding values of the patients with B-HCC or C-HCC. Perhaps due to the larger tumor size and better liver function, the NBNC-HCC group's rate of anatomical resection was significantly higher (55 vs. 33 %; $p = 0.0011$), and the resected liver volume was significantly larger (247 vs. 116 g; $p < 0.0001$) than those in the C-HCC group. Irrespective of the higher rate of more invasive operations in the NBNC-HCC group compared with the C-HCC group, the better liver function which we

reported was the most variable indicator of good postoperative patients' course in the NBNC-HCC group would pull up the short-term surgical results to the same level as those of the C-HCC group.[31]

Our data concerning the prognosis in the NBNC-HCC group after hepatic resection indicted that there were no significant differences compared with the prognoses of the B-HCC and the C-HCC groups. Multiple and distant recurrences were observed significantly more often in the NBNC-HCC group than in the C-HCC group (25 % vs. 17 %; $p = 0.0482$), and delayed recurrence (over 2 years) was observed significantly more often in the NBNC-HCC group than in the B-HCC group (24 vs. 12 %; $p = 0.0223$). These were the most important results of the present analysis. In previous reports, the DFS rate of patients with NBNC-HCC after hepatic resection was better compared with that of patients with C-HCC.[10,11] Irrespective of the low complication rate of lc in the background liver in the present NBNC-HCC group, the metachronous multicentric recurrence of HCC which would occur over 2 years after the curative resection of a primary HCC might be more frequent in the NBNC-HCC group than that in the B-HCC group. This result demonstrates that the effective treatment strategy should be established to prevent HCC occurrence from NBNC-hepatitis as early as possible.

In our series, mild fatty liver and mild liver fibrosis were found in most of the patients with NBNC-HCC (NBNC-hepatitis). Steatohepatitis should thus be considered one of the important causes of NBNC-HCC. Takai et al. summarized the importance of reactive oxidative stress (ROS) in steatohepatitis and HCC occurrence from NASH.[32] Regarding the control of ROS, hydrogen-rich water and apomycin can be expected to be possible preventive drugs against HCC occurrence from NBNC-hepatitis.[33,34] Yoshimoto et al. reported that obesity-induced gut microbial metabolites promote HCC through a senescence secretome via DNA damage of hepatic stellate cells.[35] Via the control of microbial metabolites, oral vancomycin or ursodeoxycholic acid may be effective to prevent HCC occurrence from NBNC-hepatitis.[35] Li et al. recently reported that women with NBNC-HCC had poor prognoses, and it might be worthwhile to evaluate estrogen administration for the maintenance of sex hormone balance to improve these poor outcomes.[12] We should recognize that there could be a high possibility of HCC occurrence from NBNC-hepatitis compared with B-hepatitis after curative hepatic resection, and long-term follow-ups are needed for patients with NBNC-HCC.

In conclusion, the surgical outcomes including prognosis of patients with NBNC-HCC were not significant different compared to those of patients with B-HCC or C-HCC. There was a substantial population with late recurrence among the patients with NBNC-HCC after curative hepatic resection, and thus not only long-term follow-up but also the early establishment of drugs for preventing HCC recurrence from NBNC-hepatitis are desired.

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Preemptive Thoracic Drainage to Eradicate Postoperative Pulmonary Complications after Living Donor Liver Transplantation

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BACKGROUND: Thoracic fluid retention after living donor liver transplantation (LDLT) has various negative consequences, including atelectasis, pneumonia, and respiratory distress or failure.

STUDY DESIGN: We analyzed the clinical impact of preemptive thoracic drainage in 177 patients undergoing adult-to-adult LDLT for chronic liver diseases at a single center. Recipients were divided into 2 time periods. The earlier cohort (n = 120) was analyzed for risk factors for postoperative atelectasis retrospectively; the later cohort (n = 57), with a risk factor for postoperative atelectasis, underwent preemptive thoracic drainage prospectively. The incidence of postoperative pulmonary complications was compared between these 2 cohorts.

RESULTS: Independent risk factors for atelectasis in earlier cohort were body mass index $\geq$27 kg/m^2 ($p < 0.001$), performance status $\geq$3 ($p = 0.003$) and model for end-stage liver disease score $\geq$23 ($p = 0.005$). The rates of atelectasis (21.1% vs 42.5%, $p = 0.005$) and pneumonia (1.8% vs 10.0%, $p = 0.049$) were significantly lower in later than in earlier cohort. Moreover, the mean durations of ICU stay (3.6 $\pm$ 0.2 days vs 5.7 $\pm$ 0.6 days, $p = 0.038$) and postoperative oxygen support (5.1 $\pm$ 0.8 days vs 7.1 $\pm$ 0.5 days, $p = 0.037$) were significantly shorter in the later than in the earlier cohort. There were no significant differences in the incidence of adverse events associated with thoracic drainages between these 2 cohorts.

CONCLUSIONS: Preemptive thoracic drainage for transplant recipients at high risk of postoperative atelectasis could decrease morbidities after LDLT. (J Am Coll Surg 2014;219:1134–1142. © 2014 by the American College of Surgeons)

Owing to poor preoperative clinical conditions, the extensive surgical field, long operating times, and massive blood loss and blood transfusions, liver transplant recipients are susceptible to postoperative pulmonary complications.[1-3] The most frequent are immediate postoperative pulmonary complications, including pleural effusions and atelectasis.[1,2,4] However, infectious complications, which often complicate the former, are much more serious and are responsible for a significant part of the mortality.[3,5-7]

Atelectasis is an important predisposing factor for postoperative pneumonia.[8-10] In general, if a pulmonary segment remains atelectatic for longer than 72 hours, pneumonia is almost certain to develop.[11] Thoracic fluid retention increases the risk of atelectasis by compressing the lungs.[10,12] Postoperative thoracic fluid retention will usually clear with diuresis, but this process may take a considerable period of time.[13] Moreover, postoperative fluid control is difficult after living donor liver transplantation (LDLT) owing to the small graft volume.[14] Therefore, thoracic drainage of pleural effusions may be effective in preventing postoperative atelectasis after LDLT.

This study was designed to evaluate the impact of preemptive thoracic drainage on LDLT recipients at risk for postoperative atelectasis. Additionally, the clinical impact of and risk factors for postoperative atelectasis were analyzed.

METHODS

Patients

Between January 2008 and December 2013, 177 consecutive adult-to-adult LDLTs for chronic liver diseases were

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Abbreviations and Acronyms
AUC = area under the curve
DDLT = deceased donor liver transplantation
FiO_2 = fraction of inspired O_2
LDLT = living donor liver transplantation
MELD = Model for End-stage Liver Disease
OR = odds ratio
PaO_2 = partial pressure of arterial O_2
POD = postoperative day

performed at Kyushu University Hospital. All operations were performed after obtaining informed consent from the patients and approval from the Liver Transplantation Committee of Kyushu University.

Groups and study design

Risk factors for and clinical impact of postoperative atelectasis

The 177 recipients were divided into 2 groups based on the therapeutic strategy for postoperative pleural effusion adopted at Kyushu University Hospital. The earlier cohort, consisting of 120 LDLT recipients, underwent thoracic drainage when refractory pleural effusion occurred. The later cohort, consisting of 57 recipients, underwent preemptive thoracic drainage if they had at least 1 risk factor for postoperative atelectasis (Fig. 1). Recipients with preoperative pleural effusions of grade ≥ 2 underwent preemptive thoracic drainage during both time periods. Thoracic drainage was performed by inserting a thoracic tube under mini-thoracotomy.

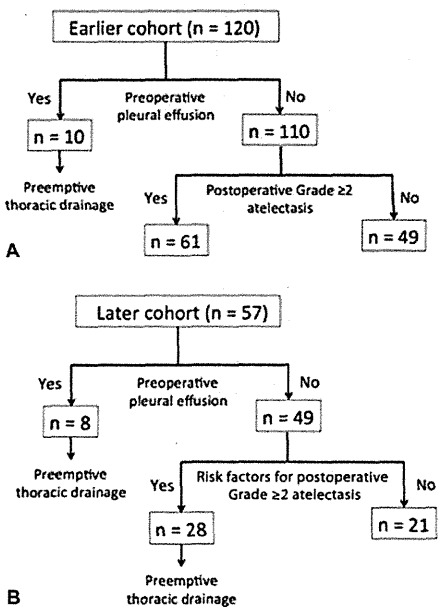

Figure 1. Schematic presentation of the 2 recipient groups of living donor liver transplant recipients. (A) Earlier cohort; (B) later cohort.

Risk factors for and the clinical sequelae of grade ≥ 2 postoperative atelectasis were examined retrospectively in the earlier cohort. Of these 120 patients, 10 had grade ≥ 2 preoperative pleural effusion; these 10 patients were excluded from analysis of risk factors and clinical effects of postoperative pleural effusion.

Validation of preemptive drainage

The incidence of postoperative pulmonary complications was compared in the 2 cohorts to validate our policy of preemptive thoracic drainage in the later cohort. Subgroup analysis was performed to assess characteristics that influenced between-group differences in clinical outcomes. Patients in each cohort were divided into 3 subgroups: those with preoperative pleural effusion, and those with and without risk factors for postoperative atelectasis. Performance status was determined using the Eastern Cooperative Oncology Group performance status scale.[15]

Preemptive thoracic drainage

Between January 2008 and April 2012, only recipients with pleural effusions of grade ≥ 2, detectable before LDLT, underwent preemptive thoracic drainage. Since May 2012, however, preemptive thoracic drainage has been performed in patients with a risk factor for postoperative atelectasis grade ≥ 2, as well as in patients with preoperative pleural effusions. All thoracic drainages in both cohorts were performed under mini-thoracotomy, in which we coagulated and divided intercostal muscles and parietal pleura along the superior edge of the rib using an electric scalpel to prevent unexpected bleeding (Supplementary video, online only). A 12-Fr catheter (Covidien Japan) was placed bilaterally under sterile aseptic conditions, with full barrier precautions. The tubes were placed in the anterior axillary line, and the catheter was attached to a closed drainage system with -10 cm water pressure suction. Chest radiography was performed after the procedure. Thoracic tubes remained in place until fluid removal over 24 hours was less than 100 mL.

Graft selection criteria and surgical procedures

The graft selection criteria for adult-to-adult LDLT[16] and the surgical procedures in both donors and recipients[17]

have been described. Splenectomy was routinely performed in patients with hepatitis C virus infection or portal hypertension.[18]

Postoperative management

All LDLT recipients were transferred to the ICU and mechanically ventilated postoperatively. The respirator was set to provide pressure-controlled ventilation with a positive end-expiratory pressure of 5 cm H_2O. To correct intraoperative fluid overload, a sufficient amount of diuretic was administered intravenously. Extubation was indicted within 24 hours after LDLT, when the ratio of the partial pressure of arterial O_2 (PaO_2) to the fraction of inspired O_2 (FiO_2) was >250 and when the patient's cardiovascular, graft, and renal conditions were stable.[6] After extubation, oxygen support was maintained until oxygen saturation of the peripheral arteries remained greater than 97% under room air. Patients were administered early enteral nutrition because of its impact on postoperative bacterial sepsis after LDLT.[19] Routine postoperative investigations included arterial blood gas tests (PaO_2, $PaCO_2$, pH, HCO^{3-}, and base excess) every 4 hours, and blood tests (complete blood count, coagulation profile, and serum liver enzymes), Doppler ultrasonography to examine blood flow in the graft vessels, and portable chest and abdominal radiographs twice daily. Patients with an uneventful course of recovery were transferred to the surgical ward on postoperative day (POD) 3. All patients underwent routine chest and abdominal CT on POD 7; if any clinical data were abnormal, roentgenographic examinations were performed.

The incidence of each grade of pleural effusion and atelectasis, as well as pneumonia, through POD 7 were assessed based on radiologic findings. To minimize the risk of bias, arterial blood gas tests, chest radiographs, and/or CT were performed at around the same time each day.

Perioperative antibacterial and immunosuppressive management have been described in detail.[6] The basic immunosuppressive regimen consisted of tacrolimus (Prograf; Astellas Pharma Inc) or cyclosporine A (Neoral; Novartis Pharma KK), and steroids, with or without mycophenolate mofetil (Cellcept; Chugai Pharmaceutical Co Ltd).

Perioperative respiratory management

Preoperative respiratory management included smoking cessation and pulmonary rehabilitation, such as respiratory muscle training, especially in patients with abnormal spirometry results. Postoperative pulmonary management included good oral hygiene, intermittent suction, adequate positional changes, nebulized bronchodilators and mucolytics after extubation, and enforcement of early postoperative ambulation.

In managing pulmonary complications, diuretics were first administered to patients with pleural effusions. Atelectasis was first managed by a combination of positional changes, such as to the prone position, elevation of positive end-expiratory pressure, breathing exercises, and suction under bronchoscopy. If atelectasis was accompanied by pleural effusions, thoracic drainage under minithoracotomy was considered. Tracheotomies were performed in patients who could not be weaned from mechanical ventilation at POD 7.

Radiologic findings

Atelectasis was classified into 3 grades, with grade 1 indicating the involvement of $\leq$1 subsegment or discoid atelectasis and grades 2 and 3 indicating the involvement of 2 and $\geq$3 subsegments, respectively (Fig. 2). Pleural effusion was also classified into 3 grades, with grade 1 indicating a loss of sharpness of the costophrenic angle and diaphragmatic profiles or subpulmonary effusion, grade 2 indicating effusion involving <25% of a hemithorax, and grade 3 indicating involvement of >25% of a hemithorax, including a massive effusion with mediastinal shift.[1]

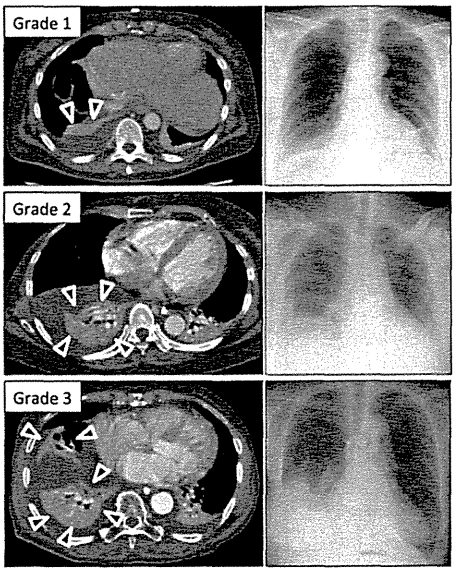

Figure 2. Chest CT and radiograph of each grade of postoperative atelectasis. Atelectasis is indicated by arrowheads. Grade 1 atelectasis is defined as involvement of $\leq$1 subsegment or discoid atelectasis; grades 2 and 3 indicate the involvement of 2 and $\geq$3 subsegments, respectively.

Table 1. Clinical Impact of Postoperative Grade ≥2 Atelectasis on Clinical Outcomes in Earlier Cohort

Factors	Postoperative grade ≥2 atelectasis: No (n = 61)	Yes (n = 49)	p Value
Pneumonia, n (%)	1 (1.6)	9 (18.4)	0.002
PaO_2/FiO_2 ratio POD 1	381 ± 11	361 ± 12	0.235
PaO_2/FiO_2 ratio POD 3	343 ± 14	332 ± 13	0.576
PaO_2/FiO_2 ratio POD 5	329 ± 28	331 ± 19	0.956
Length of mechanically ventilation, d	2.0 ± 0.9	4.7 ± 0.9	0.028
Length of oxygen support, d	5.3 ± 0.8	9.6 ± 0.9	<0.001
ICU stay, d	4.0 ± 0.8	7.3 ± 0.9	0.011
Postoperative hospital stay, d	28 ± 3	39 ± 3	0.005
Tracheotomy, n (%)	0 (0)	2 (4.1)	0.111
Reintubation, n (%)	1 (1.6)	4 (8.2)	0.103

Unless stated otherwise, data are reported as mean ± SD.
POD, postoperative day.

Infectious pneumonia was diagnosed by the combinations of radiologic findings showing new or increasing infiltrates, clinical symptoms such as fever or dyspnea, and positive cultures. Three main radiologic patterns were considered indicative of pneumonia: focal pulmonary consolidation; nodules or rapidly growing masses, with or without central cavitation; and diffuse pulmonary infiltrates with an interstitial or alveolar pattern.

Statistical analysis

All statistical analyses were performed using SAS software (JMP 11.0.1; SAS Institute Inc). Continuous variables were expressed as means ± SD and compared using Mann-Whitney U-tests. Categorical variables were compared using chi-square tests. A receiver operating characteristic (ROC) curve analysis and Youden's index were used to identify ideal cutoff values in multivariate analysis.

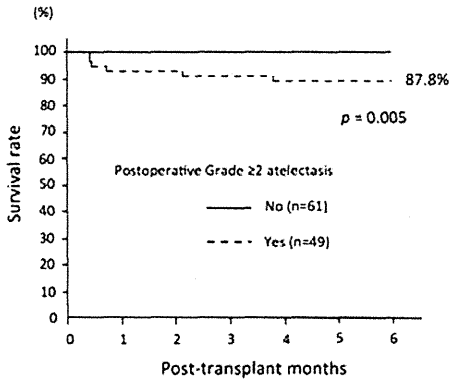

Figure 3. Six-month graft survival rates of the earlier cohort with and without postoperative grade ≥2 atelectasis.

RESULTS

Characteristics of the recipients, donors, and grafts

Demographic and clinical characteristics of all LDLT donors and recipients and the characteristics of the grafts are shown in Supplementary Table 1, online only.

Clinical sequelae of grade ≥2 postoperative atelectasis in the earlier cohort

The incidence of pneumonia was significantly higher in recipients with than without grade ≥2 postoperative atelectasis (18.4% vs 1.6%, p = 0.002). The durations of mechanical ventilation (4.7 ± 0.9 days vs 2.0 ± 0.9 days, p = 0.028), oxygen support after extubation (9.6 ± 0.9 days vs 5.3 ± 0.9 days, p < 0.001), ICU stay (7.3 ± 0.9 days vs 4.0 ± 0.8 days, p = 0.011), and postoperative hospital stay (39 ± 3 days vs 28 ± 3 days, p = 0.005) were significantly longer in patients with than without atelectasis (Table 1). The 6-month survival rate was significantly lower in recipients with than without postoperative atelectasis grade ≥2 (87.8% vs 100%, p = 0.005) (Fig. 3). The causes for mortality in the 6 recipients lost within 6 month after LDLT included respiratory failure (n = 3), retroperitoneal hemorrhage (n = 3), graft vs host disease (n = 1), and small for size syndrome (n = 1). Four of them were lost within 1 month after LDLT. There were no significant differences in the PaO_2 to FiO_2 ratio on PODs 1, 3, and 5, or in the percentages of recipients who underwent tracheotomy and reintubation.

Factors associated with grade ≥2 postoperative atelectasis in earlier cohort

Univariate analysis showed that Child-Pugh scores (10.5 ± 0.2 vs 9.5 ± 0.2, p = 0.003), Model for End-stage Liver Disease (MELD) scores (17.7 ± 0.8 vs 14.1 ± 0.8, p = 0.002) and body mass index (24.5 ± 0.4 kg/m^2 vs 23.0 ± 0.4 kg/m^2, p = 0.014) were significantly higher in patients with than without grade ≥2 postoperative atelectasis. The percentages of patients with vital capacity <80% (14.3% vs 5.0%, p = 0.034) and performance status ≥3 (46.9% vs 13.1%, p < 0.001) were significantly higher in patients with than without atelectasis, as were the amounts of transfused red cells (15.8 ± 1.9 units vs 10.6 ± 1.7 units, p = 0.044) and platelet (23.6 ± 2.3 units vs 16.3 ± 2.1 units,

Table 2. Univariate Analysis of Risk Factors for Postoperative Grade ≥2 Atelectasis

Factors	Postoperative grade ≥2 atelectasis: No (n = 61)	Yes (n = 49)	p Value
Recipient factors			
Sex, male, n (%)	30 (49.2)	17 (34.7)	0.125
Age, y	55 ± 1	55 ± 1	0.924
Primary diagnosis			0.091
Liver cirrhosis, n (%)	45 (73.8)	37 (75.5)	
Cholestatic disease, n (%)	13 (21.3)	5 (10.2)	
Others, n (%)	3 (4.9)	7 (14.3)	
Child-Pugh score, n	9.5 ± 0.2	10.5 ± 0.2	0.003
MELD score, n	14.1 ± 0.8	17.7 ± 0.8	0.002
Body mass index, kg/m^2	23.0 ± 0.4	24.5 ± 0.4	0.014
Diabetes, n (%)	9 (14.8)	7 (14.3)	0.945
Smoking, n (%)	13 (21.3)	12 (25.0)	0.650
FEV1.0% ≤ 70, n (%)	10 (16.7)	4 (8.9)	0.246
VC < 80, n (%)	3 (5.0)	7 (14.3)	0.034
Performance status ≥3, n (%)	8 (13.1)	23 (46.9)	<0.001
Donor factors			
Sex, male, n (%)	35 (57.4)	34 (69.4)	0.270
Age, y	36 ± 1	35 ± 1	0.769
ABO incompatibility, n (%)	8 (13.1)	6 (12.2)	0.892
Left lobe graft, n (%)	36 (59.0)	26 (53.0)	0.766
GV/SLV, (%)	39.2 ± 1.0	41.9 ± 1.1	0.086
GRWR	0.76 ± 0.09	0.94 ± 0.10	0.202
Recipient operation			
Operative time, min	782 ± 22	805 ± 25	0.489
Blood loss, L	3.6 ± 0.7	5.6 ± 0.8	0.054
RCC, U	10.6 ± 1.7	15.8 ± 1.9	0.044
FFP, U	17.6 ± 2.1	22.7 ± 2.4	0.113
PC, U	16.3 ± 2.1	23.6 ± 2.3	0.021
Ascites, mL	390 ± 280	1820 ± 320	0.001
Splenectomy, n (%)	52 (85.3)	36 (75.0)	0.178
Porto-systemic shunt ≥1 cm, n (%)	18 (29.5)	15 (31.3)	0.844

Unless stated otherwise, data are reported as mean ± SD.
FEV, forced expiratory volume; FFP, fresh frozen plasma; GRWR, graft/recipient weight ratio; GV, graft volume; MELD, Model for End-stage Liver Disease; PC, platelet concentrates; RCC, red cell concentrates; SLV, standard liver volume; VC, vital capacity.

p = 0.021) concentrates and the amount of ascites (1,820 ± 320 mL vs 390 ± 280 mL, p = 0.001) (Table 2).

Optimal cut-off values for atelectasis, as determined by receiver operating characteristic (ROC) curve analysis, were body mass index 27 kg/m^2 (area under the curve [AUC] = 0.62, sensitivity 51%, specificity 77%); MELD score 23 (AUC = 0.65, sensitivity 31%, specificity 93%); Child-Pugh score 11 (AUC = 0.65, sensitivity 49%, specificity 72%); ascites 500 mL (AUC = 0.64, sensitivity 44%, specificity 82%); red blood cell concentrates 6 units (AUC = 0.63, sensitivity 83%, specificity 36%); platelet concentrates 40 units (AUC = 0.60, sensitivity 21%, specificity 95%).

Multivariate analysis showed that body mass index ≥27 kg/m^2 (odds ratio [OR] 15.1, 95% CI 4.4 to 60.0, p < 0.001), performance status ≥3 (OR 7.1, 95% CI 2.0 to 28.0, p = 0.003) and MELD score ≥23 (OR 17.1, 95% CI 2.2 to 371.7, p = 0.005) were independent risk factors for postoperative atelectasis (Table 3).

Noninfectious pulmonary complications in the earlier cohort

Of the 120 patients, 103 (93.6%) experienced noninflammatory pulmonary changes during the early postoperative period, the most common being pleural effusion in 101 patients (91.8%) (Supplementary Table 2, online only). Atelectasis grade ≥2 occurred in 46 patients (41.8%), including 14 patients with atelectasis on both sides, 26 with atelectasis on the right side, and 6 with atelectasis on the left side. Of the 46 patients with atelectasis grade ≥2, 44 (95.7%) also had pleural effusions.

Demographic and clinical characteristics of the 2 cohorts

Recipient sex distribution, age, distribution of disease, MELD score, and body mass index were similar in the 2 cohorts (Supplementary Table 3, online only). The percentage of patients with performance status ≥3 was significantly higher in the later than in the earlier cohort (46.0% vs 29.2%, p = 0.025), although the percentages of patients with risk factors for postoperative atelectasis were similar in the 2 cohorts (p = 0.218).

Donors in earlier cohort were significantly younger than those in the later cohort (36 ± 1 years vs 39 ± 1 years, p = 0.020). However, there were no significant differences between groups in graft-to-standard liver volume ratio and graft-to-recipient weight ratio.

Operation times were similar in the 2 groups. Mean blood loss per patient was significantly greater in the later than in the earlier cohort (7.8 ± 1.1 L vs 4.7 ± 0.8 L, p = 0.027).

Clinical outcomes in the 2 cohorts

The percentages of patients with atelectasis (21.1% vs 42.5%, p = 0.005) and pneumonia (1.8% vs 10.0%, p = 0.049) were significantly lower in the later than in the earlier cohort (Table 4). Moreover, the mean length of ICU stay (3.6 ± 0.2 days vs 5.7 ± 0.6 days, p = 0.038) and the period with oxygen support (5.1 ± 0.8

Table 3. Multivariate Analysis of Risk Factors for Postoperative Grade ≥2 Atelectasis

Variables	Odds ratio	95% CI	p Value
Body mass index ≥27 kg/m^2	15.1	4.4–60.0	<0.001
Performance status ≥3	7.1	2.0–28.0	0.003
MELD score ≥23	17.1	2.2–371.7	0.005
PC > 40 U	6.3	0.9–58.3	0.064
RCC > 6 U	1.6	0.5–5.3	0.426
Child–Pugh score ≥11	1.5	0.5–4.7	0.526
Ascites > 500 mL	1.4	0.4–5.1	0.627
%VC < 80, %	4.3	0.6–39.5	0.141

MELD, Model for End-stage Liver Disease; PC, platelet concentrates; RCC, red cell concentrates; VC, vital capacity.

days vs 7.1 ± 0.5 days, p = 0.037) were significantly shorter in the later cohort. However, the mean length of postoperative hospital stay was similar in the 2 groups. The PaO_2 to FiO_2 ratio on POD 1 was significantly higher in the later cohort (418 ± 14 vs 372 ± 9, p = 0.005), but there were no differences between groups on PODs 3 and 5. Complications associated with intraoperative thoracic drainage did not differ significantly between the 2 cohorts. The recurrence of thoracic fluid correction with a positive culture occurred in 1 patient in the earlier cohort, and pneumothorax after drain removal occurred in 2 patients in the later cohort. The fluid correction with a positive culture was not accompanied by clinical symptoms and was successfully treated by exchanging the chest drain and administering of antibiotics; pneumothorax in both patients was successfully treated with reinsertion of a chest drain.

Subgroup analysis of clinical outcomes

The patients in each group were divided into 3 subgroups. Of the 120 patients in the earlier group, 10 (8.3%) had preoperative pleural effusion, while 56 (46.7%) had risk factors for postoperative atelectasis, and 54 (45.0%) did not. Of the 57 patients in the later group, 8 (14.0%) had preoperative pleural effusions; 28 (49.1%) had risk factors for postoperative atelectasis and 21 (36.8%) did not.

When the incidence of postoperative pulmonary complications was compared in each pair of subgroups, we observed significant differences in patients with risk factors for atelectasis. The percentages of patients with atelectasis (21.4% vs 71.4%, p < 0.001) and pneumonia (0% vs 16.1%, p = 0.025) were significantly lower in the later than in the earlier cohort. Additionally, the PaO_2 to FiO_2 ratio on POD 1 was significantly greater (421 ± 19 vs 364 ± 13, p = 0.014), and the mean length of oxygen support was significantly shorter (5.2 ± 0.9 days vs 7.7 ± 0.7 days, p = 0.029) in the later cohort (Table 5), but there was no difference in mean length of ICU stay. No differences were observed in the subgroups with preoperative pleural effusion and those without risk factors for postoperative atelectasis.

DISCUSSION

Postoperative pulmonary complications have been associated with early morbidity and mortality in liver transplant recipients.[1-7] These postoperative pulmonary complications may have serious clinical impacts due to poor patient condition, end-stage liver disease, pre-existing pulmonary abnormalities, high comorbidity rates, and immunosuppressive status.[1,2,6] Therefore, special attention should be paid to preventing pulmonary complications. This study demonstrated that preemptive thoracic drainage in LDLT recipients effectively reduced the rates of postoperative atelectasis and pneumonia and shortened the lengths of ICU stay and oxygen support.

We found that postoperative grade ≥2 atelectasis after LDLT was associated with prolonged respiratory recovery and a high mortality rate, and was an important target of

Table 4. Comparison of Clinical Outcomes in the 2 Recipient Cohorts

Factors	Earlier cohort (n = 120)	Later cohort (n = 57)	p Value
Postoperative grade ≥ 2 atelectasis, n (%)	51 (42.5)	12 (21.1)	0.005
Pneumonia, n (%)	12 (10.0)	1 (1.8)	0.049
PaO_2/FiO_2 ratio POD 1	372 ± 9	418 ± 14	0.005
PaO_2/FiO_2 ratio POD 3	340 ± 9	332 ± 15	0.615
PaO_2/FiO_2 ratio POD 5	332 ± 14	363 ± 24	0.275
Length of mechanically ventilation, d	3.2 ± 0.5	2.1 ± 0.7	0.196
Length of oxygen support, d	7.1 ± 0.5	5.1 ± 0.8	0.037
ICU stay, d	5.7 ± 0.6	3.6 ± 0.2	0.038
Postoperative hospital stay, d	33 ± 2	30 ± 3	0.373
Complications associated with intraoperative thoracic drainage, n (%)	1 (10)	2 (5.6)	0.615

Unless stated otherwise, data are reported as mean ± SD.
POD, postoperative day.

Table 5. Subgroup Analysis of Clinical Outcomes in the 2 Recipient Cohorts

Factors	Group	Earlier cohort	Later cohort	p Value
Postoperative atelectasis, grade ≥2, n (%)	P	2 (20.0)	1 (12.5)	0.671
	R (−)	9 (16.7)	5 (23.8)	0.476
	R (+)	40 (71.4)	6 (21.4)	<0.001
Pneumonia, n (%)	P	2 (20.0)	1 (12.5)	0.671
	R (−)	1 (1.9)	0 (0.0)	0.530
	R (+)	9 (16.1)	0 (0.0)	0.025
PaO_2/FiO_2 ratio on POD 1, n	P	365 ± 34	362 ± 40	0.952
	R (−)	382 ± 14	433 ± 22	0.056
	R (+)	364 ± 13	421 ± 19	0.014
PaO_2/FiO_2 ratio on POD 3, n	P	362 ± 30	382 ± 48	0.747
	R (−)	343 ± 12	304 ± 21	0.126
	R (+)	333 ± 14	340 ± 21	0.804
PaO_2/FiO_2 ratio on POD 5, n	P	357 ± 17	350 ± 20	0.791
	R (−)	311 ± 30	292 ± 52	0.766
	R (+)	339 ± 17	398 ± 30	0.101
Length of mechanical ventilation, d	P	3.9 ± 1.2	2.7 ± 1.3	0.534
	R (−)	2.1 ± 0.2	1.7 ± 0.4	0.323
	R (+)	4.2 ± 1.0	2.3 ± 1.4	0.258
Length of oxygen support, d	P	6.6 ± 2.5	7.0 ± 2.9	0.909
	R (−)	6.6 ± 0.9	4.4 ± 1.4	0.172
	R (+)	7.7 ± 0.7	5.2 ± 0.9	0.029
ICU stay, d	P	5.7 ± 1.7	5.0 ± 2.0	0.797
	R (−)	4.1 ± 0.3	3.2 ± 0.5	0.101
	R (+)	6.8 ± 1.0	4.0 ± 1.4	0.115
Postoperative hospital stay, d	P	31 ± 7	27 ± 10	0.788
	R (−)	29 ± 3	30 ± 4	0.867
	R (+)	36 ± 2	30 ± 4	0.171

Unless stated otherwise, data are reported as mean ± SD.
POD, postoperative day; P, patients with preoperative pleural effusions; R (−), patients without risk factors for postoperative atelectasis; R (+), patients with risk factors for postoperative atelectasis.

patient management. Atelectasis can be particularly problematic because it appears to be one of the primary mechanisms underlying acute lung injury[20] and impaired systemic oxygenation,[10,12] as well as being associated with prolonged ICU and hospital stay.[20] Moreover, atelectasis is thought to predispose to pneumonia,[8-10] which is also associated with a high early mortality rate[6] and prolonged mechanical ventilation and ICU stay after LDLT.[3] This study found that the incidence of pneumonia was significantly lower in the later than in the earlier cohort (1.8% vs 10.0%). All recipients with early mortality in the earlier cohort had post-transplant atelectasis. As many as 50% of those recipients (3 of 6) were lost due to respiratory failure. These results were comparable with past findings, and suggested that the prevention of atelectasis may reduce the rates of pneumonia, morbidity, and mortality.

Multivariate regression analysis showed that independent risk factors for postoperative grade ≥2 atelectasis were body mass index ≥27 kg/m^2, performance status ≥3, and MELD score ≥23. Other reports have also assessed risk factors for post-transplantation pulmonary complications.[1-7] Obesity was found to markedly reduce functional residual capacity, promoting airway closure to a greater extent than in normal weight recipients.[21] The weight of the torso and abdomen make diaphragmatic excursions difficult, especially when patients are in the supine position.[10] Owing to similar mechanisms, severe ascites may also contribute to the loss of aeration in caudal and dependent lung segments, leading to atelectasis and airway closure.[22] Liver transplant recipients with high MELD scores often have a greater incidence of pleural effusion, a need for more perioperative blood transfusions, a greater risk of fluid retention, more severely restrictive pulmonary patterns, and a greater incidence of muscle atrophy related to poor nutritional status.[2] A MELD score ≥25 was reported to be an

independent predictor of postoperative pulmonary complications.[25] To our knowledge, no studies have shown that performance status was a risk factor for postoperative pulmonary complications. A performance status ≥3 indicates that a patient is ≥50% bedridden during the daytime.[15] Immobilized patients suffer profound and persistent impairments in physical function, typically with slow and incomplete recovery.[24] These patients often lost their muscle bulk, predominantly in proximal muscle, leading to sarcopenia.[24] We have reported that sarcopenia was a prognostic factor after LDLT.[25] Although recipient age, smoking history, diabetes, and cirrhotic encephalopathy have also been identified as risk factors for postoperative pulmonary complications,[2,4,6,26] they were not found to be risk factors in this study. These risk factors for atelectasis in this study implied that the patients with atelectasis had more severe preoperative systemic status than those without it. Atelectasis in these patients might cause vital systemic damages, resulting in higher mortality.[5]

Postoperative pulmonary atelectasis after orthotopic liver transplantation is accompanied in most patients by pleural effusion.[1] Similarly, we found that 40.8% of the earlier cohort had postoperative grade ≥2 atelectasis, with 95.7% of them having pleural effusion. Under the combination of general anesthesia and prolonged placement in a supine position, intrathoracic fluid retention contributes to a decrease in functional residual capacity and compression of lung tissue, causing compressive atelectasis.[26,27] Because atelectasis has several causes, various approaches have been used to prevent this condition, according to its mechanism and cause.[12] Lung mechanics and breathing patterns are often changed postoperatively, resulting in coughing and removal of particulate matter, both of which are particular to pulmonary defense mechanisms.[10] Treatment modalities targeting these defense mechanisms include pain control, chest physiotherapy, bronchodilators, fiberoptic bronchoscopy, and DNase treatment.[10,12] We have actively used these strategies in perioperative management of patients in both groups. Positive end-expiratory pressure has also been used to prevent and reverse atelectasis.[20] However, despite these efforts, 74.5% of recipients in earlier cohort had atelectasis. Those suggested that there was a strong relationship between postoperative atelectasis and intrathoraic fluid retention after LDLT. Therefore, preemptive thoracic drainage of transudative effusions was theoretically reasonable for the prevention of postoperative atelectasis.

The rates of postoperative pleural effusion and atelectasis we observed were higher than in previous studies. Rates of pleural effusion and atelectasis in the earlier cohort were 91.8% and 74.5%, respectively, rates higher than reported incidences in other groups of orthotopic liver transplant recipients, eg, 32% to 47% and 5% to 29%, respectively,[2] and 40.9% and 29.5%, respectively.[4] These differences may be due to the greater susceptibility of LDLT than deceased donor liver transplant (DDLT) recipients to postoperative noninfectious pulmonary complications. The incidence of pulmonary infections was found to be higher in LDLT than in deceased donor liver transplant recipients, perhaps due to the smaller liver volume in the former.[8] Indeed, slower recovery of liver function, prolonged cholestasis, and persistent ascites in LDLT recipients may also be due to smaller liver volume,[28,29] suggesting that the high incidence of postoperative pulmonary complications after LDLT may be associated with small liver volumes.

Thoracic drainage under mini-thoracotomy using an electronic scalpel was extremely safe and was not associated with any serious adverse events. Thoracentesis under ultrasound guidance is associated with many risks in liver transplant recipients. Recipients' collateral veins continued to develop owing to end-stage liver disease, even after liver transplantation.[30,31] The incidence of hemothorax after tube thoracostomy was reported to be 1.8% after orthotopic liver transplantation.[31] We also previously described 2 patients with hemothorax after thoracentesis under ultrasound guidance, emphasizing the importance of proper chest tube placement. In this study, chest tube placement was a safe technique because it was performed under direct vision and hemostasis was adequate. This procedure requires adequate sterile facilities, suggesting that it be performed at the same time as LDLT.

One important limitation of this study was that it was not a concurrent controlled study. Therefore, the impact of thoracic drainage could not be compared precisely. Although a randomized controlled study is required, our subgroup analysis may be adequate. This analysis showed that preemptive thoracic drainage of LDLT recipients with at least 1 risk factor for atelectasis contributed to improvements in the later cohort. Another limitation was our inability to determine whether our preemptive strategy improved mortality. Longer-term observation is therefore required.

CONCLUSIONS

In conclusion, preemptive thoracic drainage of LDLT recipients at high risk of pulmonary complications may reduce the rates of atelectasis and pneumonia. Chest tube placement could be performed safely under mini-thoracotomy using an electronic scalpel. However, it is

yet unclear whether this strategy improves patient mortality. Further observation and experience are therefore required.

Author Contributions

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Supplementary Table 1. Demographic and Clinical Characteristics of All Recipients, Donors and Grafts

Factors	Total cases (n = 177)
Recipient factors	
Sex, male, n (%)	75 (42.3)
Age, mean, y	54.9
Primary diagnosis	
Liver cirrhosis, n (%)	130 (73.4)
HBV, n	18
HCV, n	76
Alcoholic, n	16
NASH, n	12
Cryptogenic, n	8
Cholestatic disease, n (%)	30 (16.9)
PBC, n	22
PSC, n	8
Others, n (%)	17 (9.7)
Child-Pugh score, mean	10.2
MELD score, mean	16.7
Body mass index, mean, kg/m^2	23.6
Diabetes, n (%)	25 (14.1)
Smoking, n (%)	40 (22.6)
Performance status ≥3 (%)	62 (35.0)
Donor factors	
Sex, male, n (%)	110 (62.1)
Age, mean, y	36.6
ABO incompatibility, n (%)	17 (0.1)
Left lobe graft, n (%)	99 (55.9)
GV/SLV, %	40.7
GRWR	0.82

GRWR, graft/recipient weight ratio; GV, graft volume; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SLV, standard liver volume.

Supplementary Table 2. Noninfectious Pulmonary Complications in the Earlier Cohort (n = 120), %

Factors	Total	Right	Left
Pleural effusions			
None	8.2	13.6	20.9
Grade 1	42.7	42.7	57.3
Grade 2	44.6	39.2	20.9
Grade 3	4.5	4.5	0.9
Atelectasis			
None	25.5	31.8	48.2
Grade 1	32.7	31.8	33.6
Grade 2	40.9	35.5	18.2
Grade 3	0.9	0.9	0

Supplementary Table 3. Demographic and Clinical Characteristics of the 2 Recipient Cohorts, Donors, and Grafts

Factors	Earlier cohort (n = 120)	Later cohort (n = 57)	p Value
Recipient factors			
Gender, male, n (%)	55 (45.8)	20 (35.1)	0.176
Age, mean, y	55 ± 1	54 ± 1	0.590
Primary diagnosis, n (%)			0.134
Liver cirrhosis	90 (75.0)	40 (70.2)	
Cholestatic disease	19 (15.8)	15 (26.3)	
Others	11 (9.2)	2 (3.5)	
Child-Pugh score	10.1 ± 0.2	10.2 ± 0.2	0.763
MELD score	16.2 ± 0.6	17.4 ± 0.8	0.223
Body mass index, kg/m^2	23.6 ± 0.3	23.6 ± 0.5	0.969
Diabetes, n (%)	16 (14.6)	5 (8.8)	0.159
Smoking, n (%)	28 (23.5)	12 (21.1)	0.714
FEV1.0% ≤ 70, n (%)	17 (14.9)	4 (7.4)	0.135
%VC < 80, n (%)	15 (13.2)	12 (22.2)	0.170
Performance status ≥3, n (%)	33 (29.2)	29 (46.0)	0.025
Risk factors for post-transplant atelectasis, n (%)	64 (53.3)	36 (63.2)	0.218
Donor factors			
Sex, male, n (%)	76 (63.3)	33 (58.9)	0.649
Age, y	36 ± 1	39 ± 1	0.020
ABO incompatibility, n (%)	14 (11.7)	3 (5.3)	0.177
Left lobe graft, n (%)	67 (55.8)	32 (56.1)	0.978
GV/SLV, %	40.4 ± 0.7	41.2 ± 1.1	0.546
GRWR	0.83 ± 0.05	0.79 ± 0.08	0.645
Recipient surgery			
Operative time, min	796 ± 15	823 ± 22	0.301
Blood loss, L	4.7 ± 0.8	7.8 ± 1.1	0.027
Ascites, mL	2,200 ± 940	1,990 ± 1,330	0.894

Unless stated otherwise, data are reported as mean ± SD.
FEV, forced expiratory volume; GRWR, graft/recipient weight ratio; GV, graft volume; MELD, Model for End-stage Liver Disease; SLV, standard liver volume; VC, vital capacity.

Long-Term Favorable Surgical Results of Laparoscopic Hepatic Resection for Hepatocellular Carcinoma in Patients with Cirrhosis: A Single-Center Experience over a 10-Year Period

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BACKGROUND: We first performed laparoscopic hepatic resection (Lap-Hx) for hepatocellular carcinoma (HCC) in 1994. Here we review the long-term surgical results of Lap-Hx for HCC in patients with cirrhosis over a 10-year period at a single institution.

STUDY DESIGN: Between January 2000 and December 2013, 99 patients with cirrhosis underwent open hepatic resection (Open-Hx) and 63 underwent Lap-Hx for primary HCC within the Milan criteria. We compared the operative outcomes and patient survival between the 2 groups.

RESULTS: There were no significant differences regarding patient background characteristics or tumor-related factors between the 2 groups. The morbidity rate of the Lap-Hx group was significantly lower than that of the Open-Hx group (26% vs 10%; $p = 0.0459$), and the complication rate of ascites was significantly lower (7% vs 0%; $p = 0.0077$). The mean duration of hospital stay of the Lap-Hx group was significantly shorter than that of the Open-Hx group (16 vs 10 days; $p = 0.0008$). There were no significant between-group differences regarding overall or disease-free survival.

CONCLUSIONS: Laparoscopic-Hx for HCC in patients with cirrhosis is associated with less morbidity and shorter hospital stays, with no compromise in patient survival. It may be time to consider changing the standard operation for primary HCC within the Milan criteria to Lap-Hx in patients with cirrhosis. (J Am Coll Surg 2014;219:1117–1123. © 2014 by the American College of Surgeons)

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, accounting for approximately 6% of all human cancers.[1] The mainstay of curative treatment for HCC is hepatic resection, and the surgical results of hepatic resection for HCC have significantly improved, with the mortality rate nearly reaching zero.[2] However, hepatic resection for HCC remains high risk, especially in patients with cirrhosis. As a less invasive procedure, laparoscopic hepatic resection (Lap-Hx) for HCC has gathered attention in this challenging field.[3]

We first performed Lap-Hx for HCC in patients with cirrhosis in 1994.[4] Until 2007, we selected Lap-Hx for HCC on the left lateral lobe or the peripheral ventral right lobe, and we performed liver parenchymal division through a small laparotomy after mobilization of the liver. We reported favorable short-term surgical results of Lap-Hx for HCC, with less blood loss and shorter hospital stays, with no compromise in patient survival.[5] In June 2008, pure Lap-Hx was introduced in our institution,[6] and Lap-Hx for the posterior segment, anterosuperior segment (S8), and caudate lobe was performed with the patient in the semiprone position.[7,8]

Several meta-analyses summarized the surgical results of Lap-Hx for HCC as follows: less blood loss, less frequent need for transfusion, less morbidity, a lower complication rate of ascites, a lower complication rate of liver failure,

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Abbreviations and Acronyms
HCC = hepatocellular carcinoma
Lap-Hx = laparoscopic hepatic resection
ICGR-15 = indocyanine green retention rate at 15 minutes
Open-Hx = open hepatic resection

shorter hospital stays, and no compromise in prognosis.[9-13] However, long-term (ie, more than 10 years) surgical results of Lap-Hx for HCC in patients with cirrhosis have not yet been reported.

We herein present a retrospective analysis of long-term surgical results including patients' prognoses after Lap-Hx for HCC within the Milan criteria[14] (ie, ≤5 cm in diameter in single HCC or ≤3 nodules and ≤3 cm in diameter in multiple HCCs) in patients with cirrhosis, over a 10-year period at a single institution.

METHODS

Patient characteristics

We retrospectively analyzed 653 patients with HCC who underwent hepatic resections at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, from January 2000 to December 2013. Among them, 162 patients who underwent curative hepatic resections for primary HCC within the Milan criteria were enrolled in this study. We divided this cohort of 162 patients into 2 groups; the open hepatic resection (Open-Hx) group (n = 99), and the Lap-Hx group (n = 63).

Surgical procedures and outcomes

Details of our surgical techniques of Open-Hx and patient selection criteria for hepatic resection for HCC have been reported.[15,16] Resection volume was decided based on the patients' indocyanine green dye retention rate at 15 minutes (ICGR-15) in both the Open-Hx and Lap-Hx groups. Patients with an ICGR-15 ≥ 35% were generally selected for limited resection.[16] From 1994 to 2007 in 25 patients (40%), Lap-Hx was done on the principle that parenchymal division would be performed under direct vision through a small laparotomy wound after mobilization of the liver under a carbon dioxide (CO_2) pneumoperitoneum. The CUSA system (Valleylab) was used to transect the liver parenchyma.

In almost all of the hepatic resections, the Pringle's maneuver, consisting of clamping the portal triad for 15 minutes and then releasing the clamp at 5-minute intervals, was applied; alternatively, hemivascular occlusion[17] was performed. From June 2008 in 38 patients (60%), pure Lap-Hx was introduced in our institution,[6] and Lap-Hx for the posterior segment, anterosuperior segment (S8), and caudate lobe was performed with the patient in the semiprone position.[7,8] In patients who underwent the Lap-Hx, bipolar scissors or a Biclamp under the VIO soft-coagulation system (ERBE Elektromedizin) fitted with a silicon tube dropping saline to the tip was used to transect the liver parenchyma. If transection of the liver parenchyma of S7, S8, or the right superior portion of S1 was needed in the Lap-Hx patients, an intracostal port with a balloon was placed under left-lung ventilation.[8] Types of hepatic resections in both the Open-Hx group and the Lap-Hx group are summarized in Table 1. There were no patients who underwent lobectomy or more for HCC within the Milan criteria in our series. The majority of operations performed were partial hepatic resections: 71 patients (71.7%) in the Open-Hx group and 36 patients (57.1%) in the Lap-Hx group.

Any death that occurred in the hospital after hepatic resection was recorded as a mortality. Complications were evaluated by Clavien's classification of surgical complications, and the complications with a score of grade II or more were defined as positive.[18]

Follow-up and treatment strategy for recurrent hepatocellular carcinoma

After discharge, all patients were examined for recurrence by ultrasonography and tumor markers such as α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) every month and by dynamic CT every 3

Table 1. Types of Hepatic Resection

Operative procedures	Open (n = 99)	Laparoscopic (n = 63)
Lobectomy or more		
Right liver	0	0
Left liver	0	0
Segmentectomy or more		
Left lateral	4	13
Medial	3	1
Anterior	1	0
Posterior	1	5
Subsegmentectomy or more*		
S2	0	2
S3	2	1
S5	4	1
S6	7	2
S7	2	0
S8	3	1
S5 + 6	1	1
Partials	71	36

*S, segment defined by the Couinaud's nomenclature.

Table 2. Comparisons of Patient Background Characteristics

Variables	Open (n = 99)	Laparoscopic (n = 63)	p Value
Age	65.2 ± 10.1	67.5 ± 9.5	0.1483
Male/female, n	74/25	48/15	0.8353
DM (+), n (%)	24 (24)	20 (32)	0.2977
HBs-Ag (+), n (%)	17 (17)	10 (16)	0.3813
HCV-Ab (+), n (%)	68 (68)	40 (63)	0.4952
Alb, g/dL, mean ± SD	3.99 ± 0.38	3.93 ± 0.40	0.3266
T-bil, mg/dL, mean ± SD	0.82 ± 0.32	0.86 ± 0.39	0.1263
ICGR-15, %, mean ± SD	16.1 ± 8.1	16.3 ± 8.3	0.9059
Child A/B, n	96/3	59/4	0.3187
Liver damage A/B, n	76/23	44/19	0.3293

Alb, albumin; DM, diabetes mellitus; HBs-Ag, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; ICGR15, indocyanin green retention rate at 15 min; T-bil, total bilirubin.

months.[16] The mean follow-up period after hepatic resection was 4.2 years (range 0.3 to 13.7 years) in the Open-Hx group, and 3.4 years (range 0.2 to 13.4 years) in the Lap-Hx group. When recurrence was suspected, we treated the recurrent HCC by repeat hepatic resection at any times of recurrence,[19] with ablation therapy or liodolization.[20]

Statistics

Continuous variables are expressed as the mean ± standard deviation (SD) and were compared using Student's *t*-test. Categorical variables were compared using the chi-square test. Survival curves were generated by the Kaplan-Meier method and compared using the log-rank test. All analyses were performed with JMP Pro 9.0.2 (SAS Institute Inc). Values of $p < 0.05$ were considered significant.

RESULTS

Patients' background characteristics

The patients' background characteristics are summarized in Table 2. There are no significant differences in the patient characteristics between the Open-Hx and the Lap-Hx groups, including mean age (65.2 vs 67.5 years; p = 0.1483), the positive rate of diabetes mellitus (24% vs 32%; p = 0.2977), hepatitis B surface antigen (17% vs 16%; p = 0.3813), and hepatitis C virus antibody (68% vs 63%; p = 0.4952), respectively. Concerning liver function, such as the serum level of albumin (3.99 vs 3.93 g/dL; p = 0.3266) and total bilirubin (0.82 vs 0.86 mg/dL; p = 0.1263), ICGR-15 (16.1% vs 16.3%; p = 0.9059), the ratio of Child A/B (96/3 vs 59/4; p = 0.3187) and Liver damage A/B (76/23 vs 44/19; p = 0.3293), respectively, there were also no significant differences between the 2 groups.

Short-term surgical outcomes

The patients' short-term surgical outcomes are summarized in Table 3. The mean resected liver volume in the Lap-Hx group (112.2 ± 97.3 g) was significantly larger than that in the Open-Hx group (81.2 ± 65.3 g; p = 0.0165). There were no deaths in either group, and the morbidity rate in the Lap-Hx group (10%) was significantly lower than that in the Open-Hx group (26%; p = 0.0459). Concerning the breakdown of morbidity, the positive rate of ascites in the Lap-Hx group (0%) was significantly lower than that in the Open-Hx group (7%; p = 0.0077). The duration of hospital stay in the Lap-Hx group (10.3 ± 4.4 days) was significantly shorter than that in the Open-Hx group (16.2 ± 13.4 days; p = 0.0008).

Tumor-related factors

Tumor-related factors are summarized in Table 4. There were no significant differences in tumor-related factors between the 2 groups, including the maximum tumor diameter (2.6 vs 2.5 cm; p = 0.5106), the positive rate of solitary tumor (84% vs 89%; p = 0.4593), poorly differentiated HCC (20% vs 19%; p = 0.8570), pathologic portal vein infiltration and/or intrahepatic metastasis (27% vs 19%; p = 0.4952), and stages III/IV-A (13% vs 10%; p = 0.4814), respectively. There were also no significant differences between the 2 groups regarding the tumor markers: serum levels of AFP (262.5 vs 593.4 ng/mL; p = 0.3128) and DCP (183.3 vs 127.1 mAU/mL; p = 0.1831), respectively.

Survival after hepatic resections for hepatocellular carcinoma

Disease-free survival and overall survival curves are provided in Figure 1. There were no significant differences in disease-free survival (p = 0.5196) or overall survival

Table 3. Comparisons of Short-Term Surgical Outcomes

Variables	Open (n = 99)	Laparoscopic (n = 63)	p Value
Surgical outcomes			
Operation time, min, mean ± SD	287.4 ± 83.2	299.5 ± 127.6	0.4664
Blood loss, g, mean ± SD	436.6 ± 320.7	455.7 ± 741.9	0.8221
Transfusion, n (%)	2 (2)	4 (6)	0.1612
Resected liver volume, g, mean ± SD	81.2 ± 65.3	112.2 ± 97.3	0.0165
Anatomic resection, n (%)	28 (28)	27 (43)	0.0516
Surgical margin, mm, mean ± SD	5.8 ± 6.9	7.4 ± 8.7	0.2243
Postoperative courses			
Mortality, n (%)	0 (0)	0 (0)	0.9999
Morbidity, n (%)	26 (26)	6 (10)	0.0459
Bile leakage, n (%)	2 (2)	1 (2)	0.8405
Ascites, n (%)	7 (7)	0 (0)	0.0077
Surgical site infection, n (%)	9 (9)	2 (3)	0.1249
Hospital stay, d, mean ± SD	16.2 ± 13.4	10.3 ± 4.4	0.0008

(p = 0.6791) between the 2 groups. The 2-year and 5-year disease-free survival rates were 70% and 41% in the Open-Hx group, and 68% and 33% in the Lap-Hx group, respectively. The 5-year and10-year overall survival rates were 77% and 57% in the Open-Hx group, and 78% and 69% in the Lap-Hx group, respectively. There were no port site recurrences or peritoneal seeding of HCC in the Lap-Hx group.

DISCUSSION

With advances and improvements in instruments and surgical experiences for laparoscopic surgery, there are increasing interests and options for Lap-Hx for HCC in patients with cirrhosis. The Louisville consensus statement concluded that laparoscopic left lateral sectionectomy should be considered standard practice, and it described the currently acceptable indications for Lap-Hx as patients with a solitary lesion, 5 cm or less, located in liver segment 2–6.[9] Several recent studies have reported their comparative results of Lap-Hx vs Open-Hx for HCC, and several meta-analyses summarized the surgical and oncologic outcomes of Lap-Hx as follows: less blood loss, less frequent need for transfusion, less morbidity, a lower complication rate of ascites, a lower complication rate of liver failure, shorter hospital stays, and no compromise in prognosis.[9-13]

However, in our study, the intraoperative blood loss of the Lap-Hx group (455.7 ± 741.9 g) did not significantly differ from that of the Open-Hx group (436.6 ± 320.7 g; p = 0.8221). Therefore, regarding the need for transfusion, there is no significant difference between the 2 groups (2% vs 6%; p = 0.1612). High intraperitoneal pressure caused by CO_2 pneumoperitoneum is considered to be one of the major reasons for reduced blood loss in Lap-Hx for HCC. However, generally speaking, Lap-Hx tends to be applied for limited resection to peripheral ventral small HCCs, in which hepatic resections are relatively easy to perform.[9-13] These "selection biases" were one of the potential causes of the smaller blood loss in Lap-Hx for HCC in other studies.[9,11-13] However, in our study, the resected liver volume of the Lap-Hx group (112.2 ± 97.3 g) was significantly larger than that of the Open-Hx group (81.2 ± 65.3 g; p = 0.0165), and the

Table 4. Comparisons of Tumor-Related Factors

Variables	Open (n = 99)	Laparoscopic (n = 63)	p Value
Maximum tumor diameter, cm	2.6 ± 1.1	2.5 ± 1.0	0.5106
Solitary tumor, n (%)	84 (84)	56 (89)	0.4593
Poorly differentiated HCC, n (%)	20 (20)	12 (19)	0.8570
VP and/or IM (+), n (%)	27 (27)	12 (19)	0.3356
Stage III/IVA, n (%)	13 (13)	6 (10)	0.4814
AFP, ng/mL, mean ± SD	262.5 ± 131.6	593.4 ± 205.3	0.3128
DCP, mAU/mL, mean ± SD	183.3 ± 534.5	127.1 ± 208.9	0.1831

AFP, alpha-fetoprotein; DCP, des-gamma-carboxyprothrombin; IM, pathologic intrahepatic metastasis; VP, pathologic portal vein infiltration.