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ORIGINAL SCIENTIFIC REPORT

Intraoperative High Fraction of Inspiratory Oxygen is Independently Associated with Worse Outcome After Living-Donor Liver Transplantation: A Retrospective Study

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Abstract

Background Ischemia and reperfusion injury is an important factor that determines graft function after liver transplantation, and oxygen plays a crucial role in this process. However, the relationship between the intraoperative high fraction of inspiratory oxygen (FiO_2) and living-donor-liver-transplantation (LDLT) outcome remains unclear.

Patients and Methods A total of 199 primary adult-to-adult LDLT cases in Kyoto University Hospital between January 2010 and December 2017 were enrolled in this study. The intraoperative FiO_2 was averaged using the total amount of intraoperative oxygen and air and defined as the calculated FiO_2 ($cFiO_2$). The cutoff value of $cFiO_2$ was set at 0.5.

Results Between the $cFiO_2$ <0.5 (n = 156) and ≥0.5 group (n = 43), preoperative recipients' background, donor factors, and intraoperative parameters were almost comparable. Postoperatively, the $cFiO_2$ ≥0.5 group showed a higher early allograft dysfunction (EAD) rate (P = 0.049) and worse overall graft survival (P = 0.036) than the $cFiO_2$ <0.5 group. Although the $cFiO_2$ ≥0.5 was not an independent risk factor for EAD in multivariable analysis (OR 2.038, 95%CI 0.992–4.186, P = 0.053), it was an independent risk factor for overall graft survival after LDLT (HR 1.897, 95%CI 1.007–3.432, P = 0.048).

Conclusion The results of this study suggest that intraoperative high FiO_2 may be associated with worse graft survival after LDLT. Avoiding higher intraoperative FiO_2 may be beneficial for LDLT recipients.

Introduction

In liver transplantation, ischemia and reperfusion injury (IRI) is one of the important factors that determine post-operative graft function [1]. The abrupt cessation of blood flow and subsequent ischemia decreases several antioxidants, such as glutathione, and also tissue adenosine triphosphate [2–4]. This ischemic phase itself damages the liver tissue [4]; moreover, after reperfusion, numerous cellular and molecular factors in various pathways are rapidly activated, which further aggravate the liver injury [1]. The ultimate consequence of this process is apoptotic or necrotic cell death, graft dysfunction, and graft loss [1]. From the findings of previous studies, it is now becoming clear that oxygen and its free radicals, called reactive

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oxygen species, play an important role in this process [5, 6].

Oxygen therapy was once regarded as a harmless treatment option [7]; however, several studies conducted in the field of critical care medicine have demonstrated that too much oxygenation could be harmful to the human body and that the restriction of oxygen supply would improve the outcomes of critically ill patients [8, 9]. Among patients admitted to the intensive care unit (ICU) following resuscitation of cardiac arrest, Kilgannon et al. showed that the first partial pressure of arterial oxygen (PaO_2) after ICU admission equal to or more than 300 mmHg was independently associated with increased in-hospital mortality [10]. Therefore, avoiding excessive oxygen supply is now becoming a new standard for patients' care [8].

Based on these findings, we hypothesized that excessive oxygen supply before and after graft reperfusion may influence the severity of IRI and the outcome after liver transplantation; however, this topic still remains unexplored. From the above, the aim of this study was to investigate the impact of higher intraoperative fraction of inspiratory oxygen (FiO_2) on the outcome after living-donor-liver-transplantation (LDLT).

Patients and Methods

Study Design

A total of 219 adult (≥18 years old) patients underwent primary LDLT in Kyoto University Hospital from January 2010 through December 2017. Among them, patients with posterior segment graft ($n = 8$), who died within seven days of LDLT ($n = 2$) and with preoperative pulmonary complications (hepato-pulmonary syndrome and moderate to severe pulmonary hypertension or intrapulmonary arteriovenous shunt, $n = 7$) were excluded. In addition, patients with incomplete operation records ($n = 3$) were also excluded. Ultimately, 199 patients were enrolled in this study.

The donor–recipient selection criteria, detailed surgical procedure, and regimens of postoperative immunosuppression, including blood type incompatible liver transplantation, have been described previously [11–13]. In our institute, the anesthesiology team is responsible for the intraoperative circulatory and respiratory care of patients. Although the target of intraoperative FiO_2 was set at approximately 0.4, the anesthesiologists were free to control the FiO_2 at their discretion.

All study protocols were approved by the Ethics Committee of Kyoto University (Approval number: R1473-4), and all procedures were conducted in accordance with the Declaration of Helsinki of 1996.

Data Collection

Data were retrospectively collected from patient charts. The preoperative recipient demographic data collected were age, sex, status prior to surgery (hospitalized or ICU stay), etiology of liver disease, Model for End-stage Liver Disease (MELD) score, hepatorenal syndrome, percent vital capacity (%VC), forced expiratory volume in one second/forced vital capacity (FEV1/FVC ratio), and results of blood sample tests. The donor demographic data collected were age, graft-to-recipient weight ratio (GRWR), blood type–incompatible donor, and graft type. Intraoperative parameters included operation time, blood loss, cold and warm ischemia time, portal vein pressure (PVP), intraoperative splenectomy and total volume of infusion. Postoperative parameters included in-hospital mortality, result of blood culture, acute cellular and humoral rejection within one year after LDLT, early allograft dysfunction (EAD) rate, and causes of graft loss. Postoperative platelet count until postoperative day (POD) 42 and bilirubin level until POD 7 were also collected.

The intraoperative FiO_2 usually fluctuated during the operation; therefore, to precisely assess the difference of intraoperative FiO_2 between patients, the value was averaged using the total amount of intraoperative oxygen (O_2) and air administered, i.e., the calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$.

Recipients with %VC ≥80% and FEV1/FVC ratio ≥70% were classified as having normal pulmonary function. There were 23 cases of recipients (15 and 8 cases for $cFiO_2$ <0.5 and ≥0.5 group, respectively) whose preoperative pulmonary functions were not measured due to the patient's condition.

The results of arterial blood gas analyses including the PaO_2, partial pressure of arterial carbon dioxide ($PaCO_2$), HCO_3^-, and PaO_2/FiO_2 (P/F) ratio were obtained at three time points during operation: at the start, within 30 min before or after portal reperfusion, and at the end of the operation.

Recipients' preoperative skeletal muscle mass index (SMI), visceral to subcutaneous adipose tissue area ratio (VSR), and intra-muscular adipose tissue content (IMAC) were also collected, because our team previously reported that preoperative low SMI, high IMAC, and high VSR, i.e., "positive 3 body composition markers," are independent risk factors for mortality after LDLT [14].

EAD was defined by the presence of one or more of the following: (i) total bilirubin ≥10 mg/dL on POD 7, (ii) prothrombin time-international normalized ratio ≥1.6 on POD 7, and (iii) aspartate aminotransferase or alanine aminotransferase ≥2000 IU/mL within the first seven postoperative days [15].

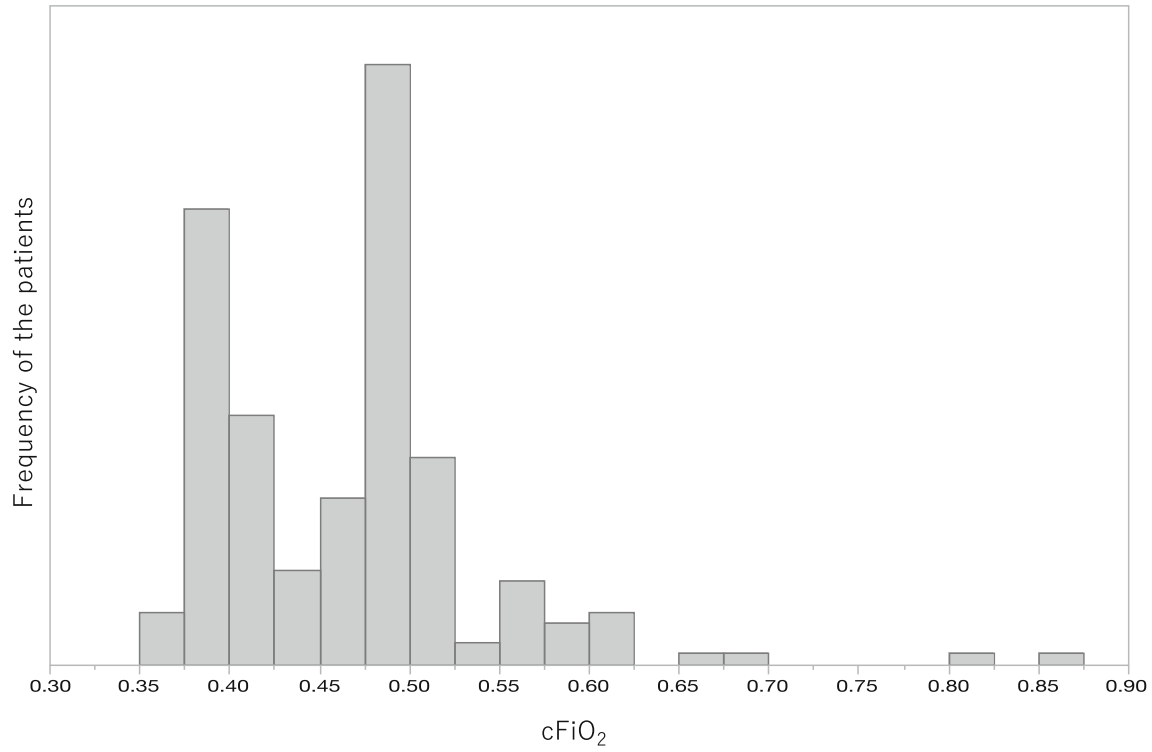


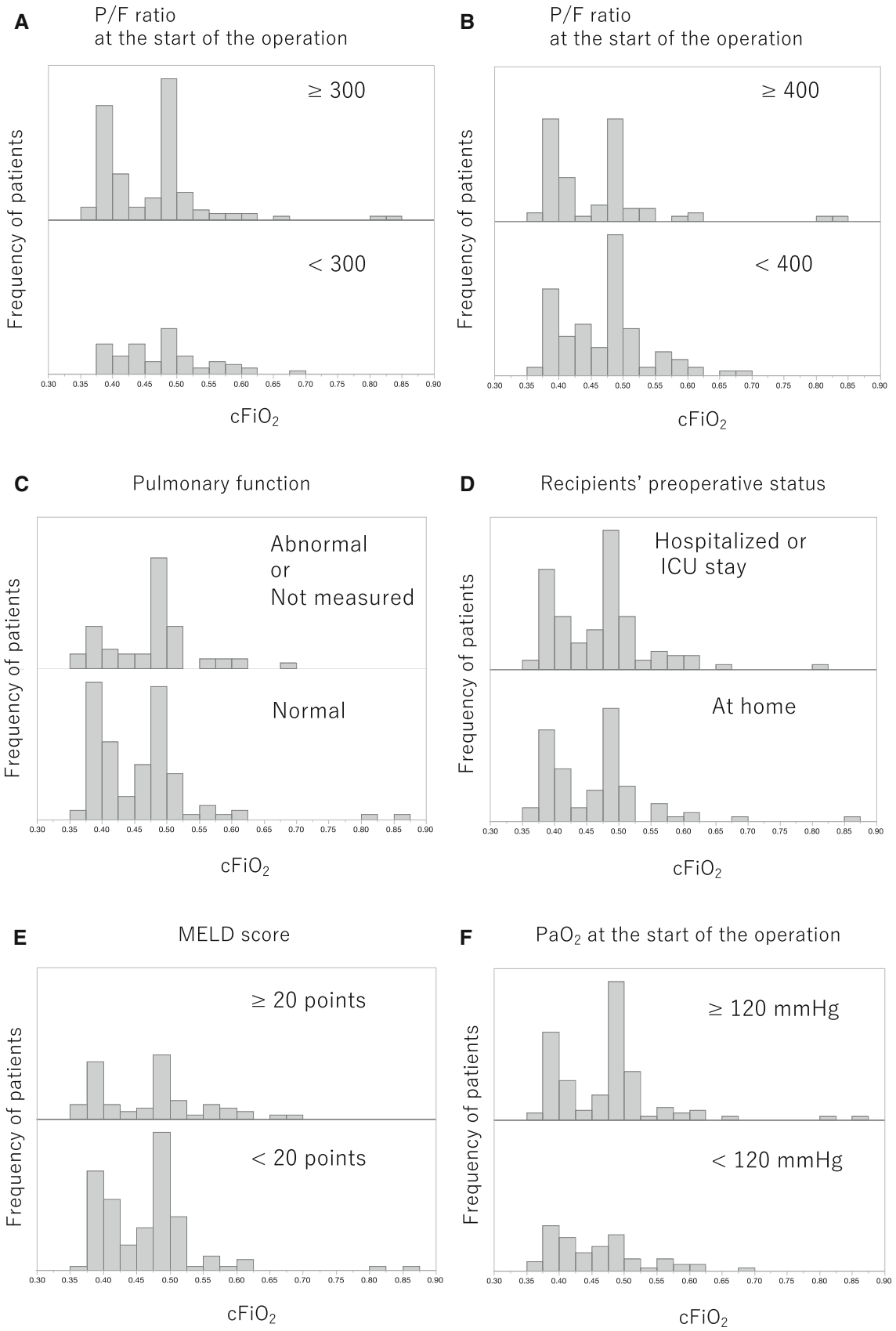
Fig. 1 Distribution of $cFiO_2$. Intraoperative FiO_2 was averaged using the total amount of intraoperative oxygen (O_2) and air administered, i.e., calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. FiO_2; fraction of inspiratory oxygen

Parameters Analyzed

First, the distribution of $cFiO_2$ was evaluated and the factors associated with the difference of $cFiO_2$ between patients were assessed. Second, based on the previous study [16], patients were divided according to the cutoff value of the $cFiO_2$ "0.5." Subsequently, the background and postoperative outcomes of patients were evaluated. Third, the prognostic factors associated with EAD were evaluated using univariable and multivariable analyses. The data included in the univariable analysis were determined according to the previous reports [17, 18]. Although the previous study has shown that a high preoperative bilirubin level is a risk factor for EAD [17], in this analysis, the clearance of total bilirubin level during the first seven days after LDLT, defined as "(preoperative bilirubin–POD7 bilirubin)/preoperative bilirubin," was used instead of a simple preoperative bilirubin level. Finally, the postoperative survival curves of recipients with the $cFiO_2$ <0.5 and ≥ 0.5 were compared. Subsequently, the prognostic factors associated with overall graft survival were analyzed using univariable and multivariable analyses. The data included in the univariable analysis were also determined according to the previous reports [14, 19–23].

Statistical Analysis

Continuous data were expressed as the median and interquartile range (IQR) and were compared using the Wilcoxon rank-sum test. Categorical data were expressed as counts, and percentages and were compared using the Fisher's exact test. The overall graft survival rate was calculated using the Kaplan–Meier method, and differences between curves were evaluated using the log-rank test. Variables with $P < 0.10$ in the univariable analysis were considered candidates for multivariable logistic regression analysis or Cox regression analysis. The results of the multivariable analysis are shown as odds ratios (ORs) or hazard ratios (HRs) with 95% confidence intervals (CIs). According to the previous recommendation of the American Statistical Association [24], we avoided describing $P < 0.05$ as "statistically significant"; instead, we described the P values as continuous quantities in the text, figures, and tables. All statistical analyses were performed using JMP Pro, version 14.0.0 (SAS Institute, Inc., Cary, NC).


A
P/F ratio
at the start of the operation
≥ 300
< 300
Frequency of patients
0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90
cFiO2
B
P/F ratio
at the start of the operation
≥ 400
< 400
Frequency of patients
0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90
cFiO2
C
Pulmonary function
Abnormal
or
Not measured
Normal
Frequency of patients
0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90
cFiO2
D
Recipients' preoperative status
Hospitalized or
ICU stay
At home
Frequency of patients
0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90
cFiO2
E
MELD score
≥ 20 points
< 20 points
Frequency of patients
0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90
cFiO2
F
PaO2 at the start of the operation
≥ 120 mmHg
< 120 mmHg
Frequency of patients
0.30 0.35 0.40 0.45 0.50 0.55 0.60 0.65 0.70 0.75 0.80 0.85 0.90
cFiO2

◀**Fig. 2** Evaluation of the factors associated with the variance of the $cFiO_2$. The distribution of $cFiO_2$ was divided according to the P/F ratio (≥or <300 and 400, **A** and **B**, respectively), recipients' pulmonary function (**C**), recipients' preoperative status (**D**), MELD score (**E**), and PaO_2 at the start of the operation (**F**). The normal pulmonary function was defined as recipients with %VC ≥80% and FEV1/FVC ratio ≥70%. Calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. FEV1/FVC, forced expiratory volume in one second/forced vital capacity; FiO_2, fraction of inspiratory oxygen; MELD, model for end-stage liver disease; PaO_2, partial pressure of arterial oxygen; P/F, PaO_2/FiO_2 ratio; %VC, percent vital capacity

Results

Distribution of $cFiO_2$ and the Factors Associated with the Variance

The $cFiO_2$ showed a bimodal distribution, and the peaks were found around 0.4 and 0.5 (Fig. 1); therefore, we evaluated the factors associated with the difference of the $cFiO_2$ between patients (Fig. 2). First, we divided the patients according to the P/F ratio at the start of the operation (Fig. 2A and B); however, both the P/F ratio ≥300 and ≥400 groups had a peak around $cFiO_2$ 0.5 and the P/F ratio <400 group also showed a peak around $cFiO_2$ 0.4. Patients were also divided according to their pulmonary function (Fig. 2C), preoperative status (Fig. 2D), MELD score (Fig. 2E), and PaO_2 at the start of the operation (Fig. 2F); however, none seemed to influence the variance of $cFiO_2$. Finally, we also assessed the trend of the $cFiO_2$ during the observational period. As shown in Fig. 3, no apparent chronological changes in $cFiO_2$ were found during this observational period.

Summary of Patients' Demographic Data (Table *1*)

Recipients were divided into those with the $cFiO_2$ <0.5 (n = 156) and ≥0.5 (n = 43). Both groups showed almost comparable preoperative recipients' background, donor factors, and intraoperative parameters. Although the P values of recipients' preoperative alanine aminotransferase and intraoperative warm ischemia time were less than 0.05, the difference in actual values was almost clinically negligible. Postoperatively, the $cFiO_2$ ≥0.5 group showed a trend toward higher EAD rate than the $cFiO_2$ <0.5 group.

Figure 4 shows the results of arterial blood gas analyses during the operation. PaO_2 was first comparable between the two groups; however, the $cFiO_2$ ≥0.5 group showed higher PaO_2 during portal reperfusion and at the end of the operation compared to the $cFiO_2$ <0.5 group (Fig. 4A). The levels of $PaCO_2$ and HCO_3^- were almost similar between the two groups throughout the operation (Fig. 4B and C). The P/F ratio was first lower in the $cFiO_2$ ≥0.5 group; however, the values became almost comparable thereafter (Fig. 4D).

Comparisons of the postoperative platelet count and total bilirubin values are shown in Fig. 5. The $cFiO_2$ ≥0.5 group showed a trend toward lower platelet count after POD5 (Fig. 5A) and higher bilirubin levels after POD3 (Fig. 5B).

Fig. 3 The trend of the $cFiO_2$ during the observational period. No apparent changes in trend were found during this observational period. Calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. FiO_2, fraction of inspiratory oxygen

Table 1 Summary of patients' characteristics

	$cFiO_2$ <0.5	$cFiO_2$ ≥0.5	
	n = 156	*n* = 43	*P*
Preoperative recipient factors			
Age, year*	54 (46–61)	53 (39–61)	0.737
Sex (male/female)	80/76	22/21	1.000
Hospitalized or ICU, *n* (%)	84 (54)	26 (60)	0.491
Positive 3 body composition markers, *n* (%)	7 (5)	1 (2)	1.000
Etiology			0.324
HBV/HCV, *n* (%)	67 (43)	13 (30)	
AIH/PBC/PSC, *n* (%)	29 (19)	7 (16)	
Biliary atresia, *n* (%)	13 (8)	4 (9)	
Other, *n* (%)	47 (30)	19 (44)	
Hepatocellular carcinoma, *n* (%)	49 (31)	11 (26)	0.574
Fulminant hepatic failure, *n* (%)	5 (3)	3 (7)	0.375
MELD score*	17 (13–20)	17 (13–27)	0.468
Hepatorenal syndrome, *n* (%)	11 (7)	6 (14)	0.213
Respiratory function			
%VC, %*	92 (78–104)	86 (69–103)	0.308
FEV1/FVC ratio, %*	83.1 (78.7–87.6)	83.4 (77.4–88.7)	0.760
Results of blood test			
AST, IU/L*	53 (33–87)	41 (27–67)	0.052
ALT, IU/L*	32 (19–53)	23 (17–35)	0.023†
Albumin, g/dL*	3.0 (2.4–3.2)	3.0 (2.4–3.2)	0.627
Total bilirubin, mg/dL*	3.9 (2.0–8.3)	3.3 (1.6–14.9)	0.814
Creatinine, mg/dL*	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.996
PT-INR*	1.5 (1.3–1.8)	1.6 (1.3–1.9)	0.440
White blood cell count, × 1000/m^3*	3.7 (2.5–5.2)	3.9 (2.7–5.9)	0.582
Hemoglobin, g/dL*	9.6 (8.5–11.5)	9.2 (8.1–10.9)	0.222
Platelet count, × 1000/μL*	64 (39–101)	66 (37–99)	0.904
Donor factors			
Age, year*	45 (31–56)	45 (34–56)	0.794
GRWR, %*	0.9 (0.7–1.1)	0.8 (0.7–1.0)	0.142
Blood type incompatible donor, *n* (%)	35 (22)	15 (34)	0.113
Graft type, left/right lobe graft	73/83	21/22	0.864
Intraoperative parameters			
Operation time, hour*	14 (12–16)	15 (12–18)	0.421
Blood loss, L*	5.7 (3.5–10.2)	6.8 (3.0–17.0)	0.326
Cold ischemia time, hour*	1.8 (1.0–2.8)	2.2 (1.1–3.6)	0.178
Warm ischemia time, min*	44 (37–54)	39 (33–50)	0.012†
PVP before abdominal closure, mmHg*	12 (10–14)	13 (11–14)	0.110
Intraoperative splenectomy, *n* (%)	65 (42)	13 (30)	0.217
Total volume of infusion, L*	13.4 (9.9–18.3)	14.8 (8.9–29.4)	0.260
Postoperative parameters			
In-hospital mortality, *n* (%)	20 (13)	8 (19)	0.330
Positive blood culture, *n* (%)	49 (31)	20 (47)	0.072
Reoperation, *n* (%)	29 (19)	14 (33)	0.060
Acute cellular or humoral rejection, *n* (%)	90 (58)	25 (58)	1.000
EAD, *n* (%)	50 (32)	21 (49)	0.049
Causes of graft loss			0.684

Table 1 continued

	$cFiO_2$ <0.5	$cFiO_2$ ≥0.5	
	n = 156	*n* = 43	*P*
Liver failure, *n* (%)	12 (35)	7 (44)	
Multiple organ failure, *n* (%)	7 (21)	2 (13)	
Sepsis, *n* (%)	10 (29)	3 (19)	
ARDS, *n* (%)	1 (3)	0 (0)	
Other, *n* (%)	4 (12)	4 (25)	

*Data are presented as the median and interquartile range. Calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. †$P$ <0.05

AIH autoimmune hepatitis; *ALT* alanine aminotransferase; *ARDS* acute respiratory distress syndrome; *AST* aspartate aminotransferase; *EAD* early allograft dysfunction; *FEV1/FVC* forced expiratory volume in one second/forced vital capacity; *FiO_2* fraction of inspiratory oxygen; *GRWR* graft-to-recipient weight ratio; *HBV* hepatitis B virus; *HCV* hepatitis C virus; *ICU* intensive care unit; *MELD* model for end-stage liver disease; *PBC* primary biliary cholangitis; *PSC* primary sclerosing cholangitis; *PT-INR* prothrombin time–international normalized ratio; *PVP* portal vein pressure; *%VC* percent vital capacity

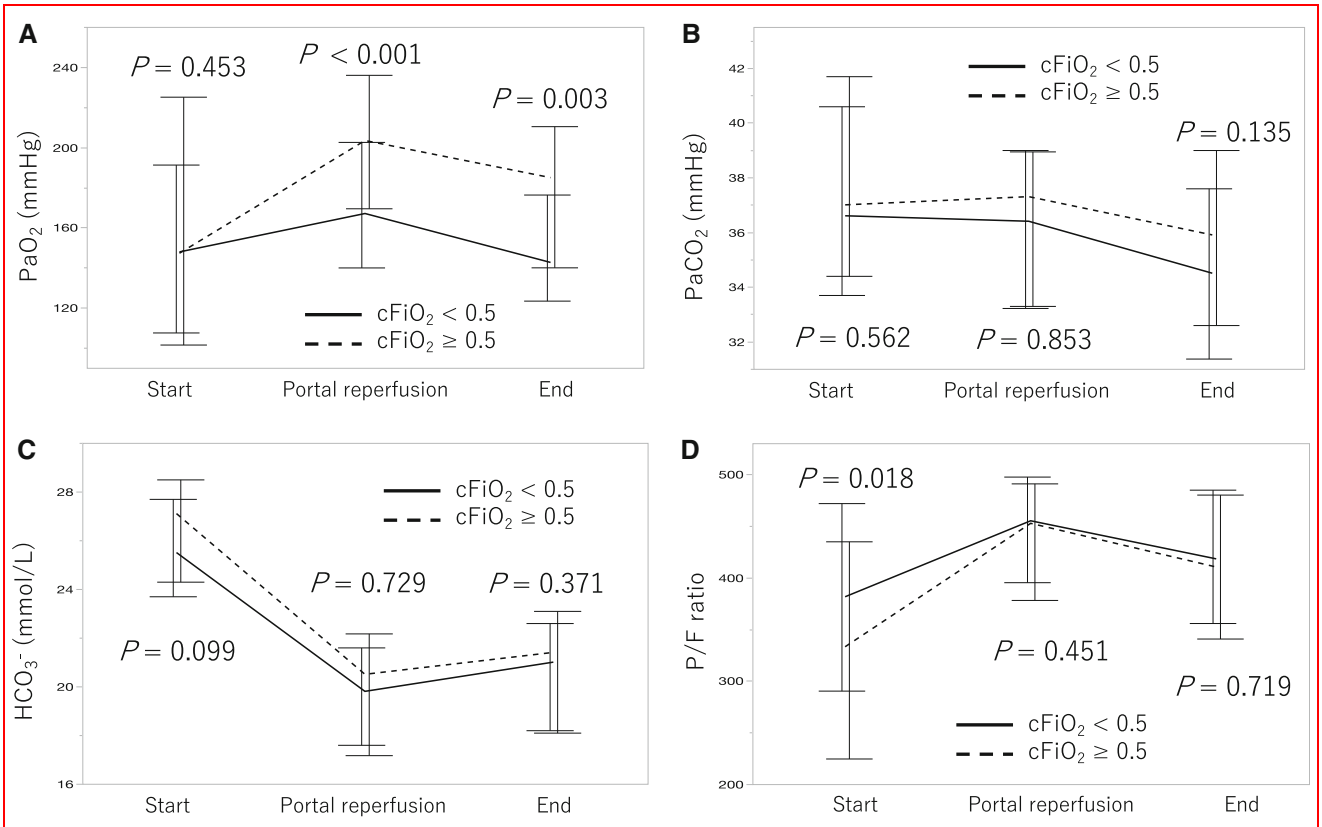


Fig. 4 The results of arterial blood gas analysis during operation. The $cFiO_2$ ≥0.5 group showed higher PaO_2 at the portal reperfusion and at the end of the operation compared to the $cFiO_2$ <0.5 group (**A**). The results of $PaCO_2$ (**B**) and HCO_3^- (**C**) were almost similar between the two groups throughout the operation. The P/F ratio was initially lower in the $cFiO_2$ ≥0.5 group; however, the value became almost comparable between the two groups during portal reperfusion (**D**). Calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. FiO_2, fraction of inspiratory oxygen; PaCO2, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; P/F, PaO_2/FiO_2 ratio

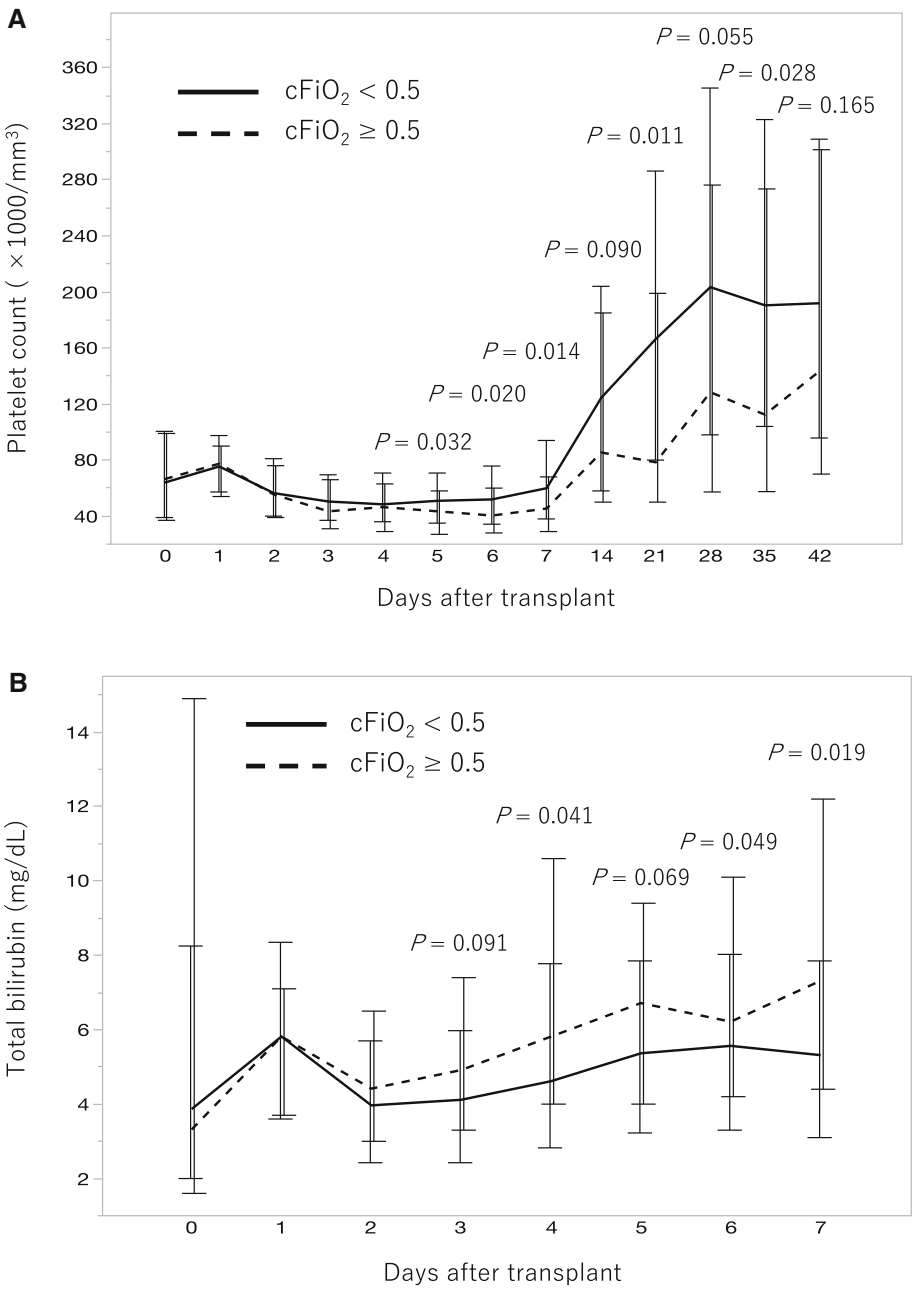


Fig. 5 Comparisons of postoperative platelet count and total bilirubin value. The $cFiO_2$ ≥0.5 group showed a trend toward lower platelet count after POD5 (**A**) and higher bilirubin levels after POD 3 (**B**). Calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. FiO_2, fraction of inspiratory oxygen

Risk Factor Analysis for EAD

Univariable analysis revealed that recipient age, gender, donor age, left lobe graft, and the $cFiO_2$ ≥0.5 were potential risk factors for EAD after LDLT (Table 2). Multivariable analysis showed that the male recipients (P = 0.048) and donor age (P = 0.023) were independent risk factors for EAD. Although the P value did not reach the statistical threshold, the $cFiO_2$ ≥0.5 was considered as a possible risk factor for EAD (P = 0.053).

Graft Survival After LDLT and Risk Factor Analysis

Figure 6 shows the overall graft survival after LDLT. The $cFiO_2$ ≥0.5 group showed worse graft survival than the $cFiO_2$ <0.5 group. Table 3 shows the results of the risk factor analysis for overall graft survival after LDLT. Univariable analysis revealed that the positive 3 body composition markers, donor age ≥40 years, GRWR <0.6% blood type incompatible donor, and the $cFiO_2$ ≥0.5 were potential risk factors for graft loss after LDLT. Multivariable analysis showed that the positive 3 body composition

Table 2 Univariable and multivariable analyses for factors associated with EAD

	Univariable analysis			Multivariable analysis		
	OR	95%CI	*P*	OR	95%CI	*P*
Recipient preoperative factors						
Recipient age, per 10 years*	0.803	0.638–1.011	0.061	0.824	0.650–1.046	0.112
Recipient sex, male	0.434	0.239–0.786	0.006	0.510	0.261–0.996	0.048†
Fulminant hepatic failure	3.205	0.743–13.834	0.119			
AST, per 1 IU/L*	0.999	0.995–1.004	0.925			
ALT, per 1 IU/L*	0.998	0.992–1.004	0.429			
Total-bilirubin clearance*‡	0.936	0.824–1.063	0.312			
Albumin, g/dL*	0.875	0.537–1.427	0.593			
Creatinine, mg/dL*	1.138	0.823–1.574	0.432			
Hepatorenal syndrome	1.692	0.622–4.602	0.303			
Donor factors						
Donor age, per 5 year*	1.116	0.999–1.247	0.049	1.146	1.016–1.292	0.023†
GRWR, per 0.1%*	0.898	0.783–1.030	0.120			
Blood type incompatible donor	0.804	0.407–1.589	0.531			
Left lobe graft	1.934	1.074–3.481	0.028	1.740	0.880–3.441	0.112
Intraoperative parameters						
Blood loss, per 1L*	0.992	0.954–1.031	0.669			
Cold ischemia time, per 1 h*	0.848	0.681–1.055	0.119			
P/F ratio at the start of operation <300	0.703	0.380–1.303	0.263			
P/F ratio at the start of operation <400	1.104	0.613–1.991	0.740			
$cFiO_2$ ≥0.5	2.024	1.020–4.018	0.044	2.038	0.992–4.186	0.053
Final PVP ≥15 mmHg	0.897	0.393–2.044	0.794			

*The factor is included in the analysis as continuous data. Calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. † *P* <0.05 on multivariate analysis. ‡The formula for total bilirubin clearance is as follows: (preoperative bilirubin–POD7 bilirubin)/preoperative bilirubin

ALT alanine aminotransferase; *AST* aspartate aminotransferase; *CI* confidence interval; *EAD* early allograft dysfunction; *FiO_2* fraction of inspiratory oxygen; *GRWR* graft-to-recipient weight ratio; *OR* odds ratio; *P/F* PaO_2/FiO_2 ratio; *PVP* portal vein pressure

markers (*P* <0.001), blood type incompatible donor (*P* = 0.046), and the $cFiO_2$ ≥0.5 (*P* = 0.048) were independent risk factors for overall graft survival after LDLT.

Discussion

The results of this study demonstrated that high intraoperative FiO_2 may be independently associated with worth graft outcome after LDLT. This is also confirmed by the fact that the $cFiO_2$ ≥0.5 group showed higher EAD rate, although the $cFiO_2$ ≥0.5 was not shown to be an independent factor in multivariable analysis.

In a previous experimental study, it was shown that perioperative hyperoxic conditions worsen liver IRI. Using a mouse partial liver ischemia–reperfusion model, Zangl et al. demonstrated that the mice under postoperative hyperoxic (FiO_2 = 0.6) conditions showed higher glutamate-pyruvate-transaminase level, reactive oxygen species, and histological injury score than the mice under normoxic (FiO_2 = 0.21) conditions [25]. Subsequently, they showed that the harmful effects of high FiO_2 were ameliorated by depletion of granulocytes or Kupffer cells or by knocking out of the p47phox unit of the NADPH-oxidase [25]. Considering that granulocytes and Kupffer cells are the main sources of reactive oxygen species, their results suggested that oxygen is a very important factor that affects IRI and that restriction of oxygen supply may decrease the severity of liver injury after ischemia–reperfusion.

In our study, the $cFiO_2$ ≥0.5 groups showed a worse overall graft survival after LDLT. Regarding short-term outcomes, the $cFiO_2$ ≥0.5 group was also associated with a higher rate of EAD. Univariable analysis showed that higher $cFiO_2$ was a potential risk factor for EAD; however, it did not reach the statistical threshold for independent risk

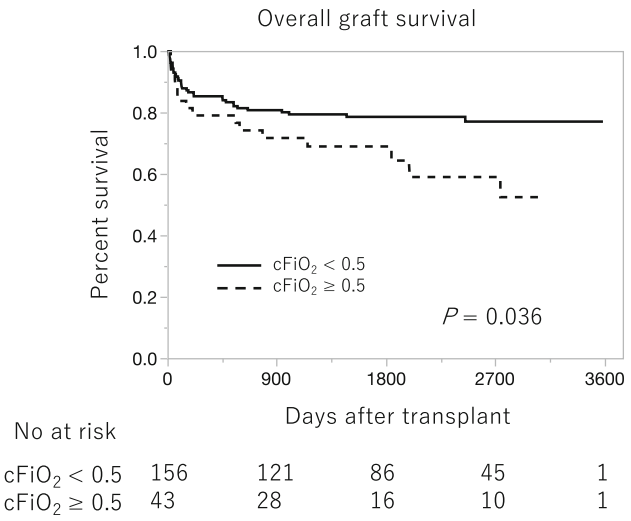


Fig. 6 The overall graft survival after LDLT. The $cFiO_2$ ≥0.5 group showed worse graft survival than the <0.5 group. Calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. FiO_2, fraction of inspiratory oxygen; LDLT, living-donor liver transplantation

factor in multivariable analysis. This may be because the difference in $cFiO_2$ between the two groups (median 0.44 for the $cFiO_2$ <0.5 group and 0.53 for the $cFiO_2$ ≥0.5 group, respectively) was not strong enough to detect the difference in the EAD rate. If we could have compared the FiO_2 0.3 and 0.8, which were used in several prospective studies [26–28], the difference in short-term outcomes might have appeared more clearly. Liver transplantation is a life-saving procedure, and recipients are usually critically ill; therefore, it would be ethically difficult to conduct a prospective study allocating patients into extremely different intraoperative FiO_2. We think the results of this study suggested the possibility that high intraoperative FiO_2 might increase the EAD rate and could lead to worse graft outcomes after LDLT.

A lower P/F ratio at the start of the operation would be the main reason for the higher oxygen supply in the $cFiO_2$ ≥0.5 group (Fig. 4D). However, in the $cFiO_2$ ≥0.5 group, the P/F ratio improved thereafter and the PaO_2 increased during portal reperfusion than in the $cFiO_2$ <0.5 group (Fig. 4A). Resolving of atelectasis by positive

Table 3 Univariable and multivariable analyses for factors associated with overall graft survival

	Univariable analysis			Multivariable analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Recipient preoperative factors						
Recipient age, per 10 years*	1.041	0.839–1.313	0.723			
Recipient sex, male	0.628	0.354–1.097	0.103			
Positive 3 body composition marker	7.232	2.918–15.503	<0.001	6.883	2.704–15.374	<0.001†
Fulminant hepatic failure	1.783	0.433–4.864	0.371			
MELD, per 1 score*	1.023	0.990–1.054	0.168			
AST, per 1 IU/L*	0.999	0.994–1.003	0.762			
ALT, per 1 IU/L*	0.999	0.993–1.003	0.845			
Total bilirubin, mg/dL*	1.008	0.976–1.034	0.612			
Albumin, g/dL*	1.276	0.807–2.006	0.296			
Creatinine, mg/dL*	1.135	0.866–1.351	0.303			
Donor factors						
Donor age ≥40 years	1.704	0.949–3.214	0.075	1.403	0.767–2.681	0.277
GRWR <0.6%	2.609	0.903–5.982	0.073	2.016	0.694–4.666	0.178
Blood type incompatible donor	2.007	1.114–3.523	0.021	1.854	1.012–3.297	0.046†
Intraoperative parameters						
Blood loss, per 1L*	0.992	0.949–1.008	0.672			
Cold ischemia time, per 1 h*	0.937	0.752–1.119	0.508			
P/F ratio at the start of operation <300	1.068	0.595–2.015	0.830			
P/F ratio at the start of operation <400	1.031	0.581–1.799	0.581			
$cFiO_2$ ≥0.5	1.868	1.004–3.331	0.047	1.897	1.007–3.432	0.048†
Final PVP ≥15 mmHg	1.013	0.414–2.129	0.976			

*The factor is included in the analysis as continuous data. Calculated FiO_2 ($cFiO_2$) was defined as $\{O_2(L) + Air(L) \times 0.21\}/\{O_2(L) + Air(L)\}$. † *P* <0.05 on multivariate analysis. *ALT* alanine aminotransferase; *AST* aspartate aminotransferase; *CI* confidence interval; *EAD* early allograft dysfunction; *FiO_2* fraction of inspiratory oxygen; *GRWR* graft-to-recipient weight ratio; *HR* hazard ratio; *MELD* model for end-stage liver disease; *P/F* PaO_2/FiO_2 ratio; *PVP* portal vein pressure

pressure ventilation or removal of a large amount of ascites or pleural effusion may be associated with improved oxygenation in the $cFiO_2 \geq 0.5$ group. As shown in the Supplementary Figure, spot FiO_2 was gradually decreased during operation even in the $cFiO_2 \geq 0.5$ group; however, the difference was smaller than that observed in the $cFiO_2 < 0.5$ group; therefore, the FiO_2 became relatively higher than expected, and the liver grafts were exposed to a higher oxygen environment in the $cFiO_2 \geq 0.5$ group. These results suggest that intraoperative FiO_2 can be reduced safely in some patients, which may lead to the suppression of IRI, lower EAD rate, and improved outcome after LDLT.

Our study has several limitations. First, the study was retrospective and conducted in a single institution. Our results should be confirmed in multicenter prospective studies. Second, it would have been more informative if we could have assessed all possible parameters in our institute during risk factor analysis for EAD and graft survival. However, due to the limited number of patients, we selected the factors included in the analysis, according to the results of previous studies. Further accumulation of cases is needed for a more accurate investigation. Last, we have to be careful about applying the results of this study to the patients undergoing LDLT. We think that these results do not mean the intraoperative FiO_2 should be kept "lower as possible." Intraoperative FiO_2 should be adjusted according to the condition of each patient and critically ill patients sometimes need higher than usual oxygen to maintain a normal oxygenation level. However, as is shown in this study, even the most of the patients in $cFiO_2 < 0.5$ group showed PaO_2 over 120 mmHg and those in $cFiO_2 > 0.5$ group showed further higher PaO_2 during LDLT; therefore, we think that FiO_2 could be reduced safely for these patients. From the above, we think that our results should be interpreted as "avoiding unnecessarily high intraoperative FiO_2 in LDLT."

In conclusion, this retrospective study suggested that intraoperative high FiO_2 might increase EAD and have some impact on graft survival after LDLT. Avoiding unnecessarily high intraoperative oxygenation may have some beneficial effects in patients undergoing LDLT.

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Declarations

Conflict of interest All authors declared no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Ethical Approval All study protocols were approved by the Ethics Committee of Kyoto University (Approval number: R1473-4), and all procedures were conducted in accordance with the Declaration of Helsinki of 1996.

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