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Acute respiratory distress syndrome after orthotopic liver transplantation☆,☆☆

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ABSTRACT

Purpose: Acute respiratory distress syndrome (ARDS) is a devastating complication with substantial mortality. The aims of this study were to identify the incidence, preoperative and intraoperative risk factors, and impact of ARDS on outcomes in patients after orthotopic liver transplantation (OLT).
Materials and methods: Adult OLT patients between January 2004 and October 2013 at our center were included. Postoperative ARDS was determined using the criteria proposed by the Berlin Definition. Multivariate logistic models were used to identify preoperative and intraoperative risk factors for ARDS.
Results: Of 1726 patients during the study period, 71 (4.1%) developed ARDS. In the preoperative model, encephalopathy (odds ratio [OR], 2.22; $P = .022$), preoperative requirement of intubation (OR, 2.06; $P = .020$), and total bilirubin (OR, 1.02; $P = .003$) were independent risk factors. In the intraoperative model, large pressor bolus was the sole risk factor for ARDS (OR, 2.69; $P = .001$). Postoperatively, patients with ARDS had a 2-fold increase in 1-year mortality, mechanical ventilation time, and length of hospital stay.
Conclusions: Acute respiratory distress syndrome occurred at a rate of 4.1% following OLT in adult patients and was associated with preoperative encephalopathy, requirement of intubation, and total bilirubin and intraoperative large boluses of pressors. Acute respiratory distress syndrome was associated with increased mortality, longer ventilation time, and hospital stay.

Acute respiratory distress syndrome (ARDS) is a clinical syndrome presenting with rapidly progressed noncardiac hypoxemia after an insult [1]. It is a common cause of respiratory failure and is viewed as one of most devastating complications after surgery [2]. Despite immense resources invested in the basic and clinical research for decades, mortality associated with ARDS remains substantially high [3].

Acute respiratory distress syndrome after orthotopic liver transplantation (OLT) was reported previously [4–6]. However, the interpretation of previous findings in today's environment is difficult. First, liver transplant is a fast-changing field. Recipients undergoing OLT are very different today from a decade ago, as are the donor organs. This is particularly true after implementation of the model for end-stage liver disease (MELD) organ allocation system in 2002 [7]. Secondly, since ARDS was first described in 1967, the diagnostic criteria and definition of ARDS have evolved greatly. In 2012, the Berlin Definition of ARDS was introduced and has been rapidly adopted by the pulmonary and critical care communities [1]. The latest definition has introduced a few new concepts and eliminated the discrepancies of the previous versions. Using a uniform term is essential in clinical research and practice. To date, a study using the Berlin Definition in patients undergoing OLT has not been reported.

Because of the paucity of development of effective treatments for ARDS, current efforts are focusing on identification of risk factors and prevention [8]. Identification of risk factors would allow clinicians to implement the preventive interventions in the early stage. We sought to use our large perioperative database to determine the incidence and risk factors (in both preoperative and intraoperative periods) of ARDS in adult patients who underwent OLT. Finally, the impacts of ARDS on postoperative outcomes were assessed.

1. Methods

The institutional review board of the University of California, Los Angeles (UCLA), approved the study and waived the informed consent. The study population consisted of all adult (≥18 years) patients who

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underwent OLT at the UCLA Medical Center between January 2004 and October 2013. Preoperative and intraoperative variables were prospectively collected and stored in the UCLA transplant database. Preoperative encephalopathy was based on a clinical diagnosis at the time of transplant surgery. Postoperative arterial blood gas analysis, chest radiographic examination, and other clinical data related to this study were collected retrospectively from the UCLA electronic medical records.

Anesthesia management followed the protocol of the UCLA anesthesia team [9]. All patients that underwent OLT were under general anesthesia with endotracheal intubation. Anesthetics generally included combined intravenous and inhalational anesthetics, neuromuscular blockages, and narcotics. In addition to American Society of Anesthesiologists standard monitors, patients were monitored with intraarterial catheter, central venous catheter, pulmonary artery catheter, and transesophageal echocardiogram. The intraoperative ventilation management was at the discretion of the attending anesthesiologist. Blood products including packed red blood cells (RBCs), fresh frozen plasma (FFP), platelets, and cryoprecipitate were used the study period. Red blood cells and FFP were administered via a rapid transfusing device. Vasoactive pressors were administered either in continuous infusion or in bolus. A large pressor bolus was described elsewhere and recorded prospectively by the treating anesthesiologist [9]. Briefly, a *large pressor bolus* was defined as total intraoperative doses of phenylephrine greater than 2 mg, epinephrine greater than 50 μg, or norepinephrine greater than 40 μg. All patients were kept intubated and transferred to the intensive care units and managed by a multidisciplinary team.

Acute respiratory distress syndrome was determined using the 2012 Berlin Definition [1]. The ARDS diagnostic criteria included the following components: within 7 days after OLT, a Pao_2/Fio_2 (P/F) ratio less than or equal to 300 mm Hg, and bilateral infiltrates on chest radiographic examination which could not be fully explained by effusions, lobar/lung collapse, nodules, cardiac origin, or fluid overload. If a patient had a diagnosis of fluid overload and the P/F ratio was improved after treatment, that patient was excluded from the ARDS group. Acute respiratory distress syndrome was divided into 3 categories based on degree of hypoxemia: mild (200 mm Hg < P/F ≤ 300 mm Hg), moderate (100 mm Hg < P/F ≤ 200 mm Hg), and severe (P/F ≤ 100 mm Hg). Preoperative, intraoperative, and donor variables were compared between patients with and without postoperative ARDS. Postoperative outcomes were compared between the 2 groups as well.

Data were expressed as mean ± SD or median (interquartile range, IQR) for continuous variables, or as proportions for nonparametric variables. If needed, continuous variables were dichotomized at the median or at a meaningful value indicated by a gap in histogram, or was grouped by quartiles. For univariate analysis, χ^2, Fisher exact test, or Student *t* test was used. Variables that showed a potential significance ($P < .1$) during univariate analyses were included in a multivariate logistic regression model. Two logistic models were used to analyze preoperative and intraoperative risk factors separately. In the preoperative model, all patients were included. In the intraoperative model, propensity score for each patient was generated by preoperative factors. Before the matching, the median propensity score of patients with ARDS was 0.058 (IQR 0.032-0.111), and the score of patients without ARDS was 0.024 (IQR 0.015-0.049). Patients were matched (1:4 ratio) by closest propensity score with caliper width equal to 0.2 of the standard deviation of the logit of the propensity score. After the matching, the median propensity scores were 0.055 (0.032-0.110) and 0.051 (0.031-0.097) for patients with and without ARDS, respectively. Afterward, intraoperative factors were compared and independent intraoperative risk factor(s) was identified using the after-match data. The odds ratio (OR) and 95% confidence interval (CI) with associated P values for each variable were reported in the logistic models. $P < .05$ was considered statistically significant in the multivariate models. Statistical analyses were performed using the Statistical Package for the Social Sciences 22.0 for Windows (IBM, Armonk, NY).

2. Results

Among 1726 adult patients who underwent OLT during the study period, 71 (4.1%, 95% CI 3.0%-5.0%) were complicated by posttransplant ARDS. Within ARDS patients, rates of mild, moderate, and severe ARDS by the Berlin Definition were 38.0%, 43.7%, and 18.3%. The majority (86%) of ARDS occurred on postoperative day 1, and the rest occurred in postoperative days 2 and 6.

The baseline and preoperative characteristics were compared between the 2 groups, and the results are summarized in Table 1. There were no significant differences in age, sex, weight, and height. However, patients with ARDS had more encephalopathy at time of transplant and history of esophageal variceal bleed compared with patients without ARDS. In addition, several indicators for severity of the liver disease such as MELD score, requirement for preoperative intubation, pressor, and hemodialysis were significantly higher in ARDS patients than in non-ARDS patients. The baseline laboratory values were not significantly different except for total serum bilirubin. The median (IQR) of baseline total bilirubin was 22.5 mg/dL (IQR 8.2-34.6) in patients with ARDS, significantly higher compared with patients without ARDS (7.4 mg/dL, IQR 2.2-25.4) ($P < .001$). The incidence of ARDS was compared among 4 serum bilirubin groups divided by the quartiles. The patients in the higher serum bilirubin quartile group were associated with the higher incidence of postoperative ARDS ($P = .001$) (Fig. 1).

Multivariate logistic analysis using preoperative factors identified 3 independent risk factors for postoperative ARDS (Table 2). Patients with preoperative encephalopathy had a 2 times increased risk of developing posttransplant ARDS compared with patients without preoperative encephalopathy. (OR, 2.22; 95% CI 1.12-4.39; $P = .022$). Similarly, patients with requirement of intubation and ventilation had 2 times higher odds to develop postoperative ARDS than patients without preoperative intubation (OR, 2.06; 95% CI, 1.12-3.79; $P = .020$). Preoperative total bilirubin concentration was significantly associated with postoperative ARDS. An mg/dL increase in serum bilirubin was associated with a 2% increase of developing postoperative ARDS (OR, 1.02; 95% CI, 1.01-4.04; $P = .003$).

To appropriately assess impact of intraoperative factors on development of ARDS, preoperative factors were matched between the ARDS and non-ARDS groups using the propensity score. Comparison of the preoperative factors using after-matching data was performed, and results are shown in Table 3. After the matching, there were no significant

Table 1
Preoperative factors between ARDS and non-ARDS patients

Variables	Non-ARDS (n = 1656)	ARDS (n = 71)	*P*
Age (y)	54.0 ± 11.2	52.0 ± 11.3	.146
Sex (male, %)	64.3	59.2	.453
Weight (kg)	79.7 ± 21.5	78.8 ± 25.4	.832
Height (cm)	169.7 ± 11.6	169.9 ± 9.9	.874
MELD score	31.4 ± 8.0	35.3 ± 8.5	<.001
Etiology for transplant			
Hepatitis C (%)	41.8	32.4	.115
Hepatitis B (%)	7.1	4.2	.348
Primary biliary cirrhosis (%)	2.6	1.4	.544
Nonalcoholic steatohepatitis (%)	5.3	11.3	.032
Acute hepatic failure (%)	5.9	9.9	.164
Alcoholic cirrhosis %)	21.4	20.0	.777
Encephalopathy (%)	41.7	75.0	<.001
Preoperative intubation (%)	21.3	52.9	<.001
Preoperative pressor (%)	12.2	34.3	<.001
Preoperative dialysis (%)	33.9	58.2	<.001
Variceal bleed (%)	33.8	46.3	.036
Baseline laboratory values			
Hematocrit (%)	29.3 ± 6.0	29.0 ± 4.5	.671
INR	1.8 ± 1.2	1.9 ± 0.6	.329
Creatinine	1.9 ± 1.9	1.7 ± 1.4	.532
Total bilirubin	14.7 ± 15.9	24.0 ± 18.4	<.001
Serum sodium	137.4 ± 5.4	137.7 ± 5.3	.304