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Predictive Factors for Reintubation following Noninvasive Ventilation in Patients with Respiratory Complications after Living Donor Liver Transplantation

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Introduction

Liver transplantation (LT) has become the mainstay for the treatment of end-stage liver disease, acute liver failure, hepatocellular cancer, and some metabolic liver diseases [1]. Liver transplantation in Japan is highly dependent on living donors because of a severe deficiency in the availability of liver grafts from deceased donors [2].

Postoperative respiratory complications (PRCs) such as atelectasis, pleural effusion, pulmonary edema, and pneumonia are frequent after LT and their incidence is reported to be between 44% and 87% [3–8]. Furthermore, persistent pulmonary edema, pleural effusion, and atelectasis have been reported to be major independent predictors of post-transplant pneumonia [5]. Thus, PRCs after transplantation negatively impact mortality [3,4,6], with recent data showing a mortality rate of 40% [9].

Noninvasive ventilation (NIV) is an effective treatment for acute respiratory failure in many conditions [10–14]. Two randomized controlled studies showed its effectiveness in patients with acute respiratory failure under immunosuppressed conditions [11,14]. On the other hand, in immunosuppressed patients who failed NIV, the rate of hospital mortality was reported to be very high.
ranging from 62% to 100% [11,15,16]. Recent data on patients with hematologic malignancies showed that the reintubation rate with NIV was almost 50% and that the mortality rate following NIV failure amounted to 69–79% [15,17]. The respiratory rate during NIV and a longer delay between admission and its first use of NIV as well as other factors were significantly associated with NIV failure [15]. However, factors related to reintubation following NIV for patients with PRCs after LT have not been documented well. In our hospital, we have successfully begun to apply NIV for respiratory complications in patients with living donor liver transplantation (LDLT) [18–21]. Although we have subsequently experienced many more cases (over 200 cases) for whom NIV was used following LDLT, reintubation has been necessary in some of these patients. Therefore, to decrease the rate of reintubation following NIV treatment after LDLT and to achieve a better prognosis, we have retrospectively examined patient data to elucidate the factors necessitating reintubation following NIV treatment. We also compared clinical outcomes between patients who did and did not require reintubation after NIV treatment following LT.

### Methods

#### Patients

From August 1999 to July 2008, 532 liver transplant recipients, aged 13 years or over, underwent LDLT at Kyoto University Hospital. Of the 200 patients who subsequently received NIV, we excluded 21 who discontinued NIV therapy because of reoperation (regardless of their respiratory status) and analyzed data on the remaining 179 patients. Fifteen of the 179 patients had infections that could be expected to be successfully treated before LT but that did result in postponement of the LT. These patients received LT after the infections were controlled as evidenced by reduced fever, blood cultures negative for bacteria, and resolution of conditions such as pneumonia, peritonitis, cholangitis, phlegmon, or enterocolitis.

After LDLT, all patients entered the Intensive Care Unit (ICU) and required invasive mechanical ventilation before weaning. Extubation was considered under the following conditions: 1) clinically stable; 2) improvement in underlying disease and its complications had improved; 3) minimal ventilator support was

### Table 1. Operative and postoperative status of 179 recipients of NIV.

| Overall (n = 179) | Reintubation (n = 43) | NIV Success (n = 136) | p value |
|-------------------|----------------------|-----------------------|--------|
| ABO Incompatible   | 45 (25.1)            | 17 (39.5)             | 28 (20.6) | 0.01 |
| APACHE II          | 16.4±4.3             | 18.5±4.8              | 15.7±3.9 | 0.0001 |
| Postoperative data:|                      |                       |        |
| Hb (g/dl)          | 9.4±1.8              | 8.7±1.6               | 9.6±1.8 | 0.005 |
| Total bilirubin (mg/dl) | 7.3±7.2 | 11.8±9.4              | 5.8±5.7 | <0.0001 |
| CRP (mg/dl)        | 4.3±3.6              | 5.6±4.0               | 3.9±3.4 | 0.005 |
| Na(mEq/l)          | 135.7±4.6            | 134.1±4.4             | 136.1±4.6 | 0.01 |
| HR (beats per minute) | 92±18               | 100±19                | 89±17   | 0.0009 |
| RR (beats per minute) | 19±8                | 22±8                  | 18±7    | 0.008 |
| Reintubation before NIV | 19 (10.6) | 9 (20.9)              | 10 (7.4) | 0.02 |
| Extubation (days)  | 3.4±5.3              | 6.6±8.1               | 2.4±3.5 | <0.0001 |
| From Extubation to NIV(days) | 2.7±7.7 | 2.9±7.9               | 2.6±6.3 | 0.80 |
| Reasons for NIV:   |                      |                       |        |
| PaO2/FIO2 ≥ 250    | 95 (53.1)            | 20 (46.5)             | 75 (55.1) | 0.32 |
| PaCO2 ≥ 45 Torr    | 40 (22.3)            | 9 (20.9)              | 31 (22.8) | 0.80 |
| Pneumonia on NIV   | 24 (13.4)            | 12 (27.9)             | 12 (8.8) | 0.001 |
| Respiratory rate ≥25/min | 28 (15.6) | 11 (25.6)            | 17 (12.5) | 0.04 |
| Atelectasis        | 31 (17.3)            | 4 (9.3)               | 27 (19.9) | 0.11 |
| Massive pleural effusion | 96 (53.6) | 25 (58.1)             | 71 (52.2) | 0.50 |
| Other reasons      | 27 (15.1)            | 8 (18.6)              | 19 (14.0) | 0.46 |
| Settings of NIV:   |                      |                       |        |
| Mode (S/T/ST)      | 1/1/177              | 0/1/42                | 1/0/135 | 0.17 |
| IPAP (cmH2O)       | 8.8±1.5              | 9.0±1.6               | 8.7±1.5 | 0.26 |
| EPAP (cmH2O)       | 4.6±1.3              | 4.2±0.5               | 4.3±0.6 | 0.54 |
| Amount of oxygen (l/min) | 8.8±3.4 | 9.7±3.2               | 8.5±3.4 | 0.04 |

mean ± SD or number (%). Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; Hb, hemoglobin; CRP, C reactive protein; Na, sodium; HR, heart rate; RR, respiratory rate; NIV, noninvasive ventilation; LDLT, living-donor liver transplantation; PaO2, partial pressure of arterial oxygen; FIO2, fraction of inspired oxygen; PaCO2, partial pressure of arterial carbon dioxide; S, spontaneous; T, timed; ST, spontaneous and timed; IPAP, inspiratory positive airway pressure; EPAP, expiratory positive airway pressure.

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Table 2. Preoperative characteristics of 179 recipients of NIV.

| Overall (n = 179) | Reintubation (n = 43) | NIV Success (n = 136) | p value |
|------------------|----------------------|-----------------------|---------|
| Male             | 92 (51.4)            | 19 (44.2)             | 73 (53.7)| 0.28    |
| Age (years)      | 48.2 ± 13.2          | 48.7 ± 12.5           | 44.3 ± 15.7| 0.19    |
| Underlying disease: |                      |                       |         |
| Hepatitis B or C, PBC, |                      |                       |         |
| Fulminant hepatitis and others |                |                       |         |
| Preoperative status: |                |                       |         |
| Residence in ICU with intubation before LT | 23 (12.8) | 11 (25.6) | 12 (8.8) | 0.004 |
| Child-Pugh (points) | 10.3 ± 2.0 | 10.8 ± 2.0 | 10.1 ± 1.9 | 0.06 |
| MELD score       | 24.2 ± 11.0         | 28.1 ± 12.1          | 22.9 ± 10.3| 0.006 |
| Chest X-ray abnormality: | 37 (20.7) | 13 (30.2) | 24 (17.6) | 0.08 |
| Controlled pre-OP infections | 15 (8.4) | 8 (18.6) | 7 (5.1) | 0.01 |

mean ± SD or number (%).

Abbreviations: ICU, Intensive Care Unit; LT, liver transplantation; MELD, model for end-stage liver disease; pre-OP, preoperative.

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Introduction of NIV

NIV was considered for all patients who received oxygen therapy or were in case of reintubation and mechanical ventilation and who met at least one of the following criteria to indicate serious PRCs: 1) ratio of the partial pressure of arterial oxygen (PaO2) to the fraction of inspired oxygen (FiO2) (PaO2/FiO2) ≤ 250 while the patient was receiving oxygen therapy; 2) partial pressure of arterial carbon dioxide (PaCO2) ≥ 45 Torr; 3) presence of pneumonia while on oxygen therapy; 4) respiratory rate > 25 breaths per minute with active contraction of accessory muscles of respiration and/or paradoxical thoraco-abdominal motion; 5) atelectasis of more than one lobe; 6) massive or uncontrolled pleural effusion after percutaneous thoracic drainage, because some of the effusion might be ascites from the abdomen by the pressure gradient [22]; and 7) other reasons. FiO2 of oxygen therapy via a nasal cannula, face mask, or reservoir face mask was calculated based on a previously published method [23]. Patients who required urgent intubation due to respiratory arrest, respiratory pauses, severe hepatic coma (above Grade 2), copious tracheal secretion and hemodynamic instability were not started on NIV.

Noninvasive Ventilation

We used a full-face mask or a nasal mask (Resmed, North Ryde, New South Wales, Australia) for NIV. Ventilation in all patients was by bilevel positive airway pressure (bilevel PAP) devices with oxygen and humidification (VPAP series Resmed) [18–21,24,25]. After the mask had been secured, the level of support was determined by the difference of the partial pressure of oxygen and expiratory positive airway pressure (EPAP) and the amount of oxygen were progressively increased until SaO2 was > 95%, accompanied by decreased respiratory rates and/or reduced activity of accessory muscles for respiration, decreased paradoxical thoraco-abdominal movement, and improvement in respiratory discomfort. When applying NIV, a doctor stayed at the bedside and observed the patient carefully while the SaO2 and electrocardiogram were monitored. Throughout the first hour, the patient’s condition was assessed repeatedly. For minor complications of NIV treatment such as skin rash, eye irritation, discomfort from the mask, air pressure, or gastric insufflations, we decreased the pressure and/or usage time of NIV, used another mask, or inserted a gastric tube. To calculate the FiO2 during NIV, we used the value from the information supplied by the manufacturer and was attached to the mask. Using this information, the FiO2 was determined from the following parameters: leakage flow rate per minute from the mask at each pressure and the oxygen flow rate per minute during NIV. If the leakage flow rate at the setting was X and the oxygen flow rate was Y, the FiO2 at the setting was: FiO2 = (X × 1.0 + Y − 0.21)/X [20].

Discontinuation of NIV

Patients for whom NIV could be discontinued because their respiratory status (including chest X-ray abnormality) had improved were assigned to the success group. The reintubated group was comprised of patients for whom NIV was not successful and who underwent reintubation with mechanical ventilation were assigned to the reintubated group. Criteria for reintubation were as follows: failure to maintain SaO2 of > 90% with a FiO2 ≥ 0.6; development of conditions necessitating endotracheal intubation to protect the upper airway (seizure, severe hepatic coma); development of copious tracheal secretions that could not be expectorated; increase in the PaCO2 accompanied by a pH of ≤ 7.30; and severe hemodynamic instability defined as systolic blood pressure < 70 mmHg.

Data Collection

Pneumonia was defined as new onset of pulmonary infiltrates with clinical symptoms (fever, cough, purulent tracheobronchial secretions, and dyspnea at rest), leukocytosis, and detection of potentially pathogenic bacteria in the sputum or bronchoalveolar lavage culture. Other infectious complications were wound infection, liver abscess, subphrenic abscess, cholangitis, peritonitis, and urinary tract infection. These were confirmed by clinical observation (fever, purulent discharge from wound, abdominal pain), and laboratory markers of inflammation with positive cultures (blood, bile, pus, and urine), and findings from chest X-rays and/or chest computed tomography. The Acute Physiology and Chronic Health Evaluation (APACHE) II score was used to assess the severity of illness at ICU admission [26]. Postoperative laboratory data presented in Table 1 represent values that were
obtained on the morning of the introduction of NIV. Arterial blood gases were obtained before the introduction of NIV, and also at the initial assessment after applying NIV (mean time ± standard deviation (SD) following NIV introduction: 3.9 ± 4.4 hours). At the initial assessment after NIV, we could not obtain arterial blood gas in 13 of the 179 patients (7.3%).

**Statistical Analysis**

Data were analyzed using JMP 9.0 (SAS Institute, Inc. Cary, NC, USA), and values are expressed as mean ± SD or absolute numbers and percentages in each group. We compared the association between the perioperative factors and the results of NIV (success group or reintubated group). Continuous variables were tested by the unpaired t test or Mann-Whitney U test. Categorical variables were compared using the χ² test or the Fisher’s exact test. A p value < 0.05 was considered to indicate statistical significance. Next, we investigated the associations between perioperative factors and reintubation. Possible predictors of reintubation were tested by univariate and multivariate logistic regression analysis. In the logistic regression analysis for reintubation, variables entered in the multivariate analysis were those yielding a p value < 0.05 by univariate analysis; p values < 0.05 in the multivariate analysis were considered statistically significant.

**Results**

**Preoperative and Postoperative Characteristics of the Patients with NIV**

The preoperative characteristics and operative and postoperative status of the 179 recipients of NIV are summarized in Tables 1 and 2, respectively. The mean model for end-stage liver disease (MELD) score was 24.2 ± 11.0 in the 179 patients. Fifteen patients had controlled preoperative infections; 5 pneumonia, 7 spontaneous bacterial peritonitis (SBP), and 1 either cholangitis, phlegmon, or enterocolitis. As mentioned above, these preoperative infections had been controlled before the LT (controlled preoperative infections) (Table 2). Before NIV treatment, 19 (10.6%) of the 179 patients had been reintubated following the LT for the

### Table 3. Outcome of 179 hospitalized recipients of NIV.

|                      | Overall (n = 179) | Reintubation (n = 43) | NIV Success (n = 136) | p value |
|----------------------|-------------------|-----------------------|-----------------------|---------|
| PaO2/FIO2 before NIV | 255 ± 114         | 263 ± 125             | 252 ± 110             | 0.60    |
| PaO2/FIO2 after NIV  | 328 ± 117         | 301 ± 120             | 338 ± 115             | 0.07    |
| PaCO2 before NIV     | 41 ± 7            | 41 ± 7                | 42 ± 7                | 0.55    |
| PaCO2 after NIV      | 41 ± 6            | 41 ± 7                | 42 ± 6                | 0.33    |
| NIV intolerant       | 16 (8.9)          | 7 (16.3)              | 9 (6.6)               | 0.06    |
| Could not tolerate NIV | 9 (5.0)        | 5 (11.6)              | 4 (2.9)               | 0.04    |
| Suspended NIV due to complications | 7 (3.9)     | 2 (4.7)               | 5 (3.7)               | 0.99    |
| Hospital mortality due to | 30 (16.8)      | 22 (51.2)             | 8 (5.9)               | <0.0001 |
| Respiratory complications | 14 (7.8)    | 11 (25.6)             | 3 (2.2)               | <0.0001 |
| Pneumonia            | 9 (5.0)           | 8 (18.6)              | 1 (0.7)               | <0.0001 |
| Aspergillosis        | 3 (1.7)           | 2 (4.7)               | 1 (0.7)               | 0.56    |
| Hemorrhage           | 2 (1.1)           | 1 (2.3)               | 1 (0.7)               | 0.42    |
| Others               | 16 (8.9)          | 11 (25.6)             | 5 (3.7)               | <0.0001 |
| Graft failure        | 6 (3.4)           | 2 (4.7)               | 4 (2.9)               | 0.63    |
| Cerebral diseases    | 2 (1.1)           | 1 (2.3)               | 1 (0.7)               | 0.42    |
| Sepsis               | 4 (2.2)           | 4 (9.3)               | 0                    | 0.003   |
| Gastrointestinal bleeding | 4 (2.2)     | 4 (9.3)               | 0                    | 0.003   |
| Hospitalization (days) | 75.5 ± 63.8     | 103.6 ± 98.0          | 66.7 ± 45.2           | 0.0008  |
| ICU stay (days)      | 9.2 ± 11.1        | 19.7 ± 15.7           | 5.9 ± 6.4             | <0.0001 |
| Duration of NIV (days) | 13.4 ± 14.3   | 6.3 ± 6.6             | 15.6 ± 15.3           | 0.0001  |
| Postoperative infections | 89 (49.7)    | 36 (83.8)             | 53 (39.0)             | <0.0001 |
| Respiratory          | 47 (26.3)         | 32 (74.4)             | 15 (11.0)             | <0.0001 |
| Others               | 66 (36.7)         | 21 (48.8)             | 45 (33.1)             | 0.06    |
| Reoperation          | 49 (27.3)         | 21 (48.8)             | 28 (20.6)             | 0.0003  |
| HAT                  | 5 (2.8)           | 2 (4.7)               | 3 (2.2)               | 0.60    |
| Biliary leak         | 12 (6.7)          | 4 (9.3)               | 8 (5.9)               | 0.49    |
| Acute cellular rejection | 28 (15.6)     | 6 (14.0)              | 22 (16.2)             | 0.81    |
| Ileus                | 6 (3.4)           | 0                     | 4 (2.9)               | 0.57    |
| ARF after LT         | 15 (8.4)          | 5 (11.6)              | 10 (7.4)              | 0.36    |

mean ± SD or number (%).

Abbreviations: NIV, noninvasive ventilation; PaO2, partial pressure of arterial oxygen; FIO2, fraction of inspired oxygen; PaCO2, partial pressure of arterial carbon dioxide; NIV, noninvasive ventilation; ARDS, Acute Respiratory Distress Syndrome; ICU, Intensive Care Unit; HAT, hepatic artery thrombosis; ARF, acute renal failure; LT, liver transplantation.

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following reasons: copious amounts of sputum that could not be expectorated, septic shock, pneumonia, tracheal hemorrhage, and respiratory muscle fatigue. NIV was introduced following the second extubation in these 19 patients (Table 1).

Noninvasive Ventilation

Reasons for application of NIV are listed in Table 1. Concerning the duration of the initial application of NIV, 137 patients (87.3%) received NIV continuously throughout the day, 17 (10.8%) 2 or 3 times per day, 1–2 hours per NIV session, and 3 (1.9%) only nocturnally. In 43 patients (24.0%), reintubation following NIV was required for the following reasons: refractory hypoxemia with pneumonia (n = 17, 39.5%), acute respiratory distress syndrome (ARDS) (n = 2, 4.7%), secretions that could not be cleared (n = 12, 27.9%), unconsciousness (n = 6, 14.0%), septic shock (n = 2), CO2 narcosis (n = 1, 2.3%), excessive tachypnea (n = 1), re-expansion pulmonary edema (n = 1), and rupture of an esophageal varix (n = 1).

Outcomes of Patients with NIV Treatment

Table 3 shows the outcome of the NIV treatment. No evidence of an obvious delay in reintubation was noted, and no severe complications such as pneumothorax, hypotension, or aspiration pneumonia were related to NIV treatment.

In both the success and reintubation groups, the baseline PaO2/FIO2 values were similar and the PaO2/FIO2 at the initial assessment after NIV therapy was higher in the success group than in the reintubation group but without significance (p = 0.07) (Table 3). However, a sub-analysis showed that in patients with pneumonia prior to application of NIV, the baseline PaO2/FIO2 was similar between groups (success group: n = 12, 284.4±118.2 vs. reintubation group: n = 12, 231.7±163.0, p = 0.37), whereas PaO2/FIO2 at the initial assessment after NIV therapy was higher in the success group than in the reintubation group (success group: n = 12, 376.8±140.1 vs. reintubation group: n = 12, 263.6±129.4, p = 0.04).

Although there was no significant between-group differences in the mean changes in PaCO2 at the initial assessment after the start of NIV therapy (Table 3), PaCO2 levels after NIV treatment significantly decreased in patients with PaCO2 ≥45 Torr (success group: n = 27, 51.0±4.5 Torr to 48.8±5.3 Torr, p = 0.008; reintubation group: n = 7, 52.3±7.2 Torr to 48.4±5.6 Torr, p = 0.02).

Eight (5.9%) of the 136 patients in whom NIV was successful died during hospitalization, while 22 (51.2%) of the 43 patients who failed NIV treatment died (p < 0.0001). NIV treatment could not be continued in 16 patients for various reasons. In 7 of the 16 patients, NIV was suspended due to complications (6 severe abdominal distension despite a nasal gastric tube; 1 concomitant ileus). Nine patients could not tolerate NIV, and the prevalence of those who could not tolerate NIV was significantly higher in reintubation group than in NIV success group (Table 3). Among the 16 patients in whom NIV discontinued, 7 were eventually reintubated and 5 of those 7 died.

The survival curve shows that patients in the reintubation group had a significantly poorer prognosis than those in the NIV success group (p = 0.0009) (Figure 1). Also, patients who failed NIV had significant longer ICU stays (19.7±15.7 days vs. 5.9±6.4, p < 0.0001).

Logistic Regression Analysis for reintubation

Among the 40 perioperative factors (those listed in Tables 1 and 2 and NIV intolerance), 16 had a significant association with reintubation in the univariate analysis (Table 4). In the multivariate forward logistic analysis of factors related to reintubation, controlled preoperative infections (odds ratio [OR] 8.88; 95% confidence interval [CI] 1.64 to 48.11; p = 0.01), ABO-incompatibility (OR 4.49; 95% CI, 1.50 to 13.38; p = 0.007), and postoperative pneumonia prior to starting NIV (OR 5.92; 95%
Discussion

Although the data were retrospective, this study of a large NIV series in one hospital showed the following significant factors that were predictive of reintubation following NIV: controlled preoperative infections, ABO blood type incompatibility, and postoperative pneumonia prior to placement on NIV. After excluding from the analysis the 19 patients who were reintubated following LDLT and were provided NIV after that second extubation, those three factors remained significant. In addition, after the start of NIV treatment in pneumonia patients, there was a significant difference not in the initial $\text{PaO}_2/\text{FiO}_2$ but in the initial assessments of $\text{PaO}_2/\text{FiO}_2$ between the reintubation and success groups.

Patients who are waiting for transplantation are usually have severely ill and are sometimes immunocompromised. Therefore, infections develop easily, which often postpones the transplantation. In this study, 15 (8.4%) of the 179 patients who had been administered NIV had an infection that had been controlled before LT. Although the LT team considered that the preoperative infection had been well controlled, this factor was revealed to be one of 3 factors predictive of reintubation following NIV. Since the number of patients with a preoperative infection ($n = 15$) was small, it was difficult to make firm conclusions as to the role of preoperative infections in the failure of NIV. In addition to control of preoperative infections as stringent as possible by LDLT teams, the future study of this issue in a greater number of patients should be done.

Prognosis of ABO-incompatible LT in adults has been reported to be inferior to compatible LT because of rejection, and especially there has been a high incidence of acute bile duct and vascular complications [27]. Although it is difficult to determine the contributions of ABO-incompatible LT to reintubation following NIV, results of the study suggest that patients with NIV following ABO-incompatible LT should be cautiously observed for PRCs, which might be influenced by several complications due to an ABO-incompatible LT.

A report from hematological parts showed that NIV treatment for respiratory failure with acute lung injury (ALI) or ARDS had a high mortality rate [17]. In the present report, the number of patients with ALI/ARDS was small and pneumonia prior to NIV treatment following LT was a significant risk factor for reintubation. In the success group and reintubated patients with pneumonia prior to NIV, the baseline $\text{PaO}_2/\text{FiO}_2$ was similar, whereas $\text{PaO}_2/\text{FiO}_2$ at the initial assessment after NIV therapy was higher in the success group than in the reintubation group. Pneumonia was already identified as a risk factor for NIV failure [28]. Therefore, we propose that if the $\text{PaO}_2/\text{FiO}_2$ does not improve in patients with pneumonia after application of NIV, reintubation should be performed early. However in this study, $\text{PaO}_2/\text{FiO}_2$ was not true but the calculated ones from the formula [20]. Therefore, the findings on $\text{PaO}_2/\text{FiO}_2$ in pneumonia patients in this study were not conclusive and this issue requires further study.

Our inclusion in the analysis of the 19 patients who were reintubated following LDLT and were then provided NIV after their second extubation might be questioned as those patients could be considered to represent a separate group of NIV post-transplant recipients. However, we included these patients in the overall analysis because we wanted to provide information for clinicians on all of our patients who received NIV treatment.

### Table 4. Univariate analysis of factors related to reintubation.

|                      | OR  | 95% CI | p value |
|----------------------|-----|--------|---------|
| Preoperative status  |     |        |         |
| Residence in ICU with intubation before LDLT | 3.6 | 1.4 to 8.8 | 0.006 |
| MELD score           | 1.0 | 1.0 to 1.1 | 0.008 |
| Comorbidity          |     |        |         |
| Controlled preoperative infectious disease | 4.2 | 1.4 to 12.4 | 0.009 |

### Table 5. Multivariate forward logistic regression analysis for reintubation.

|                      | OR  | 95% CI | p value |
|----------------------|-----|--------|---------|
| Controlled preoperative infectious disease | 8.9 | 1.6 to 48.1 | 0.01 |
| ABO compatibility: Incompatible | 4.5 | 1.5 to 13.4 | 0.007 |
| Postoperative pneumonia on NIV | 3.3 | 1.0 to 11.0 | 0.04 |

Abbreviations: OR, Odds ratio; 95%CI, 95% Confidence Interval; NIV, noninvasive ventilation.

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R square of the model 0.299
following LDLT. To determine if risk factors for reintubation following LDLT differed among these 19 patients from those in the overall study group, we performed a separate analysis and found that the same three risk factors existed for these patients as for the overall study group.

In our study, 16 patients were NIV intolerant. Seven of these patients were eventually reintubated and 5 of the 7 died. Ambrosino et al. reported that intolerance to NIV treatment was associated with NIV failure [29]. Thus, new equipment such as large masks or new types of masks [30,31] or new types of machines that alleviate the discomfort due to ventilator-related pressure or flow might be helpful to decrease the rate of intolerance to NIV.

Recently, the first review of NIV in adult liver transplantation was published [32]. Although this report was comprehensive regarding the usefulness of NIV during the perioperative LDLT stage, risk factors for reintubation following NIV treatment were not discussed, which is the topic of the current report. Previously, although we addressed the general effectiveness of NIV in both adult and infant patients [18–21,24,25], this report provides more specific information on the topic than those reports or the recent review. This retrospective study was done in an institution with extensive experience in the use of NIV [2], and the relatively high rate of use of NIV treatment could be explained by the high mean MELD scores (24.2) in the 179 patients whose data were analyzed.

Although these study patients already had relatively severe morbidity before they underwent LDLT, the rate of NIV success was 76.0%. This rate was higher or equivalent to that in immunosuppressed patients in previous reports [10,13,14]. In our institution, we set relatively mild inclusion criteria for introducing NIV, and started NIV early, partly because non-infectious respiratory complications in the patients following liver transplantation were reported as the independent risk factors of pneumonia [5] and respiratory failure might deteriorate rapidly in immunosuppressed patients after LDLT. The early introduction of NIV might result in the higher the rate of NIV success and lower hospital mortality rate.

This study had several limitations. Firstly, was the retrospective design. However, the large number of cases included in our analysis was probably sufficient to minimize this limitation. Secondly, based on several factors present in the perioperative stage, patients in the reintubated group had a more serious condition than those in the NIV success group. Therefore, success or failure might be dependent on the patients’ condition before NIV treatment. It is difficult to know how these conditions before NIV treatment influenced the success or failure of the NIV treatment. These complicated backgrounds might have caused the R square in the multivariate forward logistic regression for reintubation to be comparatively low (Table 5). However, it is important to manage NIV treatment so that success is achieved without its overuse.

In conclusion, we demonstrated that controlled preoperative infections, ABO blood type incompatibility, and postoperative pneumonia prior to the start of NIV were early predictors of NIV failure. We also revealed that in patients with postoperative pneumonia being administered NIV, PaO2/FIO2 at the initial assessment after NIV therapy was higher in the success group than in the reintubation group. We propose that if patients with a preoperative infection, ABO-incompatibility or post-operative pneumonia receiving NIV do not show improvement in the PaO2/FIO2 after NIV, early endotracheal intubation with mechanical ventilation should be considered as an alternative therapy.

Author Contributions
Conceived and designed the experiments: YC KC. Performed the experiments: HE SY TI KY MM KC. Contributed reagents/materials/analysis tools: YC TO TT TH KC. Analyzed the data: YC TH KC. Wrote the paper: YC KC.

References
1. Mullhaupt B, Dimitroulis D, Geirach JT, Clavien PA (2008) Hot topics in liver transplantation: organ allocation–extended criteria donor–living donor liver transplantation. J Hepatol 48:586–67.
2. Tanaka K, Ogura Y, Kiuchi T, Inomata Y, Uemoto S, et al. (2004) Living donor transplantation: Eastern experiences. HPB (Oxford) 6:28–94.
3. Singh N, Gayowski T, Wagner MM, Marin IR (1999) Pulmonary infiltrates in liver transplant recipients in the intensive care unit. Transplantation 67:138–44.
4. Hasegawa S, Mori K, Inomata Y, Murakawa M, Yamakoa Y, et al. (1996) Factors associated with postoperative respiratory complications in pediatric liver transplantation from living-related donors. Transplantation 62:941–7.
5. Gollieri R, Giampalma E, Morelli Lahate AM, d’Arienzo P, Jovine E, et al. (2000) Pulmonary complications of liver transplantation: radiological appearance and statistical evaluation of risk factors in 300 cases. Eur Radiol 10:169–83.
6. Durán FG, Piqueras B, Romero M, Carneros JA, de Diego A, et al. (1998) Pulmonary complications following orthotopic liver transplant. Transpl Int 11:255–9.
7. Hong SK, Hwang S, Lee SG, Lee LS, Aun CS, et al. (2006) Pulmonary complications following adult liver transplant. Transplant Proc 38:2979–81.
8. Lin CC, Chuang FR, Wang CC, Chen YS, Chen CL, et al. (2004) Early postoperative complications in recipients of living donor liver transplantation. Transplant Proc 36:2381–9.
9. Huang CT, Lin HC, Chang SC, Lee WC (2011) Pre-operative risk factors predict post-operative respiratory failure after liver transplantation. PLoS One 6:e22689.
10. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, et al. (2003) Noninvasive ventilation in severe hypoxic respiratory failure: a randomized clinical trial. Am J Respir Crit Care Med 168:1430–44.
11. Hilbert G, Grusen D, Vargaz P, Valentino R, Gihk-Siberensen G, et al. (2001) Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. N Engl J Med 344:481–7.
12. Nava S, Hill N (2009) Non-invasive ventilation in acute respiratory failure. Lancet 374:250–9.
13. Ambrosino N, Vagheggi G (2008) Noninvasive positive pressure ventilation in the acute care setting: where are we? Eur Respir J 31:874–86.
14. Antonelli M, Conti G, Buil M, Costa MG, Lappa A, et al. (2000) Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA 283:235–41.
15. Adda M, Couget I, Daumon M, Thiery G, Schlembem B, et al. (2008) Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. Crit Care Med 36:2766–72.
16. Confalonieri M, Calderini E, Terracini S, Chidini G, Celeste E, et al. (2002) Noninvasive ventilation for treating acute respiratory failure in AIDS patients with Pneumocystis carinii pneumonia. Intensive Care Med 28:1233–8.
17. Cristina GP, Antonelli M, Conti G, Ciarlone A, Rogante S, et al. (2011) Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. Crit Care Med 39:2232–9.
18. Chin K, Uemoto S, Takahashi K, Egawa H, Kasahara M, et al. (2005) Noninvasive ventilation for pediatric patients including those under 1-year-old undergoing liver transplantation. Liver Transpl 11:989–95.
19. Murase K, Chihara Y, Takahashi K, Okamoto S, Segawa H, et al. (2012) The use of noninvasive ventilation for pediatric patients following liver transplantation: Decrease in the need for reintubation. Liver Transpl 18:1217–25.
20. Chihara Y, Egawa H, Tsuboi T, Oga T, Handa T, et al. (2011) Immediate Noninvasive Ventilation May Improve Mortality in Patients with Hepatopulmonary Syndrome Following Liver Transplantation. Liver Transpl 17:144–8.
21. Takahashi K, Chin K, Ogawa K, Kasahara M, Sakasuchi T, et al. (2005) Living donor liver transplantation with noninvasive ventilation for exertional heat stroke and severe rhabdomyolysis. Liver Transpl 11:570–7.
22. Takahashi K, Chin K, Sumi K, Nakamura T, Matsumoto H, et al. (2005) Resistant hepatic hydrothorax: a successful case with treatment by nCPAP. Respir Med 99:262–4.
23. Barry A, Shapiro B (1985) Clinical application of respiratory care. Third edition. Mosby 180–187.
24. Chin K, Takahashi K, Ohmori K, Toru I, Matsumoto H, et al. (2007) Noninvasive ventilation for pediatric patients under 1 year of age after cardiac surgery. J Thorac Cardiovasc Surg 134:260–1.
25. Narita M, Hatano E, Nagata H, Yanagida A, Asechi H, et al. (2009) Prophylactic respiratory management after liver resection with bilevel positive airway pressure ventilation: Report of three cases. Surg Today 39:172–4.

26. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–29.

27. Wu J, Ye S, Xu X, Xie H, Zhou L, et al. (2011) Recipient outcomes after ABO-incompatible liver transplantation: a systematic review and meta-analysis. PLoS One 6:e16521.

28. Antonelli M, Conti G, Moro ML, Esquinas A, Gonzalez-Diaz G, et al. (2001) Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. Intensive Care Med 7:1718–28.

29. Ambrosino N, Foglio K, Rubini F, Clini E, Nava S, et al. (1995) Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: correlates for success. Thorax 50:755–7.

30. Antonelli M, Conti G, Pelosi P, Gregoretti C, Pennisi MA, et al. (2002) New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet—a pilot controlled trial. Crit Care Med 30:602–8.

31. Rocco M, Dell’Utri D, Morelli A, Spadetta G, Conti G, et al. (2004) Noninvasive ventilation by helmet or face mask in immunocompromised patients: a case-control study. Chest 126:1508–15.

32. Feltracco P, Serra E, Barbieri S, Milevoj M, Salvaterra F, et al. (2008) Noninvasive ventilation in adult liver transplantation. Transplant Proc 40:1979–82.