Early respiratory complications after liver transplantation

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Abstract
The poor clinical conditions associated with end-stage cirrhosis, pre-existing pulmonary abnormalities, and high comorbidity rates in patients with high Model for End-Stage Liver Disease scores are all well-recognized factors that increase the risk of pulmonary complications after orthotopic liver transplantation (OLT) surgery. Many intraoperative and postoperative events, such as fluid overload, massive transfusion of blood products, hemodynamic instability, unexpected coagulation abnormalities, renal dysfunction, and serious adverse effects of reperfusion syndrome, are other factors that predispose an individual to postoperative pulmonary disorders. Despite advances in surgical techniques and anesthesiological management the lung may still suffer throughout the perioperative period from various types of injury, with different ensuing ventilatory impairments, and different clinical outcomes. The incidence, etiology, pathophysiological features, clinical manifestations, preventing measures, and outcomes of post-operative respiratory disorders in this setting are also reported.

INTRODUCTION
Orthotopic liver transplantation (OLT) is currently the only definitive treatment for patients with acute liver failure and end-stage liver cirrhosis. Due to recipients’ generally poor preoperative clinical conditions, the extensive surgical field, and lengthy operating times, postop-
erative respiratory disorders are very common after OLT and significantly contribute to the related morbidity and mortality, both in the acute postoperative stage and in the long term.

Several factors are involved in the onset of postoperative pulmonary complications (PPCs), and many preoperative and intraoperative variables have been associated with different degrees of severity of respiratory impairment after OLT.

Although refinements in surgical techniques, antimicrobial prophylaxis, immunosuppression, anesthesia, and intensive care management have most likely altered the frequency and overall spectrum of post-OLT respiratory disorders, it is still common for pulmonary infiltrates, atelectasis, pleural exudates, and other radiological abnormalities to be documented on chest X-ray at any time during a patient’s stay at an intensive care unit (ICU).

All of these respiratory disorders can affect lung compliance and alveolar gas exchange and, when severe, may necessitate tracheal intubation and mechanical ventilation. In the early stages after transplantation, pulmonary complications may prolong intubation time and increase the risk of systemic infectious complications. Prolonged mechanical ventilation due to refractory respiratory failure is an extremely morbid event, as this event is a marker of poor recipient recovery, predisposes a recipient to long-term ventilator dependency, and predicts further complications.

This review focuses on the most common perioperative factors that predispose an individual to PPCs occurring early after OLT, along with these complications’ clinical manifestations and contribution to outcome. The main strategies for preventing the development of post-OLT respiratory disorders are also mentioned.

| Preoperative risk factors for post-orthotopic liver transplantation pulmonary complications |
|---|
| Recipient's age | Female sex | Smoking history | Severity of liver dysfunction (Child-Pugh class) | MELD score | Cirrhotic encephalopathy | Cerebral dysfunction | Acute renal failure | Emphysema | High systolic pulmonary artery pressure | Hypoxia, orthodeoxia | Hepatopulmonary syndrome |
| Evidence of a restrictive pulmonary syndrome | Abnormal spirometry findings | Preoperative ventilator support | Severe preoperative respiratory failure requiring mechanical ventilation | Higher value of INR | Preexisting diabetes mellitus | Impaired renal function | Preoperative MARS use | Deceased donor source of organ transplantation |

MELD: Model End Stage Liver Disease; INR: International normalised ratio; MARS: Molecular adsorbent re-circulating system.

Stage Liver Disease (MELD) scores and the incidence of PPCs has yet to be clearly elucidated, but liver transplant recipients with high MELD scores often have a higher incidence of pleural effusion, a need for more perioperative blood transfusions, a greater risk of fluid retention, severe restrictive pulmonary patterns, and muscle atrophy related to poor nutritional status. Given this higher rate of comorbidities in patients with higher MELD scores, cases of postoperative respiratory impairment or failure may be more common as well.

In a retrospective study, Huang et al found that preoperative ventilator support, diabetes mellitus, impaired renal function, and OLT with grafts from deceased donors were the most significant preoperative predictors of the risk of postoperative respiratory failure (PRF). John et al demonstrated that patients suffering from diabetes mellitus prior to liver transplantation had a higher incidence of pulmonary complications afterward than did non-diabetic patients.

The main reasons why liver recipients given a graft from a deceased donor are at a higher risk of postoperative respiratory complications relate to the higher MELD scores of such recipients compared with patients receiving grafts from living donors, the “urgent” nature of the transplantation surgery, and the greater “marginality” of cadaveric grafts.

Severe preoperative respiratory failure requiring me-
Table 2 Major intraoperative and common postoperative risk factors for post-orthotopic liver transplantation pulmonary complications

| Major intraoperative risk factors | Common postoperative risk factors |
|-----------------------------------|----------------------------------|
| Surgical procedure (wide incision) | Excessive perioperative fluid administration |
| Intraoperative fluid transfusion volume | Postoperative duration of mechanical ventilation (delayed removal of endotracheal tube) |
| Intraoperative blood transfusion volume | Acute rejection during the hospital stay |
| Perioperative fluid balance | Postoperative acute renal failure |
| Intraoperative fluid retention | Postoperative hypoproteinemia |
| Intraoperative bleeding volumes | Onset of renal insufficiency |
| Common postoperative risk factors | Poor postoperative myocardial function |
| Excessive perioperative fluid administration | Right hemidiaphragm paralysis |
| Postoperative duration of mechanical ventilation | Greater exposure to nosocomial agents |
| Postoperative hypoproteinemia | Significant decline in the recipient’s immune function |
| Onset of renal insufficiency | Surgical complications |
| Poor postoperative myocardial function | Re-interventions or need for retransplantation |

Huang et al found that OLT recipients who developed PRF had significantly different intraoperative blood loss, i.e., more patients in the non-PRF group completed the surgical procedure without needing any blood transfusions. This difference greatly influenced outcome, with patients who developed PRF staying longer in the ICU and exhibiting significantly higher morbidity and mortality rates.

Other clinical studies have demonstrated that intraoperative fluid overload is the strongest risk factor for PPCs. Jiang et al investigated the link between intraoperative and postoperative fluid therapy and early PPCs, showing that patients with net intraoperative fluid retention volumes < 5000 mL and intraoperative bleeding volumes < 800 mL had fewer PPCs than did patients needing more fluid therapy. The group that was administered less fluid intraoperatively experienced a faster postoperative recovery, with shorter times to extubation and ICU stays.

Severe reperfusion syndrome is mainly characterized by prolonged hypotension, bradycardia, hyperkalemia, vasodilation, and pulmonary hypertension and may also trigger generalized endothelial injury, resulting in acute pulmonary edema and/or acute respiratory distress syndrome (ARDS). Liver ischemia-reperfusion may lead to an increase in the levels of multiple inflammatory mediators that become active in the lungs. Inflammatory lung-liver interactions, and the activation of nuclear factor κB in particular, may be implicated in the pathogenesis of permeability-type pulmonary edema.

A greater susceptibility to interstitial lung edema can seriously impair patients’ postoperative oxygenation, worsen oxygen delivery to the newly transplanted organ, and increase the need for ventilation.

Preservation-related or graft-related factors, potentially contaminated preservation fluids, the amount of intraoperative blood transfusion, longer ischemia times, and poor initial graft function are other important factors that predispose an individual to postoperative infections that may also involve the respiratory tract.

INTRAOPERATIVE RISK FACTORS FOR POST-OLT RESPIRATORY COMPLICATIONS

OLT is a lengthy procedure that may cause numerous physiological changes, such as mechanical derangement of the chest wall and diaphragm, hydrostatic and oncotic pressure abnormalities, increases in pulmonary vascular resistance and pulmonary artery pressure, abnormal pulmonary vascular permeability, and variable coagulopathies (Table 2).

Although the administration of fluids and blood products is adjusted in an effort to ensure hemodynamic stability and to correct unanticipated coagulation abnormalities and bleeding, a significant loss of blood and fluids during OLTs may be associated with excess fluid administration and a positive fluid balance.

At the end of the transplantation procedure, significantly lower respiratory compliance than before the operation is highly suggestive of increased extravascular pulmonary water content, as demonstrated by Tallegren et al.

In a report by Lin et al, a MELD score ≥ 25 points, an intraoperative fluid transfusion volume >10 L, and an intraoperative blood transfusion volume > 4 L were all independent predictors of the risk of PPCs, whereas a fluid balance of ≤ -300 mL on the first two postoperative days appeared to be a protective factor.
movement anomalies due to transection of the abdominal oblique muscles and rectus muscles and prolonged retraction of the right hemidiaphragm, which is associated with diaphragmatic dysfunction, may result in a 50%-60% reduction in vital capacity and a 30% reduction in functional residual capacity.[21]

Early weaning from mechanical ventilation is a primary goal for a favorable outcome, but primary graft dysfunction, the need for re-laparotomy, respiratory distress syndrome, the persistence of severe encephalopathy, or surgery-related embolicgenic problems may delay removal of the endotracheal tube and correspondingly increase the risk of respiratory infections.[14]

One of the most severe, although rare, adverse effects of massive intraoperative transfusion is transfusion-related acute lung injury (TRALI), which has the potential to cause lung edema and severe postoperative respiratory distress. TRALI is particularly relevant in post-OLT patient care because this injury can lead to pulmonary infiltrates, hypoxia, and respiratory failure during or within 6 h after a blood transfusion, with no other apparent cause. According to the “two-hit” theory about the pathogenic mechanism of TRALI, a first event (e.g., sepsis or trauma) could induce pulmonary endothelial activation, cytokine release, and “neutrophil priming”. Subsequent exposure to lipids, cytokines, or antibodies associated with massive transfusion would then prompt the activation of adherent neutrophils and a release of inflammatory mediators, thus leading to lung injury.[22,23]. TRALI and acute lung injury (ALI) share the same pathophysiological pathway and clinical definition, except that TRALI is temporally and mechanistically related to the transfusion of blood or blood components. In both conditions, capillary permeability results in plasma moving into the alveolar space and causing pulmonary edema.[24].

Postoperative hypoproteinemia, the onset of renal insufficiency, and poor postoperative myocardial function can also set the stage for interstitial edema, reduce pulmonary compliance, increase the effort of breathing, and prolong the need for invasive ventilation.

Right hemidiaphragm paralysis after OLT is another complication responsible for the development of right lower lobe atelectasis. In an old study, McAllister et al.[25] found that 79% of liver recipients had right phrenic nerve injury, and approximately half of these patients also had hemidiaphragm paralysis. Phrenic nerve conduction generally tends to recover within a few months, and most patients with phrenic nerve injury and right hemidiaphragm elevation rarely develop substantial respiratory dysfunction or need more prolonged mechanical ventilator support[25,26].

A considerable risk of acute rejection invariably persists early after OLT, which is associated with a need for higher levels of immunosuppression. Acute allograft rejection demanding high-dose corticosteroids or cytolytic agents is known to raise the risk of systemic infection, which may also involve the respiratory tract.

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**Table 3  Major post-orthotopic liver transplantation pulmonary complications**

| Complication                  | Frequency |
|------------------------------|-----------|
| Pleural effusion[14,15,23]    | 32%-47%   |
| Atelectasis[4,8,12,23-24]     | 5%-29%    |
| Pulmonary edema[13,14,23,60]  | 4%-47%    |
| Acute respiratory distress syndrome[14,15,12,23,64,52] | 0.8%-42% |
| Pneumonia[14,15,12,23,64,52]  | 5%-38%    |

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**INCIDENCE AND PATHOLOGICAL FEATURES OF PPCS IN LIVER TRANSPLANT PATIENTS**

Pulmonary complications after OLT can be classified as infectious and non-infectious (Table 3). Although uncommon in the first few days, the former complications later become an important cause of overall morbidity, whereas non-infectious complications account for most early problems but have less impact on patient outcome.[27,28].

In an old study conducted by the Pittsburgh group[29], pulmonary infiltrates characterized as pulmonary edema occurred in 40% of patients; pneumonia, in 38%; atelectasis, in 10%; and ARDS, in 8%. Of the cases of infiltrates, 48% occurred within 30 d of transplantation. In total, 78% of the cases of pulmonary infiltrates and 87% of the cases of pneumonia diagnosed at the ICU involved mechanically ventilated patients.

Glanemann et al.[30] reported that 11% of liver transplant patients required ventilatory support due to pulmonary complications, and 36.1% had to be reintubated. Among the patients who developed pulmonary complications and needed reintubation, 44.6% were intubated within 24 h after OLT.

Hong et al.[31] reported that early post-OLT pulmonary infiltrates were detected in 68 of 131 liver recipients (42.7%), with pleural effusion in 50 patients (73.5%), pneumonia in 6 (8.8%), atelectasis in 6 (8.8%), pulmonary edema in 5 (7.4%), and ARDS in 1 (1.5%). Jiang et al.[32] found that 29 of 62 patients (46.77%) had pulmonary complications after OLT, including pulmonary edema (4 cases, 13.79%), acute lung injury (7 cases, 24.14%), pneumonia (14 cases, 48.28%), and ARDS (4 cases, 13.79%).

In a series described by Bozbas et al.,[4] pulmonary complications were detected in 42.1% of liver recipients; pneumonia, in 21.1%; and pleural effusion on early postoperative chest radiographs, in 32.5%. Right hemidiaphragm elevation was the most common disorder (25.4%).

**PLEURAL EFFUSIONS**

Many patients undergoing OLT develop pleural effusions that usually mainly involve the right side, with variable amounts of fluid accumulation. The effusions are transudative and unrelated to primary cardiovascular disease. Pleural effusion after OLT is generally not a serious com-
plication, but if the effusion continues to expand beyond the first week or remains isolated to the left side, the fluid should be sampled to rule out other causes. Patients with large effusions may experience shortness of breath or a nonproductive cough.

Disruption of the diaphragmatic lymphatics during hepatectomy, along with diaphragmatic defects that allow the transfer of ascites developing in the abdominal cavity directly into the pleural space, are postulated to be the principal mechanisms behind fluid accumulation\(^{[26]}\). The negative intrathoracic pressure draws ascitic fluid into the pleural space, and analysis shows that this fluid has many of the same characteristics as abdominal ascites.

Pleural effusions may expand during the first postoperative week but frequently disappear in the following weeks. These effusions are usually asymptomatic and self-limiting, and thoracentesis or chest tube placement is rarely necessary.

Persistent pleural effusions may lead to respiratory dysfunction by causing atelectasis or may predispose patients to pneumonia and prolong recovery. Effusions may also recur at any time and are occasionally a sign heralding allograft rejection.

Postoperative atelectasis can also be the result of bronchial obstruction due to changes in bronchial secretions, a defective expulsion mechanism, or a reduced bronchial caliber.

A limited intraoperative production of surfactants reduces alveolar surface tension and thus prevents the lung from stabilizing at low volumes, predisposing the lung to collapse. The residual effects of anesthetics and postoperative narcotics can cause hypoventilation, ineffective respiration, depression of the cough reflex, immobilization, and splinting.

**POST-LT PNEUMONIA**

Early nosocomial pneumonia after OLT is nearly exclusively a perioperative complication and is characterized by the presence of pulmonary infiltrate, fever, leukocytosis, and new-onset respiratory symptoms (cough, sputum, and dyspnea). When the typical radiological picture of pneumonia is identified, it is important to isolate the responsible microorganism from deep tracheal aspirate or sputum cultures or bronchoalveolar lavage cultures to prescribe the appropriate, specific treatment.

The breakdown of the muco-cutaneous defensive barriers that occurs after prolonged orotracheal intubation is a major risk factor for post-OLT pneumonia. Massive intraoperative bleeding during the transplantation procedure, the persistence of severe encephalopathy, diffuse pleural exudates, postoperative ALI/ARDS, and severe renal impairment are frequently associated with delayed weaning from mechanical ventilation and contribute to the development of infectious diseases\(^{[19,38]}\).

Other important risk factors for early pneumonia include a greater exposure to nosocomial agents, a significant decline in recipients’ immune function, surgical complications, re-interventions, and the need for retransplantation\(^{[36]}\).

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia are usually diagnosed in cases of early- or late-onset pneumonia, depending on whether the pneumonia occurs within or after the first 4-6 d of hospitalization, respectively\(^{[39]}\).

The incidence of post-LT pneumonia has been shown to vary from 5%-38%\(^{[8,10]}\). Pirat et al\(^{[8]}\) reported an incidence of 22.7% and a mortality rate of 40%. These authors found that individuals who developed pneumonia had longer times to extubation and higher mortality. In a study by Xia et al\(^{[9]}\), the overall incidence of severe pneumonia was 18.2%, with an associated mortality rate of 37.5%. Bozbas et al\(^{[4]}\) reported a higher rate of bacterial pneumonia (> 70%), with a 26% rate of fungal pneumonia; lung infections were noted in 21% of patients in their study and were responsible for 45.8% of deaths.

In a report by Weiss et al\(^{[41]}\), early HAP (within 6 d after OLTx) occurred in 15.5% of liver recipients. As in the above-mentioned reports, these cases of pneumonia were associated with prolonged postoperative mechanical ventilation, a long ICU stay, and a trend toward higher short- and long-term mortality rates.

Levesque et al\(^{[3]}\) recently reported a 22% incidence of postoperative pneumonia, and 43% of their liver recipients who had pneumonia developed respiratory failure that required mechanical ventilation. Based on a univariate analysis, the researchers found that several preoperative factors and the number of intraoperative transfusions (units of blood and fresh frozen plasma) were associated with pneumonia However, in a multivariate analysis, only a preoperative restrictive pulmonary pattern and the international normalized ratio measured prior to OLT were independent predictors of pneumonia after surgery. Ikemagi et al\(^{[10,11]}\) reported the prevalence and characteristics of bacterial pneumonia after living-donor liver transplantation (LDLT), stating that 50 of 346 patients (14.5%) experienced bacterial pneumonia after LDLT. The incidence of bacterial pneumonia was highest on postoperative day 6, whereas the incidence declined on postoperative days 8 and 9. Pneumonia was associated with a prolonged use of mechanical ventilation, a prolonged stay in the ICU, the creation of a tracheostomy, primary graft dysfunction, and a need for renal replacement therapy. The mortality rate of patients with early-onset pneumonia was 25.7%. Delayed-onset pneumonia (at least 10 d after liver transplantation) was significantly associated with graft dysfunction and resulted in a higher mortality rate (73.3%) than did early-onset pneumonia.

A wide variety of community-acquired and hospital-acquired microorganisms may be responsible for post-OLTx pneumonia, but Gram-negative pathogens dominate in the early post-transplant stages, as in the population undergoing general surgery. The Gram-negative bacteria that frequently colonize the oropharyngeal cavity are most often responsible for lower respiratory
tract infections. In liver recipients on prolonged mechanical ventilation, nosocomial pathogens, including *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella* species, *Acinetobacter* species, and *Staphylococcus aureus* (including MRSA), are usually detected in bronchoalveolar lavage samples. It is worth emphasizing, however, that the microbiological ecology may vary considerably from one ICU to another, and previous antimicrobial consumption may have a major influence on microbial ecology.

In a report by Weiss et al., in a subgroup of patients with HAP occurring within the first 4 d after ICU admission, 61.5% of the causative pathogens were Gram-negative bacilli, and 38.5% were Gram-positive cocci. Of these microorganisms, 73% were classified as community acquired. More than 30% of liver recipients had a history of hospital stays and antibiotic treatments.

Given patients’ obligatory immunosuppression, prompt isolation of the microorganisms causing post-OLT pneumonia and appropriate treatment are mandatory for a favorable outcome. An early diagnosis may not be achievable with “conventional” diagnostic techniques in certain patients, however, making it necessary to resort to more “invasive” methods. If pulmonary infiltrates persist or become worse, a histopathological diagnosis by bronchial brushing, telescope catheter culture, fiberoptic bronchoscopy with transbronchial biopsy, or even surgical pulmonary biopsy may be needed to rule out opportunistic infectious agents.

**POST-LT PULMONARY EDEMA**

Severe pulmonary edema is unusual in the early postoperative period, unless the liver recipient experiences acute-onset, severe left ventricular dysfunction or acute fluid overload in the case of renal impairment. Despite a high incidence of postoperative radiological findings suggestive of acute pulmonary edema, most episodes are clinically easily overlooked, with only a mild deterioration in gaseous exchange.

In patients with fulminant hepatic failure, pulmonary edema is an ominous sign because it may predict evolving acute lung injury.

Subclinical forms of interstitial/alveolar edema may prompt findings of a transient increase in pulmonary capillary hydrostatic pressure or hypoalbuminemia or nonspecific signs of mild or moderate lung endothelial injury. Additional causes of acute pulmonary edema include excessive amounts of fresh frozen plasma and total fluids being administered intraoperatively, postoperative changes in renal function (urine volume and serum creatinine), massive transfusions, large-volume thoracentesis, and reduced lymph flow. It has been speculated that the greater pulmonary vessel permeability associated with end-stage liver disease may be exacerbated by the systemic inflammatory reaction induced by liver transplantation.

In a study by Aduen et al., a worse preoperative MELD score could predict the risk of pulmonary edema developing soon after the transplantation procedure. Preoperative right ventricular systolic pressure, as estimated by echocardiography, was also higher in patients who developed postoperative pulmonary edema, suggesting that elevated pulmonary pressures are associated with increased interstitial lung loading.

Chen et al. postulated that nitric oxide (NO) flow-mediated vasodilation is the pathogenic mechanism behind the high incidence of pulmonary edema after LDLT. In this study, the total volume of intraoperative fluid administered was higher in patients who developed pulmonary edema, but their net fluid retention did not significantly differ from that of the patients who did not experience this complication. Pulmonary edema did not prolong the hospital stay or increase the risk of infection and was overcome by administering diuretics.

In cirrhotic patients undergoing OLT, increased blood flow in the lung may increase shear stress on the endothelium, and this phenomenon is associated with an increased release of vasodilators, including NO, prostaglandins, and endothelium-derived hyperpolarizing factors.

Pulmonary edema is diagnosed based on the strength of radiographic criteria, clinical symptoms, the PaO2/FIO2 (PF) ratio (< 300), and hemodynamic data. According to the American-European Consensus Conference (AECC) on ARDS, permeability edema may be characterized by a pulmonary artery wedge pressure < 18 mmHg, whereas the hydrostatic type is usually associated with a wedge pressure > 18 mmHg. Patients with persistent permeability-type edema may also have a higher mean pulmonary arterial pressure and a higher pulmonary vascular resistance, consistent with a resistance-dependent mechanism.

In a study by Snowden et al., patients with pulmonary edema stayed longer in the ICU and were on mechanical ventilation for longer. Aduen et al. also found that the time on mechanical ventilation and in the ICU and hospital stays were longer in patients with persistent permeability-type edema. In contrast to the situation observed for the hydrostatic type, permeability-type pulmonary edema was associated with an increase in both mean pulmonary arterial pressure and pulmonary vessel resistance. In the series, 29% of patients with persistent permeability-type pulmonary edema died, as opposed to 7% of patients who never developed pulmonary edema and 0% of patients who developed hydrostatic-type pulmonary edema.

**POST-OLT ARDS**

Post-OLT acute lung injury and even severe ARDS may develop within 24 h or the first few days after the procedure. Frequent causes of ARDS include crystalloid infusion overload, massive transfusion of blood or blood products, prolonged operating times, severe bleeding during liver removal, and severe ischemia-reperfusion syndrome. In the early postoperative course, serious systemic infections, gastric aspirations, disseminated intravascular

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Table 4  Major strategies to prevent postoperative pulmonary complications after orthotopic liver transplantation

| Preoperative strategies | Intraoperative strategies |
|-------------------------|--------------------------|
| Pulmonary rehabilitation prior to OLT | Reduction in the degree of surgical insult |
|                          | Reduction in the level of aggressiveness |
|                          | Reduction in the duration of procedure |
|                          | Reduction in the amount of blood lost |

Postoperative ventilation [50,51,56,60]

Early extubation

Lung expansion maneuvers

Deep breathing exercises

Timely execution of bronchial toilette

NIV

Chest percussion and vibration

Invasive mechanical ventilation: assisted modes with minimal sedation

OLT: Orthotopic liver transplantation; NIV: Non-invasive ventilation.

cOagulation, and other nonspecific generalized insults may also be involved.

The intraoperative transfusion of blood products, and platelets in particular, has been identified as a risk factor for a poor outcome after OLT. The negative impact cannot be explained simply by the activation of the coagulation system and platelet aggregation at the endothelium; the poor outcome most likely has to do with ischemia-related endothelial cell injury [49]. Platelets contain many cytokines and vasoactive and inflammatory mediators that are rapidly released and activated by various stimuli after reperfusion and that may affect the lung. Several other factors, such as the potential for viral transmission and bacterial contamination, the risk of alloimmunization, nonspecific immunosuppressive effects, and graft-versus-host disease, may also contribute to a worse outcome [50,51].

Pereboom et al [52] demonstrated that platelet transfusion during OLT is associated with higher postoperative mortality due to severe lung edema causing heaviness of the lungs, as described in the clinical diagnosis of TRALI or ARDS.

ARDS after OLT is a serious multifactorial complication associated with diffuse, bilateral pulmonary infiltrates of acute onset (and non-cardiogenic etiology), with a PF ratio of < 200. Based on an “old” concept, ALI was once defined as a milder form of ARDS and was distinguished by a PF ratio of between 200 and 300 [48]. Currently, according to the Berlin definition, the term ALI is avoided and replaced by mutually exclusive subcategories of ARDS based on the degree of hypoxemia. ALI is now called “mild ARDS” and applies to cases with a PF ratio of up to 201-300 mmHg, the upper limit for ALI according to the AECC definition [53].

A poorly controlled systemic inflammatory response induced by severe reperfusion syndrome, along with transfusion related-adverse events, can substantially increase the risk of postoperative pulmonary injury. Inflammatory mediators cause damage to both the alveolar and the microvascular endothelia, and this damage alters the alveolar-capillary barrier, causing extravascular fluid accumulation. This pulmonary damage results in an increase in extravascular lung water, which is one of the hallmarks of mild ARDS and ARDS [54,55].

Major clinical findings in ARDS include severely impaired pulmonary oxygen diffusion, with pulmonary edema developing in the presence of normal pulmonary capillary-filling pressures and in the absence of a marked reduction in oncotonic pressure.

ARDS is an important cause of PRF after OLT. In an old study, the reported incidence of ARDS was in the range of 4.5%-15.7%, with a mortality rate nearing 80% [57].

More than 10 years ago, Golfieri et al [58] also reported that 4%-16% of patients who developed post-OLT lung injury deteriorated to severe ARDS, and the mortality rate of these patients was as high as 80%-100%.

Treatment for ARDS is primarily supportive, with fluid restriction, lung-protective mechanical ventilation, mild hypercapnia, and optimal PEEP [57]. The use of high PEEP has raised certain concerns, however [59], because of the potentially reduced venous return in a newly engrafted liver. Given the still limited data available, the literature affords no definitive answers on the use of “permissive” PEEP in this setting.

When critical hypoxemia ensues in patients with severe ARDS, additional rescue therapies may be administered, such as inhaled NO and prostaglandins [59].

PREVENTING PPCS AFTER OLT

The period following transplantation surgery is marked by variable changes in the structure and function of the respiratory system, which can particularly affect severely debilitated patients. The normal activity of liver recipients is usually reduced due to a low physical performance status both before and after liver transplantation.

Similar to what is advisable after upper abdominal surgery, important strategies for PPC reduction may include early extubation associated with lung expansion maneuvers, which comprise incentive spirometry, deep breathing exercises, intermittent positive-pressure breathing, and continuous positive airway pressure (CPAP) [60]. Manual techniques, including chest percussion and vibration, are alternative treatment approaches if airway clearance is not sufficient (Table 4).

Early extubation is the key element to reduce PPCs and ICU stay and to speed patients’ recovery. There is a substantial body of evidence proving that patients who undergo OLT can be extubated immediately after surgery, with few pulmonary complications, a lower risk of postoperative infection, and no effect on 1- or 3-year graft survival [61].

The specific benefit of each chest physical therapy technique has not been fully evaluated, and even combining various methods does not seem to provide additional
risk reduction. However, CPAP is particularly useful for patients who cannot perform deep breathing or incentive spirometry exercises after extubation\[62\].

In the case of reduced postoperative lung volumes, the elevation of both hemidiaphragms, and lower-lobe atelectasis, the work of breathing can be consistently augmented, making it difficult to achieve and maintain postoperative ventilatory autonomy. In liver recipients who remain under invasive mechanical ventilation, ventilator use may significantly influence the disuse of muscle dysfunction. Assisted modes of ventilation with minimal sedation should be favored over “controlled” modes, as complete diaphragm rest will rapidly lead to atrophy\[63\].

Due to the important restrictive respiratory pattern of cirrhotic patients and abdominal hypertension, weaning from a ventilator after OLT can take longer because of unsatisfactory gas exchange during various T-piece trials. Rapid extubation followed by immediate noninvasive ventilation (NIV) application should be considered in this setting to shorten and accelerate the weaning process in those recipients who do not completely fulfill the criteria for safe extubation\[64,65\]. By resting and unloading the inspiratory muscles, NIV with pressure support enables both hypercapnic and hypoxic patients to improve faster and may prevent basal atelectasis induced by abdominal distension. Chest physical therapy associated with CPAP or NIV stimulates lung expansion and improves lung ventilation, thereby preventing or reducing the build-up of liquid in the pleural space.

The early and “prophylactic” use of NIV may also reduce the risk of reintubation\[66\]. Because NIV leaves the upper airways intact, this method can reduce not only bacterial colonization and nosocomially acquired infections but also hemorrhagic complications in cases of underlying coagulopathy.

Many respiratory disorders following OLT respond to specific treatments, such as hemofiltration, pleural drainage, bronchial toilette, and abdominal drainage, with expected improvements over a period of hours or days. Supporting the failing recipient with early NIV may reduce the work of breathing and maintain gas exchange while awaiting an improvement in spontaneous ventilation.

Adequate postoperative pain relief, optimal hemodynamic and fluid management, the timely execution of bronchial toilette, airway clearance maneuvers (assisted cough and expiratory airflow techniques), and trials of NIV in the case of respiratory fatigue are extremely useful to facilitate the rehabilitation process.

Postoperative pain is a major cause of shallow breathing and impaired coughing, resulting in retention of secretions, atelectasis, hypoxemia, hypercapnia, and respiratory failure, especially in patients with pre-existing lung disease. Adequate treatment of pain will prevent hypoventilation and reduce the respiratory rate. Paracetamol at reduced doses, along with rescue doses of tramadol, should be offered as a valid analgesic regimen\[66\].

The improvement of sedation management, simple interventions aiming at actively mobilizing the recipient, and increasing the amount of time out of bed are further advantageous for lung function.

Although the level of evidence for implementing multimodal preventive measures is relatively low\[67\], and although many of the procedures believed to reduce the risk of PPCs are supported by a conventional “traditional” consensus, early respiratory disorders associated with cirrhosis and transplantation surgery undoubtedly benefit from an optimized patient care program with a multidisciplinary approach.

Promising new interventions may rely on more accurate preoperative respiratory assessment, e.g., with maximal inspiratory pressure and maximal expiratory pressure measurements, quantification of the degree of respiratory muscle weakness, optimization of chronic inflammatory pulmonary disease, preoperative lung expansion maneuvers, inspiratory muscle training performed in a chest physical therapy outpatient setting or a pulmonary rehabilitation clinic in the hospital, and improvement of general health and nutritional status\[68\].

It should be noted, however, that pulmonary rehabilitation prior to OLT may be of unpredictable value, as the variable waiting times before surgery, along with malnutrition and end-stage cirrhosis-related muscle weakness, may insufficiently affect exercise capacity and are thus unlikely to reduce postoperative risk.

Additional interventions of more expected benefit include an effort to reduce the degree of surgical insult, the level of aggressiveness, the duration of the procedure, and the amount of blood lost.

Better identification of patient- and procedure-related risks of pulmonary complications, the recognition of independent predictors of PPC, and the application of a local treatment protocol in high-risk patients, may favorably influence both the incidence and the outcome of PPCs.

CONCLUSION

Many reports underscore that infectious and other PPCs are important contributors to early morbidity and mortality in liver transplant patients\[63,65\]. Despite advances in surgical techniques and anesthesiological management, the lung may still suffer throughout the perioperative period from various types of injury, with different ensuing ventilatory impairments and different clinical outcomes.

Postoperative respiratory complications are not always related to preoperative respiratory disorders, but rather may be the result of systemic inflammatory responses induced by surgical trauma, hemodynamic impairment, reperfusion syndrome, “distant” organ dysfunction, or early graft dysfunction. The severity of any PPC is also believed to depend on a recipient’s clinical condition at the time when the complication occurs\[63\]. The stress response to the surgery is maximal soon after OLT and is expressed by disrupted circulating hormone concentrations, with increased antidiuretic activity. Electrolyte abnormalities and water retention are also common at this
time due to the nephrotoxic effects of the immunosuppressants administered.

Pleural effusion, atelectasis, pneumonia, and ARDS may be severe enough to demand or prolong the need for tracheal intubation, resulting in a higher risk of nosocomial infections, longer stays at the ICU and/or in the hospital, and a worse clinical outcome[1]. The lungs are particularly vulnerable to infectious diseases after OLTx and represent the second most common site (after the abdominal cavity) of colonization by nosocomial pathogens. Infectious complications involving the respiratory tract are acknowledged to be an important cause of death in liver transplant recipients[1]. In certain old studies by Plevak et al[3] and Shieh et al[1], patients who developed pneumonia in the early postoperative period and required prolonged mechanical ventilation had a mortality rate of 43%. Singh et al[3] also reported an overall mortality rate of 28% in transplant recipients with pulmonary infiltrates in the ICU and a mortality rate of 47% after 14 d among patients with pneumonia. Bozbas et al[3] found significantly lower survival rates for patients yielding microorganisms by deep tracheal aspirate culture. The early mortality rate was higher for patients whose thoracentesis cultures were positive.

Currently, the overall 1- and 5-year survival rates after OLT are approximately 85% and 68%, respectively, with a 10-year survival rate approaching 50%[2]. Judging from the multicenter-based prospective data collected by Watt et al[3], post-transplant respiratory diseases now account for only 2.4% of all deaths. Among the deaths after OLT, those of an infectious nature (> 19%) occur earlier, and pneumonia is among the most important contributors to the overall morbidity and mortality rates.

In conclusion, numerous perioperative factors may be responsible for impaired respiratory function after OLT. It is of paramount importance to accurately identify any lung disorders because pulmonary infectious complications need to be treated rapidly and aggressively to prevent diffuse lung lesions and potential evolution into multisystem organ failure.

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