Letter to the Editor

New classification and precise prevention strategies for donor lung injury in lung transplantation

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In organ transplantation, donor organs such as the heart, liver, lungs, and kidneys inevitably suffer primary injury due to ischemia, hypoxia, cold perfusion, and the accumulation of metabolites like lactic acid (1,2). In addition, donor lungs before procurement face risks associated with prolonged mechanical ventilation and infections due to extended intensive care unit (ICU) stays (3). These unavoidable injuries during ICU stay and organ procurement are referred to as primary injury. Furthermore, lung transplantation (LTx) presents a unique challenge: the donor lung, post-transplantation, faces not only immune rejection but also potential damage from mechanical ventilation. This damage, exacerbated by the lung's initial fragility and edema, can be more severe than that caused by mechanical ventilation in non-donor lungs (4). We refer to the damage to the transplanted lung primarily caused by mechanical ventilation as secondary injury.

Additionally, the application of mechanical ventilation necessitates the use of large amounts of sedatives, muscle relaxants, analgesics, and vasoactive drugs. This can lead to respiratory muscle atrophy, diaphragm atrophy, and impacts on mediastinal vasculature (5), collectively categorized as accompanying injuries. Differentiating donor lung injuries into primary, secondary, and accompanying injuries provides a comprehensive understanding of the pathophysiology and mechanisms of donor lung damage. This categorization is crucial for developing precise prevention and treatment strategies, which can enhance donor lung protection, accelerate patient recovery, improve prognosis, and increase long-term survival rates.

New classification for the injury in LTx

The classification of donor lung injuries, as outlined in *Table 1*, provides a structured approach to understanding and addressing the various forms of damage that occur before, during, and after LTx. Each injury category—primary, secondary, and accompanying injuries—has distinct causes and implications for the overall success of the transplant.

Primary injury

This refers to the damage sustained by the donor lung before transplantation, which often results from

Table 1 Classification and common causes of donor lung injuries in lung transplantation

Classification	Define	Cause
Primary injury	Primary injury refers to the damage the donor lung experiences before transplantation. This includes injury during the donor's time in the ICU, such as intubation and infection, as well as damage sustained during the organ procurement process, including cold storage, ischemia, and hypoxia	Intubation time
		Donor lung infection
		Ischemia
		Cold storage
Secondary injury	Secondary injury refers to additional damage the donor lung experiences after transplantation, primarily due to surgical manipulation, reperfusion, and the recipient's immune response. This second wave of injury is compounded by the stress of mechanical ventilation and the immune system's attack on the transplanted lung	Mechanical ventilation-induced injury
		Reperfusion injury
		Immune-mediated injury from host rejection
Accompanying injuries	Accompanying injuries are the adverse effects associated with the use of various medications in lung transplantation	Analgesics and sedatives
		Vasoactive drugs
		Muscle relaxants
		Immunosuppressive drugs
		Antimicrobial therapy

ICU, intensive care unit.

prolonged intubation in the ICU, infections, and the organ procurement process involving ischemia and cold storage. These factors weaken the donor lung, making it more susceptible to further complications after transplantation.

Secondary injury

This damage occurs post-transplantation and is primarily due to surgical manipulation, reperfusion, and the immune response of the recipient. Mechanical ventilation exacerbates the stress on the already fragile donor lung, increasing the risk of secondary injury, such as barotrauma, volutrauma, atelectrauma, and ventilator-associated pneumonia (6-8), which can further complicate the recovery process.

Accompanying injuries

These injuries result from the use of medications such as sedatives, vasoactive drugs, muscle relaxants, immunosuppressive drugs, and antimicrobial therapies. While essential for managing transplant patients, these medications can cause adverse effects on respiratory muscles, excessive immunosuppression, and hepatic or renal impairment. Although these effects may not directly damage the donor lung, they can indirectly exacerbate lung injury, increase the risk of infection, and delay functional recovery, further compromising the patient's overall recovery.

The relationship between these types of injuries is critical. A donor lung that suffers more severe primary injury is at significantly higher risk for secondary injury post-transplantation (3). Secondary injuries can accelerate the onset of accompanying injuries. Therefore, for fragile donor lungs with primary injury, it is even more essential to reduce the occurrence of secondary injuries, which in turn can decrease drug-related accompanying injuries and reduce postoperative complications following LTx.

Innovative intervention strategies based on the new injury classification

The interventions to reduce primary injury have shown promising results, particularly through the use of *ex vivo* lung perfusion (EVLP). EVLP allows for extended preservation and assessment of donor lungs, ensuring better management of ischemic and hypoxic damage before transplantation (9). Developing biomarkers to quantify the severity of primary injuries and leveraging EVLP as a platform for such assessments will be critical in future research, particularly given the often-latent nature of primary injuries. Additionally, research into antioxidant therapies has shown potential in mitigating oxidative stress (10,11), which is a key contributor to primary injury.

However, most centers have not yet implemented the use of EVLP, and more marginal donors are being used

clinically (12), which increases the severity of primary injuries. As a result, donor lungs subjected to more severe primary injuries are particularly vulnerable to secondary injuries after transplantation, which makes reducing secondary injury critical for improving patient outcomes. To address the challenges associated with secondary injury, the First Affiliated Hospital of Guangzhou Medical University has pioneered the use of tubeless LTx in clinical practice. Tubeless LTx is an innovative anesthetic technique that avoids the need for mechanical ventilation during surgery (13,14). Instead of relying on traditional mechanical ventilation—which can exacerbate lung injury through barotrauma, volutrauma, and atelectrauma—tubeless preserves the patient's ability to breathe spontaneously throughout the procedure. By maintaining natural respiration, tubeless LTx minimizes secondary injury and associated complications. Quantitative data from our center indicate that the rate of intraoperative extubation under tubeless LTx exceeds 90%, providing quantifiable support for its benefits in LTx.

In addition to reducing mechanical ventilation-induced damage, tubeless LTx has several other advantages. The technique greatly reduces the need for sedatives, analgesics, and vasoactive drugs during surgery (13). These drugs, commonly used to manage anesthesia and hemodynamics in conventional lung transplants, are associated with various complications, including respiratory muscle atrophy, diaphragm dysfunction, and prolonged cognitive impairment. By reducing or eliminating such medications, tubeless LTx decreases the likelihood of these accompanying injuries, further enhancing patient recovery.

Postoperatively, the benefits of tubeless LTx continue to contribute to improved outcomes. With less mechanical and pharmacological intervention during ICU stay, patients experience a smoother recovery process. The reduced reliance on sedatives and analgesics lowers the risk of postoperative complications, such as delirium and respiratory muscle weakness (15). Furthermore, careful management of antimicrobial therapy helps to prevent infections while also minimizing the risk of liver and kidney damage, which can be exacerbated by excessive use of antibiotics and other medications.

Conclusions

In summary, categorizing donor lung injuries into primary, secondary, and accompanying types enhances our understanding of the mechanisms at each stage of LTx, enabling precise prevention and treatment strategies. The use of tubeless LTx exemplifies an innovative approach that effectively reduces both secondary and accompanying injuries by minimizing mechanical ventilation-induced damage and decreasing the use of potentially harmful medications. This leads to improved patient outcomes, including faster recovery and reduced complications. By applying this comprehensive injury classification and refining these techniques, we anticipate significant advancements in LTx care.

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Footnote

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