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Trajectory and Influencing Factors of Postoperative Vulnerable Symptom Clusters in Lung Transplant Recipients

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Abstract: The first three months after lung transplantation are the clinical "vulnerable period". Complications during this period often appear in the form of symptom clusters. The core includes primary graft dysfunction (PGD), infection, inflammatory response and multiple organ dysfunction, and are interconnected to form a complex network. The symptom cluster shows a clear dynamic trajectory: the risk of PGD peaks at 24 hours after surgery, and its evolution trajectory (recovery, delay, deterioration) directly affects long-term graft function; infections show a "double peak distribution", with bacteria/fungi dominant in the early stage (< 1 month) and viruses/opportunistic infections dominant in the middle stage (1–6 months), and promote each other with PGD. Influencing factors include four dimensions: donor (smoking history, infection), recipient (weakness, immune status), perioperative period (surgical method, support strategy) and postoperative management (balance of immunosuppression). In the future, dynamic prediction models and individualized management paths need to be built to improve patient outcomes.

Keywords: Lung transplantation; Symptom clusters; Postoperative complications; Trajectory

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1. Introduction

Lung transplantation, as the only radical treatment for patients with end-stage lung disease, has seen a continuous increase in its application worldwide in recent years, and the survival rate of patients has also gradually improved [1]. However, postoperative complications in the short term remain a key factor affecting prognosis, among which the management of the "vulnerable period" usually refers to the first 3 months after surgery is particularly important. During this period, patients face multiple risks such as primary graft dysfunction (PGD), infection, and acute rejection. These complications often overlap in the form of "symptom clusters", increasing the complexity of clinical management. For example, PGD is the leading cause of death within 72 hours

after surgery, with an incidence rate as high as 20%, and it often coexists with complications such as infection and renal impairment [2]. Meanwhile, infection is the leading cause of death in the first year after lung transplantation, and its risk is closely related to factors such as immunosuppression regimen, donor quality, and surgical procedures [3]. Therefore, a deep understanding of the dynamic changes of the vulnerable period symptom clusters and their influencing factors is of great significance for optimizing postoperative management and improving patient prognosis. In recent years, the number of lung transplant cases and centers in China has steadily increased, and the focus of clinical work has shifted from "being able to do it" to "doing it well", emphasizing the identification and systematic management of perioperative complications [4]. Given that the "symptom cluster" has the characteristics of multidimensional parallel and dynamic evolution across physiological, psychological, social and organ functions, it is difficult to grasp its true trajectory based on a single symptom or a single time point. Domestic clinical observations also suggest that postoperative complications occur in clusters, which have an added impact on rehabilitation and survival [5]. Multicenter data show that in 2020, about 29 centers across the country performed more than 500 lung transplants, and the perioperative (< 30 days), 1-year and 3-year survival rates were roughly in the range of 48–83% (depending on whether it is a single or double lung), suggesting that early complication control has an "anchoring effect" on long-term outcomes [4]. In addition, studies on postoperative "symptom clusters" in solid organ transplant populations (including lung transplants) have shown that symptom clusters involve four dimensions: physiological, psychological, social and organ function. A longitudinal and holistic assessment and intervention framework is needed to characterize their change trajectory [6].

2. Definition of vulnerable period and core symptom clusters after lung transplantation

2.1. The timing and clinical significance of the vulnerable period

The time range of the vulnerable period after lung transplantation is not yet unified, but most studies define it as the period within 3 months after surgery, especially the period from 72 hours to 2 weeks after surgery as the "hyperacute period" with the highest risk. The incidence of complications in this stage directly determines the short-term survival rate and long-term prognosis of patients. For example, a French study on high emergency lung transplantation (HELT) showed that the mortality rate 30 days after surgery was as high as 37.5%, and it was significantly related to factors such as preoperative mechanical ventilation and ECMO support [7]. In addition, Japanese scholars found that patients with baseline lung graft dysfunction (BLAD) had significantly longer ICU hospital stays and mechanical ventilation time, suggesting that early functional recovery delays may continue to affect the patient's recovery trajectory [8]. In the population receiving emergency/high-priority lung transplants, the perioperative complications (such as bleeding, cardiopulmonary bypass (CPB)/ECMO dependence) and infection burden are significantly increased. Multiple multicenter and single-center studies have shown that although HELT significantly reduces waiting list mortality, the risk of death during hospitalization and in the early stages (30 days–3 months) is higher than that of routinely assigned recipients, suggesting that the risk exposure in the "hyperacute phase" is more concentrated, requiring more refined perioperative management and early complication screening pathways [7,9].

The clinical significance of the vulnerable period is not only reflected in the control of short-term complications, but also closely related to long-term graft survival. For example, PGD is one of the most serious complications of the vulnerable period. Studies have shown that survivors of high-risk HELT have a significantly

higher risk of developing chronic lung allograft dysfunction (CLAD) than conventional lung transplant recipients [2]. Therefore, systematically managing the vulnerable period as a dynamic risk window is a key link in improving the overall efficacy of lung transplantation.

2.2. The composition and interaction of core symptom clusters

Cluster during the vulnerable period after lung transplantation does not exist in isolation, but rather forms a complex interactive network centered on respiratory insufficiency, infection, systemic inflammatory response, and organ dysfunction.

Respiratory failure is mainly manifested as PGD and hypoxemia. PGD is defined based on the oxygenation index (PaO_2/FiO_2) and chest imaging changes within 72 hours after surgery. Its pathological nature is similar to that of acute respiratory distress syndrome (ARDS), involving alveolar epithelial damage, release of inflammatory factors and pulmonary edema formation [2]. Studies have shown that about 55% of PGD patients will progress to BLAD, that is, they cannot reach FEV_1 and FVC ≥ 80% of the predicted value within 3 weeks after surgery, which further increases the risk of death [10]. Retrospective cohort studies suggest that when "graft failure + circulatory instability" occurs during/after surgery, sequential/bridging support with VAV ECMO can improve the weaning rate and perioperative survival, providing a feasible rescue strategy for severe PGD and respiratory and circulatory combined failure [11]. Multicenter and methodologically updated studies have further confirmed that BLAD is not an isolated event, but rather a result of the combined effects of PGD grade 3, donor/recipient factors, and perioperative procedures, suggesting that the continuous chain of "PGD severity–lung function recovery trajectory–subsequent CLAD risk" should be assessed simultaneously during the vulnerable period [12,13].

Infection is another prominent problem during the vulnerable period, including bacterial, viral and fungal infections. A study in Brazil showed that 15.7% of lung transplant recipients developed surgical site infection (SSI), of which organ/cavity infection accounted for 36.8%, and was significantly associated with factors such as prolonged operation time and positive donor bronchoalveolar lavage fluid (BALF) [14]. In addition, in pediatric lung transplant recipients, prolonged donor ischemia time (≥ 7 hours) and cardiopulmonary bypass time (≥ 340 minutes) are independent risk factors for postoperative infection [3]. Infection and PGD often promote each other: on the one hand, infection can aggravate lung tissue inflammation and induce or worsen PGD; on the other hand, the immunosuppressed state and mechanical ventilation requirements of PGD patients increase the risk of infection [15]. The spectrum of infections during the vulnerable period is time- dependent and site-specific: in the first month after surgery, donor-origin or nosocomial opportunistic infections are the main ones, followed by an increase in the burden of viral (such as CMV, influenza/RSV, etc.) and fungal infections, which are closely related to airway anastomosis complications and the intensity of immunosuppression [16,17]. Respiratory viruses cause significant mortality and readmission risk among lung transplant recipients in China. Early stratified prevention, rapid nucleic acid testing, and management of drug interactions (such as antiviral and immunosuppressant) are important measures to reduce the continuous damage of "infection-PGD-CLAD" [18]. A domestic case cohort of bacterial lung infections showed that prolonged cold ischemia time, difficulty in airway management, and exposure to drug-resistant bacteria are key modifiable factors, suggesting that perioperative antimicrobial strategies need to be dynamically optimized by combining donor and recipient culture and central epidemiology [19].

Systemic inflammatory response is a common pathway connecting various symptom clusters. Surgical trauma, ischemia-reperfusion injury, and immune activation lead to the release of a large number of inflammatory factors, which not only directly damage the lung graft but may also cause multiple organ dysfunction. For

example, the incidence of acute kidney injury (AKI) in lung transplant recipients is as high as 84.9%, of which 30.1% are severe AKI, and it is closely related to underlying diseases such as pulmonary hypertension and diabetes [20]. At the same time, AKI and PGD share pathological mechanisms such as ischemia-reperfusion and inflammatory response, forming a vicious cycle of the "cardiopulmonary-kidney axis" [21].

Recent studies on AKI indicate that perioperative volume management, hemodynamic fluctuations, ECMO use, and neurohumoral axis activation all contribute to impaired renal perfusion. Domestic reviews suggest stratified monitoring using KDIGO classification linked to biomarkers (such as NGAL) to achieve a balance between respiratory mechanics and renal protection [20,22]. In addition, the coagulation-inflammation interaction is particularly prominent in PGD/infection comorbidities: under intraoperative and perioperative anticoagulation exposure, a small number of patients develop HIT and significantly increase the risk of venous thrombosis (VTE), requiring early identification and adjustment of anticoagulation pathways by combining 4T scores and PF4 antibody testing; while VTE is not uncommon in lung transplant patients within one year, independent of HIT, and is related to metabolic factors, center procedures and transplantation procedures, as well as increased mortality and resource consumption, and early ultrasound screening and individualized prevention should be included in the pathway [23,24].

Coagulation dysfunction is not listed as a core symptom group, its role in the vulnerable period cannot be ignored. Heparin-induced thrombocytopenia (HIT) occurs in approximately 2.1% of patients and can lead to venous thromboembolism in 72% of patients, prolonging hospital stay [23]. In addition, patients with PGD often have activated coagulation system, further increasing the risk of bleeding and thrombosis [25].

The interactions of these symptom clusters significantly increase the difficulty of clinical management. For example, infection may mask the clinical manifestations of acute rejection, while adjustments to immunosuppressants may exacerbate the risk of infection. Therefore, adopting a multi-objective intervention based on a "symptom cluster" perspective is an inevitable trend in vulnerable period management.

3. The trajectory of symptom cluster changes and their dynamic characteristics

3.1. Temporal distribution and evolution of PGD

The occurrence of PGD is significantly time-dependent, with the risk peaking within 24 hours post-surgery and then gradually decreasing, but it can still persist up to 72 hours post-surgery. A Canadian study showed that 33% of lung transplant recipients developed PGD within 72 hours post-surgery, with prolonged donor cold ischemia time (≥ 6 hours) and decreased expression of ENaC channels in alveolar epithelial cells being important predictive factors [26]. In addition, the amount of red blood cells transfused during surgery and the use of inhaled pulmonary vasodilators were also associated with the severity of PGD [25]. Recent studies have emphasized that PGD is essentially an acute lung injury caused by ischemia-reperfusion, and the activation of the early inflammation-edema pathway determines the intensity and direction of its evolution within 72 hours [27].

The evolution trajectory of PGD can be divided into three types: rapid recovery type (PaO_2/FiO_2 recovers to above 300 mmHg within 72 hours after surgery), prolonged type (mechanical ventilation is still required after 72 hours), and deterioration type (progresses to ARDS and requires ECMO support). American scholars have found that HLA mismatch (especially DQ site) and donor smoking history are independent risk factors for prolonged PGD, while EVLP (extracorporeal lung perfusion) technology may improve the functional recovery of some high-risk donor lungs [28]. PGD is closely related to the occurrence of subsequent BLAD. A single-center study in Japan

showed that 55% of BLAD patients failed to achieve normal lung function within 6 months after surgery, and the reduced donor-recipient predicted vital capacity ratio was the main risk factor [8].

Organ source and assessment strategies also affect the time distribution of PGD. Analysis of national databases shows that lungs assessed/ reconditioned by EVLP have comparable overall survival to conventional direct implantation, without increasing the incidence of PGD3. In the selection of high-risk donor lungs, EVLP can serve as a bridging strategy to "delay/reduce early pulmonary edema and inflammatory response", thereby reducing the proportion of protracted/deteriorating trajectories in T24–T72 [29]. From a biological perspective, the destruction of the epithelial-endothelial barrier and the downregulation of ENaC function in donor lungs lead to alveolar fluid clearance disorders, which are considered to be the key nodes that determine the "recovery-protracted-deterioration" bifurcation in T0–T72, suggesting that targeted interventions for channel function and epithelial repair in the perioperative period are worth exploring [30]. Chinese reviews and expert experience also point out that establishing a closed-loop pathway of "72-hour continuous assessment - risk phenotype identification-early intervention" (including lung-protective ventilation, goal-oriented volume management, early external support and infection screening when necessary) can be clinically translated into higher withdrawal rates and lower complication burden [31].

3.2. Temporal characteristics and etiological changes of infection symptom clusters

The incidence of post-lung transplantation infection shows a "bimodal distribution": the first peak occurs within 1 month after surgery, mainly bacterial and fungal infections; the second peak occurs from 1 to 6 months after surgery, characterized by viral infections (such as CMV, EBV) and opportunistic infections [15]. A multicenter study in Italy showed that the infection rate in lung transplant recipients within 6 months after surgery was as high as 47.8%, with Gram-negative bacteria accounting for the highest proportion, and most of them being multidrug-resistant strains [15]. The Italian national surveillance cohort indicated that the cumulative infection rate in lung transplant recipients within 6 months was 47.8%, with the most concentrated events in the first month. Gram-negative bacilli (mainly drug-resistant *Acinetobacter baumannii*, *Aeromonas baumannii* and *Pseudomonas aeruginosa*) dominated the early lineage [15]. A review of lung transplantation bacteriology pointed out that the sources of pathogens include donor lungs, existing colonization in recipients and in-hospital exposure, and that drug resistance phenotypes are closely related to central epidemiology, emphasizing that empirical treatment should be matched with local drug sensitivity [32].

Bacterial infections, the pathogens from the donor cannot be ignored. Turkish researchers found that recipients with positive bronchial lavage fluid cultures from donors had significantly longer mechanical ventilation time after surgery (median 4 days vs. 1 day) and a 3.39-fold increase in the incidence of postoperative PGD [33]. In addition, for every hour the operation time was extended, the risk of SSI increased by 2.34 times, suggesting that intraoperative contamination may be an important source of early infection [14]. Multicenter and single-center studies have further shown that positive bronchial/bronchoalveolar lavage fluid (BAL) cultures from donors are associated with an increased risk of early lung infection and PGD in recipients, suggesting the necessity of a three-pronged screening and decolonization strategy involving the donor, recipient, and perioperative period [33]. Regarding perioperative surgical complications, recent large single-center cohort studies have linked invasive SSIs (deep/organ cavities) with poor post-transplant outcomes and provided actionable risk stratification (such as operation time, re-exploration, and transfusion volume) and procedural recommendations [34].

Among viral infections, CMV is the most common pathogen, especially in recipients with CMV serological

mismatch. The incidence of CMV infection in pediatric lung transplant recipients is 17%, while studies in elderly kidney transplant recipients show that age ≥ 65 years is an independent risk factor for CMV reactivation (OR = 2.48), suggesting that immunosenescence may exacerbate viral replication [35,36]. In addition, EBV infection is closely associated with the occurrence of post-transplant lymphoproliferative disease (PTLD), with the risk peaking within 1–2 years after surgery [37]. A multicenter retrospective study of thoracic transplantation in China suggests that differences in CMV serological background and prevention strategies can significantly affect the CMV infection burden after lung/heart-lung transplantation, supporting risk stratification to guide prevention and surveillance [38]. In the pediatric lung transplant population, individualized strategies based on CMV-specific cellular immunity and more flexible prevention durations can be considered [39]. Regarding EBV, empirical studies and authoritative reviews of adults and adolescents suggest that EBV D^+/R^- background, early high-burden replication and enhanced immunosuppression jointly determine the time-series high-risk window of PTLD, requiring dynamic nucleic acid monitoring and early immunosuppression intervention [40].

Fungal infections are most commonly caused by *Candida* and *Aspergillus*, with an incidence of about 25% within one month after surgery [35]. Due to long-term antibiotic use before surgery, cystic fibrosis (CF) patients have a significantly higher risk of fungal infection than other populations, and often present with invasive infection and extremely high mortality [41]. Contemporary studies show that invasive aspergillosis (IA) mostly occurs in the first 6 months after surgery, and the risk is significantly increased in the context of "airway anastomosis complications, chronic rejection (BOS/CLAD) and previous fungal colonization" [42]. A comparison of domestic programs shows that "targeted prevention" does not increase IA events while reducing adverse reactions, but it needs to be combined with time window and dynamic assessment of individual risk factors [18]. A single-center retrospective study in China reported that the rate of invasive fungal infection within 30 days after surgery was about 13%, which was related to the spectrum of primary diseases and perioperative exposure . This suggests that imaging, GM/BDG and bronchoscopy assessments should be combined in the early peak window, and preventive strategies should be implemented when necessary to avoid forming a vicious cycle of "infection-PGD-function not reaching peak" [43].

Overall, the early stage (0–1 month) is dominated by bacterial/Candida and surgical site/donor-related events, while the middle stage (1–6 months) is dominated by CMV/EBV and opportunistic fungi, forming a "time-pathogen" coupling, superimposed with PGD, immunosuppression intensity and airway anastomosis complications, constituting the core spectrum of infection symptoms during the vulnerable period. Based on this, a comprehensive pathway of "time-specific pathogen spectrum + antimicrobial (true) drug management + dynamic virological monitoring" should be constructed to reduce the risk of recurrence and long-term CLAD.

4. Analysis of influencing factors of symptom clusters

4.1. Donor-related factors

Donor quality is one of the key factors determining the occurrence of vulnerable period symptoms after lung transplantation, and its influence extends throughout the entire process from organ procurement and preservation to reperfusion. The influence of donor age is controversial: traditional views hold that older donors (> 55 years old) increase the risk of PGD, but the latest research shows that donor age is not significantly associated with the incidence of PGD, which may be related to the advancement of donor lung assessment technology [2]. However, Japanese scholars have found that donor-recipient age mismatch may indirectly lead to BLAD by affecting graft

size matching, and the donor-recipient predicted vital capacity ratio was significantly reduced in the BLAD group [8].

A donor smoking history is a known risk factor. A study of double lung transplant recipients showed that a donor heavy smoking history (> 20 packs / year) increased the risk of BLAD by 3.07 times, which may be related to alveolar epithelial damage and inflammatory response caused by tobacco toxins [10]. In addition, a positive BALF culture is closely associated with postoperative infection. A study in Turkey found that the median postoperative mechanical ventilation time was 4 days in donors with positive BALF cultures, which was significantly longer than that in the negative group [33].

The impact of ischemic time varies depending on surgical technique. A national study in the UK showed that when CPB was used, the risk of death increased by 13% per year for every hour of extended ischemic time, while when CPB was not used, ischemic time had no significant impact on prognosis [44]. This finding challenges the traditional "cold ischemic time < 6 hours" standard and suggests that surgical strategies may alter the ischemic tolerance of the donor lung.

Donor infection and immune status should not be ignored. A US study showed that after adopting the expanded definition of " high-risk donor" (IRD) in 2013, the proportion of non-standard infection risk donors increased from 8% to 22%, but the survival rate of recipients was not significantly different from that of standard donors [45]. This suggests that under strict monitoring, some high-risk donors can still be used safely. In addition, donor CMV serological positivity may increase the risk of recipient CMV reactivation, especially in the absence of prophylactic treatment [36].

4.2. Receptor-related factors

The recipient-side risk exposure spans from preoperative to early postoperative period and has an "amplifying" effect on the formation of vulnerable period symptom clusters (PGD, infection, AKI, etc.). First, frailty is independently associated with adverse postoperative outcomes. Recent systematic reviews suggest that multidimensional vulnerability assessment of candidates can predict post-transplant hospital stay, complications and readmission risk, and some patients can benefit from a "deterioration-improvement" trajectory 3–6 months postoperatively, suggesting that preoperative vulnerability management should be included in the perioperative pathway [46]. Second, the intensity of preoperative respiratory/circulatory support reflects the severity of the disease. Although the survival rate of patients bridging transplantation with ECMO has improved year by year, the complications, resource consumption and infection burden are higher, and refined stratification is needed in candidate selection and perioperative management [47]. In terms of immunology, HLA mismatch (especially HLA-DQ and epitope mismatch) is associated with early complications and the formation of novo donor-specific antibodies (dnDSA), increasing the risk of rejection and CLAD, suggesting that more refined compatibility assessment should be conducted in conjunction with epitope analysis [48]. Overall, the recipient side should coordinate intervention from four dimensions: "vulnerability—support strength—immuno-compatibility—inflammatory load" to reduce the cumulative effect of vulnerable period symptoms.

4.3. Surgical and perioperative management factors

Perioperative technical routes directly reshape the pathogenesis of vulnerable period symptom clusters. Regarding extracorporeal support methods, the latest meta-analysis and systematic review show that VA ECMO is superior or non-inferior to CPB in many short-term indicators (ICU hospitalization, tracheotomy, renal failure), but its impact on mortality and bleeding/transfusion is heterogeneous, suggesting that strategies should be developed in

combination with center experience and individual hemodynamics [49]. The amount of red blood cells transfused during the operation is independently correlated with PGD3 at 72 hours after the operation, and is accompanied by an increase in dialysis demand and hospitalization time. A balance should be achieved between hemostasis and transfusion thresholds [50]. In addition, prolonged operation, re-exploration and high-intensity extracorporeal support can increase infection and bleeding complications, thereby triggering the linkage of "PGD-infection-renal injury", and a dynamic balance should be achieved between organ protection and complication prevention [51].

4.4. Postoperative management and immunosuppression-related factors

The dynamic balance between postoperative immunosuppression and infection/rejection determines the "coupling strength" of vulnerable symptom clusters. The infection burden is high in the first year after lung transplantation, with CMV, drug-resistant bacteria and fungi being the core pathogens. Infection and rejection are mutually causal pathways, and imbalance can amplify the PGD-BLAD-CLAD chain [52]. The association between CMV replication and CLAD risk has been confirmed in multicenter and single-center studies, and a prevention/preemptive strategy should be implemented by combining serological stratification and PCR dynamic monitoring [53]. In terms of antifungal treatment, real-world and national data suggest that shifting from "general prevention" to "targeted prevention" can reduce adverse reactions without increasing IA events; drug selection (voriconazole/caspofungin, etc.) needs to be combined with individual risk profile and drug interaction management [54]. Calcineurin inhibitors remain the cornerstone of maintenance therapy. Tacrolimus trough concentration fluctuations are associated with increased acute rejection burden, and TDM and its interaction should be taken seriously. Compared with cyclosporine, tacrolimus has advantages in reducing acute rejection/CLAD, but diabetes and nephrotoxicity need to be weighed [55]. Chinese guidelines and reviews have formed a standardized path: emphasizing individualized induction–maintenance regimens, stratified diagnosis and treatment of rejection (cell/antibody mediated), and synergy with infection prevention and rehabilitation nursing to reduce the clustering of complications during vulnerable periods [56].

The vulnerable period after lung transplantation is a critical stage determining short-term survival and long-term graft function, characterized by the high frequency and complex interaction of multi-system complications. This article reviews the composition, dynamic trajectory, and multidimensional influencing factors of symptom clusters during the vulnerable period in lung transplant recipients. Studies have shown that PGD is the most central pathological event in this stage, forming a "symptom cluster network" together with infection, inflammatory response, and multiple organ dysfunction, exhibiting continuous evolution over time. Donor quality, recipient baseline status, surgical and perioperative management, and postoperative immunity and infection control all shape the pathogenesis of symptom clusters at different levels. In recent years, with the optimization of donor selection, the application of EVLP, and the promotion of individualized perioperative management, the overall incidence of PGD and infection has decreased, but the adverse effects of "symptom clusters" on rehabilitation and long-term survival remain prominent. Future research should focus on three aspects: First, establishing dynamic predictive models for symptom clusters based on longitudinal data to achieve precise monitoring and early intervention; second, constructing a two-way assessment system for donors and recipients to promote individualized immune and infection prevention strategies; and third, strengthening multidisciplinary collaboration and improving postoperative rehabilitation, psychological, and social support interventions to improve both physiological and functional outcomes. In summary, research on vulnerable symptom clusters after lung transplantation is shifting from "complication statistics" to "systemic physiology and holistic management" and its systematization,

dynamism, and precision will become the core direction for improving transplant efficacy in the future.

5. Conclusion

The early post-lung transplant period is characterized by a core symptom cluster, primarily comprising Primary Graft Dysfunction (PGD) and infections. This cluster exhibits a distinct temporal trajectory and is influenced by donor and recipient factors, surgical procedures, and postoperative management. Future efforts should focus on developing predictive models to inform proactive, personalized management strategies aimed at improving patient outcomes.

Disclosure statement

The authors declare no conflict of interest.

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