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Review

Neurological Complications After Heart Transplantation: From Pathophysiological Mechanisms to Emerging Management Paradigms

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Abstract

Heart transplantation (HT) is a cornerstone therapy for selected patients with end-stage heart disease. Despite substantial progress in surgical techniques, perioperative care, and immunosuppressive regimens over the past three decades, neurological complications, including immunosuppressive neurotoxicity, cerebrovascular events related to perioperative hemodynamic instability, central nervous system infections, and post-transplant lymphoproliferative disorders, remain major contributors to morbidity and mortality after HT, affecting 30%–70% of recipients. Among these, calcineurin inhibitor (CNI)-induced neurotoxicity, particularly posterior reversible encephalopathy syndrome, is one of the most prevalent and clinically challenging complications. Therefore, this review synthesizes the current understanding of these complications and emphasizes mechanistic insights into CNI-induced neurotoxicity, including blood–brain barrier disruption, mitochondrial dysfunction, and immune-mediated cerebral hypoperfusion. Furthermore, this review explores evolving diagnostic approaches, including advanced neuroimaging and emerging molecular biomarkers, and critically evaluates contemporary immunosuppressive strategies that balance therapeutic efficacy with neurological safety. Finally, we propose a novel conceptual framework, the immuno-vascular-metabolic axis, to integrate existing findings and guide future research toward personalized risk stratification and neuroprotective interventions. Overall, this review highlights the need for early recognition, multidisciplinary management, and continued innovation in immunosuppressive therapy to improve long-term outcomes in HT recipients.

Keywords: heart transplantation; neurologic manifestations; neurotoxicity syndromes; immuno-vascular-metabolic axis

1. Introduction

Heart transplantation (HT) is an established life-saving intervention for patients with refractory end-stage heart failure [1]. Over the past three decades, progress in surgical techniques, organ preservation, perioperative critical care, and immunosuppressive therapy has led to improvements in short- and long-term survival [2]. However, challenges such as rejection, infection, renal failure, cardiac allograft vasculopathy, and post-transplantation lymphoproliferative disease (PTLD) hinder the realization of optimal post-transplantation outcomes [3].

Among these challenges, neurological complications represent a particularly important and often underappreciated source of morbidity. Depending on the diagnostic criteria and study population, the reported incidence rates range from 30% to 70%, with the highest risk observed during the perioperative period [4,5]. These complications—ranging from subtle cognitive impairment to devastating stroke, encephalopathy, and central nervous system (CNS) infections [6]—can profoundly impact patients' functional status, quality of life, and long-term survival.

Pre-existing cerebral vulnerability is strongly influenced by the etiology of end-stage heart failure [7,8]. Patients with ischemic cardiomyopathy frequently harbor pre-existing cerebrovascular disease (including silent cerebral infarcts and high white matter hyperintensity burden) and are therefore predisposed to postoperative stroke and cognitive decline [9].

Patients with dilated cardiomyopathy typically experience prolonged low-cardiac-output states, which cause chronic cerebral hypoperfusion, hippocampal atrophy, and memory and executive function impairment [10]. Restrictive cardiomyopathy—particularly cardiac amyloidosis—may involve direct CNS infiltration by amyloid protein, conferring a distinct neurocognitive trajectory [11]. Congenital heart disease patients, who often survive to transplant candidacy because of advances in pediatric cardiology, present unique cerebrovascular vulnerabilities, e.g., chronic cyanosis, aberrant collateral circulation, and prior stroke from paradoxical emboli [12,13]. These etiological distinctions should inform pretransplantation neurocognitive assessment and post-transplantation neurological surveillance [14].

Despite advances in immunosuppressive regimens and surgical techniques, several fundamental questions remain unresolved. First, the precise mechanisms underlying calcineurin inhibitor (CNI)-induced neurotoxicity extend beyond simple drug toxicity and involve complex in-

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Table 1. Overview of major neurological complications following heart transplantation.

Category	Estimated incidence rate	Typical onset	Key manifestations
Immunosuppressive neurotoxicity	10%–28% (CNI-related)	Early to chronic	PRES, seizures, tremor, encephalopathy, cognitive decline
Cerebrovascular events	8%–28%	Early to chronic	Ischemic stroke, intracerebral hemorrhage, hyperperfusion syndrome
CNS infections	1%–5%	Early (1–6 months)	Meningitis, encephalitis, brain abscess (fungal, listeriosis, toxoplasmosis)
CNS neoplasms (PTLD)	2%–6%	Late (>1 year)	Lymphoma, PTLD-related lesions

CNI, calcineurin inhibitor; PRES, posterior reversible encephalopathy syndrome; CNS, central nervous system; PTLD, post-transplantation lymphoproliferative disease.

teractions among endothelial dysfunction, mitochondrial metabolic impairment, and immune-mediated cerebrovascular dysregulation [15]. Second, the optimal strategies for mitigating neurological risk without compromising graft survival are still evolving. Third, the absence of robust biomarkers for early detection and individualized risk stratification limits current clinical practice.

Herein, we provide a comprehensive and updated overview of the spectrum, pathophysiology, diagnosis, and management of neurological complications following HT. In doing so, we introduce a novel conceptual framework—the immuno-vascular-metabolic axis—to integrate disparate mechanistic insights and highlight emerging opportunities for biomarker development, neuroprotective strategies, and precision immunosuppression. By synthesizing current evidence and identifying knowledge gaps, we seek to inform clinical practice and guide future research in this critical area.

2. Spectrum and Epidemiology of Neurological Complications

Neurological complications following HT can be broadly categorized into four major entities with substantially different timings, clinical presentations, and underlying mechanisms, namely immunosuppressive neurotoxicity (e.g., posterior reversible encephalopathy syndrome (PRES)), surgery- and perioperative-related cerebrovascular events, CNS infections, and CNS neoplasms (primarily PTLD) (Table 1).

The heterogeneity of these complications necessitates a nuanced approach to diagnosis and management, which is explored in detail in the following sections.

The etiological differences between early and late neurological complications after HT merit explicit consideration. Early complications (occurring within the first month after HT) are predominantly driven by perioperative factors and include cardiopulmonary bypass (CPB)-related embolic events, hemodynamic instability leading to cerebral hypoperfusion or hyperperfusion syndrome, and acute CNI-induced neurotoxicity (particularly PRES) [16,17]. Late complications (occurring beyond six months after HT) are more commonly associated with chronic immunosuppression and include opportunistic CNS infections, PTLD, and progressive cognitive decline related to cumulative CNI exposure [18,19]. Complications occurring in the intermediate period (1–6 months) may reflect a mixture of these mechanisms, with infection risk peaking during the period of maximal immunosuppression [20]. This temporal framework informs diagnostic algorithms and guides surveillance intensity.

Special Considerations: HT in the Era of Durable Left Ventricular Assist Devices (LVADs)

The HT landscape has been fundamentally reshaped by the increasing use of durable LVADs as a bridge to transplantation. Owing to the limited donor organ availability and rising prevalence of advanced heart failure, the proportion of HT candidates receiving LVAD support before transplantation has substantially increased over the past decade [21]. Patients bridged with LVADs represent a uniquely vulnerable population, carrying a burden of pre-existing comorbidities that profoundly influence post-transplantation neurological outcomes [21].

Several LVAD-specific factors have been identified as independent predictors of post-transplantation neurological complications [22]. Sustained hypertension, particularly mean arterial pressure exceeding 85–90 mmHg, is associated with an increased risk of ischemic and hemorrhagic cerebrovascular events [23,24]. LVAD-related infections—including driveline and pump pocket infections—may serve as occult sources of systemic embolization or sepsis-related encephalopathy [25,26]. Acquired von Willebrand syndrome, a well-recognized complication of continuous-flow LVADs, creates a paradoxical predisposition to both bleeding (gastrointestinal and intracranial) and thrombosis due to high shear stress-induced platelet activation [27,28]. A prospective study of HeartMate 3 recipients demonstrated that patients with an early postoperative (<60 days) von Willebrand factor activity/antigen ratio of ≤0.7 had a 3.5–4.9-fold higher risk of late hemorrhagic stroke, compared to those with ratio >0.7 [29].

LVAD-supported patients often suffer from impaired cerebral autoregulation, probably because of chronic exposure to nonpulsatile flow and pre-existing hypertensive vasculopathy [30]. Microangiopathies and arteriovenous malformations—particularly within the gastrointestinal tract—may signal a broader systemic vasculopathy that also affects cerebral circulation [31]. Female gender and pre-existing renal dysfunction are additional risk modifiers [32,33].

Post-transplantation anticoagulation management in LVAD-bridged recipients presents unique challenges. Although LVAD explantation removes the pump-related thrombotic risk, many patients continue to require long-term anticoagulation management because of persistent risk factors such as atrial fibrillation or prior thromboembolic events. Time in therapeutic range >60%—international normalized ratio maintenance within 2.0–3.0—has been established as a benchmark for effective anticoagulation [34]. However, this target is difficult to achieve because of interactions between vitamin K antagonists and immunosuppressive agents, particularly cytochrome P450–modulating CNIs [35]. Neurological events in this population are predominantly of ischemic (embolic from residual intracardiac thrombus or arterial sources) or hemorrhagic origin [36]. The management of these complications is considerably more challenging than that in uncomplicated HT recipients, requiring decision-making coordination between transplant cardiologists, neurologists, and hematologists.

3. Immunosuppressive Neurotoxicity: Mechanisms and Clinical Spectrum

Immunosuppressive neurotoxicity is the most common neurological complication following HT, with the reported incidence rate reaching 21% in some series [37,38]. The clinical manifestations—ranging from mild tremor and headache to seizures, encephalopathy, and coma—are highly variable and often nonspecific [39]. Among the various immunosuppressive agents, CNIs, including cyclosporine A and tacrolimus (also known as FK506), are the principal culprits [40,41].

3.1 CNIs and PRES

PRES is the hallmark neurological syndrome associated with CNI exposure, affecting 10%–28% of patients [42]. Typical neuroimaging findings include vasogenic edema predominantly localized in the parieto-occipital regions, although the involvement of the frontal lobes, basal ganglia, and brainstem is increasingly recognized [43]. The pathophysiology of PRES involves the following factors.

- Endothelial dysfunction: CNIs induce endothelin release, which leads to vasoconstriction, systemic hypertension, and impaired cerebral autoregulation [44].
- Blood–brain barrier (BBB) disruption: Direct endothelial injury and downregulation of tight junction proteins increase capillary permeability and thus promote fluid extravasation [45].
- Hemodynamic factors: Pre-existing low cardiac output followed by rapid normalization after transplantation may overwhelm cerebral autoregulatory capacity and thus contribute to hyperperfusion injury [46].

PRES may also involve an aberrant T cell-mediated immune response, with endothelial activation and selective T-cell trafficking leading to regional hypoperfusion and hypoxemia [47].

3.2 Mitochondrial Dysfunction and Chronic Neurocognitive Impairment

Beyond acute PRES, emerging data suggest that chronic CNI exposure causes progressive cognitive decline. Thiankhaw et al. [15] reviewed clinical evidence of CNI-related cognitive impairment, highlighting abnormal mitochondrial fission, reactive oxygen species (ROS)-mediated neuroinflammation, and BBB breakdown. CNIs impair mitochondrial energy metabolism in experimental models and human cell lines, as reflected by reduced oxygen consumption, decreased synthesis of mitochondrial deoxyribonucleic acid (DNA)-encoded proteins, and diminished high-energy phosphate levels [48,49]. In a cohort of HT recipients, elevated plasma levels of short-chain acylcarnitines and urinary dicarboxylic acids—biomarkers suggestive of mitochondrial dysfunction—were found to be associated with worse cognitive outcomes [50]. These metabolites could serve as biomarkers of CNI neurotoxicity and inform future mitochondrial-targeted interventions. Thus, mitochondrial dysfunction may serve as both a mechanistic driver and potential therapeutic target for CNI-related neurotoxicity.

3.3 Lipophilicity, BBB Penetration, and P-glycoprotein (P-gp)

Cyclosporine A and tacrolimus are highly lipophilic, which facilitates their passive diffusion across the BBB. However, their brain accumulation is normally limited by the efflux pump P-gp at the luminal surface of brain capillary endothelial cells [51].

CNIs themselves can downregulate P-gp expression and function, creating a vicious cycle of increased drug penetration and exacerbated neurotoxicity [52,53]. This mechanism may explain the occurrence of severe neurotoxicity even in patients with therapeutic serum drug levels.

4. Surgery-Related Cerebrovascular Complications

Cerebrovascular events represent the most common nonimmunosuppressive neurological complication, occurring in 8%–28% of HT recipients [54]. The risk of these events is highest in the perioperative period, with focal ischemia, altered mental status, and seizures being the predominant presentations.

4.1 Hemodynamic Instability and Hyperperfusion Syndrome

Preoperative low cardiac output and catecholamine dependence predispose to cerebral hypoperfusion, while the post-transplantation restoration of cardiac output may paradoxically result in cerebral hyperperfusion [55]. This hyperperfusion syndrome has been linked to postoperative vascular headaches and intracerebral hemorrhage, particularly in cases of significant donor–recipient size mismatch (>30%) [56].

4.2 CPB and Neuroinflammatory Injury

Prolonged CPB time (>120 min) is an independent risk factor for postoperative stroke [57]. Elevated lactate levels during CPB, reflecting tissue hypoperfusion and metabolic stress, are similarly associated with increased neurotoxicity [58]. Beyond mechanical factors, CPB triggers a systemic inflammatory response characterized by cytokine release and complement activation, which may exacerbate pre-existing endothelial vulnerability and contribute to BBB disruption [59].

4.3 Cognitive and Hemodynamic Considerations

Beyond acute cerebrovascular events, the hemodynamic consequences of HT—including the effects of CPB and post-transplantation hemodynamic restoration—have measurable impacts on cognitive function. Advanced heart failure is associated with chronically reduced cerebral perfusion, which leads to pre-existing cognitive impairment in a substantial proportion of candidates [60]. The rapid normalization of cardiac output after transplantation may paradoxically precipitate cerebral hyperperfusion injury, particularly in patients with impaired cerebral autoregulation [46]. Prolonged CPB time (>120 min) is an independent risk factor for postoperative cognitive decline, mediated in part by CPB-induced systemic inflammatory response syndrome, microembolization, and cerebral hypoperfusion during bypass [61,62]. Post-transplantation medications, particularly CNIs and corticosteroids, further modulate cognitive function through direct neurotoxic effects and metabolic disturbances [15]. A literature-supported interpretation suggests that although many HT recipients experience improvement in global cognition compared with their pretransplantation baseline, subsets of patients—particularly those with prolonged CPB time, post-transplantation delirium, or high CNI exposure—demonstrate persistent or progressive cognitive deficits affecting executive function and memory.

4.4 Phosphodiesterase Type 5 (PDE5) Inhibitors and Neurological Outcomes

PDE5 inhibitors, such as sildenafil and tadalafil, are routinely used to manage persistent pulmonary hypertension and right heart failure after HT [50]. Beyond exerting hemodynamic effects, PDE5 inhibitors influence neurological outcomes through several mechanisms. By raising cyclic guanosine monophosphate levels, these agents promote cerebral vasodilation, enhance angiogenesis, and may offer neuroprotection in ischemic stroke models. PDE5 inhibitors (e.g., mirodenafil) markedly improve sensorimotor and cognitive recovery in rats subjected to middle cerebral artery occlusion and reduce neuronal apoptosis and degeneration, with treatment window extension boosting these benefits [63]. However, clinical data specific to HT recipients remain limited. Potential adverse neurological effects include headache (due to vasodilation) and, less commonly, nonarteritic anterior ischemic optic neuropathy (NAION) [64]. A case-crossover study estimated the odds ratio for confirmed NAION on the day after PDE5 inhibitor exposure at 2.15 (95% confidence interval: 1.06–4.34, $p = 0.03$), which indicates an approximately two-fold increased risk [65]. Given that HT recipients often have a high burden of cerebrovascular risk factors—hypertension, diabetes, and others—which are themselves risk factors for NAION, the net neurological impact of PDE5 inhibitor therapy warrants prospective investigation.

5. CNS Infections

CNS infections, although less common (1%–5%), carry a grave prognosis, with mortality rates exceeding 50% in cases of cerebral aspergillosis [18]. The risk is highest in the period of maximal immunosuppression, i.e., during the first six months after transplantation.

5.1 Etiology and Clinical Challenges

Aspergillus fumigatus, Listeria monocytogenes, and Cryptococcus neoformans are the most frequently involved pathogens [66]. Toxoplasmosis resulting from the reactivation of latent cysts in the donor heart is a unique concern in HT recipients [67]. The corresponding clinical presentation is often atypical, with headache and subtle cognitive changes being the only early signs, necessitating a high index of suspicion [68].

Cellular Mechanisms of Select Pathogens: Toxoplasma gondii reactivation typically occurs in seronegative recipients of seropositive donor hearts [69]. Immunosuppression knocks down CD8+ T-cell surveillance, leading to cyst rupture [70]. The heart carries *Toxoplasma* cysts, making HT the highest-risk procedure for donor-derived infection. D+/R− mismatch also trends toward higher mortality (HR = 3.0, $p = 0.06$) [71]. *L. monocytogenes* escapes intracellular killing by disrupting the phagosome via listeriolysin O, although Th1-type immunity normally keeps this process in check [72]. In a mouse cardiac allograft model, perioperative Listeria infection was shown to disrupt transplant tolerance through an Listeriolysin O (LLO)-dependent mechanism involving CD4+ and CD8+ T cells [73].

5.2 Risk Factors and Diagnostic Advances

Independent risk factors for CNS infection include urgent transplantation, multiple blood transfusions, younger age at transplantation, and pretransplantation extracorporeal membrane oxygenation support [74]. Molecular diagnostic techniques—including cerebrospinal fluid polymerase chain reaction for viral pathogens and serum/cerebrospinal fluid cryptococcal antigen testing—have significantly improved diagnostic yield [75]. Nevertheless, early brain biopsy remains necessary in certain cases to distinguish infection from PTLD or other mass lesions.

6. PTLD and CNS Malignancy

The cumulative risk of malignancy in HT recipients is three- to fourfold higher than in the general population because of chronic immunosuppression and oncogenic viral infections (particularly Epstein–Barr virus, EBV) in the former group [76,77]. PTLD accounts for the majority of CNS neoplasms, affecting 2%–6% of HT recipients [78,79].

6.1 Pathogenesis and Clinical Presentation

PTLD encompasses a spectrum from EBV-driven polyclonal B-cell hyperplasia to monoclonal aggressive lymphoma [80,81]. CNS involvement occurs in ~27% of PTLD cases and is often accompanied by focal neurological deficits, altered mental status, or seizures [82,83]. Risk factors include EBV seronegativity at transplant, use of T cell-depleting induction therapy, and young age [84].

6.2 Management Strategies

PTLD treatment is multimodal and risk-stratified. The reduction of immunosuppression is the first-line intervention, often leading to the regression of early lesions [85]. Progressive or high-grade disease is treated using rituximab (anti-CD20 monoclonal antibody) combined with chemotherapy or radiotherapy. Emerging data support the use of EBV-specific cytotoxic T lymphocytes in refractory cases [86]. The introduction of proliferation signal inhibitors (sirolimus and everolimus) provides a dual benefit by reducing CNI exposure and exerting direct antiproliferative effects [87].

7. Toward a Unified Framework: Immuno-Vascular-Metabolic Axis

Despite the apparent diversity of post-HT neurological complications, emerging evidence suggests convergent pathophysiological themes. Herein, we propose the immuno-vascular-metabolic axis as a unifying conceptual framework grounded in specific mechanistic interactions among allograft immunity, endothelial dysfunction, and metabolic reprogramming (Fig. 1).

- Immuno-vascular interface: CNI-induced endothelial injury involves the downregulation of tight junction proteins (claudin-5 and occludin) and activation of endothelin-1-mediated vasoconstriction [88]. Beyond direct drug toxicity, CNIs promote aberrant T-cell activation that contributes to endothelial damage and BBB disruption [89]. Conversely, allograft rejection is partly mediated by T cell–macrophage interactions that induce the proteolytic cleavage of MERTK—a key anti-inflammatory receptor on macrophages—and thus reduce efferocytosis and increase inflammatory cytokine expression [90].
- Vascular-metabolic interface: Chronic cerebral hypoperfusion, common in advanced heart failure and exacerbated by CPB-related hemodynamic stress, impairs mitochondrial oxidative phosphorylation and increases ROS production [91]. The resulting metabolic stress promotes endothelial activation and further compromises cerebral autoregulation. Recent imaging studies have demonstrated that LVAD-supported patients experience greater temporal lobe atrophy than HT recipients, suggesting that device-related hemodynamic patterns influence cerebral structural integrity [92].
- Metabolic-immuno interface: Mitochondrial dysfunction activates Toll-like receptor-mediated innate immune pathways through the release of damage-associated molecular patterns (DAMPs) [93]. Furthermore, single-cell transcriptomic evidence reveals that the metabolic polarization of macrophages (glycolysis versus oxidative phosphorylation) governs their efferocytic capacity and inflammatory phenotype, thereby directly influencing the progression of allograft vasculopathy and correlating with poorer cognitive outcomes in heart transplantation (HT) recipients [90,94].

This framework has several implications. First, it highlights the potential for shared biomarkers (e.g., endothelial microparticles (EMPs), mitochondrial DNA copy number, and inflammatory cytokines) to predict neurological risk across etiologies. Second, it suggests that neuroprotective strategies targeting endothelial stabilization (e.g., tight junction modulators) or mitochondrial function (e.g., coenzyme Q10) could have broad applicability. Third, it reinforces the need for precision immunosuppression that minimizes neurotoxicity while preserving antirejection efficacy.

8. Emerging Strategies for Risk Mitigation and Future Directions

Fig. 2 outlines emerging strategies for risk mitigation and related future development directions.

8.1 Biomarker Development

The absence of validated biomarkers for the early detection of CNI neurotoxicity, PRES, or PTLD remains a critical gap. Emerging candidates include neurofilament light chain (NfL), mitochondrial biomarkers, EMPs, and cell-free EBV DNA.

- NfL: Plasma NfL levels correlate with the severity of axonal injury [95]. In CNI neurotoxicity, NfL el-

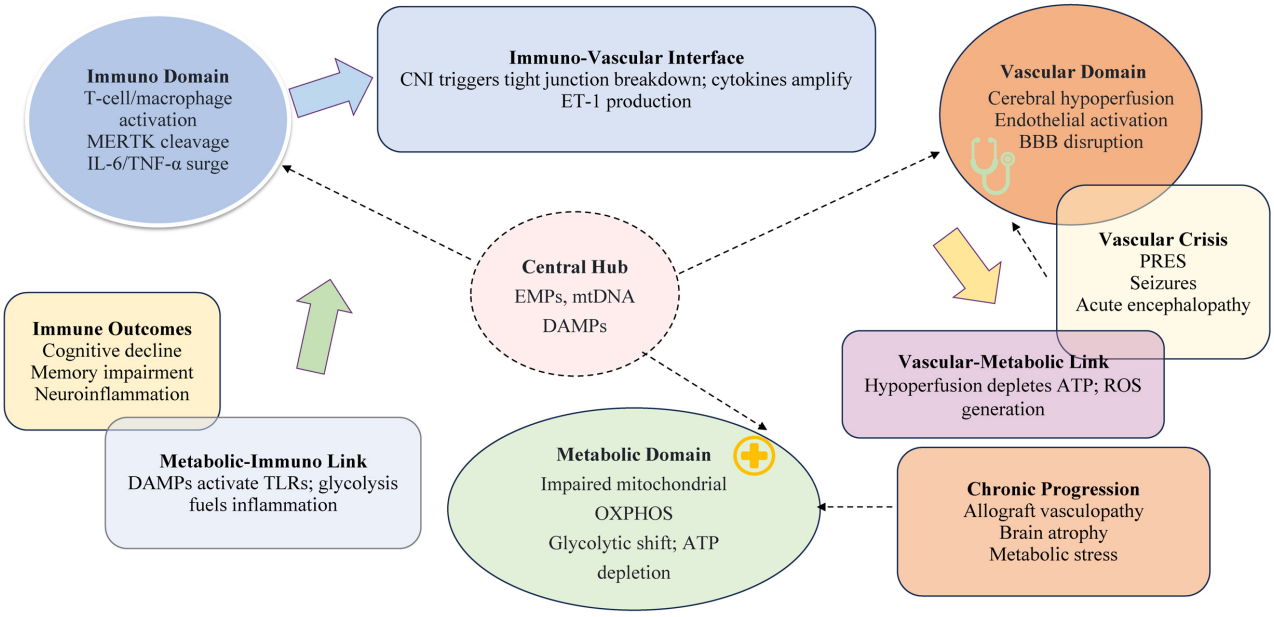


Fig. 1. Detailed mechanisms of the immuno-vascular-metabolic axis in neurological complications after heart transplantation. PRES, posterior reversible encephalopathy syndrome; ATP, adenosine triphosphate; ROS, reactive oxygen species; BBB, blood–brain barrier; OXPHOS, oxidative phosphorylation; DAMPs, damage-associated molecular patterns; TLRs, Toll-like receptors; CNI, calcineurin inhibitor; ET-1, endothelin-1; MERTK, MER proto-oncogene, tyrosine kinase; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha.

evation has been observed before the appearance of overt PRES symptoms. Animal studies indicate that serum NfL is a useful peripheral biomarker for detecting CNS toxicity and is strongly correlated with the extent of brain tissue lesions [96]. However, increased NfL levels are not a specific marker, as they can also reflect stroke, infection, and PTLD.

● Mitochondrial biomarkers include mitochondrial DNA copy number and acylcarnitine profiles for metabolic dysfunction [97]. Current translational readiness corresponds to research use only.

● EMPs: CD144+ EMPs (VE-cadherin-positive endothelial-derived extracellular vesicles) can reflect BBB endothelial injury. The plasma levels of CNS-derived endothelial extracellular vesicles were reported to be significantly elevated in patients with active multiple sclerosis, serving as a biomarker of BBB permeability and endothelial activation/injury [98]. In an Alzheimer's disease model, elevated plasma VE-cadherin (CD144) levels were found to be linked to the disruption of cerebrovascular endothelial integrity [99]. However, the ability of CD144+ EMP levels to serve as an early marker of CNI-induced endothelial injury needs prospective validation in HT cohorts.

● Cell-free EBV DNA: Quantitative polymerase chain reaction for EBV DNA in plasma is clinically available and used for PTLD surveillance. Cell-free DNA analysis can serve as a minimally invasive tool for PTLD screening and treatment monitoring. In patients with EBV-positive PTLD, the percentage of EBV reads is markedly higher than in controls (approximately 3-log difference), and an EBV read percentage above 0.0012% can indicate EBV-positive PTLD. This approach has a high negative predictive value but variable sensitivity [100]. In addition, cell-free DNA analysis can identify copy number alterations and somatic mutations in EBV-negative PTLD, with TP53 and KMT2D being the most frequently mutated genes (41%).

The prospective validation of these biomarkers in well-phenotyped HT cohorts is urgently needed to establish clinical utility and define actionable thresholds.

8.2 Advanced Neuroimaging

Beyond conventional magnetic resonance imaging, advanced techniques such as arterial spin labeling for cerebral blood flow quantification [101], diffusion tensor imaging for assessing white matter integrity [102], and quantitative susceptibility mapping for microhemorrhage detection hold promise for the earlier and more precise characterization of neurological injury [103].

8.3 Precision Immunosuppression

Individualized immunosuppressive regimens based on genetic, pharmacokinetic, and pharmacodynamic profiling may reduce neurotoxicity, as exemplified below.

● CYP3A5 genotyping can guide CNI dosing to avoid supratherapeutic concentrations [104].

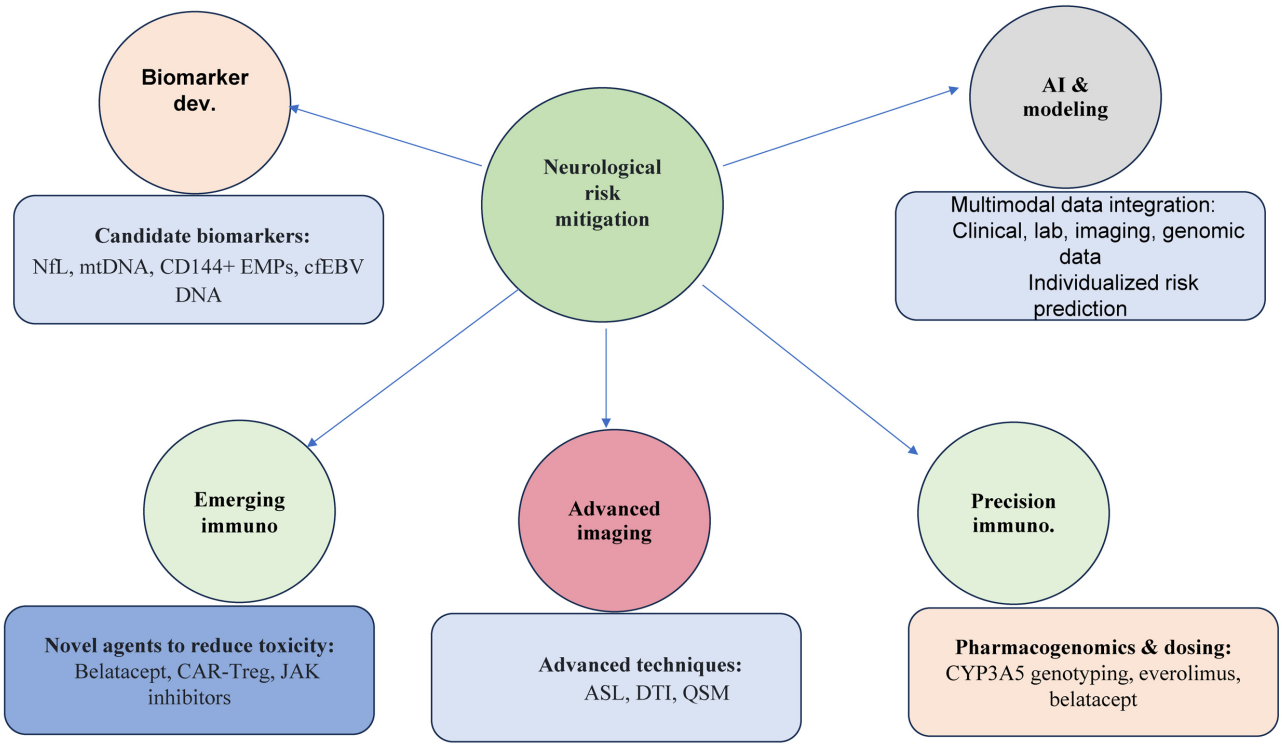


Fig. 2. Emerging strategies for risk mitigation in neurological complications after heart transplantation. NfL, neurofilament light chain; mtDNA, mitochondrial DNA; CD144+, CD144-positive endothelial microparticles; EMPs, endothelial microparticles; cfEBV DNA, cell-free Epstein–Barr virus deoxyribonucleic acid; ASL, arterial spin labeling; DTI, diffusion tensor imaging; QSM, quantitative susceptibility mapping; AI, artificial intelligence; JAK, Janus kinase; CAR, chimeric antigen receptor; CYP3A5, cytochrome P450 family 3 subfamily A member 5.

● Once-daily extended-release tacrolimus formulations may improve adherence and reduce peak-related neurotoxicity [105].

A critical comparison of alternative immunosuppressive regimens is warranted to guide clinical decision-making regarding neurological safety, as described below.

● CNI minimization strategies: Reducing CNI exposure while maintaining adequate immunosuppression may lower neurotoxicity risk [106]. However, prospective data pertaining to HT recipients are limited. Although CNI and corticosteroid minimization strategies have drawn attention in kidney transplantation, their long-term safety and effectiveness need confirmation through adequate long-term controlled trials [107].

● Mechanistic target of rapamycin (mTOR)-based approaches (everolimus and sirolimus): Conversion to mTOR inhibitors in patients with established CNI neurotoxicity or malignancy risk may preserve graft function while reducing neurological adverse effects [108]. However, mTOR inhibitors are associated with delayed wound healing and potential dyslipidemia, which may indirectly affect cerebrovascular risk [109].

The choice of regimen requires individualization based on patient-specific factors, including baseline neurological risk, rejection history, and comorbidities. A risk-benefit assessment that explicitly considers neurological outcomes should be incorporated into routine immunosuppressive management.

8.4 Emerging Immunomodulatory Approaches

Novel immunosuppressive strategies with potentially improved neurological safety profiles are under investigation, as outlined below.

● Belatacept (CTLA4-Ig) has been associated with lower rates of neurotoxicity in kidney transplantation but remains to be studied in HT [110].

● CAR-Treg (chimeric antigen receptor T-regulatory) cells can induce donor-specific tolerance without broad immunosuppression [111].

● Janus kinase inhibitors may modulate immune activation with a distinct side-effect profile [112].

8.5 Artificial Intelligence (AI) and Predictive Modeling

AI and machine learning (ML) algorithms offer transformative potential for the individualized risk prediction of neurological complications following HT. Early studies in cardiac surgery have demonstrated the feasibility of predicting postoperative delirium and stroke using AI models

[113,114]; similar approaches in HT are warranted. By integrating heterogeneous data streams—including clinical parameters, laboratory values, imaging features, genomic profiles, and continuous physiologic monitoring—AI models can identify high-risk patients before complications manifest, enabling preemptive intervention [115,116,117].

Current applications and evidence: In cardiac surgery populations, ML algorithms can predict postoperative delirium (area under the curve = 0.78–0.85) and stroke using perioperative electronic health record data [118]. For LVAD patients, AI-based predictive systems are being developed to forecast pump thrombosis, bleeding events, and neurological deterioration through the analysis of hemodynamic waveforms and sensor data [119]. In the transplant setting, single-cell transcriptomic and spatial omics data are increasingly being analyzed using computational biology approaches to decode immune cell interactions that underpin cardiac allograft vasculopathy and potentially neuroinflammatory complications [94].

Challenges and roadmap to clinical deployment: Several barriers must be addressed before AI-based neurological risk prediction can be widely implemented in HT care. These include (1) the lack of external validation across diverse transplantation centers with different patient populations and practice patterns, (2) the "black box" problem (model decisions are not easily interpretable by clinicians), (3) the heterogeneity and scarcity of data in real-world registries [120], and (4) regulatory and ethical considerations regarding AI-driven clinical decision support [121]. Prospective validation in multicenter cohorts, development of explainable AI approaches, and integration into existing clinical workflows are the necessary next steps. Within the next decade, AI-enabled risk stratification tools are expected to become part of routine transplant care, complementing clinical judgment rather than replacing it.

9. Conclusion

Neurological complications remain a formidable challenge in the management of HT recipients, affecting a substantial proportion of patients and markedly contributing to morbidity and mortality. Although our understanding of the underlying mechanisms—particularly CNI-related neurotoxicity, cerebrovascular injury, CNS infections, and PTLD—has advanced considerably, notable gaps remain in early diagnosis, risk stratification, and targeted therapy.

The proposed immuno-vascular-metabolic axis offers a novel integrative framework that may guide future research and clinical innovation. Key priorities for the coming decade include (1) the validation of multimodal biomarkers for early detection and monitoring, (2) development of neuroprotective adjuncts to existing immunosuppressive regimens, (3) application of precision medicine approaches to tailor immunosuppression, (4) special attention to the growing population of LVAD-bridged recipients with unique risk profiles, and (5) leveraging AI to enable predictive preemptive care.

Ultimately, improving neurological outcomes after HT requires a multidisciplinary approach bridging cardiology, neurology, infectious diseases, immunology, and critical care to ensure that survival gains are accompanied by optimal functional recovery and quality of life.

Author Contributions

YYH, JS, and YW conceived and designed the review study. YYH, JS, and YW conducted the literature search and review of existing studies. YYH, JS, and YW analyzed and synthesized the literature. YYH, JS, and YW wrote the manuscript. DYC contributed to the conception and design of the review, determined the overall framework, and participated in the screening, analysis, and interpretation of the literature. YPZ contributed to the literature search, data extraction, and analysis of the included studies. FWZ contributed to the acquisition, organization, and interpretation of the literature. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT-3.5 in order to check spelling and grammar of this paper. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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