

ORIGINAL RESEARCH ARTICLE

Neurological complications after heart transplantation: Incidence, risk factors, and outcomes

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Abstract

Neurological complications remain an important source of morbidity after heart transplantation, but their contemporary incidence, determinants, and clinical consequences are not fully characterized. This study evaluated the incidence, risk factors, in-hospital outcomes, and long-term survival associated with neurological complications after heart transplantation in a single-center cohort. A single-center retrospective cohort study was performed on 641 heart transplant recipients. Patients were divided according to the occurrence of post-transplant neurological complications. Neurological events were further categorized as transient or permanent neurological dysfunction. Preoperative, intraoperative, and postoperative variables were compared. To reduce overfitting, the multivariate logistic regression model was restricted to six clinically relevant variables associated with neurological complications at univariable analysis. Overall survival was evaluated using Kaplan–Meier analysis and compared with the log-rank test. Univariable Cox proportional hazards regression was performed to assess the association between neurological complications and long-term mortality. Neurological complications occurred in 65 of 641 recipients (10.1%). Transient neurological dysfunction was observed in 55 patients (8.6%), whereas permanent neurological impairment occurred in 24 recipients (3.7%). Some patients experienced both transient and persistent neurological manifestations; therefore, these categories were not mutually exclusive. Preoperative extracorporeal membrane oxygenation (ECMO) support (18.5% vs. 8.2%, $p = 0.006$), mechanical ventilation (16.9% vs. 8.7%, $p = 0.03$), previous cardiac surgery (44.6% vs. 26.6%, $p = 0.002$), and pretransplant acute kidney injury (21.5% vs. 8.5%, $p = 0.001$) were associated with a higher incidence of neurological complications. Recipients developing neurological events also exhibited higher rates of cytomegalovirus (CMV)-seropositive donors (36.2% vs. 16.6%, $p = 0.001$) and postoperative CMV infection (23.8% vs. 13.2%, $p = 0.03$). Neurological complications were associated with prolonged intensive care unit stay, increased postoperative organ dysfunction, greater transfusion requirements, and higher in-hospital mortality. At multivariate analysis, previous cardiac surgery (OR 1.81, 95% CI 1.00–3.24; $p = 0.047$), pretransplant acute kidney injury (OR 2.15, 95% CI 0.98–4.46; $p = 0.047$), donor traumatic brain injury (OR 2.34, 95% CI 1.16–4.53; $p = 0.014$), and donor CMV seropositivity (OR 2.52, 95% CI 1.36–4.56; $p = 0.003$) emerged as independent predictors of neurological complications. At a median follow-up period of 7 years (IQR, 1.2–12.7 years), recipients with neurological complications experienced significantly lower overall survival than those without neurological complications (log-rank $p <$

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0.001). Neurological complications were associated with a two-fold higher risk of long-term mortality (HR 2.06, 95% CI 1.33–3.18; $p = 0.001$). Neurological complications after heart transplantation remain a major source of postoperative morbidity and are associated with increased mortality, multiorgan dysfunction, and significantly reduced long-term survival. Previous cardiac surgery, pretransplant acute kidney injury, and CMV-seropositive donor status independently predicted neurological complications, supporting the contribution of surgical complexity, systemic vulnerability, and immunological factors to neurological risk.

Keywords: Heart transplantation; Neurological complications; Stroke; Postoperative complications; Acute kidney injury; Redo surgery; Outcomes

1. Introduction

Heart failure represents a major global health challenge, affecting more than 60 million people worldwide and accounting for substantial morbidity, mortality, and healthcare utilization.¹ Despite major improvements in pharmacological and device-based therapies, a proportion of patients progress to end-stage heart failure requiring advanced therapies. For carefully selected patients with refractory end-stage heart failure, heart transplantation remains the gold-standard treatment providing substantial improvements in survival, functional capacity, and quality of life.^{2–4} Despite more than 10,000 heart transplantations being performed worldwide annually, the persistent imbalance between organ supply and demand remains a major challenge.⁵ Over the last decades, advances in surgical techniques, donor management, organ preservation strategies, perioperative care, and immunosuppressive therapy have significantly improved outcomes after transplantation and expanded recipient eligibility criteria.⁶ Nevertheless, postoperative complications continue to exert a major influence on short- and long-term outcomes after heart transplantation. Among these, neurological complications remain a significant source of morbidity and are associated with prolonged hospitalization, increased healthcare costs, impaired functional recovery, and reduced survival.^{7,8} While disability-adjusted life years (DALYs) have not been specifically reported for neurological complications occurring after heart transplantation, the substantial global burden associated with both cardiovascular and neurological disorders underscore the importance of identifying factors associated with adverse neurological outcomes in this high-risk population.

Neurological complications after heart transplantation encompass a broad and heterogeneous spectrum of clinical entities, including ischemic stroke, intracranial hemorrhage, encephalopathy, seizures, peripheral

neurological injury, and transient neurological dysfunction. Reported incidence varies considerably across studies, ranging from approximately 5% to 20%, largely depending on differences in definitions, patient selection, and follow-up periods.^{8,9} Ischemic events represent the predominant cerebrovascular manifestation after heart transplantation and appear to occur more frequently than after conventional cardiac surgery.⁹ While some neurological events are transient and fully reversible, severe complications may result in permanent disability and have a substantial impact on quality of life and long-term outcomes. Previous studies have demonstrated that postoperative neurological events are associated with increased mortality and reduced mid-term survival after transplantation.^{7,10}

The pathophysiology of neurological injury after heart transplantation is multifactorial and differs substantially from that observed in the general stroke population.¹¹ Neurological complications may arise from perioperative cerebral hypoperfusion, thromboembolic phenomena, inflammatory activation, coagulation disturbances, and prolonged hemodynamic instability. Surgical and perioperative factors such as cardiopulmonary bypass, aortic manipulation, low-flow states, and mechanical circulatory support may further contribute to neurological vulnerability.^{8,9} Moreover, contemporary transplant recipients increasingly undergo transplantation under urgent conditions and while receiving advanced support strategies including extracorporeal membrane oxygenation (ECMO) and temporary mechanical circulatory support.

Recent large registry analyses suggest that the profile of heart transplant recipients has progressively evolved toward a more critically ill population. Increased utilization of temporary mechanical circulatory support and prioritization of patients with greater preoperative severity have been associated with a growing burden of neurological

complications and stroke after transplantation.¹² In a contemporary UNOS analysis, postoperative stroke was independently associated with markedly increased mortality after transplantation.⁶ Likewise, nationwide analyses demonstrated that heart transplant recipients experience a substantially greater risk of stroke and cardiovascular mortality than the general population.¹³

Despite increasing recognition of the clinical importance of neurological injury, available evidence remains heterogeneous and has largely focused on isolated cerebrovascular events, particularly stroke. Data addressing the broader spectrum of neurological dysfunction and identifying independent predictors in contemporary transplant populations remain limited. Therefore, the aim of the present study was to evaluate the incidence, predictors, in-hospital outcomes, and long-term survival associated with neurological complications in a contemporary single-center cohort of heart transplant recipients.

2. Methods

2.1. Study design and patient population

This retrospective observational study was based on a prospectively maintained institutional database including all consecutive adult patients who underwent orthotopic heart transplantation at the Niguarda Great Metropolitan Hospital, Milan, Italy. Consecutive adult recipients receiving heart transplant between December 2000 and February 2025 were included, resulting in a study population of 641 patients in more than 24 years of surgical activity (Figure 1).

The study was approved by the Institutional Ethics Board of Niguarda Hospital, Milan (approval number: 215-29042020; approved May 5, 2020). The approved protocol includes the prospective institutional heart transplantation database from which all study data were retrieved; therefore, no additional ethics amendment was required for patient accrual through February 2025. Due to the retrospective design and the use of anonymized clinical data, the requirement for individual informed consent was waived. Data collection and management were conducted according to institutional regulations and international ethical standards, with particular attention to privacy protection, confidentiality, and responsible use of clinical databases and biological materials. Long-term follow-up was conducted through routine outpatient visits at the institutional heart transplantation clinic. Clinical status and survival data were prospectively and regularly collected in the institutional heart transplantation database. When necessary, follow-up information was supplemented by telephone contact with patients or their relatives. This

study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The completed STROBE checklist is provided as Supplementary File.

Recipient baseline characteristics, operative variables, perioperative support strategies, postoperative outcomes and long-term follow-up data were extracted from the institutional database and cross-checked with electronic medical records when required.

2.2. Surgical management and perioperative care

Heart transplantation procedures were performed according to institutional practice and contemporary surgical standards. All transplant procedures were performed using a bicaval implantation technique under standard cardiopulmonary bypass support. Donor heart procurement and preservation followed institutional protocols and evolved throughout the study period according to contemporary practice.

For allograft preservation during transport, cardioplegic arrest was achieved using one of the following preservation solutions according to institutional preference and era-specific practice: St. Thomas cardioplegia, Custodiol (HTK), or Celsior solution.

The donor profile and procurement strategy evolved over the study period. Until 2023, all transplant procedures were performed using grafts procured from donation after brain death (DBD) donors. Beginning in December 2023, the institutional transplant program expanded to include selected donors after circulatory death.^{8,14–17}

For donation after circulatory death (DCD) procurement, normothermic regional perfusion (NRP) was routinely adopted, followed by *ex vivo* preservation using the Organ Care System (OCS) in cases involving geographical distance between donor and recipient hospitals.^{18–20} In selected cases where donor procurement and transplantation occurred within the same institution, a totally beating-heart strategy was adopted, allowing direct graft transfer without *ex vivo* transport support.²¹ To date, this approach has been performed in two cases in our institution, with very few similar cases reported worldwide.

Perioperative management evolved throughout the study period in parallel with changes in donor allocation strategies, advances in critical care, and increasing use of mechanical circulatory support. Mechanical circulatory support, including ECMO, ventricular assist devices, and temporary right ventricular support, was employed according to institutional protocols and individual clinical indications.

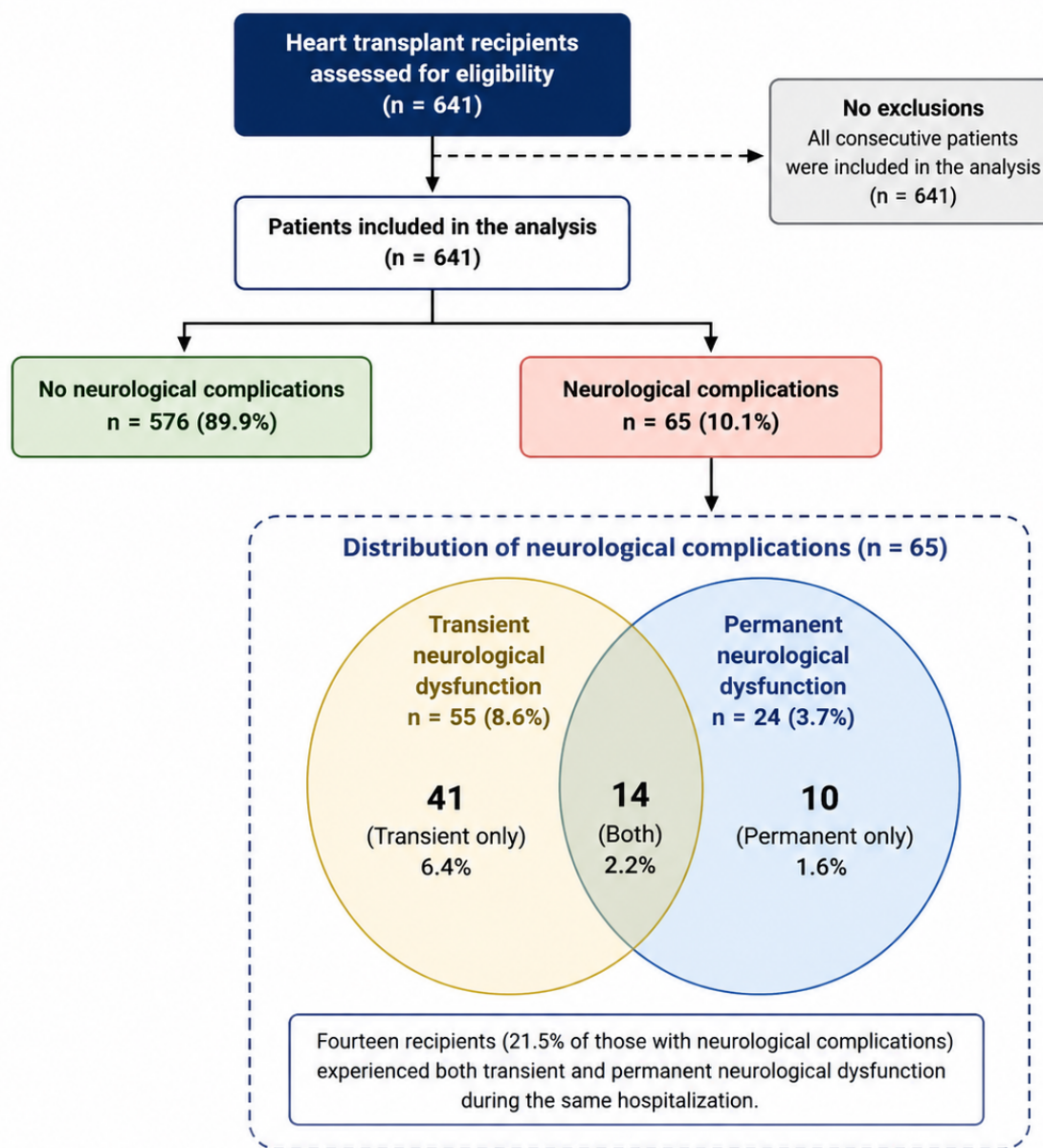


Figure 1. Study flowchart and overlap between transient and permanent neurological dysfunction. Percentages are reported relative to the total study population (n = 641).

2.3. Definition of neurological complications

The primary endpoint of the study was the occurrence of postoperative neurological complications during the index hospitalization. Secondary objectives included identifying predictors of neurological injury, assessing the associated in-hospital burden (including mortality, postoperative organ dysfunction, resource utilization, and intensive care requirements) and long-term overall survival associated with neurological complications.

Neurological complications were defined as any newly developed neurological deficit occurring after transplantation and documented during postoperative hospital stay, including stroke, transient ischemic attack, seizures, encephalopathy, delirium, peripheral neuropathy, hypoxic injury, and medication-related neurotoxicity. Events were identified through review of clinical documentation, neurological assessments, neuroimaging findings, and discharge records. Neurological consultation

was performed according to the patient's clinical course and in the presence of neurological symptoms, abnormal findings on imaging studies, or functional investigations considered clinically indicated. Diagnostic evaluation included computed tomography (CT) or magnetic resonance imaging (MRI) and additional functional examinations according to clinical judgment.

Neurological complications were further categorized into transient and permanent neurological dysfunction. Transient neurological dysfunction was defined as a neurological symptom or sign occurring after heart transplantation that completely resolved before hospital discharge without residual impairment. Permanent neurological dysfunction was defined as either persistent neurological impairment present at discharge or the presence of structural nervous system lesion documented by CT or MRI, including cerebral or spinal ischemic or hemorrhagic injury, irrespective of its clinical manifestations or functional consequences.

Because of the retrospective design and the long study period, transient neurological events were classified according to their clinical course and resolution rather than by predefined diagnostic categories. Conversely, permanent neurological dysfunction was characterized by review of the available clinical documentation and predominantly consisted of ischemic or hemorrhagic cerebrovascular events, including embolic ischemic stroke, hemorrhagic stroke, subarachnoid or subdural hemorrhage, spinal ischemic injury, hypoxic brain injury, and persistent peripheral neurological deficits. Because neurological complications were classified according to individual clinical events rather than mutually exclusive patient categories, some recipients experienced both transient neurological dysfunction and permanent neurological injury during the same hospitalization. Consequently, temporary and permanent neurological dysfunction were not mutually exclusive categories, as some recipients presented with both transient neurological manifestations and persistent neurological deficits during the same hospitalization.

This composite endpoint captures the overall burden of clinically relevant neurological complications after heart transplantation while acknowledging the heterogeneous mechanisms and prognostic implications of these events.

2.4. Other clinical definitions

Acute kidney injury was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria and was assessed according to its occurrence during the preoperative and postoperative course. Renal dysfunction requiring medical treatment or renal replacement

therapy was considered clinically relevant.^{22,23} Redo heart surgery was defined as any previous open cardiac surgical procedure performed before transplantation. Postoperative cytomegalovirus (CMV) infection was defined as clinically relevant CMV infection requiring antiviral treatment during the postoperative period according to institutional protocols and treating physician judgment. Donor and recipient CMV serostatus were assessed by routine CMV IgG serology before transplantation. CMV prevention followed the institutional protocol, consisting of antiviral prophylaxis for D+/R- recipients, prophylaxis for D-/R- recipients receiving at least two units of packed red blood cells, and a pre-emptive monitoring strategy for CMV-seropositive recipients (D+/R+ or D-/R+).

Postoperative gastrointestinal complications were defined as clinically relevant gastrointestinal events occurring during index hospitalization, including gastrointestinal bleeding, bowel ischemia, pancreatitis, ileus requiring treatment, hepatic dysfunction, or gastrointestinal perforation. Severe primary graft dysfunction was defined according to International Society for Heart and Lung Transplantation criteria as graft dysfunction occurring within 24 hours after transplantation requiring mechanical circulatory support in the absence of secondary identifiable causes.²⁴

2.5. Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation or median with interquartile range according to variable distribution. Categorical variables are presented as frequencies and percentages. Comparisons between patients with and without neurological complications were performed using Student's *t*-test or Mann-Whitney *U* test for continuous variables, as appropriate. Categorical variables were compared using Pearson chi-square or Fisher exact test. Given the exploratory nature of the univariable analyses and the number of comparisons performed, these analyses should be considered hypothesis-generating, and associations with borderline statistical significance should be interpreted with appropriate caution.

Variables associated with neurological complications in univariate analysis ($p < 0.10$) were considered candidate variables for multivariate analysis. Given the relatively limited number of neurological events, the final multivariable logistic regression model was intentionally restricted to six clinically relevant covariates to reduce the risk of overfitting while avoiding the simultaneous inclusion of variables describing overlapping aspects of pre-transplant clinical severity. Postoperative variables were not included in the predictive model because they occur after transplantation and may represent

intermediate events rather than true confounders. Because donor CMV data availability varied over the study period, an additional sensitivity analysis restricted to transplants performed from 2016 onward was performed to evaluate the robustness of the association between donor CMV serostatus and neurological complications. Results are presented as odds ratios (OR) with corresponding 95% confidence intervals (CI).

Potential multicollinearity was assessed before model construction using variance inflation factors (VIFs). Model discrimination was evaluated using the C-statistic (area under the receiver operating characteristic curve). Internal validation was performed using 1000 bootstrap resamples with optimism correction, and calibration was assessed using the optimism-corrected calibration slope. Missing values were handled according to complete-case analysis. Missing data affected primarily donor CMV IgG serostatus (40 patients, 6.2%) and, to a lesser extent, donor traumatic brain injury (11 patients, 1.7%). The final multivariate model therefore included 599 complete cases. Long-term overall survival was estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Univariate Cox proportional hazards regression was performed to estimate the association between neurological complications and long-term mortality. Hazard ratios (HRs) are reported with corresponding 95% confidence intervals (CIs). The proportional hazards assumption was assessed using Schoenfeld residuals. Statistical significance was defined as a two-sided p -value <0.05 . Descriptive statistics and univariable comparisons were performed using PSPP version 2.0.0 (GNU Project). Multivariate logistic regression, internal validation by bootstrap resampling, long-term survival analyses (Kaplan–Meier and Cox proportional hazards regression), and assessment of the proportional hazards' assumption were performed using R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria) with the rms, survival, and survminer packages.

Several measures were adopted to minimize potential sources of bias. Selection bias was reduced by including all consecutive eligible heart transplant recipients during the study period. Information bias was minimized through the use of a prospectively maintained institutional database. Standardized clinical definitions were applied for all study variables and outcomes, while multivariate adjustment, sensitivity analyses, and bootstrap internal validation were performed to reduce confounding and assess the robustness of the findings.

3. Results

A total of 641 consecutive patients underwent heart

transplantation during the study period and were included in the analysis. Neurological complications occurred in 65 recipients, corresponding to an overall incidence of 10.1% (95% CI, 8.0%–12.7%).

Among patients developing neurological complications, transient neurological dysfunction represented the most frequent presentation and occurred in 55 patients (8.6%), whereas 24 recipients (3.7% of the overall cohort) were discharged with permanent neurological impairment (Figure 1). Because some patients experienced both transient and persistent neurological manifestations during their postoperative course, these categories were not mutually exclusive. Therefore, although neurological events occurred in approximately one out of ten recipients, persistent neurological deficits at discharge remained comparatively less frequent.

Recipients' baseline characteristics are summarized in Table 1. Comparison of preoperative characteristics revealed that patients developing neurological complications exhibited a higher burden of preoperative risk factors and clinical severity. National emergency status tended to be more frequent among patients with neurological events (30.8% vs. 21.2%, $p = 0.08$). Similarly, preoperative mechanical circulatory support showed a trend toward higher prevalence in this group (41.5% vs. 30.0%, $p = 0.06$). Markers of critical preoperative condition were significantly associated with neurological complications at univariable analysis. Preoperative ECMO support was more frequently observed among patients developing neurological injury (18.5% vs. 8.2%, $p = 0.006$), as was preoperative mechanical ventilation (16.9% vs. 8.7%, $p = 0.03$). Recipients with a history of previous cardiac surgery exhibited a significantly higher rate of postoperative neurological complications compared with recipients undergoing transplantation without prior cardiac surgery (44.6% vs. 26.6%, $p = 0.002$). Patients with neurological complications also showed a significantly higher prevalence of preoperative acute kidney injury (21.5% vs. 8.5%, $p = 0.001$), while chronic kidney disease demonstrated only a trend toward significance (35.4% vs. 25.3%, $p = 0.08$). No significant differences were observed regarding age, sex distribution, pulmonary vascular resistance, baseline renal function, anticoagulation therapy, or preoperative bilirubin levels.

Donor characteristics are summarized in Table 2. Recipients developing neurological complications more frequently received grafts from male donors (78.5% vs. 64.9%, $p = 0.029$) and from donors who died following traumatic brain injury (24.6% vs. 13.0%, $p = 0.014$). In addition, recipients developing neurological complications were significantly more likely to receive grafts from CMV-

Table 1. Preoperative recipients' characteristics

	Total (<i>n</i> = 641)	Neurological complications (<i>n</i> = 65)	No neurological complications (<i>n</i> = 576)	<i>p</i>
Female, <i>n</i> (%)	198 (30.9)	18 (27.6)	180 (31.2)	0.67
National emergency status, <i>n</i> (%)	142 (22.2)	20 (30.8)	122 (21.2)	0.08
Preoperative any mechanical circulatory support, <i>n</i> (%)	200 (31.2)	27 (41.5)	173 (30.0)	0.06
Impella, <i>n</i> (%)	9 (1.4)	1 (1.5)	8 (1.4)	>0.99
VAD, <i>n</i> (%)	94 (14.7)	10 (15.4)	84 (14.6)	0.85
IABP, <i>n</i> (%)	92 (14.4)	12 (18.5)	80 (13.9)	0.35
ECMO, <i>n</i> (%)	59 (9.2)	12 (18.5)	47 (8.2)	0.006
Preoperative mechanical ventilation, <i>n</i> (%)	61 (9.5)	11 (16.9)	50 (8.7)	0.03
Redo heart surgery, <i>n</i> (%)	182 (28.4)	29 (44.6)	153 (26.6)	0.002
Antiplatelet therapy, <i>n</i> (%)	94 (14.7)	10 (15.4)	84 (14.6)	0.85
Oral anticoagulant therapy, <i>n</i> (%)	328 (51.2)	33 (50.8)	295 (51.2)	>0.99
IV heparin therapy, <i>n</i> (%)	122 (19.0)	18 (27.7)	104 (18.1)	0.06
Diabetes, <i>n</i> (%)	66 (10.3)	7 (10.8)	59 (10.2)	0.83
Chronic kidney disease, <i>n</i> (%)	169 (26.4)	23 (35.4)	146 (25.3)	0.08
Acute kidney injury, <i>n</i> (%)	63 (9.8)	14 (21.5)	49 (8.5)	0.001
Dialysis, <i>n</i> (%)	5 (0.8)	1 (1.5)	4 (0.7)	0.42
High pulmonary vascular resistance, <i>n</i> (%)	125 (19.5)	12 (18.5)	113 (19.6)	0.82
CMV IgG-seropositive, <i>n</i> (%)	490 (77.4)	54 (83.1)	436 (76.8)	0.27
D+/R- CMV mismatch, <i>n</i> (%)	23 (3.7)	2 (3.2)	21 (3.7)	>0.99
Age (years), mean ± SD	48.97 ± 11.89	49.11 ± 13.94	48.95 ± 11.65	0.92
PVR, mean ± SD	2.09 ± 1.59	2.11 ± 1.67	2.09 ± 1.58	0.91
Preoperative creatinine, mean ± SD	1.24 ± 0.78	1.44 ± 1.33	1.22 ± 0.69	0.20
Preoperative bilirubin, median (IQR)	0.8 (0.5–1.3)	0.9 (0.5–1.5)	0.8 (0.5–1.3)	0.20
BSA, mean ± SD	1.78 ± 0.2	1.79 ± 0.23	1.77 ± 0.19	0.59

Notes: Percentages were calculated excluding missing values for each variable.

Abbreviations: BSA: Body surface area; D: Donor; ECMO: Extracorporeal membrane oxygenation; IABP: Intra-aortic balloon pump; IV: Intravenous; PVR: Pulmonary vascular resistance; R: Recipient; VAD: Ventricular assist device.

positive donors (36.2% vs. 16.6%, $p = 0.001$). In contrast, recipient CMV serostatus (83.1% vs. 76.8%, $p = 0.277$) and the prevalence of donor-positive/recipient-negative (D+/R-) CMV mismatch (3.2% vs. 3.7%, $p = 1.000$) were similar between patients with and without neurological complications. No significant differences were observed regarding donor age, serum sodium, serum potassium, predicted heart mass ratio, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), or donor toxoplasma serostatus.

Intraoperative and postoperative characteristics are

summarized in Table 3. Intraoperative variables, including cardiopulmonary bypass time, CPB assistance time, and allograft ischemia time, were comparable between the two groups, suggesting that intraoperative duration factors alone did not significantly influence the occurrence of neurological complications.

In contrast, postoperative outcomes differed markedly. Postoperative neurological complications were associated with a substantially more complex postoperative course and a greater burden of systemic complications. Postoperative ECMO requirement was significantly more

Table 2. Donor characteristics

	Total (<i>n</i> = 641)	Neurological complications (<i>n</i> = 65)	No neurological complications (<i>n</i> = 576)	<i>p</i>
Male, <i>n</i> (%)	425 (66.3)	51 (78.5)	374 (64.9)	0.029
Age (years)	42.32 ± 13.7	41.91 ± 14.26	42.36 ± 13.65	0.51
Cause of death, <i>n</i> (%)				
Traumatic brain injury	91 (14.4)	16 (24.6)	75 (13.0)	0.014
Subarachnoid hemorrhage	262 (40.9)	20 (30.8)	242 (42.0)	0.06
Polytrauma	140 (21.8)	13 (20.0)	127 (22.0)	0.86
Other causes	148 (23.1)	18 (27.7)	130 (22.6)	0.3
Hypertension, <i>n</i> (%)	138 (21.5)	17 (26.2)	121 (21.0)	0.29
Type 2 diabetes, <i>n</i> (%)	9 (1.4)	1 (1.5)	8 (1.4)	0.91
COPD, <i>n</i> (%)	7 (1.1)	2 (3.1)	5 (0.8)	0.12
Serum sodium (mmol/L), mean ± SD	148.44 ± 9.36	148.17 ± 8.01	148.47 ± 9.51	0.84
Serum potassium (mmol/L), mean ± SD	3.90 ± 0.64	3.97 ± 0.61	3.90 ± 0.65	0.12
Predicted heart mass ratio, mean ± SD	1.10 ± 0.18	1.13 ± 0.17	1.09 ± 0.18	0.10
CMV IgG-positive, <i>n</i> (%)	111 (18.5)	21 (36.2)	90 (16.6)	0.001
Toxoplasma-positive, <i>n</i> (%)	49 (7.6)	6 (9.2)	43 (7.5)	0.54
HCV-positive, <i>n</i> (%)	12 (1.9)	3 (4.6)	9 (1.6)	0.07

Notes: Percentages were calculated excluding missing values for each variable.

Abbreviation: CMV: Cytomegalovirus; COPD: Chronic obstructive pulmonary disease; HCV: Hepatitis C virus.

frequent in patients experiencing neurological events (16.9% vs. 6.1%, $p = 0.001$), as was the need for temporary right ventricular mechanical circulatory support (6.2% vs. 1.7%, $p = 0.02$). Severe primary graft dysfunction was also more commonly observed in patients developing neurological complications (15.4% vs. 6.8%, $p = 0.013$). Acute kidney injury represented one of the strongest postoperative associations and occurred in 89.2% of patients with neurological complications compared with 58.5% in patients without neurological events ($p < 0.0001$). Likewise, gastrointestinal complications were more frequent among patients with neurological injury (63.1% vs. 48.9%, $p = 0.02$), and postoperative pneumonia occurred more than twice as often in this population (36.9% vs. 17.0%, $p < 0.0001$). In addition, postoperative CMV infection occurred more frequently among patients with neurological injury (23.8% vs. 13.2%, $p = 0.03$).

Neurological complications were also associated with increased postoperative resource utilization. Patients with neurological injury required longer intensive care unit (ICU) stay (median 17 [IQR 9–30] vs. 7 [IQR 5–10] days, $p < 0.001$). Because length of ICU stay may be influenced by in-hospital mortality, we performed a sensitivity analysis restricted to hospital survivors. This analysis confirmed a significantly longer ICU stay among recipients with

neurological complications (median 15 [IQR 8.8–26.5] vs. 7 [IQR 5–9] days, $p < 0.001$). Moreover, patients with neurological injury received significantly greater transfusion support, including red blood cell units (median 5 [IQR 2–15] vs. 2 [IQR 1–5] units, $p < 0.001$), fresh frozen (median 2 [IQR 0–6] vs. 0 [IQR 0–2] units, $p = 0.005$), and platelet transfusions (median 0 [IQR 0–2] vs. 0 [IQR 0–0] units, $p = 0.003$).

Finally, neurological complications were associated with significantly increased in-hospital mortality, occurring in 26.2% of patients with neurological events compared with 13.5% among patients without neurological complications ($p = 0.007$).

A multivariate logistic regression analysis was performed to identify factors independently associated with neurological complications after heart transplantation. The final model was based on 599 complete cases (42 patients excluded because of missing donor data), including 58 neurological events, corresponding to an events-per-variable ratio of 9.7:1. Missing donor data primarily involved donor CMV IgG serostatus (40 patients) and, less frequently, donor traumatic brain injury status (11 patients). To reduce the risk of overfitting, the final model was intentionally restricted to six clinically relevant

covariates. Model discrimination was acceptable, with an apparent C-statistic of 0.699 (Brier score 0.082). Internal validation using 1000 bootstrap resamples demonstrated an optimism-corrected C-statistic of 0.671 and an optimism-corrected calibration slope of 0.863, indicating only modest optimism. Multicollinearity diagnostics demonstrated no evidence of relevant collinearity among the included covariates (all variance inflation factors <1.1).

After multivariate adjustment, a history of previous cardiac surgery (OR 1.81, 95% CI 1.00–3.24; $p = 0.047$), pretransplant acute kidney injury (OR 2.15, 95% CI 0.98–4.46; $p = 0.047$), donor traumatic brain injury (OR 2.34, 95% CI 1.16–4.53; $p = 0.014$), and donor CMV seropositivity (OR 2.52, 95% CI 1.36–4.56; $p = 0.003$) remained independently associated with neurological complications. Neither preoperative ECMO support nor donor sex retained statistical significance after

multivariate adjustment (Table 4). Because exploratory analyses demonstrated substantial temporal variation in the availability of donor CMV serostatus over the study period, an additional sensitivity analysis was performed including only transplants performed from 2016 onward. In this contemporary cohort, donor CMV seropositivity remained independently associated with neurological complications (OR 5.28, 95% CI 2.08–15.40), consistent with the findings observed in the overall cohort.

Overall, these findings support the multifactorial nature of neurological complications after heart transplantation, involving interactions between preoperative clinical severity, surgical complexity, and immunological factors.

Long-term survival analysis was performed in 627 recipients with available follow-up data. Median follow-up was 7.0 years (interquartile range [IQR], 1.2–12.7 years), with a follow-up completeness of 97.8%.

Table 3. Intraoperative and postoperative characteristics

	Total ($n = 641$)	Neurological complications ($n = 65$)	No neurological complications ($n = 576$)	p
CPB time (minutes), mean $\pm$ SD	215.43 $\pm$ 76.59	221.56 $\pm$ 65.57	214.72 $\pm$ 77.78	0.50
CPB assistance time (minutes), mean $\pm$ SD	81.03 $\pm$ 44.35	79.92 $\pm$ 27.44	81.15 $\pm$ 45.80	0.85
Allograft ischemia time (minutes), mean $\pm$ SD	182.78 $\pm$ 51.91	179.03 $\pm$ 46.93	183.21 $\pm$ 52.48	0.54
IABP, n (%)	133 (20.7)	14 (21.5)	119 (20.6)	0.93
ECMO, n (%)	46 (7.2)	11 (16.9)	35 (6.1)	0.001
Right mechanical support, n (%)	14 (2.2)	4 (6.2)	10 (1.7)	0.02
AKI, n (%)	395 (61.6)	58 (89.2)	337 (58.5)	<0.001
Gastrointestinal complications, n (%)	323 (50.4)	41 (63.1)	282 (48.9)	0.02
Pneumonia, n (%)	122 (19.1)	24 (36.9)	98 (17.0)	<0.001
In hospital mortality, n (%)	95 (14.8)	17 (26.2)	78 (13.5)	0.007
Severe primary graft dysfunction, n (%)	49 (7.6)	10 (15.4)	39 (6.8)	0.013
CMV infection, n (%)	87 (14.3)	15 (23.8)	72 (13.2)	0.03
ICU stay (days), median (IQR)	7 (5–12)	17 (9–30)	7 (5–10)	<0.001
Number of RBC transfusion, median (IQR)	2 (1–6)	5 (2–15)	2 (1–5)	<0.001
Number of fresh plasma units transfusion, median (IQR)	0 (0–2)	2 (0–6)	0 (0–2)	0.005
Number of platelet units transfusion, median (IQR)	0 (0–0)	0 (0–2)	0 (0–0)	0.03
Time in ECMO (days), mean $\pm$ SD	0.6 $\pm$ 3.4	2.3 $\pm$ 8.8	0.4 $\pm$ 1.9	0.08

Notes: Percentages were calculated excluding missing values for each variable; Bold p -values indicate statistically significant differences between the tested groups ($p < 0.05$).

Abbreviations: AKI: Acute kidney injury; CMV: Cytomegalovirus; CPB: Cardiopulmonary bypass; ECMO: Extracorporeal membrane oxygenation; IABP: Intra-aortic balloon pump; ICU: Intensive care unit; RBC: Red blood cells.

Kaplan–Meier analysis demonstrated significantly reduced overall survival among recipients who developed neurological complications compared with those without neurological complications (log-rank $p = 0.00094$; Figure 2). In univariable Cox proportional hazards regression, neurological complications were associated with a more than two-fold increased risk of long-term mortality (hazard ratio [HR] 2.06, 95% confidence interval [CI] 1.33–3.18; $p = 0.001$). The proportional hazards assumption was verified using Schoenfeld residuals and was not violated (global $p = 0.64$).

4. Discussion

Neurological complications remain a clinically relevant source of morbidity after heart transplantation despite substantial improvements in surgical techniques, perioperative care, immunosuppressive strategies, and recipient selection. Previous studies have consistently shown that neurological injury after transplantation adversely affects postoperative recovery and survival.^{7,10} Although graft failure and infectious complications remain the leading causes of mortality after transplantation, neurological events continue to represent a major determinant of postoperative disability and healthcare burden.^{8,9,25}

The present study provides several important findings. First, neurological complications occurred in 10.1% of recipients, confirming that neurological injury remains relatively common in contemporary transplant practice. Importantly, only 3.7% of recipients ultimately experienced permanent neurological dysfunction, indicating that a considerable proportion of neurological events were transient and resolved during the postoperative course. Second, recipients who developed neurological complications exhibited a greater degree of preoperative clinical complexity characterized by higher rates of preoperative ECMO support, mechanical

ventilation, acute kidney injury, and previous cardiac surgery. Third, neurological events were associated with a substantially more complicated postoperative course, including prolonged intensive care stay, greater transfusion requirements, higher in-hospital mortality, and an increased burden of multiorgan dysfunction. Fourth, long-term survival analysis demonstrated significantly reduced overall survival among recipients who developed neurological complications, with a more than two-fold increased risk of long-term mortality. Fifth, CMV-related variables demonstrated a potentially relevant association with neurological injury. Patients developing neurological complications exhibited higher rates of postoperative CMV infection and were more likely to receive grafts from CMV-seropositive donors. Finally, previous cardiac surgery, preoperative acute kidney injury, donor traumatic brain injury and transplantation from CMV-seropositive donors remained independently associated with neurological complications after heart transplantation.

The overall incidence observed in our cohort is consistent with previous reports. Acampa and colleagues described cerebrovascular complication rates approaching 13%, while broader neurological complication rates ranging from approximately 5%–20% have been reported depending on study design, follow-up duration, and event definition.^{8,9,26} However, the observed incidence should be interpreted as the incidence of clinically documented neurological complications rather than the true incidence of postoperative neurological dysfunction. Neurological events were identified through retrospective review of routine clinical documentation rather than systematic neurological screening, and standardized assessments for postoperative delirium were not routinely performed. Consequently, the true incidence of postoperative neurological dysfunction, particularly transient manifestations such as delirium, was likely underestimated. Importantly, despite neurological complications occurring

Table 4. Univariate and multivariate logistic regression analysis of factors associated with neurological complications after heart transplantation

Variable	Univariable OR (95% CI)	<i>p</i>	Multivariable OR (95% CI)	<i>p</i>
Preoperative ECMO	2.13 (0.93–4.45)	0.057	1.42 (0.58–3.19)	0.415
Previous cardiac surgery	1.83 (1.03–3.18)	0.035	1.81 (1.00–3.24)	0.047
Preoperative AKI	2.88 (1.37–5.68)	0.003	2.15 (0.98–4.46)	0.047
Male donor	2.13 (1.13–4.29)	0.025	1.71 (0.89–3.52)	0.122
Donor traumatic brain injury	2.39 (1.23–4.44)	0.008	2.34 (1.16–4.53)	0.014
Donor CMV seropositivity	2.84 (1.57–5.05)	<0.001	2.52 (1.36–4.56)	0.003

Abbreviations: AKI: Acute kidney injury; CI: Confidence interval; CMV: Cytomegalovirus; ECMO: Extracorporeal membrane oxygenation; OR: Odds ratio.

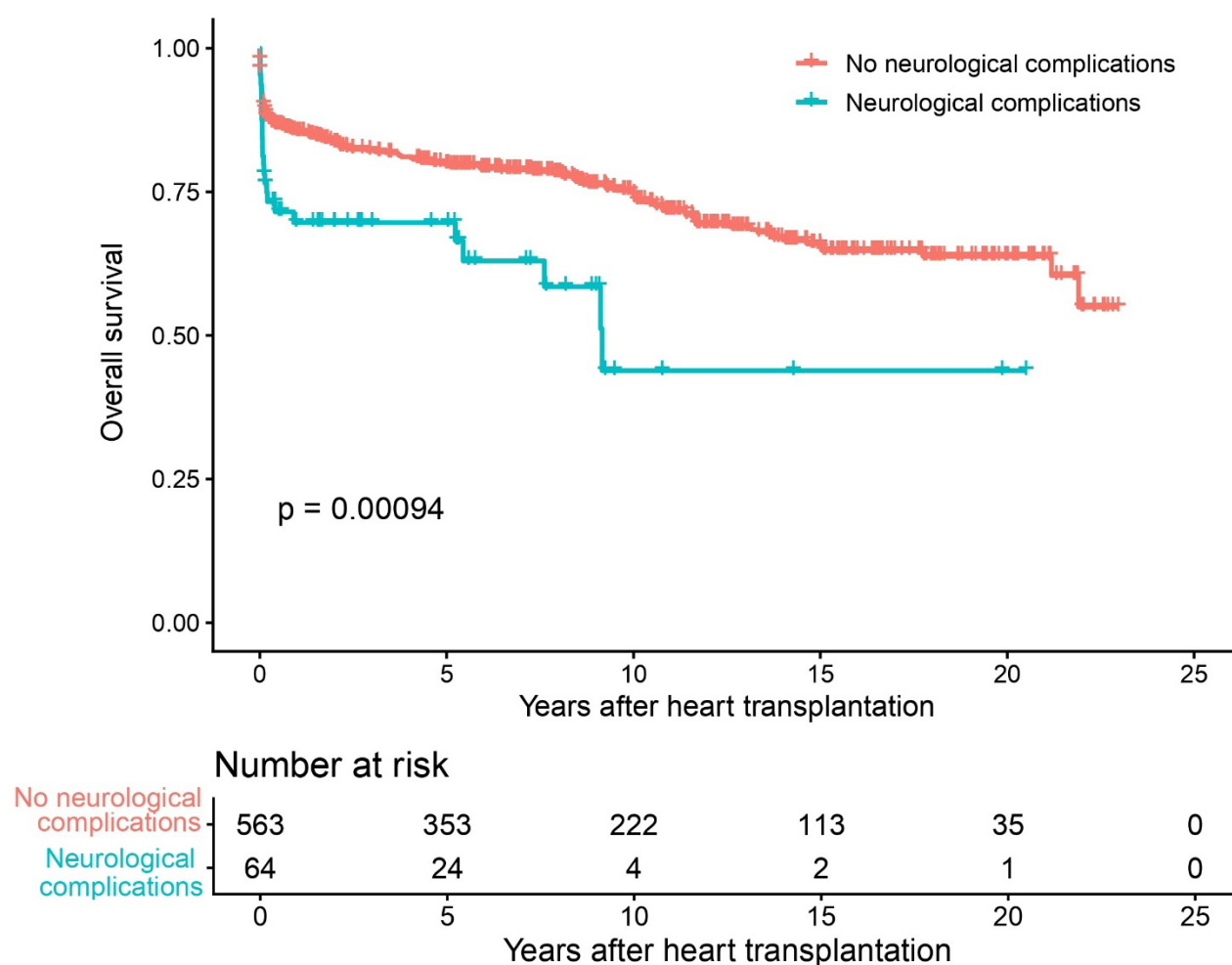


Figure 2. Kaplan–Meier estimates of long-term overall survival according to the occurrence of neurological complications after heart transplantation. Numbers at risk are reported below the graph.

in approximately one out of ten recipients, only 3.7% of patients were discharged with persistent neurological deficits. This relatively low rate of persistent disability suggests that a substantial proportion of neurological events after heart transplantation may be transient and reversible, in agreement with previous reports.^{10,26–29}

The pathophysiology of neurological injury after heart transplantation is likely multifactorial and differs from mechanisms traditionally observed in the general stroke population. Cerebral hypoperfusion, thromboembolic events, inflammatory activation, coagulation abnormalities, and perioperative hemodynamic instability have all been implicated in the development of neurological complications after transplantation.^{8,9,30} Moreover, transplantation-related neurological injury may arise through unique mechanisms including mechanical

circulatory support, prolonged low-output states, ischemia–reperfusion injury, and systemic inflammatory responses associated with major surgery.^{6,9}

One of the most relevant findings of the present study is the association between previous cardiac surgery and neurological complications. Recipients with a history of prior cardiac surgery experienced significantly higher rates of neurological injury, and previous cardiac surgery remained an independent predictor after multivariable adjustment. Prior cardiac surgery likely represents a marker of increased surgical complexity rather than merely a baseline patient characteristic. Reoperative procedures are frequently characterized by technically demanding dissections, dense mediastinal adhesions, prolonged surgical manipulation, and increased bleeding risk. These factors may contribute to embolic phenomena and

perioperative hemodynamic instability, both recognized mechanisms of cerebral injury. In heart transplantation, the impact of operative complexity may be particularly relevant. Contemporary recipients increasingly undergo transplantation after previous cardiac procedures, ventricular assist device implantation, or advanced heart failure requiring urgent support strategies. Therefore, previous surgery may amplify cerebral vulnerability during periods of perioperative instability or hypotension. Similar observations have been reported in previous studies where operative complexity and critical preoperative status emerged as important determinants of adverse outcomes.^{6,31} Importantly, the profile of heart transplant recipients has evolved substantially over the last decade. Changes in allocation policies and increasing use of temporary mechanical circulatory support have progressively shifted transplantation toward a more critically ill population.^{6,29,32–36} Registry analyses demonstrated increasing use of temporary support strategies and greater recipient complexity over time.³⁵ Consequently, identifying markers of neurological vulnerability may become increasingly relevant in current transplant practice.

Another important finding of the present study is the independent association between preoperative acute kidney injury and neurological complications. Renal dysfunction has increasingly been recognized not merely as isolated organ injury but as a marker of impaired physiological reserve and systemic vulnerability. Previous studies have consistently demonstrated that renal dysfunction is associated with increased postoperative morbidity and mortality following both cardiac surgery and heart transplantation, highlighting its role as an important determinant of adverse perioperative outcomes.^{37–39} The biological mechanisms linking renal dysfunction and neurological injury are likely multifactorial and involve a complex interplay between inflammatory, vascular, metabolic, and hemodynamic pathways. Experimental and clinical evidence increasingly supports the concept of a kidney-brain axis, whereby acute renal injury triggers systemic responses extending well beyond the kidney itself. Renal ischemia promotes the release of pro-inflammatory cytokines, including interleukin-1 beta, interleukin-6, and tumor necrosis factor alpha (TNF α), together with oxidative stress mediators that induce endothelial activation and widespread microvascular dysfunction.^{39–41} These systemic inflammatory processes have been shown to alter cerebral autoregulation, impair neurovascular coupling, increase blood–brain barrier permeability, and enhance the susceptibility of neural tissue to ischemic and hypoxic insults.^{39–42}

In parallel, acute kidney injury (AKI) is associated with disruption of blood–brain barrier integrity through endothelial injury, loss of tight junction proteins, activation of astrocytes and microglia, and increased vascular permeability. These alterations facilitate neuroinflammation, cerebral edema, and neuronal dysfunction, providing a plausible mechanistic explanation for the increased incidence of neurological complications observed in critically ill patients with renal impairment.^{39–42} Furthermore, renal dysfunction is frequently accompanied by metabolic derangements, accumulation of uremic toxins, electrolyte abnormalities, and acid-base disturbances, all of which may directly impair neuronal function and lower the threshold for encephalopathy, seizures, and other neurological manifestations.^{40,41}

Beyond inflammatory and metabolic mechanisms, renal dysfunction is also characterized by diffuse endothelial injury and microvascular disease. The kidney and the brain are highly vascularized organs with similar microvascular architecture and autoregulatory capacity, allowing them to preserve stable tissue perfusion despite fluctuations in systemic blood pressure. These same characteristics, however, also render both organs particularly vulnerable to endothelial dysfunction, microvascular injury, and hemodynamic perturbations, thereby increasing their susceptibility to ischemic damage. Consequently, pathological processes affecting the renal microcirculation often reflect generalized vascular injury and may similarly compromise cerebral perfusion. Impaired endothelial function, reduced nitric oxide bioavailability, increased vascular stiffness, and microangiopathy may collectively predispose these patients to cerebral hypoperfusion, impaired cerebrovascular autoregulation, and ischemic neurological injury.^{39,41,42}

The perioperative environment of heart transplantation may further amplify this pre-existing vulnerability. Cardiopulmonary bypass, ischemia-reperfusion injury, rapid hemodynamic fluctuations, vasopressor exposure, systemic inflammatory activation, and coagulation disturbances represent additional cerebral stressors capable of overwhelming already compromised autoregulatory and microvascular mechanisms. Moreover, the transplanted heart is initially completely denervated, with loss of both sympathetic and parasympathetic afferent and efferent pathways that normally contribute to cardiovascular homeostasis and cardiovascular reflex regulation. This unique physiological condition may further reduce the ability to compensate for acute hemodynamic changes occurring during the early postoperative period, potentially increasing cerebral vulnerability to perioperative injury.⁴³

Taken together, these observations suggest that

pretransplant AKI should not be interpreted solely as a marker of impaired renal function but rather as a surrogate of systemic endothelial dysfunction, chronic inflammation, microvascular disease, and reduced physiological reserve. The persistence of this association after multivariate adjustment in our cohort supports the concept that renal dysfunction identifies heart transplant recipients with increased neurological vulnerability, emphasizing the importance of meticulous perioperative hemodynamic optimization, preservation of renal function, and close neurological surveillance in this high-risk population.

Another important contributor to neurological complications after heart transplantation is immunosuppressive therapy, particularly calcineurin inhibitors (CNIs) such as tacrolimus and cyclosporine.^{44,45} Neurological adverse effects associated with CNIs are well recognized in solid organ transplantation and range from mild manifestations, including tremor, headache, insomnia, and paresthesia, to more severe complications such as seizures, encephalopathy, focal neurological deficits, cortical blindness, and posterior reversible encephalopathy syndrome (PRES).^{46,47} Notably, neurotoxicity may occur even in the presence of therapeutic drug levels and often presents during the early postoperative period, when transplant recipients are simultaneously exposed to multiple metabolic, hemodynamic, and pharmacological stressors. The mechanisms underlying CNI-related neurotoxicity are likely multifactorial and include endothelial dysfunction, blood–brain barrier disruption, cerebral vasoconstriction, and impaired cerebral autoregulation. Although medication-related neurotoxicity was not systematically assessed in the present retrospective study, it should be considered among the potential mechanisms contributing to postoperative neurological dysfunction after heart transplantation.

An additional finding of our study is the independent association between donor traumatic brain injury and neurological complications after heart transplantation. To our knowledge, previous studies investigating donor traumatic brain injury have primarily focused on graft function, rejection, cardiac allograft vasculopathy, and recipient survival, whereas its potential association with postoperative neurological complications has not been specifically evaluated.^{48–51} Experimental and clinical evidence indicates that traumatic brain injury triggers a complex systemic inflammatory and neurohumoral response characterized by massive catecholamine release, cytokine activation, endothelial dysfunction, coagulation abnormalities, and complement activation.^{48,51} These processes may promote myocardial injury, microvascular dysfunction, and oxidative stress, potentially impairing

donor organ quality before procurement and increasing susceptibility to ischemia–reperfusion injury after transplantation.^{48,52,53} Collectively, these mechanisms may contribute to an increased susceptibility to postoperative neurological injury during the early postoperative period, particularly in recipients exposed to additional perioperative insults. While this association should be interpreted cautiously and requires confirmation in external cohorts, our findings suggest that donor traumatic brain injury may represent an underrecognized donor-related risk factor deserving further investigation.

An additional noteworthy finding of the present study concerns CMV-related variables. Recipients receiving grafts from CMV-positive donors demonstrated significantly higher rates of neurological complications, and donor CMV seropositivity remained independently associated with neurological injury after multivariable adjustment. Conversely, although postoperative CMV infection was more frequent among recipients developing neurological complications, this association did not retain independent significance after adjustment. Importantly, the association between donor CMV IgG seropositivity and neurological complications remained significant in an additional sensitivity analysis restricted to the contemporary transplantation era (2016–2025), supporting the robustness of this finding despite temporal variation in recorded donor CMV serostatus over the study period. The mechanisms underlying this observation are likely multifactorial. CMV has increasingly been implicated in endothelial dysfunction, inflammatory activation, immune dysregulation, and prothrombotic pathways potentially contributing to cerebrovascular injury.²⁶ CMV-seropositive donor status may also reflect greater immunological burden and increased exposure to intensified immunosuppressive strategies. Furthermore, neurological vulnerability after transplantation may not only result from surgical and hemodynamic factors but also from treatment-related mechanisms.^{47,54,55} As discussed above, calcineurin inhibitors, particularly tacrolimus, have been associated with neurotoxicity and reversible neurological syndromes including posterior reversible encephalopathy syndrome.⁵⁶ These observations support the concept that neurological complications after heart transplantation likely result from complex interactions involving inflammation, vascular dysfunction, immunological activation, and perioperative injury. Interestingly, conventional procedural factors commonly associated with neurological injury in cardiac surgery, including cardiopulmonary bypass duration, post-cardiotomy support time, and allograft ischemic time, were not significantly associated with neurological complications in our cohort. Similarly, donor age, serum electrolytes, and donor-recipient size matching assessed

by predicted heart mass ratio were comparable between groups. These findings suggest that neurological injury after heart transplantation may be influenced less by isolated technical factors and more by recipient-related vulnerability and the complex physiological disturbances occurring before and after transplantation.

Markers of severe preoperative clinical condition, including ECMO support and mechanical ventilation, were significantly associated with neurological complications at univariate analysis. However, ECMO support did not remain independently associated with neurological complications after multivariable adjustment, suggesting that its effect is largely explained by the overall severity of the recipient's pretransplant clinical condition rather than by extracorporeal support itself. Recipients requiring ECMO support are exposed to systemic inflammation, coagulation abnormalities, altered cerebral perfusion, and thromboembolic burden.⁵⁷⁻⁵⁹ Previous studies similarly reported increased neurological risk among transplant recipients requiring extracorporeal support or temporary mechanical circulatory assistance.^{6,60}

Importantly, neurological complications did not appear as isolated postoperative events but rather as part of a broader syndrome of systemic deterioration. Patients developing neurological injury experienced prolonged intensive care stay, greater transfusion requirements, increased postoperative organ dysfunction, and higher mortality. More recent nationwide analyses further confirmed increased risk of stroke and cardiovascular mortality among heart transplant recipients.¹³ Neurological complications may therefore represent both a direct contributor to adverse outcomes and a marker of greater overall illness severity, although a direct causal relationship cannot be established from this observational study. Our long-term survival analysis further demonstrated that this adverse impact extends well beyond the index hospitalization, with recipients experiencing neurological complications showing significantly reduced overall survival and a more than two-fold increased risk of long-term mortality. Similar findings have been reported by Oehler and colleagues⁷, who demonstrated significantly worse postoperative outcomes and reduced survival among recipients experiencing neurological events. Van de Beek *et al.*¹⁰ identified perioperative cerebrovascular complications as the neurological event with the greatest impact on survival, and Alnsasra *et al.*²⁶ reported an independent association between stroke and long-term mortality after heart transplantation. Our findings confirm and extend these observations by demonstrating that postoperative neurological complications, considered as a whole rather than stroke alone, are associated with significantly reduced

long-term survival in a contemporary single-center cohort with a median follow-up of 7.0 years. Furthermore, unlike previous studies that primarily focused on neurological outcomes or survival separately, our study integrates the assessment of incidence, independent perioperative predictors, early postoperative burden, and long-term prognosis within the same heart transplant population. Collectively, these findings support the concept that neurological complications are not only markers of early postoperative severity but also indicators of sustained adverse prognosis after heart transplantation.

The clinical implications of these findings may be relevant. Identification of recipients at increased neurological risk before transplantation may allow implementation of individualized perioperative strategies. Particular attention may be warranted in recipients with previous cardiac surgery, pretransplant renal dysfunction, donor traumatic brain injury or CMV-related risk factors. Early neurological assessment, prompt imaging evaluation when clinically indicated, optimization of systemic perfusion, and aggressive management of postoperative organ dysfunction may contribute to reducing neurological burden. Furthermore, recipients receiving grafts from CMV-seropositive donors may represent a subgroup deserving enhanced postoperative monitoring, as earlier recognition of CMV-related complications and immunological stressors could potentially improve neurological outcomes. The observed association with impaired long-term survival further emphasizes that neurological complications should not be regarded solely as perioperative events but as markers of long-term clinical vulnerability. Strategies aimed at preventing neurological injury, together with appropriate long-term clinical follow-up of affected recipients, may therefore contribute to improving both short- and long-term outcomes after heart transplantation.

Several limitations should be acknowledged. First, this was a retrospective single-center study and therefore subject to the inherent limitations of observational analyses including residual confounding and the inability to establish causal relationships. Because multiple univariate comparisons were performed, these findings should be considered exploratory and hypothesis-generating. In particular, associations with borderline statistical significance should be interpreted cautiously and require confirmation in larger prospective studies. In addition, recipient selection, donor allocation, perioperative management, neurological surveillance, and immunosuppressive strategies reflect the standardized practice of a single experienced transplant center and may differ across institutions, potentially limiting the

generalizability of our findings. Nevertheless, the adoption of homogeneous institutional protocols throughout the study period may have reduced within-cohort variability and allowed a more consistent evaluation of factors associated with neurological complications. Moreover, the inclusion of all consecutive adult heart transplant recipients over a prolonged study period enhances the representativeness of the cohort and supports the applicability of the findings to transplant centers with similar patient populations and clinical practice. Second, surgical practice, donor allocation policies, preservation strategies, and mechanical circulatory support evolved during the long study period. In particular, the recent introduction of DCD transplantation and evolving preservation approaches may have contributed to temporal heterogeneity. Although these changes may have influenced the incidence and management of neurological complications, they also reflect the contemporary evolution of heart transplantation and enhance the real-world applicability of our findings. In addition, donor CMV serostatus was collected over a prolonged study period during which the recorded prevalence of donor CMV IgG seropositivity varied substantially. Although an additional sensitivity analysis restricted to the contemporary transplantation era confirmed the observed association, these findings should be interpreted with appropriate caution and require external validation. Third, neurological events were identified through retrospective review of clinically documented complications rather than systematic neurological assessment, and standardized neurological scales were not routinely available. Consequently, milder or transient neurological manifestations, particularly postoperative delirium, may have been underrecognized, potentially leading to an underestimation of the true incidence of neurological complications. Furthermore, neuroimaging was performed according to clinical indication. As a result, recipients with a more complicated postoperative course were more likely to undergo diagnostic evaluation, introducing the possibility of differential detection bias and increasing the likelihood of identifying structural neurological lesions in this subgroup. Fourth, although the number of neurological events limited the complexity of the multivariate model, the final model was intentionally restricted to six clinically relevant covariates to minimize the risk of overfitting. Internal validation using 1000 bootstrap resamples demonstrated only modest optimism, supporting the robustness of the model; however, external validation in independent cohorts remains necessary before these findings can be generalized. Finally, despite multivariate adjustment and internal validation, residual confounding cannot be excluded, and the observed associations should not be interpreted as evidence of causality.

5. Conclusions

Neurological complications after heart transplantation remain an important source of postoperative morbidity and are associated with prolonged ICU stay, a greater burden of multiorgan dysfunction, higher in-hospital mortality, and significantly reduced long-term survival. Although neurological events occurred in approximately one out of ten recipients, permanent neurological impairment affected only a minority of patients, suggesting that many postoperative neurological events may be transient and potentially reversible.

Previous cardiac surgery, pretransplant acute kidney injury, donor traumatic brain injury, and receipt of a graft from a CMV IgG-seropositive donor emerged as factors independently associated with neurological complications, highlighting the contribution of surgical complexity, systemic vulnerability, and immunological factors to neurological risk. These findings emphasize the importance of early and improved perioperative risk stratification, prevention and individualized management strategies to improve both short- and long-term outcomes after heart transplantation.

Future prospective multicenter studies are needed to validate the identified risk factors and better characterize the mechanisms underlying neurological injury after heart transplantation. Particular attention should be directed toward the interaction between recipient vulnerability, perioperative management, immunological factors, and treatment-related neurotoxicity. Improved understanding of these pathways may facilitate the development of targeted preventive strategies and standardized neurological surveillance protocols.

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Conflict of interest

The authors declare no conflicts of interest.

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All authors have read and agreed to the published version

of the manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Board of Niguarda Hospital (approval number: 215-29042020; May 5, 2020), and the requirement for individual informed consent was waived due to the retrospective nature of the study. Data collection and management were conducted in accordance with institutional regulations and international ethical standards, ensuring the protection of patient confidentiality, privacy, and data integrity. The institutional ethics committee approved the establishment of the database and oversees its ongoing use.

Consent for publication

The requirement for individual informed consent was waived due to the retrospective nature of the study.

Availability of data

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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