

Intraoperative Core Temperature Trajectory Phenotypes and Early Allograft Dysfunction After Liver Transplantation: A Retrospective Cohort Study

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Abstract

Background:

Static measures of intraoperative hypothermia may not capture the timing and evolution of temperature changes during liver transplantation. This study aimed to identify intraoperative core temperature trajectory phenotypes and examine their association with early allograft dysfunction (EAD).

Methods:

This single-center retrospective cohort study included adult liver transplant recipients treated between January 2016 and December 2025. Core temperature was recorded at 5-min intervals. An 18-point hybrid landmark sequence was constructed to align temperature measurements with operative phases, and latent growth mixture modeling was used to identify trajectory classes. The primary outcome was EAD. Associations between trajectory class and EAD were assessed using hierarchical logistic regression models adjusted for recipient, donor–graft, and intraoperative stress factors. Peri-reperfusion AUC below 36°C was evaluated as a complementary measure of hypothermic burden.

Results:

Among 519 eligible patients, 518 had valid temperature trajectory classification. Four trajectory phenotypes were identified. Classes 1 and 2 showed lower temperatures around reperfusion and were associated with higher odds of EAD before adjustment for intraoperative stress variables. After further adjustment for intraoperative stress factors, these associations were attenuated and were no longer statistically significant. Class 1 had higher intraoperative stress across hemodynamic, transfusion-related, metabolic, and perfusion-related domains. Peri-reperfusion AUC below 36°C showed a similar attenuation pattern.

Conclusions:

Intraoperative temperature trajectory phenotypes were associated with EAD before adjustment for intraoperative stress variables, but this association was attenuated after accounting for intraoperative stress. Lower-temperature peri-reperfusion trajectories may reflect concomitant physiological stress rather than isolated thermal exposure. External validation is required to determine their value for peri-reperfusion risk recognition.

Introduction

Liver transplantation is the definitive treatment for end-stage liver disease and a standard treatment for selected patients with acute liver failure.^[1, 2] Despite advances in surgical techniques, anesthesia, and

perioperative care, early allograft dysfunction (EAD) remains a clinically important postoperative complication. EAD reflects early graft injury and functional impairment and is influenced by recipient condition, donor–graft factors, ischemia–reperfusion injury, and intraoperative physiological stress.^[3–6]

Intraoperative temperature management is an important component of anesthetic care during liver transplantation. Recipients are susceptible to hypothermia because of extensive surgical exposure, impaired thermoregulation under anesthesia, large-volume fluid or blood product administration, cold graft implantation, and abrupt hemodynamic changes around reperfusion.^[7–11] Hypothermia may coexist with coagulopathy, bleeding, transfusion requirement, hemodynamic instability, and metabolic stress, particularly during the peri-reperfusion period.^[8, 12–14]

Previous studies have commonly assessed intraoperative hypothermia using static or threshold-based metrics, including nadir temperature, duration below 36°C, cumulative hypothermic burden, or binary hypothermia status.^[7, 8, 15, 16] Although clinically intuitive, these metrics provide limited information about the timing and evolution of temperature changes. This limitation may be particularly relevant in liver transplantation, where core temperature changes dynamically across the anhepatic phase, graft implantation, portal vein reperfusion, and early neohepatic recovery.^[7, 15, 17, 18]

A trajectory-based approach may complement conventional hypothermia metrics by capturing phase-specific thermal patterns over time.^[10, 15, 19, 20] Latent growth mixture modeling provides a data-driven method to identify subgroups of patients with distinct longitudinal temperature patterns.^[20, 21] However, intraoperative temperature trajectories during liver transplantation have not been well characterized, and their relationship with EAD and concurrent intraoperative stress remains unclear.

Therefore, we conducted a single-center retrospective cohort study of adult liver transplant recipients with repeated intraoperative core temperature measurements. Using an 18-point hybrid landmark model and latent growth mixture modeling, we identified intraoperative temperature trajectory phenotypes and examined their association with EAD. We also evaluated peri-reperfusion AUC below 36°C as a complementary measure of hypothermic burden.

Methods

Study design and population

This single-center retrospective cohort study included adult patients who underwent liver transplantation at Ningbo Medical Center Lihuili Hospital between January 2016 and December 2025. Patients were eligible if intraoperative core temperature data were available. Patients were excluded if they had baseline core temperature < 36.0°C, insufficient perioperative or postoperative records, or no valid temperature trajectory classification. Patients with indeterminate EAD status or missing covariates were excluded from the corresponding regression models. A total of 568 patients were screened, 519 were included in the eligible analytic cohort, and 518 had valid trajectory classification.

Intraoperative temperature measurement and surgical phase annotation

Core temperature was monitored intraoperatively using a nasopharyngeal temperature probe and recorded electronically at 5-min intervals. Key operative time points were extracted from anesthesia and surgical records: skin incision (T3), portal vein clamping (T4), portal vein reperfusion (T5), and wound closure (T6).

Three operative phases were defined: the diseased liver phase from T3 to T4, the anhepatic phase from T4 to T5, and the neohepatic phase from T5 to T6.

Perioperative temperature management

Perioperative temperature management followed institutional standard practice, including passive insulation with blankets, forced-air warming, and warming of intravenous fluids, blood products, and irrigation fluids. Warming intensity was adjusted intraoperatively according to core temperature and clinical condition. Because detailed time-varying warming intensity was not consistently quantifiable, it was not included as an independent covariate in the primary models.

Construction of the 18-point hybrid landmark temperature sequence

To standardize temperature trajectories across patients with different operative durations, an 18-point hybrid landmark sequence was constructed. The sequence combined proportional landmarks within operative phases and fixed early post-reperfusion time points.

The 18 landmarks were DLP0, DLP25, DLP50, DLP75, T4, AHP25, AHP50, AHP75, T5, PR5, PR10, PR15, PR20, PR30, PR60, Late50, Late75, and T6. DLP0 corresponded to skin incision, DLP25–DLP75 represented proportional points within the diseased liver phase, and T4 corresponded to portal vein clamping. AHP landmarks represented proportional points within the anhepatic phase, with T5 corresponding to portal vein reperfusion. PR5 to PR60 represented fixed time points 5 to 60 min after portal vein reperfusion. Late50 and Late75 represented the 50% and 75% proportional landmarks from 60 min after portal vein reperfusion to wound closure. Temperatures at each landmark were obtained from recorded values or linearly interpolated using adjacent 5-min measurements when needed. Interpolation was performed within the observed operative interval only, and no extrapolation beyond the recorded period was performed.

Temperature trajectory modeling

Latent growth mixture modeling was used to identify intraoperative temperature trajectory phenotypes based on the 18-point landmark sequence, as this approach can identify latent subgroups with distinct longitudinal patterns.^[20] Models with 2 to 5 classes were compared. Model selection was based on

information criteria, entropy, class proportions, and clinical interpretability.^[21, 22] Each patient was assigned to the trajectory class with the highest posterior probability.

Exposure variables

The primary exposure was intraoperative temperature trajectory class. Class 4, the higher-temperature stable trajectory, was used as the reference category in regression analyses.

The complementary exposure was peri-reperfusion AUC below 36°C. This was calculated from portal vein clamping to 60 min after portal vein reperfusion using actual elapsed time between adjacent temperature measurements. AUC below 36°C was calculated as the time-integrated area of $\max(0, 36^{\circ}\text{C} - \text{observed temperature})$ using the trapezoidal rule and was expressed in $^{\circ}\text{C}\cdot\text{min}$. It was entered into regression models per 10°C·min increase. If wound closure occurred before 60 min after portal vein reperfusion, AUC was calculated within the available observed interval without extrapolation.

Outcomes

The primary outcome was early allograft dysfunction (EAD), defined according to the Olthoff criteria.^[23] EAD was considered present if at least one of the following criteria occurred: total bilirubin ≥ 10 mg/dL on postoperative day 7, international normalized ratio ≥ 1.6 on postoperative day 7, or alanine aminotransferase or aspartate aminotransferase > 2000 IU/L within the first 7 postoperative days.

Secondary postoperative outcomes included postoperative AKI, postoperative renal replacement therapy, postoperative artificial liver therapy, ICU length of stay, hospital length of stay, total hospitalization cost, reoperation, 30-day mortality, and 90-day mortality. These outcomes were assessed in supplementary analyses to describe the broader postoperative outcome profile across temperature trajectory classes. Postoperative AKI was defined using the available components of the KDIGO criteria.^[24] The most recent preoperative creatinine value was used as baseline. AKI was diagnosed if serum creatinine increased by ≥ 26.5 $\mu\text{mol/L}$ within 48 h after surgery, reached ≥ 1.5 times baseline within the first 7 postoperative days, or if new postoperative renal replacement therapy was initiated.

Covariates

Covariates were selected according to clinical relevance and grouped into recipient, donor–graft, and intraoperative stress domains.

Recipient factors included age, sex, MELD-Na, and albumin. Donor–graft factors included graft type, cold ischemia time, and donor liver steatosis. Graft type was categorized as DBD, DCD-related, and living donor graft. DCD-related grafts included DCD and DBCD grafts.

Intraoperative stress factors included duration of MAP < 65 mmHg, anhepatic phase duration, and red blood cell transfusion. Additional intraoperative stress variables, including estimated blood loss, lowest

MAP, norepinephrine use, operative duration, lactate levels, and urine output, were compared descriptively across trajectory classes.

Statistical analysis

Continuous variables were summarized as median and interquartile range, and categorical variables as number and percentage. Across trajectory classes, continuous variables were compared using the Kruskal–Wallis test, and categorical variables were compared using the chi-square test or Fisher’s exact test, as appropriate.

Trends across trajectory classes were evaluated by treating trajectory class as an ordered thermal-severity variable from Class 4 to Class 1.

Associations between temperature trajectory class and EAD were assessed using logistic regression. Hierarchical models were constructed as follows: Model 1 was unadjusted; Model 2 adjusted for recipient factors; Model 3 further adjusted for donor–graft factors; and Model 4 further adjusted for intraoperative stress factors. Overall P values for trajectory class were obtained using likelihood-ratio tests. Trend tests were performed by modeling trajectory class according to increasing thermal severity.

Associations between peri-reperfusion AUC below 36°C and EAD were examined using logistic regression models. Model A was unadjusted. Model B adjusted for recipient and donor–graft factors. Model C additionally adjusted for intraoperative stress factors.

Complete-case analysis was used for regression models. Patients with indeterminate EAD status or missing covariates required for a given model were excluded from that model. Complete-case sample sizes were therefore allowed to vary across models.

All tests were two-sided, and $P < 0.05$ was considered statistically significant. Latent trajectory modeling was performed using Mplus version 7.0. Other statistical analyses were performed using SPSS version 27.0.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Ningbo Medical Center Lihuili Hospital (Approval No. KY2025SL438-01). The requirement for written informed consent was waived because of the retrospective design. The study was registered with the Chinese Medical Research Registration and Filing Information System (No. MR-33-25-056511). All organs were procured through voluntary citizen donation via the China Organ Transplant Response System (COTRS), in accordance with national allocation standards.

Results

Study cohort

After screening, 519 patients were included in the eligible analytic cohort (Fig. 1). Among them, 518 had valid temperature trajectory classification and were used for trajectory-based analyses. Complete-case samples for the EAD regression models differed by covariate availability, with 513 patients in Model 1, 508 in Models 2 and 3, and 505 in Model 4.

Identification of temperature trajectory phenotypes

Latent growth mixture models with 2 to 5 classes were compared using information criteria, entropy, and class proportions. AIC, BIC, and aBIC decreased with increasing class number, and entropy remained high across the candidate models. Although the 5-class solution had the lowest information criteria, the 4-class solution was retained for subsequent analyses based on class size, clinical interpretability, and avoidance of over-fragmentation. The 4-class solution was selected as the primary model because it provided clinically interpretable and adequately sized classes, despite the lower information criteria of the 5-class solution (Table 1). The final class proportions were 11.8%, 24.5%, 36.1%, and 27.6%.

Figure 2 shows the four mean temperature trajectories derived from the 18-point hybrid landmark model. Class 1 had the lowest temperature trajectory, particularly during the anhepatic and early neohepatic phases. Class 2 showed a low-temperature recovery pattern, Class 3 followed an intermediate pattern, and Class 4 maintained the highest and most stable temperature profile.

Table 1
Fit indices for temperature trajectory models

Classes	AIC	BIC	aBIC	Entropy	Class proportions
2	13026.367	13336.615	13104.898	0.97	34.2% / 65.8%
3	9792.528	10260.026	9910.864	0.971	17.6% / 41.1% / 41.3%
4	7948.586	8573.332	8106.725	0.973	11.8% / 24.5% / 36.1% / 27.6%
5	6958.360	7740.355	7156.302	0.975	10.2% / 18.9% / 26.6% / 24.3% / 19.9%
Notes: AIC, Akaike information criterion; BIC, Bayesian information criterion; aBIC, sample-size-adjusted Bayesian information criterion.					

Lines represent mean core temperature trajectories for each class across the 18 hybrid landmarks. Vertical dashed lines denote phase boundaries. DLP, diseased liver phase; AHP, anhepatic phase; NHP, neohepatic phase.

Recipient and donor–graft characteristics according to trajectory class

Table 2 summarizes recipient and donor–graft characteristics across the four temperature trajectory classes. Among recipient characteristics, MELD-Na differed across classes, with higher median values in

Classes 1 and 2. Age, sex, ASA class, albumin, total bilirubin, creatinine, INR, and primary diagnosis were not significantly different across classes.

Among donor–graft characteristics, donor age, graft type, cold ischemia time, and warm ischemia time differed across trajectory classes. The proportion of DCD-related grafts was highest in Class 1, and cold and warm ischemia times were longer in Class 1 than in the other classes. Donor liver steatosis was similar across classes.

Table 2
Baseline characteristics by trajectory class

Characteristic	Overall	Class 1	Class 2	Class 3	Class 4	P value
Age, years	54.0 (47.0–61.0)	53.0 (45.0–59.0)	56.0 (49.0–61.5)	54.0 (47.0–61.0)	53.0 (47.5–59.5)	0.273
Male sex, n (%)	410 (79.2)	47 (77.0)	95 (74.8)	146 (78.1)	122 (85.3)	0.169
ASA class III–IV, n (%)	334 (64.5)	41 (67.2)	90 (70.9)	116 (62.0)	87 (60.8)	0.287
MELD-Na	13.0 (9.0–22.0)	16.0 (11.0–24.0)	15.0 (10.0–24.0)	12.0 (9.0–19.5)	13.0 (9.0–22.0)	0.026
Albumin, g/L	33.6 (29.9–39.0)	33.5 (30.6–36.3)	33.5 (29.4–38.9)	33.7 (29.6–39.2)	33.7 (30.6–39.1)	0.712
Total bilirubin, µmol/L	42.9 (20.4–210.2)	79.4 (23.6–201.2)	49.3 (22.9–227.6)	40.9 (19.6–169.3)	38.8 (18.0–246.3)	0.321
Creatinine, µmol/L	66.8 (54.6–86.3)	69.1 (55.5–100.0)	68.5 (56.2–89.9)	66.5 (53.3–83.2)	64.2 (53.9–80.8)	0.316
INR	1.4 (1.1–1.9)	1.5 (1.2–1.9)	1.4 (1.1–2.0)	1.3 (1.1–1.9)	1.4 (1.1–2.1)	0.348
Hepatic malignancy/HCC	229 (44.2)	17 (27.9)	57 (44.9)	86 (46.0)	69 (48.3)	0.249
Cirrhosis/decompensated cirrhosis	196 (37.8)	29 (47.5)	46 (36.2)	71 (38.0)	50 (35.0)	
Liver failure	86 (16.6)	13 (21.3)	22 (17.3)	27 (14.4)	24 (16.8)	
Cholestatic/biliary/metabolic/benign	7 (1.4)	2 (3.3)	2 (1.6)	3 (1.6)	0 (0.0)	
Donor age, years	45.0 (33.0–	49.0 (35.0–	44.0 (36.0–	47.0 (33.5–	41.0 (30.0–	0.046

Notes: Values are median (interquartile range) or n (%). Overall n = 518; Class 1 n = 61, Class 2 n = 127, Class 3 n = 187, and Class 4 n = 143. Overall P values were obtained using Kruskal–Wallis tests for continuous variables and chi-square tests for categorical variables. Percentages were calculated using available non-missing data unless otherwise specified. Graft type was categorized as DBD, DCD-related (DCD + DBCD), and living donor. Diagnosis groups were collapsed using a prespecified hierarchy: hepatic malignancy/HCC, liver failure, cirrhosis/decompensated cirrhosis, and cholestatic/biliary/metabolic/benign disease. ASA, American Society of Anesthesiologists; DBCD, donation after brain and circulatory death; DBD, donation after brain death; DCD, donation after circulatory death; INR, international normalized ratio; MELD-Na, Model for End-stage Liver Disease incorporating sodium.

Characteristic	Overall	Class 1	Class 2	Class 3	Class 4	P value
	53.0)	55.0)	51.0)	54.0)	50.5)	
DBD graft	222 (42.9)	16 (26.2)	44 (34.6)	92 (49.2)	70 (49.0)	< 0.001
DCD-related graft	269 (51.9)	43 (70.5)	78 (61.4)	87 (46.5)	61 (42.7)	
Living donor graft	27 (5.2)	2 (3.3)	5 (3.9)	8 (4.3)	12 (8.4)	
Donor liver steatosis, %	0.0 (0.0– 0.0)	0.0 (0.0– 0.0)	0.0 (0.0– 0.0)	0.0 (0.0– 0.0)	0.0 (0.0– 0.0)	0.259
Cold ischemia time, min	316.0 (240.0– 420.0)	360.0 (290.0– 480.0)	330.0 (225.0– 480.0)	306.0 (240.0– 419.5)	300.0 (239.0– 390.0)	0.019
Warm ischemia time, min	4.0 (0.0– 10.0)	7.0 (0.0– 10.0)	6.0 (0.0– 9.5)	0.0 (0.0– 10.0)	0.0 (0.0– 9.0)	0.016

Notes: Values are median (interquartile range) or n (%). Overall n = 518; Class 1 n = 61, Class 2 n = 127, Class 3 n = 187, and Class 4 n = 143. Overall P values were obtained using Kruskal–Wallis tests for continuous variables and chi-square tests for categorical variables. Percentages were calculated using available non-missing data unless otherwise specified. Graft type was categorized as DBD, DCD-related (DCD + DBCD), and living donor. Diagnosis groups were collapsed using a prespecified hierarchy: hepatic malignancy/HCC, liver failure, cirrhosis/decompensated cirrhosis, and cholestatic/biliary/metabolic/benign disease. ASA, American Society of Anesthesiologists; DBCD, donation after brain and circulatory death; DBD, donation after brain death; DCD, donation after circulatory death; INR, international normalized ratio; MELD-Na, Model for End-stage Liver Disease incorporating sodium.

Association between temperature trajectory class and EAD

In the unadjusted complete-case cohort, EAD occurred in 31 of 59 patients in Class 1 (52.5%), 57 of 127 patients in Class 2 (44.9%), 61 of 185 patients in Class 3 (33.0%), and 40 of 142 patients in Class 4 (28.2%). Table 3 summarizes the association between temperature trajectory class and EAD across hierarchical logistic regression models. Compared with Class 4, Classes 1 and 2 were associated with higher odds of EAD in the unadjusted model, after adjustment for recipient factors, and after further adjustment for donor–graft factors. Class 3 was not significantly associated with EAD across these models.

After additional adjustment for intraoperative stress factors, the associations for trajectory class were attenuated and no longer statistically significant. In the fully adjusted model, the overall P value for trajectory class was 0.242, and the P value for trend was 0.077.

Table 3
Temperature trajectories and early allograft dysfunction

Model	Adjustment	No. of patients / EAD events	Class 1 vs Class 4, OR/aOR (95% CI); P value	Class 2 vs Class 4, OR/aOR (95% CI); P value	Class 3 vs Class 4, OR/aOR (95% CI); P value	Overall P	P for trend
Model 1	Unadjusted	513 / 189	2.82 (1.51–5.29); P = 0.001	2.08 (1.25–3.44); P = 0.005	1.25 (0.78–2.02); P = 0.352	0.001	< 0.001
Model 2	Recipient factors	508 / 188	2.83 (1.49–5.38); P = 0.001	2.03 (1.22–3.40); P = 0.007	1.26 (0.77–2.04); P = 0.357	0.002	< 0.001
Model 3	Recipient + donor–graft factors	508 / 188	2.14 (1.10–4.14); P = 0.024	1.77 (1.04–3.02); P = 0.035	1.11 (0.67–1.84); P = 0.673	0.037	0.005
Model 4	Model 3 + intraoperative stress factors	505 / 188	1.49 (0.73–3.04); P = 0.271	1.71 (0.97–2.99); P = 0.062	1.14 (0.67–1.93); P = 0.636	0.242	0.077

Notes: Class 4 was the reference category. Values in the class-specific columns are OR/aOR (95% CI); P value. Model 2 adjusted for age, sex, MELD-Na, and albumin. Model 3 further adjusted for graft type, cold ischemia time, and donor liver steatosis. Model 4 further adjusted for duration of MAP < 65 mmHg, anhepatic phase duration, and red blood cell transfusion. Overall P values were obtained using likelihood-ratio tests. Trend tests coded trajectory classes according to increasing thermal severity from Class 4 to Class 1. aOR, adjusted odds ratio; CI, confidence interval; EAD, early allograft dysfunction; MAP, mean arterial pressure; MELD-Na, Model for End-stage Liver Disease incorporating sodium; OR, odds ratio.

Intraoperative stress variables according to trajectory class

Table 4 summarizes selected intraoperative stress variables across the four temperature trajectory classes. Estimated blood loss, red blood cell transfusion, lowest MAP, duration of MAP < 65 mmHg, norepinephrine use, total operative duration, lactate levels, and urine output differed significantly across classes.

Class 1 had higher estimated blood loss, greater red blood cell transfusion, lower lowest MAP, longer duration of MAP < 65 mmHg, higher anhepatic lactate, and lower urine output than the other classes. Anhepatic phase duration did not differ significantly across classes. Significant trends across increasing thermal severity were observed for most intraoperative stress variables, except anhepatic phase duration.

Table 4
Intraoperative stress variables by trajectory class

Variable	Overall	Class 1	Class 2	Class 3	Class 4	P overall	P for trend
Estimated blood loss, mL	1000 (600–1500)	1800 (1000–3000)	1000 (600–1800)	800 (500–1500)	800 (500–1250)	< 0.001	< 0.001
Red blood cell transfusion, mL	1300 (600–2000)	1800 (900–2600)	1400 (600–2100)	1300 (600–2000)	1150 (600–1800)	0.016	0.007
Lowest MAP, mmHg	55 (50–61)	50 (46–56)	55 (50–60)	56 (52–61)	57 (52–62)	< 0.001	< 0.001
Duration of MAP < 65 mmHg, min	50 (10–115)	105 (40–195)	50 (12–115)	48 (15–105)	35 (6–100)	< 0.001	< 0.001
Norepinephrine use, n (%)	451 (87.1)	57 (93.4)	118 (92.9)	154 (82.4)	122 (85.3)	0.017	0.017
Anhepatic phase duration, min	51 (44–61)	56 (45–66)	51 (44–62)	51 (43–60)	50 (44–60)	0.231	0.115
Total operative duration, min	440 (380–525)	428 (358–501)	409 (350–498)	440 (390–524)	480 (410–543)	< 0.001	< 0.001
Lactate during anhepatic phase, mmol/L	2.9 (2.2–4.1)	3.7 (2.8–5.0)	2.9 (2.2–4.3)	2.7 (2.1–3.6)	2.8 (2.1–4.3)	< 0.001	0.024
Urine output, mL	1500 (974–2100)	1155 (738–1862)	1500 (868–2100)	1442 (952–2000)	1700 (1200–2300)	0.002	< 0.001

Notes: Values are median (interquartile range) or n (%). Class sizes: overall n = 518, Class 1 n = 61, Class 2 n = 127, Class 3 n = 187, and Class 4 n = 143. Overall P values were obtained using Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. P for trend was calculated by treating trajectory classes as an ordered thermal-severity variable from Class 4 to Class 1. IQR, interquartile range; MAP, mean arterial pressure.

Peri-reperfusion hypothermic burden according to trajectory class

Peri-reperfusion AUC below 36°C differed across trajectory classes and was highest in Class 1 (Fig. 3).

Box-and-jitter plot showing peri-reperfusion AUC below 36°C across the four temperature trajectory classes. Boxes indicate the median and interquartile range, and dots represent individual patients. Group differences were assessed using the Kruskal–Wallis test. Higher AUC values indicate greater peri-reperfusion hypothermic burden. AUC, area under the curve.

Association between peri-reperfusion hypothermic burden and EAD

Table 5 summarizes the association between peri-reperfusion AUC below 36°C and EAD across hierarchical logistic regression models. AUC below 36°C was associated with higher odds of EAD in the unadjusted model and remained significant after adjustment for recipient and donor–graft factors.

After additional adjustment for intraoperative stress variables, the association was attenuated and was no longer statistically significant. In the fully adjusted model, the adjusted OR per 10°C·min increase in AUC below 36°C was 1.01 (95% CI, 0.98–1.05; P = 0.458).

Table 5
Peri-reperfusion hypothermic burden and EAD

Model	Adjustment	No. of patients	EAD events, n	OR / adjusted OR (95% CI)	P value
Model A	Unadjusted	513	189	1.05 (1.02–1.08)	0.002
Model B	Adjusted for recipient and donor–graft factors: age, sex, MELD-Na, albumin, graft type, cold ischemia time, and donor liver steatosis	508	188	1.04 (1.01–1.07)	0.020
Model C	Model B plus intraoperative stress variables: duration of MAP < 65 mmHg, anhepatic phase duration, and red blood cell transfusion	505	188	1.01 (0.98–1.05)	0.458
Notes: Outcome was early allograft dysfunction. Peri-reperfusion AUC below 36°C was entered per 10°C·min increase and calculated from portal vein clamping to 60 min after portal vein reperfusion using actual elapsed time between adjacent temperature measurements. Model B adjusted for age, sex, MELD-Na, albumin, graft type, cold ischemia time, and donor liver steatosis. Model C additionally adjusted for duration of MAP < 65 mmHg, anhepatic phase duration, and red blood cell transfusion. Patients with indeterminate EAD status or missing model covariates were excluded. AUC, area under the curve; CI, confidence interval; EAD, early allograft dysfunction; MAP, mean arterial pressure; MELD-Na, Model for End-stage Liver Disease incorporating sodium; OR, odds ratio.					

Discussion

Principal findings

In this retrospective cohort of liver transplant recipients, the 18-point hybrid landmark model identified four intraoperative temperature trajectory phenotypes with graded peri-reperfusion hypothermic burden. Lower-temperature trajectories were associated with higher odds of EAD after adjustment for recipient and donor–graft factors, but these associations were attenuated after additional adjustment for intraoperative stress variables. A similar attenuation pattern was observed for peri-reperfusion AUC below

36°C, suggesting that hypothermic burden and trajectory patterns should be interpreted in the context of concurrent intraoperative stress.

Temperature trajectories as dynamic peri-reperfusion phenotypes

Conventional hypothermia metrics, such as nadir temperature, duration below a threshold, or cumulative hypothermic burden, primarily summarize the depth and/or duration of hypothermia but provide limited information about its timing and temporal evolution.^[17, 25] This distinction is relevant in liver transplantation, where temperature changes occur around the anhepatic phase, portal vein reperfusion, and early neohepatic recovery.

By aligning repeated measurements to phase-specific landmarks, the 18-point hybrid model characterized hypothermia as a dynamic peri-reperfusion phenotype rather than a single summary exposure. Peri-reperfusion AUC below 36°C provided a complementary quantitative measure of thermal burden by summarizing the cumulative depth and duration of hypothermia during the peri-reperfusion window.^[26, 27] Together, these measures describe related but distinct dimensions of thermal vulnerability: trajectory analysis preserves temporal information, whereas AUC quantifies cumulative hypothermic burden.

Hypothermic trajectories, intraoperative stress, and EAD

The attenuation after adjustment for intraoperative stress variables suggests that the trajectory–EAD association should be interpreted in the context of concurrent peri-reperfusion stress. In liver transplantation, hypotension, transfusion requirement, metabolic derangement, and perfusion-related changes may act not only as confounders but also as clinical features of the same vulnerability state.^[28–30]

This interpretation is supported by the higher stress profile observed in Class 1. Given the observational design and the close interrelationship among temperature, perfusion, transfusion, and graft-related factors, this study cannot determine whether hypothermia is a contributor to, consequence of, or marker of peri-reperfusion vulnerability.

Clinical implications

These findings support considering temperature trends together with hemodynamic stability, transfusion requirement, metabolic status, urine output, and graft-related risk factors when assessing peri-reperfusion risk. Whether such trajectory information can improve clinical decision-making requires prospective validation.

Figure 4 provides a schematic summary of the proposed clinical interpretation of the temperature trajectory phenotypes. In this framework, Classes 1 and 2 represent higher hypothermic-burden trajectories, whereas Classes 3 and 4 represent lower hypothermic-burden trajectories. The figure links

these trajectory patterns with associated intraoperative stress features and potential clinical response domains.

Schematic summary of intraoperative temperature trajectory phenotypes, associated intraoperative stress features, and potential clinical response domains. Classes 1 and 2 were considered higher hypothermic-burden trajectories, whereas Classes 3 and 4 were considered lower hypothermic-burden trajectories. EAD, early allograft dysfunction; MAP, mean arterial pressure; RBC, red blood cell.

Limitations

Several limitations should be acknowledged. First, this was a single-center retrospective study, and causal inference cannot be made. Second, the trajectory classes were derived from latent growth mixture modeling and require external validation. Although the 5-class solution had lower information criteria, the 4-class solution was selected based on class size and clinical interpretability, which may involve some degree of subjectivity. Third, complete-case analyses may have introduced selection bias, particularly because sample sizes varied across regression models according to covariate availability. Fourth, intraoperative temperature, hemodynamic instability, transfusion burden, and metabolic stress were closely interrelated. Therefore, adjustment for intraoperative stress variables should be interpreted as contextual adjustment rather than definitive causal adjustment, and the present models cannot distinguish confounding, collinearity, or mediation. Finally, although standardized warming measures were used, detailed time-varying warming intensity, hemodynamic management, transfusion practice, and other center-specific intraoperative interventions were not fully captured. Therefore, residual confounding related to intraoperative management cannot be excluded.

Conclusions

In this single-center retrospective cohort, intraoperative temperature trajectory phenotypes were associated with EAD after liver transplantation before adjustment for intraoperative stress variables. This association was attenuated after accounting for intraoperative stress, suggesting that lower-temperature peri-reperfusion trajectories may reflect concomitant physiological stress rather than isolated thermal exposure. These findings support the potential value of phase-aligned temperature trajectories for peri-reperfusion risk recognition, but external validation is required.

Abbreviations

Number	Abbreviation	Full Form
1	EAD	Early allograft dysfunction
2	AUC	Area under the curve
3	LGMM	Latent growth mixture modeling
4	DLP	Diseased liver phase
5	AHP	Anhepatic phase
6	NHP	Neohepatic phase
7	PR	Post-reperfusion
8	MAP	Mean arterial pressure
9	RBC	Red blood cell
10	AKI	Acute kidney injury
11	KDIGO	Kidney Disease: Improving Global Outcomes
12	ICU	Intensive care unit
13	MELD-Na	Model for End-stage Liver Disease incorporating sodium
14	ASA	American Society of Anesthesiologists
15	INR	International normalized ratio
16	DBD	Donation after brain death
17	DCD	Donation after circulatory death
18	DBCD	Donation after brain and circulatory death
19	OR	Odds ratio
20	aOR	Adjusted odds ratio
21	CI	Confidence interval
22	IQR	Interquartile range
23	AIC	Akaike information criterion
24	BIC	Bayesian information criterion
25	aBIC	Sample-size-adjusted Bayesian information criterion
26	COTRS	China Organ Transplant Response System
27	ALT	Alanine aminotransferase
28	AST	Aspartate aminotransferase

Declarations

Human Ethics and Consent to Participate declarations

This retrospective cohort study was conducted in compliance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Ningbo Medical Center Lihuili Hospital (approval no. KY2025SL438-01). Given the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

The name of ethics committee: Ningbo Medical Center Lihuili Hospital Ethics Committee.

The institute: Ningbo Medical Center Lihuili Hospital.

Consent for Publication

Not Applicable.

Availability of data and materials

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

Competing Interests

We have reviewed the journal's policy on competing interests and hereby confirm the following. All authors of this manuscript declare that they have no financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work. This includes, but is not limited to, employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding relevant to the subject of this study.

Clinical trial number: not applicable.

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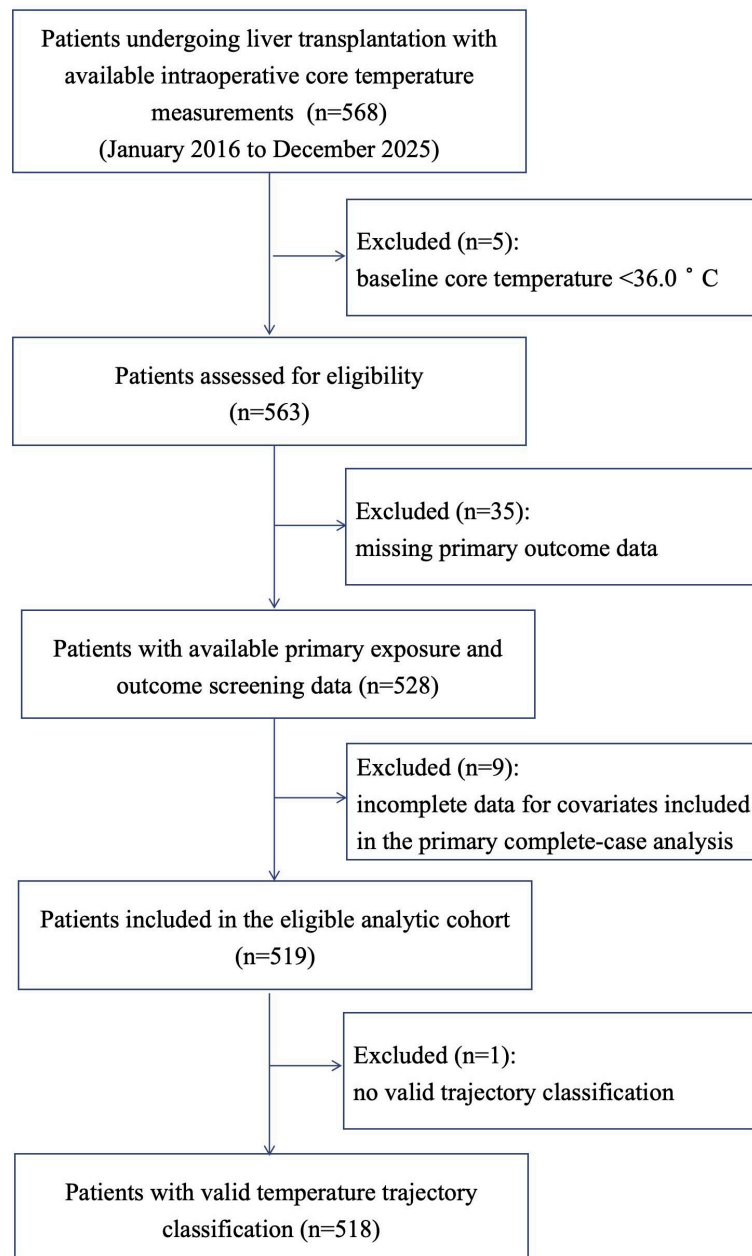
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Figures



Note:
Complete-case samples for the EAD regression models were: Model 1, n=513 with 189 EAD events; Model 2, n=508 with 188 EAD events; Model 3, n=508 with 188 EAD events; and Model 4, n=505 with 188 EAD events.

Figure 1

Flow diagram of patient selection.

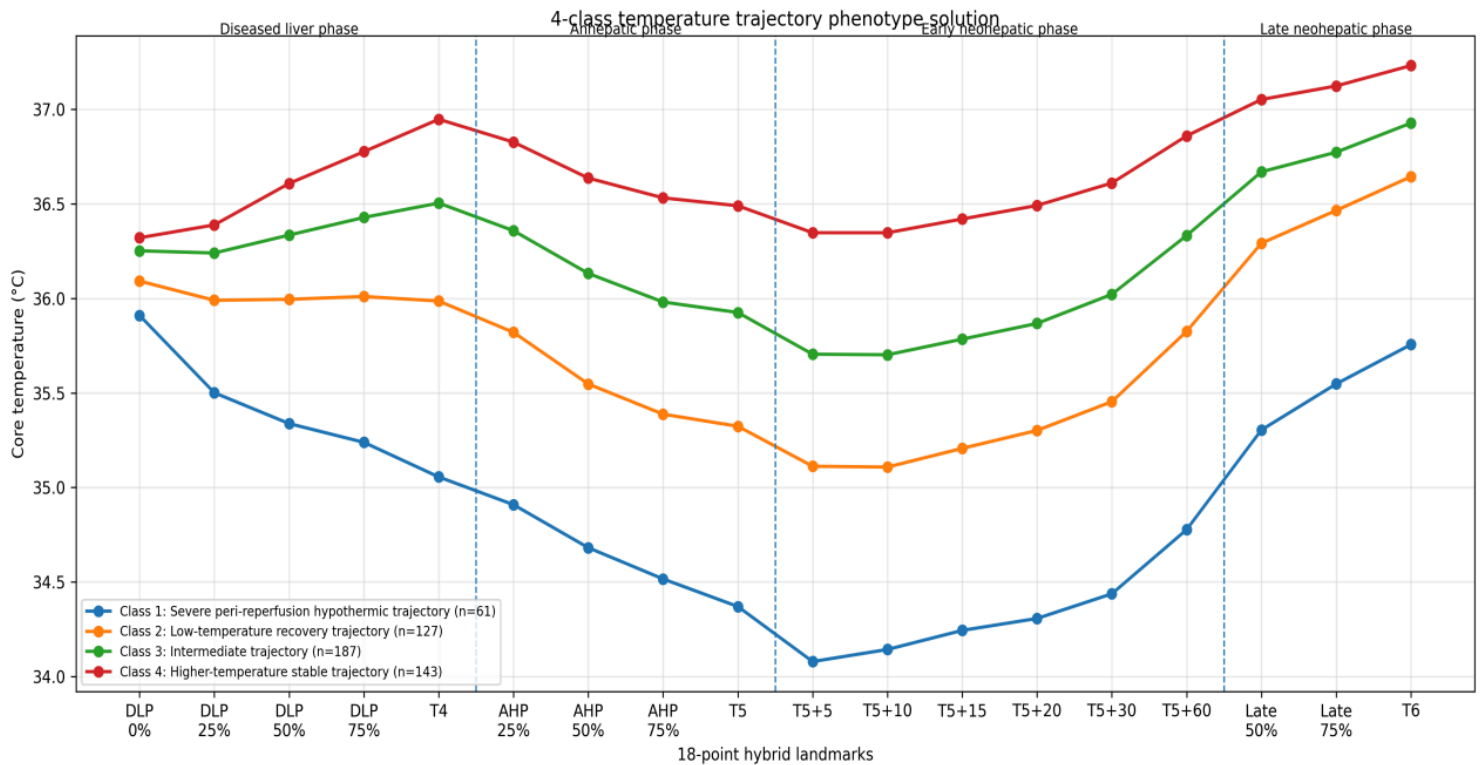


Figure 2

Four intraoperative core temperature trajectory phenotypes based on the 18-point hybrid landmark model.

Lines represent mean core temperature trajectories for each class across the 18 hybrid landmarks. Vertical dashed lines denote phase boundaries. DLP, diseased liver phase; AHP, anhepatic phase; NHP, neohepatic phase.

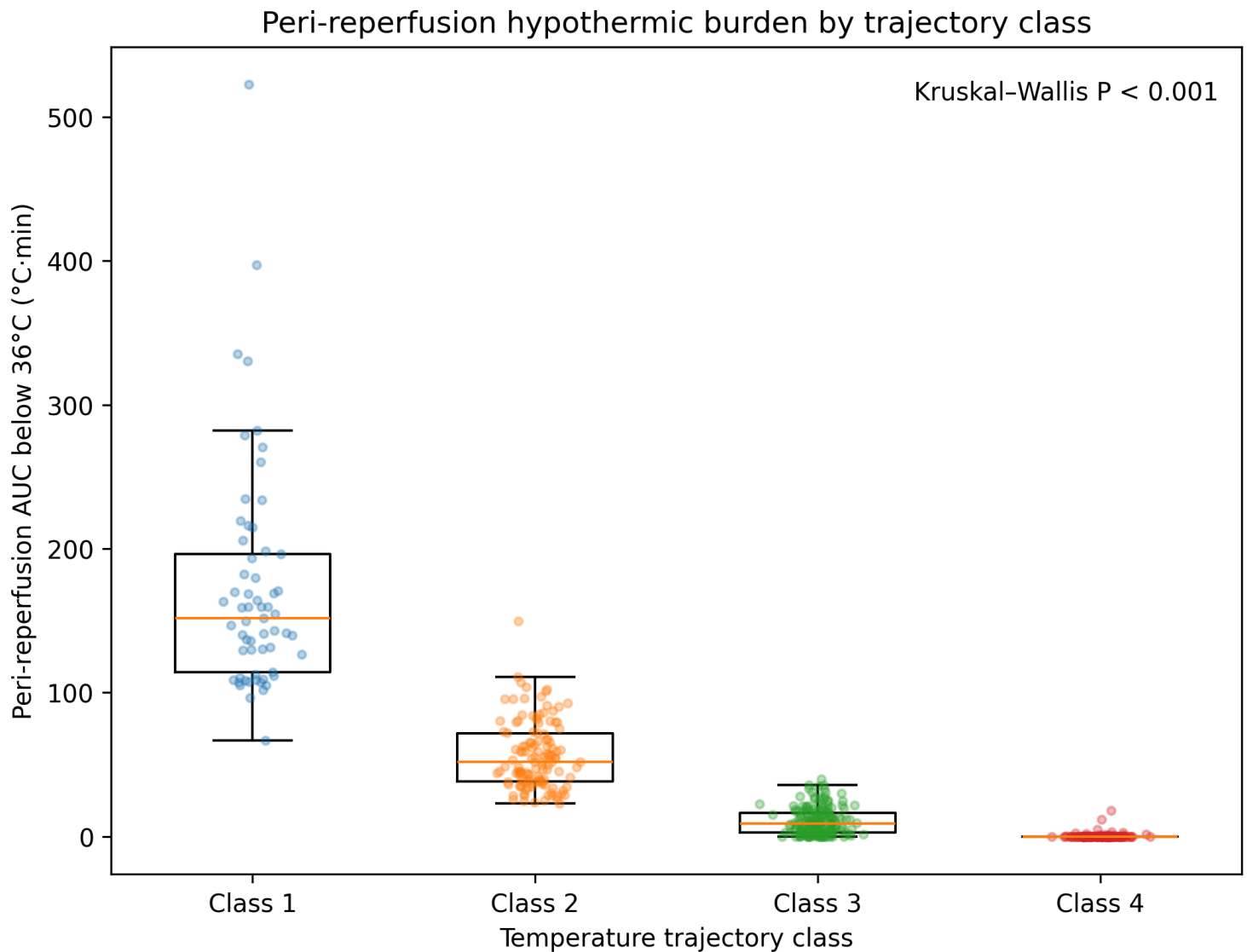


Figure 3

Peri-reperfusion hypothermic burden by temperature trajectory class.

Box-and-jitter plot showing peri-reperfusion AUC below 36°C across the four temperature trajectory classes. Boxes indicate the median and interquartile range, and dots represent individual patients. Group differences were assessed using the Kruskal–Wallis test. Higher AUC values indicate greater peri-reperfusion hypothermic burden. AUC, area under the curve.

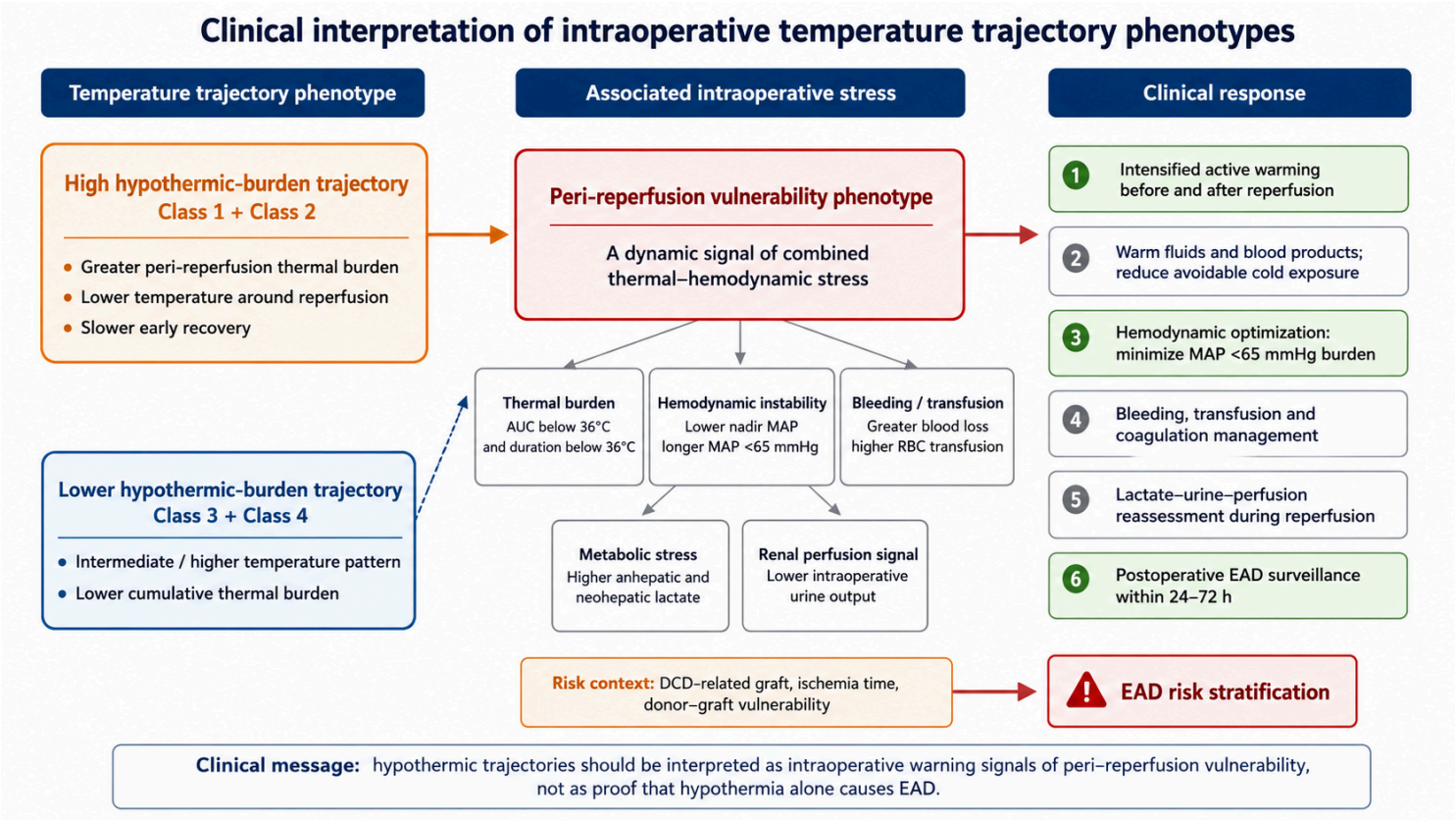


Figure 4

Proposed interpretation of temperature trajectory phenotypes

Schematic summary of intraoperative temperature trajectory phenotypes, associated intraoperative stress features, and potential clinical response domains. Classes 1 and 2 were considered higher hypothermic-burden trajectories, whereas Classes 3 and 4 were considered lower hypothermic-burden trajectories. EAD, early allograft dysfunction; MAP, mean arterial pressure; RBC, red blood cell.

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