Time-Dependent Effects of Normothermic and Mild Hypothermic Cardiopulmonary Bypass on the De Ritis Ratio

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Abstract

Aim: This study aims to comparatively evaluate the effects of normothermic and mild hypothermic cardiopulmonary bypass (CPB) strategies on liver function in coronary artery bypass grafting (CABG) operations through the dynamics of the De Ritis ratio.

Methods This retrospective study included 150 patients who underwent CABG with either normothermic (35–37 ˚C, n=75) or mild hypothermic (28–34 ˚C, n=75) CPB. Liver function parameters (AST, ALT, De Ritis ratio, GGT, bilirubin) were assessed at the prebypass, postbypass, and postoperative time points. Statistical analysis was performed using SPSS software, with significance set at $p<0.05$.

Results: While De Ritis ratios were comparable during the prebypass period ($p=0.751$), significantly higher values were observed in the mild hypothermic group during both the postbypass ($p=0.032$) and postoperative ($p=0.048$) periods. A significant time-dependent increase in De Ritis ratio was found in both groups ($p<0.01$). Moreover, a higher proportion of patients in the mild hypothermic group had a De Ritis ratio >2.0 in the postoperative period. The De Ritis ratio showed a negative correlation with GGT at all time points ($p<0.001$) and a positive correlation with total bilirubin during the prebypass ($p<0.001$) and postoperative ($p=0.006$) periods. Female patients consistently showed higher De Ritis ratios than males ($p < 0.05$).

Conclusions: The normothermic CPB strategy was associated with lower De Ritis ratios compared to hypothermia. The De Ritis ratio may serve as an early indicator of liver function in cardiovascular surgery. Normothermic perfusion may offer hepatoprotective benefits and could be preferred in patients at high risk for liver dysfunction.

***Keywords**: Cardiopulmonary bypass; normothermia; hypothermia; De Ritis ratio; AST/ALT; hepatic injury*

1. Introduction

Cardiopulmonary bypass (CPB) is an indispensable technique used to temporarily support systemic circulation and oxygenation during cardiac surgery. The temperature protocols applied during CPB, namely normothermia and hypothermia, can directly influence the physiological responses of target organs.[1–3]

Findings regarding the organ-protective effects of different temperature strategies during CPB remain controversial. Some studies suggest that hypothermia may reduce ischemic injury by decreasing metabolic rate[4], whereas others indicate that normothermia ensures more effective organ perfusion and better preserves the function of various organs, particularly the heart and liver[5]. Therefore, the selection of an appropriate temperature strategy is of critical importance, especially for organs that are sensitive to ischemia-reperfusion injury, such as the liver.[6,7]

The liver is directly affected by the thermal variations applied during CPB due to its high metabolic activity and microcirculatory sensitivity. Normothermic perfusion has been reported to better preserve hepatic energy reserves and to result in more moderate increases in transaminases such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT), thereby reducing hepatocellular injury.[8] In contrast, although hypothermic CPB decreases metabolic demands, it may also lead to reduced hepatic blood flow and impaired microcirculation, potentially resulting in more pronounced cellular damage.[9]

In this context, the AST/ALT ratio, commonly known as the De Ritis ratio, has emerged as a specific biochemical marker for assessing the type and severity of hepatic injury.[10] While ALT is primarily cytosolic in origin, AST is derived from both cytosolic and mitochondrial sources. A De Ritis ratio below 1 is typically associated with mild and reversible hepatocellular damage, whereas a ratio above 1 may indicate more extensive or mitochondrial-level injury.[11] This ratio is not only valuable in

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evaluating liver function but also serves as a prognostic marker in the postoperative period.[12]

Several studies involving CPB have reported significant elevations in AST and ALT levels, accompanied by increases in the De Ritis ratio.[13] However, the number of studies specifically examining the impact of temperature strategies on the De Ritis ratio during CPB remains limited.

Therefore, a comparative analysis of the effects of normothermic and mild hypothermic perfusion strategies on liver function and the De Ritis ratio is essential to better understand how temperature management during bypass affects hepatic health. In this study, we investigated the temporal changes in the De Ritis ratio among patients undergoing coronary artery bypass grafting (CABG) with CPB and whether these changes differed according to the temperature strategy employed.

2. Materials and Methods

2.1. Study design and ethical approval

This study was conducted using a retrospective and cross-sectional design. Data were obtained from archived medical records of patients who underwent isolated elective coronary artery bypass grafting (CABG) at the Department of Cardiovascular Surgery, Harran University Hospital, between January 2020 and May 2025. Ethical approval for the study was granted by the Clinical Research Ethics Committee of Harran University (Date: 14.07.2025, Number: HRÜ-25.13.16).

2.2. Participant selection

Patients aged between 18 and 80 years who had undergone CABG surgery alone, had no diagnosis of active liver disease, hematologic disorders, or malignancy in the preoperative period, and had complete biochemical data were included in the study. Patients were excluded if they underwent emergency surgery, had concomitant valve procedures, a history of liver disease, or incomplete biochemical records. A total of 150 patients meeting the inclusion criteria were divided into two groups according to the temperature strategy applied during CPB: normothermic (n=75; 35–37 °C) and mild hypothermic (n=75; 28–34 °C). The selection of temperature strategy was based on the clinical discretion of the attending surgeon and perfusion team; researchers did not intervene in this process.

2.3. Data collection and evaluated parameters

Biochemical parameters were assessed based on laboratory data obtained at three distinct time points: the prebypass period (after anesthesia and before initiation of CPB), the postbypass period (immediately after termination of CPB), and the postoperative period (within the first 24 hours following surgery). The evaluated parameters included AST, ALT, De Ritis ratio, gamma-glutamyl transferase (GGT), total bilirubin, and direct bilirubin levels. The De Ritis ratio was calculated by dividing the AST level by the ALT level.

2.4. Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY) and Python version 3.10. The distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. For non-normally distributed data, median and interquartile range (IQR) values were calculated. Between-group comparisons were performed using the Mann–Whitney U test, while within-group time-dependent changes were analyzed using the Friedman test. Correlations between parameters were evaluated using Spearman correlation analysis. A p-value of <0.05 was considered statistically significant for all tests.

3. Results

3.1. Demographic and operative data

The demographic characteristics and operative parameters of the patients included in the study are presented in Table 1.

Table 1

Baseline demographic and operative parameters of the patient groups

Parameter	Normothermic (n=75)	Mild Hypothermic (n=75)	p
Gender (M/F)	47 / 28	45 / 30	0.998
Age (years)	59.73 ± 11.29	60.76 ± 9.71	0.5515
Height (cm)	164.80 ± 8.73	164.33 ± 9.60	0.7561
Weight (kg)	77.44 ± 15.91	73.96 ± 13.70	0.1535
Body Surface Area (m^2)	1.87 ± 0.18	1.82 ± 0.18	0.1458
Flow Rate (L/min)	4.50 ± 0.44	4.40 ± 0.43	0.1742
Cross-Clamp Time (min)	78.24 ± 36.21	89.16 ± 38.14	0.0742
Perfusion Time (min)	105.42 ± 35.46	119.48 ± 52.95	0.0584

Both groups exhibited similar characteristics in terms of anthropometric parameters such as age, height, weight, and body surface area (BSA). The distribution of sex was balanced between the groups, with no statistically significant difference observed (p=0.998). Regarding operative variables, although the mean cross-clamp time and perfusion time were longer in the mild hypothermic group, these differences did not reach statistical significance (p=0.074 and p=0.058, respectively). Mean pump flow values were also comparable between the groups (p=0.174). Collectively, these findings indicate that the two patient groups were homogeneous in terms of baseline characteristics (p>0.05).

3.2. Temporal changes in the De Ritis Ratio and intra-/intergroup comparisons

The comparative analysis results of the De Ritis ratio at different time points in the normothermic and mild hypothermic CPB groups are presented in Table 2.

Table 2

Comparison of the De Ritis Ratio between normothermic and mild hypothermic groups across time points

Parameter	Normothermic (n=75)	Mild Hypothermic (n=75)	p-value
De Ritis Ratio (Prebypass)	1.67 ± 1.12	1.72 ± 1.05	0.751
De Ritis Ratio (Postbypass)	2.14 ± 1.89	2.45 ± 2.30	0.032*
De Ritis Ratio (Postoperative)	2.89 ± 3.45	3.12 ± 4.10	0.048*

The Mann–Whitney U test was used to compare differences between the two independent groups (Normothermic vs. Mild Hypothermic)

As shown in Table 2, no significant difference was observed between the groups during the prebypass period (p=0.751). However, in the mild hypothermic group, the De Ritis ratio was significantly higher in both the postbypass and postoperative periods (p=0.032 and p=0.048, respectively). These findings suggest that hypothermia may have a more pronounced effect on liver enzyme dynamics, particularly during the reperfusion phase.

Intragroup changes in the De Ritis ratio across different time points are presented in Table 3.

Table 3

Intragroup statistical comparisons

Comparison	p-value	Significant Difference
Normothermic: Within-group changes over time	<0.001*	Postoperative > Postbypass > Prebypass
Mild Hypothermic: Within-group changes over time	0.002*	Postoperative, Postbypass > Prebypass

The Friedman test was used to analyze the dependent measurements across the three time points (Prebypass, Postbypass, Postoperative) within the same group.

Significant increases in the De Ritis ratio over time were observed within both groups. In the normothermic group, the postoperative De Ritis ratio was significantly higher than both the postbypass and prebypass values (p<0.001). In the mild hypothermic group, the De Ritis ratios in the postbypass and postoperative periods were significantly higher than those in the prebypass period (p=0.002).

Temporal changes and relative increases in the De Ritis ratio within each group are presented in Table 4.

Table 4

Time-dependent changes and relative increases in the de ritis ratio within groups

Group	Time Point Comparison	Relative Increase (%)
Normothermic	Prebypass → Postbypass	+28%
Normothermic	Postbypass → Postoperative	+35%
Mild Hypothermic	Prebypass → Postbypass	+42%
Mild Hypothermic	Postbypass → Postoperative	+27%

In the normothermic group, the De Ritis ratio increased by approximately 28% from the prebypass to the postbypass period. In the subsequent postoperative period, this increase reached 35%. In the mild hypothermic group, the De Ritis ratio rose by 42% from the prebypass to the postbypass period and by 27% from the postbypass to the postoperative period. These findings indicate a marked time-dependent increase in the De Ritis ratio in both groups.

3.3. Analysis of subgroups with De Ritis Ratio >2.0

Table 5 presents the time-dependent percentage distribution of patients with a De Ritis ratio greater than 2.0.

Table 5

Percentage of patients with De Ritis Ratio >2.0 over time

Time Point	Normothermic (%)	Mild Hypothermic (%)
Prebypass	25	28
Postbypass	38	51
Postoperative	40	58

In both groups, the proportion of patients with a De Ritis ratio >2.0 increased following surgery, with a notably higher percentage observed in the mild hypothermic group during the postoperative period, reaching 58%—a significant difference compared to the normothermic group.

3.4. Biochemical correlations

Spearman correlation analyses between the De Ritis ratio and GGT, total bilirubin, and direct bilirubin were calculated for each time point (prebypass, postbypass, and postoperative), and the results are presented in Table 6.

Table 6

Correlations between the De Ritis Ratio and GGT, total bilirubin, and direct bilirubin parameters

De Ritis (Time Point)	Parameter	Spearman r	p-value
Prebypass	GGT	−0.386	0.000**
	Total Bilirubin	0.300	0.000**
	Direct Bilirubin	0.024	0.773
Postbypass	GGT	−0.362	0.000**
	Total Bilirubin	0.119	0.145
	Direct Bilirubin	−0.138	0.088
Postoperative	GGT	−0.344	0.000**
	Total Bilirubin	0.221	0.006*
	Direct Bilirubin	0.178	0.028*

The Spearman correlation test was used to evaluate the relationship between the De Ritis ratio and GGT, total bilirubin, and direct bilirubin levels. GGT: Gamma-glutamyl transferase.

According to the Spearman correlation analysis, a significant negative correlation was observed between the De Ritis ratio and GGT levels across all time points (Prebypass: $r = -0.386$, $p < 0.001$; Postbypass: $r = -0.362$, $p < 0.001$; Postoperative: $r = -0.344$, $p < 0.001$). This finding suggests that individuals with lower GGT levels tend to have higher De Ritis ratios. Additionally, a positive correlation was identified between the De Ritis ratio and total bilirubin, particularly during the prebypass ($r = 0.300$, $p < 0.001$) and postoperative ($r = 0.221$, $p = 0.006$) periods. Correlations with direct bilirubin were generally weak and reached statistical significance only in the postoperative period ($r = 0.178$, $p = 0.028$).

3.5. Gender-based evaluation

When the De Ritis ratio was analyzed based on sex, female patients exhibited higher mean De Ritis ratios than male patients across all time points (Table 7).

Table 7

Comparison of the De Ritis Ratio according to gender

Time Point	Mean De Ritis (Male)	Mean De Ritis (Female)	p-value
Prebypass	1.43 ± 0.75	1.74 ± 1.02	0.0433 *
Postbypass	1.84 ± 0.92	2.59 ± 1.55	0.0002 **
Postoperative	2.06 ± 1.19	2.44 ± 1.47	0.0884

This difference was found to be statistically significant particularly in the prebypass ($p = 0.0433$) and postbypass ($p = 0.0002$) periods. Although the mean value in the postoperative period was also higher in females, the difference did not reach statistical significance ($p = 0.0884$).

4. Discussion

4.1. Effect of temperature strategy on temporal changes in the De Ritis Ratio

In this retrospective analysis of CABG patients, we found that CPB significantly increased the De Ritis ratio in both normothermic and hypothermic strategies, with a more pronounced elevation in the hypothermic group during the postbypass and early postoperative periods (p=0.032 and p=0.048). These results suggest that mild hypothermia may exacerbate hepatic enzyme release compared to normothermia. Since baseline and operative parameters were comparable, the observed differences are likely due to temperature strategy. Both groups showed a progressive rise in De Ritis from prebypass to postoperative phases (p<0.01), indicating a general hepatic stress response to CPB. Notably, De Ritis >2.0 was observed in 58% of hypothermic and 40% of normothermic patients postoperatively, implying greater hepatocellular injury with hypothermic CPB, particularly during reperfusion.

4.2. Literature comparison and pathophysiological perspective

Our findings support the notion that CPB contributes to hepatic injury. Postoperative transaminase and bilirubin elevations remain common in cardiac surgery, with hyperbilirubinemia reported in 10–40% of cases[14]. This reflects a multifactorial insult, including oxidative stress, systemic inflammation, and centrilobular ischemia during CPB, followed by reperfusion damage upon rewarming[15,16]. In our cohort, hypothermic patients likely experienced more severe hepatic ischemia due to reduced splanchnic perfusion under hypothermia. Intraoperative studies confirm decreased hepatic venous flow during hypothermic CPB, which may predispose the liver to hypoxia and subsequent enzyme release during reperfusion. Normothermic CPB, by preserving organ perfusion and oxygenation, may reduce this insult[17]. Previous studies have shown that normothermia is associated with better hepatic outcomes and lower oxidative stress[17,18]. Although some earlier reports noted no significant enzyme differences between groups, those involved shorter bypass times and lower-risk populations. In our study, slightly longer CPB duration in the hypothermic group may have exacerbated enzyme release[14]. Overall, perfusion temperature appeared to influence De Ritis trajectories independently, suggesting that avoiding unnecessary hypothermia may reduce hepatic stress in CABG. By elucidating the link between CPB management and liver enzyme dynamics, this work contributes to the broader effort of minimizing organ injury in cardiac surgery and improving perioperative care standards[19]. The evidence to date indicates that normothermic CPB is at least as safe and effective as hypothermia for the heart and other organs[19], and our findings suggest an added benefit in terms of hepatic protection.

The De Ritis ratio remains a valuable marker of liver injury. While ALT is cytosolic, AST also exists in mitochondria; thus, severe injury with necrosis elevates AST disproportionately[11]. Ratios above 2 suggest extensive damage or ischemic hepatitis. In our study, the hypothermic group showed higher ratios post-CPB, indicating more severe hepatocyte stress during reperfusion. This aligns with prior findings where AST rose threefold post-CPB, particularly in patients with worse outcomes[20]. Similar surges have been linked to "shock liver" in adults[11]. That many of our patients exceeded an De Ritis ratio of 2.0, especially under hypothermia, underscores its utility in detecting significant hepatic insult and guiding postoperative monitoring.

4.3. Evaluation of clinical findings with supporting parameters and the role of gender

We also evaluated secondary factors affecting the De Ritis ratio. A notable finding was its inverse correlation with GGT levels across all time points ($r \approx -0.35$ to -0.38, $p<0.001$), suggesting a hepatocellular rather than cholestatic enzyme release pattern. This is consistent with acute ischemic or toxic liver injury, where transaminases rise while GGT remains stable. Postoperatively, De Ritis showed a mild positive correlation with total bilirubin ($r \approx 0.22$, $p=0.006$), indicating greater hepatocyte injury in patients with higher bilirubin levels, an association also reported in previous studies of CPB, related hepatopathy[14]. Direct bilirubin correlated weakly with De Ritis, suggesting minor impairment in conjugation or excretion.

Demographically, female patients exhibited consistently higher De Ritis ratios than males, with significant differences in prebypass and early post-bypass phases. This aligns with epidemiological data showing women generally have higher De Ritis ratios despite lower absolute enzyme levels[21]. One explanation is men's typically higher ALT, possibly due to muscle mass or liver fat[22]. In our cohort, the preoperative ratio was higher in women (~1.74 vs. 1.43), and this trend persisted post-CPB. While not necessarily indicating greater injury, it highlights the need to consider sex-based enzyme kinetics when interpreting De Ritis levels[21].

4.4. Limitations

Several limitations should be acknowledged. First, as a retrospective single-center study, our analysis is subject to selection bias and relies on the accuracy of medical records. We did not have direct measures of hepatic blood flow or oxygenation during CPB, so our mechanistic explanations are inferred from enzyme data and existing literature. While the two patient groups were demographically and clinically similar, there was a trend toward longer cross-clamp and perfusion times in the hypothermic group. Although not statistically significant, this could have contributed to greater liver enzyme release, since longer CPB duration is known to worsen hepatic ischemia. The sample size (n=150) provides moderate power, but a larger cohort or randomized trial would be ideal to confirm that temperature alone drives the observed differences in De Ritis ratio. Additionally, we focused on biochemical markers; we did not formally assess clinical liver outcomes such as postoperative hepatic dysfunction scores or longer-term liver health.

Finally, our findings are limited to comparisons between mild systemic hypothermia (28–34 °C) and near-normothermic perfusion, and it remains uncertain whether deeper hypothermia or alternative cooling protocols would result in more pronounced hepatic effects. Despite these limitations, our study sheds light on the hepatic implications of perfusion temperature during CABG and suggests a potential benefit of normothermic CPB in reducing immediate hepatocellular injury.

5. Conclusion

In conclusion, maintaining normothermic perfusion during CABG appears to mitigate the acute hepatic stress compared to mild hypothermic CPB. Both strategies lead to an increase in the De Ritis ratio postoperatively, indicating that cardiopulmonary bypass inherently causes transient hepatocellular injury. However, the hypothermic CPB group showed significantly greater elevations in the De Ritis ratio in the early reperfusion period, reflecting a more pronounced release of liver enzymes. These results suggest that even moderate hypothermia can exacerbate ischemia-reperfusion injury to the liver, whereas normothermic CPB appears to exert a more protective effect on hepatic function in the immediate postoperative period. From a clinical perspective, adopting normothermic CPB, when feasible, could be beneficial for patients, particularly those with pre-existing liver vulnerability, by lessening the degree of hepatic enzyme disturbance. The De Ritis ratio itself proved to be a useful indicator of liver injury dynamics in this setting; a ratio above 2.0 was common after on-pump surgery and more frequent under hypothermic conditions, potentially serving as a red flag for significant hepatocellular stress. Overall, our study reinforces that perfusion temperature is an important modulator of end-organ response during cardiac surgery. Future prospective studies or randomized trials are warranted to confirm these findings and determine whether the biochemical advantages of normothermic CPB translate into improved clinical outcomes. Additionally, further research into protective strategies for the liver during CPB (such as optimized perfusion flow, pharmacological agents, or ischemic preconditioning) may help improve patient recovery, regardless of the temperature strategy employed.

Statement of ethics

Ethical approval for the study was granted by the Clinical Research Ethics Committee of Harran University (Date: 14.07.2025, Number: HRÜ-25.13.16).

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

This Data and materials are available to the researchers.

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