Preoperative Inflammatory Biomarkers Identify Dexamethasone Responders in Cardiac Surgery: A Post Hoc Analysis of the DECS Trial

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Key Points Summary

- **Question**: Do pre-op NLR and SII (i) stratify postoperative risk and (ii)) identify patients more likely to benefit from dexamethasone?
- **Findings**: Higher NLR & SII were prognostic for major complications. Exploratory thresholding suggested SII ≥770 identified a subgroup that exhibit greater benefit from dexamethasone vs placebo.
- **Implication:** Routine pre-op CBC-derived indices may support biomarker-enriched trials and targeted perioperative immunomodulation in cardiac surgery.

BACKGROUND

- **Clinical Problem:** Cardiac bypass (CPB) provokes systemic inflammation associated with postoperative complications[1]
- **Prior Evidence:** In the Dexamethasone for Cardiac Surgery (DECS) trial, dexamethasone did not reduce major composite adverse events, suggesting benefit may vary by baseline inflammatory state[2]
- **Gap**: Benefit may be concentrated in patients with heightened pre-op inflammatory phenotype[3]
- **Approach**: Neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) are routinely available CBC-derived biomarkers linked to adverse postoperative outcomes[4]
- **Objective**: To test whether pre-op NLR & SII are (1) prognostic for complications and (2) predictive of dexamethasone benefit, including threshold exploration.

Methods

Study Design & Data Source

- **Inclusion/Exclusion:** Post hoc analysis of the DECS trial (NCT00293592)
- **Cohort**: Patients enrolled at University Medical Center Utrecht with available preoperative CBC values needed to compute NLR and SII.
- **Regulatory**: IRB waiver of consent; all outputs de-identified.

Exposure & Outcome

- **Exposures**: Dexamethasone vs placebo, per original randomization
- **Outcome**: 30-day composite of death, myocardial infarction, stroke, renal failure, or respiratory failure (original primary composite endpoint).

Statistical Analyses

- **Balance / baseline descriptions:** Baseline characteristics were compared between arms using linear regression and Pearson χ^2 tests. Per a prespecified analysis plan, multivariable adjustment was planned if baseline imbalance was detected (p<0.10).
- **Prognostic associations**: To address distribution skew, logistic regression models estimated associations of log-NLR and log-SII with the primary outcome.

$$NLR = \frac{Absolute\ neutrophil\ count}{Absolute\ lymphocyte\ count} \qquad SII = \frac{Absolute\ neutrophil\ count \times platelet\ count}{Absolute\ lymphocyte\ count}$$

- **Effect modification:** Models included treatment × biomarker interaction terms using both linear and restricted cubic splines.
- **Threshold exploration**: Johnson–Neyman approach was used to identify biomarker values where the estimated treatment effect differed from 0 (one-sided α=0.05, directional hypothesis).
- **Threshold-based subgroup comparisons:** Within above threshold-defined subgroups, outcomes were compared using χ^2 tests; treatment effects were summarized as NNT when applicable.
- **Significance / reporting**: Statistical significance was defined as two-sided p<0.05 for primary inference

Results

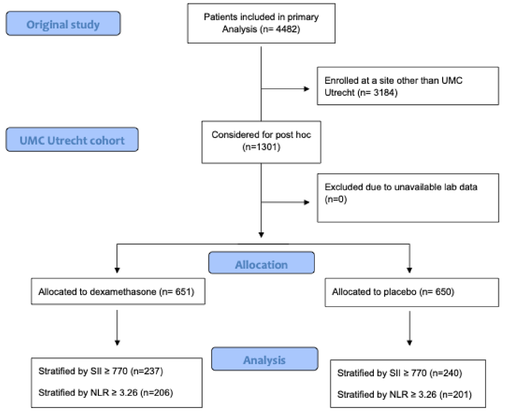

Figure 1: Cohort selection, randomization, and biomarker stratification.

	Placebo 650 (50.0%)	Dexamethasone 651 (50.0%)	Total (1,301)	Test
Age, yes	65.850 (11.3)	65.740 (11.8)	65.795 (11.5)	0.864
Gender, Male	449 (69.1%)	465 (71.4%)	914 (70.3%)	0.354
Body Mass Index, kg/m²	26.8 (4.2)	26.9 (4.1)	26.8 (4.1)	0.473
Hypertension, yes	363 (55.8%)	346 (53.1%)	709 (54.5%)	0.329
Diabetes, yes	125 (19.2%)	140 (21.5%)	265 (20.4%)	0.308
Treatment for pulmonary disease, yes	64 (9.8%)	81 (12.4%)	145 (11.1%)	0.137
Cerebrovascular accident, yes	68 (10.5%)	78 (12.0%)	146 (11.2%)	0.385
Peripheral artery disease, yes	47 (7.2%)	61 (9.4%)	108 (8.3%)	0.162
Preoperative creatinine µmol/l	99.0 (44.8)	98.6 (33.8)	98.8 (39.7)	0.855
Recent myocardial infarction (<90 days), yes	57 (8.8%)	59 (9.1%)	116 (8.9%)	0.853
Left ventricular function:				
Good (>50%)	483 (74.3%)	469 (72.0%)	952 (73.2%)	
Moderate (30-50%)	141 (21.7%)	152 (23.3%)	293 (22.5%)	
Poor (<30%)	26 (4.0%)	30 (4.6%)	56 (4.3%)	0.636
EuroScore (IQR)*	4 (3-7)	5 (3-7)	4 (3-7)	0.244
Beta-blockers, yes	441 (67.8%)	455 (69.9%)	896 (68.9%)	0.425
Statins, yes	183 (28.2%)	208 (32.0%)	391 (30.1%)	0.135
Reoperation, yes	32 (4.9%)	41 (6.3%)	73 (5.6%)	0.281
Procedure duration, min	204.1 (78.9)	206.1 (108.6)	205.1 (94.9)	0.713
CPB time, min	116.1 (61.7)	116.0 (67.9)	116.1 (64.9)	0.974
Cross-clamp time, min	86.7 (47.7)	86.5 (49.6)	86.6 (48.7)	0.964
Deep hypothermic circulatory arrest, yes	3 (0.5%)	5 (0.8%)	8 (0.6%)	0.479
Cell saver, yes	130 (20.0%)	164 (25.2%)	294 (22.6%)	0.025
Tranexamic acid, yes	451 (69.4%)	444 (68.2%)	895 (68.8%)	0.646
NLR (SD)	3.009 (1.7)	2.993 (1.7)	3.001 (1.7)	0.869
SII (SD)	780.0 (631.1)	780.671 (558.4)	780.4 (595.6)	0.985

Table 1: Baseline characteristics of included patients.

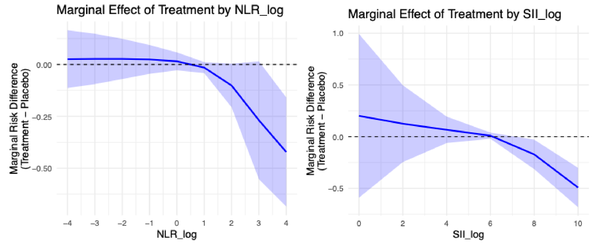

Table 2: Marginal effect of dexamethasone across log-transformed NLR (left panel) and SII (right panel). The blue lines represent estimated marginal effects, while shaded areas indicate 95% confidence intervals. Negative values indicate a treatment benefit.

- **Study Population**: 1,301 (29.1% of DECS patients) were included (**Fig. 1**); baseline characteristics were similar (p > 0.1) between arms (**Table 1**).
- **Biomarker Associations**: Higher NLR & SII were both associated with increased odds of the primary outcome (log-NLR OR 1.99, 95% CI 1.27–3.11, P<0.001; log-SII OR 1.59, 95% CI 1.10–2.30, P=0.013).
- **Dexamethasone-Biomarker Interaction**: Marginal risk difference became more favorable with higher biomarker values (**Fig. 2**)
- **Thresholds**: Thresholds for SII and NLR were 770 and 3.26, respectively.
- **Above-threshold subgroup**: Above SII threshold, dexamethasone was associated with fewer composite events (NNT 17; **Table 3**).

	Above NLR Threshold Patients			Above SII Threshold Patients		
	Placebo (n=201)	Dexamethasone (n=206)	RR (95% CI)	Placebo (n=240)	Dexamethasone (n=237)	RR (95% CI)
Primary Study Endpoint	23 (11.4 %)	17 (8.25 %)	0.721 (0.397–1.31)	27 (11.3%)	12 (5.06%)	0.450 (0.234–0.867)
Components of the Primary Study Endpoint						
Death	9 (4.48 %)	6 (2.91 %)	0.650 (0.236–1.79)	8 (3.33%)	6 (2.53%)	0.759 (0.268–2.16)
Myocardial infarction	6 (2.99%)	1 (0.485%)	0.163 (0.020–1.34)	6 (2.50%)	1 (0.422%)	0.169 (0.020–1.39)
Stroke	4 (1.99 %)	2 (0.971 %)	0.488 (0.090–2.63)	5 (2.08%)	2 (0.844%)	0.405 (0.079–2.07)
Renal failure	6 (2.99 %)	5 (2.43 %)	0.813 (0.252–2.62)	6 (2.50%)	4 (1.69%)	0.675 (0.193–2.36)
Respiratory failure	9 (4.48 %)	9 (4.37 %)	0.976 (0.395–2.41)	12 (5.00%)	5 (2.11%)	0.422 (0.151–1.18)

Table 3: Primary Study End Point and Components of the Primary Study End Point in the Dexamethasone and Placebo Groups for above threshold patients.

Discussion & Conclusions

- **Final Takeaway**: A higher pre-op inflammatory phenotype is associated with increased risk of major postoperative complications and may identify patients more likely to benefit from dexamethasone, supporting future biomarker-enriched perioperative trials.
- **Strengths**: Leverages the largest RCT dataset in this setting; uses routinely available, low-cost biomarkers; demonstrates both prognostic and treatment-effect–modifying signal for a clinically meaningful endpoint.
- **Limitations:** Post hoc/hypothesis-generating; single-center subset; not generalizable to other steroid regimens/doses; thresholds were derived and evaluated in the same dataset (risk of overfitting).

References

1. Bain CR, Myles PS, Corcoran T, et al. Anaesthesia. 2023;78:356–370.
2. Dieleman JM, Nierich AP, Rosseel PM, et al. JAMA. 2012;308:1761–1767.
3. Wier J, Jones IA, Palmer R, et al. J Bone Joint Surg Am. 2025;107:163–173.
4. Jones IA, Wier J, Chen MS, et al. J Am Acad Orthop Surg. 2024;32:e1315–e1323.