ORIGINAL ARTICLE

Predictive Value of Postoperative Neutrophil-Lymphocyte Ratio for Major Adverse Cardiac Events Following Off-Pump CABG with Preoperative Dexamethasone: A Retrospective Analysis from a Randomized Controlled Trial

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ABSTRACT

Introduction:The neutrophil-lymphocyte ratio (NLR) is a known predictor of major adverse cardiac events (MACE) after coronary artery bypass grafting (CABG). However, its prognostic value in patients receiving preoperative dexamethasone remains uncertain. This study aimed to determine the optimal cut-off value of 24-hour postoperative NLR for predicting MACE in off-pump CABG (OPCAB) patients who received preoperative dexamethasone. **Methods:** This study is a single-center retrospective secondary analysis of data derived from a previously conducted randomized controlled trial (RCT). For this current observational study, a specific cohort of 60 OPCAB patients was retrospectively selected from the parent RCT, focusing on those who had received preoperative dexamethasone. This cohort comprised 12 patients who developed MACE and 48 who did not. The primary outcome for this analysis was the occurrence of MACE postoperatively, and the NLR was measured within the first 24 hours after surgery. **Results**: Patients who developed MACE had significantly higher postoperative NLRs. Receiver operating characteristic analysis showed an area under the curve (AUC) of 72.9%. A cut-off value of 16.24 for NLR provided a sensitivity of 91.7%, specificity of 58%, positive predictive value of 35.5%, negative predictive value of 96.9%, and a risk ratio of 10.29 (95% CI: 1.42–74.79). No significant adverse effects related to dexamethasone were noted. **Conclusion**: An NLR cut-off of 16.24 may serve as a reliable early predictor of MACE in OPCAB patients receiving preoperative dexamethasone, indicating that NLR retains prognostic value even with anti-inflammatory premedication.
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INTRODUCTION

The neutrophil-lymphocyte ratio (NLR), indicative of inflammation, holds significance across various medical conditions, particularly in cardiovascular diseases. Neutrophils are key players in acute inflammation, and their ratio to lymphocytes has been associated with prognostic implications in clinical settings. Several studies have explored the prognostic role of NLR in predicting adverse events following cardiac surgeries. 1-8 Such as a study by Silberman et al.2, stated that higher NLR is related to higher mortality and postoperative adverse events such as myocardial infarction, arrhythmia, stroke, and renal failure. Another study by Papa et al.3, also showed that elevated NLR was found to be associated with adverse outcomes and reduced survival of patients presenting with a wide spectrum of coronary disease, including stable coronary artery disease. Gibson et al. also stated that elevated NLR to be a predictor of both operative and postoperative mortality of patients that underwent coronary artery bypass grafting surgery (CABG), while total white blood cell alone was not a predictor.4 All of these studies have gave association of NLR prognostic value for patients that underwent cardiac surgeries including CABG.3,4

However, the administration of corticosteroids such as dexamethasone, commonly used preoperatively to reduce inflammation and improve surgical outcomes, introduces potential confounding effects on NLR's prognostic capacity. Dexamethasone exerts potent immunomodulatory actions by suppressing neutrophil activation, inducing lymphocyte apoptosis, and altering leukocyte trafficking, which can significantly modify peripheral blood cell counts and inflammatory markers.5-10 This immunosuppressive effect may lower NLR values, potentially masking or altering its predictive accuracy for major adverse cardiac events (MACE) post-CABG. Conflicting evidence exists regarding corticosteroids' impact on inflammatory biomarkers and clinical outcomes in cardiac surgery; some studies report reduced inflammatory responses and improved outcomes,1,12 while others suggest potential adverse effects including hyperglycemia and increased infection risk, which may indirectly influence NLR dynamics and prognostic utility. 13-16

Given these uncertainties, it remains unclear whether postoperative NLR retains its predictive value in patients receiving preoperative dexamethasone. This study aims to address this gap by determining the cut-off value of 24-hour postoperative NLR in predicting MACE specifically in patients undergoing off-pump CABG (OPCAB) with preoperative dexamethasone therapy. It is important to note that this investigation represents a secondary exploratory analysis nested within a larger single-center, parallel-group, superiority randomized controlled trial (RCT) evaluating the overall effectiveness of dexamethasone in cardiac surgery. The primary RCT focuses on clinical outcomes related to dexamethasone administration, whereas this substudy specifically explores the prognostic role of NLR within the dexamethasone-treated subgroup.

Methodology

Study Design

This study is a retrospective, observational secondary analysis of data derived from a previously conducted double-blind, parallel-group, superiority randomized controlled trial (RCT) at the National Cardiovascular Center Harapan Kita, Indonesia (registration number: LBB.01.01/VII/239/KEP.050/2018). The parent RCT enrolled consecutive adult patients undergoing either off-pump (OPCAB) or on-pump (ONCAB) coronary artery bypass grafting between July 1st, 2018 and January 20th, 2019. Patients were randomized in a 1:1 ratio using Research Randomizer version 4.0 software to receive either intravenous dexamethasone (1 mg/kg, maximum 100 mg) or placebo (0.9% NaCl) administered preoperatively. Randomization was stratified by surgical technique (OPCAB vs ONCAB) and allocation concealment was maintained using sealed opaque envelopes. Both participants and care providers, as well as outcome assessors, were blinded to group allocation. Full details of the parent trial design, including inclusion and exclusion criteria, blinding procedures, and primary outcomes, are available in in other studies that have been published.1,2

For this current retrospective, observational substudy, our primary objective was to investigate the association between postoperative NLR and the MACE within a specific cohort of patients. Therefore, this analysis does not focus on the original randomization comparison of dexamethasone versus placebo. Instead, we retrospectively identified all patients from the parent RCT who underwent OPCAB surgery and who had received preoperative dexamethasone. The cohort for this specific analysis was then analyzed as a single group, based on the occurrence of MACE.

The inclusion criteria for this substudy were: (1) adult patients (age 18–75 years), (2) elective OPCAB surgery, (3) receipt of preoperative dexamethasone per protocol, and (4) postoperative NLR measured within 24 hours after surgery. Exclusion criteria included: (1) incomplete clinical or laboratory data, (2) intraoperative conversion to ONCAB, (3) preoperative systemic inflammation indicated by fever or leukocytosis (≥15,000 cells/mm), (4) active infections such as sepsis, (5) malignancy, (6) recent myocardial infarction, (7) history of cardiopulmonary resuscitation, (8) additional intraoperative procedures (valve, large vessel, or septal repair), (9) severe organ dysfunction (grade 4 congestive heart failure, kidney failure, severe respiratory failure, or stroke with complications), (10) previous cardiac surgery, and (11) withdrawal of consent. These exclusions were designed to minimize confounding factors affecting preoperative NLR levels. The final cohort included 60 OPCAB patients, with 12 developing MACE and 48 without. The selection process is detailed in Figure 1.

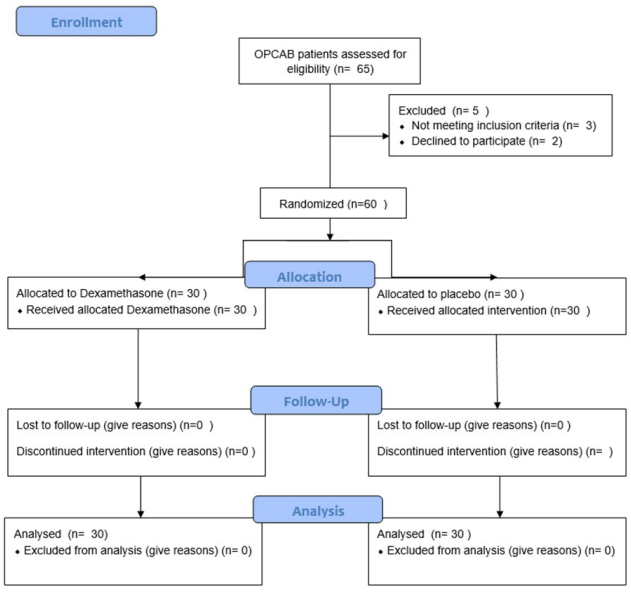

Figure 1: Diagram of patients selection, randomization, and analysis.

Outcomes and Data Collection

The primary outcome for this analysis was the occurrence of MACE during the postoperative period, as defined in the parent protocol.1,2 MACE encompassed death, myocardial infarction, stroke, arrhythmia, respiratory failure, and kidney failure. NLR was measured from routine blood samples collected within 24 hours postoperatively. Baseline demographic, clinical, and perioperative data were extracted from the RCT database.

Blinding

In the parent RCT, allocation concealment and double-blinding were maintained for participants, care providers, and outcome assessors. For this secondary analysis, to minimize potential bias, outcome assessors (for any data collection or adjudication in this substudy, if applicable) and data analysts were blinded to the original dexamethasone/placebo group allocation from the parent RCT during data extraction and statistical analysis. This ensured that the assessment of NLR and MACE, and the subsequent statistical analysis, was performed independently of the original randomized treatment assignment.

Sample Size and Power

As this study is a retrospective secondary analysis utilizing an existing cohort from a previously conducted RCT, the sample size for this substudy was determined by the availability of eligible patients who met our specific inclusion criteria. For the analysis of the NLR cut-off value in predicting MACE within this cohort, a post-hoc power calculation was performed to assess the statistical power of our derived sample size. Based on an assumed minimum meaningful correlation coefficient (r) of 0.5 between NLR and MACE occurrence, with an alpha ($Z\alpha$) of 1.64 (for a one-sided test) and a beta ($Z\beta$) of 1.28 (corresponding to a power of 90%), the minimum required sample size to detect this correlation was calculated to be 31 patients. After accounting for a 10% potential data loss, a sample size of 34 patients would be required. Our final cohort included 60 OPCAB patients, providing sufficient power to assess this correlation and the predictive performance of NLR for MACE within our specified assumptions. All sample size calculations were performed using standard statistical formulas and were based on effect sizes and standard deviations derived from published studies.17-19

Statistical Analysis

Data distribution was assessed for normality using the Kolmogorov-Smirnov test. Continuous variables with normal distribution were presented as mean ± standard deviation (SD), while those with non-normal distribution were expressed as median with range or interquartile range (IQR). Categorical variables were summarized as counts and percentages. Group comparisons for continuous variables were performed using the unpaired t-test if data were normally distributed, or the Mann-Whitney U test if data were non-normally distributed. For categorical variables, the Chi-square test or Fisher's exact test was used as appropriate.

The predictive performance of postoperative NLR for MACE was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) with 95% confidence intervals (CI) was reported to quantify discrimination ability. The optimal NLR cut-off value was determined using the Youden index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and relative risk (RR) with 95% CIs were calculated to assess diagnostic accuracy.

Baseline characteristics were compared between groups, and as no significant differences were observed, multivariable logistic regression was deemed unnecessary for confounder adjustment.

Missing data were handled using complete case analysis (CCA), whereby only participants with complete data for all variables included in the analysis were considered. This approach assumes that data are missing completely at random (MCAR), meaning the probability of missingness is unrelated to observed or unobserved data. Although CCA may reduce the sample size and statistical power, it provides unbiased estimates under the MCAR assumption and is widely used in clinical research when the proportion of missing data is low. No imputation methods were applied. All statistical analysis were performed using the Statistical Product and Service Solution (SPSS) version 21 software.

Results

This study included 60 subjects, 12 experienced MACEs, while 48 did not. None were excluded due to the complete follow-up for all subjects included. The subject's demographic data are displayed in Table 1. All patients' demographics did not differ significantly between the two groups. In addition, the most common MACE events were arrhythmias (13.3%) and myocardial infarction (5%).

Table I: Demographics of the study subjects

Variable	Group MACE (n = 12)	Group non-MACE (n = 48)	P-value
Age (mean ±SD; year)	62.8 ± 7.0	59.3 ± 7.7	0.619
Sex (n (%))			
Male	9 (75.0)	38 (79.2)	0.754
Female	3 (25.0)	10 (20.8)	
Weight (mean ±SD; kg)	68.3 ± 11.0	67.7 ± 11.3	0.900
Height (mean ±SD; cm)	160.3 ± 8.8	161.4 ± 7.3	0.592
Body mass index (mean ±SD; kg/m^2)	26.5 ± 3.5	25.9 ± 3.5	
Obese (≥28; n (%))	4 (33.3)	12 (25.0)	
Overweight (23-27.9; (n (%))	6 (50.0)	26 (54.1)	0.442
Normal (17.5-22.9; n (%))	2 (16.7)	10 (20.8)	
Underweight (<17.5; n (%)))	0 (0.0)	0 (0.0)	
Comorbid types (n (%))			
Hypertension	10 (83.3)	41 (85.4)	0.386
Diabetes Mellitus	8 (66.7)	27 (56.2)	
Comorbidity amounts (n (%))			
5	1 (8.3)	3 (6.3)	
4	4 (33.3)	19 (39.5)	
3	3 (25.0)	19 (39.5)	0.202
2	4 (33.3)	4 (8.3)	
1	0 (0.0)	3 (6.3)	
Creatinine Preoperative (mean ±SD; mg/dL)	1.2 (0.5 – 2.8)	1.1 (0.6 – 2.3)	0.613
>1.3 mg/dL (n (%))	3 (25.0)	13 (27.0)	
≤ 1.3 mg/dL (n (%))	9 (75.0)	35 (63.0)	
Number of obstructions (n (%))			
2	2 (16.7)	6 (12.5)	0.704
3	10 (83.3)	42 (87.5)	
Total Graft (n (%))			
1	0 (0.0)	1 (2.0)	
2	6 (50.0)	13 (27.0)	0.430
3	6 (50.0)	32 (66.7)	
4	0 (0.0)	2 (4.1)	
MACE (n (%))	12 (20.0)		
Arrhythmia (n (%))	8 (13.3)	-	
Myocardial infarction (n (%))	3 (5.0)	-	-
Renal failure (n (%))	2 (3.3)	-	
Respiratory failure (n (%))	1 (1.7)	-	
Stroke (n (%))	0 (0.0)	-	

Table 2 suggests that preoperative NLR between the two groups are not significantly different, with a mean difference (MD) of 0.23 (95% CI -0.23 to 0.70, p=0.082)]. Conversely, the post-operative NLR mean for the MACE group is significantly higher than the non-MACE group, with MD of 4.76 (95% CI 0.87 to 8.66, p=0.015). This data showed that both groups have similar preoperative NLR value and preoperative dexamethasone did not influence the NLR postoperative cut-off value in predicting MACE.

Table II: The relationship between NLR value and MACE based on the subject group

Variable	MACE	n	Mean ± Deviation	Mean Difference	CI 95%		Median (min-max)	p-value
					min	max		
NLR pre	Yes	12	2.1 ± 0.5	0.2	-0.2	0.7	2.0 (1.3 – 2.8)	0.082
	No	48	1.9± 0.8				1.7 (0.9 – 4.7)	
NLR post	Yes	12	21.1± 0.5	4.8	0.9	8.7	21.6 (11.2 – 26.3)	0.015
	No	48	16.4± 6.3				15.1 (5.2 – 29.3)	

The 24-hour postoperative AUC NLR value of the dexamethasone group, respectively, to MACE had an area of 72.9% (95% CI 59.1-86.7%), p-value = 0.015, and sensitivity and specificity of 75% each (Figure 2). The following are the selected 24-hour postoperative NLR cut-off values (Table 3)

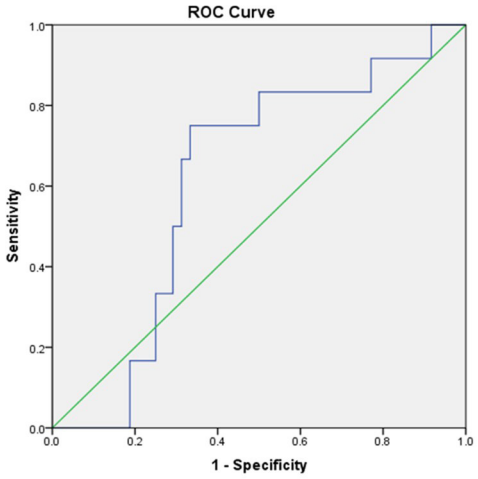

Figure 2: AUC- ROC graph of 24-hours postoperative NLR in dexamethasone group respectively to MACE

Table III: Cut-off values of 24-hours postoperative NLR in dexamethasone group respectively with MACE

No.	*Positive if Greater Than or Equal To*[a]	*Sensitivity*	*Specificity*	No.	*Positive if Greater Than or Equal To*[a]	*Sensitivity*	*Specificity*
1	4.1914	1.000	0.000	31	16.7791	0.833	0.583
2	6.4144	1.000	0.021	32	17.4907	0.750	0.583
3	7.8076	1.000	0.042	33	17.7591	0.750	0.604
4	8.2008	1.000	0.063	34	17.9406	0.750	0.625
5	8.5396	1.000	0.083	35	18.3975	0.750	0.646
6	9.2128	1.000	0.104	36	18.7282	0.750	0.667
7	9.8275	1.000	0.125	37	18.8129	0.750	0.688
8	9.9859	1.000	0.146	38	18.8954	0.750	0.708
9	10.0984	1.000	0.167	39	19.5225	0.750	0.729
10	10.1863	1.000	0.188	40	20.3314	0.750	0.750
11	10.3600	1.000	0.208	41	20.5613	0.667	0.750
12	10.7424	1.000	0.229	42	21.0122	0.667	0.771
13	11.0885	1.000	0.250	43	21.4680	0.583	0.771

CONTINUE

Table III: Cut-off values of 24-hours postoperative NLR in dexamethasone group respectively with MACE. (CONT.)

No.	*Positive if Greater Than or Equal To*[a]	*Sensitivity*	*Specificity*	No.	*Positive if Greater Than or Equal To*[a]	*Sensitivity*	*Specificity*
14	11.2756	0.917	0.250	44	21.5193	0.500	0.771
15	11.4450	0.917	0.271	45	21.6757	0.500	0.792
16	11.8518	0.917	0.292	46	22.3003	0.417	0.792
17	12.4158	0.917	0.313	47	23.1472	0.333	0.792
18	12.6345	0.917	0.333	48	23.6189	0.333	0.813
19	13.0686	0.917	0.354	49	23.7905	0.333	0.833
20	13.5609	0.917	0.375	50	24.1479	0.250	0.833
21	13.6421	0.917	0.396	51	24.6948	0.167	0.833
22	13.8310	0.917	0.417	52	25.4562	0.167	0.854
23	14.3633	0.917	0.438	53	26.0427	0.167	0.875
24	14.7767	0.917	0.458	54	26.1569	0.167	0.896
25	14.8679	0.917	0.479	55	26.2640	0.083	0.896
26	15.1003	0.917	0.500	56	26.5337	0.000	0.896
27	15.4661	0.917	0.521	57	26.7856	0.000	0.917
28	15.6735	0.917	0.542	58	26.9499	0.000	0.938
29	15.9399	0.917	0.563	59	27.8177	0.000	0.958

The selected NLR cut-off value postoperatively was 16.24. This cut-off value was chosen due to its high sensitivity to rule out MACE in post-CABG patients with preoperative dexamethasone therapy. The sensitivity value is 91.7%, a specificity of 58.3% (Table 3), a positive predictive value of 35.5%, and a negative predictive value of 96.6%. This yields a Relative Risk (RR) of 10.29 (95% CI: 1, 42-74.79) with a p-value of 0.002 (Table 4).

Table IV: Relationship between NLR with MACE in subjects administered with dexamethasone.

			MACE			Relative Risk	95% CI	Nilai p
	Present		None					
	n	%	N	%				
NLR post	16.24	11	**35.5**	20	64.5	10.3	1.4-74.8	**0.002**
	<16.24	1	3.4	28	**96.6**			
	Total	12	20.0	48	80.0			

Discussion

Numerous studies have demonstrated the prognostic value of the NLR for postoperative outcomes following CABG, including MACE. However, to date, no research has specifically examined the NLR cut-off value and its association with MACE in patients receiving preoperative dexamethasone therapy.1-7,11,13 The immunomodulatory effects of dexamethasone, which effectively improve clinical outcomes and control postoperative inflammatory responses, raise uncertainty about whether dexamethasone alters NLR values and consequently affects its predictive accuracy.1,7,20,21 Our study addresses this gap by demonstrating that the mean postoperative NLR in the MACE group was significantly higher than in the non-MACE group, with a mean difference of 4.76 (95% CI 0.87 to 8.66, p=0.015), indicating that preoperative dexamethasone does not diminish the prognostic value of postoperative NLR for predicting MACE. Although, our NLR cut-off is higher than that reported by Sevuk et al.(cut-off: 8.34)22, who evaluated postoperative NLR in relation to post-pericardiotomy syndrome rather than MACE, reflecting differences in clinical outcomes assessed. Nonetheless, our higher sensitivity strengthens the utility of this cut-off as a prognostic indicator. Additional studies by Silberman et al.3 and Papa et al.4 corroborate our findings, showing that elevated NLR is associated with increased mortality and adverse postoperative events including myocardial infarction, arrhythmia, stroke, and renal failure, as well as reduced survival across a spectrum of coronary artery disease. Gibson et al.5 further demonstrated that elevated NLR, but not total white blood cell count, predicted both operative and postoperative mortality in CABG patients. While these studies support the prognostic value of NLR in cardiac surgery broadly, none have defined specific postoperative NLR cut-off values in patients receiving preoperative dexamethasone, highlighting the novelty of our work.

Supporting our findings, Nakamura et al.2 reported that established inflammatory markers such as C-reactive protein (CRP), procalcitonin, and interleukin-6 (IL-6) were significantly elevated in CABG patients experiencing MACE who received placebo in both on-pump and off-pump CABG. This further validates the role of inflammatory biomarkers, including NLR, in prognostication. Our analysis revealed an area under the curve (AUC) of 72.9% (95% CI: 59.1–86.7%, p=0.015) for postoperative NLR predicting MACE in the dexamethasone group, indicating reasonable discriminatory ability.

However, the key limitation that need to be higlighted is that the optimal NLR cut-off value of 16.24, with a sensitivity of 91.7% and specificity of 58%, its modest specificity (58.3%) and low positive predictive value (35.5%) restrict its clinical utility for confirming risk. This means that a low NLR is effective for excluding patients at risk of MACE, but a high NLR does not reliably confirm increased risk, as many patients with elevated NLR will not experience MACE. When comparing with the available CABG-specific literature, there is limited evidence directly reporting NLR cut-off values, sensitivity, and specificity for predicting MACE. For example, Garganeeva et al.23 found that while the NLR alone had a low discriminatory value for MACE after CABG (AUC=0.566, p=0.363), the combination of NLR with growth differentiation factor-15 (GDF-15) was significantly associated with adverse cardiovascular events, suggesting that NLR alone may not be sufficiently specific for risk confirmation in this population. Another study in post-CABG patients undergoing percutaneous coronary intervention found that pre-procedural NLR was not significantly different between those with and without MACE, and did not provide strong predictive value for MACE on its own.24 Additionally, Atasoy and Guven (2025) demonstrated that NLR was an independent predictor of postoperative atrial fibrillation after off-pump CABG, but did not provide specific cut-off values or detailed sensitivity/specificity for MACE prediction.25

Thus, current CABG-specific previous studies supports the prognostic association of NLR with MACE, but also highlights its limited specificity and the need for combination with other biomarkers or clinical factors to improve predictive accuracy. There is a lack of robust CABG studies reporting optimal NLR cut-off values with both high sensitivity and specificity for MACE, underscoring the importance of cautious interpretation and the need for further research in this area.

Limitations

This study has limitations that warrant consideration. First, the single-center design and small cohort size (n=60) may limit the generalizability of our findings to broader populations, particularly in regions with differing demographic or clinical profiles. For example, genetic, dietary, or comorbid factors unique to the Indonesian population (e.g., higher prevalence of diabetes mellitus or rheumatic heart disease) could influence NLR dynamics.26,27 Second, while our findings suggest that postoperative NLR is associated with MACE in CABG patients, the predictive performance of NLR as a standalone marker is limited due to its low specificity. In addition, the relatively small sample size, particularly the limited number of MACE events (n=12), may restricts

statistical power and raises the possibility of effect size overestimation. Our study also only assessed short-term postoperative outcomes and did not include long-term follow-up data such as 30-day or 6-month MACE rates. This limits the ability to evaluate the prognostic value of NLR for predicting adverse events over extended periods, which is important for clinical decision-making. These results should therefore be considered preliminary and hypothesis-generating, necessitating validation in larger, longer follow up cohorts. Furthermore, while our results suggest NLR retains prognostic utility post-dexamethasone, external validation in multi-center cohorts is needed to confirm its applicability across diverse settings.

Future applications

Clinically, our findings suggest that postoperative NLR remains a robust prognostic marker for MACE even in the context of dexamethasone's anti-inflammatory effects. This dual benefit of dexamethasone improving clinical outcomes and controlling inflammation while NLR retains prognostic utility offers a cost-effective and widely accessible tool for early risk stratification. The identified NLR threshold of 16.24 could assist clinicians in identifying high-risk patients who may benefit from enhanced monitoring such as serial troponin measurements or hemodynamic support, tailoring postoperative therapies including intensified statin regimens or anti-inflammatory agents, and informing shared decision-making regarding rehabilitation plans.28 However, several important considerations should be noted. The retrospective nature of this subgroup analysis introduces potential selection bias and confounding, as inclusion was based on the availability of postoperative NLR measurements and receipt of dexamethasone, which may not fully represent the parent randomized controlled trial (RCT) population. Hence, future RCT is recommended to perform. Furthermore, the follow-up period was limited to the duration of hospitalization, preventing assessment of the long-term prognostic value of postoperative NLR. Therefore, extended follow-up in future research is necessary to evaluate the sustained predictive utility of NLR beyond the immediate postoperative period. Future studies incorporating multiple centers and ethnically diverse cohorts are essential to confirm and extend these findings, ensuring the generalizability of the NLR cut-off across different populations, surgical practices, and cardiovascular risk profiles. Additionally, investigations into how dexamethasone dosing or timing, such as single versus multiple doses, modulates NLR's predictive accuracy would provide valuable insights.29 Finally, exploration of NLR in combination with other biomarkers, including CRP or IL-6, may improve risk prediction models and further enhance clinical decision-making.30

Conclusion

Twenty-four hours postoperative NLR with an optimal cut-off of 16.24 may serve as a useful marker for predicting MACE in patients undergoing off-pump CABG with preoperative dexamethasone therapy. However, given the limited discriminatory value of NLR alone for MACE prediction after CABG due to its low specificity, these findings should be considered preliminary and hypothesis-generating. Further large-scale, multi-center studies with longer follow-up are needed to validate the prognostic utility of NLR in this clinical setting and to determine its role in combination with other biomarkers or risk models.

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