

# Retrospective Evaluation of the Pre- and Postoperative Neutrophil-Lymphocyte Ratio as a Predictor of Mortality in Patients Who Underwent Coronary Artery Bypass Grafting

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## ABSTRACT

**Background:** We aimed to investigate the neutrophil-lymphocyte ratio (NLR) as a predictor of mortality in patients, who had undergone on-pump and off-pump coronary artery bypass grafting (CABG).

**Methods:** This retrospective study comprised of 457 patients, who underwent CABG (323 on-pump and 134 off-pump) between January 2014 and October 2019. Preoperative, postoperative (PO) 1st hour, PO 1st day, and PO 5th day neutrophil-lymphocyte ratios were calculated. The patients were compared, according to demographic, laboratory, and clinical data. A receiver operating characteristics curve was applied to estimate a cut-off value of NLR for mortality.

**Results:** The on-pump group was older ( $P = 0.001$ ), had a lower Euroscore II ( $P = 0.036$ ), had a higher graft number ( $P < 0.001$ ), intensive care unit stay ( $P = 0.001$ ), and all PO NLRs, except preoperative NLR. There were 14 (3.06%) patients with mortality. Overall ( $N = 457$ ), PO 1st hour ( $P = 0.001$ ), PO 1st day ( $P < 0.001$ ), and PO 5th day ( $P = 0.016$ ) NLRs were considerably higher in patients with mortality. While none of the NLRs revealed significant difference in the off-pump group, PO 1st hour ( $P = 0.004$ ) PO 1st day ( $P < 0.001$ ), and PO 5th day ( $P = 0.007$ ) NLRs were higher in patients with mortality in the on-pump group. The increase in odds ratio of PO NLR was higher in patients with mortality in the overall group of PO 1st hour and in the on-pump group of PO 1st hour and PO 1st day. The best combination of sensitivity and specificity was reached at a cut-off value of 6.4 for PO 1st hour NLR and 31.8 for PO 1st day NLR.

**Conclusions:** As an indicator of inflammatory state, NLR readily can be used as a predictor of mortality. Regardless of the CABG technique used, postoperative 1st hour and postoperative 1st day NLR  $>6.4$  and  $31.8$ , respectively, are highly related to mortality.

## INTRODUCTION

Besides corruption of hemostasis and blood rheology [Butler 1993], the negative impact of the use of cardiopulmonary bypass (CPB) on morbidity and mortality through exacerbating the systemic inflammatory response [Butler 1993] has partially declined the casualness of the use of CPB. These unfavorable impacts of the use of CPB have made off-pump CABG a favorable alternative in select patients [Buffolo 1996; Calafiore 2001; Plomondon 2001].

As an indicator of systemic inflammation, neutrophil-lymphocyte ratio (NLR) has attracted attention in the last decade [Abanoz 2021; Ünal 2013]. The NLR, both preoperative and postoperative values, was studied as a predictor of outcome in many situations of cardiac surgery patients, not only in adults but also in patients with congenital heart disease [Abanoz 2021; Aldemir 2015; Şişli 2016; Weedle 2019]. However, there is a controversy about whether the outcome of a patient undergoing cardiac surgery can be predicted by the preoperative NLR or not. Lacking the consistent results in the literature, the aims of the current study were first to investigate the relationship between NLR and mortality and second to compare the difference of NLR as a predictor of outcome between the patients, who had undergone on-pump and off-pump CABG.

## PATIENTS AND METHODS

**Ethical approval:** The ethical approval of the current retrospectively designed study was obtained from the Ethical Committee of Non-Invasive Clinical Research at Osmangazi University Faculty of Medicine on 10 December 2019 (Approval number: 2019-318).

**Study population:** A total of 457 patients, who underwent CABG between January 2014 and October 2019, were included in the study. Patients' demographic, clinical, and laboratory data were collected from the medical archive. The study population was divided into two groups; patients who underwent off-pump CABG and patients who received on-pump CABG.

The patients who had undergone redo CABG or received a concomitant surgical procedure, such as valve replacement, carotid endarterectomy, were excluded from the study. Besides, patients with a chronic or an acute renal failure (serum creatinine

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>1.5), an immunological disease, a cancer, low ejection fraction less than 30%, a previous stroke, and coagulopathy were excluded due to the fact these conditions have the potential to lead to a disarrangement in neutrophil and lymphocyte counts.

**Surgical procedure:** All patients underwent surgery under general anesthesia. A central venous catheter and radial artery line was placed for hemodynamic monitoring. Steroids were not used in the perioperative period. For off-pump CABG patients, a bolus dose of 150 IU/kg heparin was administered before the left internal mammary artery and great saphenous vein were harvested for grafting. Octopus (Medtronic Inc. Minneapolis, Minnesota, USA) was used for cardiac stabilization. The decision for the use of an intra-coronary artery shunt was given by the surgeon. After completion of the procedure in off-pump CABG patients, the heparin either was partially or not neutralized.

In the on-pump patients, with administration of 300 IU/kg intravenous heparin, the surgery was performed under standard aortic and right atrial cannulation, using two-stage venous cannula. A non-pulsatile continuous flow cardiopulmonary bypass machine and Maquet Quadrox Oxygenator (Maquet Inc, USA) were used for cardiopulmonary bypass. Also, no steroid was added to the pump at prime solution or during the CPB. The patient's body was cooled down to

30°C. Following aortic cross-clamping, cardiac quiescence was achieved with antegrade cold blood cardioplegia. After completion of the distal anastomoses, proximal anastomoses were performed on the beating heart after removal of the aortic cross-clamp. The heparin was 50-80% neutralized with protamine sulfate. After completion of the surgical procedure, all patients were transferred to the intensive care unit with mechanical ventilation support. Patients electively were separated from mechanical ventilation, according to individual hemodynamic status.

**Laboratory values:** As a routine clinical protocol, total blood count study is performed in all patients during the preoperative preparation, 1st hour after surgery, 1st day after surgery, and 5th day after surgery periods.

**Statistical analyses:** The PSPP, version 1.2 (2013 Free Software Foundation, Inc) was used for statistical analysis. The continuous variables were evaluated for normal distribution using Shapiro-Wilk test, and they were presented as mean ± standard deviation. The categorical variables were presented as frequency and percentage. The comparison of the continuous variables was performed with independent-samples t test. The distribution of the categorical variables between the groups was compared using Chi-square test with Yate's continuity correction, or Fischer's exact test. Receiver

Table 1. Comparison of the demographic and clinical data of the groups

| Variable                            | On-Pump (N = 323) | Off-Pump (N = 134) | P-value             |
|-------------------------------------|-------------------|--------------------|---------------------|
| Age, years                          | 62.8±8.4          | 59.9±8.8           | 0.001 <sup>a</sup>  |
| Male                                | 272 (84.2)        | 108 (80.6)         | 0.374 <sup>b</sup>  |
| Diabetes mellitus                   | 159 (49.2)        | 65 (48.5)          | 0.889 <sup>b</sup>  |
| Systemic hypertension               | 202 (62.5)        | 75 (56)            | 0.191 <sup>b</sup>  |
| Hyperlipidemia                      | 163 (50.5)        | 57 (42.5)          | 0.123 <sup>b</sup>  |
| COPD                                | 17 (5.3)          | 9 (6.7)            | 0.541 <sup>b</sup>  |
| Recent MI                           | 76 (23.5)         | 44 (32.8)          | 0.040 <sup>b</sup>  |
| LVEF                                | 45.3±6.9          | 40.3±3.0           | <0.001 <sup>a</sup> |
| Euroscore II                        | 4.30±1.05         | 4.54±1.08          | 0.036 <sup>a</sup>  |
| Preop. NLR                          | 2.6±1.2           | 2.8±1.7            | 0.166 <sup>a</sup>  |
| Postop. 1st hour NLR                | 9.2±3.2           | 8.1±4.8            | 0.007 <sup>a</sup>  |
| Postop. 1st day NLR                 | 24.3±10.1         | 20.7±8.7           | <0.001 <sup>a</sup> |
| Postop. 5th day NLR                 | 4.1±1.6           | 3.7±1.8            | 0.001 <sup>a</sup>  |
| Graft number                        | 2.8±0.6           | 1.9±0.7            | <0.001 <sup>a</sup> |
| Postoperative IABP                  | 11 (3.4)          | 3 (2.2)            | 0.718 <sup>c</sup>  |
| Mechanical ventilation time (hours) | 7.3±6.3           | 6.9±7.1            | 0.643 <sup>a</sup>  |
| Inotropic needed                    | 46 (14.2)         | 23 (17.2)          | 0.427 <sup>b</sup>  |
| ICU stay (day)                      | 2.3±0.7           | 2.0±0.2            | 0.001 <sup>a</sup>  |
| Mortality                           | 10 (3.1)          | 4 (3)              | 1.0 <sup>c</sup>    |

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NLR, neutrophil lymphocyte ratio. <sup>a</sup>Independent-samples t-test, <sup>b</sup>Chi-square test, <sup>c</sup>Fischer's exact test with continuity correction

operating characteristics curve analysis was performed to determine a cut-off value of NLR for mortality. A *P*-value of less than 0.05 was considered significant.

## RESULTS

Demographic and clinical data of the patients are presented in Table 1. (Table 1) For a total of 457 patients, the mean age of the off-pump group was significantly lower than

that of the on-pump group (*P* = 0.001). There was no statistically significant difference between the two groups, in terms of gender, diabetes mellitus, hyperlipidemia, systemic hypertension, and chronic obstructive pulmonary disease (COPD). European system for cardiac operative risk evaluation (Euroscore II) score was significantly higher in the off-pump group (*P* = 0.036). The mean number of bypass grafts per patient was considerably higher in the on-pump group (*P* < 0.001).

As for the postoperative outcomes (Table 1), there was no statistical difference between the two groups in terms of the

Table 2. Neutrophil Lymphocyte ratio and mortality relationship

| Overall                    | Mortality (+) (N = 14) | Mortality (-) (N = 443) | <i>P</i> -value* |
|----------------------------|------------------------|-------------------------|------------------|
| Preop NLR                  | 3.2±1.7                | 2.6±1.4                 | 0.203            |
| Postoperative 1st hour NLR | 13.3±3.9               | 8.7±3.7                 | 0.001            |
| Postoperative 1st day NLR  | 40.4±11.5              | 22.8±9.4                | <0.001           |
| Postoperative 5th day NLR  | 5.2±3.0                | 3.9±1.6                 | 0.016            |
| On-Pump                    |                        |                         |                  |
| Preop NLR                  | 3.3±1.9                | 2.6±1.2                 | 0.063            |
| Postoperative 1st hour NLR | 14.0±4.1               | 9.0±3.1                 | 0.004            |
| Postoperative 1st day NLR  | 44.8±9.3               | 23.7±9.5                | <0.001           |
| Postoperative 5th day NLR  | 5.7±3.5                | 4.0±1.5                 | 0.007            |
| Off-Pump                   |                        |                         |                  |
| Preop NLR                  | 3.2±1.0                | 2.8±1.8                 | 0.528            |
| Postoperative 1st hour NLR | 11.3±2.8               | 8.0±4.8                 | 0.093            |
| Postoperative 1st day NLR  | 30.3±10.1              | 20.4±8.5                | 0.144            |
| Postoperative 5th day NLR  | 3.9±0.5                | 3.5±1.8                 | 0.239            |

\*Independent samples t test

Table 3. Neutrophil lymphocyte ratio index for preoperative value regarding mortality

| Overall                          | N          | Mortality (+) | Mortality (-) | <i>P</i> -value* |
|----------------------------------|------------|---------------|---------------|------------------|
| Postop 1st hour versus Preop NLR | 14 vs. 443 | 5.2±3.1       | 4.1±4.3       | 0.208            |
| Postop 1st day versus Preop NLR  | 13 vs. 443 | 15.7±8.7      | 10.4±7.1      | 0.008            |
| Postop 5th day versus Preop NLR  | 10 vs. 443 | 1.7±1.1       | 1.9±4.8       | 0.582            |
| On-Pump                          |            |               |               |                  |
| Postop 1st hour versus Preop NLR | 10 vs. 313 | 5.6±3.3       | 4.0±1.9       | 0.013            |
| Postop 1st day versus Preop NLR  | 9 vs. 313  | 17.6±8.7      | 10.8±6.4      | 0.047            |
| Postop 5th day versus Preop NLR  | 7 vs. 313  | 1.8±1.3       | 1.8±1.0       | 0.971            |
| Off-Pump                         |            |               |               |                  |
| Postop 1st hour versus Preop NLR | 4 vs. 130  | 4.2±2.7       | 4.2±7.3       | 0.994            |
| Postop 1st day versus Preop NLR  | 4 vs. 130  | 11.3±8.0      | 9.4±8.4       | 0.642            |
| Postop 5th day versus Preop NLR  | 3 vs. 130  | 1.5±0.8       | 2.3±8.8       | 0.869            |

\*Independent samples t test.

rate of postoperative IABP, mechanical ventilation time, inotropic support needed, and mortality. However, the intensive care unit stay was significantly higher in on-pump group ( $P = 0.001$ ). Although preoperative NLR ( $P = 0.166$ ) did not reveal significant differences between the groups, the postoperative 1st hour, 1st day, and 5th day NLR ( $P = 0.007$ ,  $P < 0.001$ , and  $P = 0.001$ , respectively) were considerably higher in the on-pump group.

The NLR values for the patients with and without mortality is presented in Table 2. (Table 2) In the overall, while the preoperative NLR did not reveal significant differences between the patients with and without mortality ( $P = 0.23$ ), the postoperative 1st hour ( $P = 0.001$ ), 1st day ( $P < 0.001$ ), and 5th day ( $P = 0.016$ ) NLR were significantly higher in patients with mortality. As for the same variables, the comparative outcomes were resembling in patients who had undergone on-pump CABG. However, in patients who received off-pump CABG, there was no considerable difference, regarding NLRs between the patients with and without mortality.

With the aim of ascertaining the change in the odds ratio of the postoperative 1st hour, 1st day, and 5th day NLR, they were indexed to the preoperative NLR value. (Table 3) Only the postoperative 1st day/preoperative NLR index (15.7 versus 10.4 times) was found to increase significantly in patients with mortality ( $P = 0.008$ ). While there was no significant change in NLR index values in patients who received off-pump CABG, the 1st hour (5.6 versus 4.0 times,  $P = 0.013$ ) and 1st day (17.6 versus 10.8 times,  $P = 0.047$ ) postoperative NLR/preoperative NLR index was significantly higher among patients with mortality who received on-pump CABG. (Figure 1)

In receiver operating characteristics (ROC) curve analysis among all patients, the cut-off values of NLR with highest combination of sensitivity and specificity values for mortality were reached at 1.37 for preoperative NLR, 6.4 for postoperative 1st hour NLR, 31.8 for postoperative 1st day NLR, and 2.4 for postoperative 5th day NLR. (Figure 2) (Table 4)

However, only postoperative 1st hour (sensitivity 1.0, specificity 0.26, area under the curve:  $0.81 \pm 0.05$ ,  $P = 0.001$ ) and postoperative 1st day NLR (sensitivity 1.0, specificity 0.82, area under the curve:  $0.92 \pm 0.02$ ,  $P < 0.001$ ) values were found to be significant. In the on-pump group, while the postoperative 1st hour and 24th hour NLRs were found to be significant at a cut-off value 6.37 (area under the curve:  $0.80 \pm 0.09$ ,  $P = 0.007$ ) and 31.79 (area under the curve:  $0.93 \pm 0.03$ ,  $P < 0.001$ ), respectively, only the postoperative 24th hour NLR at a cut-off value of 31.3 with 1.0 sensitivity and 0.89 specificity (area under the curve:  $0.92 \pm 0.03$ ,  $P = 0.012$ ) was significant in the off-pump group.

## DISCUSSION

The relationship between inflammatory markers and cardiovascular diseases has been shown in many studies to date. Among these markers, in addition to NLR being both cheap and easy to obtain, which makes it a useful tool [Abanoz 2021; Erdolu 2020; Gibson 2007], it is advocated that the NLR

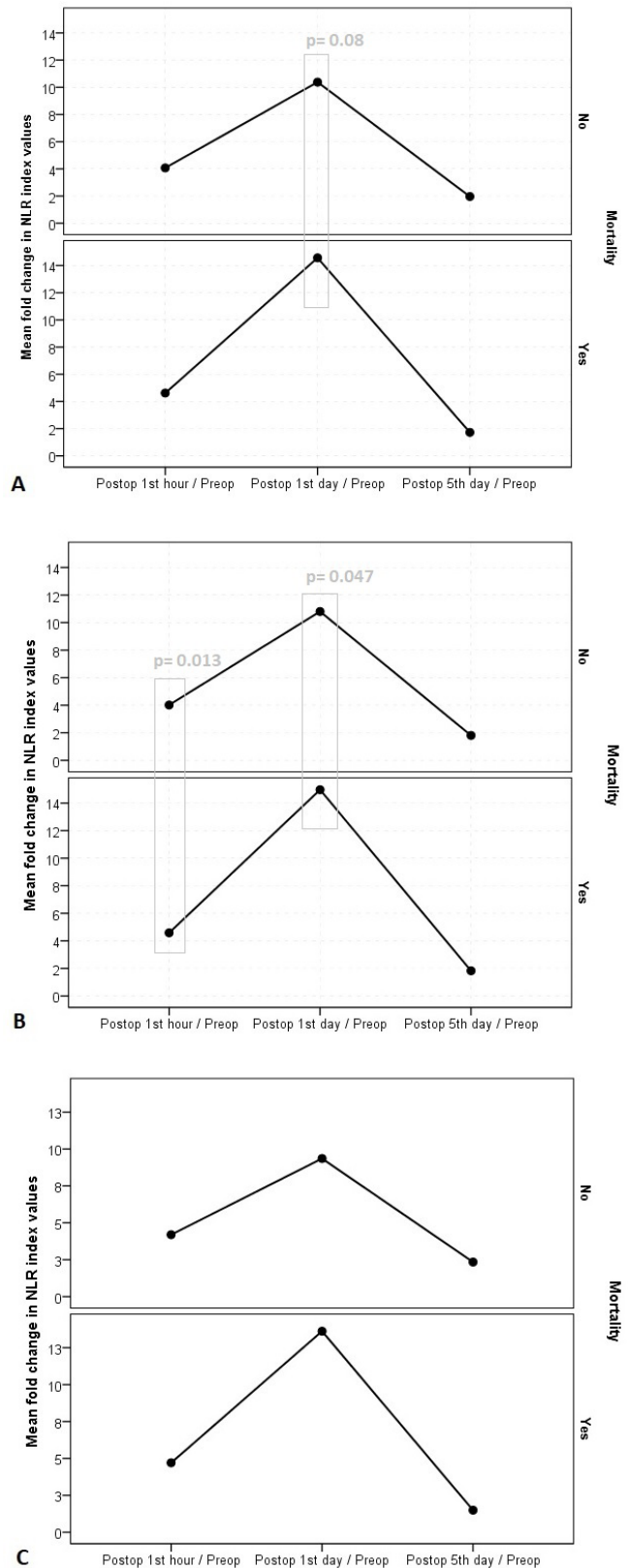


Figure 1. The change of NLR according to preoperative NLR value regarding in-hospital mortality in overall (A), in on-pump (B), and off-pump (C) patients.

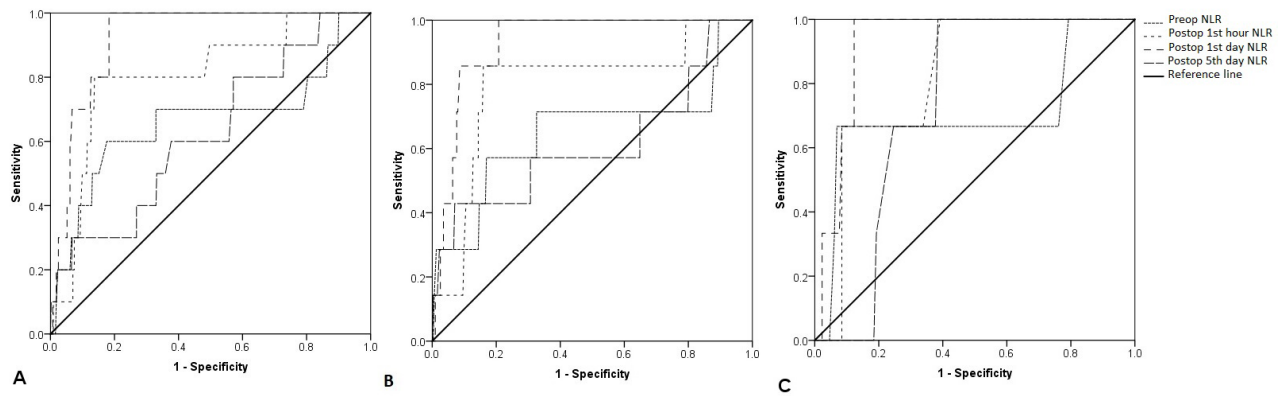


Figure 2. Receiver operating characteristics curve of neutrophil-lymphocyte ratios in overall (A) and in patients who received on-pump (B) and off-pump (C) CABG.

Table 4. The cut-off values of neutrophil-lymphocyte ratios for mortality

| NLR                      | Sensitivity | Specificity | AUC         | P-value |
|--------------------------|-------------|-------------|-------------|---------|
| <b>Overall</b>           |             |             |             |         |
| Preop. >1.37             | 1.0         | 0.90        | 0.66 ± 0.11 | 0.078   |
| Postop. 1st hour >6.4    | 1.0         | 0.26        | 0.81 ± 0.05 | 0.001   |
| Postop. 24th hour >31.8  | 1.0         | 0.82        | 0.92 ± 0.02 | <0.001  |
| Postop. 5th day >2.4     | 1.0         | 0.16        | 0.63 ± 0.09 | 0.178   |
| <b>On-Pump</b>           |             |             |             |         |
| Preop. >1.37             | 1.0         | 0.11        | 0.65 ± 0.14 | 0.163   |
| Postop. 1st hour >6.37   | 1.0         | 0.21        | 0.80 ± 0.09 | 0.007   |
| Postop. 24th hour >31.79 | 1.0         | 0.79        | 0.93 ± 0.03 | <0.001  |
| Postop. 5th day >2.32    | 1.0         | 0.11        | 0.61 ± 0.13 | 0.305   |
| <b>Off-Pump</b>          |             |             |             |         |
| Preop. >1.59             | 1.0         | 0.21        | 0.70 ± 0.19 | 0.234   |
| Postop. 1st hour >8.7    | 1.0         | 0.61        | 0.82 ± 0.08 | 0.057   |
| Postop. 24th hour >31.3  | 1.0         | 0.89        | 0.92 ± 0.03 | 0.012   |
| Postop. 5th day >3.28    | 1.0         | 0.62        | 0.74 ± 0.06 | 0.161   |

offers the strongest value as a predictor of cardiovascular risk in coronary artery patients [Abanoz 2021; Ünal 2013; Zouridakis 2000]. Although NLR has a prognostic value associated with complications and survival after cardiovascular surgery [Abanoz 2021; Ünal 2013], its value in off-pump and on-pump CABG has not adequately been investigated. As an overview of our results, the preoperative NLR was not found to be a significant predictor of mortality, neither the overall, nor between the off-pump and on-pump groups (Table 1). As presented in Table 2, while the postoperative NLRs significantly increased in both groups, the increase was more pronounced in patients with mortality who received on-pump CABG. On the other hand, the postoperative NLRs in off-pump patients with and without mortality were not significant.

Other than surgical trauma and myocardial arrest, use of CPB increases the burden of acute systemic inflammatory

response [Weedle 2019]. Neutrophilia and relative lymphocytopenia are believed to be the indicators of a negative outcome [Zouridakis 2000; Arruda-Olson 2009]. In the literature, preoperative and postoperative NLRs were associated with an increased immediate- and medium-term mortality after CABG [Ünal 2013; Nashef 2012; Shahian 2009]. Furthermore, the NLR, as a marker of inflammatory burden, is suggested to predict complications, such as postoperative acute kidney injury [Kim 2015], length of hospital stay [Giakoumidakis 2017], and mortality [Ünal 2013; Gibson 2007; Nashef 2012; Shahian 2009; Sinan 2016]. In the current series, as revealed in Table 1, not the preoperative NLR but the postoperative NLR values were higher in patients who received on-pump CABG. As it was anticipated, the significance of the difference became more pronounced in the postoperative 1st day. Additionally, the persistence of the increased

inflammatory state was observed not only in the postoperative first hour but also in the postoperative first day and the fifth day NLRs. When it was considered that the Euroscore II of the patients in the off-pump group were higher, their length of intensive care unit stay was lower than that of the on-pump group. This situation can be explained in great part due to the fact that the patients in the off-pump group were significantly younger and received fewer bypass grafts, which indirectly indicates that their extensiveness of the coronary artery disease was lower. In our opinion, the burden of the systemic inflammatory response, as it was advocated by Aldemir et al. [Aldemir 2015], which became apparently lower in the off-pump group within the postoperative first hour, has a significant influence on the lower length of intensive care unit stay.

The literature comprises a variety of studies regarding that the preoperative NLR can be used as a predictor of postoperative morbidity and mortality [Calafiore 2001; Abanoz 2021; Ünal 2013; Şişli 2016; Gibson 2007; Giakoumidakis 2017; Silberman 2018; Wada 2017]. The literature comprised of studies in which the prognostic value of preoperative NLR was investigated, and the relationship between preoperative NLR and increased immediate-term morbidity and long-term mortality rates were noted [Abanoz 2021; Silberman 2018; Giacinto 2019]. Contrary to our results (Table 2), some authors found a significant difference in preoperative NLR and executed it as an important predictor of postoperative mortality [Ünal 2013; Gibson 2007; Wada 2017]. However, resembling the results of Aldemir et al. [Aldemir 2015], it can be inferred that the inflammatory state of the patients in the preoperative period was appropriate and without significant difference, neither in terms of mortality nor between the patients who received on-pump and off-pump CABG. This situation can be an explanation for our finding of insignificant difference, in terms of preoperative NLRs between the groups.

Besides surgical stress, CPB imposes an additional burden of systemic inflammation through circulation of blood within foreign surface [Calafiore 2001; Weedle 2019; Giakoumidakis 2017; Giacinto 2019]. Moreover, the dilution effect of the CPB leads to a decrease in leukocyte count while neutrophilia occurs, which further results in an increase in NLR [Moen 1997]. In comparison to on-pump CABG, off-pump CABG technique has an advantage of lower systemic inflammatory burden and lower mortality rate [Buffolo 1996; Ehsan 2004; Mathison 2000], which was observed in our study. Overall, the increase in NLR, which initially starts within the first hour of surgery, was found to be directly related to mortality regardless of the technique applied (Tables 2 and 3). From another point of view, it was observed that this significant difference was highly related to the application of on-pump CABG because there was no considerable difference in the mean NLRs, regarding mortality in the off-pump group. Furthermore, as revealed in Table 3, the index values as an indicator of increase in odds ratio of NLR in the off-pump group was not significantly differed in patients with and without mortality. On the other hand, it was found that both the mean postoperative NLRs and their index values revealed a significant increase in the on-pump group. In the on-pump

CABG group with mortality, the increase in NLRs were 5.6 and 17.6, respectively. It is recommended that patients with multiple comorbidities be operated through off-pump technique, providing that their clinical and coronary anatomy is suitable for its application [Buffolo 1996; Magee 2003]. In our study, although the Euroscore II of the patients who had undergone off-pump CABG was significantly higher, the mortality rate did not reveal a significant difference between the groups, which reveals a favorable influence of off-pump CABG on outcome. Although open to debate and impossible to apply all CABG patients, it can be inferred with the current study's findings that insistence of avoiding the performance of CABG surgery under CPB seems to be favorable but in suitable cases, indeed.

Supporting the findings of Abanoz et al. [Abanoz 2021] in which the cut-off value was found to be 2.4, Silberman et al. estimated a cut-off value [Silberman 2018] for NLR as 2.6, which was advocated as an independent predictor of operative and long-term mortality with a hazard ratio of 2.15 and 1.19, respectively. The cut-off value of preoperative NLR was found to be 3.36 and concluded as an independent predictor of mortality [Gibson 2007]. Azab et al. [Azab 2013] found preoperative NLR  $\geq 3$  as an independent predictor mortality in the long-term. In our study, the best combination of sensitivity and specificity in the overall, on-pump, and off-pump groups were found at the cut-off values of 1.37, 1.37, and 1.59, respectively. However, as revealed in Table 4, none of them were found a significant predictor for mortality with an inadequate area under the curve values. When the median values of preoperative NLRs in the overall, on-pump, and off-pump groups in our study were evaluated, it is apparent that the preoperative NLRs could not have reached to those levels. Thus, it can be inferred that in comparison to the estimated values of preoperative NLRs for mortality in the studies of Gibson et al. [Gibson 2007], Ünal et al. [Ünal 2013] and Azab et al. [Azab 2013], the lower-leveled values of the preoperative NLRs can be the reason of the insignificant results in the current study.

One of the main limitations of our study is the use of retrospective data collected from a single center, which inevitably led to a selection bias. The NLR was used regardless of lymphocyte and neutrophil values when examining postoperative values. Also, a limited number of complications were examined after the operation and short-term follow up was performed.

In conclusion, as an indicator of inflammatory state, NLR can readily be used as a predictor of mortality. Regardless of the CABG technique used, postoperative 1st hour and postoperative 1st day NLR  $>6.4$  and  $31.8$ , respectively, is highly related to mortality.

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