

The importance of inflammatory parameters in predicting deep sternal wound infections after open heart surgery

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the relationship between the development of deep sternal wound infection after open heart surgery and inflammatory parameters obtained from routine biochemical tests.

METHODS: A total of 280 patients who underwent cardiac surgery with median sternotomy between January 2015 and January 2020 were examined retrospectively. Patients who developed deep sternal wound infection were identified as "Group 1," and those who did not develop deep sternal wound infection were identified as "Group 2."

RESULTS: There were 70 patients with a mean age of 61.6±9.9 years in Group 1 and 210 patients with a mean age of 62.7±9.8 years in Group 2. As a result of the analysis, it was found that the presence of concomitant chronic obstructive pulmonary disease, concomitant diabetes mellitus, blood and blood product transfusion, postoperative 2nd day C-reactive protein, postoperative 1st day neutrophil-to-lymphocyte ratio, and delta neutrophil-to-lymphocyte ratio was found as independent predictive factors of postoperative deep sternal wound infection development ($p=0.043$, $p=0.012$, $p=0.029$, $p=0.009$, $p=0.002$, and $p<0.001$; respectively). As a predictor of deep sternal wound infections development, postoperative 1st day neutrophil-to-lymphocyte ratio cutoff value was 11.2 (area under the curve [AUC] 0.598; $p=0.014$; 60% sensitivity, and 65.2% specificity), and delta neutrophil-to-lymphocyte ratio cutoff value was 9.6 (AUC 0.716; $p<0.001$; 57.1% sensitivity, and 73.8% specificity).

CONCLUSIONS: Deep sternal wound infection development can be predicted with inflammatory parameters such as neutrophil-to-lymphocyte ratio and C-reactive protein that are obtained from cheap and easily available routine biochemical tests.

KEYWORDS: Cardiac surgery. C-reactive protein. Inflammation. Sternum. Postoperative wound infections.

INTRODUCTION

One of the significant unwanted complications after open heart surgery is sternum wound infections. This infection is basically divided into two — deep and superficial infections. In superficial infections, the skin and subcutaneous soft tissues are involved, and the muscle and bone structures are involved in deep sternal wound infections (DSWI). Hospitalization is longer and the treatment costs are increasing in both cases¹⁻³. Thanks to the early detection of postoperative sternal wound site infections with clinical and laboratory data, it is of vital importance to apply preventive treatments, proper antibiotherapy, and early surgical treatments⁴.

The inflammatory response that occurs as the natural defense mechanism of the body against surgical processes is an important factor in postoperative morbidity and mortality. The preoperative inflammatory status of the patient also affects the inflammatory response to surgery and thus postoperative results^{5,6}. The aim of this study was to investigate whether inflammatory parameters obtained from routine biochemical tests are predictors for the development of DSWI,

which is one of the complications that increase morbidity and morbidity after open heart surgery.

METHODS

Study design and patient selection

The patients who underwent cardiac surgery by the same surgical team between January 2015 and January 2020 at the University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, and Cardiovascular Surgery Clinic were scanned retrospectively. A total of 280 patients who underwent elective cardiac surgery with cardiopulmonary bypass (CPB) and median sternotomy were included in our study. The local ethics committee approval was obtained (approval number: 2011-KAEK-25 2020/05-01).

In our study, the patients we considered as DSWI consisted of patients in whom the wound infection passed through the skin and subcutaneous tissues and the muscles in the sternal region were involved or the infection spread to the mediastinum,

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on March 29, 2022. Accepted on June 12, 2022.

and 70 patients were included in the study as “Group 1.” For the control group, among the patients who did not develop DSWI, 210 patients were randomly selected in the computer environment according to the protocol numbers using the random number table by looking at the data in the similar literature (to show the significant difference with 80% power and 5% Type-1 error) and included in the study as “Group 2.” Patients with a history of emergency surgery or cardiac surgery, who were not in the age range between 18 and 80, who had only superficial sternum wound site infection, who had undergone off-pump surgery, chronic inflammatory disease, hematological disease, or who received steroid treatment were excluded from the study.

Laboratory measurements

Blood samples were obtained from the peripheral venous structures of all patients. Complete blood count and biochemical measurements were made with automatic analyzers (Coulter LH780, USA, and Coulter AU5800, USA). The preoperative, postoperative 1st day (Po1), and postoperative 2nd day (Po2) neutrophil-to-lymphocyte ratio (NLR) values were calculated. Delta NLR values were calculated by subtracting the preoperative NLR value from the highest NLR value of Po1 and Po2.

Preoperative preparation and postoperative follow-up

All the body shaves were made with a shaving machine one day before the surgery and bathed with chlorhexidine solutions. In the perioperative process, the skin of patients was stained with 10% polyvinylpyrrolidone iodine (Batticon[®]). Perioperative surgical prophylaxis was initiated with 1–2 g of IV cefazolin. On the first 2 postoperative days, 1–2 g of IV cefazolin was applied at 6-h intervals. Unless the specialist for infection diseases had any additional recommendations, cefazolin prophylaxis was discontinued on the Po2. The surgical wound dressing was performed using 10% polyvinylpyrrolidone iodine (Batticon[®]), and if there were no other conditions, wound sites were left open on the Po2 and later.

Statistical method

SPSS 21.0 was used for the analysis of the data. Mean and standard deviation values were calculated using descriptive methods for continuous and ordinal data. The Shapiro-Wilk test was used for the normality distribution. The Student's t-test was used for data showing normal distribution, and the Mann-Whitney U test was used for data that did not meet the normal distribution. Frequency and percentage analyses were performed for nominal data. After comparing the data, the chi-Square test was

used. A multivariate logistics regression analysis was conducted to analyze predictors of postoperative DSWI development (in univariate analysis, variables with a p-value below 0.100 were included). A p-value below 0.05 was deemed statistically significant. The receiver operating characteristic (ROC) analysis was performed for Po1-NLR and delta NLR values to predict DSWI development.

RESULTS

A total of 280 patients were included in this study. Group 1 had 70 patients with a mean age of 61.6±9.9 years, and there were 210 patients in Group 2 with a mean age of 62.7±9.8 years. In the evaluation of the preoperative characteristics of the groups, the number of patients with diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and body mass index >30 kg/m² were significantly higher in Group 1 (p<0.001, p=0.021, and p=0.039, respectively) (Table 1).

When the laboratory parameters were compared, the preoperative NLR value was found to be significantly higher in Group 1 (p=0.044). While the neutrophil, CRP, and NLR values in Po1 were significantly higher in Group 1 (p=0.014, p=0.021, and p<0.001, respectively), lymphocyte values were significantly lower (p=0.005). NLR and CRP values in Po2 were found to be significantly higher in Group 1 (p=0.003 and p<0.001, respectively). During this period, lymphocyte values were significantly lower in Group 1 (p=0.014). The delta NLR value was found to be significantly higher in Group 1 (p<0.001) (Table 2).

The comparison of perioperative and postoperative characteristics of the patient groups is presented in Table 1. Blood and blood product transfusion amount, mechanical ventilation need for more than 48 h, and hospitalization times were significantly higher in Group 1 (p=0.005, p=0.017, and p<0.001, respectively).

Multivariate logistic regression analysis was performed to predict postoperative DSWI development (Table 3). In the analysis performed, COPD, DM, blood and blood product transfusion, Po2-CRP, Po1-NLR, and delta NLR were identified as independent predictors of postoperative DSWI development (p=0.043, p=0.012, p=0.029, p=0.009, p=0.002, and p<0.001, respectively). In the ROC analysis, the cut-off value for Po1-NLR was found to be 11.2 (AUC 0.598, 95%CI 0.518–0.687; p=0.014, 60% sensitivity, and 65.2% specificity), and the cutoff value for delta NLR was 9.6 (AUC 0.716; 95%CI 0.648–0.784; p<0.001; 57.1% sensitivity, and 73.8% specificity).

Table 1. Demographic, preoperative, perioperative, and postoperative clinical characteristics of the patients.

Preoperative variables	Group 1 (n=70)	Group 2 (n=210)	p-value
	n mean±SD/median (IQR) (%)	n mean±SD/median (IQR) (%)	
Age (years)	61.6 ±9.9	62.7±9.8	0.294 ^b
Gender (female)	17 (24.3)	68 (32.3)	0.260 ^a
Hypertension	39 (55.7)	126 (60)	0.528 ^a
Hyperlipidemia	20 (28.5)	68 (32.3)	0.671 ^a
COPD	20 (28.5)	28 (13.3)	0.021 ^a
Diabetes mellitus	32 (45.7)	41 (19.5)	<0.001 ^a
Smoking	35 (50)	85 (40.4)	0.163 ^a
BMI (>30 kg/m ²)	24 (34.2)	42 (20)	0.039 ^a
Ejection fraction (%)	51.5±9.8	50±10.1	0.407 ^b
EuroSCORE II	1.9 (0.5–5.4)	1.5 (0.5–4.9)	0.214 ^c
Perioperative and postoperative variables			
CPB time (min)	83 (36–126)	78 (44–158)	0.318 ^c
CABG	44 (62.8)	138 (65.7)	0.497 ^a
AVR or MVR or MRA or AVR+MVR	6 (8.5)	24 (11.4)	0.503 ^a
Combined surgery	20 (28.5)	48 (22.8)	0.747 ^a
Blood and blood product transfusion (unit)	7 (5–18)	5 (4–9)	0.005 ^c
Inotropic support	20 (28.5)	38 (18)	0.071 ^a
Prolonged mechanical ventilation (>48 h)	19 (27.1)	29 (13.8)	0.017 ^a
Length of hospital stay (day)	18 (15–78)	7 (6–21)	<0.001 ^c
Length of stay in the ICU (day)	2 (2–7)	2 (2–5)	0.317 ^c

Bold indicates statistically significant values. a: χ^2 test; b: Student's t-test; c: Mann-Whitney U test. SD: standard deviation; IQR: 25–75th percentile; COPD: chronic obstructive pulmonary disease; BMI: body mass index; CPB: cardiopulmonary bypass; CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MVR: mitral valve replacement; MRA: mitral ring annuloplasty; ICU: intensive care unit.

DISCUSSION

In our study, we evaluated the relationship between inflammatory parameters and the development of postoperative DSWI in patients who underwent open heart surgery. As a result of the analysis, it was found that COPD, DM, blood and blood product transfusion, Po2-CRP, Po1-NLR, and delta NLR were found to be independent predictive factors for postoperative DSWI development. Among the inflammatory parameters, which were evaluated as the priority targets of our study, a one-unit increase in the Po2-CRP variable increased the risk of DSWI development 1.675 times, a one-unit increase in the Po1-NLR variable increased the risk of DSWI development 1.779 times, and a one-unit increase in the delta NLR variable increased the risk of DSWI development 3.192 times.

The DSWI is a serious and life-threatening complication that can be observed after open heart surgery with median sternotomy. It was reported that the incidence is 0.5–6% and the 1-year mortality associated with DSWI is 25.4%^{2,7}. Inflammatory processes play a role in the pathogenesis and

progression of DSWI. NLR is an inflammatory biomarker and is also deemed to be an indicator of subclinical inflammation. It is known that neutrophil numbers in the circulation increase, and there is a decrease in the numbers of lymphocytes in the presence of systemic inflammation or inflammatory response, and therefore, NLR also increases⁸⁻¹⁰. There are studies in the literature investigating the relationship between preoperatively evaluated NLR and postoperative complications. Gurbuz et al. conducted a study on 751 elective coronary artery bypass grafting (CABG) patients and reported that preoperative NLR was an independent predictive factor for the postoperative long-term major adverse cardiac and cerebrovascular event⁹. In our study, preoperative NLR levels were found to be significantly higher in our patient group who developed DSWI, but it was not found to be a predictive factor for DSWI development.

An acute inflammatory response is induced during surgical procedures, which may cause complications in the postoperative period^{11,12}. Especially, this inflammatory response

Table 2. Laboratory variables of the patients.

Variables	Group 1 (n=70)	Group 2 (n=210)	p-value
	Median (IQR)	Median (IQR)	
Pre-WBC (10 ³ /μL)	7.4 (4.1–11.2)	7.2 (3.8–10.2)	0.347 ^c
Pre-hemoglobin (g/dL)	12.7 (10.1–16.5)	12.5 (10.7–16.8)	0.545 ^c
Pre-platelet (10 ³ /μL)	234 (148–477)	242 (144–476)	0.298 ^c
Pre-neutrophil (10 ³ /μL)	4.7 (2.7–8)	4.4 (2.2–7.6)	0.196 ^c
Pre-lymphocyte (10 ³ /μL)	1.4 (1–4.2)	1.8 (1.1–4.4)	0.098 ^c
Pre-creatinine (mg/dL)	1 (0.6–1.9)	1.2 (0.6–2)	0.214 ^c
Pre-urea (mg/dL)	19 (10–46)	17 (11–38)	0.474 ^c
Pre-CRP (mg/dL)	9.5 (3.2–41.3)	8.9 (2.9–42)	0.320 ^c
Pre-NLR	3.4 (0.7–6.5)	2.9 (0.8–6.1)	0.044^c
Po1-WBC (10 ³ /μL)	10.8 (6–16)	10.2 (5.3–17.4)	0.271 ^c
Po1-hemoglobin (g/dL)	9.4 (8.4–11.2)	8.9 (7.9–12)	0.118 ^c
Po1-neutrophil (10 ³ /μL)	8.3 (5.4–12.9)	7.8 (5.1–11.4)	0.014^c
Po1-lymphocyte (10 ³ /μL)	0.7 (0.2–1.7)	0.9 (0.4–2.4)	0.005^c
Po1-CRP (mg/dL)	48.5 (12–150)	43.9 (9–138)	0.021^c
Po1-NLR	11.9 (4.8–27.2)	9.9 (4.4–25.1)	<0.001^c
Po2-WBC (10 ³ /μL)	11.5 (7.7–17.1)	11.1 (7.3–16.9)	0.211 ^c
Po2-hemoglobin (g/dL)	10.1 (8.9–12.3)	9.6 (8.5–12.9)	0.490 ^c
Po2-neutrophil (10 ³ /μL)	9.7 (5.4–14.8)	9.2 (5.3–13.7)	0.094 ^c
Po2-lymphocyte (10 ³ /μL)	1 (0.5–2.3)	1.2 (0.6–2.7)	0.014^c
Po2-CRP (mg/dL)	102.5 (34–311)	89.9 (29–294)	<0.001^c
Po2-NLR	9.8 (3.5–21.6)	8.9 (3.4–19.2)	0.003^c
Delta NLR	9.8 (4.2–25.2)	7.8 (2.8–21.8)	<0.001^c

Bold indicates statistically significant values. c: Mann-Whitney U test. IQR: 25–75th percentile; Pre: preoperative; Po1: postoperative 1st day; Po2: postoperative 2nd day; WBC: white blood cell; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio.

Table 3. Multivariate logistic regression analysis to determine predictors of postoperative DSWI development.

Variables	Multivariate analysis		
	p-value	OR	95%CI Lower-upper
BMI (>30 kg/m ²)	0.124	0.657	0.495–1.022
COPD	0.043	0.593	0.456–0.798
Diabetes mellitus	0.012	1.184	1.032–1.446
Inotropic support	0.156	0.778	0.456–1.114
Blood and blood product transfusion	0.029	0.798	0.659–0.991
Prolonged mechanical ventilation (>48 h)	0.057	0.865	0.691–1.138
Po1-CRP	0.217	0.797	0.544–1.009
Po2-CRP	0.009	1.675	1.214–2.229
Pre-NLR	0.239	0.796	0.654–1.002
Po1-NLR	0.002	1.779	1.554–3.191
Po2-NLR	0.071	0.983	0.697–1.598
Delta NLR	<0.001	3.192	2.997–7.734

Bold indicates statistically significant values. OR: odds ratio; CI: confidence interval; BMI: body mass index; COPD: chronic obstructive pulmonary disease; Pre: preoperative; Po1: postoperative 1st day; Po2: postoperative 2nd day; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio.

occurs in cardiac surgery due to CPB¹³. This may cause surgical site infections and sepsis. It was shown in previous studies that postoperative NLR value, as well as preoperative NLR value, may be a predictor of complications, which may also develop. In their study, Kim et al. found that the NLR value evaluated immediately after open heart surgery and the NLR value evaluated on the Po1 were associated with postoperative mortality due to all reasons throughout one year¹⁴. In our study, we investigated the effects of Po1-NLR and Po2-NLR values and found that both NLR values were significantly higher in the patient group developing DSWI. However, we found that only the Po1-NLR value was a predictor in the multivariate analysis.

In the light of all these evaluations, studies have been carried out on the delta NLR value obtained from the difference between the NLR value after surgical operations or interventional procedures and the NLR value in the preoperative period¹⁵. Rich et al. included 1019 hepatocellular patients in their study and reported that the delta NLR value, which they described as the difference between the NLR values before and after the treatment, was the independent predictor of mortality¹⁶. In a study by Li et al., delta NLR was associated with major adverse cardiovascular events independently after percutaneous coronary interventions¹⁷. In our study, the delta NLR value was found to be a predictive factor of DSWI development.

There have been studies in the literature examining CRP levels and the development of postoperative complications¹². In their study on 185 off-pump CABG patients, Kim et al. reported that there was a significant relationship between elevated preoperative CRP and the development of major postoperative complications, including the development of DSWI⁵. In our study, the Po1-CRP and Po2-CRP levels were significantly higher in our DSWI developing patient group, and the Po2-CRP variable was a predictor of DSWI development.

The comorbidities of the patients affect surgical field infections. DM affects wound healing negatively depending on the changes in the microvascular area^{18,19}. DM was significantly higher in the patient group with DSWI in our study, and it was

a predictor of DSWI development. In various studies, COPD has been shown to be a risk factor for DSWI development. This is often associated with tissue hypoxia due to COPD³. We also found that having concomitant COPD is an independent predictor of DSWI development. It is already known that increased blood and blood product transfusion may cause many complications in the perioperative and postoperative periods²⁰. We found that increased blood and blood product transfusion was a predictor of DSWI development.

The primary limitations of our study were the retrospective design and being a single-centered study. It had a relatively small sample size to make strong and generalizable interpretations. Preoperative length of stay is known as a modifiable risk factor for DSWI development in open heart surgery²¹. In this respect, it is another limitation that the preoperative length of stay status of the patients was not added to the analyses.

CONCLUSIONS

The DSWI, which develops after open heart surgery with a median sternotomy, is a rare but feared complication. It is important that the predictors of this complication are known, risky patients are detected early, and preventive treatments are applied for the treatment of this complication. Our analysis performed for this purpose showed that COPD, DM, blood and blood product transfusion, Po2-CRP, Po1-NLR, and delta NLR are independent predictive factors for DSWI development after open heart surgery.

AUTHORS' CONTRIBUTIONS

KP: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **ABT:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **AAP:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **MTG:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

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