Evaluation of the Effect of Lymphocytes, Platelets, Monocytes on the Development of Acute Renal Failure and Atrial Fibrillation After Open Heart Surgery: A Retrospective Study

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Abstract

Background

Cardiac surgery is the most well-known treatment for cardiovascular diseases, including coronary artery and valvular heart diseases. Following cardiac surgery, systemic inflammatory responses are induced due to myocardial arrest, surgical trauma and cardiopulmonary bypass (CPB), which lead to greater complications and poorer outcomes in patients. There is growing evidence, that evaluating cellular markers in cardiac surgery patients are promising messengers of inflammation and could predict post-operative inflammatory events.

In this study, for the first time, hematological parameters and the ratio of inflammatory cells before, during, and after cardiac surgery are assessed to predict inflammatory complications, such as: acute renal injury (AKI) and atrial fibrillation (AF).

Material and Methods

This retrospective study was performed on patients, who underwent elective open-heart surgery; they referred to Imam Khomeini Hospital in Ahvaz during November 2014 - March 2017. The profiles of 400 cardiac surgery patients, who underwent CABG were scanned to evaluate the relationship between hematological parameters, cellular-inflammatory indexes, and inflammatory events before, during, and after cardiac surgery. In this study, AKI was diagnosed based on KIDGO criteria; Electro Cardiogram (ECG) was also used to diagnose AF. The specificity and sensitivity of biomarkers were assessed through the receiver operating characteristic curve (AUROC).

Results

According to the results, the post-operative NLR was significantly associated with AKI (P-Value: 0.03). Serum markers, including BUN and sCr levels were also significantly correlated with AKI and Non-AKI patients in all post-operative periods (P-Value: 0.0001). Hb core related antigen (HbCr) was also associated with AKI as a hematological parameter.

Conclusions

The findings of this study claimed, that post-operative NLR is significantly associated with the occurrence of AKI; it has also the acceptable sensitivity and specificity results. HbCr levels in the postoperative period also has relatively acceptable sensitivity and specificity concerning AKI.

1. Introduction

As a significant health burden, cardiovascular diseases are one of the leading causes of death globally, affecting more than 600,000 people annually (1). Coronary artery disease and atherosclerosis are considered the most prevalent cardiovascular diseases (2). So far, many risk factors have been identified

concerning the pathogenesis of cardiovascular events, which appropriate treatment strategies have been used for them in accordance with the relevant mechanisms (2, 3). Inflammation, thrombosis, consumption of fatty foods, inactivity, and many other factors are involved in cardiovascular disease development (4). Clearly, improvements in understanding the responsible mechanisms for cardiovascular events have reduced adverse mortality rates (5-7). Therefore, the treatment of these patients varies according to the type of disease pathogenesis, and includes anti-inflammatory drugs and anticoagulants, such as clopidogrel, ticlopidine, and prasugrel (8).

Cardiac surgery is another treatment mechanism in cardiovascular patients. Although this method improves patients' clinical condition; due to its invasive effects, it is associated with a series of complications (9). It may be associated with adverse changes in organ systems, which can be initiated at surgery and persist into the post-operative recovery period. Previous studies have reported that the occurrence of inflammation after cardiac surgery is one of the main challenges for cardiologists (10). The inflammatory response following cardiac surgery may be due to blood products transfusion and the use of anesthetics (10, 11).

Cardiopulmonary bypass (CPB) is a crucial procedure for most cardiac surgeries. It has been routinely used since 1953 (Fou 1997), allowing surgeons to undertake more complex and longer surgery than the previous beating cardiac techniques. However, CPB such as cardiac arrest and surgical trauma is associated with systemic inflammatory response syndrome (SIRS); these patients often spend time in the cardiovascular intensive care unit (CVICU) (12, 13).

Acute renal injury (AKI) is another major problem after cardiac surgery, which is associated with several inflammatory mediators. Implicated factors in the AKI aetiology in cardiac surgery are broadly described as pre-operative, intraoperative, and post-operative factors (14, 15). AKI occurs in 30% of patients after heart surgery, with 1-2% requiring renal replacement therapy. It is noteworthy that AKI independent of other risk factors is associated with an increased risk of death up to 10 years after cardiac surgery, even in patients whose renal parameters return to baseline levels (16). Therefore, the ability to predict and prevent these complications is critical to reduce patient complications, and optimize health resources. Another concern associated with cardiac surgery is atrial fibrillation (AF), which is considered the most common arrhythmia after cardiac surgery and occurring 30-40% after CABG surgery, 50% after valvular surgery, and up to 64% after combination surgery (17). This arrhythmia is associated with an increased risk of stroke, heart failure, extended hospital stays and increased costs (18).

Because of the increased incidence of inflammation after cardiac surgery, researchers have focused on diagnostic factors, which can predict post-operative inflammation in these patients. On the other hand, the use of invasive methods to predict the clinical status of patients is threatening. Therefore, non-invasive methods are preferred for patients undergoing cardiac surgery. The stimulation and initiation of immune responses following cardiac surgery include cellular, molecular and clinical aspects. Identifying the effects of inflammatory cells and cytokines involved in immune responses can be influential in diagnostic and prognostic processes development in patients undergoing cardiac surgery; it guides to

select the effective therapeutic methods. Evaluating valuable laboratory markers and preventive measures to control immune responses will certainly help to manage and improve patients' conditions.

From a cellular perspective, increased white blood cells (WBCs) count is one of the most well-known inflammation predictors (4, 19). Neutrophils, lymphocytes, monocytes, platelets, and endothelial cells (ECs) are among the primary inflammatory cells, regulating inflammatory status through inflammatory cytokines and other stimulants before and after surgery (19-21). Platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and monocyte-lymphocyte ratio (MLR) are valuable prognostic markers, that predict inflammation in various clinical situations (22, 23). Based on previous studies, these inflammatory recognized markers are associated with clinical outcomes, inflammatory status, or morbidity and mortality in cardiac surgery patients (24, 25).

In addition, evaluation of these markers is not time-consuming and is economically optimal for patients. Extensive studies have reported, that NLR can be used as a prognostic marker to predict AF, AKI, increased length of hospital stay, adverse outcomes, and post-operative mortality (26). Since elevated levels of these laboratory markers predict inflammation before cardiac surgery, the use of pre-operative anti-inflammatory agents can prevent systemic inflammatory responses after cardiac surgery (27).

1. Aims of Study

The occurrence of CPB, AKI, AF, or other inflammatory complications post-cardiac surgery is multifactorial, and is not yet fully understood. However, increased inflammation following cardiac surgery undoubtedly leads to more significant complications and poorer outcomes in patients. In previous studies, the diagnostic value of NLR in predicting complications after cardiac surgery has been investigated. In this retrospective study, for the first time in Khuzestan province, the diagnostic value of the inflammatory cellular markers (NLR, PLR, and MLR) concerning inflammatory complications before, during, and after cardiac surgery (including CPB, AKI, AF, etc.) was evaluated. Also, in this study the sensitivity and specificity of these biomarkers have been evaluated from both diagnostic and prognostic perspectives.

The innovative and practical objectives of this study have been classified below;

- Evaluation of inflammatory cells (including neutrophils, lymphocytes, and monocytes) before, during, and after cardiac surgery.
- Association of NLR, PLR, and MLR with the occurrence of AKI and AF before, during, and after cardiac surgery.
- Comparison of cellular-biomarkers to diagnose or predict inflammatory complications following cardiac surgery.
- Sensitivity and specificity of cell biomarkers, that are significantly associated with heart problems.

2. Material And Methods

2.1- Study Subjects and Specimen Collection

This retrospective study was performed on patients, who underwent elective open-heart surgery; they referred to Imam Khomeini and Golestan Hospitals in Ahvaz between November 2014- March 2017. In order to evaluate the relationship between AKI and cellular-inflammatory indexes, including NLR, PLR, and MLR in patients undergoing cardiac surgery, the profiles of 400 patients, who underwent CABG were scanned and studied. Inflammatory cells count data (including lymphocytes, monocytes, platelets, and neutrophils) were obtained from patients' records. BUN and serum creatinine (sCr) levels (before and after cardiac surgery) were also extracted from patient's profile in the hospital.

After heart surgery, inflammatory events and related clinical symptoms were carefully monitored to assess their statistical correlation with cellular biomarkers. After obtaining written consent from patients, who underwent elective open-heart surgery and receiving the ethical code from the ethics committee of Ahvaz Jundishapur University of Medical Sciences, data analysis started. This study is based on the approval of the Medical Ethics Committee of Jundishapur Ahvaz University (IR.AJUMS.REC.1399.131).

2.2- Inclusion & Exclusion Criteria

Monitoring inflammatory events after cardiac surgery and assessing the prognostic values of biomarkers required screening for several intervening criteria. The inclusion criterion included, patients who had undergone open-heart surgery using the CPB method. Exclusion criteria included reoperation, valvular disease due to endocarditis, death of patients 48 hours after cardiac surgery, age under 18 years, and patients who had not undergone CPB or underwent surgery before surgery for other reasons. In addition, history and other findings of cardiac surgery patients were collected, which will be discussed in the following sections.

2.3- Hematological Parameters and Clinical Information

To analyze hematological parameters, 5-7 ml of venous blood were taken from patients and collected into dipotassium ethylenediaminetetraacetic acid (K2EDTA)-anticoagulated tubes. Pre and post-operative hematological parameters such as hemoglobin (Hb) and platelet, lymphocyte, neutrophil, and monocyte counts were collected by reviewing patients' information profiles. PLR was calculated by dividing the count of the platelets to lymphocytes. By the same procedure, NLR and MLR were calculated, by dividing the number of neutrophils and monocytes to the number of lymphocytes, respectively. In order to evaluate the relationship between AKI and cellular-inflammatory indexes, the profiles of 400 patients, who underwent CABG were scanned and studied.

2.4- History and Other Findings of Cardiac Surgery Patients

Demographic and clinical information, which affect the conditions of the undergoing cardiac surgery, including age, sex, history of smoking, diabetes, hypertension, hyperlipidemia and left ventricular ejection fraction (LVEF) were reviewed and recorded. Pre and post-operative other laboratory parameters including, serum creatinine (sCr) and serum urea levels were collected by reviewing patients' profiles.

In this study, the hypertension report in patients was dependent on the following two conditions: 1- Blood pressure higher than 140/90 mmHg, and 2- Use of antihypertensive drugs. Patients with the history of smoking were also included in the study, provided that they had not quit smoking in the year before cardiac surgery. In the present study, patients with fasting blood sugar above 126 mg/dl or taking antidiabetic drugs were considered as subjects with the history of diabetes. Patients with total cholesterol > 220 mg/dl and LDL > 130 mg/dl or patients taking lipid-lowering medications were also classified as hyperlipidemia patients.

2.5- Diagnosis of AKI and AF

Finally, 339 patients, who underwent CABG with CPB and had the creatinine (Cr) <1.5 mg/dL were selected and participated. AKI was diagnosed by changing initial Cr levels relative to sCr levels after cardiac surgery, and based on Kidney Disease Improving Global Outcomes criteria (KDIGO). In this study, the highest sCr level in the first three days after cardiac surgery was used to diagnose AKI compared to baseline sCr level (the patient's last sCr measured before cardiac surgery). It is noteworthy, that urine output was not used to diagnose AKI, as it may be altered by administered diuretics during anesthesia and CPB.

So, the following criteria were used for the AKI diagnosis in patients undergoing cardiac surgery;

- Increased level of sCr ≥ 0.3 mg/dL within 48 hours of cardiac surgery.
- Increased level of sCr ≥ 1.5 times of baseline within three days of cardiac surgery.

After AKI diagnosis, patients who developed AKI after cardiac surgery were classified as "AKI patients" (Group 1), and those with kidneys normal function after cardiac surgery were classified as "Non-AKI patients" (Group 2). In parallel with the diagnosis of AKI, Electro Cardiogram (ECG) was used to diagnose AF in these patients. Irregular rhythm in the absence of detectable P-waves, lasting more than 30 seconds on the ECG or recording 12-lead on post-operative ECG was considered as post-operative atrial fibrillation (POAF).

2.6- Statistical Analysis

All profiles of patients were collected by census and statistically analyzed (About 400 cases). This study's variables included quantitative and qualitative data, which former were reported as mean $\pm$ standard deviation (mean $\pm$ SD). Chi-square statistical method was used to measure nominal data. An independent sample t-test was also used to measure quantitative data during the period between pre and post operative. Pearson correlation was also used to examine the relationship between the measured factors. In order to quantify the strength of associations and their statistical significance, as well as account for negative associations, odds ratios and chi-squared/Fisher's exact test were performed.

Regression analysis and AUROC were performed by selecting a step-by-step variable to assess the sensitivity and specificity of biomarkers. Statistical analyses were performed using GraphPad Prism v. 7

(GraphPad Software Inc, CA, USA). Peak integration and analytical method validation were performed using ABSciex Multiquant Software Version 2.0. P-value <0.05 was considered statistically significant in all the analysis, and the OR of 95 % was calculated as confidence interval (95% CI).

3. Results

To evaluate the relationship between inflammatory events and NLR, PLR, and MLR indices, the medical profile of 400 patients were reviewed. The demographic information, clinical and laboratory data of these patients were registered and presented in Table 1. In the following, we will discuss the relationships between cellular, hematological and clinical biomarkers with inflammatory events in pre and post-operative phases. It should be noted, that pre and post-operative findings were classified chronologically as follows;

a) Pre-operative

b) Post-operative: within one, two, and three days of cardiac surgery (1b, 2b, and 3b)

c) When discharged from the hospital

3.1 Pre-operative Hematological Findings and Meaningful Criteria

In the current study, patients with post-operative AKI were classified as group I (AKI patients); patients, whose kidneys functioned normally after surgery were classified as group II (Non-AKI patients). According to this classification, group I and group II included 84 and 151 patients, respectively. Statistical analyzes revealed, that the age of AKI patients ($61.91 \text{ years} \pm 9.7 \text{ SD}$) was significantly higher than Non-AKI ones ($57.53 \text{ years} \pm 11.83 \text{ SD}$), and there was a statistically significant relationship (P-Value: 0.009).

The values of all clinical features except body mass index (BMI) and ejection fraction (EF) without significant correlation were higher in Non-AKI patients (Table 1). According to AKI and Non-AKI classifications, laboratory findings and hematological parameters were analyzed and compared in both groups of patients (Table 2). Based on the statistical results, pre-operative platelet count was significantly higher in Non-AKI patients (P-Value: 0.008). Conversely, without statistical correlation, pre-operative Hb, Hct, Hb core related antigen (HbCr), RBCs, WBCs, Neutrophils, platelets, and absolute lymphocyte count (ALC) were also higher in Non-AKI patients.

3.2 Post-operative Hematological Parameters and Serum Markers

Based on the category mentioned in the previous section, post-operative cellular biomarkers and hematological indexes were evaluated in both groups (Table 3). After statistical analysis, some cellular and hematological biomarkers were significantly different in these two groups; in some cases were significantly associated with the absence of AKI. According to the results, the lymphocyte (P-Value: 0.025) and platelet count (P-Value: 0.048) in the post-operative phase in the Non-AKI group were significantly higher (Table 4). Also, the NLR index (P-Value: 0.03) and HbCr levels (P-Value: 0.0001) were

significantly higher in patients without AKI (Table 5). On the other hand, post-operative sCr and BUN levels were statistically higher in patients with AKI (P-Value: 0.0001) (Table 5). Another post-operative hematological parameters have been summarized in Table 3.

To evaluate sensitivity of post-operative hematological parameters, regression analysis was performed. Accordingly, seventeen variables were selected as independent predictors. Among the hematological parameters just like serum markers (BUN and sCr), significant relationships were found for the Hct and HbCr in post-operative patients (Table 6). According to the post-operative duration, a statistically significant relationship was identified between Hct-2b and post-operative patients (P-Value: 0.027, df: 1). It is necessary to mention, that HbCr-a (pre-operative parameter) was also detected significantly in these patients (P-Value: 0.049, df: 1).

BUN and sCr levels as serum markers were also significantly associated with these patients. BUN-2b (P-Value: 0.002, df:1), sCr-1b (P-Value: 0.000, df:1), sCr-2b (P-Value: 0.013, df:1), sCr-3b (P-Value: 0.000, df:1) and sCr-c (P-Value: 0.000, df:1) had a significant statistical correlation. Similar to HbCr-a, BUN-a (P-Value: 0.002, df:1) and sCr-a (P-Value: 0.000, df:1) had a statistically significant relationship with these patients (Table 6).

3.3- Sensitivity and Specificity of Hematological and Serum Markers

Sensitivity and specificity of cellular biomarkers and hematological parameters were assessed separately to predict the occurrence of AKI at different time points after cardiac surgery. AUROC comparison was used to predict HbCr levels in all stages and determine sensitivity and specificity of this parameter (Figure 1). The AUROC of HbCr-2b was significantly more than for all others (AUROC: 0.701, 0.623 to 0.779, P-Value: 0.000). The AUROC of HbCr-a without a statistically significant relationship was less than all (AUROC: 0.536, 0.455 to 0.616, P-Value: 0.369).

Mentioned evaluations were also performed for serum markers (BUN and sCr); the results of the sCr's evaluation showed, that sCr-3b was significantly more than others (AUROC 0.842, 0.790 to 0.893, P-Value: 0.000). The AUROC of sCr-a without a statistically significant relationship was less than that of all (AUROC 0.519, 0.442 to 0.597, P-Value: 0.625). In parallel, the results of BUN analysis revealed, that the AUROC of BUN-3b was significantly more compared to others (AUROC 0.711, 0.640 to 0.782, P-Value: 0.000).

3.4- Sensitivity and Specificity of Cellular Biomarkers

Sensitivity and specificity of lymphocyte and platelet count were also analyzed to predict the occurrence of AKI. Lymphocyte counts were assessed at all time points after cardiac surgery. The analysis results revealed, that lymphocyte count-c was significantly higher than the others (AUROC 0.590, 0.514 to 0.667, P-Value: 0.023); lymphocyte count-a without a statistically significant relationship was less than of all (AUROC 0.489, 0.409 to 0.568, P-Value: 0.780). The results of platelet count analysis in the time periods after surgery showed, that the AUROC of platelet count-a was significantly more than for all others

(AUROC 0.597, 0.520 to 0.674, P-Value: 0.015), and the AUROC of platelet count-1b without a statistically significant relationship was less than of all (AUROC 0.533, 0.456 to 0.610, P-Value: 0.404).

Following the evaluation of the relationships between cell count and AKI occurrence, important cell ratios were also examined. On this basis, among the NLRs evaluated in the post-operative periods, NLR-c was significantly more than others (AUROC 0.601, 0.524 to 0.678, P-Value: 0.012). The AUROC of NLR-1b without a statistically significant relationship was less than of all (AUROC 0.498, 0.418 to 0.578, P-Value: 0.964). AUROC comparison to predict NLR of all stages has been displayed in Figure 2. With the same pattern, the sensitivity and specificity of PLR in post-operative patients were compared with NLR (Figure 3). The findings revealed, that the AUROC of NLR-c was significantly more than PLR-c (AUROC 0.587, 0.510 to 0.663, P-Value: 0.030).

4. Discussion

Cardiovascular diseases are a significant health burden in the world. Approximately 180,000 deaths occurred due to cardiovascular disease, accounting for a third of all deaths in the UK, in 2010 (28). Various risk factors are involved in the pathogenesis of these diseases. With improvements to understand the responsible mechanisms for cardiovascular complications, adverse mortality rates have fallen. The pathogenic mechanisms, that lead to organ injury are multifactorial, including inflammatory, hemodynamic, and direct damage (e.g., embolic to the heart, brain, lung, and gut or nephrotoxic to the kidney). Health benefits are achieved by reducing major risk factors, such as smoking cessation, exercise and improvements in preventative measures (e.g., enhanced blood pressure control, lipid-lowering agents, long-term antiplatelet therapy, and optimized blood glucose) in conjunction with healthy eating (29).

Nowadays, cardiac surgery and CPB are the most effective treatment methods, but also have inevitable side effects. Prescribing anesthetics, transfusing blood products and CPB can stimulate immune system and trigger a chain of immune responses. These threatening factors gradually enhance numbers of neutrophils and increase concentrations of pro-inflammatory cytokines (IL-6, IL-8, TNF α) and neutrophil elastase. Increases in cellular permeability and the additional fluid load of CPB lead to increased extravascular lung water and pulmonary edema (30, 31). Systemic immune responses in patients undergoing CABG with CPB, specifically cardiac surgery, leads to the activation of p38 MAP kinase in circulating leukocytes by phosphorylation, and ROS induction. In addition, induction of ROS and activation of p38 MAP kinase occurred before CPB commencement (32, 33).

Inflammatory problems following cardiac surgery and CPB, including AKI and AF are among the most important concerns of the international community. In addition, myocardial infarction is one of the leading causes of death in post-operative patients. Studies have revealed, that a post-operative myocardial infarction incidence occurs in 2-3% of patients following cardiac surgery (34, 35). In recent years, various predictors and biomarkers have been measured to predict inflammatory events after cardiac surgery. For instance, cardio-specific proteins (CK-MB) and troponins are the mainstay markers of

cellular damage. Additionally, heart-type fatty-acid-binding protein (hFABP) is an emerging rapid marker of myocardial infarction (36).

There are consistently higher markers of myocardial injury in association with on-pump surgery compared to off-pump surgery (36, 37). Discovery of early predictors of inflammatory events following cardiac surgery, which are also economic, has been the goal of many researches.

Over the years, various hypotheses have been tested to predict inflammatory problems after surgery. From a cellular perspective, extensive studies have been performed on cells involved in inflammation and cytokines secretion. One of the most challenging observations in inflammatory processes is changes in hematological indexes, serum markers, poikilocytosis, and changes in inflammatory cells' count. Tracing any of these criteria may lead to the discovery of a new path in the process of predicting and diagnosing of inflammatory events before heart surgery. Extensive researches focusing on cellular biomarkers has attempted to predict inflammatory problems following heart surgery, including AF, POAF, and AKI.

In 2015, Kim et al. examined the relationship between NLR and AKI post-cardiac surgery with CPB in a statistical population of 590 patients, where 28.1% developed AKI in the first seven post-operative days. The results of the study by Kim et al. revealed, that immediate post-operative and day one NLR (NLR-a) were significant predictors of AKI. In another study in 2019, Rebecca et al. reported, that there was no significant relationship between day one NLR (NLR-a) and AKI occurrence (26). However, their results confirmed day 2 NLR, and found a significant link between raised day 2 NLR (NLR-2b) and AKI (P-Value: 0.041). However, pre-operative NLR did not predict post-operative AKI, and pre-operative NLR was not significantly associated with AKI (P-Value: 0.283) (38).

A prominent common finding in many studies is AKI occurrence in the first postoperative days. Therefore day one and day two NLR (NLR-1b and NLR-2b) would not be clinically useful in predicting AKI after cardiac surgery. Some other studies have identified the association between cellular biomarkers and patient mortality as the main focus of the study. For example, the findings of Bin Mahmood et al.' study In 2019 showed, that LNR was a more stable measurement over time than NLR; LNR demonstrated a stronger association with mid-term mortality (39). They also reported, that low LNR was associated with increased baseline morbidity, increased cardiopulmonary bypass time, and increased post-operative ICU length of stay.

Recent studies have even identified WBC counts as a valuable cellular marker for detecting cardiac complications. Studies in this area have shown a strong correlation between pre-operative WBC count and cardiac death, including studies explicitly focused on CABG (39, 40). The study by Gibson et al. also claimed, that among patients undergoing CABG, increased NLR was a strong predictor of post-operative mortality (P-Value: 0.001, HR: 1.12 per unit, and 95% CI: 1.06–1.18) (41). In this area, study conducted by Tan et al. reported that increased risk of re-intubation were associated with pre-operative NLR (P-Value: 0.003, OR: 6.29, and 95% CI: 1.85–21.4) (25). In addition, the results of their studies confirmed a significant relationship between higher pre-operative NLR values and increased mortality after cardiac surgery (P-Value < 0.00001, HR: 1.85, and 95% CI: 1.46–2.36) (25, 42).

Numerous studies have been performed on absolute inflammatory cell count and the ratio of these cells. The results of a study by Durmus et al. revealed, that NLR as an independent risk factor of myocardial injury is a more precise predictive marker than ALC and ANC following non-cardiac surgery (24).

4.1- Considerations and Limitations

This study had some advantages compared to previous ones; In the present study, the inclusion criteria were broader, and findings were more acceptable and reliable. The study results can be the cornerstone for conducting more clinical practices and future researches. In addition, the statistical population in this study was more extensive than other similar recent ones, which makes the results of statistical analysis more realistic.

It should be noted, that the absence of patients who did not undergo CPB or underwent surgery before surgery, as an essential exclusion criterion caused the study population to be purely composed of cardiac surgery patients. However, this retrospective study inherently had its limitations. The process of POAF diagnosing might limited this study. As the use of 12-lead ECG for POAF diagnosis was user-dependent, it is possible that the short episodes of AF may not be detected or may be incompletely recorded.

4.2- Conclusions and Recommendations

In this study, for the first time, hematological parameters and cellular biomarkers were evaluated to predict inflammatory problems following cardiac surgery (Table 3). Accordingly, blood indexes, cell counts and the ratio of inflammatory cells (NLR, PLR, and MLR) were assessed before, during, and after cardiac surgery. On the other hand, the sensitivity and specificity of these markers were evaluated for early detection and prediction of AKI in patients.

In this study, serum markers (BUN and sCr levels) and some blood cell counts, such as platelet were significantly associated with AKI. A slight increase in pre-operative platelet count was detected statistically in Non-AKI patients (P-Value: 0.008). The same significant correlation was clearly observed in platelet count within three days of cardiac surgery (platelet counts-c.) (P-Value: 0.048). Both groups of patients (AKI and Non-AKI patients) in all post-operative periods (P-Value: 0.0001 BUN and sCr levels were significantly correlated) (Table 5). Post-operative HbCr, like serum markers was significantly associated with AKI in all periods after cardiac surgery (P-Value of HbCr-1b, 2b, and 3b: 0.0001, and P-Value of HbCr-c: 0.002) (Table 3).

According to the analysis, the sensitivity and specificity of HbCr-1b, HbCr-2b, and HbCr-3b seemed desirable to suspecting AKI (Figure 1). Among inflammatory cell biomarkers, the post-operative NLR-c was significantly associated with AKI (P-Value: 0.03) (Table 5). Evaluation of sensitivity and specificity of NLR showed relatively acceptable results (Figure 3).

Given the critical need for effective prognostic, diagnostic and therapeutic methods to control inflammatory problems following heart surgery, it is recommended to evaluate the hematological, cellular,

and clinical aspects with a new perspective; it will maximize the efficiency of preventive processes, and minimize patient mortality rates.

Declarations

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Conflict of interest

The authors declare no conflict of interest.

Authors' Contributions

Dr. Fatemeh Javaherforoosh Zadeh conceived the manuscript and revised it. Mohsen Maleknia and Hadi Rezaeeyan wrote the manuscript and prepared tables. All authors participated in preparing the final draft of the manuscript, revised the manuscript, and critically assessed the academic contents. All authors have read and approved the manuscript's content and confirmed the accuracy or integrity of any parts of the work.

COMPLIANCE WITH ETHICAL STANDARDS

All the procedures performed in the studies involving human participants were in accordance with ethical standards of the local ethics committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1399.131) as well as 1964 Helsinki declaration.

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Tables

Table 1. Demographic and Clinical findings of patients.

Patient's Characteristics	Group I, AKI Patients (N=84)	Group II, Non-AKI Patients (N=151)	P-Value
Age, Years (mean $\pm$ SD)	61.91 $\pm$ 9.7	57.53 $\pm$ 11.83	0.009
Male (%)	41 (33.6%)	81 (66.4%)	0.254
Female (%)	44 (38.6%)	70 (61.4%)	0.254
BMI (Kg/m ²) (mean $\pm$ SD)	28.72 $\pm$ 5.22	27.21 $\pm$ 3.75	0.096
Hypertension (%)	66 (78.6%)	104 (69.8%)	0.097
Diabetes mellitus (%)	38 (47.5%)	70 (47.9 %)	0.530
Smoking (%)	20 (25.6 %)	40 (28.8%)	0.370
Hyperlipidemia (%)	42 (49.4%)	68 (45%)	0.717
EF (%) (median; min-max)	42.5 (20-60)	40 (20-60)	0.35
History of atrial fibrillation (%)	29 (34.1%)	46 (30.5%)	0.334
History of MI (%)	16 (18.8%)	38 (25.2%)	0.461
History of CVA (%)	7 (8.2%)	8 (5.3%)	0.632
Peripheral Vascular disease	0 (0%)	1 (0.7%)	0.746
Previous Heart Surgery	1 (1.2%)	4 (2.6%)	0.742
History familial diseases	71 (83.5%)	131 (86.8%)	0.767

Abbreviation: AKI: acute kidney injury; BMI: body mass index; EF; ejection fraction; MI: myocardial infarction; CVA: cerebrovascular accident.

Table 2. Patient's preoperative laboratory/hematological findings.

Pre-operative Parameters	Group I (AKI patients)	Group II (Non-AKI patients)	P-Value
Hb (g/dl)	11.23 ± 2.4	11.52 ± 2.3	0.245
Hct (%)	33.74 ± 7.2	35.17 ± 6	0.06
MCV (fl)	85.04 ± 7	83.5 ± 10.91	0.221
MCH (pg)	28.26 ± 2.91	27.9 ± 3.75	0.292
MCHC (g/dl)	33.14 ± 1.9	32.58 ± 2.3	0.107
RBCs count (×10 ⁶)	4.06 ± 1.26	4.48 ± 3.5	0.057
WBCs count (×10 ³)	9.47 ± 3.6	9.87 ± 7.2	0.660
Lymphocytes count (%)	19.96 ± 13.7	22.68 ± 13.7	0.106
Neutrophils count (%)	83 ± 10.2	68.96 ± 16.58	0.093
Platelets count (×10 ³)	192.5 ± 71.75	216.198 ± 71.22	0.008
BUN (mg/dl)	19.68 ± 6	19.23 ± 6	0.584
sCr (mg/dl)	1.01 ± 0.177	1.00 ± 0.172	0.619
ANC	0.78 ± 0.08	0.71 ± 0.05	0.356
ALC	0.016 ± 0.01	0.019 ± 0.02	0.203
NLR	8.4 ± 12.9	6.36 ± 6.6	0.062
PLR	175.4 ± 188.38	150.93 ± 89.6	0.936
HbCr	11.37 ± 3.07	11.75 ± 2.7	0.117

*All data have been provided with mean and standard deviation (mean ± SD).

Abbreviation: RBCs: red blood cells; WBCs: white blood cells; Hb; hemoglobin; Hct: hematocrit; MCV: mean cell volume; MCH: mean cell hemoglobin; MCHC: mean corpuscular hemoglobin concentration; BUN: blood urea nitrogen; ANC: absolute neutrophil count; ALC: absolute Lymphocyte count; NLR: neutrophil-lymphocyte ratio; sCr: serum creatinine.

Table 3. Patient's post-operative hematological indexes.

Post-operative parameters / duration	Group I (AKI patients)	Group II (Non-AKI patients)	P-Value
Hb (g/dl) 1b	9.66 ± 1.73	9.61 ± 1.7	0.935
Hb (g/dl) 2b	9.31 ± 1.64	9.37 ± 1.75	0.863
Hb (g/dl) 3b	9.02 ± 1.53	9.0 ± 1.8	0.463
Hb (g/dl) c	9.7 5± 1.36	10.16 ± 5.12	0.985
Hct (%) 1b	29.07 ± 5.29	29.97 ± 5.62	0.745
Hct (%) 2b	29.15 ± 6.89	29.34 ± 6.12	0.778
Hct (%) 3b	27.15 ± 3.61	28.43 ± 6.27	0.127
Hct (%) c	29.9 ± 3.93	30.16 ± 6.27	0.609
MCV (fl) 1b	85.36 ± 5.15	89.3±62.25	0.475
MCV (fl) 2b	85.51 ± 5.27	84.35 ± 8.27	0.272
MCV (fl) 3b	84.34 ± 8.29	84.12 ± 10.20	0.860
MCV (fl) c	95.57 ± 85.23	84.28 ± 9.32	0.136
MCH (pg) 1b	28.23 ± 2.96	28.08 ± 5.84	0.629
MCH (pg) 2b	28.06 ± 2.68	29.26 ± 19.73	0.838
MCH (pg) 3b	27.89 ± 2.4	27.71 ± 3.05	0.800
MCH (pg) c	28.80 ± 5.82	27.94 ± 2.87	0.484
MCHC (g/dl) 1b	32.72 ± 1.91	32.38 ± 2.5	0.177
MCHC (g/dl) 2b	32.32 ± 1.98	32.4 3± 1.71	0.812
MCHC (g/dl) 3b	32.43 ± 2.1	34.24 ± 22.25	0.828
MCHC (g/dl) c	32.43 ± 2.25	32.36 ± 1.81	0.857
HbCr 1b	8.57 ± 5.65	9.91 ± 2.47	0.0001
HbCr 2b	7.91 ± 2.5	9.66 ± 2.5	0.0001
HbCr 3b	7.71 ± 2.63	9.32 ± 2.6	0.0001
HbCr c	9.19 ± 2.5	10.8 ± 9.03	0.0020

* Post-operative findings were classified chronologically as follows; **a)** Pre-operative, **b)** Post-operative: within one, two, and three days of cardiac surgery (1b, 2b, and 3b), **c)** When discharged from the hospital.

Abbreviation: Hb; hemoglobin; Hct: hematocrit; MCV: mean cell volume; MCH: mean cell hemoglobin; MCHC: mean corpuscular hemoglobin concentration; Hb core related antigen (HbCr).

Table 4. Cell count of patient’s post-operative.

Post-operative parameters / duration	Group I (AKI patients)	Group II (Non-AKI patients)	P-Value
RBCs Count (×10 ⁶) 1b	3.93 ± 4.42	3.89 ± 4.38	0.844
RBCs Count (×10 ⁶) 2b	3.77 ± 3.63	4.31 ± 4.8	0.106
RBCs Count (×10 ⁶) 3b	3.33 ± 0.93	3.75 ± 3.12	0.137
RBCs Count (×10 ⁶) c	3.50 ± 0.389	3.73 ± 2.40	0.791
WBCs Count (×10 ³) 1b	12.81 ± 3.94	12.61 ± 4.42	0.530
WBCs Count (×10 ³) 2b	13.35±3.81	13.37 ± 6.95	0.393
WBCs Count (×10 ³) 3b	13.57 ± 3.89	13.2±4.35	0.388
WBCs Count (×10 ³) c	10.54 ± 3.53	10.36 ± 3.81	0.453
Lymphocytes Count (%) 1b	10.81 ± 10.31	10.254 ± 8.74	0.698
Lymphocytes Count (%) 2b	11.61 ± 8.76	13.95 ± 14.42	0.209
Lymphocytes Count (%) 3b	12.81 ± 7.61	14.18 ± 13.72	0.369
Lymphocytes Count (%) c	21.86 ± 7.47	23.45 ± 8.23	0.025
Neutrophils Count (%) 1b	81.64±12.77	82.4 ± 11.11	0.447
Neutrophils Count (%)2b	81.15 ± 9.38	80.04 ± 10.07	0.576
Neutrophils Count (%)3b	77.99 ± 11.73	78.13 ± 12.01	0.727
Neutrophils Count (%)c	65.77 ± 11.25	63.93 ± 9.75	0.053
Platelet Count (×10 ³) 1b	175.14±52.73	206.39 ± 263	0.464
Platelet Count (×10 ³) 2b	170.84 ± 49.51	182.11 ± 54	0.196
Platelet Count (×10 ³) 3b	165.61 ± 48.35	179.16 ± 66.21	0.257
Platelet Count (×10 ³) c	229.65 ± 83.31	246.82 ± 73.6	0.048
ANC 1b	0.1065 ± 0.037	0.1062 ± 0.043	0.511
ANC 2b	0.1103 ± 0.036	0.1101 ± 0.066	0.408
ANC 3b	0.1074 ± 0.037	0.1057 ± 0.049	0.673
ANC c	0.0705 ± 0.0314	0.068 ± 0.032	0.289
ALC 1b	0.0125 ± 0.01	0.0115 ± 0.009	0.742
ALC 2b	0.0141 ± 0.0108	0.015 ± 0.0112	0.293

ALC 3b	0.0162 ± 0.0096	0.0168 ± 0.014	0.347
ALC c	0.022 ± 0.01	0.023 ± 0.01	0.798

* Post-operative findings are classified chronologically as follows; **a)** Pre-operative, **b)** Post-operative: within one, two, and three days of cardiac surgery (1b, 2b, and 3b), **c)** When discharged from the hospital.

Abbreviation: RBCs: red blood cells; WBCs: white blood cells; ANC: absolute neutrophil count; ALC: absolute Lymphocyte count.

Table 5. Serum and cell biomarkers in post-operative patients.

Post-operative parameters / duration	Group I (AKI patients)	Group II (Non-AKI patients)	P-Value
BUN (mg/dl) 1b	24.78 ± 8.39	20.24 ± 6.06	0.0001
BUN (mg/dl) 2b	25.84 ± 9.68	20.89 ± 6.51	0.0001
BUN (mg/dl) 3b	28.24 ± 9.94	21.46 ± 7.19	0.0001
BUN (mg/dl) c	21.52 ± 8.07	18.5 ± 6.18	0.0001
sCr (mg/dl) 1b	1.26 ± 0.32	0.99 ± 0.16	0.0001
sCr (mg/dl) 2b	1.39 ± 1.52	1.00 ± 0.18	0.0001
sCr (mg/dl) 3b	1.34 ± 0.34	0.97 ± 0.18	0.0001
sCr (mg/dl) c	1.12 ± 0.25	0.99 ± 0.17	0.0001
NLR 1b	13.85 ± 13.44	12.34 ± 7.32	0.751
NLR 2b	10.68 ± 7.52	9.95 ± 9.84	0.134
NLR 3b	8.24 ± 4.58	8.17 ± 5.71	0.395
NLR c	3.65 ± 2.7	4.22 ± 5.16	0.030
PLR 1b	227.83 ± 237.62	241.87 ± 464.9	0.145
PLR 2b	162.9 ± 115.62	158.02 ± 119.36	0.754
PLR 3b	126.3 ± 70.65	134.21 ± 88	0.689
PLR c	140.2 1± 200	140.57 ± 138	0.230

* Post-operative findings were classified chronologically as follows; **a)** Pre-operative, **b)** Post-operative: within one, two, and three days of cardiac surgery (1b, 2b, and 3b), **c)** When discharged from the hospital.

Abbreviation: BUN: blood urea nitrogen; sCr: serum creatinine; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.

Table 6. Regression analysis of hematological parameters and serum markers in pre/post-operative patients.

Parameters	B	S.E.	Wald	df	Sig.	Exp (B)
Hct 2b	0.119	0.054	4.881	1	0.027	1.028
BUN 2b	-.101	.033	9.563	1	0.002	.904
sCr 1b	-5.925	1.640	13.057	1	0.000	.003
sCr 2b	-4.821	1.950	6.111	1	0.013	.008
sCr 3b	-9.954	1.827	29.672	1	0.000	.000
sCr c	-6.801	1.817	14.006	1	0.000	.001
HbCr a	- 0.121	0.062	3.887	1	0.047	0.886
BUN a	0.100	0.032	9.637	1	0.020	1.105
sCr a	21.938	3.551	38.176	1	0.000	0.002

*Variable(s) entered on step 1: Hct 2b, BUN 2b, sCr 1b, sCr 2b, sCr 3b, sCr c, HbCr a, BUN a, and sCr a.

*Pre/Post-operative findings were classified chronologically as follows; **a)** Pre-operative, **b)** post-operative: within one, two, and three days of cardiac surgery (1b, 2b, and 3b), **c)** When discharged from the hospital.

Abbreviation: BUN: blood urea nitrogen; sCr: serum creatinine; HbCr: Hb core related antigen.

Figures

Diagonal segments are produced by ties.

Test Result Variable(s)	Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
HbCr-a	0.536	0.041	0.369	0.455	0.616
HbCr-1b	0.701	0.040	0.000	0.623	0.779
HbCr-2b	0.686	0.037	0.000	0.613	0.758
HbCr-3b	0.689	0.037	0.000	0.617	0.762
HbCr-c	0.623	0.040	0.002	0.544	0.701
The test result variable(s): HbCr-a, HbCr-1b, HbCr-2b, HbCr-3b, and HbCr-c has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

* HbCr1, HbCr2a, HbCr2b, HbCr2c, and HbCr3 are equivalent to HbCr a, HbCr 1b, HbCr 2b, HbCr 3b, and HbCr c, respectively.

Abbreviation: HbCr: Hb core related antigen.

Figure 1

Sensitivity and specificity of HbCr to predict AKI occurrence in post-operative patients. Comparison of HbCr a, HbCr 1b, HbCr 2b, HbCr 3b, HbCr c and the logistic regression model to predict the occurrence of AKI in post-operative patients. As it is evident, the AUROC of HbCr 2b (AUROC: 0.701, 0.623 to 0.779, P-Value: 0.000) was significantly more than others.

Diagonal segments are produced by ties.

Test Result Variable(s)	Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NLR-a	0.567	0.039	0.094	0.491	0.643
NLR-1b	0.498	0.041	0.964	0.418	0.578
NLR-2b	0.556	0.039	0.167	0.478	0.633
NLR-3b	0.543	0.040	0.284	0.465	0.621
NLR-c	0.601	0.039	0.012	0.524	0.678
The test result variable(s): NLR-a, NLR-1b, NLR-2b, NLR-3b, NLR-c has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

* NLR1, NLR2, NLR3, NLR4, and NLR5 are equivalent to NLR-a, NLR-1b, NLR-2b, NLR-3b, and NLR-c, respectively.

Abbreviation: NLR: neutrophil-lymphocyte ratio.

Figure 2

Sensitivity and specificity of NLRs in the post-operative periods to predict the occurrence of AKI. A logistic regression model performed a comparison between NLR-a, NLR-1b, NLR-2b, NLR-3b, and NLR-c to predict post-operative AKI occurrence. The results showed, that this biomarker is significantly more than others (AUROC 0.601, 0.524to 0.678, P-Value: 0.012), and NLR-1b without a statistically significant relationship was less than of all (AUROC 0.498, 0.418 to 0.578, P-Value: 0.964).

Test Result Variable(s)	Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PLR-c	0.452	0.041	0.230	0.372	0.533
NLR-c	0.587	0.039	0.030	0.510	0.663
The test result variable(s): PLR-c, NLR-c has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.					
a. Under the nonparametric assumption					
b. Null hypothesis: true area = 0.5					

* NLR5, and PLR5 are equivalent to NLR-c, and PLR-c, respectively.

Abbreviation: NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio.

Figure 3

Comparison between sensitivity and specificity of NLR-c and PLR-c to predict AKI occurrence in post-operative patients. The sensitivity and specificity of PLR-c in post-operative patients were compared with NLR through logistic regression model; the results proved, that the AUROC of NLR-c was significantly more than PLR-c (AUROC 0.587, 0.510 to 0.663, P-Value: 0.030).

Supplementary Files

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