

The Ir indicator and its modification Im in patients operated on for infective endocarditis – usefulness in operative risk prognosis and postoperative therapy assessment



Wskaźnik Ir i jego modyfikacja Im u pacjentów operowanych z powodu infekcyjnego zapalenia wsierdza – przydatność w prognozowaniu ryzyka operacji i ocenie skuteczności leczenia pooperacyjnego

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Abstract

Introduction: Anemia is a part of the endocarditis clinical presentation. C-reactive protein is one of the widely available inflammatory markers, which contributes to the diagnostic and prognostic process of infective endocarditis (IE). Both mentioned parameters are connected by the newly proposed risk indicator Ir.

The aim of the study was to assess its usefulness in patients subjected to cardiac surgery due to IE. We also evaluated the clinical application of the modified risk indicator Im.

Material and methods: The study involved 29 patients operated on for IE in the Cardiosurgical Clinic in Lodz. All laboratory examinations (CRP, RBC, Hb) and proper calculations were carried out: preoperatively, on the 3rd, 7th, 12th and 21st postoperative day. Patients were divided into 2 groups: without (A) or with (B) complications. The end points of prognostic significance were: decrease, respiratory or circulatory failure over 72 h, the time of hospitalization and stay in the intensive care unit (ICU).

Results: Postoperative complications were found in 17 (58.62%) patients. A statistically significant increase of Ir and Im was observed on the 3rd postoperative day (the highest values for the non-complicated group). The peak increase was noted on the 7th day in the group with complications. The risk indicators began to decrease earlier in group A. The blood parameters decreased significantly on the 3rd day and started to elevate significantly from the 12th day. The perioperative mortality reached 10.34% (3) of patients.

Streszczenie

Wstęp: Anemia jest jedną ze składowych infekcyjnego zapalenia wsierdza. Białko C-reaktywne (*C-reactive protein* – CRP) należy do szeroko dostępnych markerów zapalnych, odgrywających rolę w rozpoznaniu i prognozowaniu u pacjentów z infekcyjnym zapaleniem wsierdza (IZW). Oba parametry łączy nowy wskaźnik ryzyka – Ir.

Cel pracy: Ocena przydatności Ir u pacjentów operowanych z powodu IZW. Oceniono także kliniczną przydatność zmodyfikowanego wskaźnika ryzyka – Im.

Materiały i metody: Badaniem objęto 29 pacjentów operowanych w Klinice Kardiochirurgii w Łodzi z powodu IZW. Wszystkie badania laboratoryjne (RBC, Hb, CRP) oraz odpowiednie obliczenia (Ir i Im) wykonano przed operacją oraz w 3., 7., 12. i 21. dobie pooperacyjnej. Pacjenci zostali podzieleni na 2 grupy: A – bez powikłań, B – z powikłaniami. Za punkty końcowe o znaczeniu predykcyjnym przyjęto: zgon, niewydolność oddechową lub krążenie > 72 godz., czas hospitalizacji i pobytu na oddziale intensywnej terapii (OIT). Przeanalizowano wystąpienie powikłań w przebiegu pooperacyjnym. Uwzględniono ilość przetaczanych preparatów krwi i krwiopochodnych.

Wyniki: Powikłania pooperacyjne wystąpiły u 17 pacjentów (58,62%). W 3. dobie pooperacyjnej stwierdzono istotny statystycznie wzrost Ir i Im (szczyt dla grupy niepowikłanej). W grupie z powikłaniami najwyższy wzrost przypadł dopiero na 7. dobie. W grupie A oba wskaźniki zaczęły obniżać się już w 7. dobie. W grupie B istotny spadek nastąpił dopiero w 12. dobie. Odnotowano istotny spadek parametrów krwi – RBC i Hb w 3. dobie

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Conclusions: The prognostic value for postoperative complications was proved for Ir and Im. Their superiority to CRP was found.

Key words: risk indicators, infective endocarditis, valvular prosthesis implantation.

Introduction

Infective endocarditis (IE) remains a disease of high mortality, reaching even 10-50%, despite appropriate antibiotic therapy [1]. Anemia is one of the clinical signs of endocarditis. It is a consequence of a long-lasting disease process and bacterial infection. The release of cytokines (mainly IL-6) is a response to the existing inflammatory process and it exerts a double effect. The cytokines stimulate synthesis of the acute phase proteins, including hepcidin, which despite its antimicrobial properties, is the main hormone regulating iron metabolism [2]. Furthermore, cytokines directly inhibit the medullary erythropoiesis. Inflammatory markers, including widely available C-reactive protein (CRP), are popular tools for monitoring patients with IE. They have also become indispensable for fast and proper diagnosis [3, 4], which plays a key role in complicated cases or those with a dramatic course [5].

The new risk indicator Ir, developed by B. Kraśnicka-Sokół *et al.* [6], joins the two above mentioned parameters. Diagnostic as well as prognostic value is assigned to it. Using this indicator the researchers have revealed a high-risk patient group, which should be qualified for earlier surgical intervention. Among patients involved in the mentioned study almost half underwent surgical treatment.

As a purpose of the study we decided to verify the risk indicator Ir among patients subjected to cardiac surgery due to valvular defects caused by endocardial infection. We have also modified the proposed Ir formula by replacing hemoglobin (Hb) by the red blood cell count (RBC). We evaluated the obtained modified indicator (Im) in clinical practice and tried to establish the threshold value for this parameter. Eventually we compared both of the indicators.

Material and methods

This study was retrospective. In the study there were involved 29 patients admitted to the Cardiac Surgery Clinic of the Medical University of Lodz. For the group of 20 patients operated on subsequently in the clinic, the analysis and calculations were conducted retrospectively. Then 9 patients, admitted and operated on for IE, were enrolled in the study. Diagnosis of infective endocarditis was based on Duke's criteria [7]. The average time from the first symptoms to the final diagnosis was 24-30 days. The assessed group consisted of 16 men and 13 women. The average age was 52.14 ± 15.11 . The average ejection fraction was 57.77%.

i istotny wzrost od 12. doby. W okresie okołoperacyjnym przetoczono 1 pacjentowi średnio 2,7 j. koncentratu krwinek czerwonych i 1,17 j. świeżo mrożonego osocza. Śmiertelność pooperacyjna wyniosła 10,34% (zmarło 3 pacjentów).

Wnioski: Wykazano prognostyczną wartość Ir i Im co do pooperacyjnych powikłań oraz stwierdzono wyższość obu parametrów nad CRP.

Słowa kluczowe: wskaźniki ryzyka, infekcyjne zapalenie wsierdza, implantacja sztucznej zastawki.

Fourteen (14, 48.3%) patients were qualified as functional NYHA class III. In 8 (27.6%) patients heart failure in NYHA class IV was diagnosed. In the perioperative period a standard for IE antibiotic therapy, according to the cultures and antibiograms, was administered to the patients. Patients' characteristics are presented in Table I.

In the study population there were 11 (38%) artificial mitral valves (MVR) implanted. In 12 (41.38%) cases an aortic valve replacement (AVR) was carried out (bioprostheses). In 1 (3.45%) case mitral annuloplasty was performed and in the others complex procedures were conducted. All procedures included 3 redo surgeries. Heart protection was obtained with a cold crystalloid cardioplegic solution given antegrade (average 1519 ml). The average perfusion time was 104.56 min and the aortic cross-clamping time was 77.31 min. Although patients were given preoperative antibiotic therapy and the preoperative blood cultures were negative the valvular material collected intraoperatively was sent for microbial examination.

The analysis also included the amount of blood and blood-derived preparations (PRBC – packed red blood cells) transfused in the intra- and postoperative period. The mode of the surgery – emergent, urgent or scheduled – was also taken into account. Complications in the early postoperative period were also analyzed, inter alia respiratory or circulatory insufficiency lasting over 72 h (the necessity of mechanical ventilation or use of intra-aortic balloon counterpulsation – IABP), duration of stay in the intensive care unit (ICU) and complete hospitalization time.

Tab. I. Patients' preoperative characteristics including more significant comorbidities

Comorbidities	Number of patients
history of stroke	5
peripheral embolism	3
renal diseases	3
coronary artery disease (including history of myocardial infarction)	3
cancer in the past history	2
diabetes/IGT	4
pulmonary disease	5
history of sepsis	2
history of steroids use	3

For each patient the value of the new risk indicator I_r was calculated, according to the formula proposed by B. Kraśnicka-Sokół *et al.* [6]:

$$I_r = \frac{CRP \left[\frac{mg}{l} \right]}{Hgb \left[\frac{g}{dl} \right] - \beta} \times 10, \text{ where } \beta = 6 \text{ g/dl.}$$

Then the modified indicator was calculated, as shown below:

$$I_m = \frac{CRP \left[\frac{mg}{l} \right]}{RBC \left[\frac{mln}{\mu l} \right] - \alpha} \times 10^{12} \text{ (*multiplier } 10^{12} \text{ is a result of units harmonization) } I_r [mg], \text{ where } \alpha = 2.5 \text{ mln}/\mu l.$$

2.5 mln/ μ l was accepted as the RBC threshold for which mortality risk is high (on the basis of the MHC formula, where the average hemoglobin value 25 pg and the hemoglobin concentration 6 g/dl were posited), which approximately reflects the content of hemoglobin – 6 g/dl.

All collected data (CRP, RBC and Hb) and appropriate calculations (I_r and I_m) were performed at consecutive check points: preoperatively, and on the 3rd, 7th, 12th and 21st postoperative day.

Patients were divided into 2 groups: A, without complications (12); and B, any complication during hospitalization (17).

The obtained data were statistically analyzed. The program SPSS version 9.0 was used. For all collected data mean values with standard deviations and median values were determined. Shapiro-Wilk's test was used for evaluation of the accordance with normal distribution. For comparison of the quantitative values with normal distribution Student's t-test was used. The nonparametric values were compared with χ^2 test. Correlation of both risk indicators (I_r vs. I_m) was evaluated with Spearman's correlation test. The dependency between CRP, RBC and Hb at consecutive control points was studied. The value $p < 0.05$ was considered as statistically significant.

Results

Comparison of the preoperative RBC with the value from the 3rd postoperative day revealed a statistically significant (SS) decrease ($p = 0.00011$). Analogical dependency was found for Hb (SS, $p = 0.0005$). Erythrocytes and hemoglobin started to increase from the 12th postoperative day (SS, $p = 0.004$ and $p = 0.01$). There were no statistically significant differences in morphological parameters (RBC and Hb) between groups A (without complications) and B (with complications) (comparison of the average values of RBC and Hb in both groups for each control point, $p > 0.05$) (Tables II, III).

In the perioperative period the average 2.7 PRBC and 1.17 units of FFP (fresh frozen plasma) were transfused to each patient. In the early postoperative period coagulation disorders were diagnosed in 2 patients. In 1 patient massive coagulation disturbances required 9 units of cryoprecipitate and 9 units of platelet concentrates (besides PRBC and FFP). Moreover, in 2 patients rethoracotomy was conducted because of the increased drainage. In the early postoperative period complications occurred in 17 (58.62%) patients. Complications included cardiac arrhythmias, coagulation disorders, low output syndrome, cardiogenic shock (requiring catecholamines and/or IABP usage), perioperative stroke, respiratory insufficiency, acute renal failure, hydrothorax, sternal dehiscence, and pneumonia. In 6 patients complex complications were present.

The CRP peak occurred on the 3rd postoperative day (SS, $p = 0.001$). After that time it started to decrease (SS, 7th vs. 12th day, $p = 0.006$). This is compatible with our previous studies concerning inflammatory markers in patients with IE [8]. In the group with complications CRP levels were higher at each control point (SS, on the 7th and 21st postoperative day, $p = 0.019$ and $p = 0.026$). However, the variability of this parameter was identical in both groups (peak on the 3rd day and gradual decrease from that control point).

In both groups we observed differences in alterations of I_m and I_r . The maximal increase of both indicators occurred

Tab. II. Mean values of assessed morphological parameters, CRP and the prognostic indicators for the group without complications (A)

Parameter	Before surgery	3 rd postoperative day	7 th postoperative day	12 th postoperative day	21 st postoperative day
RBC	3.84	3.30	3.48	3.85	4.27
Hb	11.31	9.82	10.14	11.13	12.28
CRP	22.41	91.73	59.60	32.47	13.61
I_r	59.93	251.72	164.00	76.30	21.40
I_m	28.41	118.78	81.47	30.10	7.60

Tab. III. Mean values of assessed morphological parameters, CRP and the prognostic indicators for the group with postoperative complications (B)

Parameter	Before surgery	3 rd postoperative day	7 th postoperative day	12 th postoperative day	21 st postoperative day
RBC	4.02	3.58	3.35	3.64	3.90
Hb	11.77	10.53	9.80	10.47	10.90
CRP	59.02	145.10	121.56	67.50	64.68
I_r	136.71	363.28	426.78	187.58	191.36
I_m	67.63	213.91	303.50	95.85	74.44

on the 7th postoperative day in the group with complications, while in the group without complications it occurred on the 3rd postoperative day. But just on the 3rd postoperative day we noted a statistically significant increase in both groups (SS, Ir $p = 0.02$ for group B and $p = 0.013$ for group A, Im $p = 0.015$ for group B and $p = 0.016$ for group A). However, the increase of Ir > 300 and Im > 200 was associated with complications within the next days. On the 12th day we noted a sudden decrease of these parameters in the group with complications (SS, Ir $p = 0.036$ for Ir and $p = 0.028$ for Im), while in the group without complications both indicators began to decrease on the 7th day (SS, for Ir 7th vs. 12th day $p = 0.005$ and 12th vs 21st day $p = 0.026$, for Im respectively, $p = 0.012$ and $p = 0.019$). Both indicators (Ir and Im) also had higher values for each control point in the group with complications. For the preoperative measurements Ir >100, which was compatible with the results of B. Kraśnicka-Sokół *et al.* [6] and Im > 60, which we established in our study, was helpful in prognosticating early complications. Statistical significance was confirmed only for the 21st postoperative day (SS, $p = 0.017$). In group B we observed an Ir increase at the last control point of 3.78 (NS, $p = 0.52$) (Figs. 1-4).

Three (10.34%) patients were operated on in an urgent mode. The perioperative mortality was 10.34 % (3 patients). It concerned 2 patients operated on in an urgent mode and 1 demanding surgery during the same hospitalization. In 2 (6.9%) patients respiratory insufficiency lasting over 72 h and demanding prolonged mechanical ventilation and continuation of the treatment in another department occurred. In 2 (6.9%) patients IABP usage was essential. The average duration of the ICU stay was 3.8 days, while the average hospitalization time was 34.45 days (for group B respectively, 4.3 and 32.64, for group A 3.25 and 36.2; NS, respectively $p = 0.13$ and $p = 0.28$).

Discussion

The clinical efficacy of the risk indicator (Ir) in the preoperative period is not questionable. However, its reliability in the postoperative period seems to be much more controversial. Cardiosurgical procedures are connected not infrequently with considerable intraoperative blood loss, which imposes transfusion of the blood and blood-derived preparations, disturbing the variability depending on the infective process. Despite this, in our observation the course of morphological parameters was proceeding

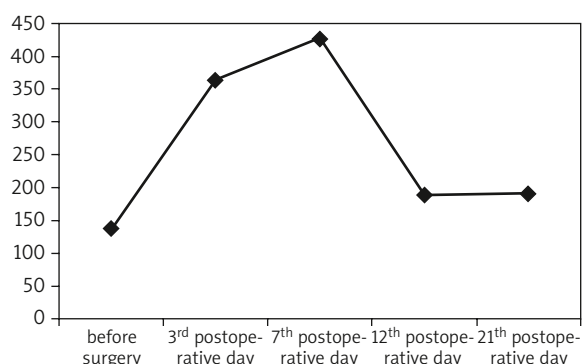


Fig. 1. Changes of Ir at consecutive control points for the group with complications. (description in the text)

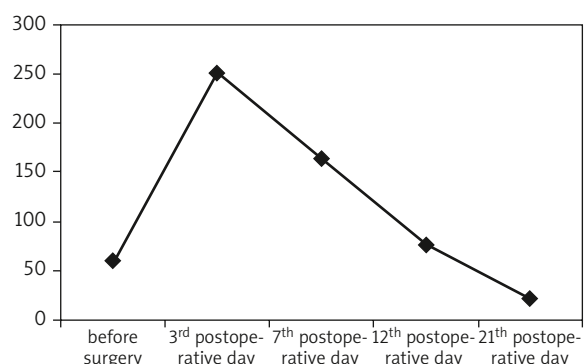


Fig. 2. Changes of Ir at consecutive control points for the group without complications. (description in the text)

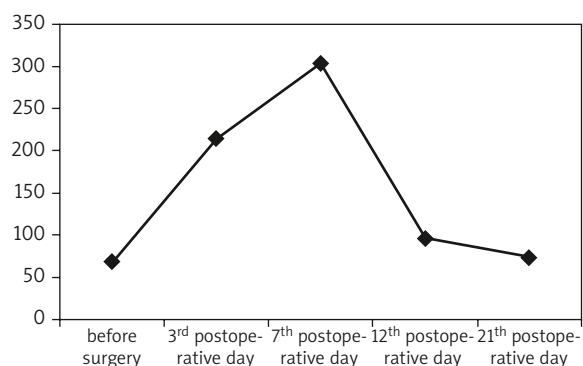


Fig. 3. Changes of Im at successive control points for the group with complications. A lower increase of this parameter than the Ir increase can be seen on the 3rd postoperative day, while on the 21st its decrease is more clear than the one for Ir

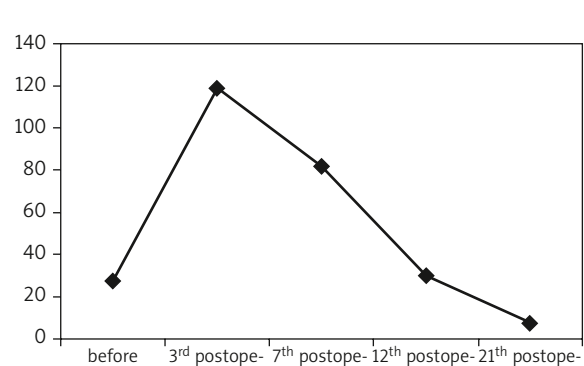


Fig. 4. Changes of Im at successive control points for the group without complications. In the uncomplicated group the Im and Ir curve are compatible

analogically like CRP (an increase after the operation and significant decrease on the 12th day). However, it must be said that the majority (only 15 PRBC from 78 in total transfused were given in the operating theater during surgery) of blood and blood-derived preparations were transfused already in the postoperative period (mainly in the ICU, that is the first 3-4 days).

Hb and RBC are the principal parameters measured in anemia. However, depending on the cause of anemia their alterations proceed distinctly. We decided to check if RBC in prognosis in cardiosurgical patients with IE will significantly impact the indicator's alterations. As it turned out, both parameters I_r (Hb) and I_m (RBC) are equivalent. As emphasized in the study by B. Kraśnicka-Sokół *et al.* [6] for outcome evaluation and as we proved in the above study, for the prediction of postoperative complications, the most important is to confirm low morphological parameters with coexisting high CRP values.

The I_r as well as I_m indicator values are linearly proportional to CRP level. However, concerning sudden alterations of this parameter, it seems to influence much more both indicators than the blood morphology does.

The majority of complications appeared in the first postoperative week, when both indicators as well as CRP remained high. The higher preoperative I_r >100 (according to B. Kraśnicka-Sokół's study) was indeed concerned with a higher risk of complications and also, as we confirmed in our study, with a higher risk of postoperative complications. However, as we analyzed the postoperative course in patients with I_r >100, it turned out that in 2 (among 8) cases no complications occurred after the surgery. On the other hand, in 11 patients with I_r < 100 complications occurred.

We additionally observed that in operated patients with postoperative complications (despite the CRP decrease) both indicators did not have a lowering tendency after the 3rd day and their values were significantly higher. In our opinion the value > 300 for I_r and > 200 for I_m on the 3rd postoperative day can be predictive for the occurrence of complications in the first week following surgery. In the group of patients involved in our study both indicators had important input in monitoring the postoperative treatment, which moreover is well reflected by Figures 1-4.

Our observation can suggest that (I_m value in the group with complications) I_m > 60 may be predictive for a complicated postoperative course. Both indicators show mutual dependency.

The influential disadvantage of our study is the fact that all kinds of complications were collected together: neurological, circulatory, respiratory and coagulative. We decided to make that simplification due to the small study population. Results of the Nomura A *et al.* [9] study revealed that one of the complications – heart failure, neurological complications (CNS) or peripheral and central embolism – is an independent risk factor for 90-day mortality.

It must also be underlined that occurrence of major complications depended strongly on the previous patient's characteristics (Table I), which is any way a common fact,

repeatedly emphasized by other authors [10]. Prosthetic valve endocarditis is a well-known risk factor of postoperative complications [11, 12]. In our observation all 3 patients after redo procedures had complications.

It is worth mentioning that coexisting anemia may be a consequence of comorbidities such as renal insufficiency, which not only leads to anemia, but also hinders blood parameters' normalization. Furthermore, in the group of our patients two had diagnosed deficiency anemia. I_r and I_m indicators thereby include the patient's condition as a consequence not only of progression of endocardial infection but also other diseases.

Conclusions

The prognostic value of I_r indicator for prognosing complications in the postoperative period for patients operated on for IE was proved.

Analogical usefulness for I_m indicator was proved and the preoperative value of I_m > 60 was estimated as predictive for complicated postoperative course.

Both indicators were useful in monitoring the efficacy of postoperative treatment.

Both indicators, connecting morphological and inflammatory parameters, more properly reflect the patient's clinical condition than the isolated assessment of a singular parameter such as CRP.

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