EVOLUTION OF INFLAMMATORY MARKERS IN PATIENTS WITH PROSTHETIC JOINT INFECTION TREATED WITH *STIMULAN*

F. Dimofte[1], Cristina Serban[2], G. Țocu[3], Iulia Filip[2], Laura Bezman[1], B. M. Ciuntu[4*], Irina Mihaela Abdulan[5], M. Guliciuc[2], D. Firescu[2]
"Dunărea de Jos" University Galați, Romania
Faculty of Medicine and Pharmacy
1. Department of Orthopedy
2. Department of General Surgery
3. Department of Laboratory Medicine
"Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania
Faculty of Medicine
4. Department of Surgery (I)
5. Department of Medical Specialties (I)
[*]Corresponding author. E-mail: bogdanmciuntu@yahoo.com

EVOLUTION OF INFLAMMATORY MARKERS IN PATIENTS WITH PROSTHETIC JOINT INFECTION TREATED WITH *STIMULAN* (Abstract): Total hip arthroplasty is a commonly performed procedure with a known risk of postoperative infection. Diagnosing an infection after total hip arthroplasty can be challenging, as there are no consistently reliable preoperative tests for infection in patients requiring a revision arthroplasty. This study **aimed** to assess the common investigative methods for diagnosing infection at the site of a previous arthroplasty and the evolution of these biomarkers in patients treated with biocomposite and traditional surgical treatment. **Materials and methods:** We conducted a prospective analysis of pre- and postoperative investigations used to diagnose infection in 44 patients admitted from January 2017 to September 2023 at the "Sf. Apostol Andrei" County Clinical Emergency Hospital of Galati. **Results:** Our study group included 31.81% women and 68.19% men. The most common symptoms experienced by patients were pain and functional incapacity of the lower limb. Only ESR and CRP were elevated in all patients at admission. Their values decreased postoperatively, and determinations at two and six weeks postoperatively showed normalization of ESR, while CRP remained slightly elevated. **Conclusions:** The biological modifications were generally typical when considering the preoperatory moment, with notable rapid improvement in inflammatory status within the first six weeks post-surgery. The novel approach that includes bio composites seems to have major clinical impact on the future management of prosthetic joint infections given the cure rate and the general evolution. **Keywords:** PROSTHETIC JOINT, INFLAMMATORY MARKERS, INFECTION, BIOCOMPOSITE.

After joint replacement surgeries, most patients find relief from preoperative pain and disability. While the surgeries are generally successful and lead to high patient satisfaction, it's important to be aware of the associated risks. Infection is one of the

most concerning complications of this type of operation.

In addition, it can be challenging to confirm a diagnosis of prosthetic joint infection (PJI) after total hip arthroplasty (THA). Patients with this type of infection often do not display typical signs and symptoms, such as fever, chills, or elevated white blood cell count.

In some cases, microorganisms enter the joint during the insertion of the prosthesis (direct inoculation), while in others, bacteria travel to the joint through the bloodstream (hematogenous spread).

Some bacteria, like coagulase-negative staphylococci, have low virulence and can persist due to prosthetic material and biofilm. These infections usually cause a chronic low-grade infection with few systemic symptoms. On the other hand, diseases caused by high-virulence organisms, such as Staphylococcus aureus, can lead to severe conditions like septicemia and bacterial endocarditis (1).

Staphylococci species are the most common causative organisms of joint infections, followed by streptococci, enterococci, and Gram-negative bacteria. Gram-negative bacteria account for about 8% of cases (2).

The erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count are said to have low reliability as indicators of prosthetic joint infection (3). However, these indicators can be influenced by age and medical conditions. An ESR greater than 30 mm/h and a CRP greater than 10 mg/L are considered elevated levels (4). The sensitivity and specificity of ESR and CRP can vary widely in the available literature. If both the ESR and CRP are normal, however, the probability of infection is around 3% (5).

This research is part of a larger study evaluating the efficacy of using an antibiotic-loaded bio composite (*Stimulan*) in addition to conventional treatment. One of the objectives of this original research was to evaluate the inflammatory biologic profile and its evolution in this category of patients. To our knowledge, this is the first research of its kind in our country, with a major clinical impact on the future management of prosthetic joint infections.

MATERIALS AND METHODS

We carried out a retrospective study from January 2017 to September 2023 at the "Sf. Apostol Andrei" County Clinical Emergency Hospital of Galati. Our research involved patients who were hospitalized for hip arthroplasty.

During the specified period, 44 out of 4,244 hip arthroplasty surgeries were included in this study. The study focused on patients with hip arthroplasty-related infections who were treated with the biocomposite *Stimulan* in addition to the classical surgical treatment.

Patients with chronic inflammatory conditions, those with malignancy, or patients who had previously received antibiotic treatment before surgery were excluded based on the criteria.

Data on age, gender, BMI, laboratory results, type of intervention, progression, and post-surgery outcomes were collected.

A patient was considered to have an infected THA if they met any of the following criteria (6):

1. Presence of a sinus tract communicating with the prosthesis

2. Isolation of a pathogen by culture from two separate tissue or fluid samples obtained from the affected prosthetic joint

3. Any four of the following six criteria:

a. Elevated serum erythrocyte sedimentation rate (ESR) or serum C-reactive protein (CRP) concentration

b. Elevated synovial white blood cell (WBC) count.

c. Elevated synovial neutrophil percentage (polymorphonuclear leukocyte % [PMN%])

d. Presence of purulence in the affected joint

e. Isolation of a microorganism in one culture of periprosthetic tissue or fluid

f. Greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at 400 times magnification.

In order to be included in this study, all the patients completed an informed consent form. The ethics approval was received in 2022 (no. 33/23.12.2022 issued by the Ministry of National Education-Faculty of Medicine and Pharmacy, "Dunărea de Jos" University of Galati, Romania).

The statistical analysis of the patients data was performed using the *SPSS program version 20.0* and the calculation of the chi square test, as follows: $p<0.05$, the statistical value is moderately significant (S, 95% c); $p<0.01$, the statistical value is very significant (S, 99% confidence); $p<0.001$, the statistical value is highly significant (HS, 99.9% confidence); $p> 0.05$, the statistical value is not significant (NS).

RESULTS

From a total of 4,244 patients admitted for hip arthroplasty, 76 were diagnosed with an infection associated with the surgical intervention, and from those, in 44 cases, *Stimulan* was used complementary to the classical surgical treatment.

Our study group included 31.81% women and 68.19% men. Women were older, had a bigger BMI. In their case, the infection appeared later, and the hospitalization was shorter. DAIR procedure was preferred in most women, while in the case of men, there was an equal percentage DAIR versus two-stage revision. All the characteristics of the study group are presented in the first table.

TABLE I.

Characteristics of the study group

		Total Group (n-44)	Female (n-14)	Male (n-30)	P
Age (mean ± SD) (years)		66.77±12.02	72.02±11.59	63.30±11.57	0.04
Living environment	Urban	18 (40.90%)	6 (42.85%)	12 (40%)	0.65
	Rural	26 (59.10%)	8 (57.15%)	18 (60%)	0.57
BMI		27.79±3.42	30.22±3.37	26.67±2.83	0.0007
Temperature		36.62±0.75	36.32±0.85	36.76±0.84	0.12
Time between the initial surgery and the onset of infection (days)		387 (127.5;720)	429 (150;817.5)	360 (112.5;750)	0.65
Hospitalization days		18.5 (10;46.5)	15.5 (8;48)	21.5 (10;44.25)	0.51
Nasal culture test		5 (11.36%)	0 (0%)	5 (16.66%)	-
Pharyngeal culture test		3 (6.81%)	0 (0%)	3 (10%)	-
Urine culture		2 (4.54%)	0 (0%)	2 (6.66%)	-
DAIR		25 (56.81%)	10 (71.42%)	15 (50%)	0.18
Two-stage revision		20 (45.45%)	4 (28.57%)	15 (50%)	0.38

BMI, Body Mass Index; DAIR, Debridement, antibiotics, and implant retention.

Upon admission, the most common symptoms experienced by patients were pain and functional incapacity of the lower limb. In addition, prolonged standing resulted also in discomfort/pain (fig. 1).

The main aspects of the wound are described in fig. 2.

Before surgery, WBC values varied from 2290/mm^3 to 16600/mm^3, only 40.90% of the patient having elevated levels. Only ESR and CRP were elevated in all patients at admission (fig 3).

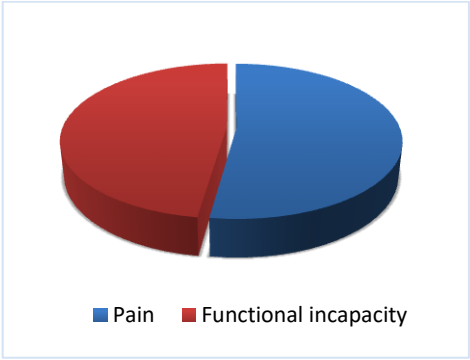

Fig. 1. Symptoms at admission

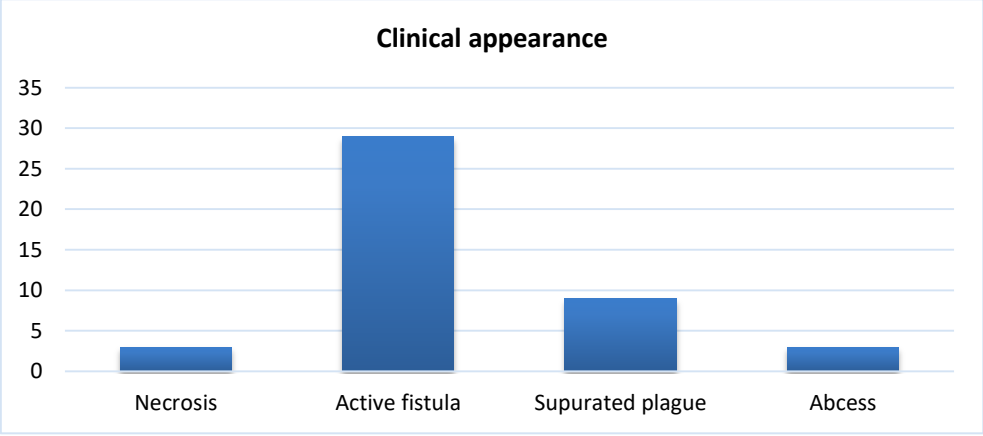

Fig. 2. Aspect of the plague

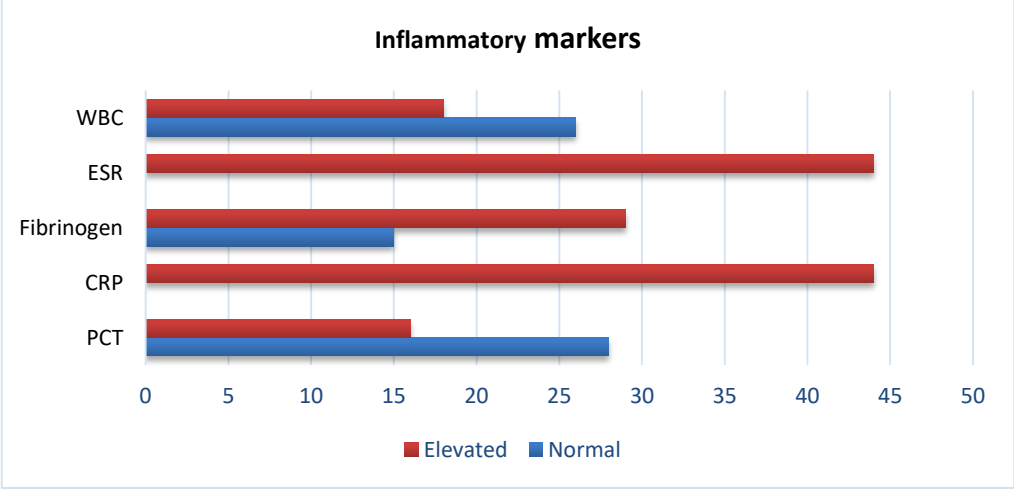

Fig. 3. Inflammatory markers upon admission

The evolution of the laboratory parameters showed a significance difference in the case of the ESR, CRP and hemoglobin (tab. II).

When we analyzed the pathogens involved in the infection, the most frequent were Methicillin-resistant Staphylococcus aureus-MSSA (34%), coagulase-negative staphylococcus-SCN-MRS (20.45%) and Methicillin-susceptible *Staphylococcus* MSS (9.09%). 4 cases had negative antibiograms (fig. 4).

TABLE II.

Evolution of the laboratory parameters

	Before intervention	2 weeks after intervention	6 weeks after intervention	P
WBC	8798 (7297;10230)	7620 (6242.25;9445)	8626 (6732;10532)	0.75
ESR	80 (61.25;120)	21.11 (15;22)	19.5 (15.25;25)	< .00001
CRP	174(147.25;223.25)	11.5 (8.07;29.25)	8.25 (4.31;9.36)	< 0.00001
Fibrinogen	455 (302.25;573)	365.5 (321.25;436.25)	321.75(257.5;385.75)	0.000043
PCT	0.66±2.08	0.17±0.54	0.07±0.05	0.06
Hemoglobin	12.70±2.08	12.36±2.22	11.50±2.17	0.009
Glycemia	104.40±23.30	108.29±31.40	103.20±21.11	0.80
Urea	41.88±16.90	38±15.47	38.29±13.23	0.27
Creatinine	1.12±0.36	1.05±0.36	1.13±0.45	0.84

WBC, white blood cells; ESR, erythrocytes sedimentation rate; CRP, C reactive protein; PCT, procalcitonin.

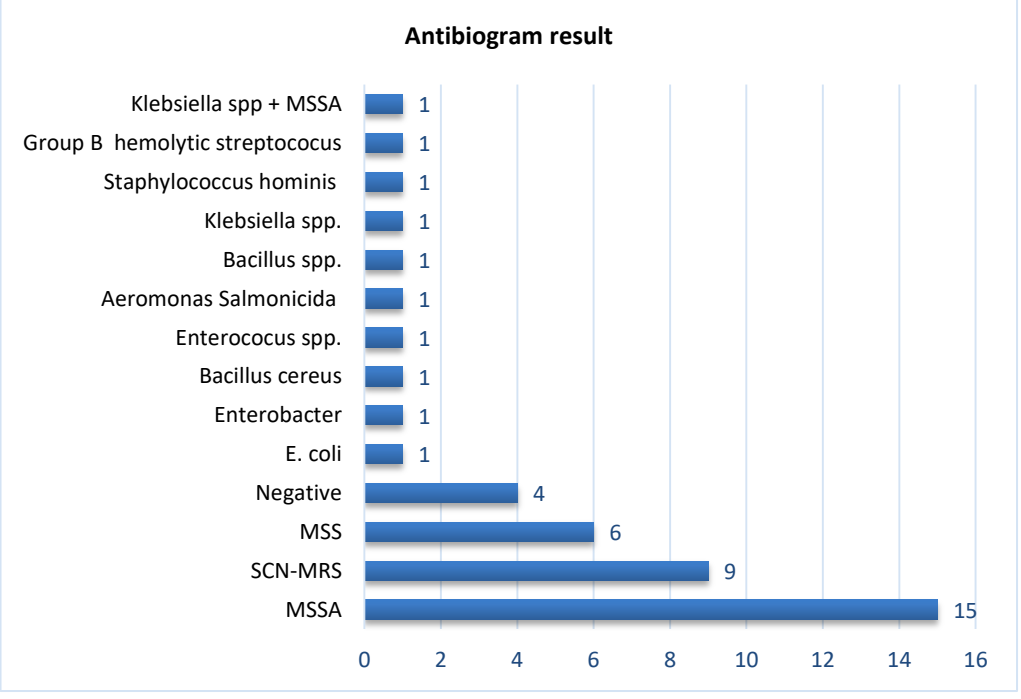

Fig. 4. The pathogens involved in the infection.

DISCUSSION

In recent arthroplasty developments, there has been a focus on gender-specific implants for the hip and knee to account for potential anatomical differences between males and females (7). Specifically, regarding the hip, attention is given to the femoral side as there are differences in the location of the femoral head center and the shape and size of the femoral canal based on gender. Females generally have a lower offset, or a smaller femoral axis compared to male. With aging, females also tend to experience increased femoral medullary width and greater bone loss at the medial calcar and lateral cortex compared to males (8). Currently, available implant designs offer various options in stem length and diameter, neck offset, and neck length but it remains unclear whether gender makes a difference in the outcome of the patents after the hip surgery. Using nongender-specific implants, creates a difference in implant survivorship in the long-term? Are there any differences in implant-related complications?

The Swedish Total Hip Replacement Register and other large registries have demonstrated that the revision rates for hip replacements have been consistent for both men and women over the years. Additionally, the reasons for hip replacement revisions have also been similar between men and women (9).

In addition to the anatomical aspect, recent studies have begun to emphasize the psychological impact, quality of life and impact on daily activities. However, research is very limited (10).

In the present study, there are some differences between the female and male groups that are worth discussing. Women tend to undergo joint arthroplasty at an older age, possibly due to a heightened apprehension of surgery and a tendency to delay the procedure in order to minimize the impact on their caregivers' responsibilities.

BMI was higher in women, and the time interval between the first intervention and presentation to hospital for the symptoms mentioned was also longer. We have no data to confirm whether the time interval to the onset of the infectious complication was longer, or patients delayed presentation to hospital.

After the primary THA intervention, the patients declared they were called for follow-up at 14 days, at which time the sutures were removed. No intermediate follow-ups were performed until the current presentation.

At the time of the current presentation, laboratory tests and pelvis / hip X-ray were performed. In most of the cases, the X-ray did not show any specific modifications.

Detecting PJI continues to be a significant challenge for orthopedic practitioners. Research by Virolainen *et al.* (11) suggests that there is no single laboratory test currently available to accurately diagnose PJI before revision arthroplasty. Common laboratory tests such as ESR, WCC, and CRP, which are typically used as initial diagnostic tools for PJI, are not consistently reliable. Therefore, it is widely acknowledged that there is a pressing need to discover new and dependable indicators of inflammation that can facilitate the prompt and accurate diagnosis of PJI (12).

The C-reactive protein is a substance produced by the liver in response to inflammation, infection, and neoplasm. After surgery, its levels peak two to three days later and return to normal around three weeks post-surgery. Currently, most ex-

perts recommend using both the blood erythrocyte sedimentation rate and C-reactive protein level as markers for evaluating patients with a suspected prosthetic joint infection. When both markers test negative, the likelihood of infection is very low.

Following a standard joint arthroplasty, the erythrocyte sedimentation rate initially increases, peaks at five to seven days postoperatively, and then gradually returns to preoperative levels over three to twelve months.

In our study, both inflammatory markers were elevated preoperatively. Their values decreased postoperatively, and determinations at 2 and six weeks postoperatively showed normalization of ESR, while CRP remained slightly elevated. The results are different from those published in the literature, where ESR often remains slightly elevated until the end of the first year after the procedure (13), this aspect may be due both to the use of the bio composite and to the particularities of each individual patient.

In arthroplasty patients, the time taken for plasma CRP levels to return to normal after surgery has been reported as 2 (14), 3 (15) or 6-8 weeks (16), whereas White *et al.* (17) reported that, at the first follow-up visit after discharge from hospital, the CRP levels had returned to normal, although the exact time-period was not reported.

Plasma fibrinogen is a key coagulation indicator traditionally used to assess venous thrombus embolism and to regulate inflammation associated with several organ infections (18, 19). Previous research has shown that plasma fibrinogen is closely linked to the diagnosis of PJI also, with Xu *et al.* (20) being the first to show that plasma fibrinogen levels are elevated in PJI compared to aseptic failure.

The latest findings indicate that coagulation-related markers show potential for diagnosing PJI. Coagulation-related indicators offer a simple, relatively inexpensive, and noninvasive diagnostic approach compared to other tests. Additionally, coagulation function testing is a standard practice following admission. The primary function of the coagulation system is to facilitate hemostasis, and it has a close connection to infection. This system plays a role in preventing the spread of viruses through the coagulation cascade (21). Synovitis can generate significant amounts of fibrin, and the breakdown of fibrin can lead to heightened indicators with subsequent inflammatory effects (22).

The white blood cell count is a commonly used lab test that can indicate the presence of infection or inflammation. While the WBC count alone cannot definitively diagnose a specific disease, it is a valuable tool in diagnosing many diseases (23). While some studies suggest that the serum WBC count can be useful in diagnosing prosthetic joint infection (PJI), other research has conflicting findings (24, 25).

Toosi *et al.* (26) investigated the effectiveness of using white blood cell count to diagnose periprosthetic joint infection. The study revealed that the sensitivity of WBC count in diagnosing PJI was 55%, and the specificity was 66%. These findings align with the widespread opinion that serum WBC count and differential have limited utility and should not be relied upon when evaluating patients suspected of having PJI.

In our study, white blood cells were elevated in only 40% of the patients, this agrees with the results in the literature. There were no statistically significant differences between the three determinations.

The usefulness of serum procalcitonin in diagnosing periprosthetic joint infection is limited, unlike its effectiveness in detecting systemic bacterial infection. Busch *et al.* (27) conducted a study that revealed serum PCT to have low sensitivity (13%) in diagnosing PJI. Additionally, a recent meta-analysis by Yoon *et al.* (28) concluded that serum PCT plays a minimal role in the evaluation of patients with suspected PJI.

In the current study, only 16 patients showed elevated procalcitonin levels. It's important to mention that there was a consistent decrease in the levels of this marker in the postoperative follow-up assessments. The renal function remained stable, with slight postoperative increases in urea and creatinine, which later normalized.

Despite experiencing significant inflammatory symptoms, preoperative glycemic values remained below 200 mg/dL for diabetic patients and below 140 mg/dL for non-diabetic patients. These levels showed a noticeable decrease in the weeks following the surgery. Similar to other major surgeries, patients with diabetes have a higher risk of postoperative complications. Stress-induced high blood sugar is frequently seen in surgical patients and is typically caused by hormonal responses and inflammatory mediators. Elevated blood sugar levels can be due to medications, stress, poor glucose tolerance, or unmanaged diabetes. However, the patients we studied had well-managed blood sugar levels after surgery.

THA is linked to reduced hemoglobin levels, largely due to blood loss during the operation. These low Hb levels following surgery could potentially hinder the healing of surgical wounds (29-31). In our study, hemoglobin values were maintained at an average of 12.36 g/L, with a slight decrease at 6 weeks postoperatively.

PJI involves a complicated interaction between germs, mostly bacteria and sometimes fungi, and the body's immune response. Even a small number can start a PJI, as disease-causing organisms can stick to the surfaces of joint replacement components and create biofilms. The bacteria usually come from the skin's microbial community and may enter during the implantation surgery. Alternatively, these pathogens can infect the implant after surgery through the bloodstream or direct contact with nearby infected tissues (32).

Staphylococci species are the most frequent causative organisms. In our study, staphylococci account for 66% of PJI cases, confirming the previous studies' data.

The overall data of the patients included in the study seem to follow the evolution of the biological parameters of patients in previous studies, where no additional treatment (biocomposite) to the classical technique was used. The pain management and the quality of healing were important elements in the outcome analysis (33-35).

The advantages are however preserved, given the overall results and the increased cure rate.

The limitations of the study are the small number of patients, although it can be considered a positive aspect given the low infection rate.

CONCLUSSIONS

The impact of periprosthetic joint infection on patients is significant, affecting them physically, socially, and emotionally while also leading to increased healthcare costs, patient suffering, and higher mortality rates. In this study, involving 45 patients who underwent surgical reintervention and received a biocomposite following total hip

arthroplasty, the biological progression was generally typical when considering the preoperatory changes, with notable rapid improvement in inflammatory status within the first six weeks post-surgery.

However, diagnosing PJI is challenging as there is no universally accepted definition, and it can occur anywhere from 4 weeks to 2 years after the initial surgery. Additionally, the current tests used for diagnosis may only be useful in combination. The ideal scenario would be the discovery of a single biomarker with high sensitivity for accurately diagnosing PJI and relate to the evolution during the post-operative period.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

ACKNOWLEDGMENTS

The author Bogdan Mihnea Ciuntu contributed equally to the first and corresponding authors.

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