Genij Ortopedii. 2023;29(5):512-517.

Original article

https://doi.org/10.18019/1028-4427-2023-29-5-512-517

Hematological markers of periprosthetic joint infection after revision total hip arthroplasty

E.L. Matveeva, A.G. Gasanova✉, E.S. Spirkina, S.N. Luneva, A.M. Ermakov

Ilizarov National Medical Research Centre for Traumatology and Orthopedics, Kurgan, Russian Federation

Corresponding author: Anna G. Gasanova, gasanova.08@mail.ru

Abstract

Analysis of clinical and laboratory tests is essential for monitoring the course of infectious complications after total hip arthroplasty (THA). **The objective** was to assess the reliability of differences in hematological parameters in patients with periprosthetic joint infection (PJI) for monitoring the infectious process. **Material and methods** Patients with acute (lasting 21.8 days on average) and chronic (lasting for 26.3 months on average) PJI were screened for hematological parameters on admission and during treatment in order to control the course of the purulent-inflammatory process. **Results** Preoperative parameters demonstrated mild anemia in patients with acute PJI, and the hemoglobin concentration was normal in patients with chronic PJI. Patients of both groups showed normal total leukocyte count. ESR and C-reactive protein levels were many times higher than the threshold values. The C-reactive protein level was more than 2 times higher in patients with acute PJI than that in patients with a chronic infection. The ratio of ESR / C-reactive protein was normally greater than 5 units, from 3 to 4.5 in chronic PJI and from 1.5 to 2.3 in acute PJI. Discussion Examination of pre- and postoperative clinically significant parameters is practical for identification of the criteria to assess the risk of chronic PJI. **Conclusion** Patients with acute PJI need no additional clinical and laboratory examination, integral laboratory parameters can be employed for accurate assessment of the extent of inflammation in a purulent wound.

Keywords: hip joint, revision total hip arthroplasty, blood, periprosthetic joint infection

For citation: Matveeva E.L., Gasanova A.G., Spirkina E.S., Luneva S.N., Ermakov A.M. Hematological markers of periprosthetic joint infection after revision total hip arthroplasty. *Genij Ortopedii*. 2023;29(5):512-517. doi: 10.18019/1028-4427-2023-29-5-512-517

INTRODUCTION

Prosthetic joint infection (PJI) following total joint replacement surgery is a serious complication that negatively impacts patients' lives and is financially burdensome for healthcare providers. This is associated with high relapse rates and a significant risk of mortality among elderly patients [1, 2]. Lack of efficacy of the PJI treatment can be caused by limited data on the period of formation of an irreversible bacterial attachment to the endoprosthestic surface [3]. Effectiveness of treatment using different therapies remains low with failure of 24-75 % treated for PJI [4-6]. There is a wide range of infection diagnostic tools to mitigate the impact of disease. A clinical and laboratory diagnostic algorithm would facilitate the optimal treatment option for the patient and lower risk of recurrence [7-10].

New clinical and laboratory criteria for diagnosing PJI was discussed at the 2nd International Consensus Meeting on Musculoskeletal Infection (Philadelphia, 2018) [11-15]. Clinical recommendations of the Ministry of Health of the Russian Federation on "Prevention of infections in the area of surgical intervention" indicate the need for clinical (complaints, anamnesis, physical examination), hematological (leukocyte level, ESR, CRP), cytological (leukocyte level, neutrophils), microbiological and radiological (radiography, fistulography and CT, if needed) examinations [16]. Clinical and biochemical blood tests are performed for severity of the purulent process. Anemia, hypoproteinemia, thrombocytosis and hyperfibrinogenemia are the most characteristic signs of PJI [17]. Alterations in D-dimer, lipopolysaccharide-binding protein and presepsin (sCD14-ST) were noted in addition to the classic changes in acute phase proteins (interleukin-1, interleukin-6) [18-23].

The combination of ESR (> 30 mm/h) and CRP (> 10 mg/l) was the most sensitive diagnostic criterion indicating infection in 90-100 %, as reported earlier [24-26]. The diagnostic role of the parameters was not so high with low grade infection [27, 28]. We thought it was necessary to evaluate these data for different types of PJI (acute and chronic) with comparison of a large amount of literature data on the diagnosis of PJI including acute-phase hematological parameters. The objective was to assess the reliability of differences in hematological parameters of patients with PJI of the hip for monitoring the infectious process.

MATERIAL AND METHODS

Hematology blood tests of patients with PJI of the hip treated between 2005 and 2020 by one surgical team at the Federal State Budgetary Institution "National Medical Research Ilizarov Center for Trauma and Orthopaedics" Ministry of Health of the Russian Federation were analyzed. Exclusion criteria included inconsistency with the age group and incomplete data in the medical record, malignant and decompensated chronic diseases. Inclusion criteria included age, diagnosis, duration and severity of the disease. The disease was diagnosed based on physical examination and laboratory testing. Informed consent was given prior to inclusion in this study by all patients. The study received a favourable opinion from the relevant research ethics committee of the Federal State Budgetary Institution "Ilizarov National Medical Research Centre for Traumatology and Orthopaedics" Russian Ministry of Health.

The mean age of the patients was 54.7 ± 12.7 years (Me, 56; 95 % CI 52.7 to 56.8; IQR 46-65), with 36 % (n = 53) of patients aged 60 years and over, with males of 56 % (n = 82). On admission, 71 % (n = 105) of patients were diagnosed with a fistulous form of PJI, 9 % (n = 13) had open wounds and 20 % (n = 29) had swelling and hyperemia of the postoperative suture. Infection was observed in 78 % (n = 114) after primary joint replacement and in 22 % (n = 33) after revision surgery. Absolute signs of PJI were diagnosed in 114 (77.5 %) patients with the presence of a fistulous tract communicating with the joint cavity and/or with a pathogen strain with the same phenotype isolated from two biological samples. Relative signs were identified in 33 (22.5 %) patients with an average IMC score of 5.96 ± 2.70 (range, 2 to 14); Me, 6.0; 95 % CI 5.0 to 6.9; MQR 2.1-3.5, as mentioned in protocol of the 2nd International Consensus Meeting on Musculoskeletal Infection. Based on the nature of the infectious process, patients were divided into 2 groups. Group 1 (n = 28; 19 %) included patients with acute PJI (mean infectious period of 21.8 days; Me, 22; 95 % CI from 19.7 to 24.0; IQR 17-27.5). Group 2 included patients with chronic PJI (n = 119 or 81 %, respectively) (mean infectious period of 26.3 months, Me, 13; 95 % CI 20.5 to 32.3; IQR 8-35).

Data on isolated gram-positive (44 and 55 %) and gram-negative (7 and 10 %) bacteria are presented in Table 1 for comparison between the groups. Nearly every third (29 %) case of acute PJI was caused by methicillin-resistant strains of epidermal staphylococcus, and microbial associations (p = 0.04) and strains of methicillin-resistant staphylococci MRSE (p = 0.03) were common for acute cases as compared to chronic PJI.

The American Society of Anaesthesiologists physical status classification was used to assess a patient's overall health. Severe comorbidities were recorded in 56 % (n = 82) and 7 % of patients had no prior documented comorbidity. Hematological parameters of the patients were examined on admission and during treatment in order to monitor the dynamics of the disease. The equipment employed for the study included Hitachi/BM 902 automated analyzer (Japan, registration No. 2000/564 Ministry of Health of the Russian Federation); the Beckman automated Paragon protein chemistry analyzer (USA, registration no. 2005/282); Stat Fax spectrophotometer (registration no. 2004/1258). The reference intervals were referred to as normal ranges by clinical laboratories. Nonparametric statistical methods were used to process the data; significant differences were assessed in the groups using the Wilcoxon test. The samples were checked for normal distribution; differences were considered statistically significant at $p < 0.05$. Statistical processing was based on electronic database generated with Microsoft Excel integrated module AtteStat 1.0.

Table 1

Microbiological characteristics of patients with acute and chronic PJI of the hip joint

Evaluation criteria	Characteristics of patients with PJI (n = 147)		Statistical significance (p)
Type of PJI	Acute PJI (n = 28)	Chronic PJI (n = 119)	
Average manifestation of infection	21.8 (13-28) days	26.3 (1-204) months	–
Gram-positive bacteria	43 % (n = 12)	55 % (n = 66)	P = 0.23
Gram-negative bacteria	7 % (n = 2)	10 % (n = 12)	P = 0.64
Microbial associations	46 % (n = 13)	27 % (n = 32)	P = 0.04*
No growth detected	4 % (n = 1)	8 % (n = 9)	P = 0.46
MRSA	7 % (n = 2)	12 % (n = 14)	P = 0.48
MRSE	29 % (n = 8)	13 % (n = 15)	P = 0.03*
ESBL	7 % (n = 2)	3 % (n = 4)	P = 0.36
P. aeruginosa	11 % (n = 3)	10 % (n = 12)	P = 0.92

Note: statistically significant differences in the level of polymicrobial infection (p = 0.04) and MRSE strains (p = 0.03) were identified in the groups.

RESULTS

Clinically significant parameters of inflammation and postoperative blood loss were the most informative laboratory tests. Table 2 included hemoglobin and total leukocyte count, ESR and C-reactive protein; other hematological parameters were within the reference values and are not reported.

Preoperative measurements showed mild anemia in patients with acute PJI (hemoglobin Me 118 g/L, IQR 105-121) and normal hemoglobin values in patients with chronic PJI (hemoglobin Me 136.5 g/l, IQR 101-156). Patients of both groups had normal leukocyte count. ESR (average 61.5 ± 29.7 mm/h calculated using the Westergren method) and CRP (average 24.3 ± 23.5 mg/l) showed much higher values than the ESR and CRP threshold. C-reactive protein level was more than twice higher in patients with a short period of infection than in patients with a chronic infectious process.

Hemoglobin values were comparable in both groups and, as expected, below the preoperative level; they remained at the lower limit of normal at 7-10 postoperative days. Total leukocyte count was within the reference range in patients of both groups increasing insignificantly at 1-3 days of surgery. ESR and C-reactive protein levels were significantly higher than normal throughout the observation period and were statistically higher in patients with a chronic course of the inflammatory process than in patients with acute infection.

Table 2

Preoperative laboratory blood test performed in patients with PJI of the hip

Description	Acute PJI (n = 28)	Chronic PJI (n = 119)
Hb, g/L	Me 118 IQR (105-121)	Me 136.5 IQR (101-156)
WBC, 10^9/L	Me 6,3 IQR (6.2-7.2)	Me 7.7 IQR (6.2-8.8)
ESR, mm/h	**Me 52***# IQR (48-61)	Me 40.5* IQR (19.5-79.5)
CRP, mg/L	**Me 26***# IQR (10-64)	Me 11.5* IQR (6-18)
ESR /CRP, units	**Me 2.03***# IQR (1.5-2.3)	**Me 3.6*** IQR (3.0-4.5)

Note: *parameters having statistically significant differences with reference values at a significance level of $p < 0.05$; #, parameters having statistically significant differences between groups at a significance level of $p < 0.05$.

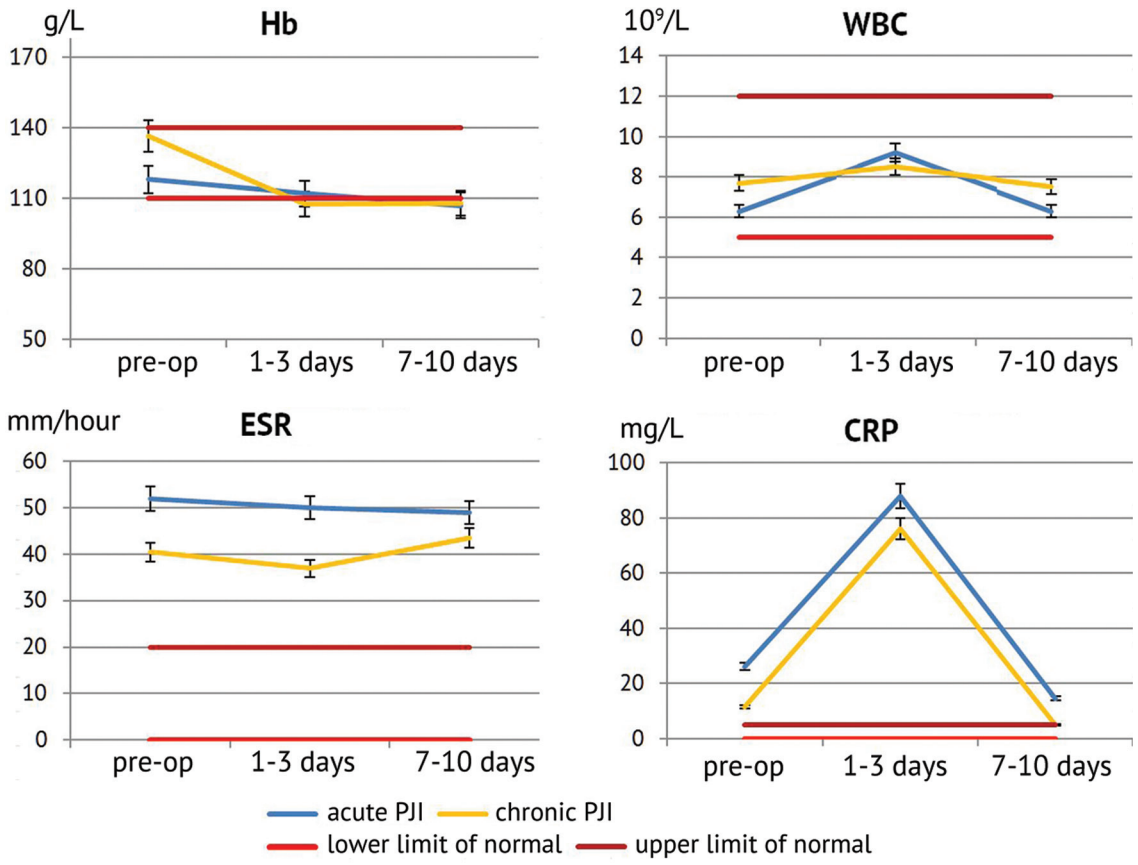

Fig. 1 Hematological parameters of patients of group 1 and group 2 measured preoperatively and at different time points: Hb, hemoglobin; WBC, white blood cells; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

DISCUSSION

Complete resolution of the acute inflammatory process and total repair is the optimal way to address complications in the form of PJI after total hip replacement. Chronic PJI represents a huge challenge for physicians. Analysis of clinically significant pre- and postoperative parameters may help surgeons to make an appropriate choice of criteria for assessing the risk of chronic PJI. Preoperative and dynamic observations of major clinically significant hematological tests in patients with acute (mean infectious period of 21.8 days) and chronic (duration on average 26.3 months) PJI showed a high ESR level, one of the nonspecific markers of inflammation. The ESR values were several times higher than the reference range and amounted to 520 % in group 1 and 405 % in group 2. Similar findings were recorded for C-reactive protein, another nonspecific marker of the inflammatory response. C-reactive protein level was higher than the reference range in patients of both groups. However, the differences between the groups were more significant. The average values were 2.3 times higher in patients with acute inflammation than those in patients with chronic inflammation. A close relationship between hemoglobin and the activity level of the inflammatory process was reported [29, 30]. Although a decreased hemoglobin level is a most common cause of chronic inflammation, the patients showed some signs of anemia in the acute period. There might be no association between local clinical manifestations of purulent surgical disease and a WBC count [31]. The WBC count was within normal range preoperatively and increased early post-surgery and at 7-10 days in patients of both groups. It is known that leukocytes are the main line of defense against bacterial agents and one of the main criteria for assessing the degree of a purulent-inflammatory process, and the studied hematological parameters do not allow a differential assessment between acute and chronic inflammatory processes during revision hip arthroplasty. Leukocytes represent the body's initial line of defense against bacterial agents and one of the main criteria for assessing the degree of an inflammatory process. The hematological parameters explored do not allow a differential assessment between acute and chronic inflammation during revision THA. This opportunity is often provided by the use of integral laboratory indicators, and some researchers propose interesting mathematical models that make it possible to more accurately assess the degree of inflammation in a purulent wound [32, 33, 34]. The opportunity is often provided by integrated laboratory parameters, and some researchers report interesting mathematical models for more accurate assessment of the extent of inflammation in a purulent wound [32, 33, 34]. In our series, ESR/C-reactive protein ratio was used for the calculations. A normal ratio has been calculated as greater than 5 units, chronic PJI is characterized by a ratio ranging from 3 to 4.5 units and acute PJI has a range from 1.5 to 2.3. The use of the ESR/C-reactive protein ratio, leukocyte counts including the body resistance index, the leukocyte to ESR ratio index, the blood leukocyte shift index [5-7] requires no additional economic costs, giving advantages in predicting risks and potential indirect economic benefits.

CONCLUSION

The combination of clinical and laboratory parameters of PJI after primary THA has a high diagnostic value. However, the importance of clinical and laboratory methods is significantly reduced in the presence of low-virulent pathogens. Effectiveness of debridement prior to revision arthroplasty of large joints or timely detection of the latent phase of PJI remains an essential issue. Our findings have shown a unidirectional change in hematological parameters of patients with acute and chronic PJI during the first 10 days of revision arthroplasty. The dynamics in parameters was characterized the body's stereotypical reaction to surgery in both groups. Laboratory diagnostic methods of standard preoperative procedures allowed no prediction on the transition of the clinical form of acute PJI to the chronic stage. The strategy for improved outcomes of revision arthroplasty should focus on improved diagnostic algorithms for a comprehensive examination of patients prior to revision surgery to facilitate timely identification or elimination of latent PJI and adjustment of treatment plan if needed.

Conflict of interest *None declared.*

Funding *The work was carried out at the "National Medical Research Ilizarov Centre for Traumatology and Orthopaedics" of the Ministry of Health of Russia and supported by the institution.*

REFERENCES

1. Rozhkov NI, Ermakov AM, Burtsev AV, et al. Analysis of the economic and clinical effectiveness of one- and two-stage revisions in the treatment of periprosthetic infection of the hip joint (literature review). *Genij Ortopedii*. 2022;28(6):842-851. doi: 10.18019/1028-4427-2022-28-6-842-851.2
2. Tryapichnikov AS, Kamshilov BV, Kolotygin DA, Belokrylov NM. Outcomes of two-stage revision arthroplasty in the treatment of patients with periprosthetic hip infection (retrospective cohort study). *Genij Ortopedii*. 2022;28(2):173-178. doi: 10.18019/1028-4427-2022-28-2-173-178
3. Zubavlenko RA, Babushkina IV, Ulyanov VYu, et al. Features of diagnostics of biofilm (session) implant-associated infectious complications of knee arthroplasty. *Quantum Satis*. 2022;5(1-2):56-59. (In Russ.)
4. Kukovenko GA, Elizarov PM, Alekseev SS, et al. Importance of the Algorithm for Diagnosis of Late Deep Periprosthetic Hip Infection. *Travmatologiya i ortopediya Rossii* [Traumatology and orthopedics of Russia]. 2019;25(4):75-87. (In Russ.) doi: 10.21823/2311-2905-2019-25-4-75-87
5. Gallo J, Kamínek M. Předoperační diagnostika infekcí kloubních náhrad [Preoperative diagnosis of prosthetic joint infection]. *Acta Chir Orthop Traumatol Cech*. 2011;78(6):510-8.
6. Stogov MV, Sudnitsyn AS, Kireeva EA, Kliushin NM. New laboratory tests for evaluating the effectiveness of the method of transosseous osteosynthesis for treatment of patients with chronic osteomyelitis of the foot bones. *Genij Ortopedii*. 2022;28(2):194-199. doi: 10.18019/1028-4427-2022-28-2-194-199
7. Winkler T, Trampuz A, Renz N, et al. Classification and algorithm for diagnosis and treatment of hip periprosthetic infection. *Travmatologiya i ortopediya Rossii* [Traumatology and orthopedics of Russia]. 2016;22(1):33-45. (in Russ.) doi: 10.21823/2311-2905-2016-0-1-33-45
8. Panteleev AN, Bozhkova SA, Preobrazhensky PM. Diagnosis of periprosthetic joint infection in revision total knee arthroplasty: review. *Department of Traumatology and Orthopedics*. 2022;(2):106-120. pp.106-120. doi: 10.17238/2226-2016-2022-2-106-120
9. Matveeva EL, Gasanova AG, Ermakov AM. Serum biochemical parameters of patients with periprothetic joint infection of the hip in carbohydrate metabolism disorders. *Genij ortopedii*. 2022;28(2):200-203. doi: 10.18019/1028-4427-2022-28-2-200-203
10. Kaminskiy AV, Matveyeva EL, Gasanova AG, et al. Analysis of Biochemical Parameters of Blood Serum in Patients with Revision Hip Arthroplasty and Disorder of Carbohydrate Metabolism. *Science of the young (Eruditio Juvenium)*. 2023;11(1):5-14. doi: 10.23888/HMJ20231115-14
11. Frank RM, Cross MB, Della Valle CJ. Periprosthetic joint infection: modern aspects of prevention, diagnosis, and treatment. *J Knee Surg*. 2015;28(2):105-12. doi: 10.1055/s-0034-1396015
12. Koh IJ, Cho WS, Choi NY, et al. How accurate are orthopedic surgeons in diagnosing periprosthetic joint infection after total knee arthroplasty?: A multicenter study. *Knee*. 2015;22(3):180-5. doi: 10.1016/j.knee.2015.02.004
13. Parvizi J, Tan TL, Goswami K, et al. The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria. *J Arthroplasty*. 2018;33(5):1309-1314.e2. doi: 10.1016/j.arth.2018.02.078
14. Schwarz EM, Parvizi J, Gehrke T, et al. 2018 International Consensus Meeting on Musculoskeletal Infection: Research Priorities from the General Assembly Questions. *J Orthop Res*. 2019;37(5):997-1006. doi: 10.1002/jor.24293
15. Ji B, Xu E, Cao L, et al. The method and result analyses of pathogenic bacteria culture on chronic periprosthetic joint infection after total knee arthroplasty and total hip arthroplasty. *Zhonghua Wai Ke Za Zhi*. 2015 Feb;53(2):130-134. (In Chinese)
16. Sheraliyev TU, Fedorov YeA, Gol'nik VN, Pavlov VV. *Periprosthetic infection in hip arthroplasty: features of modern etiology, problems and prospects for diagnosis: monograph*. Krasnoyarsk: Scientific and Innovation Center; 2021;229. (In Russ.) doi: 10.12731/978-5-907208-50-6.
17. Petrova NV. Evidence-based diagnosis of implant-associated infection in orthopedic surgery. *Russian Journal of Spine Surgery* [Khirurgiya Pozvonochnika]. 2012;(1):74-83. (In Russ.) doi: 10.14531/ss2012.1.74-83
18. Klimovitskiy VG, Vakulenko AV. The main indicators of blood in the diagnosis of infectious complications of endoprosthesis of the hip joint. *Travma*. 2008;9(2):123-126.
19. Ghanem E, Parvizi J, Burnett RS, et al. Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty. *J Bone Joint Surg Am*. 2008;90(8):1637-43. doi: 10.2106/JBJS.G.00470
20. Pfitzner T, Krocker D, Perka C, Matziolis G. C-reactive protein. An independent risk factor for the development of infection after primary arthroplasty. *Orthopade*. 2008;37(11):1116-20. (in German) doi: 10.1007/s00132-008-1342-1
21. Husain TM, Kim DH. C-reactive protein and erythrocyte sedimentation rate in orthopaedics. *U. Penn. Orthop J*. 2002;15:13-16.
22. Berbari E, Mabry T, Tsaras G, et al. Inflammatory blood laboratory levels as markers of prosthetic joint infection: a systematic review and meta-analysis. *J Bone Joint Surg Am*. 2010;92(11):2102-2109. doi: 10.2106/JBJS.I.01199
23. Friedrich MJ, Randau TM, Wimmer MD, et al. Lipopolysaccharide-binding protein: a valuable biomarker in the differentiation between periprosthetic joint infection and aseptic loosening? *Int Orthop*. 2014;38(10):2201-2207. doi: 10.1007/s00264-014-2351-9
24. Koudela K Jr, Geigerová L, Hes O, Koudela K Sr. Comprehensive diagnosis of infection in revision total replacements of large joints. *Acta Chir Orthop Traumatol Cech*. 2010;77(5):425-431. (In Czech)
25. Costa CR, Johnson AJ, Naziri Q, et al. Efficacy of erythrocyte sedimentation rate and C-reactive protein level in determining periprosthetic hip infections. *Am J Orthop* (Belle Mead NJ). 2012;41(4):160-5.
26. Schinsky MF, Della Valle CJ, et al. Perioperative testing for joint infection in patients undergoing revision total hip arthroplasty. *J Bone Joint Surg Am*. 2008;90(9):1869-1875. doi: 10.2106/JBJS.G.01255
27. Xu HY, Zha JN, Bao NR. Clinical value of the ECT bone scan in diagnosis of prosthesis infection for revision. *Zhongguo Gu Shang*. 2015;28(3):219-221. (in Chinese)
28. McArthur BA, Abdel MP, Taunton MJ, et al. Seronegative infections in hip and knee arthroplasty: periprosthetic infections with normal erythrocyte sedimentation rate and C-reactive protein level. *Bone Joint J*. 2015;97-B(7):939-944. doi: 10.1302/0301-620X.97B7.35500

29. Kasatov AV, Trefilova YuV, Gorovits ES, Timasheva OA. Dynamics of clinical laboratory test indices in patients with postoperative sternal and costal osteomyelitis. *Permskiy meditsinskiy zhurnal*. 2015;32(1):18-23. doi: 10.17816/pmj32118-23.
30. Mirzoyev SZ, Kholmurodova ZA, Tulaganova SM, Alimova NA. Features of rheumatoid arthritis in patients with reduced hemoglobin levels. *Vestnik Avitsenny*. 2013;15(4):68-71. doi: 10.25005/2074-0581-2013-15-4-68-71
31. Rybdylov DD, Khitrikheyev VYe. Application of leucocyte index of inflammation in purulent surgery. *Vestnik Buryatskogo gosudarstvennogo universiteta*. 2011;12:62-64. (In Russ.)
32. Rybdylov DD. Leukocytic index of inflammation. *Byulleten' Vostochno-Sibirskogo nauchnogo tsentra Sibirskogo otdeleniya Rossiyskoy akademii meditsinskikh nauk*. 2010;2(72):84-85. (In Russ.)
33. Chepeleva MV, Klyushin NM, Ermakov AM, Ababkov YuV. Interleukin-6 in predicting the course of postoperative period in patients with periprosthetic infection of the hip. *Sibirskij nauchnyj medicinskij zhurnal*. 2015;35(4):45-48. (In Russ.)
34. Chepeleva MV, Volokitina EA, Karmatskikh OL. The informative evidence of immunological indices in the early postoperative period during the hip endoprosthetics. *Genij Ortopedii*. 2004;(4):58-62. (In Russ.)

The article was submitted 12.05.2023; approved after reviewing 06.06.2023; accepted for publication 25.08.2023.

Information about the authors:

1. Elena L. Matveeva – Doctor of Biological Sciences, Leading Researcher, matveevan@mail.ru, https://orcid.org/0000-0002-7444-2077;
2. Anna G. Gasanova – Junior Researche, gasanova.08@mail.ru, https://orcid.org/0000-0001-7734-2808;
3. Elena S. Spirkina – Junior Researche, spirkina.82@mail.ru, Shttps://orcid.org/0000-0003-2506-2657;
4. Svetlana N. Luneva – Doctor of Biological Sciences, Professor, Leading Researcher, luneva_s@mail.ru, https://orcid.org/0000-0002-0578-1964;
5. Artem M. Ermakov – Candidate of Medical Sciences, Head of the Clinic, Researcher, ema_cab@mail.ru, https://orcid.org/0000-0002-5420-4637.

Contribution of the authors:

Matveeva E.L., Ermakov A.M., Luneva S.N. – the concept and design of the study.
Matveeva E.L., Gasanova A.G., Spirkina E.S. – collection and processing of material.
Gasanova A.G., Spirkina E.S. – statistical processing.
Matveeva E.L., Luneva S.N. – writing text.
Ermakov A.M., Matveeva E.L., Luneva S.N., Gasanova A.G., Spirkina E.S. – editing.