The role of culture-negative infection among infectious complications after total knee arthroplasty

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Abstract

Introduction Diagnosis of chronic periprosthetic joint infection (PJI) is difficult with the clinical signs of periprosthetic inflammation showing no growth of microorganism in the biomaterial. The frequency of culture-negative infection can reach 42.1%. The objective of the study was to analyze outcomes of two-stage treatment of chronic PJI of the knee joint depending on the etiology of the infectious process. Material and methods A retrospective analysis of outcomes was produced for 105 patients: group I (n=50) showing no growth of microorganisms and group II (n = 75) demonstrating positive growth of pathogens. Knee PJI was diagnosed according to the 2018 ICM criteria. A favorable outcome suggested absence of recurrence for at least two years after reimplantation of endoprosthesis, arthrodesis, "life with a spacer" without signs of infection. Results Culture-negative infection was detected in 29.1 % (n = 50). Patients in the group were 1.5 times more likely to receive antibiotic therapy prior to admission and had average levels of CRP, ESR and articular leukocyte count being 1.5-2 times less than those in group II. Staphylococci (69.8 %) including MRSE (75 %) was the leading pathogen in group II. Recurrence of infection was 3.4 % in group I and 16.9 % in group II (p = 0.0928), the two-stage treatment was successful in 96.7 % and 74 %, respectively (p = 0.0064). Discussion Causes for the lack of growth of microorganisms in biological materials included previous antibiotic therapy, wound drainage, violations of the rules for sampling of biological material, absence of media for the growth of atypical microorganisms and the ability of microorganisms to form biofilms on implant surfaces. An emergency histological examination of the affected tissues was practical during surgery in doubtful situations for adequate surgical approach. The results of a meta-analysis (2023) showed that the replacement of an infected endoprosthesis was more effective for the treatment of a culture-negative infection compared to debridement and preservation of implant. Conclusion The culture-negative infection group in our series showed better success rate of a two-stage treatment of PJI using implant replacement and broad-spectrum empiric antibiotic therapy at a two-year follow-up period. The negative microbiological result in the group could be caused by antibacterial drugs administered prior to diagnosis of PJI.

Keywords: periprosthetic joint infection, culture-negative infection, culture-positive infection, revision arthroplasty, inflammation markers, knee joint

INTRODUCTION

Diagnosis of chronic periprosthetic joint infection (PJI) does not cause difficulties in the presence of wound dehiscence, sinus tract communicating with the joint space or prosthesis, phenotypically identical microorganisms isolated from two or more samples of biological material in combination with clinical and laboratory signs of inflammation. However, in some cases, the clinical presentation of prosthetic joint infection is not confirmed by the growth of the microorganism in the biological material. The infection is called culture-negative with the prevalence ranging from 7 to 42.1 % [1-4]. A particular interest in culture-negative infection (CNI) is associated with the problems of pathogen verification, selection and duration of antibiotic therapy.

The results of treatment of infection depending on the presence or absence of the pathogen growth are controversial. Mortazavi S.M. et al. (2011) reported the incidence of recurrence after two-stage reimplantation was 4.5 times greater in the CNI group as compared with cases of PJI treatment in patients with an established etiology of the infectious process [5]. However, in their systematic review, M. Reisener, C. Perka (2018) concluded that CNI PJI had the same or even better outcomes than culture-positive infection. The rate of successfully treated infections varied from 85 % to 95 % in all included studies. The two-stage exchange arthroplasty had the best outcome, based on the infection-free survival rate of 95 %, five years after treatment. [1]. Choi H.R. et al. (2013) reported higher success rate of infection control in the culture-negative group (p = 0.006, n = 40) in comparison with positive culture results (n = 135) [6]. By contrast, Huang R., Hu C.C. (2012) reported no differences in outcomes for both types of PJI.
The authors retrospectively analyzed 55 cases of CNI and 295 cases of culture-positive infection (CPI) and found an overall infection control rate in both groups being 73% at minimum 1-year followup after two-stage exchange arthroplasty and postoperative vancomycin therapy [7]. The conflicting data on the outcomes of culture-negative PJI and the lack of domestic publications on the topic were the reason for this study.

The objective was to conduct a comparative analysis of the outcomes of two-stage treatment of PJI of the knee joint, depending on the known or unknown etiology of the infectious process.

MATERIAL AND METHODS

Outcomes of 103 patients with chronic PJI after primary or revision total knee arthroplasty were retrospectively reviewed between 2017 and 2021 based on data from the medical information system. The study included patients who underwent the first stage of a two-stage treatment with the removal of the prosthesis and placement of a spacer impregnated with an antibiotic. A diagnosis of PJI relied on the criteria developed by the 2018 International Consensus Meeting (ICM) [8]. Synovial fluid culture yielded no growth of pathogenic bacteria in 35 cases out of 103 outpatients with PJI. Positive growth of microorganisms with intraoperative biological material was seen in 5 cases out of 35 inpatients. The cases were divided into two groups. Group I (n = 30) included cases of PJI with no growth of microflora (CNI), group II (n = 73) consisted of cases with a positive growth of pathogens (CPI) in synovial fluid sample by preoperative aspiration, surgical specimens of tissue biopsy and/or swabs from the construct removed. Patients were examined by gender, age, proportion of patients with systemic conditions and BMI (Table 1).

A synovial fluid sample was collected from the knee joint in a sterile syringe under aseptic conditions without the use of local anesthetics. Delivery of the biomaterial was performed within 05-60 minutes. A quantitative calculation of the cellular composition with differentiation of leukocytes was produced in the laboratory and the punctate was bacteriologically examined. The aspirate was added to the aerobic and anaerobic vials of the Bact/Alert 3D analyzer. With the punctate volume being less than 1 ml, inoculation was produced in pediatric analyzer bottles or in broths prepared in a routine way.

Reeseeding on solid nutrient media (Columbian, chocolate, Shedler, Saburo agars) was performed with culture growth detected in analyzer vials or broth after 5-10 days. To isolate microorganisms from microbial biofilms, the prosthetic components obtained intraoperatively were processed in a BRANSON 8510 ultrasound machine (USA) for 5 min. at a frequency of 40 ± 2 kHz, followed by inoculation of swabs on nutrient media and on analyzer flasks. The cultures were incubated for 14 days creating conditions for the culturing aerobes, anaerobes, capnophiles and fungi. Species identification of pathogens and sensitivity was performed using an automatic bacteriological analyzer Vitec 2-compact (Bio Merieux, France) and semi-automatic analyzer Multiskan FC [9].

The duration of antibiotic therapy at the stage of debridement and reimplantation was at least 6 weeks (2 weeks intravenously, 4 weeks orally). CPI patients received etiotropic therapy and CNI patients received empiric antibiotic therapy (vancomycin and cefoperazone/sulbactam administered intravenously for 2 weeks, levofloxacin orally for 4 weeks at the stage of debridement and the therapy was combined with rifampicin after reimplantation) [10]. The database was based on medical records including:

- concomitant pathology (systemic diseases);
- the history of previous treatments of PJI including courses of antibacterial drugs;
- signs of generalized infection: septicemia, multiple organ failure, fever;
- local manifestations of edema, hyperemia, hyperthermia, fistula on admission to the first stage of debridement including individual symptoms and in combination.

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group I, abs. number (%)</th>
<th>Group II, abs. number (%)</th>
<th>P &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66.1 (95 % CI: 62.6-69.2)</td>
<td>64.1 (95 % CI: 62.3-65.6)</td>
<td>0.2251</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>7 (23.3)</td>
<td>28 (38.4)</td>
<td>0.1737</td>
</tr>
<tr>
<td>female</td>
<td>23 (76.7)</td>
<td>45 (61.6)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.9 (95 % CI: 30.9-34.1)</td>
<td>32.9 ± 5.2 (95 % CI:31.7-34.0)</td>
<td>0.9116</td>
</tr>
<tr>
<td>Patients receiving antibiotic therapy before admission, %</td>
<td>16 (53.3)</td>
<td>26 (35.6)</td>
<td>0.1845</td>
</tr>
<tr>
<td>Systemic diseases (rheumatoid arthritis, undifferentiated arthritis)</td>
<td>3 (10.0)</td>
<td>9 (12.3)</td>
<td>1.0000</td>
</tr>
</tbody>
</table>
Laboratory blood tests (leukocyte count, ESR, CRP and D-dimer), articular aspirate (leukocyte count, stab neutrophils (SNF), bacteriological examinations (from 1 to 3 consecutive samples of joint fluid taken preoperatively, intraoperative biopsy specimens, joint fluid if any, swabs from metal constructs removed) were evaluated. In 3 cases in group I and in 9 cases in group II, the results of a Sterility blood test was performed for 3 patients of Group I and 9 patients of Group II with signs of a systemic inflammatory reaction with increased blood procalcitonin over 1.0 ng/ml. Effective debridement suggested absence of clinical and laboratory signs of an infectious and inflammatory process at the time of admission to the second stage of treatment. A favorable outcome of the two-stage treatment suggested no recurrence of PJI for at least 2 years after implantation of the prosthesis or arthrodesis or "life with a spacer" without signs of infection.

Statistical methods. The data were recorded in the form of spreadsheets, the visualization of the data structure and analyzed using the MS Office Excel, 2007 software (Microsoft, USA) and the Graf Pad program. A normality test using the Kolmogorov-Smirnov criterion was performed to determine quantitative parameters. The mean and standard deviation with 95% CI were used to describe a parameter with a normal distribution. The Mann–Whitney test was employed to compare quantitative parameters between the groups. Categorical data (gender, type of PJI, outcome) were described using conditional codes of categories that could not be measured and were not subject to ranking. Fisher's exact test was used to assess the effectiveness of the treatment in the groups. Differences in the parameters between groups were considered statistically significant at p < 0.05.

RESULTS

The proportion of CNI in the sample was 29.1 % (n = 30). Despite the absence of statistically significant differences (p = 0.1845), patients with negative cultures were 1.5 greater more those in group II receiving antibiotic therapy at the preadmission stage. PJI developed in 93.3 % (n = 28) in group I and in 87.7 % (n = 64) in group II (p = 0.5025) after primary TJR. The rest of the patients developed the complication after revision procedures for non-infectious causes. The diagnosis of PJI was confirmed (Fig. 1) in 98.6 % of patients in group II and in 76.7 % in group I (p = 0.0006) using the ICM diagnostic criteria (2018). The data for the diagnosis of PJI were not demonstrative (n = 6) or negated an infectious process (n = 1) in another 23.3 % of cases with CNI. There was 1.4 % (n = 1) of such cases in the comparison group.

![Fig. 1 PJI detected with ICM diagnostic criteria (2018)](image)

Staphylococci (69.8 %) were the leading pathogen among causative CPIs. Although no MRSA strains were isolated in the cases, a high proportion of MRSE was identified in the total number of coagulase-negative staphylococci (Fig. 2).

The species of gram-negative microorganisms were presented in the form of a monoculture of *E. coli*, *Achromobacter xylosoxidans*, *Burkholderia cepacia*, *Enterobacter cloacae*, in microbial associations – *Acinetobacter baumannii*. 
Table 2

Preoperative laboratory measurements in groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I (n = 30)</th>
<th>Group II (n = 73)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood serum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>45.9 ± 26.7</td>
<td>64.2 ± 29.2</td>
<td>0.0029</td>
</tr>
<tr>
<td>SRP (mg/l)</td>
<td>33.6 ± 40.9</td>
<td>76.1 ± 64.1</td>
<td>0.0002</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>2672.8 ± 1663.8</td>
<td>2392.6 ± 1383.7</td>
<td>0.4231</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte</td>
<td>aspiration 1</td>
<td>aspiration 2</td>
<td>aspiration 3</td>
</tr>
<tr>
<td>(cells/µL)</td>
<td>16221.4 ± 25920.0</td>
<td>12885.8 ± 27912.7</td>
<td>18876.5 ± 25286.1</td>
</tr>
<tr>
<td>SNP 1 (%)</td>
<td>aspiration 1</td>
<td>aspiration 2</td>
<td>aspiration 3</td>
</tr>
<tr>
<td></td>
<td>88.6 ± 7.6</td>
<td>88.8 ± 6.8</td>
<td>90.8 ± 6.8</td>
</tr>
</tbody>
</table>

Table 3

Mean laboratory measurements of patients with CNI (n = 30) with confirmed and non-confirmed PJI according to ICM criteria (2018)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PJI confirmed (n = 23)</th>
<th>PJI Not confirmed (n = 7)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood serum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>53.8 ± 27.0</td>
<td>24.3 ± 7.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>SRP (mg/l)</td>
<td>43.7 ± 44.5</td>
<td>8.2 ± 6.3</td>
<td>0.0022</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>2753.7 ± 1687.8</td>
<td>2418.4 ± 1687.7</td>
<td>0.6569</td>
</tr>
<tr>
<td>Synovial fluid – aspiration 1</td>
<td>22532.1 ± 28420.8</td>
<td>444.6 ± 849.8</td>
<td>0.0026</td>
</tr>
<tr>
<td>SNP 1 (%)</td>
<td>88.6 ± 7.6</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

The pathogen isolated in 5 cases (6.8 %) group II only from the intraoperative material included *S. aureus* (n = 3), *E. faecalis* (n = 1) and *S. haemolyticus* (n = 1). The growth of strains obtained from preoperative aspiration, *S. aureus* (n = 2) and coagulase-negative staphylococci (n = 2) was not confirmed in four cases (5.5 %) by examination of intraoperative material.

The average interval between surgical stages of PJI treatment and II was 2.5 months (CI = 95 %; 1.2-4.9) in group I and 2.8 month (CI = 95 %; 0.2-17.5) in group II. Recurrence of PJI was detected in 12.3 % (9 out of 73) of patients in group II after debridement (Fig. 3).

There were 3.3 and 7.8 % patients in groups I and II who refused from the second stage of treatment. The reasons for “living with a spacer” included the patient’s unwillingness to accept the treatment plan (arthrodesis after placement of a spacer block, n = 3), absolute contraindications to surgical treatment because of concomitant pathology (n = 2), patient’s refusal from surgical treatment after coronavirus infection (n = 1). Indications for arthrodesis included large defects of the soft tissues and/or bones that form the knee joint due to previous operations, contractures.

Reimplantation was performed in 96.7 % and 80.8 % of patients in groups I and II, respectively. The average follow-up period after the second stage of re-arthroplasty was 40.1 months. (CI = 95 %; 6.2-77.7) in group I and 29.4 months (CI = 95 %; 0.5-57.5) in group II, p = 0.0197. Recurrent PJI with the need for repeated debridement were diagnosed in 3.4 and 16.9 % (p = 0.0928) of cases in groups I and II, respectively. The average period from implantation of the prosthesis to recurrent PJI was 20.8 months in patients with
CPI (CI = 95 %; 1.7-48.2) and 11.9 months (n = 1) in a patient with CNI.

Recurrent PJI was caused by S. aureus (n = 8 out of 20), coagulase-negative staphylococci (n = 4), streptococci (n = 3), gram-negative bacteria (n = 2), polymicrobial infection (n = 3). Strepotococcus agalactiae was isolated in one case with CNI who showed a poor outcome. The etiology of recurrent CPI was similar to the etiology of PJI at the stage of debridement in 26.3 % of cases (5 out of 19): S. aureus was isolated in three cases and E. coli and Strepotococcus spp. were isolated in 1 case. Inconsistent etiology of CPI in 9 cases was caused by absent growth of microorganisms at subsequent stages of debridement with present signs of PJI. Substitution of microflora during relapses occurred in 5 patients with CPI (Table 4).

<table>
<thead>
<tr>
<th>Primary PJI</th>
<th>Recurrent PJI</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>S. aureus + S. epidermis MRSE</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>S. aureus + Strepotococcus oralis</td>
</tr>
<tr>
<td>S. aureus</td>
<td>Acinetobacter baumannii + E. faecalis</td>
</tr>
<tr>
<td>S. epidermidis MRSE</td>
<td>Staphylococcus lugdunensis</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>Corynebacterium jeikeium</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Researchers have been interested in studying outcomes of CNI of prosthetic joints and reasons behind the absent growth of pathogens in biological material, as evidenced by scientific publications for the key phrase "Culture-Negative Periprosthetic Joint Infection" in the PubMed database of all known microorganisms [25]. The prevalence of suspected culture-negative PJI was 96.7 % (1 out of 30) and 74 % (19 out of 73) in groups I and II, respectively (p = 0.0064) (Fig. 3).

The ability of microorganisms, such as staphylococci and Pseudomonas aeruginosa to form a biofilm on the surface of implants from planktonic forms to be a barrier to the detection is an important problem in identifying PJI pathogens [21, 22]. The presence of the viable but not cultivated forms in biofilms is another factor hindering identification of bacteria. Such cells temporarily lose their ability to grow on conventional bacteriological media, but can restore their metabolic activity under certain conditions [23, 24].

In addition to that, S. aureus can exist intracellularly when internalized into osteoblasts and osteocytes leading to a failure in identifying the pathogen. Molecular diagnostic methods using DTT technologies and PCR sequencing have evolved in addition to cultural methods for identifying pathogens. The latter allows the identification of organisms by highly efficient parallel sequencing of all microbial DNA present and comparison of the generated sequence scanning with a bioinformatic database of all known microorganisms [25]. The statistics with the number of tissue samples (at least 3-5 needed) or from non-infected tissue [20], increased sample transportation time, non-compliance with incubation periods, or lack of media for the growth of atypical microorganisms. In our series, the obvious reason for the lack of microorganism growth included the use of antibiotics prior to diagnosis of PJI, which was found in 50 % of cases in group I. Collection of biomaterial for microbiological examination, prosthetic components are treated with ultrasound and incubated for at least 14 days providing conditions for culturing aerobes, anaerobes, capnophiles and fungi.

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of molecular diagnostic methods include the high cost and impossibility of detecting sensitivity to antibiotics. Repeated sampling for microbiological research can be offered to improve identification of pathogens in the absence of microorganism growth through incubation of cultures for at least 14 days, ultrasonic treatment of implants refraining from antibiotics prior to sampling [26].

Despite the improvement of PJI diagnostic criteria (ICM, 2018), demonstrating high sensitivity (97.7 %) and specificity (99.5 %) [8] with the possibility of verifying the infectious process in the absence of microorganism growth in the biological materials, diagnosis of CNI is still difficult. In our series, the total ICM score was less than 5 in 7 cases with an established diagnosis of CNI; there were no differences in the level of D-dimer. The diagnosis of PJI in the group of patients was based on radiological criteria for early instability of the prosthesis with zones of osteolysis or resorption. An emergency histological examination of the altered tissues can help to verify the diagnosis during surgery and decide on the optimal surgical strategy (one-stage rather than two-stage revision). The method offered by L. Morawietz et al. for determining more than 23 neutrophilic granulocytes in 10 high-power fields allows differential diagnosis of aseptic and infectious endoprosthesis loosening [27]. According to the literature, an emergency histological examination has a sensitivity of 95-98 %, a specificity of 98-99 %.

An automating technique using the CD15 focus score and the CD 15 quantifier computer program has been described with the sensitivity of 83 %, specificity of 86.4 % and an accuracy of 84.6 % [28]. This method allows for the diagnosis of PJI caused by low-virulence pathogens to be verified within a short period of time, in contrast to microbiological examination. Immunohistochemical examination of the CD15 antigen on the surface of neutrophils significantly increase the accuracy of PJI diagnosis, as reported by Silantieva T.A. et al. in 2021 exploring infected periprosthetic membranes [29]. Li H., Yang R., Geng L. (2014) suggested describing CNI that the infectious process with a negative culture was characterized by a slow onset and a moderate inflammatory response. In our series, the average levels of CRP, ESR and the leukocyte count in the joint fluid were reduced by 1.5 to 2 times in the CNI group than in the comparison group, which confirms the hypothesis of foreign colleagues.

A systematic meta-analysis of CNI outcomes including a review of 8 English-language articles was published in 2018 [30]. The pooled culture-negative infection rate was 11 % (n = 504) with a success rate of 85-95 % with no difference in success rates with CPI. The results of a recent meta-analysis, which included 30 studies, demonstrated a similar or better efficacy in the treatment of CNI in comparison with the culture-positive PJI group with success rate of 81 % and 76.4 %, respectively [30]. One of reasons for the success of CNI treatment may include absence of infection in the prosthetic joint or presence of low-virulence microorganisms that are easier to treat than highly virulent germs, such as methicillin-resistant Staphylococcus aureus [6].

S. aureus is reported in the literature as playing a leading role in the development of PJI [31-34]. Tan TL (2018) reported 219 cases of CNI with methicillin-susceptible S. aureus accounting for 38.5 % (10/26) of recurrent PJI with positive microbiological growth [14]. The results of our study also confirm the leading role of S. aureus in the etiology of CPI, both newly diagnosed (32.9 %) and relapsed (50 %). MRSE staphylococci that account for 75 % of all isolated coagulase-negative staphylococci are essential for etiology of PJI. With S. aureus and methicillin-resistant coagulase-negative staphylococci being the leading causative agents of PJI in our series the rationale for the mandatory use of vancomycin as part of the initial empirical antibiotic therapy in combination with cefoperazone / sulbactam was essential for expanding the spectrum of antimicrobial activity. Bejon P. et al. (2010) described 62 cases of CNI with a two-stage debridement success rate of 83 % over 5.75 years of follow-up [31]. In our series, a successful treatment outcome was achieved in 96.7 % and 74 % of cases (p = 0.0064) with culture-negative and culture-positive PJI, respectively at a two-year follow-up.

Most studies have shown the advantage of two-stage revision arthroplasty over radical surgical debridement with preservation of the endoprosthesis in patients with CNI. Tan TL et al. (2018) reported the infection arrested in 71.2 % and 55.6 % of cases, respectively [14]; Berbari E.F. et al. (2007) described success in 94 and 71 % of cases, Huang R. et al. (2012) could achieve efficient treatment in 70 % and 50 % of observations, respectively. Only Malekzadeh D. et al. (2010) reported comparable results in the treatment of 135 cases of CNI with 78 % cumulative incidence free of treatment failure at 5 years followup being similar for CNI and CPI PJI regardless of the implant retention or removal [15]. The results of a recent meta-analysis (2023) suggested that surgery with the replacement of an infected endoprosthesis with one-stage or two-stage revision was more effective for the treatment of CNI compared with debridement and implant retention with the recurrence rate of 11.5, 16.1 and 22.2 % of cases, respectively [30].
CONCLUSION

In our series, the use of antibacterial drugs prior to diagnosis of PJI was the most obvious reason for the lack of growth of microorganisms. The findings indicated the high efficiency of two-stage revision arthroplasty, broad-spectrum empiric antibiotic therapy administered for culture-negative infection of the knee joint, which amounted to 96.7 % success at a 2-year follow-up, which statistically significantly exceeded outcomes with culture-positive infection with an established etiology with success rate of 74 %.

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REFERENCES


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Bozhkova S.A. – reviewing and editing the article, control.
Pchelova N.N. – conceptualization, research.
Preobrazhenskaya E.V. – methodology, validation, formal analysis, visualization.
Lyubimov E.A. – conceptualization, research.

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