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Method of predicting the outcome of surgical treatment in Dupuytren's contracture based on leukocyte formula indices

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Abstract

Introduction World literature indicates the relevance of predicting the outcomes of Dupuytren's contracture (DC) treatment, including those based on laboratory methods. There are no comparative studies of the results of surgical DC treatment based on preoperative peripheral blood counts in the available literature.

The **purpose** of the work was to identify possible differences in preoperative leukocyte counts in DC with different outcomes of surgical treatment one year after surgery and to evaluate their prognostic significance.

Materials and methods The analysis of medical records of 52 DC patients operated on in the Hand Surgery Clinic of the Ilizarov Center in 2021–2022 was conducted. The results were assessed using the Khan scale, as well as by calculating the contracture reduction index (CRI). The subgroup included 111 patients with fair and poor results, the remaining 41 were included in subgroup 2 with good and excellent results.

Results According to the CRI values, the subgroups were in non-overlapping ranges. The percentage of eosinophils and basophils (B + E) in subgroup 1 was higher than in subgroup 2 ($p < 0.05$). ROC analysis of the "CRI — (B + E)" model revealed an area under the curve of more than 0.7 at $p < 0.01$, specificity of 100 %, sensitivity of less than 60 %. In patients with (B + E) < 1.2 %, the rate of excellent and good results one year after surgery was 95.23 %, with (B + E) ⩾ 1.2 % 70.00 % ($p < 0.05$).

Discussion The role of eosinophils and basophils in the development of fascial fibromatosis is unknown, but it has been established that interleukins IL-4 and IL-13 secreted by mast cells, basophils and eosinophils directly contribute to the activation of myofibroblasts and the development of fibrosis.

Conclusion In (B + E) < 1.2 %, a favorable outcome is predicted for both open and minimally invasive surgeries; at (B + E) ⩾ 1.2 % there is a high probability of progressive postoperative fibrosis, which justifies the choice of radical open interventions (hypodermectomy or dermofasciectomy) and the use of antifibrotic therapy in the postoperative period.

Keywords: Dupuytren's contracture, basophils, eosinophils, preoperative prognosis

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INTRODUCTION

Dupuytren's contracture (DC) is a consequence of palmar fascial fibromatosis (PFF), a ibroproliferative disease that primarily affects the fascial framework of the palms and fingers on the ulnar side of the hand. The main manifestations — nodes and fibrous chords — thicken and shorten the palmar-digital fascia and integumentary tissues, which leads to the formation of persistent flexion contractures of the finger joints. The majority of patients are males aged 40 to 80 years; about 3 % of them become disabled [1].

The etiology and PFF pathogenesis remain a matter of debate, with well-known risk factors including genetic predisposition, manual labor, alcohol and smoking, hypertension, and diabetes [2].

The most commonly used treatments for DC include collagenase injections, needle fasciotomy, and various types of open fasciectomy [3], which aim to destroy or remove pathological formations and correct hand deformity. Recurrence of contractures (growth in total extension deficit by more than 30°) is noted in 85 % of patients after needle fasciotomy and in 20 % after open partial fasciectomy over a five-year follow-up period [4].

Some authors classify contracture recurrences as late postoperative complications along with the spread and progression of fascial fibromatosis [5]. To optimize the treatment tactics for DC patients with, a technology for predicting late postoperative complications has been proposed based on the analysis of 39 factors that determine the patient's biological status and lifestyle, as well as the technical and surgical components of operations and rehabilitation treatment [6]. To develop a prognostic approach, a number of studies were conducted on potential laboratory markers of PFF activity: antibodies to connective tissue components [7, 8], matrix metalloproteinases [9], and circulating fibrocytes [10].

A study of 19 patients with DC found that the level of gene expression of matrix proteinases in tissue samples can be used to predict the outcome of treatment one year after surgery [11]. However, circulating matrix metalloproteinases did not correlate with postoperative extension deficit [12], so the problem of preoperative prediction of the outcome of DC treatment based on laboratory methods has not been solved to date. However, there are no data from comparative studies of surgical treatment outcomes based on preoperative peripheral blood parameters in the available literature.

The **purpose** of the work was to identify possible differences in preoperative leukocyte counts in DC patients with different outcomes of surgical treatment one year after surgery and to evaluate their prognostic significance.

MATERIALS AND METHODS

An analysis of preoperative leukocytograms and of treatment results was performed in 52 patients with DC, operated on at the hand surgery clinic of the Ilizarov Center in the period from 2021 throughout 2022.

The analysis of preoperative peripheral blood tests was performed based on the Nomenclature of the Ministry of Health of the Russian Federation (Order No. 804n): A12.05.121 "Differential leukocyte count (leukocyte formula)", which corresponds to the determination of the concentration of leukocytes in peripheral blood and differentiation of the main five types of leukocytes (neutrophils, eosinophils, basophils, lymphocytes, monocytes) by a hematology analyzer, as well as the calculation of their percentage. For the possible detection of immature leukocytes, atypical and blast cells, the automatic analysis is supplemented by "manual" microscopy of stained peripheral blood smears.

All patients underwent open partial fasciectomy with neurolysis and arteriolysis of the vascular-nerve bundles according to the indications (contracture of the metacarpophalangeal joint of 30° or more and contracture of the proximal interphalangeal joint regardless of the angle size [13]). In contracture of the proximal interphalangeal joint of more than 30°, fasciectomy was supplemented with arthrolysis [14]. In persistent contractures of grade II and grades III–IV, the operated rays were fixed in the Ilizarov mini-fixator during the healing period of the surgical wound. If full extension of the fingers was not achieved immediately during the operation due to contraction of the integumentary tissues and vascular-nerve bundles, dosed extension in the Ilizarov fixator was used, which started after the surgical wound healing. Once full extension of the joints had been reached, the fixator was blocked for at least 14 days, after which dynamic fixation was used: patients developed passive movements in the joints during the day, and the fixator was blocked at night. The duration of inpatient treatment varied from 9 to 14 days without fixator application and the fixation of the Ilizarov mini-apparatus was used from 17 to 42 days in the distraction application. After discharge, patients were recommended rehabilitation treatment.

The treatment results were assessed 6 and 12 months after surgery using the Khan et al. scale [15], as well as by calculating the contracture reduction index (CRI), expressed as a percentage of the difference between the initial sum of contracture angles and the sum of angles after surgery to the initial sum of angles [16].

Clinical and demographic characteristics of the studied group of patients are presented in Table 1. Based on the analysis of treatment results using the Khan et al. scale [15], patients with satisfactory and poor results were assigned to group 1 (n = 11), and patients with good and excellent results were included in group 2 (n = 41).

Table 1

Clinical and demographic parameters of studies patients

Parameter	Patients (n = 52)
Age — Me (Q1; Q2)	60 (58; 60)
Male to female ratio	5:1
Duration of disease since initial manifestations — Me (Q1; Q2)	8 (4; 14)
Contractures in stage III–IV, %	70.59
Patients under age of 50 years, %	49.02
Involvement of both hands, %	76.9
Interventions due to recurrence, %	23.53
Rate of multiple contractures (three or more digits), %	25.49
Contractures of ray V, %	74.51

The studies were conducted in accordance with the ethical standards of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" with amendments.

Microsoft Excel 2010 spreadsheets and the Attestat computer program (version 9.3.1) were used for statistical processing of quantitative data. The Shapiro-Wilk criterion was used to test the hypothesis of normal distribution. In some samples, the distribution differed from normal, so the data in the tables are presented as medians and quartiles - Me (Q1; Q3). Hypotheses about differences were tested using the nonparametric Mann-Whitney test, applicable for comparisons of different-sized samples.

RESULTS

According to the CRI values, the groups were in non-overlapping ranges: patients with satisfactory and poor results had a contracture reduction index of 62 % or less, and in patients with good and excellent results, this indicator varied from 64 to 100 %.

The preoperative leukocytogram values (Table 2) did not differ from normal values, but a significant difference was revealed between the groups: the percentage of eosinophils and basophils in group 1 was higher than in group 2 ($p < 0.05$).

Table 2

Preoperative leukocytogram values (Me (Q1; Q3)) of patients based on the magnitude of the reduction index (RI) of Dupuytren's contracture one year after surgery

Group/ parameter	Whole sample	Group 1 (RI ⩽ 62 %)	Group 2 (RI 64 — 100 %)	*P*
	n = 52	*n* = 11	*n* = 41	
Leucocytes (× 10^9/l)	6.65 (5.31; 8.16)	5.91 (5.05; 8.67)	6.75 (5.45; 8.05)	0.66
Neutrophils (%)	56.50 (51.8; 62.4)	55.65 (55.45; 62.85)	56.50 (52.00; 6.40)	0.73
Lymphocytes (%)	35.00 (29.00; 39.95)	33.10 (29.30; 37.65)	35.00 (29.00; 40.00)	0.63
Monocytes (%)	7.15 (6.00; 8.20)	7.20 (6.50; 8.20)	7.15 (5.80; 8.20)	0.74
Eosinophils (%)	1.55 (0.70; 2.00)	2.05 (1.50; 3.05)	1.00 (0.00; 2.00)	0.02*
Basophils (%)	0.00 (0.00; 0.40)	0.35 (0.10; 0.50)	0.00 (0.00; 0.25)	0.01*

Note * — statistically significant differences according to the Mann – Whitney test ($p < 0.05$)

A similar intergroup difference was noted for the absolute content of eosinophils and basophils. Immature forms of leukocytes did not exceed reference levels; young, plasmatic and blast cells were absent in most patients, and did not exceed reference levels in solitary cases.

ROC analysis of the RIDC — (B + E) model revealed its good quality (area under the curve more than 0.7 at $p < 0.01$), high specificity (100 %), but only satisfactory sensitivity (less than 60 %).

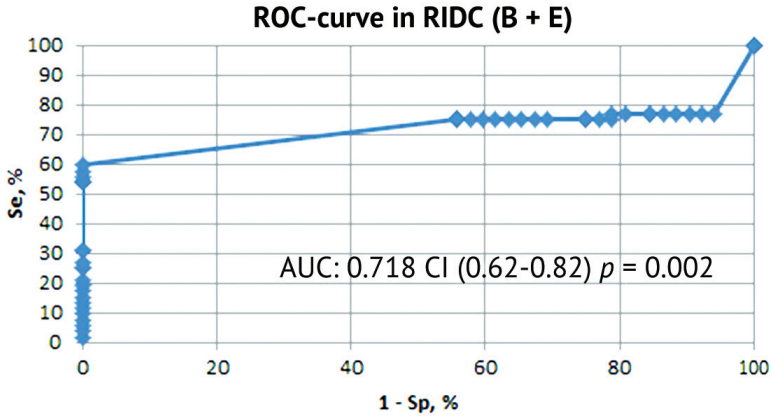

Fig. 1 Diagnostic value of preoperative total relative content of basophils and eosinophils (B+E) in the assessment of RIDC one year after surgery. Threshold 1.2 %; Sensitivity 59.62 %; specificity 100.0 %

At the next stage of the study, all patients were divided into groups based on the (B + E) value. There were 21 patients with a value lower than the threshold, and 31 patients with a value equal to or greater than the threshold. As shown by the data in Table 3, the groups did not have significant differences in clinical and demographic characteristics.

However, in patients with (B + E) < 1.2 %, the rate of excellent and good results one year after surgery was 95.23 %, and in patients with (B + E) ⩾ 1.2 % it was only 70 % ($p < 0.05$).

Table 3

Clinical and demographic characteristics of patients based on the value of the sum of basophils and eosinophils in peripheral blood before surgery

Parameters	Group		*p*
	(B + E) < 1,2 (*n* = 21)	(B + E) ⩾ 1,2 (*n* = 31)	
Age —Me (Q1; Q2) (min–max)	61.5 (58; 64) (51–71)	59 (54.5; 65) (23–75)	0.30
PFF duration	6.5 (5; 15) (1.5–20)	10 (4; 14.5) (2–40)	0.63
Patients under 50 years of age, %	40.90	53.57	0.52
Contracture severity — Me (Q1; Q2) (min–max)	3 (2; 3) (1–4)	3 (2.5; 3) (1–4)	0.77
Rate of patients with two-side involvement of PFF	81.82	78.57	0.79
Number of digits with impaired function — Me (Q1; Q2) (min–max)	1 (1; 2) (1–5)	2 (1;3) (1–4)	0.51
Patients that underwent second surgery, or more operations, %	27.27	46.43	0.18

DISCUSSION

The work presented, was the first comparative analysis of preoperative leukocytograms in patients with DC with different outcomes of surgical treatment one year after the operation. The studied pool of patients was characterized by a typical median age and gender ratio, typical duration of the disease, a high percentage of patients with severe contractures (more than 70 %), a large number of patients with signs of Dupuytren's diathesis (half of whom were affected at the age under 50 years and 77 % had lesions in both hands). More than 20 % of patients had operations for relapses, more than 25 % had contractures of three or more fingers and almost 75 % had contractures of the ray V.

Preoperative peripheral blood tests did not reveal any deviations in the absolute number of leukocytes. As is known, in such cases, the analysis of the leukocyte formula for relative content of the main types of leukocytes does not lead to erroneous results.

The results of surgical treatment were assessed using the qualitative scale of Khan et al. [15] and the quantitative indicator of the contracture reduction index. According to the qualitative scale, excellent and good results (*n* = 41) included complete restoration of motion or minor limitations of flexion-extension function that did not affect daily activities. The RIDC in such patients ranged from 64 to 100 %. None of those patients met the expert consensus definition of relapse as an increase in contracture of any treated joint by at least 20° within a year after surgery compared to six weeks after surgery [17]. In patients with fair and poor treatment results (*n* = 11), the contracture reduction index had negative dynamics within a year after surgery, confirming relapse.

According to some authors, DC relapses in the first year after surgery develop in cases where "operations were performed with violations of hand surgery guidelines" [18]. However, our study revealed significant differences in preoperative leukocytograms in groups of patients with different treatment outcomes. Apparently, the treatment outcome is also affected by the predisposition of patients to different patterns of wound healing.

As is known, eosinophils and basophils, along with mast cells, helper lymphocytes and macrophages, participate in inflammatory reactions of the second type, characteristic not only of allergies and parasitic invasions, but also of many other diseases. This type of immune reactions also regulates tissue reparation, including the restoration of epithelial barriers after damage [19, 20]

Eosinophils, comprising one to 5 % of peripheral blood leukocytes, are normally present in many tissues, performing homeostatic functions [21], including directly activating mast cells [22]. Basophil is the rarest blood cell, which normally comprises 0.5 % of leukocytes [23]. Unlike tissue basophils (mast cells), residents of connective tissue, short-life basophils of peripheral blood, are usually not present in tissues; their tissue traffic is associated with specific functions [24].

It has been previously established that the fascia of DC patients contains 12 times more mast cells than normal fascia [25], and not only their numerical density increases, but also their morphofunctional quantitative parameters, such as the area and index of degranulation with contractures of grades III–IV, compared with contractures of grades I–II, [26]. The role of eosinophils and basophils in the development of fascial fibromatosis is unknown, but it has been established that interleukins IL-4 and IL-13, secreted by mast cells, basophils, and eosinophils [27], directly contribute to the activation of myofibroblasts and the development of fibrosis [28].

As our study showed, patients with low and high total relative content of basophils and eosinophils in peripheral blood had no differences in clinical and demographic indicators. However, the proportion of fair and poor treatment results was significantly higher in the group with (B + E) ⩾ 1.2 %. Therefore, the total relative content of basophils and eosinophils in peripheral blood ⩾ 1.2 % in the preoperative period is an independent predictor of relapse of the fibroproliferative process in patients operated on for DC.

The results of ROC analysis indicate an average prognostic significance of this indicator due to a specificity of lower than 60 %; however, in combination with another leukocyte index (lymphocyte-monocyte ratio), which allows predicting the progression of DC and has a high prognostic significance [29], it can be used in preoperative prediction of treatment outcomes in DC patients [30].

Here are clinical cases with the use of this prediction method.

Case 1 Patient H., 71 years old, was admitted for treatment to the Ilizarov Center in November 2021 with the diagnosis: bilateral palmar fascial fibromatosis, acquired deformity of digits II-V of the left hand, DC stage IV (total deformity angle 190°). Concomitant diseases: stage 3 hypertension, chronic heart insufficiency, atrial fibrillation outside of paroxysm, late stage of Bechterev disease.

History of the disease: was ill for 8 years; initially, movement limitations and persistent contractures in the left hand developed, then in the right one; did not seek treatment for 5 years. On 07.03.18, he underwent surgery at the Ilizarov Center for acquired deformity of the fifth finger of the right hand, DC grade III. He was satisfied with the treatment result. According to the archival medical records, the lymphocyte-monocyte index was 5.8 (higher than the threshold value, which did not indicate a progressive nature of the disease at that time), the total content of eosinophils and basophils was 1 %, which indicates a probability of obtaining a good and excellent result of the operation of 95.23 %. At the time of the patient's admission due to the deformity of the left hand, the restoration of flexion-extension movements of the operated fifth finger of the right hand was almost complete.

The total contracture angle of ray V of the left hand before the operation was 190°. According to the preoperative blood test (2021), the lymphocyte-monocyte index was 5.75 (higher than the threshold value, which also does not indicate a progressive nature of the disease at the moment). The total content of eosinophils and basophils was 1.0 %, which indicates a probability of obtaining a good and excellent result of the operation of 95.23 %.

On 18.10.21, the following surgery was performed: excision of the fibrously altered palmar aponeurosis in the projection of rays II–V of the left hand, arthrolysis of the proximal interphalangeal joint of finger V, skin grafting of the palmar surface of ray V of the left hand with local tissues, osteosynthesis of ray V with the Ilizarov mini-fixator.

At the patient's follow-ups 6 and 12 months after the surgery, the total angle of deformation on the left hand decreased from 190° to 60° and 45°, respectively, and the contracture reduction index was 0.68 and 0.76. The latter value corresponded to an excellent result of surgical correction and coincided with the positive preoperative prognosis based on peripheral blood indices, despite the extreme severity of the disease (multiple contracture of digits II–V, grade IV).

Case 2 Patient U., 36 years old, was admitted for treatment to the Ilizarov Center with the diagnosis: palmar fascial fibromatosis, acquired deformity of the right hand, combined DC and digit V of the left hand in grade II–III (total deformity angle 90°).

According to the preoperative blood test, the lymphocyte-monocyte index was 5.39 (higher than the threshold value, which does not indicate a progressive nature of the disease at the moment). However, the total content of eosinophils and basophils was 2.8 % (higher than the threshold value of 1.2 %) and indicated that the probability of obtaining a good and excellent result of the operation is no more than 70.00 %.

On 26.01.22, the operation included excision of the fibrously altered palmar aponeurosis in the projection of ray V of the right hand, arthrolysis of the proximal interphalangeal joint of digit V, skin grafting of the palmar surface of ray V of the left hand with local tissues, osteosynthesis of ray IV with the Ilizarov mini-fixator.

A 6-month follow-up revealed a total contracture angle of 30°, and after 12 months it was 90°. The contracture reduction index one year after the operation was 0°, which corresponded to a poor result.

In this clinical case, the prognosis about a decreased probability of good and excellent results of the operation due to the high total content of eosinophils and basophils was confirmed.

CONCLUSION

Available prognostic criteria for detecting DC progression and recurrence have been developed. The lymphocyte-monocyte ratio and the total relative content of basophils and eosinophils were used as prognostic criteria. If the lymphocyte-to-monocyte ratio is more than 3.1, surgical treatment tactics (minimally invasive fasciotomy or open fasciectomy options) is chosen based on the local status, age, comorbidity and patient preferences. If the lymphocyte-to-monocyte index is less than 3.1, a prognosis is made about a high probability of fascial fibromatosis progression, which is an additional indication for radicalization of the surgical treatment method: open hypodermofasciectomy and dermofasciectomy. If the total relative content of eosinophils and basophils is less than 1.2 %, a prognosis is made about a favorable outcome of minimally invasive and open surgical interventions. If a total relative content of eosinophils and basophils is 1.2 % or more, there is a high probability of progressive postoperative fibrosis and the development of cicatricial contracture, therefore, in the immediate postoperative period, enhanced therapy of the edematous-inflammatory syndrome is necessary, and in the late period, antifibrotic therapy [31, 32].

The application of the developed criteria does not require material costs, but they have prognostic value and are important for refining treatment tactics, so it is advisable to use them in wide clinical practice.

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