LUND UNIVERSITY
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ERYSIPELAS

Risk factors of recurrency and the clinical course of events.

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Abstract

Background: Erysipelas is a common infection that often reoccurs, but only a few studies have investigated risk factors for recurrent episodes. How the natural course of events in the infection corresponds to the inflammatory signs is not well described.

Objective: The aim of this study was to indentify risk factors for recurrent erysipelas and the possibility to study the course of events from an objective point of view.

Methods: The study was divided in one retrospective and one prospective part. In the retrospective study, medical records were reviewed from patients diagnosed with erysipelas at the Department of Infectious Diseases at Skåne University Hospital in Lund from January 2007 to December 2010. Patients with single episode erysipelas were compared with patients suffering from recurrent episodes regarding risk factors and general characteristics.

In the prospective study, patients admitted to the Department of Infectious Diseases at Skåne University Hospital in Lund for erysipelas in upper or lower extremity were included. Repeated examinations of inflammatory signs such as temperature of the the skin, area of erythema and circumference were performed on the affected as well as the contra lateral extremity for comparison.

Results: In the retrospective study, 511 patients were included and divided into two groups, single episode erysipelas (n=370) and recurrent erysipelas (n=141). Risk factors identified for recurrent erysipelas were malignancy (p=0.006), venous insufficiancy (p=0.036), lymph oedema (p<0.000) and previous regional operation (p<0.000).

In the prospective study, 18 patients were included. All measured parameters showed significant difference between inclusion day and day 7. Temperature of the skin was the most rapid parameter react, showing difference alredy at day 3-4. At the later follow up visit, temperature and circumference still showed difference between the extremities and only the erythema had disappeared.

Conclusions: Risk factors for recurrent erysipelas were identified. The symptoms of erysipelas are possible to measure and show a variation over time. These findings may contribute in monitoring clinical improvement in future studies regarding treatment effects and prognostic factors.

Introduction

Erysipelas is a common infection of the superficial layer of the skin, while cellulitis and necrotizing fasciitis also involve the subcutaneous tissue. It is defined as an acute onset of local signs of inflammation such as progressing erythema, associated with pain and swelling, clearly demarcated from the surrounding tissue. In the typical case erysipelas also manifests with systemic symptoms such as fever, chills and malaise and sometimes accompanied by nausea and vomiting [1, 2]. The most frequent pathogen is beta-hemolytic group A streptococcus, but it may also be caused by group B, C and G streptococci [1]. *Staphylococcus aureus* is also debated and suspected as a pathogen [3]. The most common location for the infection is the lower limb, about 80% of all cases. Less common is upper limb, head and other locations [4]. The severity of erysipelas varies from cases with mild infection *e.g.* outpatients to severe hospitalized cases, including fatal outcome [5]. How the natural course of events in erysipelas corresponds to the inflammatory signs is not well described.

There are various risk factors reported for erysipelas including disruption of the cutaneous barrier, venous insufficiency, lymph oedema and being overweight [6, 7]. Recurrent erysipelas is common, according to a previous study 29% of patients with erysipelas were observed with recurrent episode in an average three year follow-up time [8]. Few previous studies have compared general characteristics and risk factors for patients with recurrent erysipelas and single episode erysipelas. Significant risk factors for recurrent erysipelas have been identified, including venous insufficiency, lymph oedema, *tinea pedis*, previous regional surgical intervention and being overweight [8-10]. This common infection causes both suffering and medical expenses that should motivate appropriate prevention [7, 11].

Aim of study

The study is divided in one retrospective and one prospective part. In the retrospective study, patients with single episode erysipelas and patients with recurrent erysipelas were compared regarding risk factors and general characteristics. In the prospective study the possibility of objectively measuring signs of inflammation and thus monitor the dynamic inflammatory process in erysipelas was investigated.

Materials and methods

Retrospective study

We retrospectively reviewed medical records from patients diagnosed with erysipelas in the Department of Infectious Diseases at Skåne University Hospital in Lund during the time period from January 2007 to December 2010. Patients were both hospitalized and treated as outpatients. The patients were divided into two groups for comparison, single episode erysipelas (SEE) and recurrent erysipelas (RE). SEE consisted of patients with erysipelas without a history of previous episodes (medical records and anamnestic information). RE consisted of patients with more than one episode of erysipelas registered during the study period, or anamnestic information of previous episode outside the study period. Medical records from the two groups were compared regarding background disorders known or suspected as risk factors for erysipelas [6, 7] as well as local risk factors and general characteristics. All parameters are shown in appendix 1. Malignancy included both prior and present occurrence of all types. Previous regional operation was defined as surgical interventions at the area affected by erysipelas or adjacent locations. As a number of patients from the RE group was registered for more than one episode during the study period, the medical record from the first recurrent episode that occurred within the study period was selected for comparison with the SEE group. The Chi2-test was used to compare categorical data and the Mann-Whitney test was used to compare continuous data between the two groups. A P-value less than 0.05 was considered statistically significant.

Prospective study

A prospective case study was performed on patients with erysipelas of the leg or arm. All subjects were patients admitted to emergency treatment at the Department of Infectious Diseases at Skåne University Hospital in Lund, during the time period 23

of January to 2 of May 2012. The diagnosis erysipelas was validated within 72 h, by a senior physician specialized in infectious diseases.

Modus operandi

The following parameters were examined repeatedly on the target limb as well as the corresponding area on the contra lateral extremity: local status, skin temperature, area (cm^2) of affected skin (area), circumference (cm), colour of the affected skin and status of regional lymph nodes. In addition, vital parameters were measured and self-estimated pain score (score 0-10, where 0 is no pain and 10 the greatest pain). Careful visual inspection and thorough searching for skin barrier defects was performed at inclusion. Examination took place at day 0, 1, 3-4, 7 and later a follow up visit, after inclusion. The follow up visit was performed at day 31 in median (range day 18 to 36). C-reactive protein (CRP) was measured at day 0, 3-4 and 7.

Surface temperature was measured in the middle of the affected skin and proximally within the borders of erysipelas with a digital infrared instrument (Mini temp, Ingeniörsfirma Torsten Berg). Colour of the skin was measured with NCS Colour Scan instrument (NCS colour AB, Stockholm). The subjects sat down with their lower extremities stripped of clothes in horizontal position for at least five minutes, and were systematically interviewed about their present symptoms and relevant medical history. In the case of erysipelas of the arm, subjects sat straight, arms hanging by their side. Statistical analysis was performed using Wilcoxon nonparametric t-test with a P-value less than 0.05 considered statistically significant.

Both studies were approved by an ethics committee and in the prospective study, all subjects gave their written informed consent to participate. In the retrospective study, informed written consent was waived.

Results

Retrospective study

During the study period, 601 patients were registered with the diagnose erysipelas. Among them we excluded 90 patients due to medical records that could not be retrieved, initial erysipelas diagnose that changed to other diagnose during the episode, and non acute patient visits. The remaining 511 patients were divided into two groups, single episode erysipelas (SEE) and recurrent erysipelas (RE)**.** SEE group consisted of 370 patients, 215 (58.1%) males and 155 (41.9%) females. The mean age was 57.9 years (range 18-97, median 59.5 years). 216 patients (58.4%) were hospitalized (average 6.5 days, +/- 5.0 days) and 154 patients treated as outpatients. The RE group was registered for 211 episodes during the study period and consisted of 141 patients, 77 males (54.6%) and 64 females (45.4%). The mean age was 61.5 years (range 19-92, median 63 years). 62 (44.0%) patients were hospitalized (average 6.3 days +/- 4.1 days) and 79 patients treated as outpatients. The anatomical location most affected by erysipelas altogether was the lower extremity (69.1%), followed by upper extremity and the head as summarized in table 1. Other locations as breast, genitalia and trunk were less common. There were no statistically significant difference between the two groups regarding age and gender. Risk factors and outcome from the two groups are summarized in table 2. Among general risk factors, statistical significant difference could be seen for malignancy ($p=0.006$). Local risk factors with statistical significant difference were lymph oedema ($p<0.000$), venous insufficiency ($p=0.036$), previous operation ($p<0.000$) and occurrence of wounds ($p=0.038$), with the last mentioned more frequent in the SEE group. In majority of hospitalized patients, treatment consisted of intravenous penicillin (56.5%), followed by oral penicillin. Most of the outpatients were initially treated with oral penicillin, sometimes after one initial dose of intravenous penicillin.

Table 1

Anatomical location

	SEE n=370 (%)	RE n=141 (%)	All n=511 (%)
Lower extremity	65.9	77.3	69.1
Upper extremity	16.8	11.3	15.3
Head	12.7	5.0	10.6
Other	4.6	6.3	5.1

Distribution of anatomical locations

Table 2

Risk factors

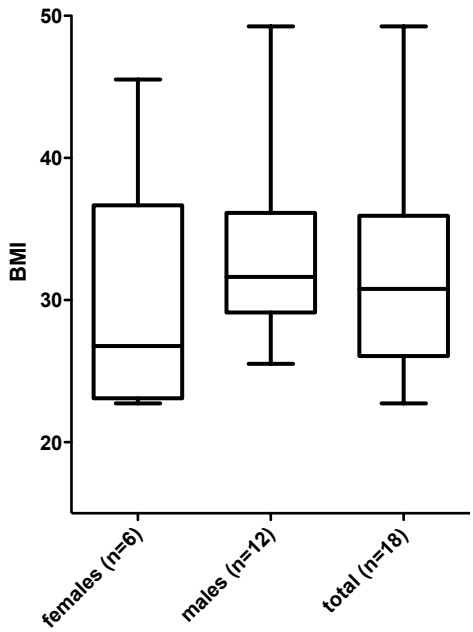
General Risk factors	SEE n=370 (%)	RE N=141 (%)	All N=511 (%)
Malignancy	14.9	25.5 (p=0.006)	17.8
Diabetes	14.1	17.7	15.1
Cardiovascular disease	15.4	14.9	15.3
COPD	5.9	2.1	4.9
Dermatological disease	11.6	14.9	12.5
Local risk factors			
Tinea Pedis	2.7	4.3	3.1
Wound	49.2 (p=0.038)	39.0	46.4
Venous Insufficiency	4.6	9.9 (p=0.036)	6.1
Lymph oedema	2.2	12.1 (p<0.000)	4.9
Regional operation	17.3	34.8 (p<0.000)	22.1
CABG	4.6	8.5	5.7
Arterial Insufficiency	3.5	5.7	4.1
Polyneuropathy	3.2	2.8	3.1
Radiation Therapy	4.9	7.8	5.7

Distribution of risk factors. P-values only shown for significant results.

Prospective study

18 patients were included, twelve males and six females with a median age of 61 years. Among the 18 subjects there were six smokers and six patients with diabetes mellitus type 2. Body Mass Index (BMI) was 31 in median (figure 1). At the time of inclusion, seven subjects met the criterion of SIRS [12] (appendix 2) and 13 were hospitalized. Eleven suffered from recurrent erysipelas. The two females with erysipelas of the arm were operated for breast cancer with subsequent lymph oedema, whilst the man with affected upper extremity suffered from nothing the like. The great majority of subjects reported symptoms of chills (n=14), fever (n=12), and malaise (n=15). Clinical examination showed lymphadenopathy of the regional lymph nodes in 13 subjects (swelling n=13, tenderness n=8). Ten subjects presented with some kind of wound at the target extremity. Five out of the eight without wounds showed various skin barrier defects *e.g.* heel fissures. Furthermore in nearly half (n=7) of the ones with lower extremity erysipelas, suspected intertriginous mycosis and/or onychomycosis were seen. Data were excluded from two patients examined day 2 and day 5 respectively because of the inadequate time of examination. Furthermore erysipelas reoccurred in two patients, wherefore their follow up examination data were excluded. Valid number of subjects examined day 0 (n=18), day 1 (n=16), day 3-4 (n=12), day 7 (n=10) and follow up (n=10).

Figure 1



The values of the control extremity were subtracted from the values of the affected extremity resulting in a difference between extremities for each and every time of examination as shown in table 3. The differences were compared between days for the various parameters. Circumference showed significant difference between day 0 versus day 7 and day 0 versus follow up. The area also showed significant difference between day 0 versus day 7 and day 0 versus follow up, as did the pain evaluation. Statistical results are shown in table 4. However, difference in temperature changed between day 0 versus day 3, day 1 versus day 3-4 and day 3-4 versus day 7 (table 5). CRP decreased significant between each time of measurement (table 6). The results of the colour measurements were complex and a proper way to compare the values for affected and unaffected extremity could not be found.

Table 3

Median of differences

	Day 0	Day 1	Day 3-4	Day 7	Follow up
Valid (n)	18	16	12	10	10
Temperature (C°)	3.25	2.70	1.63	0.68	0.50
Area (cm²)	1195	1265	750	995	0
Circumference (cm)	4.00	2.50	3.00	3.75	1.50
Measured data, median and (range).					
Pain Score	3◆ (0-10)	3 (0-10)	2.5 (0-9)	1.5 (0-9)	0 (0-3)
CRP (mg/L)	126.5 (0.6-342)	--	60.0 (8-245)	9.35 (5-125)	--

Median of differences between affected and control extremity and measured pain score and CRP.

◆(n=17)

Table 4

Comparison of differences for parameters and days.

Day	0 vs 1	0 vs 3-4	0 vs 7	0 vs follow up
Temperature	P=0.257	P<0.000*	P=0.002*	P=0.002*
Area	P=0.375	P=0.105	P=0.008*	P=0.004*
Circumference	P=0.381	P=0.102	P=0.012*	P=0.012*
Pain score	P=1.000	P=0.570	P=0.010*	P=0.012*

* Exact significance (two-tailed).

Table 5

Comparison of differences for temperature and days.

Day	0 vs 1	1 vs 3-4	3-4 vs 7	7 vs follow up
Temperature	P=0.257	P=0.006*	P=0.004*	P=0.469

* Exact significance (two-tailed).

Table 6

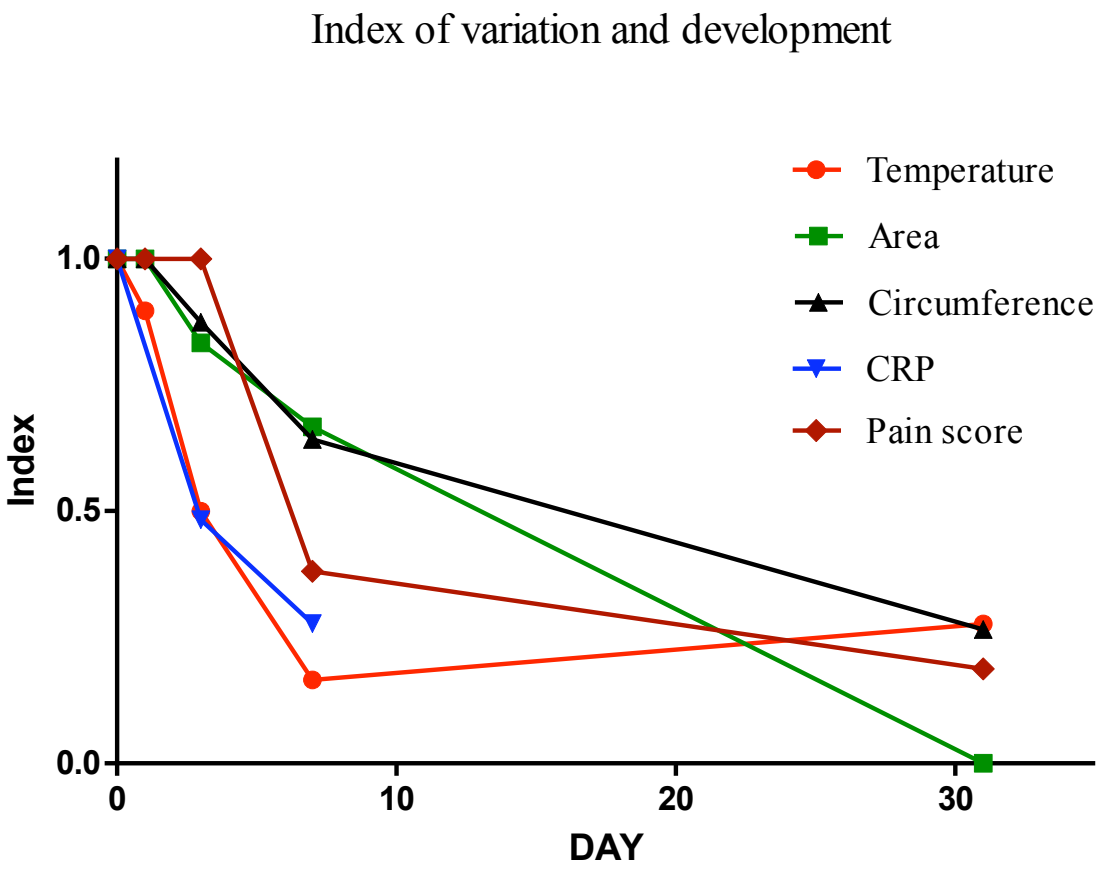
Comparison of CRP and days.

Day	0 vs 3-4	3-4 vs 7	0 vs 6-8
CRP	P=0.049*	P=0.031*	P=0.047*

* Exact significance (one-tailed).

To facilitate the visual comparison between parameters, the difference in temperature, circumference, area, pain score and CRP was indexed and given the value 1 at inclusion day shown in figure 2. In addition the original values in units are shown for the day of inclusion (index=1) in appendix 3.

Figure 2



Indexed differences between affected extremity and control
in temperature, area, cirfumerence and variation in CRP and pain score.

Discussion

Retrospective study

In this retrospective study, malignancy, lymph oedema, venous insufficiency and previous regional operation were found to be risk factors for recurrent erysipelas. There are only a few previous studies regarding risk factors for recurrent erysipelas [8, 9]. Malignancy was not reported as a risk factor in those studies, but our other findings consist with their results in general. We were not able to determine whether being overweight is a risk factor or not as previously found [9]. This was due to a great lack of information about height and weight in the medical records. We also suspect that data of *tinea pedis* is unreliable in our material as in the local status record it was rarely commented. The results for malignancy and regional operation may be connected with lymph oedema. Malignancy, for example breast cancer, often requires operation, which could lead to subsequent lymph oedema [13]. This connection could maybe explain why malignancy and regional operation were found to be risk factors for recurrent erysipelas. However, cases in both groups suffered from a variety of malignancies and regional operation included a wide range of procedures, and therefore the connection may be doubtful.

The higher rate of wounds in the SEE group was an unexpected finding. Disruption of the cutaneous barrier has been shown to be a great risk factor for erysipelas [6]. Perhaps the occurrence of a wound plays a less important role in the RE group for development of erysipelas, as they in general are more burdened with risk factors.

In this study, the RE group consisted of both patients with recurrent episodes within the study period and patients with a history of previous erysipelas before the study period. We found this division most logic since there are no criteria described for recurrent erysipelas regarding the time interval between each episode. There are most likely patients in the SEE group who in the future will suffer from recurrent episodes. These potential RE patients may falsely heighten and distort the distribution of risk factors in the SEE group. Nonetheless we found significant differences between the groups.

The strength of this study is the large number of cases and it is the largest one in Sweden investigating recurrent erysipelas.

The limitations of this study are several. It is a retrospective study and therefore the available information is restricted to medical records. Data for examined parameters were sometimes not to be found. Some patients were excluded due to medical records that were missing. The significant difference for regional operation between the groups may be questioned, as the definition for regional operation was arbitrary.

Prospective study

To our knowledge, the dynamics of inflammatory signs and clinical course of events in erysipelas is poorly described. The results of our measurements over time show a variation that most likely reflects the dynamic process and the clinical course of events in erysipelas. The general tendency for normalization between the affected extremity and the control extremity could be seen for all parameters during the acute phase and recovery period. In relation, CRP decreased rapidly from inclusion day to day 6-8, which correlates and supports our findings (figure 2).

Temperature was the most rapid parameter to approach normalization, showing less difference between the extremities already at day 3-4. The temperature was the only parameter to show significant difference between day 1 to 3-4 and 3-4 to 7 (table 5). Circumference, area, and self-estimated pain score showed no alteration until day 7. At the follow up examination, only the area and pain score had fully normalized, but temperature and circumference still showed a difference between the extremities. We consider three plausible theories. Firstly, the time for follow up examination was set too soon, perhaps there is a longer recovery period than 31 days (range 18 to 36 days). Secondly, there could be a normal variation regarding temperature and circumference between extremities, which have not been investigated in this study. Thirdly, that erysipelas could cause or be caused by regional lymph drainage impairment on the affected extremity, which has been a theory in previous studies [14, 15]. This could explain the differences between extremities.

From this study, we suggest that temperature is the most sensitive parameter when monitoring changes of inflammation within the first week. Circumference and area are still important parameters, but perhaps more blunt in describing the dynamics of the inflammatory process.

Colour measurement may contribute with valuable information, but due to the complexity of colour models, we found it hard to compare differences in our study.

We believe that the method used in this study is a new and sophisticated approach to observe the clinical course of events in erysipelas, especially when compared to less objective methods, such as describing length of hospitalization [16]. The most optimal treatment for erysipelas is yet to be found [17] and this method may contribute in future clinical studies of erysipelas when evaluating the effects of different treatment options. In this study it has not been investigated whether measured values contained prognostic information. It could be plausible that differences between extremities reflect the severity of erysipelas, for example, more severe cases may show greater differences.

However, the study design ought to be refined, if possible measuring the parameters in a shorter interval to survey the course of events in detail. Further studies are needed to evaluate possible prognostic use.

The strength of this innovative study is the prospective method. The examinations were performed standardized and by only two trained examiners. The subjects could be regarded as representative in the aspect of general characteristics.

The limitations of this study depend partly of the study design and the time of disposition. The selection of patients may not be representative for erysipelas in general as general practitioners treat many patients. However, the material could be representative for patients admitted to hospitals. There were patients dropping of during the study period, hence at the latter examination days less data were collected. A control group had made it possible to evaluate the normal variation of our parameters on healthy patients.

Conclusion

Erysipelas is a common infection that often reoccurs. Risk factors for patients with recurrent episodes have been identified as malignancy, lymph oedema, venous insufficiency and previous regional operation. A new way of evaluating the course of events in erysipelas by measuring skin temperature, circumference, area and pain score have been discovered. We suggest considering this method in future studies of erysipelas when evaluating treatment options as well as studying the clinical course of events and prognostic factors.

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Appendix

Appendix 1

The following parameters were registered for all patients:

Date, recurrency, age, sex, height, weight, outpatient/hospitalized, number of visits if outpatient, length of hospitalization, time from debute of symptoms to treatment, affected anatomical region and symptoms.

Initial values for: temperature, heart rate, blood pressure, respiratory rate and initial laboratory analysis: Hb, White blood cell count, CRP, platelet count and blood creatinine level.

Anticoagulant treatment, immunosupressive treatment, dermatologic diseases, tinea pedis, occurence of wounds, previous operations and types, CABG, previous malignancies and types, radiation therapy, arterial insufficiency, venous insufficiency, lymph oedema, diabetes, polyneuropathy, cardiovascular diseases, COPD, systemic diseases, penicillin drug reaction, antibiotic treatment, other medical treatment, blood culture, wound culture and complications.

Appendix 2

SIRS

Patient	Temperature (C˚)	Respiratory rate (breaths per minute)	Heart rate (beats per minute)	White blood cell count (10^9/L)	Total number of SIRS criteria
1	37,8	24	77	11,2	1
2	38	28	70	7,6	0
3	38,5	24	96	11,7	3
4	36,8	16	103	9,9	1
5	37	23	100	10,4	2
6	36,7	16	72	14,2	1
7	36,7	20	68	10,1	1
8	36	22	90	24,9	2
9	36,8	20	90	10,7	0
10	36,6	20	88	9,3	0
11	36,1	12	77	12,1	1
12	37,4	13	60	7,2	0
13	38,5	20	119	11,3	2
14	36,3	12	72	17,8	1
16	38,6	13	106	11,1	2
17	37,4	15	104	20,3	2
18	38,1	25	81	13	3
19	37,3	20	84	17	1

Appendix 3

Values at inclusion day

		Temperature (C°) affected extremity	Temperature (C°) control extremity	Temperature (C°) difference	Circumference (cm) difference	Area (cm²) difference
N	Valid	18	18	18	18	18
	Missing	0	0	0	0	0
Mean		36.1	33.2	2.9	4.9	1469
Median		36.2	33.1	3.3	4.0	1195
Minimum		33.3	28.8	-0.10◆	1.0	0
Maximum		38.3	35.9	5.1	22.0	5074
Percentiles	25	35.3	32.5	1.6	1.9	656
	50	36.2	33.1	3.3	4	1195
	75	37.3	34.1	4,1	5.3	1725

Difference refers to the values of the affected extremity minus the control extremity. ◆Affected lower than control.