Clinics in Oncology

Research Article
Published: 22 Jan, 2024

The Clinical Picture of Patients with the Ultra-Extremely Low and Extremely High Total Level of Serum IgE in the Material of the Provincial Hospital in Opole from 2013-2023

Warmuzińska A[1] and Tubek S[2]*

[1]Department of Imaging Diagnostics, Provincial Hospital in Opole, Poland

[2]Clinical Department of Hematology, Hematological Oncology and Internal Medicine, Provincial Hospital in Opole, University of Opole, Poland

Abstract

Aim: There is growing interest in the importance of low serum total IgE level in the recent years due to data showing its relation to immune system dysfunction syndromes and susceptibility to malignant neoplastic diseases.

Material and Method: Within the period 01/01/2013 and 31/08/2023, 13,907 determinations of total serum IgE were performed in the analytical laboratory of the Provincial Hospital in Opole. It should be noted that this research was not a routine one.

In the retrospective study presented here, it was decided to compare clinically two groups - those with the ultra-extremely low IgE level (<0.1 U/l), i.e. virtually undetectable, and the extremely high IgE (defined as >10,000 U/l).

Results: Women predominated in the group with ultra-extremely low IgE, men in the group with extremely high IgE. Clinically, respiratory conditions predominated in the first group, skin conditions in the second. Immunodeficiencies were more common in the first group, and likewise - to a lesser extent - oncological concerns.

Conclusion: We propose that the IgE values <0.1 U/l should be defined as ultra-extremely low (or undetectable), the values between 0.1 and 0.5 as extremely low, and the values between 0.6 and 2.0 as low. Further observations should identify the clinical features and risk of significant health concerns in these individual patient groups.

OPEN ACCESS

Correspondence:
Sławomir Tubek, Clinical Department of Hematology, Clinical Hematology and Internal Diseases, Voivodship Hospital, Institue of Medical Sciences, Opole University, Opole, Poland

Received Date: *22 Dec 2023*
Accepted Date: *15 Jan 2024*
Published Date: *22 Jan 2024*

Citation:
Warmuzińska A, Tubek S. The Clinical Picture of Patients with the Ultra-Extremely Low and Extremely High Total Level of Serum IgE in the Material of the Provincial Hospital in Opole from 2013-2023. Clin Oncol. 2024; 9: 2050.

ISSN: 2474-1663

Introduction

Interest in the significance of low total level of serum IgE level has been growing in the recent years due to data demonstrating its relationship with immune system dysfunction syndromes and susceptibility to neoplastic diseases [1-6]. In both cases, we are dealing with the broad concept of immune system dysfunction syndrome. High level of total IgE, in turn, are thought to improve prognosis in the selected groups of oncology patients. Furthermore, there are perspectives for the use of allegro-oncological insights in the oncological treatment processes and the side effects of immunotherapy of neoplastic diseases [7-10].

Knowledge of the differences in response to a treatment depending on the blood IgE level may have an impact on the individualization of the treatment for specific diseases [11].

The normal level of serum IgE is below 100 U/l - within the range of 2 (2.5) -100 U/l. In the literature, the values below 2.0 U/l to 2.5 U/l are considered the low or extremely low levels of total IgE. The extreme high levels are regarded the values above 1000 [1] or above 10,000 [1,6,12,13], or above – 20,000 [12,14] U/l.

As the group of individuals with the total IgE values below 2.0 U/l to 2.5 U/l may be clinically significantly heterogeneous due to a presence of tissue IgE, it is suggested that the IgE values below this limit should be more accurately determined [5].

In the retrospective study presented here, it was decided to compare clinically two groups - those with the ultra-extremely low level of IgE (<0.1 U/l), i.e. practically undetectable, and the extremely high IgE level (defined as >10,000 U/l).

Material and Method

Within the period 01/01/2013 until 31/08/2023, 13,907 determinations of the total IgE in the serum were performed in the analytical laboratory of the Provincial Hospital in Opole. It should be noted that this test was not a routine one.

According to the data referred to above, among these determinations, there were 377 results below 2.0 U/l, with 65 ultra-extremely low results (<0.1 U/l), i.e. practically undetectable. Whereas, results above the level defined as the extremely high - at the level above 20,000 U/l - 6 determinations, and at a level above 10,000 - 49 determinations, above 1,000 to 713.

We sought to compare the clinical picture of patients with the ultra-extremely low (undetectable) IgE (defined as <0.1 U/l) and the extremely high IgE (defined as >10,000 U/l).

Results

Bronchial hyperresponsiveness conditions - diagnosed during a hospitalization as bronchial asthma, chronic obstructive pulmonary disease or overlapping conditions of these conditions were counted together. This was a significant health problem in the group with the low serum IgE level - as indicated by the frequency of hospitalization at the pulmonology department, which is derived from the number of chest/lung CT scans performed in these patients. Only in this group was significant bronchial wall destruction - bronchiectasis – diagnosed (Table 1).

In the bibliography, there are far more frequent reports of extremely high serum IgE level (PubMed of 16/10/2023 - "extremely high IgE" phrase - 257) than of the low one - respectively "extremely low total level of serum IgE" - 18.

Below the brief clinical characteristics of both groups (Table 2).

Despite the relatively small size of the study groups, statistical analyses were conducted (Table 3).

The analyses were carried out using the IBM SPSS Statistics 29 software, which included the chi-square test of independence, the student's t test for independent samples and the Mann-Whitney U test. The significance level was taken as the threshold $\alpha=0.05$. In turn, the effect sizes obtained were interpreted according to the Cohen's proposal.

Firstly, we compared the significance of differences in age and sex among patients with both high and low IgE coefficients. Patients with a low coefficient were those whose IgE was below a value of

Table 1: The comparison of the two groups of patients - with the low IgE <0.1 U/l and the high IgE >10000 U/l (data in the comment from the statistical analysis presented below).

Chosen parameters	Low IgE <0.1 U/l	High IgE >10000 U/l	Comment
Quantity of determinations	65	49	
Number of patients	44	33	
Women	26–59.1%	6-18.2%	
Men	18–40.9%	27–81.8%	p<0.001
Immune system dysfunction syndrome*	40–90.9%	26–78.8%	undetermined
Bronchiectasis	10–22.7%	0	
Neoplastic disease	12– of which 6 - lymphoma 27.5/13.6%	5– of which 3 - lymphoma 15.1/9.1%	undetermined
Bronchial asthma/COPD**	10-22.7%	10–30.3%	undetermined
AD***	2–4.5%	16–48.5%	p<0.001
psoriasis	1	3	
sarcoidosis	2	0	
urticaria	1	0	
coeliac disease	3	0	
RA****	3	2	
Inflammatory bowel disease (IBD)	1 (Crohn's disease)	1 (ulcerative colitis)	
Wagener's granuloma	3	0	
Diagnosed CVID*****	8 (antibody deficiency)	1 (lymphocyte deficiency)	
Scabies	0	7	
Pulmonary CT scan performed	29–65.9%	5–15.1%	
PD#	25	3	p<0.001
DD#	2	26	p<0.001
HD#	7	3	
Other entity#	10	1	

*immune system dysfunction syndrome = broad term including diagnosed immunodeficiencies, allergic diseases, autoimmune diseases, chronic inflammatory conditions, frequent recurrent infections, neoplastic diseases; ** chronic obstructive pulmonary disease; ***atopic dermatitis; **** rheumatoid arthritis; *****common-variable-immunodeficiency; # Department of the most frequent hospitalizations; PD: Department of Pulmonology; DD: Department of Dermatology; HD: Department of Hematology; other unit: Department of Internal Diseases, Hospital Outpatient Clinics

Table 2: Characteristics of individual patients with the ultra-extremely low level of serum IgE<0.1 U/l.

S.No	Sex/age at the time the ultra-low level of IgE was determined (cumulatively)	Health problems according to medical records	Main (most frequent)* place of hospitalisation/treatment
1	K 18	AD, allergic rhinitis	DD
2	K 20	Bronchial asthma	PP
3	K 22	CVID, coeliac disease	HD, PG
4	K 23	CVID, Crohn's disease	HD
5	K 23	CVID, ataxia-telangiectasia syndrome, cholestatic hepatitis, mental retardation, death at the age of 24 due to pneumonia	HD
6	K 34	coeliac disease	-
7	K 36	CVID, CPD, sinusitis, bronchiectasis, cryptogenic organizing pneumonia - CPD, diffuse large B-cell lymphoma of the stomach, tonsillectomy, recurrent conjunctivitis, mental retardation	HD/PD
8	K 37	Coeliac disease, Fe deficiency	PG
9	M 41	CVID, recurrent bronchitis	HD
10	M 41	Sarcoidosis, COPD, kidney stones,	PD
11	K 43	CVID, recurrent respiratory infections	HD
12	K 47	Bronchial asthma/COPD, aortic defect	PD
13	M 50	Leukopenia under observation	PH
14	M 53	Psoriasis, interstitial lung lesions, collagenosis under observation	DD/PD
15	M 55	Sarcoidosis, psoriasis, fibrotic lung lesions	PD
16	K 54	Wegener's granulomatosis, bronchial asthma, chronic renal failure, dialysis therapy	HD
17	K 59	Good's syndrome, CVID, bronchiectasis	HD
18	M 61	Urticaria	DD
19	K 63	Chronic bronchitis, psoriasis	DD
20	K 64	Wegener's granulomatosis, bronchiectasis	PD
21	M 65	CLL, Wegener's granulomatosis, bronchiectasis, chronic bronchitis, secondary immunodeficiency	HD/PD
22	M 65	Bronchial asthma/COPD, bronchiectasis	PD
23	M 65	Pulmonary fibrosis, autoimmune cholangitis, cirrhosis, type 2 diabetes, AITD	PD
24	M 66	Pleural abscess, IE in medical history, recurrent bronchitis	PD
25	K 66	Lymphoma, CLL, pneumonia, type 2 diabetes, lymphoma infiltration in the lungs, circulatory failure, atherosclerosis	PD/HD
26	M 67	CVID, bronchiectasis, post PTCA, type 2 diabetes, ulcerative colitis	HD
27	M 67	COPD, medical history of kidney cancer, chronic renal failure, dialysis,	PD
28	M 70	CLL, suspected ANL, recurrent bronchitis, lung infiltrates,	PD/HD
29	M 70	Right lung tumour, bladder cancer, CPOD, type 2 diabetes, bronchiectasis,	PD
30	K 70	interstitial pneumonia, RA, COPD, bronchiectases	PD
31	K 71	Pneumonia post COVID-19,	PD
32	M 71	Lung tumour, CNS metastasis, atherosclerosis,	PD
33	K 72	interstitial pneumonia,	PD
34	M 73	Bronchial asthma/COPD, atherosclerosis, chronic pancreatitis	PD
35	K 75	Glandular carcinoma, lung cancer, hypertension, type 2 diabetes	PD
36	K 75	Bronchial asthma/COPD, type 2 diabetes, HA, pneumonia, bronchiectasis	PD
37	M 76	Right lung adenocarcinoma, bronchiectasis, CML within observation,	PD
38	K 77	Bronchial asthma/COPD	PP
39	M 78	B-cell CLL, secondary immunodeficiency, bronchial asthma, rhinitis, atherosclerosis,	HD/PD
40	K 81	Lung cancer, CNS metastases, RA,	PD
41	K 83	CLL, bronchiectasis, secondary immunodeficiency, allergic rhinitis	PD/HD
42	K 86	respiratory infection	PD
43	K 87	Bronchial asthma, right lung cyst, RA,	PD
44	K 92	Pneumonia, COPD, type 2 diabetes, atherosclerosis	PD

*- at the Provincial Hospital in Opole - department of the most frequent hospitalizations; PD: Pulmonology Department; DD: Dermatology Department; HD: Hematology Department; POC: Pulmonology Outpatient Clinic; HOC: hematology Outpatient Clinic; AD: Atopic Dermatitis; CVID: Common Variable Immunodeficiencies; CLL: Chronic Lymphocytic Leukemia; AITD: Autoimmune Thyroiditis; CML: Chronic Myeloid Leukemia; RA: Rheumatoid Arthritis; DM t2: type 2 Diabetes

0.10. In turn, among patients with the higher IgE level, the coefficient ranged from a few to several thousand (M=17391.70; Mdn=14664.00; SD=9318.12). The Tables 1 and 2 show the results for the analyses of age differences, while the Table 3 shows the variations by sex (Table 4, 5).

The analyses conducted on the age variation of the compared samples, showed that there were no significant differences using both the mean (Table 1) and median (Table 2). The effect size measures obtained, however, varied at the level of a weak difference between the mean (d>0.20) or median (r>0.10), suggesting that those with the high IgE level may have been slightly younger compared to patients with the low IgE severity. However, this effect was very weak and within the statistical error limit. The final decision was made that there were no differences between the groups as regards an age (Table 6).

The analyses conducted confirmed a statistically significant sex variation in patients with different IgE severity. It turned out that patients with the high IgE index were significantly more likely to be men, who accounted for more than three quarters of the sample of patients with the high IgE severity. In contrast, women predominated among patients with the low IgE level; however, the difference in proportions was less than 20 percent. The effect size measure obtained, Yul's φ, indicated a moderate strength of the relationship between the IgE level and patient's sex.

In a further step, the variation of patients by place of hospitalization was presented, followed by the variation of conditions present according to the IgE level. For the variation in place of hospitalization, the Fisher-Freeman-Halton exact test with the Bonferroni correction for pairwise comparisons was used as an alternative to the Chi-square test of independence when observing a low expected value and multiple categories compared, and the results are presented in the Figure 1. For the analysis of differences in prevalent conditions, the Chi-square coefficient or Fisher's exact test was used when low expected values were observed in more than 20% of cells, and logistic regression was used to trace the interaction between the IgE level and patient's sex due to the observation of significant differences in sex count. The results for the differentiation of conditions are presented in the Table 4.

The analyses of differences as regards patients' hospitalization department showed statistically significant differences (p<0.001; V=0.77), who's the Cramer's V coefficient effect size indicated a very strong relationship between hospitalization site and the IgE level. Pairwise comparisons using the Bonferroni correction for multiple comparisons showed that patients with the low IgE were 56% more likely to be at the pulmonology department and 18.2% more likely to be at the hematology department. In contrast, patients with the high IgE level were significantly more likely (72%) to be admitted to the dermatology department. No differences were found in the admission of patients to other departments (Table 7).

The results, presented in the Table 4, showed that there was no statistically significant interaction between sex and IgE level. This means that the obtained significance coefficient p values for the main effect of IgE were sufficient to assess the presence of differences. Observing the main effects, it was found that only in the case of AD there were statistically significant differences, which were characterized by a moderate level of association between the IgE level and the occurrence of AD, as confirmed by the magnitude of Yul's φ coefficient. It appeared that patients with the high IgE level were more than ten times more likely to have a confirmed diagnosis of AD (48.5%) compared to patients with the low IgE (4.5%). In case of other diseases, the incidence was similar in both groups, based on the data collected.

Discussion

The extremely low IgE and the extremely high IgE are two sides of the same coin [15] - immune dysfunction syndrome (immune system dysfunction, immune system dysregulation). How do they differ, however (Table 1)?

Two extreme groups were initially selected for the comparison, with the ultra-extremely low IgE level of <0.1 kU/l (i.e. virtually undetectable) and the extremely high IgE level of >10,000 kU/l. Under this assumption, the study groups were compared quantitatively, while also meeting the assumed criterion of extreme results.

At first glance, the groups differ in the place of hospitalization, which indicates the leading clinical issue - hospitalization in the pulmonology department, respiratory lesions - with the ultra-extremely low IgE and hospitalization in the dermatology department, skin lesions - with the extremely high IgE.

The group with the extremely high level of serum IgE was dominated by men, the group with the ultra-extremely low IgE by women. Perhaps this is related to baseline physiologically higher IgE values in men [1]. The mechanisms for this phenomenon are not clear, perhaps there is a higher baseline capacity for immunosuppression in the female sex due to a biological role in reproductive function (pregnancy).

For the diagnosis of AD (atopic dermatitis), the difference in incidence in the two groups was statistically significant - the incidence was higher in the group with the extremely high level of serum IgE. From the point of view of the role of IgE, this should not seem strange. What may seem strange, however, is the difference between the group with the ultra-extremely low IgE currently described and the group from the literature [15] defined as IgE<2.0 kU/l. In our group with the ultra-extremely low IgE, urticaria occurred in only one patient and AD in two, which was much more common in the earlier study [15]. The authors of this publication themselves, when describing the frequent occurrence of skin lesions in patients with the low IgE similar to those with the high IgE, draw attention to the possible heterogeneity of the group they describe, suggesting the need to differentiate it according to the specific IgE values below 2 kU/l, as a serum IgE deficiency so defined does not imply a tissue IgE deficiency [5,15], which may be at sufficient levels to stimulate mast cells. A deficiency of the tissue IgE can occur with the virtually undetectable serum IgE level [5] - and then the skin lesions are virtually absent, as in the case of the group under study by us.

The diagnosed primary immunodeficiency syndrome was present in 8 (18.2%) patients in the ultra-extremely low IgE group (including Good's syndrome, ataxia-telangiectasia syndrome, among others) and in 1 (0.03%) patient in the extremely high IgE group (Netherton syndrome). Similarly, a broad immune dysfunction syndrome - defined as the occurrence of allergies, autoimmunity, frequent, recurrent, severe infections, the appearance of neoplastic diseases - was present in 40 (90.9%) in the first and 26 (78.8%) in the second group of patients.

A diagnosed neoplastic disease was present in 12 (27.5%) patients

Table 3: Characteristics of individual patients with the extremely high level of serum IgE >10000 U/l.

S. No	Sex/age at the time the ultra-low level of IgE was determined (cumulatively)	Health problems according to medical records	Main (most frequent)* place of hospitalisation/treatment
1	M 19	AD	DD
2	K 23	AD	DD
3	M 20	AD, bronchial asthma	DD
4	M 26	AD, erythroderma, treated biologically - baricitinib, family medical history - father - psoriasis	DD
5	M 27	AD, Besner's prurigo diathesis, biologically therapy- dupilumab	DD
6	M 29	AD	DD
7	K 31	AD, Besner's prurigo diathesis, liver hemangioma - 40 mm diameter	DD
8	M 33	AD	DD
9	M 38	AD, bronchial asthma, AITD	DD
10	M 39	AD	DD
11	M 46	Erythroderma, AD, congenital fish scales, ALK+ anaplastic large cell lymphoma - skin infiltration, immunodeficiency, cytotoxic and NKT lymphocyte deficiency, right testicular seminoma, hepatitis C, death, - retrospective - Netherton Syndrome	DD/HD
12	M 53	AD, erythroderma, eczema of the lower legs, chronic pancreatitis, splenic artery pseudoaneurysm, esophageal varices, necrosis of the transverse colon, death	DD, SD, ICU
13	M 54	Neck and mediastinal lymphadenopathy - without a final diagnosis of a specific neoplastic disease during hospitalization, venous thrombosis of the lower extremities, COPD, atherosclerosis, myocardial infarction	PD
14	M 56	Psoriasis vulgaris, erythroderma, suspected lymphoma, generalized lymphadenopathy, bronchial wall thickening, psoriatic arthritis, bronchial asthma, RA	DD, PD
15	M 58	Right lung tumor, lymphadenopathy, COPD, emphysema - large emphysematous blisters up to 75 mm in diameter, circulatory failure	PD
16	M 60	AD, bronchial asthma	AR
17	K 60	AD, bronchial asthma, hypoacusis, pulmonary embolism, hypertension	DD
18	M 61	Scabies	DD
19	M 64	AD, contagious ecthyma, CTCL with Sezary's cells (Sezary syndrome), lymphocytic vasculitis (ICD-10 - C84)	DD
20	M 65	Prurigo nodularis, lymphomatoid papulosis under observation, histopathology - angiokeratoma, suspected Fabry disease	DD
21	M 65	Psoriasis, lymphocytic infiltration in the skin, chronic renal failure, alcohol use syndrome, nephrotic syndrome, COPD, type 2 diabetes	DD
22	M 66	Psoriasis, cutaneous lymphoma - suspicion, metabolic syndrome	DD
23	M 66	Suspected hyper-IgE syndrome, AD since childhood, bronchial asthma, eosinophilia, lymphadenopathy for diagnosis, suspected lymphoma, death before lymphadenopathy diagnostics	DD, PD, HD
24	M 67	Scabies	DD
25	K 68	Skin erythematous conditions, ulcerative colitis, AITD, chronic renal failure, dialysis, bronchial asthma, RA, osteoporosis, circulatory failure	DD, IDD, PD
26	M 69	AD, erythroderma	DD
27	M 70	Severe bronchial asthma of the eosinophilic type, bronchial wall thickening (on the CT scan), chronic sinusitis, atherosclerosis	PD, HD
28	M 72	COPD, pneumonia, circulatory failure	PD
29	K 82	Scabies, bronchial asthma, type 2 diabetes, obesity, circulatory insufficiency, nodular prurigo	DD
30	M 82	Scabies	DD
31	M 83	Scabies, erythroderma, atrial fibrillation	DD
32	K 85	Scabies, eosinophilia	DD
33	K 89	Scabies	DD

* - at the Provincial Hospital in Opole - department of the most frequent hospitalizations; PD: Pulmonology Department; DD: Dermatology Department; HD: Hematology Department; POC: Pulmonology Outpatient Clinic; HOC: Hematology Outpatient Clinic; AD: Atopic Dermatitis; CVID: Common Variable Immunodeficiencies; CLL: Chronic Lymphocytic Leukemia; AITD: Autoimmune Thyroiditis; CML: Chronic Myeloid Leukemia; RA: Rheumatoid Arthritis; DM t2: type 2 Diabetes

in the ultra-extremely low IgE group (of which six had lymphoma - 13.6%) and in five (15.1%) patients in the extremely high IgE group (of which three had lymphoma - 9.1%), showing no statistical difference between the study groups.

Similarly in the case of obstructive airway conditions - bronchial asthma and CPOD (22.7 *vs.* 30.3%), with bronchiectasis found only in the group with ultra-extremely low IgE (22.7%), which may have been associated with a greater propensity for bacterial superinfection

Table 4: Differentiation of mean age of patients according to the IgE level using the student's t test for independent samples.

Dependent variable	Low IgE (*n*=44)		High IgE (*n*=33)		*t*	*df*	*p*	95% *CI*		*Cohen's d*
	M	SD	M	SD				LL	UL	
Age	59.55	19.71	55.33	20.52	0.91	75	0.365	-4.99	13.41	0.21

Annotation: n: number of observations; M: Mean; SD: Standard Deviation; t: value of test statistic; df: degrees of freedom; p: statistical significance; CI: Confidence Interval for the difference between means; LL and UL: Lower and Upper Limits of the confidence interval; Cohen's term d - strength of effect index

Table 5: Differentiation of median age of patients according to the IgE level using the Mann-Whitney U test for independent samples.

Dependent variable	Low IgE (*n*=44)		High IgE (*n*=33)		*U*	*Z*	*p*	*r*
	Mdn	*IQR*	*Mdn*	*IQR*				
Age	65.5	29	60	33	618	-1.11	0.266	0.13

Annotation: n: number of observations; Mdn: Median; IQR: Interquartile Range; Z: value of test statistic; p: statistical significance; r: strength of effect index

Table 6: Differentiation of the sex index of patients according to the IgE level.

Test variable	Low IgE		High IgE		*p*	φ
	n	%	*n*	%		
Men	18	40.90%	26	78.80%	0.001	0.38
Women	26	59.10%	7	21.20%		

Annotation: n: number of observations; p: statistical significance; φ: strength of effect index

Table 7: Differentiation of the proportion of conditions among patients according to the IgE level and the interaction of sex with the IgE level.

Variable	Response	Low IgE		High IgE		*p* IgE	φ	*p* Sex x IgE	*OR* [95% CI]
		n	%	*n*	%				
Asthma	None	34	77.30%	23	69.70%	0.453	0.09	0.226	4.39 [0.40; 48.08]
	Occurred	10	22.70%	10	30.30%				
Neoplastic disease	None	32	72.70%	29	87.90%	0.105	0.18	0.229	5.62 [0.34; 93.24]
	Occurred	12	27.30%	4	12.10%				
Lymphoma	None	38	86.40%	30	90.90%	0.725	0.07	1	—
	Occurred	6	13.60%	3	9.10%				
Immune system dysfunction syndrome	None	4	9.10%	7	21.20%	0.19	0.17	0.41	3.99 [0.15; 107.22]
	Occurred	40	90.90%	26	78.80%				
AD	None	42	95.50%	17	51.50%	<0.001	0.51	1	—
	Occurred	2	4.50%	16	48.50%				

Annotation: n: number of observations; p: statistical significance; φ: strength of effect index; OR: Odds Ratio represented by Exp(B); 95% CI: Confidence Interval of odds ratio with 95% probability of true result

in the bronchi, and its detection with more frequent chest CT in this group.

According to population-based observations, the low IgE level is thought to predispose to neoplastic processes [3-7], hence the interest in the question of whether immunotherapies with anti-IgE antibodies could potentially lead to an increased incidence of neoplastic diseases in the group treated [8].

In the retrospectively analyzed groups - neoplastic processes were present in both, and when scabies was excluded as a cause of the extremely high level of serum IgE - the difference between the groups decreases (from 27.5% *vs.* 15.1% to 27.5% *vs.* 19.2%). Perhaps the differences were statistically significant with a much larger group size.

Autoimmune problems were present in both groups, qualitatively different, but without the possibility of statistical analysis. In the group with the ultra-extremely low IgE, autoimmune problems such as sarcoidosis or granulomatosis with polyangiitis were observed, while in the group with the extremely high IgE, psoriasis was observed more frequently.

While our study has some limitations due to its retrospective nature (including not routinely testing the serum IgE levels of all inpatients or outpatients, regardless of the reason for hospitalization or advice), it is important to separate from the group with the extremely low IgE (<2.0-2.5 kU/l) - the group with the ultra-low IgE (<0.1), which appears to be suggested in the earlier studies [1,15].

For the purpose of more accurately determining the prognostic utility of the low IgE level - as a risk factor for immune dysfunction with a tendency to autoimmune phenomena or the appearance of neoplastic diseases [1-10,15-18], methods for the more precise determination of serum IgE below the limit of 2 kU/l should be routinely introduced, as suggested previously. In our retrospective material, such determinations took place, which will enable a clinical assessment in the designated few ranges between <0.1 and <2.5 kU/l (in increments of 0.5) and, despite the shortcomings of retrospective observation, will perhaps become the subject of a subsequent paper.

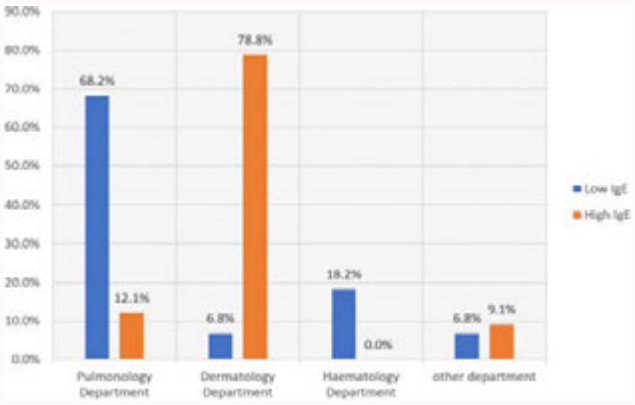

Figure 1: Differentiation of the place of hospitalization depending on the IgE level.
Key: X axis: Pulmonology Department, Dermatology Department, Hematology Department, other department. Y axis: Low IgE, High IgE

Furthermore, as indicated by studies, skin tests would additionally need to be performed, which may additionally indirectly indicate the insufficient levels of tissue IgE to stimulate mast cells [15-18].

In summary, in our opinion, in order to make future observations comparable and to determine the relevance of their results, the levels of IgE deficiency - both laboratory and clinical ones - should be defined to provide a basis for inferring the degree of immune system dysregulation and the degree of immunodeficiency.

We propose that the IgE values <0.1 U/l should be defined as the ultra-extremely low (or undetectable), values between 0.1 and 0.5 as the extremely low and values between 0.6 and 2.0 as low ones. Skin tests used for allergy diagnosis or skin reaction to a polysaccharide vaccine [17,18] would complement the clinical assessment of the low IgE level and its prognostic significance, especially in combination with the patient's family medical history.

References

1. Patel MB, Smith JK, Chi DS, Krishnaswamy G. Regulation and dysregulation of immunoglobulin E: A molecular and clinical perspective. Clin Mol Allergy. 2010;8:3.
2. Lawrence MG, Palacios-Kibler TV, Workman LJ, Schuyler AJ, Steinke JW, Payne SC, et al. Low serum IgE is a sensitive and specific marker for Common Variable Immunodeficiency (CVID). J Clin Immunol. 2018;38(3):225-33.
3. Matricardi PM. The very low IgE producer: Allergology, genetics, immunodeficiencies, and oncology. Biomedicines. 2023;11:1378.
4. Ferastraoaru D, Bax HJ, Bergmann C, Capron M, Castells M, Dombrowicz D, et al. AllergoOncology: Ultralow IgE, a potential novel biomarker in cancer— A position paper of the European Academy of Allergy and Clinical Immunology (EAACI). Clin Transl Allergy. 2020;10:32.
5. Ferastraoarua D, Jordakievab G, Jensen-Jarolim E. The other side of the coin: IgE deficiency, a susceptibility factor for malignancy occurrence. World Allergy Organ J. 2021;14:100505.
6. Ferastraoaru D, Rosenstreich D. IgE deficiency and prior diagnosis of malignancy: Results of the 2005-2006 National Health and Nutrition Examination Survey. Ann Allergy Asthma Immunol 2018;121(5):613-8.
7. Wang A, Wan P, Hebert JR. Atopic allergic conditions and prostate cancer risk and survival in the Multiethnic Cohort study. Br J Cancer. 2023;129:974-81.
8. McCraw AJ, Chauhan J, Bax HJ, Stavraka C, Osborn G, Grandits M, et al. Insights from IgE immune surveillance in allergy and cancer for anti-tumour IgE treatments. Cancers. 2021;13:4460.
9. Di Gioacchino M, Della Valle L, Allegra A, Pioggia G, Gangemi S. AllergoOncology: Role of immune cells and immune proteins. Clin Transl Allergy. 2022;e12133.
10. Fereydouni M, Motaghed M, Ahani E, Kafri T, Dellinger K, Metcalfe DD, et al. Harnessing the anti-tumor mediators in mast cells as a new strategy for adoptive cell transfer for cancer. Front Oncol. 2022;12:830199.
11. Guida G, Bertolini F, Carriero V, Levra S, Sprio AE, Sciolla M, et al. Reliability of Total Serum IgE Levels to Define type 2 High and Low Asthma Phenotypes. J Clin Med. 2023;12:5447.
12. Wollenberg A, Thomsen FS, Lacour JP. Targeting immunoglobulin E in atopic dermatitis: A review of the existing evidence. World Allergy Organ J. 2021:14:100519.
13. Scala E, Condorelli AG, Scala A, Caprini E, Didona B, Paganelli R, et al. IgE sensitization profile in patients with Netherton syndrome. Int Arch Allergy Immunol. 2022;183(12):1291-6.
14. Zhang Q, Boisson B, Béziat V, Puel A, Casanova JL. Human hyper-IgE syndrome: Singular or plural? Mamm Genome. 2018;29(7-8):603-17.
15. Picado C, García-Herrera AP, Hernández-Rodríguez J, Vlagea A, Pascal M, Bartra J, et al. Skin manifestations in patients with selective immunoglobulin E deficiency. J Clin Med. 2022;11:6795.
16. Levin TA, Ownby DR, Smith PH. Relationship between extremely low total serum IgE levels and rhinosinusitis. Ann Allergy Asthma Immunol. 2006;97(5):650-52.
17. Ferastraoaru D, Goodman B, Rosenstreich D. Higher rates of malignancy in IgE deficient patients with negative immediate hypersensitivity skin tests. Ann Allergy Asthma Immunol. 2021;126:194-5.
18. Noonan E, Streasser MD, Makin T, Williams A, Al-Hazaymeh A, Routes JM, et al. Impaired response to polysaccharide vaccine in selective IgE deficiency. J Clin Immunol. 2023;43(6):1448-54.