Serum immunoglobulins in non-Hodgkin's lymphoma patients

Planinc-Peraica, Ana; Ostojić Kolonić, Slobodanka; Radić-Krišto, Delfa; Dominis, Mara; Jakšić, Branimir

Source / Izvornik: **Collegium Antropologicum, 2010, 34, 407 - 411**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:464851

Coll. Antropol. **34** (2010) 2: 407–411
Original scientific paper

Serum Immunoglobulins in non-Hodgkin's Lymphoma Patients

Ana Planinc-Peraica[1,3], Slobodanka Ostojić Kolonić[1,3], Delfa Radić-Krišto[1], Mara Dominis[2,3] and Branimir Jakšić[1,3]

[1] Department of Medicine, »Merkur« University Hospital, Zagreb, Croatia
[2] Department of Clinical Pathology, »Merkur« University Hospital, Zagreb, Croatia
[3] University of Zagreb, School of Medicine, Zagreb, Croatia

A B S T R A C T

Serum proteins and immunoglobulin (Ig) findings in 119 non-Hodgkin's lymphoma (NHL) patients were analysed. Out of them 96 (81%) patients had B non-Hodgkin lymphoma (B-NHL), and 23 (19%) T-NHL. Indolent type of NHL was more frequent (77 patients, 65%), then aggressive type of NHL (42 patients, 35%). Most patients had normal serum protein concentration, the increased protein concentration was seen in 17% of patients while decreased concentration was noticed in 7% of patients. Hypoalbuminaemia was more frequent (43%) then hyperalbuminaemia (1%). In contrast to albumin, low levels of other protein fractions (alpha1-, alpha2-, and beta-globulin) were rather rare (0.6%, 4%, and 3% of patients, respectively) and high levels were frequent (23%, 37%, and 8%, respectively). Polyclonal hyperimmunoglobulinaemia was more frequent finding than hypoimmunoglobulinaemia. In 29% patients higher IgG level and in 25% patients higher IgA level were found. IgM hypoimmunoglobulinaemia (22%) was more frequent than IgG (11%) and IgA (8%) hypoimmunoglobulinaemia. M-spike in serum protein electrophoresis was found in 11 (7%) patients. The statistically significant association was not found between serum Ig concentration and lymphoma malignancy grade as well as between serum Ig concentration and immunologic origin of lymphoma. T-NHL patients have more often IgA concentration level above or under normal values than B-NHL patients ($p<0.05$).

Key words: *non-Hodgkin's lymphoma, serum immunoglobulins, serum proteins*

Introduction

Non-Hodgkin's lymphomas (NHL) are tumours of the immune system causing very often the alteration of immune function in affected patients which is not surprising because one function of the immune system is the production and secretion of immunoglobulin molecules. Immunoglobulin production depends on normal B- and T-cell interactions and may be estimated by measuring serum immunoglobulin levels[1]. Although there are evidence that altered immunity is a risk factor for development of non-Hodgkin lymphoma, the analysis of immune function after the diagnosis of NHL do not show the immunological conditions before the development of lymphoma[2]. The papers with laboratory findings in patients with NHL are rather scarce. Although there are some studies dealing with this problem it is hard to compare data from these studies because some old classifications of NHL were used[3].

The aim of the present study was to analyze serum immunoglobulin levels in NHL patients in order to find out whether certain histological types could be characterised by the particular immmunoglobulin profile.

Patients and Methods

In retrospective study from 5 years period serum immunoglobulin levels were analysed in 119 consecutive untreated adult patients with NHL in Department of Medicine, »Merkur« University Hospital in Zagreb, Croatia. Diagnosis of NHL was established immunohistologically on samples of lymph node, spleen, or other tissues. Patient with haematological criteria for acute lymphatic or chronic lymphocytic leukaemia were excluded from this study.

Received for publication November 24, 2009

According to the WHO classification[4] all patients were grouped as indolent or aggressive type, and according to lymphoma cells origin in T- and B-NHL groups, respectively. Serum protein electrophoresis was performed on acetate cellulose Cellogen, Chemtron. For immunoglobulin quantitation radial immunodiffusion method with Tri-Partigen plates Behringwerke and heterologous anti-human immunoglobulin antisera were used. Serum immunoglobulin findings at diagnosis were compared among different histologic and immunologic groups. Null hypothesis was tested (at alpha=0.05) using the χ^2 for frequency tables, one-way analysis of variance and Kruskal-Wallis rank test.

Results

Clinical and morphologic characteristics of NHL patients are shown in Table 1. Out of 119 patients in 96 (81%) patients B-NHL was diagnosed, and in 23 (19%) T-NHL. Indolent type of NHL was more frequent (77 patients, 65%), then aggressive type of NHL (42 patients, 35%). Median age was 56 years, range 15 to 88 years. Male to female ratio was 1.6:1.

Summarized laboratory findings of all our patients are presented in Table 2. Although median of serum protein and immunoglobulin levels are in normal range, some patients had extremely low or high value of these parameters.

TABLE 1
NON-HODGKIN'S LYMPHOMA PATIENTS' CHARACTERISTICS

Age	Median	56 y
	Range	15–88 y
Sex	Men	74 (62%)
	Women	45 (38%)
	M:F	1.6:1
Histology (grade of malignancy)	Indolent	77 (65%)
	Aggressive	42 (35%)
Immunological type	T-NHL	23 (19%)

TABLE 3
PATIENTS DISTRIBUTION ACCORDING TO TOTAL PROTEIN, ALPHA1-, ALPHA2-, AND BETA2-GLOBULIN CONCENTRATION

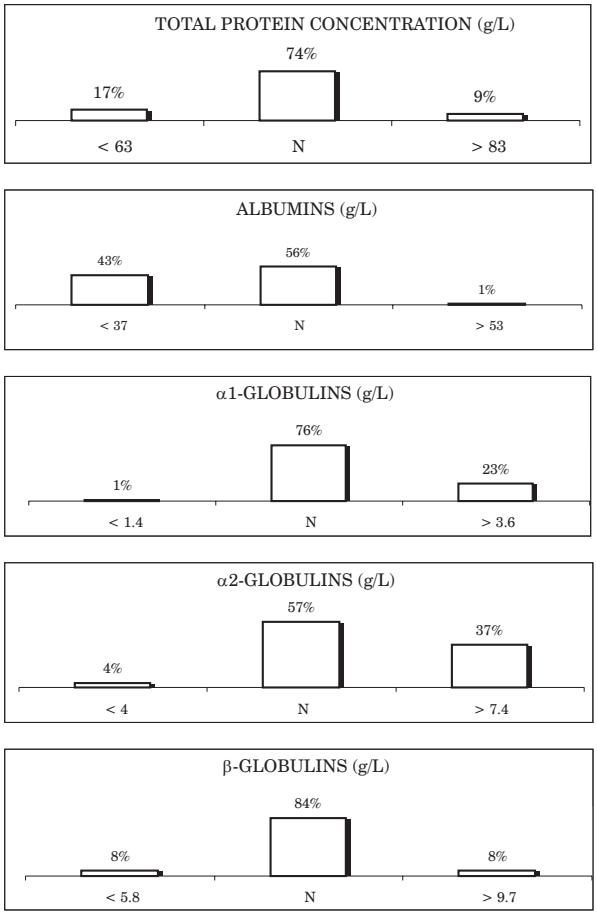
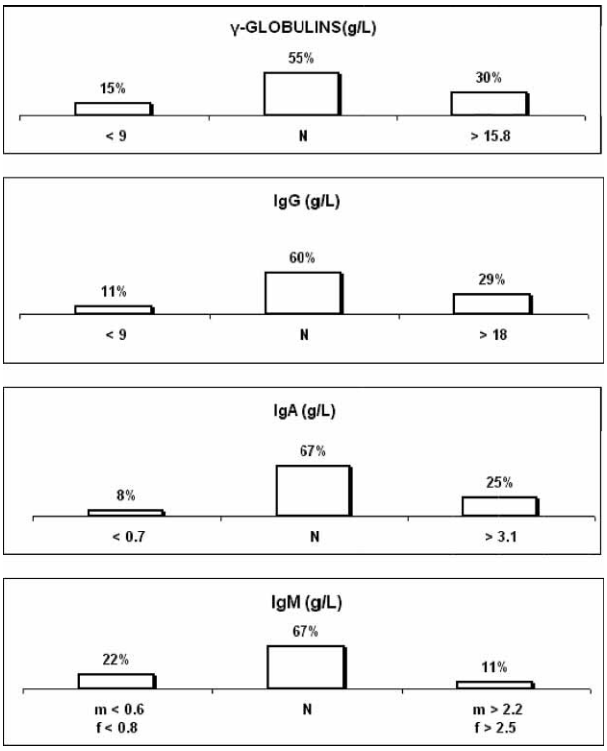


TABLE 2
SERUM PROTEINS AND IMMUNOGLOBULINS IN NHL PATIENTS AT DIAGNOSIS (N=119)

Variables	$\overline{X}$	SD	Min	Max	Med	Normal values
Totpr (g/L)	70.8	9.27	45	108	71	64–82
Alb (g/L)	30.09	5.87	19.2	50.1	39.4	36–52
α_1 (g/L)	2.91	0.89	1.2	6.7	2.7	1.5–3.5
α_2 (g/L)	6.98	2.11	1.9	14.8	6.6	4.1–7.3
β (g/L)	7.72	1.42	3.9	13.1	7.9	5.8–9.6
γ (g/L)	15.05	7.16	5.5	57.6	13.3	10.0–15.7
IgG (g/L)	16.46	8.77	1.2	60	14.3	10.0–17.0
IgA (g/L)	2.83	2.99	0.1	31.1	2.4	0.8–3.0
IgM (g/l)	1.32	0.93	0.2	5.8	1	0.7–2.4

$\overline{X}$ – mean value, SD – standard deviation, Max – maximum value, Min – minimum value, Med – median, Totpr – total serum protein, Alb – albumin, α_1 – alpha$_1$-α_2 – alpha$_2$$\beta$– beta-globulin, γ – gama-IgG – immunoglobulin G, IgA – immunoglobulin A, IgM – immunoglobulin M

TABLE 4
PATIENTS DISTRIBUTION ACCORDING TO SERUM GAMMA-GLOBULINS AND IMMUNOGLOBULIN G, A AND M



Distribution of patients with aberrant findings of serum proteins, immunoglobulin G, A, and M is presented as percentage of all patients with NHL (Table 3). Most patients had normal concentrations of the measured parameters. Hypoproteinaemia was found in 17% patients, and hyperproteinaemia in 9% patients. Hypoalbuminaemia was more frequent (43%) than hyperalbuminaemia (1%). Contrary to albumins, low serum concentrations of alpha1-globulin, alpha2-globulins, and beta-globulin fraction were found in 0.6%, 4%, and 3% of patients, respectively. High serum concentrations of alpha1-, alpha2-, and beta-globulin fractions were more frequent (23%, 37%, and 8%, respectively) in our NHL patients.

Hypogammaglobulinaemia was found in 15%, and hypergammaglobulinaemia in 30% NHL patients at diagnosis (Table 3). In contrast to IgM with higher frequency of patients with hypogammaglobulinaemia (22%), the frequency of patients with hyperglobulinaemia of IgG, and IgA was higher (29% and 25%, respecitvely) then the frequency of patients with hypogammaglobulinaemia (11% and 8%, respectively) (Table 4). »M«-spike in serum protein electrophoresis was found in 11 (7%) patients with NHL. High levels of immunoglobulin G and A were found in 29% and 25% patients, respectively. Hypoimmunoglobulinaemia was found to be more frequent in class IgM than in class IgG and class IgA (22%, 11% and 8% respectively) (Table 4). Highly significant correlation between gammaglobulins and IgG concentration was found ($r=0.85$, $p<0.00001$).

The statistical significance of the association between serum immunoglobulin concentration and histological and immunological findings was analysed with Kruskal-Wallis test. Statistically significant association was found between prognostic groups of histology and altered, total serum protein findings, albumins, as well as $alpha_2$-globulins. Aggressive NHL patients had lower concentrations of serum proteins ($p=0.05$), albumins ($p<0.01$), as well as higher concentrations of serum $alpha_2$-globulins ($p<0.05$) than indolent NHL patients (Table 5). Statistically significant association was found between immunology of lymphoma, serum $alpha_2$-globulins, and immunoglobulin A. B-NHL patients have significantly more often aberration in serum concentration of immunoglobulin A than T-NHL patients ($p<0.05$). On the other side T-NHL patients have more often higher concentrations of $alpha_2$-globulins ($p<0.05$) (Table 5).

Significant association between malignancy type NHL and the concentration of any immunoglobulin were not established. The same was true when immunological finding of lymphoma was correlated with the concentration of total serum proteins, albumins, $alpha_1$-globulins, beta-globulins, gamma-globulins, immunoglobulin G, and immunoglobulin M.

Discussion

Laboratory findings of serum proteins are variable and nonspecific for NHL. In our study hypoalbuminaemia was the most frequent aberration in serum protein findings, followed by increased serum $alpha_2$-globulin level, hypergammaglobulinaemia and increased serum $alpha_1$-globulin level. Only sporadic cases of nephritic syndrome associated with lymphoma disease were publisher. Higher $alpha_2$-globulin serum concentration is rel-

TABLE 5
ASSOCIATION OF SERUM PROTEIN FINDINGS AND SERUM IMMUNOGLOBULINS WITH HISTOLOGICAL AND IMMUNOLOGICAL FINDINGS OF LYMPH NODES IN NHL PATIENTS

Variable	Prognostic group – histological type of lymphoma	Prognostic group – immunological origin of lymphoma
Total proteins	Aggressive-NHL – lower serum protein concentration $p=0.05$	NS
Albumins	Aggressive-NHL – lower serum albumins $p<0.01$	NS

atively frequent finding (37%) in our patients while in the other authors' studies in well differentiated lymphocytic lymphoma only 25% patients have the same findings[5]. Measurement of serum albumin concentration has been proven relevant in assessing prognosis in another lymphoproliferative entity – multiple myeloma. Serum albumin concentration has been included in the recently published and widely used International Staging System (ISS) prognostic classification in multiple myeloma[6]. This significance of serum albumin as prognostic factor in multiple myeloma is connected with possible renal demage and consequent low level of serum albumin concentration.

The alterations of cellular and/or humoral immunity in NHL patients are not uncommon[7–15]. In NHL patients intrinsic B-cell defects, increased T-cell or monocyte suppressor activity, and diminished T-helper activity may also contribute to the hypogammaglobulinaemia[9,16–19]. Hypogammaglobulinaemia was seen in 5% of patients with well differentiated lymphocytic lymphoma and in 45% patients with chronic lymphocytic leukaemia[11]. The hypogammaglobulinaemia that occurs in lymphoproliferative disorders is generally mild and is usually seen in the terminal stage, when massive neoplastic infiltration of bone marrow and lymphatic tissues develops[7,8,16,20–22].

M-spike in serum protein electrophoresis is not a frequent finding except in solid organ transplant patients with post-transplant lymphoproliferative disorder[3,23–25]. In our investigation M-spike was found in 7% of NHL patients that is higher than expected in Caucasian general population 50 yeas of age or older[26]. In some subsets of NHL, the monoclonal gammapathy was detected more frequently than in our study[27,28].

In our study the most frequent hypoimmunoglobulinaemia is in class IgM (22%), followed by class IgG (11%) and IgA (8%). Two recent reports showed than IgM and IgA were also decreased in patients with NHL[10,14]. IgG levels were not decreased in one study[10], but decreased in the others[14,24]. Low serum IgG level (<10g/L), low total immunoglobulins on presentation were significantly associated with short survival[8]. In the study aimed to check whether the NHL patients have reduced IgA level and that allergy or atopy is associated with a reduced risk of lymphoma[10,14,19,29], it was reported that all immunoglobulin class levels are decreased in NHL patients[15]. The greatest difference between patients with NHL and controls was seen in IgG. Patients with B-cell NHL had consistenly lower median IgG levels than controls for all immunoglobulin types[14,15].

Our patients have more often polyclonal hyperimmunoglobulinaemia than hypoimmunoglobulinaemia. In 29% patients we found increased IgG concentration, and in 25% increased IgA concentration. The most frequent aberration seen by other authors was high IgA concentration[11]. At clinical presentation, patients with lymphoproliferative disorders tended to have higher levels of IgM[1,30], and IgG[1].

In our study statistically significant association between histological type of NHL and total serum proteins was found. Patients with aggressive type of lymphoma had significantly more often lower serum protein concentration. It is possible that the aggressive malignant disease infiltrates organs decreasing protein synthesis or it enhances the protein loss and/or degradation. The same results are obtained analyzing the statistical correlation between histological type of NHL, and serum albumins. The patients with aggressive type of lymphoma had more often lower concentration of serum albumins. The explanation for this finding may be the same as for the correlation of type of NHL and total serum proteins.

In our study it was found statistically significant association between the histological type of lymphoma and $alpha_2$-protiens as well as between immunological type of lymphoma and serum $alpha_2$-protiens. In aggressive type NHL patients it was found more often higher $alpha_2$-protein concentration as well as in T-NHL. $Alpha_2$-protien fraction in protein electrophoresis consists of several proteins that are acute phase reactants. Both type of lymphoma have aggressive clinical course and may cause higher $alpha_2$-protein production. In the relevant literature we have not found similar analyses.

We have not found statistically significant association between immunological type of lymphoma and total serum proteins, as well as between immunological origin of lymphoma and serum albumins. In other hand, it was found statistically significant correlation between immunological origin of lymphoma and serum IgA. Patients with B-NHL have significant more often IgA concentration aberration than T-NHL patients. It was not found correlation between histological type of lymphoma and serum immunoglobulins. In one old article it was published the correlation between histologic type of lymphoma and IgA level. The authors found higher concentration of immunoglobulin G and A in patients with diffuse in comparison with the patients with follicular NHL according Rappaport's classification[3].

In our study correlation between immunoglobulin G and M and immunologic origin of NHL was not noticed. The statistical analysis of immunoglobulin level and histological type of lymphoma did not show any correlation.

Conclusions

A number of statistical analyses showed a higher or lower degree of statistical significance correlations. These results give a description of system, but not the insight into pathogenesis and manifestations of disease. It is necessary to perform a prognostic analysis to assess clinical reference of particular variable.

Over the last few years new immunoassays have emerged that allow the measurement of free immunoglobulin light chains in serum to a level of 2–4mg/L and provide a much greater sensitivity than older methods, such as immunofixation, which is able to detect free immunoglobulin light chains at a minimum concentration of 100–150 mg/L[25,31].

REFERENCES

1. MALIK AR, TAYYIB M, TASNIM T, DITTA A, CHAUDHARY NA, Pak Postgrad Med J, 13 (2002) 114. — 2. GRULICH AE, VAJDIC CM, COZEN W, Cancer Epidemiol Biomarkers Prev, 16 (2007) 405. — 3. LICHTENSTEIN A, TAYLOR CR, Am J Clin Pathol, 74 (1980) 12. — 4. HARRIS NL, JAFFE ES, DIEBOLD J, FLANDRIN G, MULLER-HERMENLINK HK, VARDIMAN J, LISTER TA, BLOOMFIELD CD, J Clin Oncol, 17 (1999) 3835. — 5. PANGALIS GA, NATHWANI BN, RAPPAPORT H, Cancer, 39 (1977) 999. — 6. GREIPP PR, SAN MIGUEL J, DURIE BG, CROWLEY JJ, BARLOGIE B, BLADE J, BOCCADORO M, CHILD JA, AVET-LOISEAU H, KYLE RA, LAHUERTA JJ, LUDWIG H, MORGAN G, POWLES R, SHIMIZU K, SHUSTIK C, SONNEVELD P, TOSI P, TURESSON I, WESTIN J, Clin Oncol 23 (2005) 3412. — 7. ECONOMIDOU J, TERZOGLOU K, ANAGNOSTOU D, NIKIFORAKIS EM, PAPAJANNIS A, Scand J Haematol, 33 (1984) 123. — 8. PARKER D, ALISON DL, BARNARD DL, CHILD JA, DOVEY G, FARISH J, NORFOLK DR, O'BRIEN CJ, PARAPIA LA, SHARP J, Hematol Oncol, 12 (1994) 15. — 9. PASCALI E, Europ J Haematol, 56 (1996) 114. — 10. ELLISON-LOSCHMANN L, BENAVENTE Y, DOUWES J, BUENDIA E, FONT R, ALVARO T, KOGEVINAS M, DE SANJOSE S, Cancer Epidem Biomark Prevent, 16 (2007) 1492. — 11. KYLE RA, RAJKUMAR SV, Immunol Rev, 194 (2003) 112. — 12. SUN X, PETERSON LA, GONG Y, TRAYNOR AE, NELSON BP, Modern Pathology, 17 (2004) 389. — 13. TSAI DE, AQUI NA, TOMASZEWSKI JE, OLTHOFF KM, AHYA VN, KOTLOFF RM, BLOOM RD, BROZENA SC, HODINKA RL, STADTMAUER EA, SCHUSTER SJ, NASTA SD, PORTER DL, LUGER SM, KLUMPP TR, Clin Transplant, 19 (2005) 644. — 14. GRULICH AE, VAJDIC CM, RIMINTON S, HUGHES AM, KRICKER A, AMSTRONG BK, J Natl Cancer Inst, 99 (2007) 1417. — 15. BIGGAR RJ, CHRISTIANSEN M, ROSTGAARD K, EKSTRÖM SMEDBY K, ADAMI HO, GLIMELIUS B, HJALGRIM AH, MELBYE M, Int J Cancer, 124 (2009) 2616. — 16. PASCALI E, PEZZOLI A, Acta Haematol, 75 (1986) 193. — 17. OSTOJIĆ KOLONIĆ S, PRAŠEK-KUDRNA K, ROSO V, RADIĆ-KRIŠTO D, PLANINC-PERAICA A, DŽEBRO S, KARDUM-SKELIN I, JAKŠIĆ B, Coll Antropol, 34 (2010) 75. — 18. MARTIN W, ABRAHAM R, SHANAFELT T, CLARK RJ, BONE N, GEYER SM, KATZMANN JA, BRADWELL A, KAY NE, WITZIG TE, Translational Research, 149 (2007) 231. — 19. MELBYE M, SMEDBY KE, LEHTINEN T, ROSTGAARD K, GLIMELIUS B, MUNKSGAARD L, SCHÖLLKOPF C, SUNDSTRÖM C, CHANG ET, KOSKELA P, ADAMI HO, HJALGRIM H, J Natl Cancer Inst, 99 (2007) 158. — 20. JAKŠIĆ B, JAKŠIĆ A, PLANINC-PERAICA A, MINIGO H, VITALE B, Libri Oncologici, 14 (1985) 73. — 21. CHAPEL H, GRIFFITHS H, BRENNAN V, BUNCH C, LEA J, LEE M, Immunol Invest, 20(1991) 187. — 22. MARTINEZ-MAZA O, BREEN EC, Curr Opin Oncol, 14 (2002) 133. — 23. COLLS BM, LORIER MA, N Z Med J, 82 (1975) 221. — 24. GRIBBEN JG, CARDOSO AA, SCHULTZE JL, NADLER LM, Leukaemia, 11 (1997) S31. — 25. PRATT G, Br J Haematol, 141 (2008) 413. — 26. KYLE RA, RAJKUMAR SV, Br J Haematol, 134 (2006) 573. — 27. KATSIKIS PD, PAVLIDIS NA, PAPADOPOULOS NM, BAI M, MOUTSOPOULOS HM, Anticancer Res, 10 (1990) 1719. — 28. WÖHRER S, STREUBEL B, BARTSCH R, CHOTT A, RADERER M, Clin Cancer Res, 10 (2004) 7179. — 29. ECKSCHLAGER T, PRŮSA R, HLADÍKOVÁ M, RADVANSKÁ J, SLABÝ K, RADVANSKÝ J, Neoplasma, 51 (2004) 261. — 30. ROBERTS-THOMSON PJ, NIKOLOUTSOPOULOS T, SMITH AJ, Pathology, 34 (2002) 356. — 31. GUENET L, DECAUX O, LECHARTIER H, ROPERT M, GROSBOIS B, La Rev med inter, 28 (2008) 689.

A. Planinc-Peraica

Department of Medicine, »Merkur« University Hospital, Zajčeva 19, 10000 Zagreb, Croatia
e-mail: ananas2907@hotmail.com

SERUMSKI IMUNOGLOBULINI U BOLESNIKA SE NE-HODGKINOVIM LIMFOMOM

SAŽETAK

Analizirali smo nalaze serumskih bjelančevina i imunoglobulina (Ig) u 119 bolesnika sa ne-Hodgkinovim limfomom (NHL). U 96 (81%) bolesnika dijagnosticiran je B-NHL, a u 23 (19%) T-NHL, mnogo češće indolentni tip (77 bolesnika, 65%), nego agresivni tip (42 bolesnika, 35%). U većine bolesnika koncentracija serumskih bjelančevina je bila u granicama normale. Povišena koncentracija serumskih bjelančevina je nađena u 17%, a snižena u 7% bolesnika. Hipoalbuminemija je mnogo češća (43%) nego hiperalbuminemija (1%). Za razliku od serumskog albumina, niske razine drugih proteinskih frakcija su vrlo rijetke (0.6% bolesnika ima snižene alfa1-, 4% bolesnika ima snižene alfa-2 i 3% bolesnika ima snižene beta-globuline), a povišene znatno češće (23% alfa-1, 37% alfa-2 i 8% beta-globulini). Poliklonalna hiperimunoglobulinemija je češća nego hipoimunoglobulinemija. U 29% boelsnika nađena je povišena razina IgG i u 25% bolesnika povišena razina IgA. Hipoimunoglobuinemija IgM (22%) je mnogo češća nego IgG (11%) i IgA (8%). U 11 (7%) bolesnika u elektroforezi serumskih bjelančevina nađena je monoklonalna gamapatija. Nije nađena statistički značajna povezanost između koncentracije serumskih imunoglobulina i stupnja malignosti limfoma kao niti između koncentracije serumskih imunoglobulina i imunološkog porijekla limfoma. Bolesnici sa T-NHL imaju češće koncentraciju IgA iznad ili ispod normalnih vrijednosti nego bolesnici s B-NHL ($p<0,05$).