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# Prediction of survival in non-Hodgkin lymphoma based on markers of systemic inflammation, anemia, hypercoagulability, dyslipidemia, and Eastern Cooperative Oncology Group performance status

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**Abstract**

Background: The International Prognostic Index and its modifications are used to estimate prognosis in non-Hodgkin lymphoma. However, the outcome is often different in patients with similar index scores. Aim: The aim of this study was to elaborate a prognostic model for patients with mature B-cell non-Hodgkin lymphoma using a combination of predictive markers. Material and methods: The study included 45 patients with mature B-cell non-Hodgkin lymphoma. Before the administration of treatment, clinical and laboratory parameters were measured. After the 35-month follow-up period, overall survival was studied in relation to the data obtained at initial examination. Results: We revealed nine adverse predictive markers for overall survival of enrolled patients: Eastern Cooperative Oncology Group (ECOG) performance status >1; erythrocyte sedimentation rate >30 mm/h; levels of hemoglobin <120 g/L, fibrinogen ≥6 g/L, interleukin-6 ≥2 pg/mL, tumor necrosis factor ≥1.45 pg/mL, soluble fibrin monomer complexes >4 mg/dL, high-density lipoprotein cholesterol <1.03 mmol/L in men, and <1.29 mmol/L in women; and short activated partial thromboplastin time. A prognostic model for the estimation of the risk of death within the ensuing 1.5–2 years in patients with non-Hodgkin lymphoma was constructed.
Conclusion: Markers of inflammation, anemia, hypercoagulability, dyslipidemia, and poor ECOG status are associated with worse survival in patients with mature B-cell non-Hodgkin lymphoma.



**Keywords:**
non-Hodgkin lymphoma, prognosis, hypercoagulability, inflammation, dyslipidemia

## Introduction

Estimation of disease prognosis is very important, especially in malignancies, which helps to determine viable treatment strategies. For this purpose, the International Prognostic Index (IPI), the Mantle Cell Lymphoma IPI, the Follicular Lymphoma IPI, and other indexes are used in some types of non-Hodgkin lymphoma (NHL). However, in patients with identical prognostic indexes, different disease courses are often observed [1]. On the other hand, we do not have universal prognostic factors for all types of NHL, although there are different data in the literature about new predictive markers in some concrete NHL cases [2, 3]. It is known that systemic inflammation, hypercoagulability, and dyslipidemia play a vague role in pathogenesis, progression, and complications of NHL [4–7]. The aims of our study were to estimate the risk of death of patients with mature B-cell NHL in relation to various clinical, proinflammatory, hemostatic, and biochemical parameters and thereafter construct a prognostic model using a combination of predictive markers.

## Material and Methods

The study involved 45 patients with mature B-cell NHL: 26 men and 19 women aged 26–80 years (the median age was 60 years; the interquartile interval was 53–65 years). Criteria for exclusion from the study were the following: infectious and other inflammatory diseases, thrombosis and thromboembolism during the previous 3 months, treatment with anticoagulants, and surgical intervention or radiotherapy for the previous 2 weeks.

The majority of patients had diffuse large B-cell lymphoma – 23 (51.1%); others were diagnosed with the following: small lymphocytic lymphoma – 2 (4.4%), marginal zone lymphoma – 3 (6.7%), mantle cell lymphoma – 2 (4.4%), follicular lymphoma – 2 (4.4%), lymphoplasmocytic lymphoma – 4 (8.9%) and chronic lymphocytic leukemia (CLL) – 9 (20.0%) patients. The following Ann Arbor stages of the disease were identified in 30 patients with NHL (after the exclusion of 4 patients with lymphoplasmocytic lymphoma and 2 patients with relapse): stage I – 4 (13.3%) patients, stage II – 8 (26.7%) patients, stage III – 4

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(13.3%) patients, and stage IV – 14 (46.7%) patients. Among the 9 patients with CLL, according to the Rai staging system, stage II was established in 1 (11.1%) patient, stage III in 3 (33.3%) patients, and stage IV in 5 (55.6%) patients.

Clinical and laboratory studies were performed before the onset of first-line chemotherapy in 19 (42.2%) patients, before the next cycle of first-line chemotherapy regimen in 15 (33.3%) patients and before the next cycle of second-line chemotherapy regimen in 11 (24.4%) patients. Laboratory examination of the enrolled patients was carried out at the Institute of Blood Pathology and Transfusion Medicine of the NAMS of Ukraine, a specialized clinical and diagnostic laboratory. Serum levels of the proinflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor (TNF), were measured using an enzyme-linked immunosorbent assay with the A-8768 "Interleukin-6-ELISA-BEST" and A-8756 "α-TNF-ELISA-BEST" reagent kits (VECTOR-BEST, Ukraine), respectively. The following blood coagulation parameters were estimated: plasma fibrinogen levels (Clauss method), prothrombin time, prothrombin index, and activated partial thromboplastin time (APTT) by the chronometric method using the Coag-Chrom 3003 coagulometer (Bio-Ksel, Poland); levels of soluble fibrin monomer complexes (SFMCs) by the ortho-phenanthroline test (Technology-Standard, Russia); and levels of highly sensitive d-dimer by immunoassay using the reagent kit D-9120 "D-dimer-ELISA-BEST" (VECTOR-BEST, Ukraine). Elevated levels of SFMCs (a marker of thrombin generation; >4 mg/dL), d-dimer (a product of fibrin degradation during fibrinolysis; >250 mg/L), and shortened APTT were considered as hypercoagulability [8, 9]. In 11 (24.4%) patients with d-dimer levels >500 mg/L, Doppler ultrasound of the lower extremities was performed, which ruled out venous thrombosis in all of them. Parameters of lipid metabolism, such as levels of triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-Ch), and low-density lipoprotein cholesterol, were measured using standard enzymatic methods.

The overall functional state of patients, as a quantitative reflection of their state of health and daily activity, was evaluated using a system developed by the Eastern Cooperative Oncology Group (ECOG). The ECOG performance status defines scores ranging from "0" to "5", where score 0 means total health and score 5 indicates death.

### Statistical analysis

In order to identify the predictive markers, we performed analyses of overall survival (OS) using the Kaplan–Meier method. OS was defined as the time from study enrollment until death from any cause. Cox's *F*-test was used to detect the relationship between the studied parameters and OS. Cumulative 1-year and 2-year survival was determined by the life table method. Subsequently, a multivariate Cox proportional-hazards regression model was used, with OS as the dependent variable. To construct a model that predicts survival, the Wald method was used for calculation of the diagnostic coefficients of every factor. Chi-squared test and Cox's *F*-test were used to compare the OS in different risk groups. In order to find correlations, the Kendall tau ($\tau$) test was used. *P*-values had to be <0.05 to indicate statistical significance. For statistical analysis of the results, the software package "Statistica for Windows 6.0" (Statsoft, USA) was used.

## Results

After enrollment in the investigation, patients were treated with aggressive chemotherapy regimens in 26 (57.8%) cases; among these, 22 cases were treated with CHOP-like regimens: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), R-CHOP (with addition of rituximab), and R-CHOEP (with addition of rituximab and etoposide) and four cases with other regimens: R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin), Hyper-CVAD (course A: cyclophosphamide, vincristine, doxorubicin, and dexamethasone; course B: methotrexate and cytarabine), and four cases with other regimens: R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin), Hyper-CVAD (course A: cyclophosphamide, vincristine, doxorubicin, and dexamethasone; course B: methotrexate and cytarabine), and gemcitabine regimens). A total of 19 (42.2%) patients received less-aggressive regimens, such as CVP (cyclophosphamide, vincristine, and prednisone), R-CVP (with addition of rituximab), FC (fludarabine and cyclophosphamide), R-FC (with addition of rituximab), R-DC (rituximab, dexamethasone, and cyclophosphamide), BR (bendamustine and rituximab), and rituximab or chlorambucil alone. During the 35-month follow-up period (the median was 23 months), response to treatment was achieved in 26 (57.8%) patients, including a complete remission in 21 (46.7%) patients (with further development of relapse in 4 of them) and a partial response in 5 (11.1%) patients. The disease was stable in 2 (4.4%) patients, and it progressed in 1 (2.2%) patient; meanwhile, 16 (35.6%) patients died.

We estimated the OS of patients in relation to all the studied parameters, which were recorded at the time of initial examination. Significant relations were established with nine clinical and laboratory markers, such as ECOG score, erythrocyte sedimentation rate (ESR), APTT, and levels of hemoglobin, IL-6, TNF, fibrinogen, SFMCs, and HDL-Ch.

The survival of patients was analyzed in relation to their functional state, according to the ECOG scale. The patients' ECOG scores were assigned as follows: Grade 0: seven (15.6%) patients; Grade 1:27 (60.0%) patients; Grade 2: three (6.7%) patients; Grade 3: five (11.1%) patients; and Grade 4: three (6.7%) patients. ECOG grade >1 was found in 11 (24.4%) patients. It indicated low functional capacity and was associated with significantly worse OS. Over the 35 months of follow-up, the cumulative proportion surviving among the 11 patients with ECOG >1 was 36.4%, which was significantly lower than the cumulative proportion surviving (73.3%) among the 34 patients with ECOG grades 0–1 ($p = 0.010$).

On the basis of the analysis of associations between the OS of patients with NHL and markers of anemia, systemic inflammation, hypercoagulability, and dyslipidemia, laboratory predictors of death were established (Tab. I).

Anemia with hemoglobin levels <120 g/L was detected in 22 (48.9%) patients. Among these patients, anemia was mild in 15 (68.2%) patients, moderate in six (27.3%) patients, and severe in one (4.5%) patient. The survival of patients in relation to the level of hemoglobin was estimated. According to the cumulative proportion

surviving for 1 year and 2 years, OS was significantly worse in patients with anemia (Tab. I). A negative correlation was found between hemoglobin levels and ECOG scores in the examined patients (Tab. II), which reflects the relationships between predictive biomarkers. We also found a weak negative correlation between hemoglobin and IL-6 levels (Tab. II).

A decrease in OS was associated with ESR >30 mm/h before the onset of treatment (Tab. I). This value indicates B symptoms of tumor, intoxication, and systemic inflammatory response and was observed in 11 (28.2%) out of the 39 examined patients.

We evaluated the OS of patients in relation to serum levels of IL-6. Using Wald's sequential analysis, we determined that the threshold level of IL-6 that predicted better survival was 2.0 pg/mL. Comparing the OS in subgroups of patients with IL-6 levels either more than or less than 2.0 pg/mL (28 and 17 patients, respectively), the cumulative proportion of OS was found to be significantly lower in the first subgroup (Tab. I).

We estimated the OS of patients with NHL in relation to the TNF levels. A subgroup of 10 (22.2%) patients had levels of TNF ≥1.45 pg/mL, and in the remaining 35 (77.8%) patients, the serum TNF level was undetectable. The OS of patients in the first subgroup was significantly worse compared to patients in the second one (Tab. I).

Reduction in OS was associated with levels of fibrinogen ≥6 g/L. This level was established empirically and was close to the upper interquartile value of 5.62 g/L. In eight (17.8%) patients with such levels, the cumulative proportions of OS for 12 and 24 months were significantly lower than in the subgroup of 37 (82.2%) patients with fibrinogen levels <6 g/L (Tab. I).

In the examined patients, features of systemic inflammation were associated with hypercoagulability, which was confirmed by significant direct correlations between levels of TNF and d-dimer, as well as between ESR and levels of IL-6, on the one hand, and SFMC levels, on the other hand (Tab. II).

***Table I. Overall survival of patients with non-Hodgkin lymphoma depending on levels of laboratory markers***

| Markers | Cumulative proportion surviving for 12 months, % | Cumulative proportion surviving for 24 months, % | Cox's F-test, p |
|---|---|---|---|
| Hemoglobin <120 g/L | 63.7 | 42.9 | 0.030 |
| Hemoglobin ≥120 g/L | 73.5 | 64.4 | |
| ESR >30 mm/h | 45.8 | 26.0 | 0.042 |
| ESR ≤30 mm/h | 78.9 | 67.7 | |
| IL-6 ≥2.0 pg/mL | 62.6 | 45.0 | 0.002 |
| IL-6 <2.0 pg/mL | 80.7 | 70.0 | |
| TNF ≥1.45 pg/mL | 45.8 | 22.0 | 0.040 |
| TNF undetectable | 78.7 | 66.9 | |
| Fibrinogen ≥6 g/L | 45.0 | 0 | 0.010 |
| Fibrinogen <6 g/L | 77.1 | 68.8 | |
| SFMC >4 m/dL | 47.7 | 34.3 | 0.002 |
| SFMC ≤4 mg/dL | 87.7 | 73.3 | |
| APTT <30 s | 57.0 | 31.0 | 0.042 |
| APTT ≥30 s | 78.5 | 68.3 | |
| HDL-Ch low | 53.0 | 39.1 | 0.033 |
| HDL-Ch normal* | 83.5 | 68.1 | |

*APTT – activated partial thromboplastin time; ESR – erythrocyte sedimentation rate; HDL-Ch – high-density lipoprotein cholesterol; IL-6 – interleukin-6; SFMC – soluble fibrin monomer complex; TNF – tumor necrosis factor. * HDL-Ch levels ≥1.03 mmol/L in men and ≥1.29 mmol/L in women.*

***Table II. Correlations between the studied parameters in patients with non-Hodgkin lymphoma (Kendall's tau test)***

| Pairs of variables | | *p*-Values |
|---|---|---|
| APTT | d-dimer | 0.00002 |
| ESR | SFMC | 0.022 |
| IL-6 | SFMC | 0.006 |
| TNF | d-dimer | 0.014 |
| HDL-Ch | TNF | 0.019 |
| HDL-Ch* | d-dimer* | 0.045 |
| HDL-Ch | ECOG scores | 0.044 |
| Hemoglobin | ECOG scores | 0.008 |
| Hemoglobin | IL-6 | 0.053 |

*APTT – activated partial thromboplastin time; ECOG – Eastern Cooperative Oncology Group; ESR – erythrocyte sedimentation rate; HDL-Ch – high-density lipoprotein cholesterol; IL-6 – interleukin-6; SFMC – soluble fibrin monomer complex; TNF – tumor necrosis factor. * In women.*

In 19 (42.2%) patients, there were increased levels of SFMCs (>4 mg/dL). It was found that the OS of these patients was worse compared to the OS of patients with levels of SFMCs ≤4 mg/dL, as evidenced by the significantly lower cumulative proportion surviving (Tab. I).

APTT values shorter than the reference value of 30 s were noted in 15 (33.3%) patients. An inverse correlation between levels of d-dimer and APTT was found (Tab. II). This correlation confirms that short APTT can be considered as a marker of hypercoagulability, since, according to the literature, it is associated with increased thrombin generation [8]. We found that shortened APTT was a predictor of worse outcome for patients with NHL because the cumulative proportion of OS was significantly lower among them in comparison to the OS of patients in whom the APTT was within reference values (Tab. I).

HDL-Ch level <1.03 mmol/L in men and <1.29 mmol/L in women is considered to be low according to the definition of the International Federation of Diabetes. Such a low concentration of HDL-Ch was detected in 18 (40.0%) patients: 8 females and 10 males. Low levels of HDL-Ch were associated with worse OS in the examined patients (Tab. I). Levels of HDL-Ch correlated inversely with d-dimer levels in women, as well as TNF levels and ECOG scores in both genders (Tab. II).

Thus, estimation of Kaplan–Mayer survival curves over the maximum 35-month follow-up period allowed the detection of unfavorable prognostic factors for OS in patients with NHL, including the following: hypercoagulability markers, such as SFMC levels >4 mg/dL and APTT shorter than 30 s; laboratory features of systemic inflammation, such as levels of fibrinogen ≥6 g/L, IL-6 ≥2 pg/mL, TNF ≥1.45 pg/mL, ESR >30 mm/h, and anemia with hemoglobin levels <20 g/L; features of dyslipidemia, such as low HDL-Ch levels <1.03 mmol/L in men and <1.29 mmol/L in women; and poor performance status with ECOG scores >1.

Subsequently, we analyzed these nine predictive markers in a multivariate Cox proportional-hazards regression model. We determined that the independent predictors of OS were SFMC level >4 mg/dL, IL-6 level ≥2 pg/mL, and ECOG status score >1 ($p$ = 0.0001).

***Table III. The prognostic model for determination of overall survival of patients with non-Hodgkin lymphoma***

| No | Predictors | Death before 18 months (n) | Censored after 18 months (n) | Score | Corrected score | Kullback information quantity |
|---|---|---|---|---|---|---|
| 1 | ECOG grade 0–1 | 9 | 23 | –1.966 | –2 | 0.322 |
| | ECOG grade >1 | 7 | 3 | 5.788 | 6 | 0.966 |
| | | | | | | =1.288 |
| 2 | Hemoglobin ≥120 g/L | 5 | 16 | –3.113 | –3 | 0.491 |
| | Hemoglobin <120 g/L | 11 | 9 | 2.810 | 3 | 0.491 |
| | | | | | | =0.982 |
| 3 | ESR ≤30 mm/h | 7 | 19 | –1.859 | –2 | 0.288 |
| | ESR >30 mm/h | 6 | 4 | 4.239 | 4 | 0.575 |
| | | | | | | =0.863 |
| 4 | IL-6 <2 pg/mL | 2 | 14 | –6.690 | –7 | 1.604 |
| | IL-6 ≥2 pg/mL | 14 | 10 | 3.222 | 3 | 0.688 |
| | | | | | | =2.292 |
| 5 | TNF = 0 pg/mL | 10 | 23 | –1.509 | –1.5 | 0.195 |
| | TNF >0 pg/mL | 6 | 3 | 5.119 | 5 | 0.649 |
| | | | | | | =0.844 |
| 6 | Fibrinogen <6 g/L | 10 | 26 | –2.041 | –2 | 0.375 |
| | Fibrinogen ≥6 g/L | 6 | 0 | | 3 | 0.563 |
| | | | | | | =0.938 |
| 7 | SFMC ≤4 mg/dL | 4 | 19 | –4.078 | –4 | 0.890 |
| | SFMC >4 mg/dL | 10 | 7 | 4.237 | 4.5 | 1.001 |
| | | | | | | =1.891 |
| 8 | APTT ≥30 s | 8 | 16 | –1.249 | –1 | 0.083 |
| | APTT <30 s | 8 | 8 | 1.761 | 2 | 0.167 |
| | | | | | | =0.250 |
| 9 | HDL-Ch normal* | 7 | 18 | –3.590 | –3.5 | 0.984 |
| | HDL-Ch low | 9 | 8 | 1.023 | 1 | 0.059 |
| | | | | | | =1.043 |

*APTT – activated partial thromboplastin time; ECOG – Eastern Cooperative Oncology Group; ESR – erythrocyte sedimentation rate; HDL-Ch – high-density lipoprotein cholesterol; IL-6 – interleukin-6; SFMC – soluble fibrin monomer complex; TNF – tumor necrosis factor.*

** HDL-Ch levels ≥1.03 mmol/L in men and ≥1.29 mmol/L in women.*

Based on these results, a predictive model was developed for estimating the risk of death using the Wald method. To determine the diagnostic coefficients of every factor, taking into consideration that all deaths occurred within a period of 18 months, we compared the clinical and laboratory parameters of all dying patients with the same parameters in patients censored after 18 months (Tab. III). Scores from the proposed nine markers are summarized for each patient. The result is defined as a risk of death within 1.5–2 years, which is evaluated and divided into the following risk categories according to the summarized score: low risk: score <-10; low–

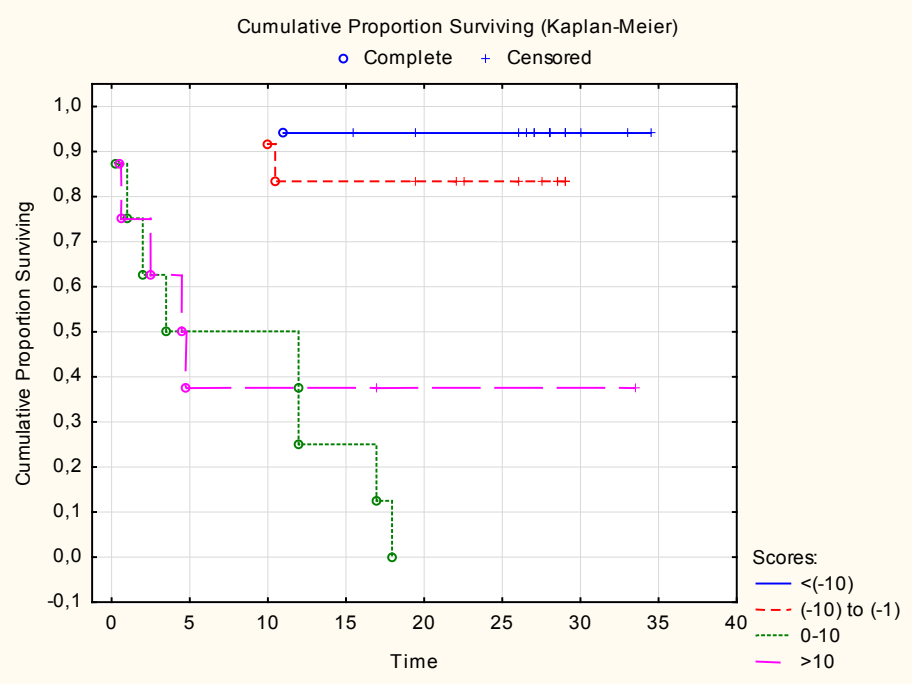


***Fig. 1. Overall survival of patients with non-Hodgkin lymphoma depending on the score of the predictive model (chi-square = 23.9, df = 3, p = 0.00003), df – degrees of freedom***

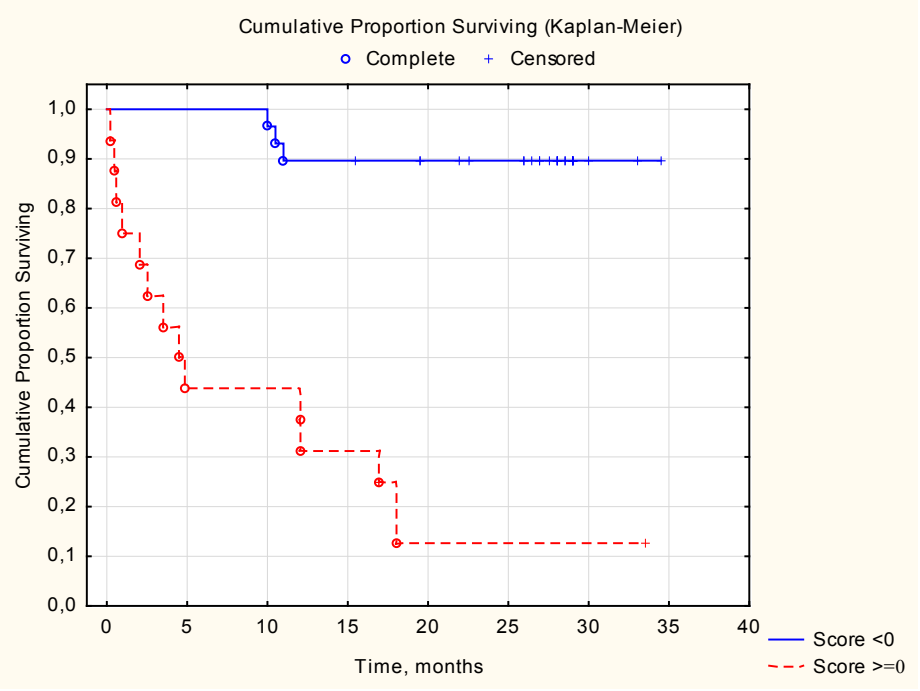


***Fig. 2. Overall survival of patients with non-Hodgkin lymphoma depending on the score of the predictive model <0 and ≥0 (Cox's F-test, p < 0.00001)***

intermediate risk: score from –10 to –1; high risk: score from 0 to 10; and very high risk: score >10.

In the cases with score <–10 (in 17 patients), the cumulative proportion of OS was 86.1% during the 12-month period and 75.1% over 24 months; in the case of scores ranging from –10 to –1 (in 12 patients), it was 73.3% and 58.8%, respectively; in the case of scores from 0 to 10 (in eight patients), it was 38.3% and 0%, respectively; and in the case of scores >10 points (in eight patients), it was 26.0% and 4.1%, respectively (Fig. 1).

Within the group of all examined patients, 0 points can be considered as the threshold of prognostic model scores, because the survival was similar in two subgroups with score <–10 and scores ranging from –10 to 0 (i.e., <0), and in two subgroups with scores from 0 to 10 and >10 (i.e., ≥0), as seen in Fig. 1. Having divided all patients into two groups with scores <0 (29 patients) and ≥0 (16 patients), the cumulative proportion of OS in the first group was 85.1% for 12 months and 78.3% for 24 months, and in the second group, 37.7% and 5.1%, respectively. The difference between the two groups was highly significant (Cox's *F*-test, $p < 0.00001$) (Fig. 2).

## Discussion

In the composition of the incidence of hematological malignancies in Ukraine, the incidence of mature lymphoid neoplasms was 52.1%, including 18.6% NHL and 22.4% CLL [10]. In recent years, the prognosis of these diseases has improved significantly due to the use of modern polychemotherapy and biological agents. For example, more than half of patients with diffuse large B-cell lymphoma may have long-term disease-free survival when treated with CHOP and R-CHOP regimens; however, one-third of patients experience relapsed or refractory malignancy after standard therapy [1]. Prognosis in mature lymphoid neoplasms is based on the results of molecular genetic studies, clinical staging (International Staging System (ISS), Ann Arbor, Rai, and Binet), and estimation of IPI and its modifications for different types of NHL. However, in patients with identical prognostic indicators, differences in consequences of a disease are often found. Therefore, the prognosis is supplemented by a number of predictive biomarkers, and investigations are aimed at finding new prognostic factors that would allow determination of the degree of risk in each case, creating the basis for individually tailored therapy [2, 3]. However, recommendations regarding the prognostic value of some markers of systemic inflammation, disorders of blood coagulation, and dyslipidemia in patients with different types of mature lymphoid neoplasms have not yet been elaborated.

The microenvironment of malignancies plays an important role in tumor growth and metastasis because tumor cells produce proinflammatory cytokines, such as IL-6, IL-1A, IL-8 and others. Systemic inflammatory response in patients with mature lymphoid neoplasms is one of the causes of anemia (anemia of chronic disease), which was partly confirmed by the weak inverse correlation between levels of hemoglobin and IL-6 in our study. Anemia reflects an unfavorable prognosis of tumor course [11, 12]. Decreased hemoglobin level is taken into account for CLL staging by the Rai and Binet methods, as well as for prognosis in patients with Waldenstrom's macroglobulinemia in International Prognostic Staging System for Waldenstrom's macroglobulinemia in the Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI-2. It should be noted that according to the model proposed by Khorana [13], anemia with hemoglobin levels <100 g/L is associated with an increased risk of thrombosis in patients with malignant tumors, including lymphomas, and development of thrombosis may affect prognosis [14]. Our study established that hemoglobin level <120 g/L is an unfavorable predictive marker in patients with different types of NHL.

According to the literature data, blood cytokine levels are important for predicting the survival of patients with hematological neoplasms, in particular, those with NHL [3, 4]. This is due to the influence of cytokines on the proliferation, differentiation, and migration of tumor and stromal cells, as well as on the regulation of communication between a tumor and its stroma, and the interaction of a tumor with its extracellular matrix [15]. Proinflammatory cytokines change the anticoagulant properties of the endothelium to procoagulant ones, which promotes the peritumoral formation of fibrin deposits as "a scaffold" for the invasive growth of malignant cells [16, 17].

It should be noted that the relationship between levels of cytokines and survival is studied, as a rule, in patients with concrete mature lymphoid neoplasms, such as diffuse large B-cell lymphoma [3]. We clarified the universal significance of some cytokine levels in predicting the course of many types of NHL. Our study revealed the relationship between worsening survival of patients with different types of NHL and systemic inflammation, reflected by the increased ESR and altered levels of fibrinogen, IL-6, and TNF. Dependence between the level of TNF-α and life expectancy was also observed in patients with other hematological neoplasms, in particular, in those with myelodysplastic syndrome [18]. According to the literature, TNF levels are positively associated with the degree of NHL malignancy [5]. Barilka et al. [12] showed that increased levels of TNF-α can induce the development of anemia already in the early stages of CLL. According to Patel and Patel [19], TNF-α promotes proteolysis, loss of adipose tissue, and a decrease in protein and lipid synthesis.

Our studies revealed that laboratory features of systemic inflammation are associated with hypercoagulability. Similar data are available in literature sources [20]. It has been established that hypercoagulability can be induced by malignant cells, both directly and indirectly through tumor-associated cytokines that are produced by macrophages or endothelial cells, and IL-6 is defined as a key regulator of paraneoplastic thrombocytosis and hyperfibrinogenemia [21]. The presence of IL-6 in the blood and levels of TNF-α >0.285 pg/mL are considered to be associated with the risk of venous thromboembolism [22]. In patients with mature lymphoid neoplasms, there are often elevated levels of hypercoagulability markers, such as fibrin degradation products, d-dimer, and tissue factor [6]. Hypercoagulability in these patients is associated with increased predisposition to thrombosis, which significantly impairs prognosis [23]. Thus, inflammation is one of the leading mechanisms in the development of hypercoagulability and thrombi, which can contribute to or lead to lethal outcomes.

The current study revealed the relationship between hypercoagulability and unfavorable prognosis in NHL. In patients with NHL without thrombotic complications, hypercoagulability

markers, such as increased levels of SFMCs and shortened APTT before the administration of chemotherapy, were significant predictors of worse OS. Similar results were obtained by Rubio-Jurado et al. [6] and Bi et al. [2], who revealed that high levels of d-dimer before the onset of treatment for NHL correlated with adverse clinical features and incomplete response to treatment and, as such, predicted worsening of patients' survival. According to the literature, hypercoagulability can directly or indirectly promote tumor progression and metastasis [21, 24].

It is known that dyslipidemia contributes to the development of atherosclerotic changes in the arteries, causing ischemic diseases that are among the leading causes of death in the world. Patients with NHL often suffer from coincident cardiovascular diseases, the progression of which is frequently caused by lipid metabolism disorders. The association of dyslipidemia with prognosis of NHL has not yet been studied.

According to the literature, HDL has anti-inflammatory actions, which are implemented on the cellular and molecular levels [25]. Low concentrations of HDL-Ch are associated with systemic inflammation, which contributes to atherogenesis and thrombosis [7, 26]. It has been reported that HDL has a protective effect against thrombosis due to inhibition of platelet activation and endothelial dysfunction, promotion of endothelial-dependent vasodilation, and reduction of thrombin generation by enhancing the anticoagulant properties of protein C [27]. Population studies demonstrate an inverse association between plasma HDL levels and the incidence of venous thromboembolism [28]. We confirmed the associations between levels of HDL-Ch and markers of inflammation and hypercoagulability.

The current study found that decreased level of HDL-Ch was a predictor of worse OS of patients with NHL. This result is in line with the literature data, in which low level of HDL-Ch is associated with the risk of death, sepsis, and malignant tumors [29].

Among the clinical functional parameters, ECOG performance status is used in Prognostic System IPI and Mantle Cell Lymphoma IPI. Our study revealed that it has a self-dependent value in NHL prognosis.

The revealed correlations between the studied parameters confirm the data in the literature about interactions among systemic inflammation, hypercoagulability, and dyslipidemia, which may play a role in the worsening of the functional ability of patients with NHL and their survival.

Consequently, the results of the performed study substantiate the use of ECOG performance status, hemoglobin concentrations, ESR, APTT, as well as levels of fibrinogen, SFMCs, IL-6, TNF, and HDL-Ch, obtained before treatment administration, as additional prognostic criteria for estimation of death risk in patients with different types of NHL. We propose to evaluate the risk of death within the following 1.5–2 years using these parameters together and calculating the summarized score.

## Conclusions

In patients with NHL, markers with a negative predictive value for OS are the following: laboratory features of systemic inflammation and tumor intoxication, such as levels of fibrinogen ≥6 g/L, IL-6 ≥2 pg/mL, TNF ≥1.45 pg/mL, ESR >30 mm/h, and anemia with hemoglobin levels <120 g/L; hypercoagulable state with levels of SFMCs >4 mg/dL and short APTT; low HDL-Ch levels <1.03 mmol/L in men and <1.29 mmol/L in women; as well as ECOG status score >1. Three of the established markers are independent predictors: ECOG score and levels of SFMCs and IL-6. The prognostic model for estimation of the risk of death within the ensuing 1.5–2 years was thus created, which included the above-mentioned nine predictive markers.

## Registration of clinical trials

The research was conducted in accordance with the research plan of the State Institution "Institute of Blood Pathology and Transfusion Medicine of the NAMS of Ukraine" (Lviv). It is a piece of research conducted by the Department of Hematology in association with the Laboratory Group working on the topic "Establishing a complex of prognostic factors for assessment of the disease course and stratification of treatment plans in patients with chronic lymphocytic leukemia" (state registration number: 0116U000176).

### *Authors' contributions*

ID, OT, YD – performed the study and analyzed the data.
ID, OT, YD, ZK – had a substantial contribution to the conception and design of the work. OT, ID – drafted the manuscript. OT, YD, ZK – critically revised the manuscript for important intellectual content. ID, OT, YD, ZK – had a substantial contribution to the acquisition, analysis and interpretation of data for the work.

### *Conflict of interest*

Conflicts of interest relevant to this article are not reported.

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### *Ethics*

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/ EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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