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THE IMPACT OF ANTICARDIOLIPIN ANTIBODIES AND HEMOSTASIS ON PATIENTS WITH NON-HODGKIN LYMPHOMA

321.10. HEMATOLOGY AND BLOOD TRANSFUSION

Summary of the Habilitation Thesis in Medicine

Chișinău, 2026

The thesis was developed in the Department of Internal Medicine, Discipline of Hematology and member institutions of the Founding Consortium of the Doctoral School in the field of Medical Sciences

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CONCEPTUAL LANDMARKS OF RESEARCH

The topicality and importance of the topic addressed. The importance of the topic derives from the high morbidity of non-Hodgkin lymphoma (NHL) both globally and nationally [1, 2]. The incidence of NHL in the Republic of Moldova (RM) is 5.92 per 100,000 population [3], and globally the incidence of NHL is estimated to increase by 43% by 2040 [2].

Modern treatment of NHL allows for prolongation of life, cure, but at the same time, complications associated with the disease have an impact on the quality of life [4, 5]. Hemostasis disorders associated with NHL develop severe complications, limit treatment options and outcomes, and alter their quality of life [6, 7]. The associated risk of thrombosis is 4 times higher in patients with malignancy versus the general population [8]. Early detection of hemostatic disorders and their associated risk is possible thanks to the implementation of screening tests, scores and other tools [9, 10].

Despite advances in understanding the pathogenesis of aberrant antibody (ab) synthesis, the ability to identify patients at increased risk of thrombosis or hemorrhage remains a challenge. Currently, there are no reliable models to accurately predict these risks in patients with NHL [11]. In the last decade, it has been demonstrated that some thromboses in NHL have been associated with elevated levels of anticardiolipin (aCL) antibodies, which recognize as non-self-antigen plasma proteins capable of binding anionic phospholipids expressed or coupled by vascular endotheliocytes, platelets, monocytes [12, 13]. It is necessary to predict the risk of thrombosis in asymptomatic carriers of aCL antibodies, and risk stratification seems to be the fundamental element, including in patients with NHL [14]. Detection of antibodies expressed in hematological malignancies may be asymptomatic. The pathogenic role of aCL antibodies in NHL remains a subject of debate [15], and their routine testing in NHL remains uncertain [16].

Biomedical criteria for evaluating the effectiveness of NHL treatment become even more important in terms of assessing the patient's quality of life [17]. Among the Major Initiatives of the European Cancer Control Plan is the "*A Better Life for Cancer Patients*" Initiative [18]. The review of the specialized literature reflects the lack of unified criteria for assessing the quality of life of patients with NHL - a prognostic indicator for survival. Meta-analysis of 39 clinical studies revealed that lymphoma and its treatment lead to severe suffering, and in 36% of cases manifest symptoms that condition adverse changes in the patient's professional life [19]. In the Republic of Moldova, there is the lack of collection and reporting of quality of life indicators for NHL patients. This situation could be explained by the underestimation of the significance of these indicators, the priority direction remaining to be considered therapeutic efficacy expressed by cure.

Purpose of the paper: Studying the impact of anticardiolipin antibodies and hemostasis on subjects with NHL to optimize medical management**.**

The objectives of the research: 1.Determination of the frequency of IgG, IgM aCL antibodies, antiβ2glycoprotein I IgG, IgM antibodies, LA in patients with NHL; 2. Research on hemostasis of patients with NHL and aCL antibodies in relation to type, disease stage, age and gender; 3. Estimation of hemostasis in patients with NHL and aCL antibodies according to the stage of treatment and its effectiveness; 4. Assessing the risk of thrombotic and/or hemorrhagic complications in patients with NHL; 5. Researching the quality of life of the patient with NHL at the stage of establishing the diagnosis and later during the specific treatment; 6. Reliability of instruments to assess quality of life, treatment compliance, satisfaction and general well-being in NHL; 7. Development of the risk assessment model for thrombotic events in patients with NHL and aCL antibodies.

Synthesis of scientific research methodology.

The study was conducted in 2020–2025 at the Hematology Discipline, "Nicolae Testemițanu" SUMPh, Hematology Department of Oncological Institute of the Republic of Moldova, with the support of ANCD, Postdoctoral Programs, project no. 24.00208.8007.02/PD. The research protocol was approved by the Ethics Committee of USMF "Nicolae Testemițanu" (minutes no. 32 of 28.01.2020).

Historical, chronological, mathematical, and biostatistical research methods were used. The review of the literature was carried out in a qualitative and analytical study. To achieve the proposed objectives, 2 studies were conducted: descriptive prevalence studies and prognostic cohort studies. The database was statistically processed using Microsoft Excel, Epi Info – 7.2, EpiMax Table, Graphpad Prism ver. 9.3.0. and RStudio programs. This research was possible to carry out in collaboration with the surgical departments, the Pathological Anatomy department, the Hematology Department, the Clinical Laboratory, "Immunology and Molecular Genetics" Laboratory of Oncological Institute, "Sante Clinic", the Medical Rehabilitation department of the Oncological Institute.

Scientific novelty and originality: For the first time in the RM, a sample of NHL patients was evaluated to estimate the impact of aCL antibodies and hemostasis, the risk of hemostatic complications depending on NHL type, tumor size, disease stage, ECOG, treatment, age and gender. An innovative topic was the proposal of a model for assessing the risk of hemostasis disorders in NHL with positive aCL antibodies. For the first time in the RM, the reliability of the instruments for assessing the quality of life, treatment compliance, satisfaction and general well-being of NHL patients was assessed. The results of scientific research were implemented in the research process, methodological and clinical activity in the Hematology Department of the Oncological Institute and in the didactic process of continuous training at the Hematology Discipline of the "Nicolae Testemițanu" SUMPh.

Important problem solved in that field. Through the analysis of NHL-specific factors, the applied treatment and individual factors with impact on the hemostasis of the patient with NHL and aCL antibodies, an evaluation algorithm model was developed for an optimal prophylaxis approach. Quality of life and psychosocial well-being of patients with NHL were assessed. Practical recommendations for multidisciplinary teams of hematologists and clinical psychologists are presented.

Theoretical significance. The data obtained on the impact of aCL antibodies and hemostasis on NHL patients, as well as their quality of life, will allow stratification into risk groups with the association of hemostatic complications and will be actively used in the creation of algorithms and recommendations in their conduct.

Application value. By analyzing the factors with possible impact on hemostasis in patients with NHL, the main causes with risk of hemostasis dysregulation that require an optimal prophylaxis approach were identified. Based on the data obtained, a model for assessing the risk of thrombotic events in patients with NHL and aCL antibodies was created. Practical recommendations for multidisciplinary teams of hematologists and clinical psychologists are presented.

Main results submitted for support:

1.Aberrant synthesis of aCL antibodies, antiβ2GPI antibodies, LA in NHL patients was assessed in 16.2% of cases versus an average of 5% of cases among people from the general potentially healthy population, in whom aCL antibodies are assessed.

2.Not all positive tests for aCL antibodies, LA, antiβ2GPI antibodies have clinical significance manifested by thrombosis, which demonstrates that hemostasis disorders in NHL are multifactorial.
3.The dimensions of the concept of transient synthesis of aCL antibodies, LA and antiβ2GPI antibodies in oncological diseases have also been demonstrated in NHL, so their synthesis does not qualify as a classic APS.
4.The Khorana score had the weakest discrimination ability (AUC=0.55, p=0.52), suggesting that it does not reliably distinguish thrombotic patients, and the ThroLy score showed moderate discrimination ability (AUC = 0.66), but nevertheless did not reach statistical significance (p=0.08). The Carpini score had the best results (AUC=0.68, p=0.048), apparently being the most reliable predictor with the highest odds ratio, significant association with thrombosis, and the best AUC.
5.The model for assessing the risk of thrombosis in patients with NHL and aCL antibodies has value for stratifying patients at highest risk of VTE and for selecting those who require additional testing, more thorough monitoring, or thromboprophylactic treatment.
6.The reliability of the instruments for assessing quality of life, treatment compliance, satisfaction and general well-being in NHL established prior to the research coincided with the actual one determined by self-assessment in real conditions through dynamic surveillance of respondents in the same unit of time and does not require additional scarce resources.

Approval of scientific results. The main results were presented, discussed and approved at the joint meeting of the Department of Oncology and the Discipline of Hematology of the "Nicolae Testemițanu" SUMPh (16.01.2026), at the Scientific Seminar of Profile 321 General Medicine; specialty 321.10 Hematology and Hemotransfusion (11.03.2026), as well as through active participation in 24 national and international scientific forums, including: Научно-практическая конференция Ассоциации директоров центров и институтов онкологии и рентгенорадиологии стран СНГ и Евразии *«ОНКОРЕАБИЛИТАЦИЯ. СОВРЕМЕННЫЕ ТЕНДЕНЦИИ И ПЕРСПЕКТИВЫ»* (Moscova. Rusia. 2020), *,,CONFER"* Iași. România (2020, 2024), *The 23-rd BALKAN MEDICAL DAYS. The Romanian National Section of the Balkan Medical Union*. București. România. (2021, 2025), *The XXVI th - NATIONAL CONFERENCE OF CLINICAL HEMATOLOGY AND TRANSFUSION MEDICINE*. România. (2019, 2022), *SOHO Annual Meeting* Houston. SUA (2020, 2021), *SOHO 2nd ITALIAN CONFERENCE*. Roma. Italia. (2020), *Conferenței a XVIII cu participare internațională «Злокачественные лимфомы»*. Moscova. Rusia. (2020, 2021), a *61-a conference HAEMATOCON 2020*. India. (2020), *British Society for Haematology* (*BSH)* (2021), *The 4th Annual Meeting of the International Academy for Hematology (IACH)* (2021), *The 6th Translational Research Conference Lymphoid Malignancies*. (ESH) (2021), ediția a V-a *,,Prevalența și controlul cancerului - o continuă provocare"*. Chișinău. RM. (2020), Conferința Științifică Anuală a USMF „Nicolae Testemițanu'' Chișinău, RM (2020, 2021, 2022, 2023), Ședința Societății de Respirologie din RM *,,VIAREMO"* (2020, 2021), *I Congres de Geriatrie și Gerontologie din RM*. Chișinău (2021), *al 2-la Congres Național cu participare Internațională a Societății Tromboză și Hemostază* (2025).

Publications on the topic of the thesis. The basic materials of the thesis were published in 72 scientific papers, including 1 monograph, 4 chapters in monographs, 25 articles, 42 abstracts published in collections of papers at scientific events abroad and nationally; 6 innovation patents, 24 presentations and oral communications at various scientific events with international participation (16 national and 8 abroad).

Thesis volume and structure. The thesis was presented on 226 pages of electronic text and is divided into: introduction, 5 chapters, discussions, 9 conclusions and 14 recommendations, bibliographical index (347 titles), 104 figures, 59 tables, 26 annexes.

Keywords: Non-Hodgkin lymphomas, anticardiolipin antibodies, hemostasis, prognostic score, thrombosis, hemorrhage, risk factors, compliance, psychological well-being, quality of life.

THESIS CONTENT

1. PATHOPHYSIOLOGICAL ASPECTS OF THE IMPACT OF aCL ANTIBODIES AND HEMOSTASIS ON PATIENTS WITH NHL

NHL is a heterogeneous group of lymphoproliferative malignancies [20]. aPL antibodies are a heterogeneous family that includes aCL antibodies, anti-β2GPI antibodies, and LA antibodies [21, 22]. These antibodies serve not only as "biomarkers", but also as "culprits" by recognizing as an antigenic target β2GPI, expressed on the surface of endotheliocytes and platelets. Endotheliocytes, selected among the basic target cells of aCL antibodies, create a bridge between the molecular level of these antibodies and the tissue and organ level of pathological changes [23].

The question arises whether the presence of antibodies increases the thrombotic risk in patients with NHL? The mechanisms mediating the synthesis of aCL antibodies, LA, antiβ2GPI antibodies in NHL are poorly understood: they do not seem to correlate with thrombotic events or other clinical manifestations of antiphospholipid syndrome (APS), although thromboses associated with antibodies may be the first manifestation of NHL, which will alter the quality of life [24]. Not all positive tests for antibodies are clinically significant. Their coexistence can create a major prothrombotic state [8, 16, 25, 37-39].

The presence of antibodies is indisputable, but it remains an unresolved issue whether their presence is a “phenomenon” or whether it directly contributes to the development of thrombosis. Phospholipid synthesis by malignant cells represents targets for aCL antibodies, LA, antiβ2GPI antibodies [26-30].

IgG is historically considered more relevant than IgM, but IgM reflects a low risk of thrombosis [31-33]. Major risk for thrombosis is suspected when the association of antibodies is detected, regardless of IgG or IgM isotype, called the “double aPL profile” and the “triple aPL profile” [34]. The Nepalese study (2023) observed a significant association between aCL antibodies synthesis and advanced tumor stage [35], a fact not confirmed by Rimesh (2020) [36]. The relevance of the impact of aCL antibodies in oncology has been studied, but there is still insufficient focus on the implications for patients who develop NHL, especially the relationship between these synthesized antibodies and the conditioning of prothrombotic states [27, 40]. The focus of study could be directed towards an individualized management of NHL patients.

The pathogenesis of thrombosis in NHL is dependent on: the inflammatory component, hemostatic deregulation, fibrinolytic deficiency, cellular and vascular dysfunctions [41]. The lack of complete clinical and laboratory data limits the assessment of all risk factors with reference to individual NHL [42]. Evaluation of the presence and severity of inflammation by assessing the leukocyte count, CRP, ESR, fibrinogen, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) [43]. The variables NLR, PLR, ESR, CRP, and LDH were significantly higher in lymphoma patients with VTE than in athrombotic patients, respectively, parameters reflecting the level of inflammation have the ability to identify patients with malignant lymphoma at risk of VTE [44]. However, their predictive performance and reliability have not been evaluated in patients with NHL.

Management of the risk of developing hemostasis disorders in NHL embodies consecutive stages [45, 46]: highlighting NHL-specific risk factors; assessing their impact; applying relevant and useful tools for influencing and monitoring the action of risk factors; implementing prophylactic strategies based on guidelines, practical recommendations and national clinical protocols; individual evaluation of the results of prophylaxis already applied. Currently, there are no reliable models for maximum prediction of thrombosis risk in patients with NHL [47].

2. EXPRESSION OF COMORBIDITIES, COMPLIANCE AND QUALITY OF LIFE OF PATIENTS WITH NHL

Modern medicine is faced not only with optimizing innovations in personalized diagnostic and therapeutic conduct, but also with the problem of ensuring patient compliance with prescribed therapy [48]. At the national level, there is a lack of information and reliable studies on treatment compliance in NHL. Identifying and formulating factors with a negative impact on compliance, educating patients about its importance, and rational therapeutic interventions are current issues in the RM. Comorbidity has a negative impact on the survival of patients with NHL [49-50]. Less well known are the pathogenetic and clinical particularities, their impact on treatment management and the specific mortality of patients with NHL and comorbidities.

Response to treatment and survival of patients with NHL are the basic biomedical criteria for evaluating treatment effectiveness must be complemented by measures of quality of life, which carry increasing importance in NHL management. However, they do not reflect the psychoemotional, social well-being and daily functional capacities of the patient with NHL [51-53]. The European Beating Cancer Plan (2021) includes improving the quality of life of cancer survivors [54]. Alabdaljabar (2022) highlighted 3 major issues impacting NHL survivors: quality of life, uncertainty about the future, and potential physical health complications [55]. The quality of life of patients with NHL has become an increasingly important task in oncohematology [56], but less proposed at the national level. The lack of collection and reporting of quality of life indicators in malignant hematological diseases, including NHL in the RM, could be explained by the underestimation of their significance, the basic direction remaining to be considered therapeutic efficacy.

II RESEARCH MATERIALS AND METHODS

According to the set purpose and objectives, prospective, longitudinal, descriptive prevalence and prognostic cohort studies were conducted (2020–2025).

The sample of 161 respondents represented a balance between the desired statistical power and practical feasibility. In order to achieve the proposed objectives and identify the answers to the hypotheses put forward, the following were carried out:

1. Descriptive prevalence study, by segregating the study group by characteristics/values, using collection procedures, with primary analysis and data characteristics, such as determining the frequency of aCL antibodies, antiβ2GPI antibodies, LA in patients with NHL.

2. Prognostic cohort study for time surveillance and evaluation of the impact of aCL antibodies, hemostasis on patients with NHL, estimation of quality of life, treatment compliance, impact of comorbidities, satisfaction and general well-being of patients with NHL.

Inclusion criteria: over 18 years old, confirmed NHL, obtaining informed consent and ensuring follow-up availability.

Exclusion criteria: aged <18 years, patient refusal to participate in the study, presence of other comorbidities with possible association with aCL antibodies synthesis (collagenosis, Covid19), lack of possibility of evidence in dynamics (death, treatment in other hospitals, abroad).

The research concept and design was developed based on the objectives identified to achieve the intended purpose.

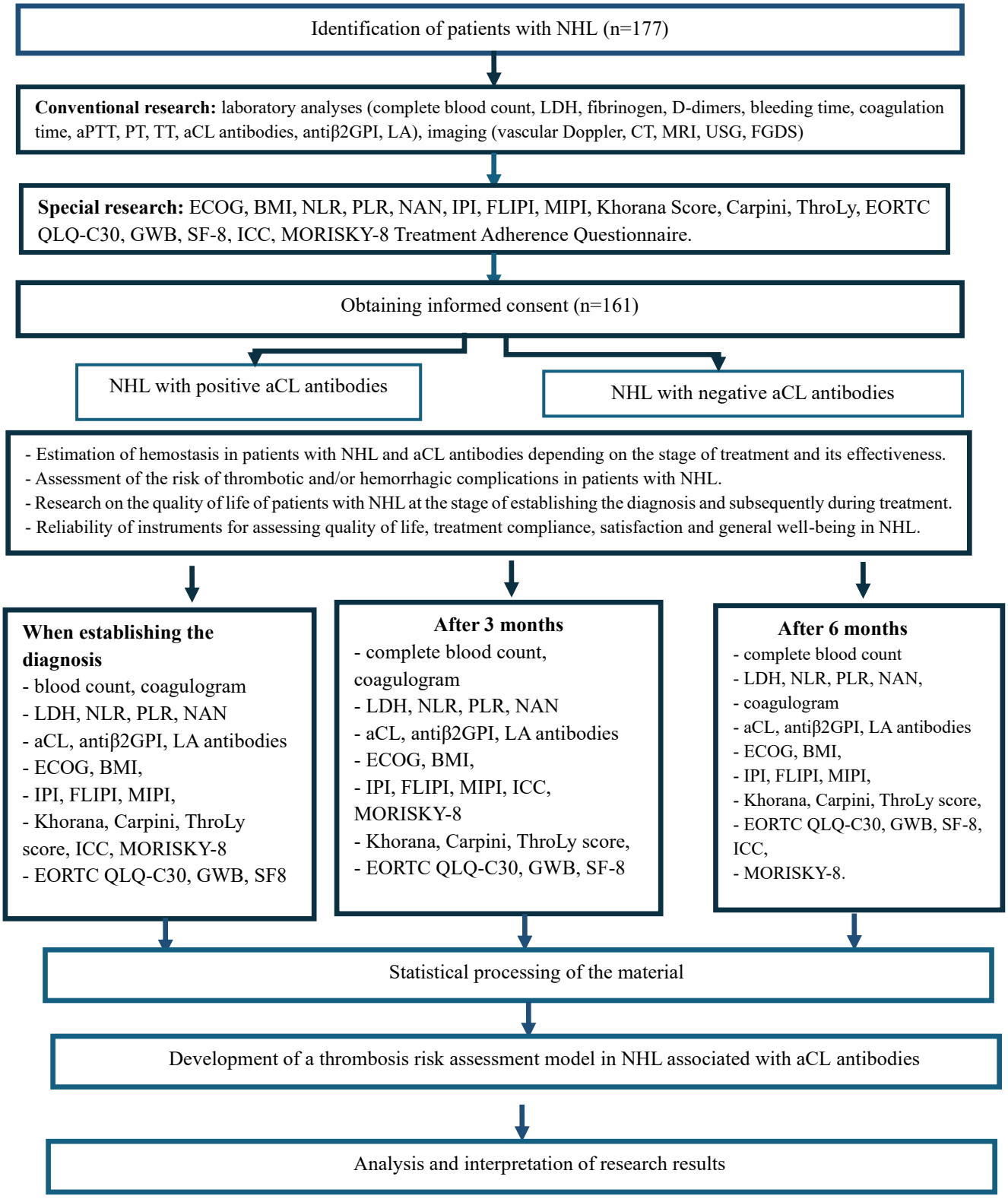

Figure 1. Research design

The database was statistically processed using electronic techniques to evaluate the degree of relationship in the study sample according to the proposed objectives, using Microsoft Excel, Epi Info – 7.2, EpiMax Table, Graphpad Prism ver. 9.3.0. and RStudio programs. The following were used: (n)-absolute values and (%) percentages; descriptive summaries-means, medians, standard deviations, minimum and maximum values; multiple regression and logistic regression by calculating the odds ratio (OR) and the 95% confidence interval (CI); p-value confidence coefficient values; Mann Whitney U test; Wilcoxon rank test; Pearson's Chi-squared test; Fisher's exact test; ANOVA method; Holm's test (Holm-Sidak test); Dunn's test.

Table 1. Characteristics of the research group

Parametrs	**Pacients n, %, 95% CI**
Age (years)	24-82
Sex	
Women	77 (48%) (95% CI, 40-56)
Men	84 (52%) (95% CI, 44-60)
NHL types	
Agressive	91 (56.5%) (95% CI, 48-64)
Indolente	70 (43.5%) (95% CI, 36-52)
The cell substrate	
B	157 (97.5%) (95% CI, 93-99)
T	4 (2.5%) (95% CI, 0.80-6.6)
NHL stages	
Localized (I-II)	55 (34.2%) (95% CI, 27-42)
Advanced (III-IV)	106 (65.8%) (95% CI, 58-73)
Symptoms of intoxication	
A	80 (49.7%), (95% CI, 42-58)
B	81 (50.3%), (95% CI, 42-58)
NHL oncet	
Nodal	91 (56.5%) (95% CI, 49-64)
Extranodal	70 (43.5%) (95% CI, 36-52)

III aCL ANTIBODIES, ANTIβ2 GP I ANTIBODIES, LA ANTIBODIES IN PATIENTS WITH NHL

3.1. Determining the frequency of aCL antibodies, antiβ2GPI antibodies, LA in patients with NHL

Based on the database analysis, positivity of antibodies was found in 16.2% (95% CI, 10.8-23) cases: LA in 80.7% (95% CI, 60-93) cases, aCL IgM and antiβ2GPI IgM antibodies in 15.4% (95% CI, 4.36-35) cases each, antiβ2GPI IgG antibodies in 3.8% (95% CI, 0.1-19.6) cases with a totally heterogeneous incidence between single positivity in 88.5% (95% CI, 70-97.6), double positivity in 7.7% (95% CI, 1-25) and triple positivity in 3.8% (95% CI, 0.1-19.6) cases. IgM antibodies clearly prevailed over IgG antibodies in a ratio of 8:1.

aCL antibodies, β2GPI antibodies, AL were positive in patients aged 24-71 years, with a median age of 50.5 years versus seronegative NHL patients with a median recorded age of 59.5 years**.**

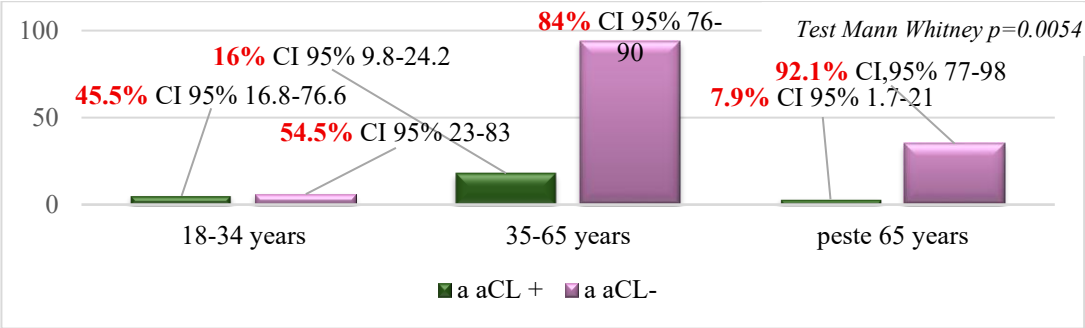

Figure 2. Correlation between age category and antibody association.

A statistically insignificant result was obtained when analyzing NHL patients with positive aCL antibodies, antiβ2GPI antibodies, LA according to gender: 53.8% (95% CI, 33-73) men and 46.2% (95% CI, 27-67) women. Women predominated in 15.4% (95% CI, 4.3-35) versus 3.8% (95% CI, 0.1-19.6) men in the age group 18-45 years. The estimated *RR* of association of aCL antibodies, antiβ2GP-1 antibodies, LA antibodies synthesis depending on NHL type is 1.46 with 95% CI, 1.07-1.85, and the OR is 3.005 with 95% CI, 1.17-7.7, and the RR of association of aCL antibodies, antiβ2GP-1 antibodies, LA synthesis in the case of aggressive NHL development depending on stage is 0.82 with 95% CI, 0.54-1.4, and the OR is 0.67 with 95% CI, 0.26-1.9.

Table 2. Characterization of patients with NHL according to aCL antibodies, antiβ2GPI antibodies and LA positivity or negativity

Parametrs	Patients with NHL and positive ab (26) abs (%) CI 95%	Patients with NHL and negative ab (135) abs(%) CI 95%	P value (*Fisher exact*)
NHL types	*RR* 1.46 CI 95%, 1.07-1.85, *OR* 3.01 CI 95%, 1.17-7.71.		*0.03*
Aggressive	20 (76.9) 56-91	71 (52.6) 43.8-61	
Indolente	6 (23.1) 9-43.7	64 (47.4) 39-56	
The cell substrate			*0.0006*
B	26 (100)	131 (97) 93-99	
T	-	4 (3) 0.8-7.4	
NHL stages	*RR* 0.62 CI 95%, 0.41%-1.03%, *OR* 0.45 CI 95%, 0.19%-1.09%.		*0.07*
Localized (I-II)	13 (50) 30-70	42 (31) 23-40	
Advanced (III-IV)	13 (50) 30-70	93 (69) 60-76.5	
Symptomes of intoxication	*RR* 1.08 CI 95%, 1.73%-1.77%, *OR* 1.15 CI 95%, 0.5%-2.62%.		*0.83*
A	12 (46) 27-66.7	68 (50.4) 41-59	
B	14 (54) 33-73	67 (49.6) 41-58.3	
NHL onset	*RR* 1.46 CI 95%, 1.07-1.85, *OR* 3.01 CI 95%, 1.17-7.71.		*0.03*
Nodal	20 (77) 56-91	71 (52.6) 43.8-61	
Extranodal	6 (23) 9-43.7	64 (47.4) 39-56	

The leader among seropositive aggressive NHL was DLBCL in 55% (95% CI, 31.5-77) of cases, ABS versus GSB in a ratio of 2:1. The nodal onset of NHL with antibodies was predominant in peripheral lymph nodes in 65% (95% CI, 41-85) of cases, followed by mediastinal lymph nodes in 25% (95% CI, 9-49) of cases, and abdominal lymph nodes in 10% (95% CI, 1.2-32) of cases. It is important to emphasize that out of 70 extranodal locations, the association of antibodies was estimated in 23% (95% CI, 22-96) of cases with high specificity in the gastrointestinal system (stomach, spleen, nasopharynx) in 66.6% (95% CI, 4.4-35) of them and the genitourinary system (uterus, kidneys) in 33.4% (95% CI, 0.4-77) of patients.

3.2. Research on hemostasis in patients with NHL and aCL antibodies, antiβ2GPI antibodies and LA according to clinical and paraclinical criterias, stage and efficacy of the applied treatment

Hemostasis disorders were estimated in 13% (95% CI, 8.3-19.2) cases: thrombosis in 85.7% (95% CI, 64-96.9) (p=0.01) and 14.3% (95% CI, 3-36) bleeding events, in a ratio of 6:1. In 72.2% (95% CI, 46.5-90) of cases the age ranged from 24 to 61 years with aggressive NHL with their prevalence in the age category of 35-65 years. Indolent NHL complicated with thrombosis was estimated at 27.8% (95% CI, 9.7-53) of respondents aged between 49-77 years. Thrombosis developed more frequently in men - 72.2% (95% CI, 46.5-90) of cases versus in women - 27.8% (95% CI, 9.7-53) of cases (p=0.004, Mann-Whitney U test). Of aggressive NHL complicated with thrombosis, DLBCL was found in 83% (95% CI, 52.6-98) of cases. The *RR* was 1.5 and the *OR* was 3.7, although in this study the difference did not reach statistical significance (Fisher's exact test, p=0.11). In the case of hemorrhages, an equal distribution was observed between patients with aggressive and indolent NHL, in a ratio of 1:1. Thrombosis developed more frequently in local NHL stages (I-II) in 61% (95% CI, 35.8-83) cases versus disseminated stages (III-IV) in 39% (95% CI, 17-64), and depending on B symptoms, they were present in 66.7% (95% CI, 41-87) cases.

Not all subjects with NHL and positive aCL antibodies, antiβ2GPI antibodies and LA developed thrombosis, but it is possible that among patients with NHL and thrombosis there are patients who are seronegative for these antibodies.

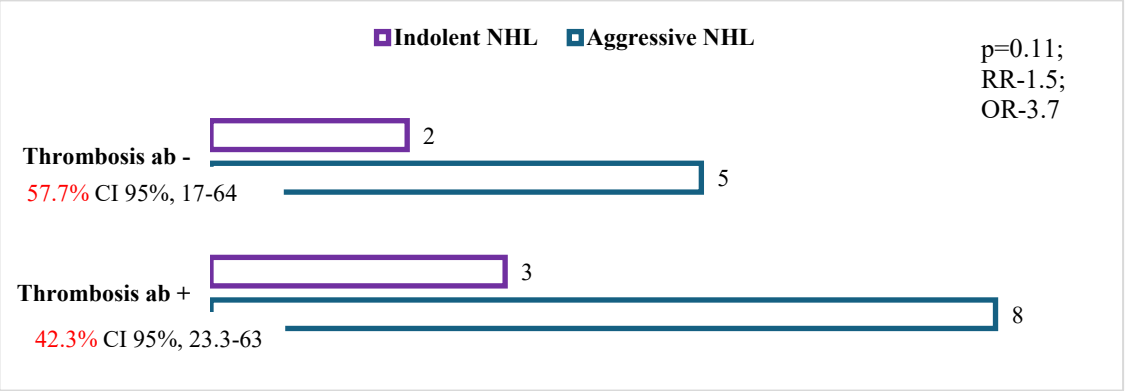

Figure 3. NHL associated with thrombosis according to aCL antibodies, antiβ2GPI antibodies and LA positivity

Of the 26 respondents with NHL and positive aCL antibodies, antiβ2GPI antibodies and LA, thrombotic events were estimated to be 42.3% (95% CI, 23-63), and of the total number of thrombosis these respondents constituted 61.1% (95% CI, 36-83). In patients with NHL complicated by thrombosis, unipositivity was estimated in 72% (95% CI, 39-94). Cases of double positivity (aCL IgM antibodies+LA and aCL IgM antibodies + antiβ2GPI IgM antibodies) and triple positivity (LA+aCL IgM antibodies+antiβ2GPI IgG antibodies) induced hemostasis dysregulation.

Thrombosis developed more frequently in men - 82% (95% CI, 48-97) of cases versus in women in 18% (95% CI, 8-19) cases (p=0.041, Mann-Whitney U test). In patients with NHL and positivity of aCL, antiβ2GPI and LA antibodies, but who did not develop thrombosis - 20 (12.5%) (95% CI, 8-19) patients, no statistical difference was observed according to gender, with an equal involvement in a 1:1 ratio.

The locations of VTE in the 18 patients were: deep VT of the lower extremities in 39% (95% CI, 17-64) of cases, jugular VT in 33% (95% CI, 13.3-59) of cases, deep VT of the upper extremities and subclavia in 11% (95% CI, 1.4-35) of cases each, portal VT in 6% (95% CI, 0.02-3.4) of cases. Thus, in 64% of cases, VT developed "atypically" localized. In 61.1% (95% CI, 35.7-82.7) VT was assessed with a median interval of 3-4 weeks. In 38.9% (95% CI, 17.3-64.3), VT developed during first-line treatment with a follow-up time of up to 6 months.

Table 3. Correlation of thrombotic events with positive ab and NHL variables

Parametrs	**Thrombosis (n=18)**		**Absence of thrombosis (n=143)**	
	ab + abs (%),CI 95%	ab - abs (%), CI 95%	ab + abs (%),CI 95%	ab - abs (%),CI 95%
Oncet				
Nodal (n=91)	11 (61), 39-94	7 (39), 29-96	9 (6.7), 3-12	64 (47), 38-56
Extranodal (n=70)	-	-	6 (4.4), 1.6-9.4	64 (47), 38-56
Tumor size	*p=0.1*			
< 7cm (n=61)	5 (28) 9.7-53	3 (17) 3.5-41	6 (8) 3-17	47 (64) 52-75
≥ 7 cm (n=30)	6 (33) 13-59	4 (22) 6.4-48	3 (4) 0.9-11	17 (24) 14-35
IPI (n=83)	n=12		n=71	
intermediate, (n=48) high intermediate, high and very high	4 (33), 6.4-48	3 (25), 3.5-41	5 (7), 3.5-23	36 (51), 60-86
intermediate low and low (n=35)	3 (25), 3.5-41	2 (17), 0.7-19	6 (8), 6.6-33.6	24 (34), 51-83
LDH	*p=0.69*			
Normal (n=87)	2 (11), 1.4-35	5 (28), 10-53	6 (4), 1.6-9	74 (52), 43- 60
Increased (n=74)	9 (50), 26- 74	2 (11), 1.4-35	9 (6), 3-12	54 (38),30- 46
ECOG	*p=0.001*			
0-1 (n=103)	8 (44), 22-69	2 (11) 1.4-35	11 (8), 4- 13	82 (57), 49-66
2-4 (n=58)	3 (17), 3.6-41	5 (28), 10-53	4 (3), 0.8-7	46 (32), 25-41
CCI	*p=0.067*			
0-2 (n=108)	10 (56), 31- 78	5 (28), 10-53	10 (7), 3.4-12	83 (58), 49-66
3-7 (n=53)	1 (5.5), 0.1- 27	2 (10.5), 1.4-35	5 (3), 1.1-8	45 (32), 23-40
BMI	*p=0.11*			
< 30 kg/m^2 (n=104)	8 (44), 22-69	4 (22), 6.4-48	7 (5), 1.9-10	85 (59), 51-68
> 30 kg/m^2 (n=57)	4 (22), 6.4-48	2 (11) 1.4-35	8 (6), 2.4-11	43 (30), 23-38

Informative note: IPI-International Prognostic Index; BMI-Body Mass Index; LDH-Lactate dehydrogenase; ECOG-Performance Status.

IV RISK OF HEMOSTASIS DISORDERS IN NHL

4.1. Assessing the risk of associated hemostasis disorders in patients with NHL

Following the analysis of patients with lymph node NHL according to the development of thrombosis, we suspected a higher rate of thrombosis association in patients with mediastinal onset.

Table 4. NHL correlation according to location of tumor onset and thrombosis

Lymph nodes	**Thrombosis**	**Absense of thrombosis**
Mediastinum	54.6%	12.5%
Other groups	45.5%	76%

p value = 0.02 Fisher test

Only 13.3% (95% CI, 3.8-31) patients with aggressive NHL and anemia developed thrombosis, but in the absence of aCL antibody synthesis. Thrombocytosis was present in 50%

(95% CI, 26-74) of patients with thrombosis, and an additional 10% (95% CI, 3.3-22) of them also tested positive for aCL antibodies. The leukocyte count at the diagnosis of NHL was not associated with the risk of thrombosis or with the positivity of aCL antibodies, anti-β2GPI antibodies, or LA in this study (p=0.38). Among patients with NHL and thrombosis, 33.3% (95% CI, 13.3–59) had multiple procoagulant factors such as positive aCL antibodies, antiβ2GPI antibodies, LA and leukocytosis. There was a statistically insignificant difference between the median 1.4 (mean 6.3, 95% CI, 4.7–17.5) of leukocytes in NHL with thrombosis and their median in the absence of thrombosis—1.84 (mean 12.6 (95% CI, 7.7–17.5)) (Mann-Whitney U test, p=0.21). Among seropositive patients, the mean leukocyte count at diagnosis was 1.57 (mean value 6.03, 95% CI, 0.4–11.6), while seronegative patients had a mean leukocyte count of 1.9 (mean value 13.2, 95% CI, 875.95%). Also, the difference between the 2 groups did not reach statistical significance (Mann-Whitney U test, p=0.38), suggesting that the leukocyte count at NHL diagnosis was not associated with the risk of thrombosis or with the positivity of aCL antibodies, antiβ2GPI antibodies, LA antibodies in this study.

The correlation of increased NAN with thrombosis was present in 14.8% (95% CI, 4.1-33.7) cases, and 50% (95% CI, 6.8-93) of them had positive aCL antibodies, antiβ2GPI antibodies, LA antibodies, although this difference did not reach statistical significance (p=0.18). In particular, the results of a t-test performed using the same data lead to a significant p-value of 0.03, hinting at the validity of the observed differences.

In 72.2% (95% CI, 46.5-90.3) cases of NHL with increased NLR, thrombosis developed, among which 53.8% of seropositive patients were found. In a ratio of 4:1, an increased NLR is attested in aggressive NHL as opposed to indolent NHL (Chi-square test, p<0.0001). Patients with aggressive NHL would have a higher thrombogenic risk (p=0.0703). A comparison of the NLR ratio between patients with thrombosis with a median of 3 (mean value of 13.27, 95% CI, 5.1–31.7) and without thrombosis with a median of 2 (mean value of 3.2, 95% CI, 2.45–4), denotes a higher NLR among NHL patients with thrombosis (p=0.0703 Mann-Whitney test).

A mean PLR of 183 (105-254) was in seropositive aggressive NHL and thrombosis, versus the mean PLR value in seronegative aggressive NHL and thrombosis, which was evidently 877 (112-1500). Seropositive NHL, without thrombosis the mean PLR value - 287 (30-1100) in aggressive NHL and 137 (7-337) in indolent NHL (p=0.0617). In seropositive NHL, hyperfibrinogenemia was present in 42.3% (95% CI, 23-63) cases, associated with thrombosis in 36.4% (95% CI, 11-69) of aggressive NHL (p=0.13), with a potential association between fibrinogen level and the risk of thrombosis in NHL (p=0.02). Every 4th patient with NHL and elevated D-dimer presented an eminent prothrombotic risk. Seropositivity was associated in 22% (95% CI, 11.2-37) cases of NHL and elevated D-dimer, 50% of whom developed thrombotic complications, of which 77.8% (95% CI, 40-97) aggressive NHL versus 22.2% (95% CI, 2.8-60) indolent NHL (p=0.002). Bleeding time, coagulation time, aPTT, PT provided an assessment of coagulation, but did not fully describe the hemostatic changes associated with NHL and did not correlate with the positivity of aCL antibodies, antiβ2GPI antibodies, LA antibodies and did not constitute a predictive marker.

4.2. Assessment of the risk of thrombosis by applying the Khorana, Carpini, ThroLy scores

When evaluating the dynamics of the Khorana score, no significant differences were observed, recording a constant number of patients with NHL in the high-risk group 19.9% (95% CI, 14-27); 15.5% (95% CI, 10-22) and 15.5% (95% CI, 10-22), respectively. The same picture

was also in the group of patients with NHL with intermediate risk of developing thrombosis 80% (95% CI, 73-86); 84.5% (95% CI, 78-90) and 84.5% (95% CI, 78-90), respectively (Chi2, 1.44, g.l.=2, p=0.48). Of the high and very high risk categories of association of thrombotic complications, those with aggressive NHL were the priority: 30% (95% CI, 23-38) and 21.1% (95% CI, 15-28), respectively (aggressive NHL vs. indolent NHL, intermediate Carpini risk vs. high-very high risk; Chi^2, 11.61, g.l.=1, p=0.0007). This allowed the identification of aggressive NHL with a higher risk of developing thrombosis according to the Carpini score. According to the same score, an uneven distribution of the 18 (11.1%) (95% CI, 6.8-17) NHL patients with thrombosis according to the level of risk according to the Carpini score. The vast majority, 66.7% (95% CI, 41-87) of patients were in the high and very high risk group. Among the 19.9% (95% CI, 14-27) of respondents estimated according to the Carpini score in the intermediate risk group, they did not develop thrombotic hemostasis disorders. The evaluation after 3 months shows a risk of thrombosis in the same percentage of 47.2% (95% CI, 39.3-55), 41% (95% CI, 33-49), respectively. The evaluation at 6 months showed a positive dynamics of the risk of developing thrombosis by increasing by 18% (95% CI, 12.4-25) the number of patients with low risk, ultimately constituting 59% (95% CI, 51-67) of patients (Chi^2, 14.63, g.l.=4, p=0.0055).

To compare the ability of the Carpini, ThroLy and Khorana clinical scores to predict thrombosis, simple logistic regression was used to analyze the relationship between each score and thrombotic events.

Table 5. Comparative presentation of Khorana, Carpini, ThroLy scores

Scale	β1 (IÎ 95%)	*p*-value	Odds Ratio (OR, IÎ 95%)
Khorana	0.36 (-0.4 – 1.1)	0.33	1.4 (0.67 – 3.0)
ThroLy	0.88 (-0.01 – 1.83)	0.05	2.4 (0.99 – 6.2)
Carpini	1.044 (0.09 – 2.18)	0.04	2.8 (1.1 – 8.9)

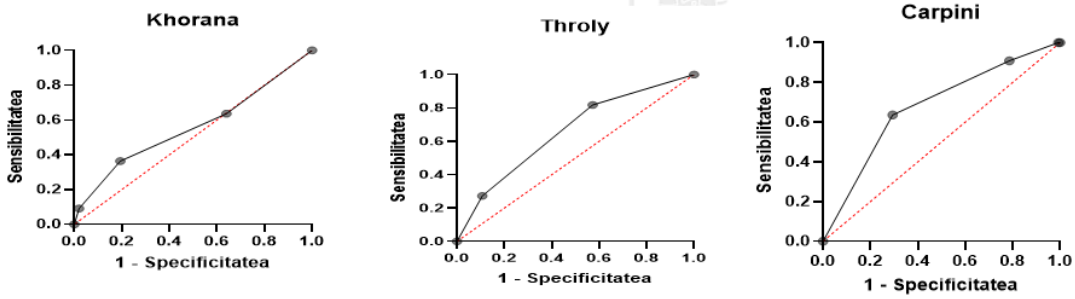

Figure 4. Specificity and sensitivity of the Khorana, ThroLy, Carpini scores.

The Khorana score demonstrated the weakest discrimination ability (AUC=0.55, p=0.52), suggesting that it did not reliably distinguish thrombotic patients in our study. The ThroLy score showed moderate discrimination ability (AUC=0.66), but nevertheless, did not reach statistical significance (p=0.08). Overall, the Carpini score performed best (AUC=0.68, p=0.048), appearing to be the most reliable predictor in this data set, with the highest odds ratio, significant association with thrombosis, and the best AUC. However, the current dataset is limited in sample size, which may affect the generalizability of the results and the performance of the scoring systems. Consistent with previous findings, the Khorana and ThroLy scores in NHL did not demonstrate satisfactory thrombotic prediction performance. A plausible explanation could be the high rate of antithrombotic prophylaxis in our patients.

4.3. Development of a model for assessing the risk of thrombotic events in patients with NHL and aCL antibodies, antiβ2GPI antibodies, LA antibodies

A model for assessing the risk of thrombosis involved the evaluation of individual clinical, laboratory, and patient factors. Risk factors were identified as similar variables with comparable hazard ratios, where possible, that would have a prothrombogenic impact in patients with NHL and positive antibodies. From the very beginning, the minor prothrombogenic risk group was excluded, on the grounds that the development of a malignancy (NHL) or seropositivity, according to multiple validated international instruments, places the patient in the minor risk group.

Based on the above data, it was decided to develop an internally validated thrombosis risk prediction model in NHL patients, using currently available clinical and laboratory variables measured at the time of diagnosis, including antibodies positivity. According to data from the specialized literature, as well as our own deductions, the model included: sex, BMI, NHL type (aggressive/indolent), B symptoms, IPI score, platelet count, fibrinogen, NLR, seropositivity (positive for ≥1 antibody).

Some potential predictors were excluded because they were correlated or redundant, especially variables that are components of the IPI (e.g., age, stage, LDH, performance status, extranodal sites).

Given the limited number of thrombotic events in the study, model estimation was performed using penalized ridge logistic regression to reduce overfitting and stabilize coefficient estimates. Internal validation was performed using bootstrap resampling (B = 1000) to estimate optimism-corrected measures of calibration and discrimination.

Calibration (figure 5) was summarized using the intercept with the calibration origin (ideally 0) and the calibration slope (ideally 1), and discrimination was summarized using Somers' Dxy, with conversion to the area under the receiver operating characteristic curve (AUC) as AUC=0.5+Dxy/2AUC=0.5+Dxy/2AUC=0.5+Dxy/2.

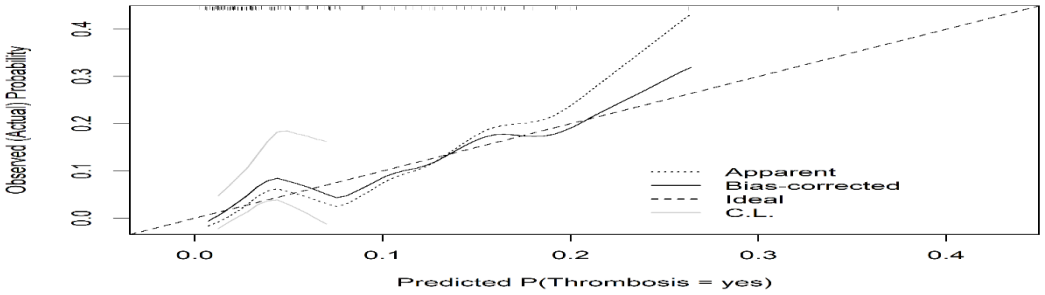

Figure 5. Calibration of the penalized logistic regression model for thrombosis. The dashed diagonal indicates the ideal calibration. *The dotted line shows the apparent calibration in the development cohort. The solid line shows the calibration corrected with bootstrap optimism (B = 1000). The check marks represent the predicted probability distribution (n = 161)*

The final model (with a chosen penalty = 2) demonstrated acceptable internal calibration (optimism-corrected intercept 0.1; slope 1.03; Table 6) and moderate discrimination (optimism-corrected AUC of approximately 0.75).

Table 6. Internal validation parameters (corrected with bootstrap optimism) of the thrombotic event risk assessment model

Metric	Estimate	Lower 95	Upper 95
Calibration interception	0.101774072	-1.191288102	1.783738847
Calibration slope	1.030829831	0.502503694	1.622231756
AUC	0.752763647	0.581335388	0.874828925

For clinical interpretability, the predicted thrombosis probabilities from the final model were further synthesized using a two-level risk stratification scheme (Figure 6 and Table 7). Patients were grouped into lower predicted risk (predicted probability ≤ 0.15) or higher predicted risk (predicted probability > 0.15). In this cohort of responders, the high-risk group comprised 19/161 patients (11.8%) and had an observed thrombosis rate of 31.6% (6/19), while the low-risk group comprised 142/161 patients (88.2%) with an observed thrombosis rate of 3.5% (5/142).

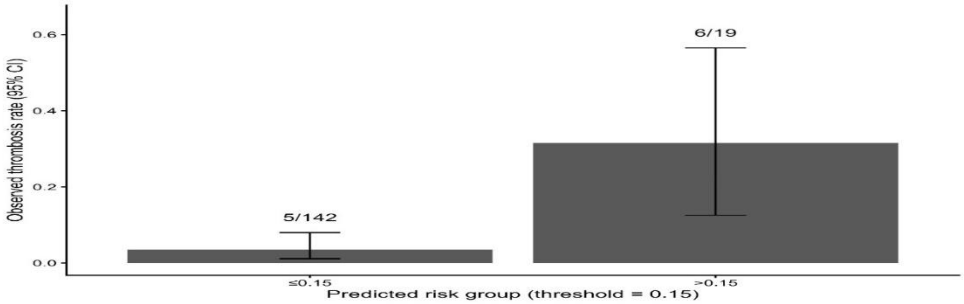

Figure 6. Observed thrombosis rates in two model-based risk groups. Patients were stratified according to predicted probability of thrombosis (≤0.15 vs >0.15). Bars show observed event rates with exact 95% confidence intervals; labels indicate events/total

Table 7. Model-based risk stratification for thrombosis prediction based on a probability threshold of 0.15.

LIKELIHOOD	Total	Events	observed_rate	Medium_expected risk
<0.15	142	5	0.035211	0.044786562
>0.15	19	6	0.315789	0.244226751

A key limitation of this model was the small number of thrombosis in the study cohort. Although ridge penalty and bootstrap internal validation were used to mitigate overfitting and estimate optimism-corrected performance, the model was only internally validated, and its transferability to other contexts is unknown. Therefore, external validation (ideally in an independent cohort) is required before clinical implementation. The value of the model for assessing the risk of thrombosis in patients with NHL and aCL antibodies is not a "universal" one and cannot override clinical judgment. This prediction model of thrombotic events in patients with NHL and aCL antibodies, antiβ2GPI antibodies, LA antibodies is challenging and is oriented for thromboprophylaxis, but does not take into account the bleeding risk. Also, this prediction model was developed in a cohort of patients with the same malignant hemopathy, respectively, it represented the group of patients who can be considered for preventive measures. This model would have application for stratifying and recognizing patients at highest risk of VTE and those who could benefit most from thromboprophylactic intervention. Our study was oriented towards the development and formal validation of the model, but at the same time it could be used in particular to identify patients with NHL and aCL antibodies, at increased risk of VTE prior to the possible complication and to select the group of NHL patients for additional testing, closer monitoring or thromboprophylactic treatment.

V. TOOLS FOR ASSESSING TREATMENT COMPLIANCE AND QUALITY OF LIFE IN PATIENTS WITH NHL

5.1. Estimating treatment compliance in patients with NHL

The dynamic assessment of treatment adherence by self-assessment by completing the MORISKY-8 Questionnaire did not register any obvious changes (figure 5.1; Chi^2 Test, 0.8 (g.l.=4), p=0.93).

The average level of treatment compliance increased from 45.4% (95% CI, 37.5-53.4) of patients to 47.8% (95% CI, 40-56) and then to 49.7% (95% CI, 41.7-57.7) of respondents. The low level of compliance tended to decrease insignificantly from 18% (95% CI, 12.4-24.8) to 15.6% (95% CI, 10.3-22) of patients, and then to 14.9% (95% CI, 9.8-21.4) cases. The number of patients with a high degree of compliance showed insignificant deviations, registering with the same frequency of 36.6% (95% CI, 29-44.6) of patients in Ev I and II, and then reduced to 35.4% (95% CI, 28-43.3) of patients in cases of evaluation at the completion of the first line of therapy.

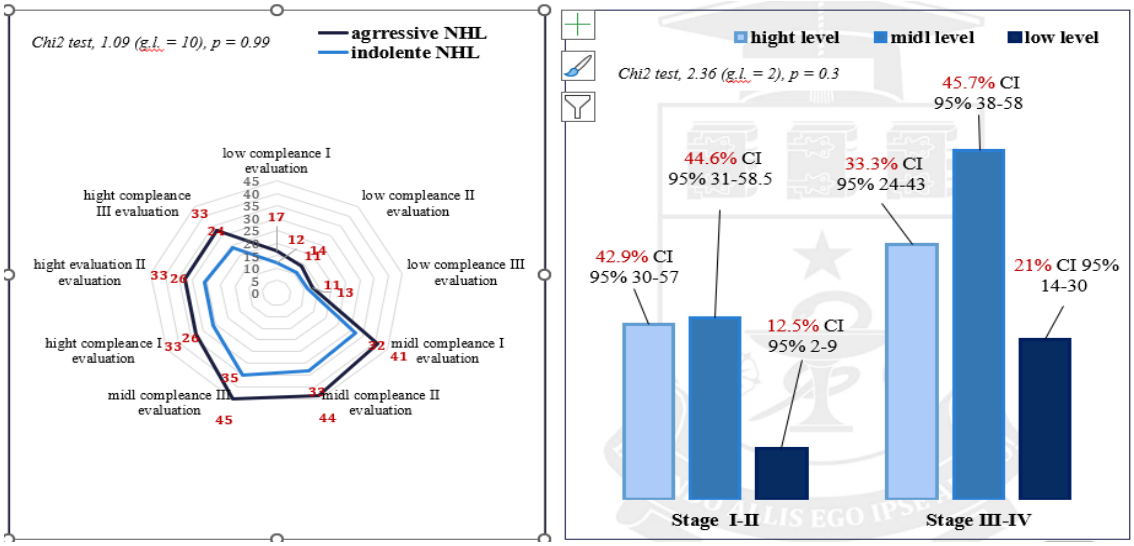

Figure 7. Compliance level according to NHL type and stage.

Depending on gender, the level of treatment compliance assessed in dynamics determines the prevalence of two extreme levels (high and low) in men with a percentage distribution of 21%-21.7% for high level and 8%-10% for low level of compliance, in contrast to the same levels recorded in women 13.7%-15% and 6.8%-8% (Chi^2 Test, 9.94 (g.l.=10), p=0.45).

Independent of age, during the dynamic evaluation, average compliance with treatment was more frequently assessed, followed by the number of patients with high compliance with treatment (Chi^2 Test, 10.97 (g.l.=10), (p=0.36).

There were no significant differences (Chi^2 Test, 1.09 (g.l.=10), (p=0.99) in the level of compliance depending on the aggressive or indolent type of NHL. Among patients with local stages (I-II) of NHL-34.8% (95% CI, 27.5-42.7), high and medium compliance levels prevailed in the same percentage distribution of 14.9% (95% CI, 10-21) and 15.5% (95% CI, 10-22), and low compliance level was estimated in only 4.4% (95% CI, 1.8-8.8) cases. It is important to emphasize an uneven characterization of patients with NHL in generalized stages (III-IV) depending on the level of compliance, with an increase in the percentage of subjects with low compliance – 13.7% (95% CI, 8.8-20) (Chi^2, 2.36, g.l.=2, p=0.3).

5.2. Estimating the quality of life of patients with NHL and the reliability of assessment tools

EORTC QLQ-C30 (VERSION 3)

The global quality of life scale (QLQ) had a median score of 67, with a range of 17 to 100, with a mean of 61 (95% CI, 58–64), corresponding to an average global level. In 43% (95% CI, 35-51) of cases, an average level of QLQ (50-69 points) was estimated, followed by 30% (95%

CI, 24-38) of cases of a low level of QLQ (<50 points) and 27% (95% CI, 20-34) of cases of a high level of QLQ (70-100 points). The functional health status scale (FS) was investigated before treatment initiation, with a mean score of 80 (range, 3–10, mean, 72, 95% CI, 69–76). The pretreatment symptom health status scale (SS) recorded a mean score of 26 (range, 3–85, mean, 31, 95% CI, 28–33).

Age did not have a significant influence on QLQ in NHL patients. Patients younger than 65 years of age—74.5% (95% CI, 67-81) of respondents had a median QLQ of 67, range 17-100 (Mann-Whitney U test, p=0.7044). Patient age did not significantly influence FS values, with those younger than 65 years of age having similar SF levels (median, 80, range, 13.3-100) compared to those over 65 years of age (median, 80, range, 3.3-100, Mann-Whitney U test, p=0.48). Age had no impact on SS in primary NHL patients (Mann-Whitney U p=0.5).

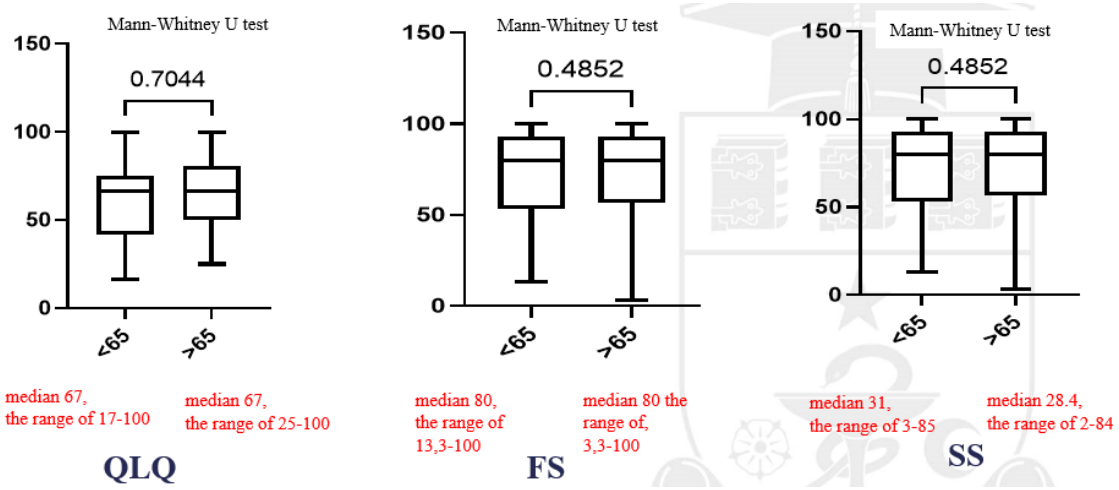

Figure 8. QLQ, FS, SS according to age of NHL patients.

Patient gender did not have a significant impact on QLQ (p=0.8), FS (p=0.8), SS (p=0.4). Low SS (< 50 points) was estimated in 85.7% (95% CI, 79-91) of patients including 45.3% (95% CI, 38-53) of men and 40.4% (95% CI, 33-48) of women.

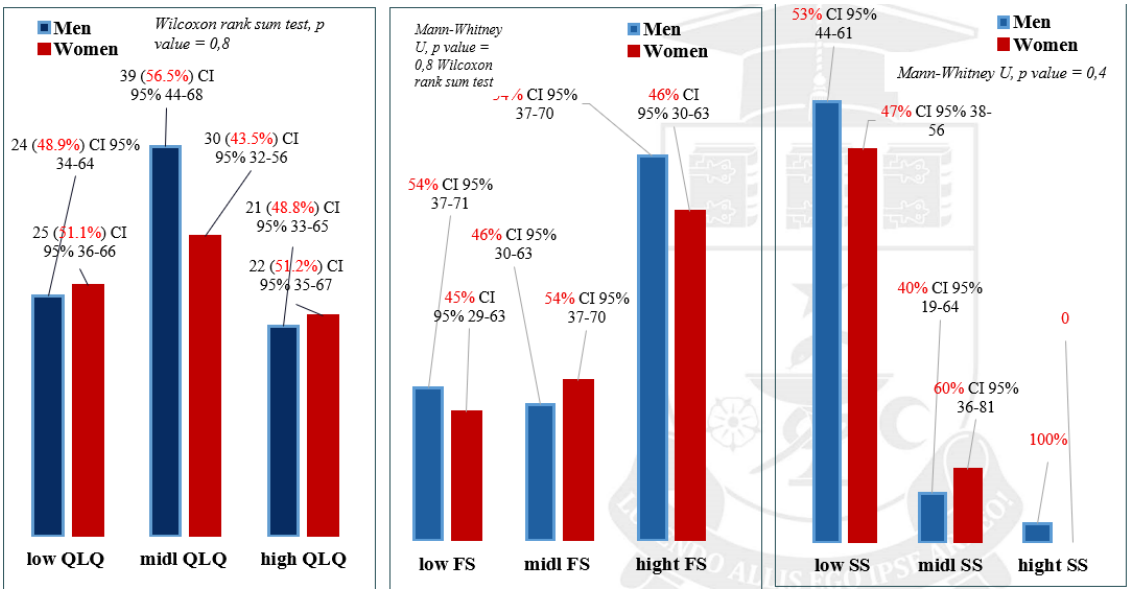

Figure 9. QLQ, FS, SS according to gender of patients with NHL.

A higher QLQ was in indolent NHL—mean of 65 (95% CI, 60-70), versus QLQ in aggressive NHL—mean of 58 (95% CI, 54-62), although the difference obtained did not reach statistical significance with a nonparametric test (p=0.051). A non-significantly higher level of SF was in indolent NHL-mean of 72.5, as opposed to aggressive NHL-mean of 70, and a lower level of SF was estimated in aggressive NHL-14.9% (95% CI, 10-21) of cases versus indolent NHL-5.7% (95% CI, 3.5-12). High SS of symptomatology was in patients diagnosed with aggressive NHL, but despite a trend towards a higher SS score in patients with aggressive NHL, no statistically significant association was observed (p=0.2).

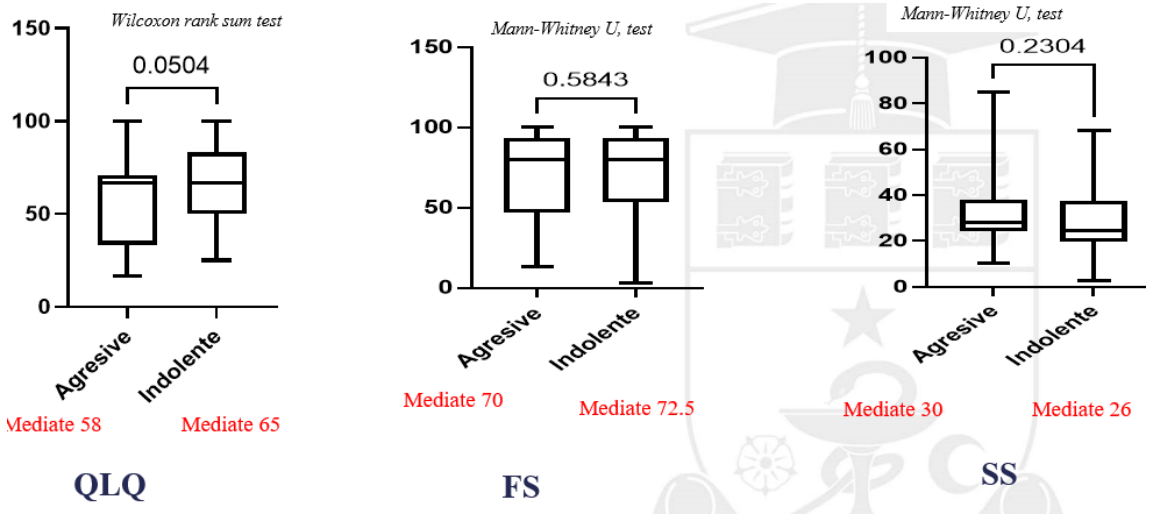

Figure 10. QLQ, FS, SS depending on NHL type.

NHL stage (localized I-II or generalized III-IV) (Wilcoxon rank sum test, p=0.9), presence of symptoms B versus their absence – A (Wilcoxon rank sum test, p=0.7; 0.5) do not influence QLQ, FS, SS levels.

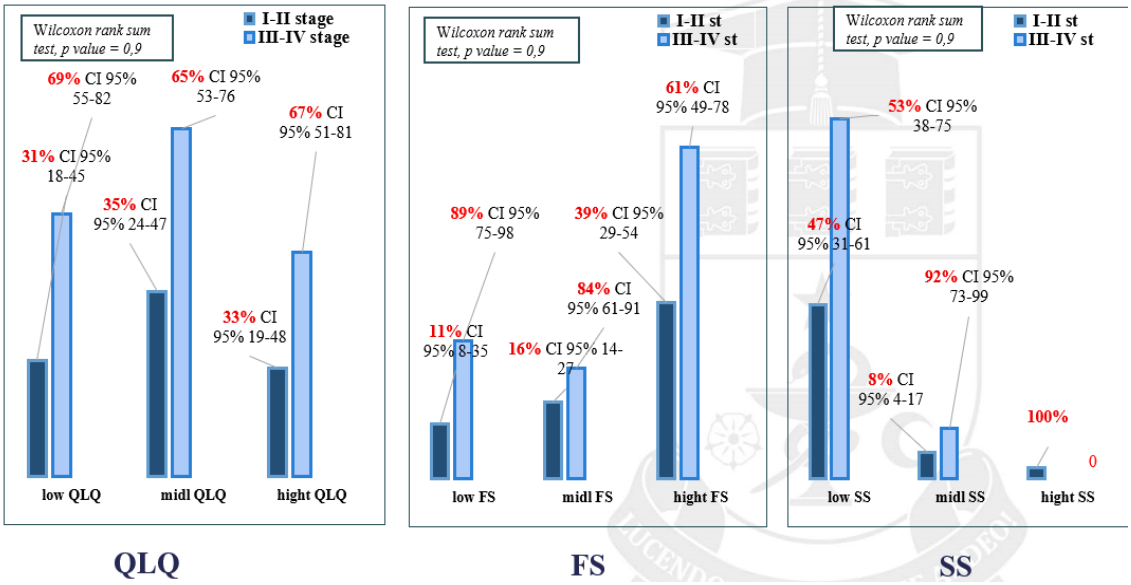

Figure 11. QLQ, FS, SS according to NHL stage.

42.2% (95% CI, 34.5-50) of patients with a low IPI (0-1) with a median of 66.7, mean of 65.7, (95% CI, 61-71) QLQ versus 57.8% (95% CI, 50-65.5) of patients with an intermediate and high IPI (2-5), with a median of 58.3, mean of 57.7, (95% CI, 54-62) showed significantly lower

levels of QLQ (p=0.02), indicating the role and impact of IPI. A lack of relationship between IPI and SF (p=0.2) and SS (p=0.16) was estimated.

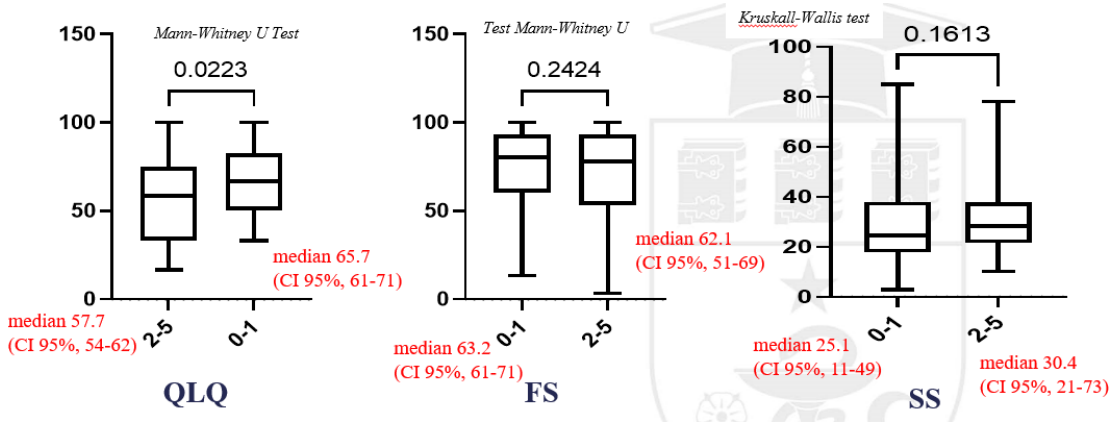

Figure 12. QLQ, FS, SS according to IPI.

Similarly, the NHL patient's ICC also had no impact on QLQ (p>0.9), on FS (Kruskal-Wallis test, p=0.2), despite the presence of an apparent trend of higher FS in patients with a higher ICC, and on SS (p=0.3).

Analysis of the distribution of NHL patients according to nodal versus extranodal onset and QLQ revealed a uniform distribution of patients with low and high nodal onset QLQ of 17.4% (95% CI, 12-24) patients each. In all 3 variations of QLQ, patients with nodal versus extranodal onset NHL prevailed. A more obvious gap was estimated among respondents with a low QLQ score: 17.4% (95% CI, 12-24) patients with nodal onset NHL versus 10% (95% CI, 5.8-15.6) patients with extranodal location of the primary tumor focus, in a ratio of 1.8:1.

Interpretation of the characterization of NHL responders according to tumor focus location did not demonstrate an association with SF (p=0.8) and SS (p>0.9).

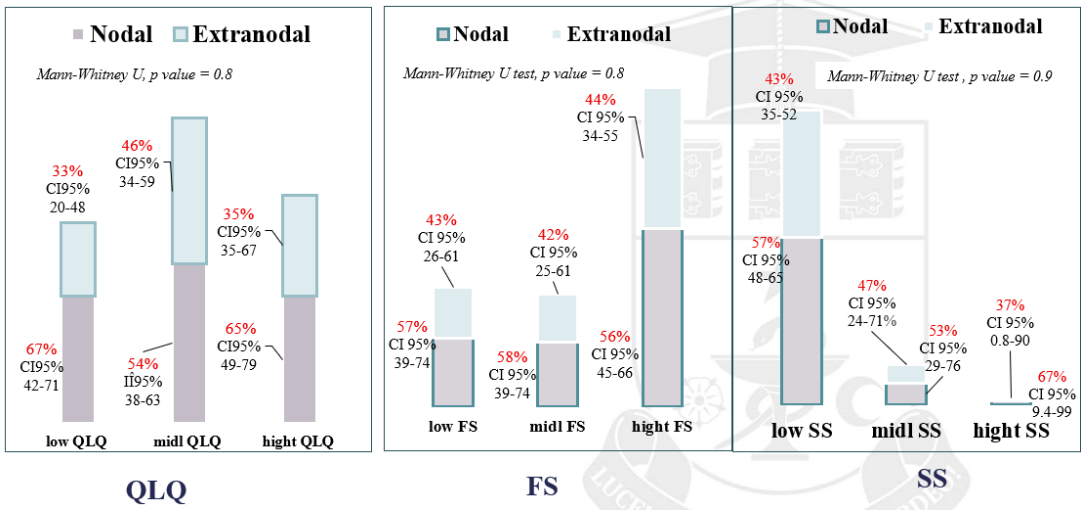

Figure 13. QLQ, FS, SS depending on the location of the primary tumor focus.

GENERAL PSYCHOLOGICAL WELL-BEING (GWB)

The GWB score before treatment initiation (GWB1) was 56 (range 32–101, mean 59, 95% CI 57–62), corresponding to a high overall mean level of stress. The most common level of stress was recorded in 59% (95% CI 51–67) of patients, followed by a low level of stress in 25% (95% CI 19–32) and, more rarely, 16% (95% CI 11–23) of patients with a medium level of stress. In the self-reported assessment of GWB2 and GWB3 scores over time, stress levels were significantly

reduced following the treatment program (Kruskall-Wallis test with multiple comparisons using Dunn's corrected test) (Figure 14).

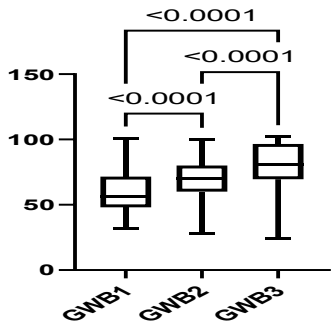

Figure 14. Psychological well-being of the patient with NHL over time

Independently of the environment of origin, a high level of psychoemotional stress prevailed in 59% (95% CI, 51-67) of cases: urban-53.7% (95% CI, 43-64) and rural-46.3% (95% CI, 36-57). Reduced stress level over 6 months reached satisfactory values in 71.4% (95% CI, 64-78) of respondents: urban-53% (95% CI, 43.5-62), rural-47% (95% CI, 38-56). A difference depending on the environment of origin, in a ratio of 2.6:1 was appreciated in the case of the analysis of the distribution of NHL patients with high stress levels assessed over time.

A high level of stress develops in all primary patients regardless of gender: women-55.8% (95% CI, 45.2-66), men-44.2% (95% CI, 34-55). GWB was higher in men-67.5% (95% CI, 51-81) of cases versus in women in 32.5% (95% CI, 18.6-49) of cases. The evaluation after 6 months notes a positive dynamic by reducing to 15.5% (95% CI, 10-22) cases of high stress: 64% (95% CI, 42.5-82) women and 36% (95% CI, 18-57) men, but also the increase in respondents with psychoemotional well-being to 71.4% (95% CI, 64-78) of patients among 59.1% (95% CI, 49.6-68) of men and 29.2% (95% CI, 32-50) of women (figure 15).

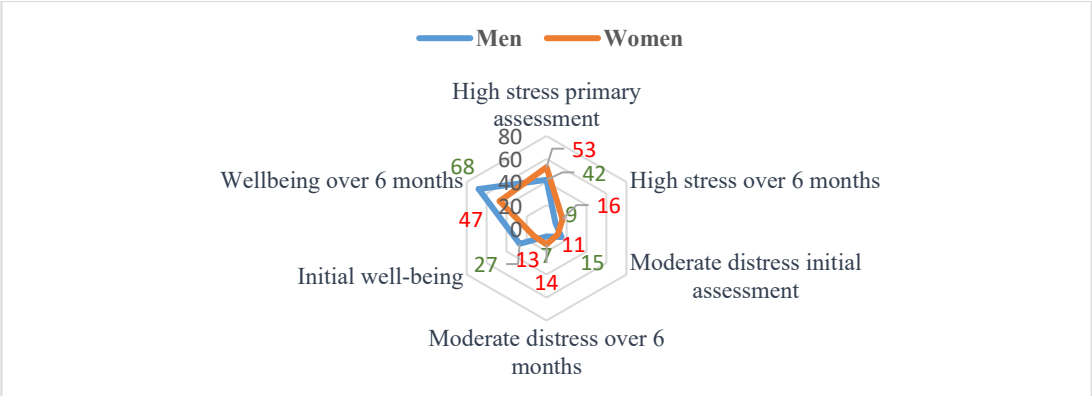

Figure 15. Psychoemotional well-being assessed on-going by gender in NHL.

High stress in respondents who are in the age category over 65 years and 35-65 years, being established in 60.5% (95% CI, 43-76) and 53% (95% CI, 43-62.5) of cases, respectively. All young patients aged 18-34 years assessed themselves as developing a high level of stress following self-assessment.

In 64.8% (95% CI, 54-74.6) of cases of high stress level in aggressive NHL compared to 36.2% (95% CI, 39-63.5) of patients with indolent NHL with the same psychoemotional state. In the case of initially assessed average distress 17.6% (95% CI, 10.4-27) patients with aggressive NHL versus 14.3% (95% CI, 7-25) patients with indolent NHL. Similarly, a predominance of cases with aggressive NHL with high stress and medium distress was observed at the time assessment over 6 months from the initiation of specific treatment for malignant lymphoma. However, it is encouraging that the number of patients decreases to 25 (15.5%) (95% CI, 10-22) with aggressive

NHL and indolent NHL with such psychoemotional disorders: 80% (95% CI, 59.3-93) respondents with aggressive NHL with high stress versus 20% (95% CI, 6.8-40.7) respondents with indolent NHL.

Table 8. Psychoemotional state assessed over time according to NHL stage

Psycho-emotional well-being	GWB1		GWB3	
	Stages I-II abs, %, CI 95%	Stages III-IV abs, %, CI 95%	Stages I-II abs, %, CI 95%	Stages III-IV abs, %, CI 95%
High stress	29 (52.7) 39-66	68 (64) 54-73	9 (16.3) 3-10	17 (16) 9.6-24
Medium distress	11 (20) 10.4-33	14 (13.2) 7.4-21	7 (12.7) 5.2-24	14 (13.2) 7.4-21
Psycho-emotional well-being	15 (27.3) 16-41	18 (22.8) 10-25	39 (71) 57-82	75 (70.8) 61-79
Total	55 (100)	106 (100)	55 (100)	106 (100)

Note: CI – confidence interval; n – number of patients (absolute); % – number of patients in percentage; GWB1 – psychoemotional well-being at primary assessment; GWB3 – psychoemotional well-being at assessment 6 months after initiation of first-line treatment.

SHORT FORM (SF-8)

The physical health scale (physical domain–PhD) was investigated in 161 NHL patients during the first interview, with a mean score of 63.8 (range, 20-100, mean, 56, 95% CI, 51-62). The mental health scale (mental domain–MD) in the same group of eligible study respondents had a mean score of 55.3 (range, 15-100, mean, 47, 95% CI, 41-54). Given that scores > 50 indicate a better state of health, and scores < 50 represent a low quality of life, we can see that in both domains (PhD and MD) a good state of health is appreciated on average.

Independently of the type of NHL aggressive or indolent, an alteration in the quality of life of the patients studied with a score < 50 is observed mainly due to MD versus PhD in a ratio of 2:1 – 37 (23%) (95% CI, 17-30) versus 19 (11.8%) (95% CI, 7.3-18) cases.

Table 9. Value of PhD and MD scores (< 50 or > 50) depending on NHL type

SF-8	patients	Aggressive NHL		Indolente NHL	
		Scor < 50 abs, %, CI 95%	Scor > 50 abs, %, CI 95%	Scor < 50 abs, %, CI 95%	Scor > 50 abs, %, CI 95%
PhD	161	11 (12) 6.2-21	80 (88) 79.4-94	8 (11.4) 5-21	62 (88.6) 79-95
MD		23 (25.3) 17-35	68 (74.7) 64-83	14 (20) 11-31	56 (80) 69-88

Note: FD – physical domain, MM – mental domain, CI – confidence interval, % - frequency

The evaluation of these scores according to NHL types does not show a statistical difference (Wilcoxon rank sum test, p=0.9), but nevertheless the lowest scores in both domains were estimated in patients with aggressive NHL.

GENERAL CONCLUSIONS

1. aCL antibodies, antiβ2GPI antibodies, LA antibodies were detected in 16.2%: single positivity-88.5%; double positivity-7.7% and triple positivity-3.8%, with the prevalence of IgM vs IgG (8:1), only in B-cell NHL, aggressive 76.9% (p=0.03) (RR of 1.46), with lymph node onset 77%, with median age 50.5 years (p=0.0054), independent of stage (p=0.07), B symptoms (p=0.83) (RR of 1.08).
2. Hemostasis disorders were in 13% of cases: hemorrhages (14.3%) and thrombosis (85.7%) (p=0.01), with atypical localization (61%), only in the venous system, at a mean age of 50.5 years (p=0.34), more frequent in men (72%, p=0.0041), only in B-cell NHL, aggressive 72% RR 1.5 (p=0.11), mediastinal (RR of 1.3, OR of 5.07, p=0.02), with dimensions ≥ 7 cm (p=0.1), in stages I-II 39% (p=0.07) and B symptoms 66.7% (p>0.99), in the first 4-6 months of disease onset (100%).
3. Among patients with seropositive NHL, 42.3% of thromboses are found, representing 61.1% of all thromboses, with unipositivity in 72%, predominantly with nodal onset 61%,

≥ 7 cm (p=0.1), aggressive NHL 83.3%, ECOG 2-4 in 61% (p=0.1), ICC 0-2 in 55.5%, BMI < 30 kg/m2 in 44.4%.

4. During the application of specific therapy, regression of aCL antibodies, antiβ2GPI antibodies and LA antibodies was recorded in accordance with the positive dynamics of NHL, regardless of the aggressive or indolent subtype (92.3%/7.7%/8.3%).
5. The association of thrombocytosis, increased ANC, average PLR of 183, hyperfibrinogenemia, increased Ddimers and LDH with the synthesis of aCL antibodies, antiβ2GPI antibodies, LA antibodies presents a greater potential for the development of thrombosis.
6. The Khorana score demonstrated the weakest discrimination ability (AUC=0.55, p=0.52), suggesting that it does not reliably distinguish thrombotic patients, and the ThroLy score showed moderate discrimination ability (AUC = 0.66), but nevertheless, did not reach statistical significance (p=0.08). The Carpini score performed the best (AUC=0.68, p=0.048), apparently being the most reliable predictor with the highest odds ratio, significant association with thrombosis, and the best AUC.
7. Age (p=0.7; 0.48; 0.5), gender (p=0.8, 0.8; 0.4), ICC (p>0.9; 0.2; 0.3), NHL stage (p=0.9; > 0.9; 0.9), B symptoms (p=0.7; 0.5; 0.5) had no impact on the EORTC QLQ, SF, SS suggesting that other factors could determine the different score levels. According to GWB, psychoemotional stress was reduced on the background of treatment (p<0.0001), independently of the environment of origin, gender, stage of the disease. High stress was found more often in 18-40 years and >70 years (21.1% each), in aggressive NHL (36.7%) According to SF-8, a good health status was observed, but lower scores were observed in aggressive NHL (p=0.9). The degree of compliance with treatment during the dynamic evaluation did not register obvious changes, with average compliance prevailing, followed by high and low compliance (Chi^2 Test, 0.8 (g.l.=4), p=0.93), independent of gender (Chi^2 Test, 9.94 (g.l.=10), p=0.45), age (Chi^2 Test, 10.97 (g.l.=10), p=0.36), and NHL type (Chi^2 Test, 1.09 (g.l.=10), p=0.99).
8. The predictive reliability of the instruments for assessing quality of life, treatment compliance, satisfaction and general well-being in NHL established prior to the research coincided with the operational one determined by self-assessment in real conditions through time surveillance of respondents during the same period of time and does not require additional scarce resources.
9. The model for assessing the risk of thrombotic events in patients with NHL and aCL antibodies has value for stratifying patients at highest risk of VTE and for selecting those who require additional testing, closer monitoring, or thromboprophylactic treatment.

RECOMMENDATIONS FOR HEMATOLOGISTS

1. Integration of aCL determination in primary NHL patients for individualized stratification of patients into risk groups for early and late thrombotic complications.
2. Implementation of the risk assessment model for thrombotic events in patients with NHL and aCL antibodies.
3. Monitoring the profile of clinical variables with demonstrated prothrombotic risk such as the development of aggressive, B-cell NHL, intermediate, high intermediate, high and very high IPI with lymph node conglomerate, particularly mediastinal, in the first 9 months from the onset of the disease through the mandatory perspective of laboratory variables
4. Development and implementation of personalized prophylactic strategies (drug, mechanical, etc.) to reduce the risk of factors impacting hemostasis.
5. Periodic, individual evaluation of the results of prophylaxis already applied with adjustment of strategies depending on the evolution of NHL: complete remission, partial remission or disease progression.

RECOMMENDATIONS FOR HEMATOLOGISTS REGARDING ENSURING TREATMENT COMPLIANCE

1. Develop educational strategies adapted to the age group, the level of education of the patient with NHL regarding the optimal management of symptoms, the profile of associated adverse reactions by providing information regarding the role of treatment and the evolution of the disease depending on the presence/absence of treatment.
2. Development of behavioral strategies with application through education of NHL patients with reference to the importance of high levels of compliance with treatment.
3. Individualization of therapy so as to bring about minimal acceptable changes on the part of the NHL patient in the lifestyle through a joint doctor-patient decision.
4. Implementation of self-management adherence programs (in groups, online, etc.) in order to support persistence in treatment.
5. Creating an additional support "tool" (patient calendar, reminder messaging for doctor visits, outpatient medication administration, etc.) for good treatment adherence and long-term disease control.

RECOMMENDATIONS FOR CLINICAL PSYCHOLOGISTS

1. Expand early psychological counseling services (online or in person) provided to patients with NHL, their caregivers, and families to accept the malignant nature of NHL, cognitively and emotionally to ensure their quality of life.
2. Adjustment from the perspective of the NHL patient in the community, such as personal problems, abilities to adapt to new demands associated with increased caregiving demands, inability to return to work, financial constraints, marital stress, etc.
3. Developing a coordinated plan for physiological, cognitive, behavioral, emotional, and relational care for survivors, maximally personalized with psychosocial support and assistance included.

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