Azienda Ospedaliera Nazionale
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Alessandria

IL RISCHIO DI TROMBOSI NEI PAZIENTI CON LINFOMA

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BACKGROUND

Table 1
Incidence of thromboembolic complications in hematologic malignancies.

Disease	Overall incidence	Reference
MGUS	6%	Sallah et al. [27]
	3%	Kristinsson et al. [29]
Myeloma	10%	Skralovic et al. [28]
	10%	Barlogie et al. [31]
Lymphoma	5-10%	Rickles et al. [2]
High-grade non-Hodgkin lymphoma	11%	Mohren et al. [22]
	7,5%	Sgarabotto et al. [71]
Low-grade non-hodgkin lymphoma	6%	Mohren et al. [22]
	3%	Sgarabotto et al. [71]
Hodgkin lymphoma	7%	Mohren et al. [22]
	3%	Sgarabotto 2008
Myelodysplastic syndromes	6,5%	Sgarabotto et al. [71]
Acute leukemia	6%	De Stefano et al. [6]
	2%	Ziegler et al. [4]
	12%	Mohren et al. [5]

Elice & Rodeghiero, Thromb Res 2012

BACKGROUND

Risk of VTE in patients with NHL seems to be similar to what observed in high risk solid tumors: in retrospective studies VTE incidence in patients with NHL ranges from 5 to 15%

Falanga A et al.; JCO, 2009
Ku GH et al.; Blood, 2009
Melillo L et al.; Acta Haematol, 2007
Kwaan HC et al.; Thromb Hemost , 2007
Caruso V et al.; Blood, 2006
Blom JW et al.; JAMA, 2005

BACKGROUND

blood®
2010 115: 5322-5328
doi:10.1182/blood-2010-01-258624 originally published online April 8, 2010

Thrombotic complications in adult patients with lymphoma: a meta-analysis of 29 independent cohorts including 18 018 patients and 1149 events

Vanesa Caruso, Augusto Di Castelnuovo, Susana Meschengieser, Maria A. Lazzari, Giovanni de Gaetano, Sergio Storti, Licia Iacoviello and Maria Benedetta Donati

<u>Meta-analysis</u>:

-VTE incidence: 6.5%
-VTEs more frequent in high-grade NHL and in pts with advanced disease
-most VTEs occur within 3-6 months from diagnosis

BACKGROUND

Thrombosis Research(2012):130(3);e6-e12

Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: Results from a prospective cohort study with Asian population

Lee Chun Park[1], Sook-young Woo, Seonwoo Kim, Hyejin Jeon, Young Hyeh Ko, Seok Jin Kim, Won Seog Kim

[1]*Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.*

-cohort of 686 lymphoma pts (NHL + HL)
-VTE incidence 7.9% (NHL > HL)
-median time of VTE development: 1.97 months
-risk factors for VTE:

- **age > 60 years**
- **CNS involvement**
- **chemotherapy (no VTE in untreated pts)**

LYMPHOMA-ASSOCIATED VTE

- **Increased morbidity and mortality**
- **Prolonged hospitalization**
- **Use of anticoagulant drugs**
- **Bleeding-related complications**
- **Incresed risk of recurrent VTE**
- **Interruption or modification therapy for the primary disease**

VTE RISK AND LYMPHOMA CHARACTERISTICS

- **NHL > HL**

Lee Chun Park. *Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: Results from a prospective cohort study with Asian population*. Thrombosis Research(2012):130(3);e6-e12

- **High-grade compared with low-grade**

Caruso V. *Thrombotic Complications in adult patients with lymphoma: a meta-analysis of 29 independent cohorts including 18018 patients and 1149 events. Blood 2010: 115 : 5322-5328*

- **Tumor stage**

Lee Chun Park. *Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: Results from a prospective cohort study with Asian population*. Thrombosis Research(2012):130(3);e6-e12

- **Tumor site.**

Highest incidence of VTE in primary central nervous system lymphoma and mediastinal lymphoma

Colombo R. *Thrombosis and hemostatic abnormalities in hematological malignancies. Clin Lymp Myeloma Leuk 2014;14:441-450*

- **Higher incidence of venous thrombosis than of arterial events (84 vs 16)**

Caruso V. *Thrombotic Complications in adult patients with lymphoma: a meta-analysis of 29 independent cohorts including 18018 patients and 1149 events. Blood 2010: 115 : 5322-5328*

FACTORS PREDISPOSING

- **The first three months of therapy**

Colombo R. *Thrombosis and hemostatic abnormalities in hematological malignancies.* Clin Lymp Myeloma Leuk 2014;14:441-450

- **Therapeutic agents (anthracycline based regimens)**

Lee Chun Park. *Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: Results from a prospective cohort study with Asian population*. Thrombosis Research(2012):130(3);e6-e12

- **Infectious complications**

Rickles Fr. Mechanism of cancer-induced thrombosis in cancer.Pathophysio Haemost Thromb 2006;35(1-2):103-110

- **Thrombophilia**

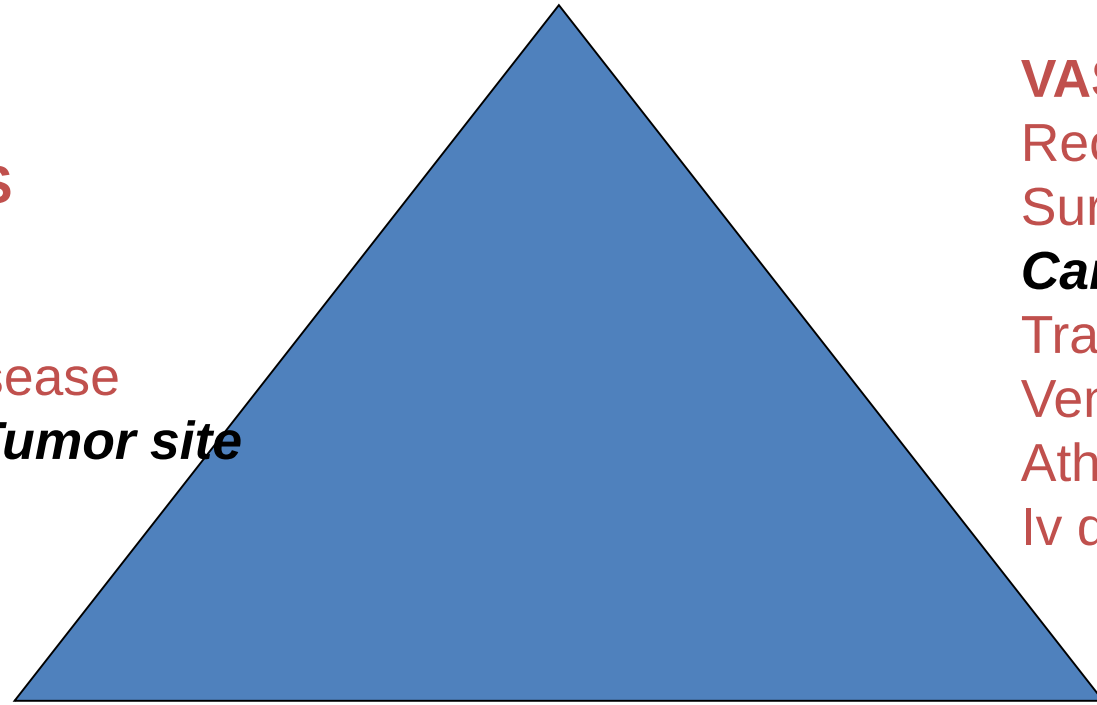
Blom JW . *Malignancies, phrothrombotic mutations, and the risk of venous thrombosis. JAMA 2005;293:715-722*
Genvresse **L.** *Prevalence and clinical significance of anticardiolipin and anti-beta2GP1antibodies in limphoma. Eur J of hematology 2002;68:322-332.*

- **Central venous device**

Conlan MG. *Catheter-related thrombosis in patients with refractory lymphoma undergoing autologous stem cell trasplantation. Bone Marrow Transplant 1991;7:4235-240.*

Virchow's triad in NHL

Risk factor are cumulative



VENOUS STASIS

Obesity

Immobility

Chronic Heart Disease

Tumor stage & Tumor site

VASCULAR INJURY

Reccurent VTE

Surgery

Cancer treatment

Trauma

Venipuncture

Atherosclerosis

Iv drug administration

HYPERCOAGULABILITY

Malignancy

Bleeding disorders

Hereditary risk factors

Anderson FA, Jr.Spencer, Circulation, 2003 : 107 ;9-16

THROMBOPROPHYLAXIS IN CANCER PATIENTS

In hospitalized patients (ASCO/ACCP)

Lyman GH. *American Society of Clinical Oncology. Venous thromboembolism prophylaxis and treatment in patients with cancer:American Society of Clinical Oncology clinical practice guideline update 2014. J Clin Oncol 2015:33:654 656.*

Kahn SR. American College of Chest Physician . Prevention of VTEin non surgical patients; antithrombotic therapy and Prevention of Thrombosis, 9 th ed;American College of Chest Phisician Evidenced-based Clinical Practise guidelines. Chest 2012:141;e195S-226S

Khorana Score for patients in outpatient settings (ASCO/ESMO)

Mandalà M. *ESMO Guidelines Working Group. Management of venous thromboembolism in cancer patients :ESMO Clinical Practice Guidelines. Ann Oncol 2011: 22:vi85vi92. J Thrombosis Hemostasis 2010: 8, 202 204*

THROMBOPROPHYLAXIS IN NHL PATIENTS

- **No specific guidelines**
- **No validated risk assessment model**
- **Largely underulitized**

Risk of thrombocytopenia from disease and/or chemotherapy

- **An accurate estimate of individual patient's VTE risk is important to target thromboprophylaxis in high risk patients**

PREDICTIVE MODEL

blood®
2008 111: 4902-4907
doi:10.1182/blood-2007-10-116327 originally published online January 23, 2008

Development and validation of a predictive model for chemotherapy-associated thrombosis

Alok A. Khorana, Nicole M. Kuderer, Eva Culakova, Gary H. Lyman and Charles W. Francis

Table 1. Khorana Score

Khorana Score	Risk score
Site of cancer	
very high risk (stomach, pancreas)	2
high risk (lung, lymphoma, etc)	1
PLTs ≥ 350 x 10^9/l pre-chemo	1
Hb < 10 g/dl or use of r-EPO	1
WBC > 11 x 10^9/l pre-chemo	1
BMI 35 kg/m^2 or more	1
Low risk	0 points
Intermediate risk	1-2 points
High risk	≥ 3 points

validated in solid tumors for risk of VTE development

KS IN NHL

- **Only 328 lymphoma patients were included in the study**
- **Arterial thrombotic events were not evaluated**
- **Lymphoma characteristics (stage, site, extranodal) were not considered**
- **A criticism of KS is the fact that its value could be limited by the effect of bone marrow involvement by lymphoma on platelets and leukocyte counts**

A PROPOSAL OF PREDICTIVE MODEL

RESEARCH ARTICLE

AJH

Development and validation of multivariable predictive model for thromboembolic events in lymphoma patients

Darko Antic,[1,2*] Natasa Milic,[3,4] Srdjan Nikolovski,[1] Milena Todorovic,[1,2] Jelena Bila,[1,2] Predrag Djurdjevic,[5,6] Bosko Andjelic,[1,2] Vladislava Djurasinovic,[1] Aleksandra Sretenovic,[1] Vojin Vukovic,[1] Jelena Jelicic,[1] Suzanne Hayman,[7] and Biljana Mihaljevic[1,2]

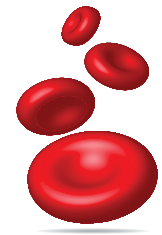


TABLE IV. Predictive Model for TE in Lymphoma Patients

Patient characteristics	Assigned score
Previous VTE/AMI/stroke	2
Reduced mobility (ECOG 2-4)	1
Obesity (BMI $>$ 30 kg/m^2)	2
Extranodal localization	1
Mediastinal involvement	2
Neutrophils $<1 \times 10^9$/L	1
Hemoglobin level $<$ 100 g/L	1

AMI, acute myocardial infarction; BMI, Body mass index; VTE, venous thromboembolic events.

Low risk	0-1
Intermediate risk	2-3
High risk	>3

EMERGING MARKERS

- **Thrombin generation**
- **Procoagulant Microparticles**
- **Solubile P-selectina**
- **D-Dimer**

Khorana Score and Histotype as Predictors of Early Thrombosis in NHL. A Pooled Data Analysis of 12 Clinical Trials of Fondazione Italiana Linfomi.

Roberto Mario Santi[1], M.Ceccarelli[2], E.Bernocco[1], C.Monagheddu[2], A.Evangelista[2], F. Valeri[1], F.Monaco[1], U.Vitolo[4], S.Cortelazzo[5], MG.Cabras[6], M.Spina[7], L.Baldini[8], C.Boccomini[4], A.Chiappella[4], A.Bari[9], S.Luminari[9], C.Visco[10] M.Calabrese[11], A.Levis[11], L.Contino[1], G.Ciccone[2] and M.Ladetto[1].

Preliminary results were presented in abstract form at the 2015 ASH Meeting (Orlando, FL, USA) and at 2016 EHA Meeting (Copenhagen Danemark, UE) and at the 2016 8th International Conference on Thrombosis and Hemostasis issues in cancer (Bergamo, Italy EU)

PATIENT & TRIAL CHARACTERISTICS

Table 2. Pts characteristics by trial

	DLCL04	DCLC10	FLE09	FOLL05	FOLL12	HEARTH01	INFL08	INFL09	MCL0208	R-benda-frail	R-BAC	REAL07	TOTAL
N° pts	399	33	79	504	129	47	38	68	256	41	57	66	1717

Table 5. Pts distribution according to experimental phase of clinical trials and NHL histology

Trial	NHL histotype	Study phase	Pts no	Pts contribution to the study (%)
R-BENDA FRAIL	DLBCL	II	41	2.39
DLCL10	DLBCL	II	33	1.92
REAL07	DLBCL	II	66	3.84
HEARTH01	DLBCL	II	47	2.74
DLCL04	DLBCL	III	399	23.24
TOTAL DLBCL No			586	
TOTAL DLBCL %				34.13
INFL09	INFL	II	68	3.96
INFL08	INFL	II	38	2.21
TOTAL INFL No			106	
TOTAL INFL %				6.17
MCL0208	MCL	III	256	14.91
RBAC	MCL	I/II	57	3.32
TOTAL MCL No			313	
TOTAL MCL %				18.23
FOLL05	FL	III	504	29.35
FOLL12	FL	III	129	7.52
FLE09	FL	II	79	4.60
TOTAL FL No			712	
TOTAL FL %				41.47
Total			1717	100

PATIENT CHARACTERISTICS

Table 4. Pts general characteristics at baseline		
		TOTAL
	N	1717
Gender	1717	
Male		1007 (59%)
Female		710 (41%)
Age (years)	1717	57 (49;66)
Hb (g/dl)	1632	13.0 (11.5;14.2)
PLTs (10^9/l)	1612	224 (169;298)
WBC (10^9/l)	1618	7.1 (5.6;10.3)
BMI	1411	25 (22;28)
r-EPO	1348	
No		1224 (91%)
Yes		124 (9%)
KS	1189	
1		689 (58%)
2		359 (30%)
3		123 (10%)
4		18 (2%)
KS	1189	
≤ 2		1048 (88%)
≥ 3		141 (12%)
Histotype	1717	
DLBCL		586 (34.13%)
FL		712 (41.47%)
INFL		106 (6.17%)
MCL		313 (18.23%)

METHODS

Table 3. VTE - CTCAE V4.0

Grade	Definition
1	Venous thrombosis (i.e. superficial thrombosis)
2	Venous thrombosis (i.e. uncomplicated deep vein thrombosis), medical intervention indicated
3	Thrombosis (i.e. uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated
4	Life-threatening (i.e. pulmonary embolism, cerebrovascular event, arterial insufficiency), hemodynamic or neurologic instability, urgent intervention indicated

- **VTE definition and grading stated according to standard criteria of toxicity**
- **analysis limited to the first 6 months from treatment start (as the majority of VTEs develops in this period)**
- **analysis restricted to VTEs (excluding arterial events)**
- **sensitive sub-analysis excluding trials with lenalidomide administration during the first 6 months of treatment**

RESULTS

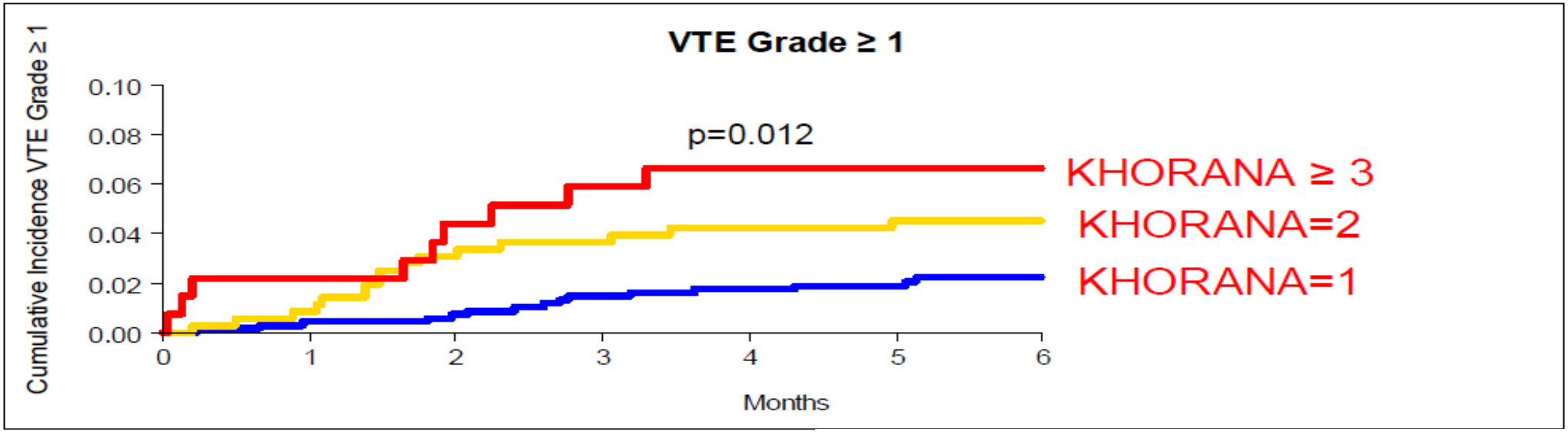


Table 8. Cumulative incidence of VTE of any grade at 6 months

VTE grade ≥ 1	Cumulative incidence at 6 months (CI 95%)	Gray test p
Total pts (n° = 1717)	2.9% (2.1 – 3.8)	-
Pts with available KS (n° = 1189)	3.4% (2.4 – 4.4)	-
KS = 1 (n° = 689)	2.2% (1.1 – 3.3)	p = 0.012
KS = 2 (n° = 359)	4.5% (2.3 – 6.7)	
KS ≥ 3 (n° = 141)	6.6% (2.4 – 10.8)	

Table 9. Cumulative incidence of VTE grade ≥ 3 at 6 months

VTE grade ≥ 3	Cumulative incidence at 6 months (CI 95%)	Gray test p
Total pts (n° = 1717)	1.1% (0.6 – 1.6)	-
Pts with available KS (n° = 1189)	1.3% (0.6 – 1.9)	-
KS = 1 (n° = 689)	0.7% (0.1 – 1.4)	p = 0.048
KS ≥ 2 (n° = 500)	2.0% (0.8 – 3.3)	

cumulative incidence of VTE at 6 months by KS

RESULTS

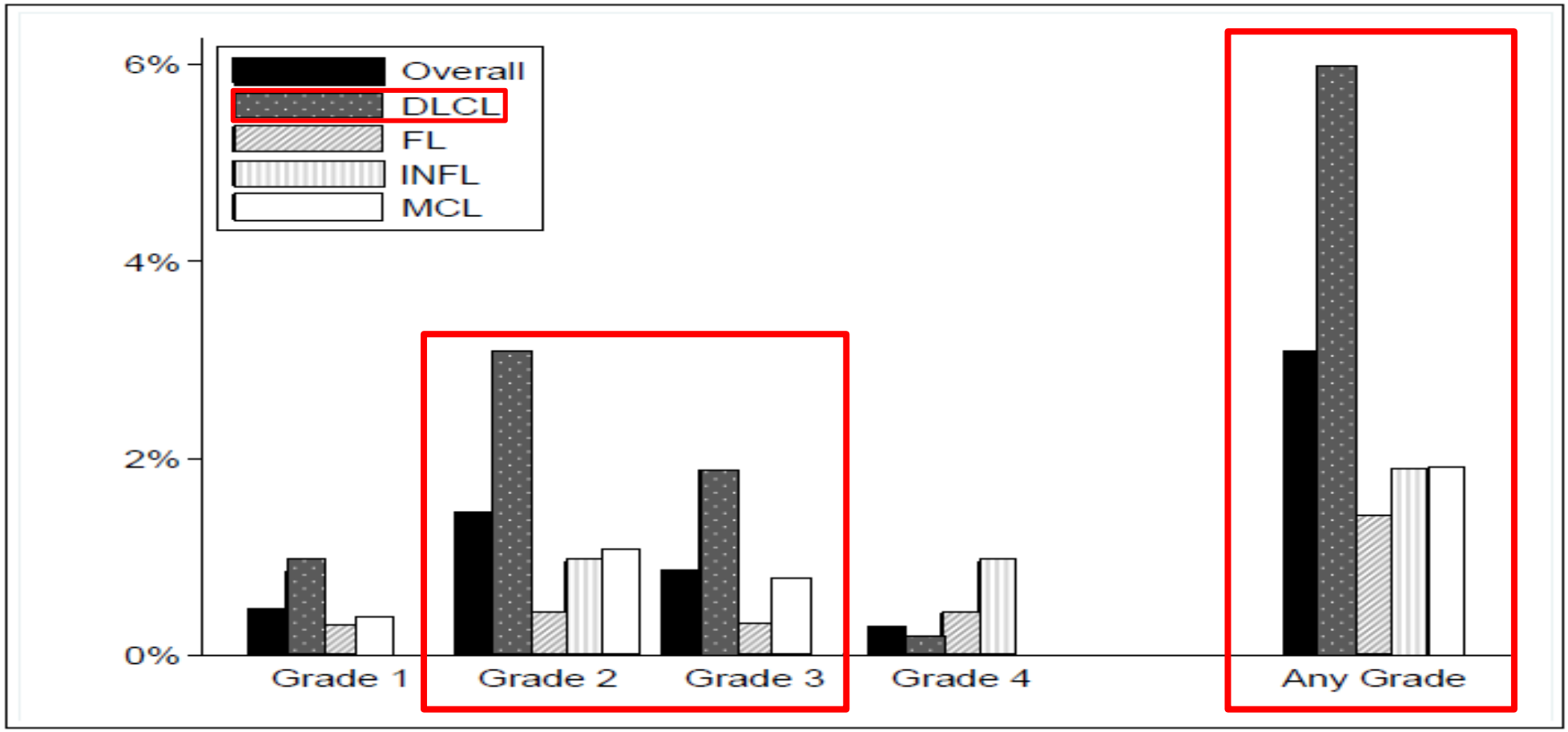
VTE incidence by grouping pts by KS (≤ 2 vs ≥ 3)

Table 10. Incidence of VTE of grade ≥ 1 at 6 months

	Pts No	VTE No	%
KS			
≤2	1048	31	2.96
≥3	141	10	7.09
missing	528	5	0.95
NHL histotype			
DLBCL	586	29	4.95
FL	712	10	1.40
INFL	106	2	1.89
MCL	313	5	1.60
Total	1717	46	2.68

incidence of VTE grade ≥ 1 at 6 months

RESULTS



- **stratification of VTE incidence by NHL histotype**
- **increased overall VTE incidence in DLBCL histotype (particularly grade 2 and 3 VTE events)**

RESULTS

Table 12. Fine & Gray multivariate analysis for VTE risk

	HR (CI95%)	p value
KS ≥ 1 (adj)		
KS = 1 (ref)	1	-
KS ≤ 2	2.00 (0.85 – 4.71)	0.147
KS ≥ 3	3.87 (1.50 – 10.00)	0.049
Histotype (adj)		
FL (ref)	1	-
DLBCL	2.58 (1.01 – 6.55)	0.023
INFL	1.13 (0.24 – 5.31)	0.875
MCL	0.47 (0.1 – 2.17)	0.332

multivariate analysis for VTE risk at 6 months by KS and histotype

KS and DLBCL histotype are independently associated to an increased risk of VTE at 6 months from treatment start

RESULTS

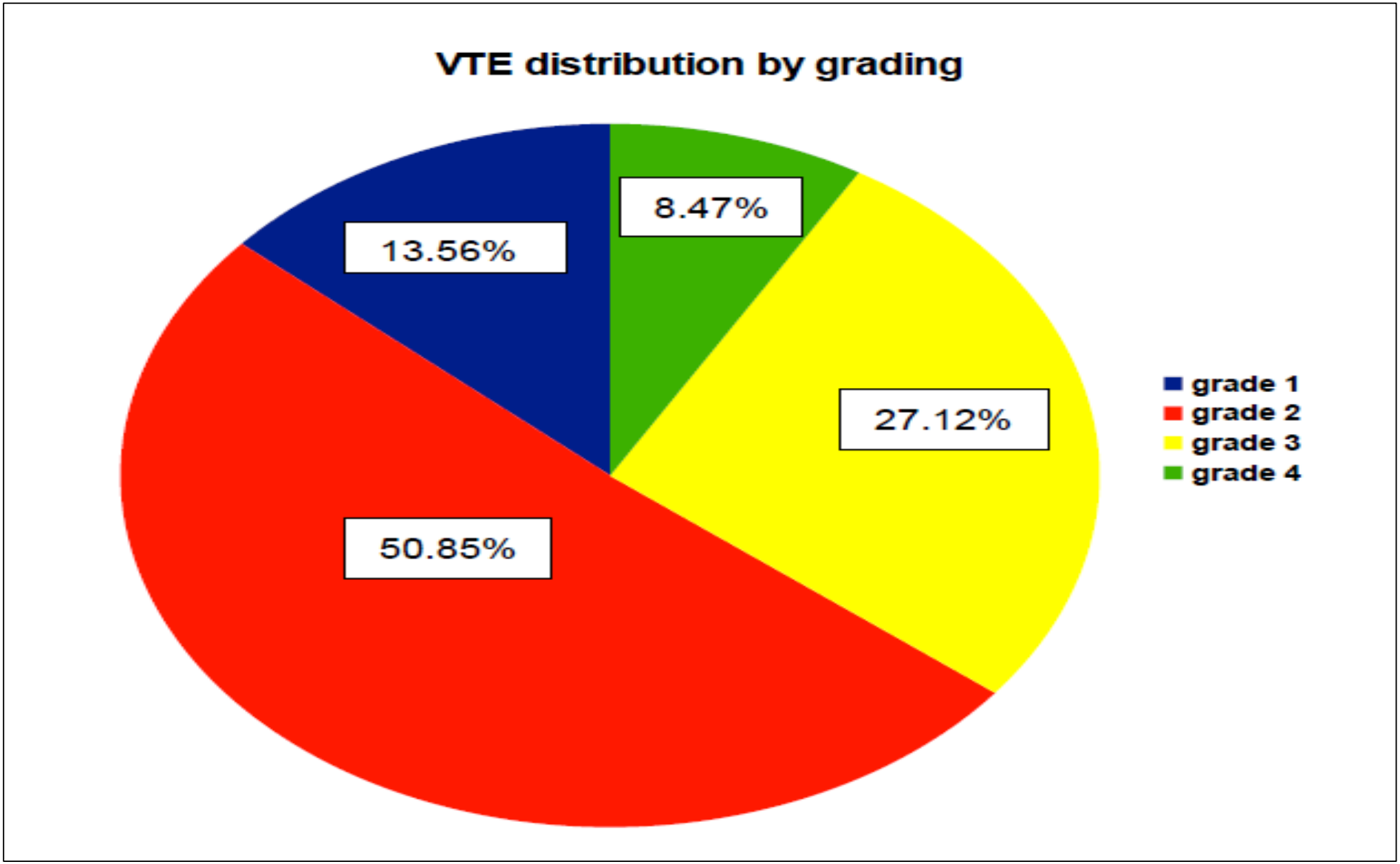
Table 13. Ordinal logistical regression model for VTE risk.

	OR (CI95%)	p value
KS (unit increase)	1.85 (1.23 – 2.80)	0.031
Histotype		
FL (ref)	1	-
DLBCL	2.45 (1.11 – 5.42)	0.027
INFL	1.13 (0.24 – 5.44)	0.876
MCL	0.65 (0.17 – 2.44)	0.523

ordinal logistic regression model for VTE risk at 6 months by KS and histotype

the increase of 1 point in KS resulted in an increased risk of VTE at 6 months from treatment start

RESULTS


VTE distribution by grading
8.47%
13.56%
27.12%
50.85%
grade 1
grade 2
grade 3
grade 4

CONCLUSIONS

- **Risk of VTE in patients with NHL seems to be similar to what observed in high risk solid tumor**

- **The incidence of VTE is influenced by many factors, including the type and the stage of lymphoma, antitumor therapies, the use of central venous devices**

- **Thromboprophylaxis is largely underutilized**

- **An accurate estimate of individual patient's VTE risk is important to target thromboprophylaxis in high risk patients**

CONCLUSIONS

- **No validated risk assessment model**
- **KS seems able to identify the patients affected by NHLs with high risk of VTE**
- **The risk of VTE need to be further refined by exploring VTE-associate biomarkers such as D-dimer, thrombin generation assay and fibrinogen levels.**