EVALUATION OF CURRENT CLINICAL MODELS FOR RISK OF PROGRESSION FROM MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE TO MULTIPLE MYELOMA OR RELATED MALIGNANCIES IN 2028 PERSONS FOLLOWED IN THE CZECH REPUBLIC

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INTRODUCTION

- Monoclonal gammopathy of undetermined significance (MGUS) is a non-malignant condition associated with a risk of progression to multiple myeloma (MM) or related disorders.
- There are currently 2 clinical models predicting progression from MGUS to MM (1).
- The Mayo Clinic model uses levels and type of serum monoclonal protein (M-protein) and serum free light chain ratio (sFLC) (2).
- The Spanish PETHEMA model uses flow cytometry of bone marrow plasmocytes (BMPC) and the presence of DNA aneuploidy (3).

PURPOSE

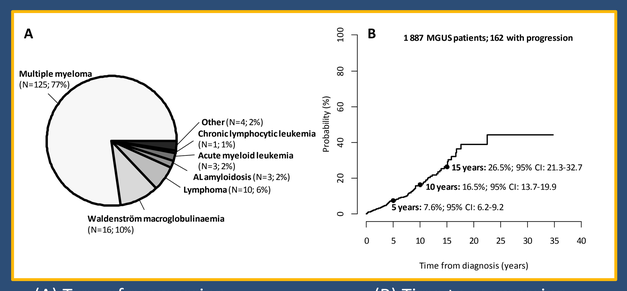
- To estimate the cumulative risk of hematologic disorders occurring during the follow-up of our cohort.
- To validate known clinical models suggested by the Mayo Clinic group and the Spanish PETHEMA group for the risk of progression from MGUS to MM or related malignancies.
- To establish a new risk model by the Czech Myeloma Group (CMG model) with better prediction of low-risk MGUS group.

GROUP

- Data for this study were obtained from the Registry of Monoclonal Gammopathies (RMG) acquired from hematologic centers of the Czech Republic.
- MGUS diagnosis was made according to IMWG criteria.
- In total, 2028 persons with MGUS were enrolled in the RMG study from May 2007 to June 2013.
- A total of 93% (1887/2028) of persons were evaluated with median 4 years.

RESULTS I

- Malignancies developed in 8.6% (162/1887) cases (Figure 1A).
- The risk of progression was 1.5% at 1 year, 7.6% at 5 years and 16.5% at 10 years after diagnosis (Figure 1B).



(A) Type of progression (B) Time to progression

1.Kyle RA, Durie BG, Rajkumar SK, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 2010;24:1121-1127.
2.Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smouldering multiple myeloma. Blood 2008;111:785-789.
3.Pérez-Persona E, Vidriales MB, Mateo G, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smouldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood 2007;110:2586-2592.

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RESULTS II

Figure 2:The key predictors factors of progression

N (%)	Without progression	Progression to tumor	p[1]
Total (N=1887)	**N=1725**	**N=162**	
Age (at diagnosis)			
60-69 vs. younger than 50	47/561 (7.7%)	1.78 (1.04-3.05)	0.036
older than 69 vs. younger than 50	52/571 (8.3%)	2.55 (1.49-4.36)	**0.001**
MIG in serum			
normal	1529 (94.0%)	97 (6.0%)	**<0.001**
abnormal (>15g/l)	172 (74.8%)	58 (25.2%)	
Bone marrow infiltration			
normal	1049 (92.5%)	85 (7.5%)	**<0.001**
abnormal (> 5%)	128 (78.0%)	36 (22.0%)	
Immunoparesis			
One Ig lower vs. other	41/319 (11.4%)	2.06 (1.43-2.99)	**<0.001**
Both Ig lower vs. other	22/97 (18.5%)	3.06 (1.94-4.85)	**<0.001**
Any Ig lower vs. other	63/416 (13.2%)	2.78 (1.99-3.90)	**<0.001**
FLC index			
normal	831 (97.0%)	26 (3.0%)	**<0.001**
abnormal (<0.26 or >1.65)	575 (87.7%)	81 (12.3%)	
Hemoglobin	1455 (92.5%)	118 (7.5%)	0.014
normal			
abnormal (<120g/l)	265 (88.0%)	36 (12.0%)	
LDH			
normal	1021 (94.5%)	59 (5.5%)	**<0.001**
abnormal (>3.75ukat/l)	564 (88.0%)	77 (12.0%)	
Type of paraprotein			
normal	1198 (91.7%)	109 (8.3%)	0.594
abnormal (non IgG)	520 (90.9%)	52 (9.1%)	

1 Tested by ML Chi-square test

Mayo model

Distribution of MGUS persons according to risk groups based on the Mayo Clinic model confirmed predictive power of Mayo Clinic model based on our data although isotype of M- protein was not found as independent predictor (Figure 3).

Modified PETHEMA model

Immunoparesis instead of DNA aneuploidy was used together with the presence of abnormal plasma cells (aPCs) to validate the modified PETHEMA model. We confirmed predictive power of this model based on our data (Figure 3).

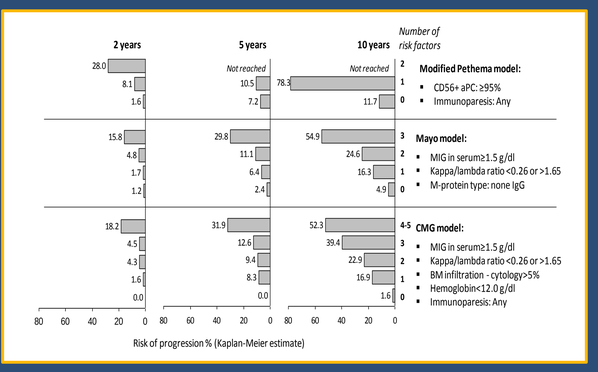
CMG model

Based on the 5 parameters with independent predictive value in the univariate analysis (immunoparesis, serum M-protein quantity ≥ 1.5 g/dL, BMPC > 5%, abnormal sFLC ratio and serum level of hemoglobin < 12.0 g/dL) we proposed a new CMG model (Figure 3).

Figure 3: Comparison of risk models

No. of risk factors	Overall rate of progression N (%)	HR (95% CI)	p	Kaplan-Meier's estimate of risk of progression % (95% CI) at: 2 years	10 years
Modified Pethema model[1]					
0 (N=245)	8 (3.3%)	*reference*		1.6 (0.5-4.9)	11.7 (4.8-26.9)
1 (N=80)	11 (13.8%)	3.98 (1.60-9.91)	**0.003**	8.1 (3.7-17.3)	78.3 (40.1-98.9)
2 (N=11)	2 (18.2%)	14.23 (2.86-70.76)	**0.001**	28.0 (7.2-76.2)	-
Mayo model[2]					
0 (N=571)	13 (2.3%)	*reference*		1.2 (0.5-2.6)	4.9 (2.5-9.5)
1 (N=593)	41 (6.9%)	2.59 (1.39-4.84)	**0.003**	1.7 (0.9-3.2)	16.3 (11.1-23.7)
2 (N=296)	42 (14.2%)	4.79 (2.56-8.93)	**<0.001**	4.8 (2.8-8.1)	24.6 (17.6-33.8)
3 (N=26)	9 (34.6%)	12.97 (5.52-30.48)	**<0.001**	15.8 (6.2-36.8)	54.9 (27.8-85.7)
CMG model[3]					
0 (N=311)	2 (0.6%)	*reference*		0.0 (-)	1.6 (0.2-11.1)
1 (N=307)	21 (6.8%)	9.59 (2.25-40.90)	**0.002**	1.6 (0.6-4.1)	16.9 (10.6-26.3)
2 (N=210)	25 (11.9%)	15.80 (3.74-66.80)	**<0.001**	4.3 (2.1-8.3)	22.9 (13.9-36.5)
3 (N=93)	13 (14.0%)	22.76 (5.13-101.02)	**<0.001**	4.5 (1.7-11.5)	39.4 (22.2-63.0)
4-5 (N=35)	11 (31.4%)	63.17 (13.99-285.36)	**<0.001**	18.2 (8.6-36.3)	52.3 (28.3-80.8)

Figure 4: **Risk of progression in 2, 5 and 10 years for modified Pethema, Mayo and CMG model**



CONCLUSIONS:

We confirmed validity of previously considered clinical models for the risk of progression from MGUS to MM by the Mayo Clinic group and the Spanish PETHEMA group (model used for SMM).

The created CMG model for the risk of progression from MGUS to MM or related malignancies was established with an advantage for better identification of MGUS persons at low risk (87% of persons with risk of progression below 10% in 5 years) as well as few persons at the highest risk of progression.