Risk Factors for Progression in MGUS and SMM

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Jacksonville, Florida

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No conflicts to disclose

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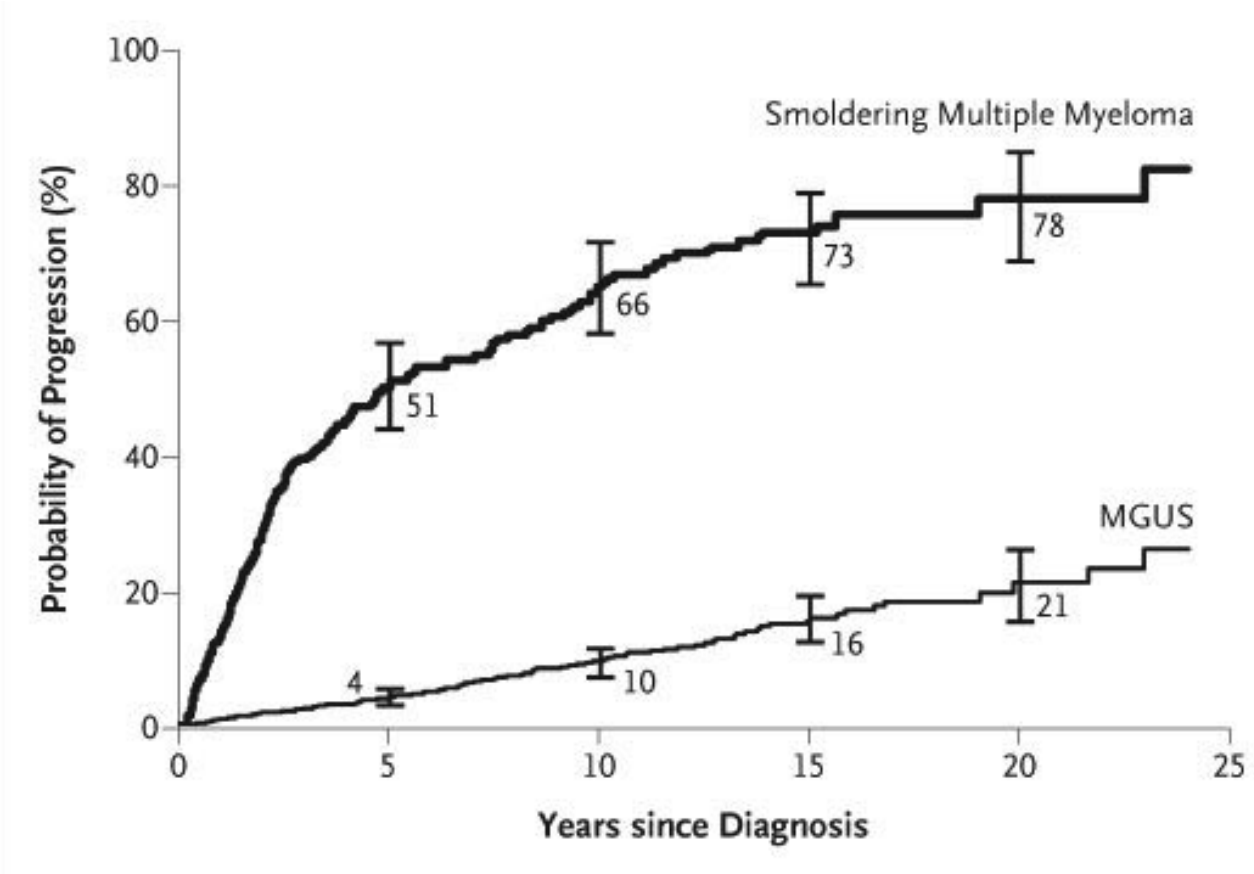
Progression in MGUS and SMM



Kyle RA et al. N Engl J Med 2007;356:2582-90.

The NEW ENGLAND JOURNAL of MEDICINE

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MGUS

Type of MGUS	Type of Progression	Risk of Progression
Non IgM MGUS (IgG, IgA)	Myeloma, Plasmacytoma	1% per year
IgM MGUS	Waldenstrom Macroglobulinemia	1.5% per year
LC-MGUS	Light Chain Myeloma	Not known

All can progress to AL amyloidosis

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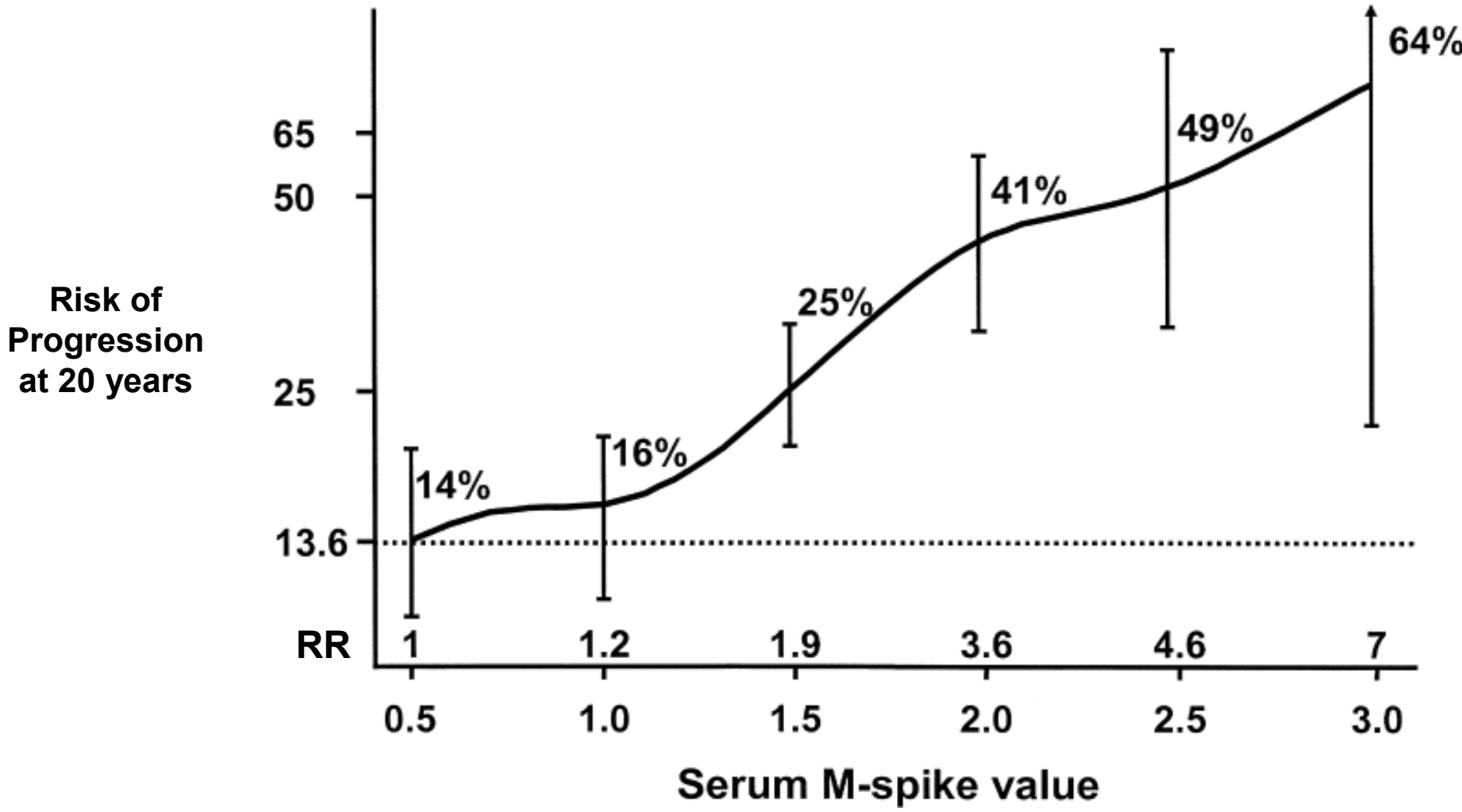
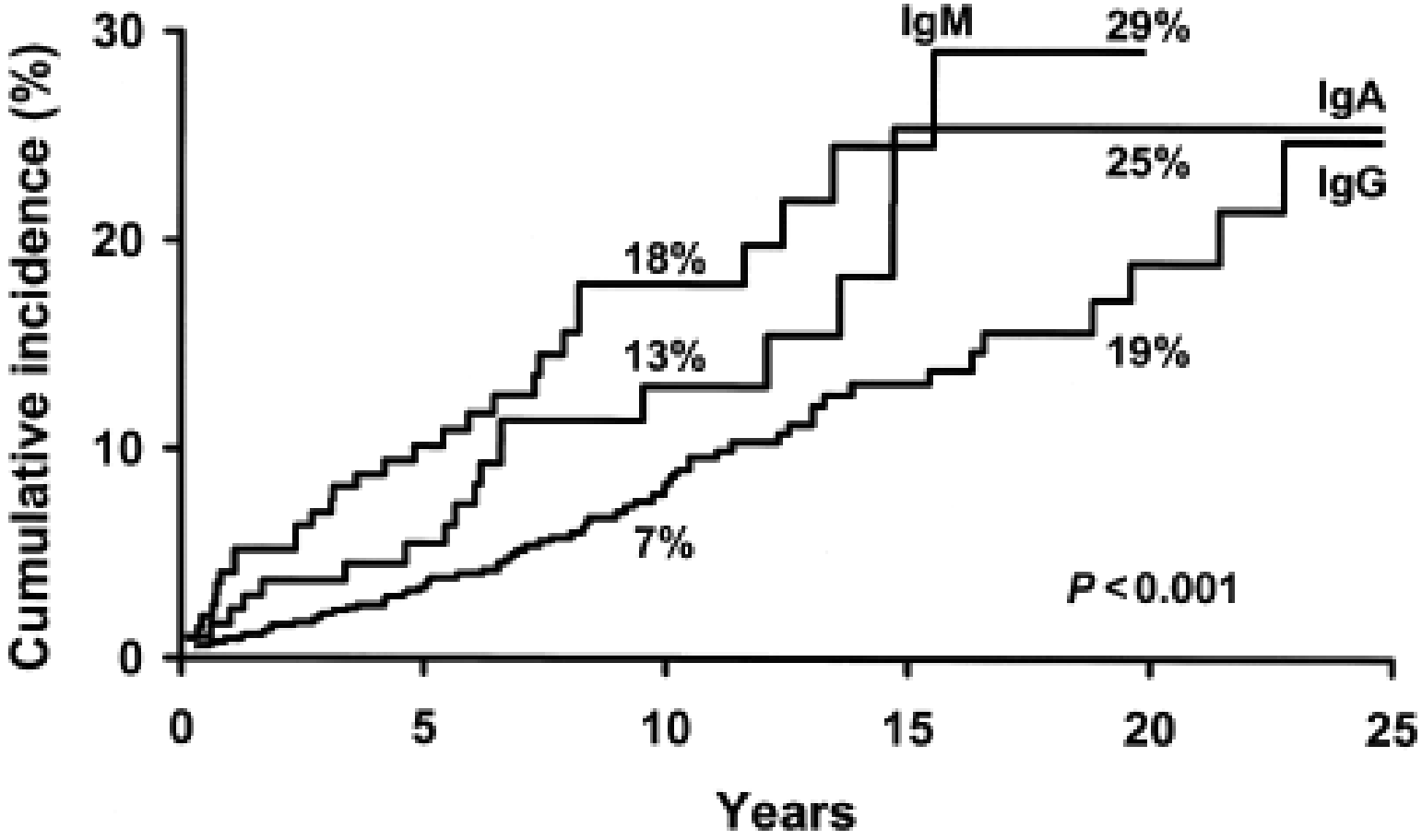
Risk Factors for Progression of MGUS: Size of M spike and Absolute Risk of Progression to Malignancy



Kyle RA and Rajkumar SV. Immunol Rev. 2003;194:112-139

Risk Factors for Progression of MGUS: Size of M spike and Absolute Risk of Progression to Malignancy



Kyle RA et al. N Engl J Med 2002;346:564-69

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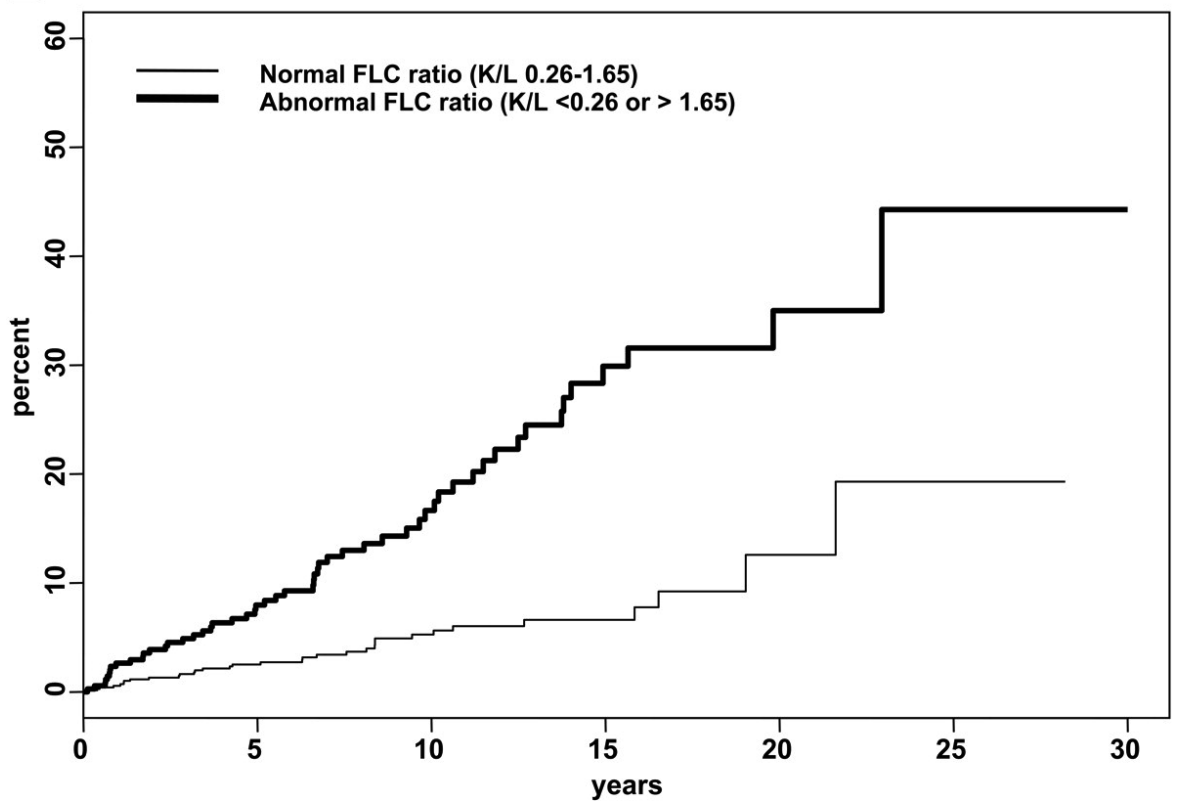
Risk Factors for Progression of MGUS: Abnormal FLC Ratio and Absolute Risk of Progression to Malignancy

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Rajkumar, S. V. et al. Blood 2005;106:812-817

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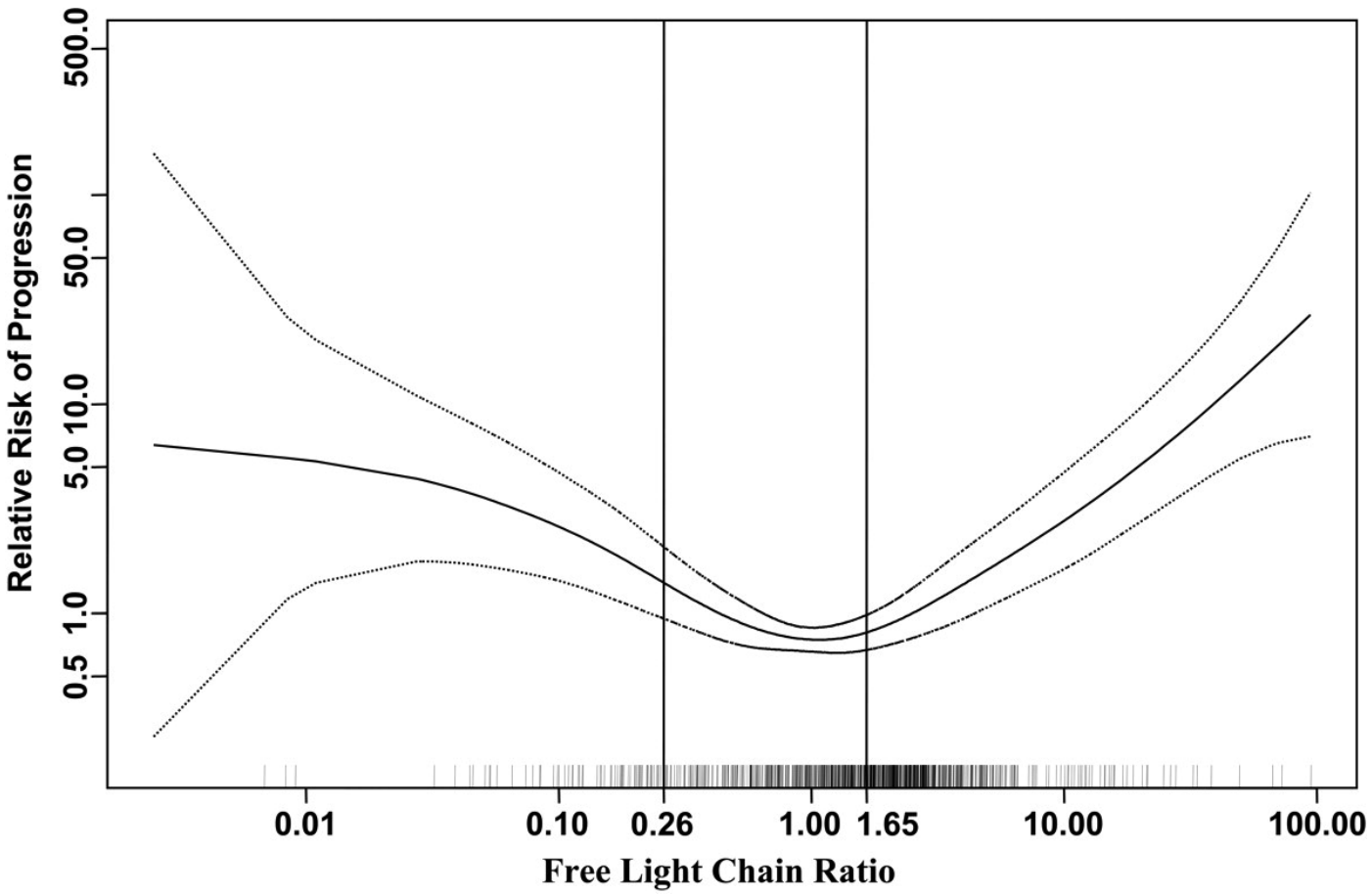
Effect of increasingly abnormal FLC ratio on the relative risk of progression of monoclonal gammopathy of undetermined significance to multiple myeloma or related disorder

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY



Rajkumar, S. V. et al. Blood 2005;106:812-817

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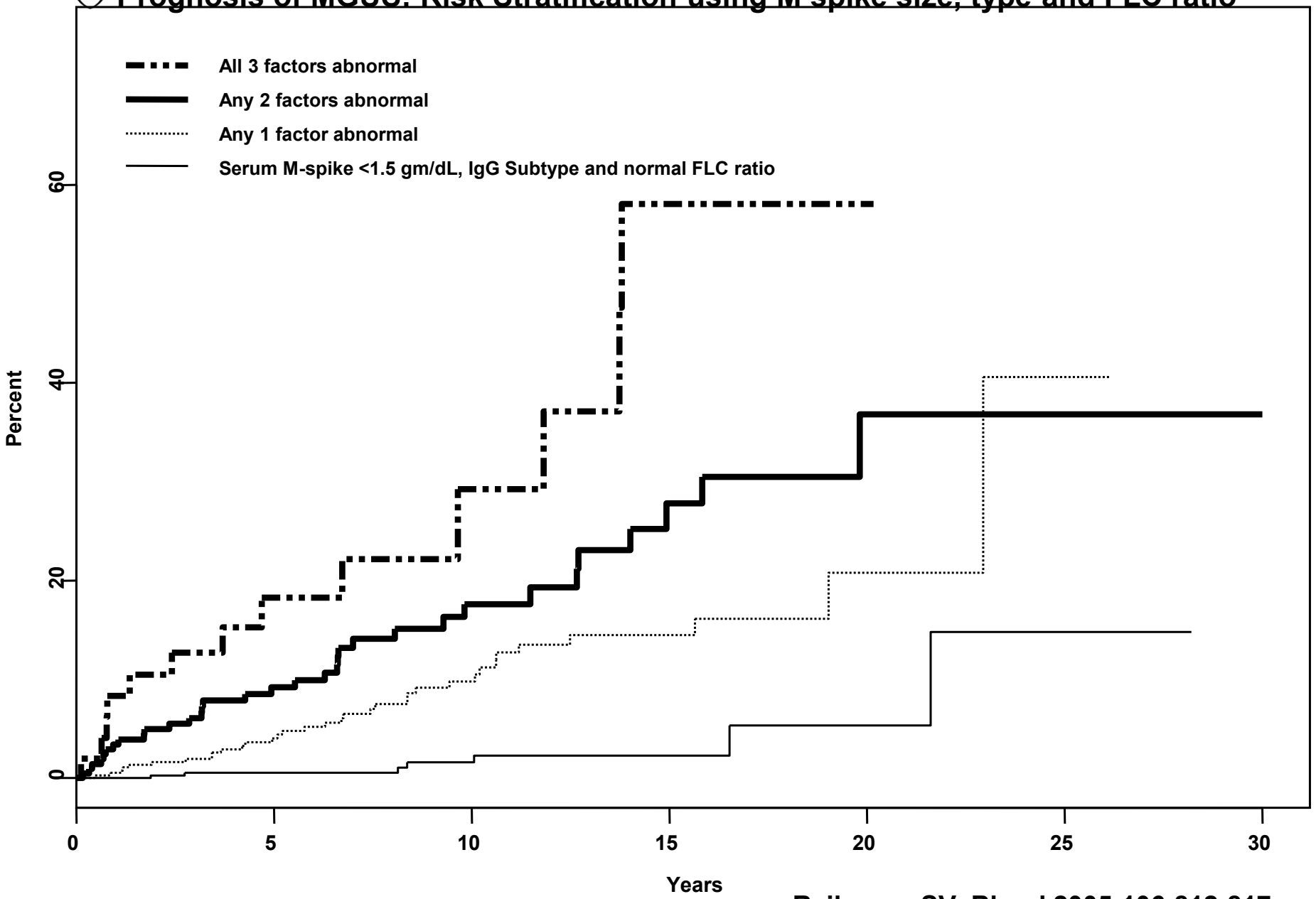
Prognosis of MGUS: Risk Stratification using M spike size, type and FLC ratio



Rajkumar SV. Blood 2005;106:812-817

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Risk Stratification of MGUS

Risk Group	No. of patients	Relative risk	Absolute risk of progression (ARP) at 20 years	ARP at 20 years with death as a competing risk
Risk stratification model				
Low-risk **(No risk factor)**	**449**	**1**	**5%**	**2%**
Low-Intermediate-risk **(Any 1 factor)**	**420**	**5.4**	**21%**	**10%**
High-Intermediate-risk **(Any 2 factors)**	**226**	**10.1**	**37%**	**18%**
High-risk **(All 3 factors)**	**53**	**20.8**	**58%**	**27%**

Rajkumar SV et al. Blood 2005;106:812-817

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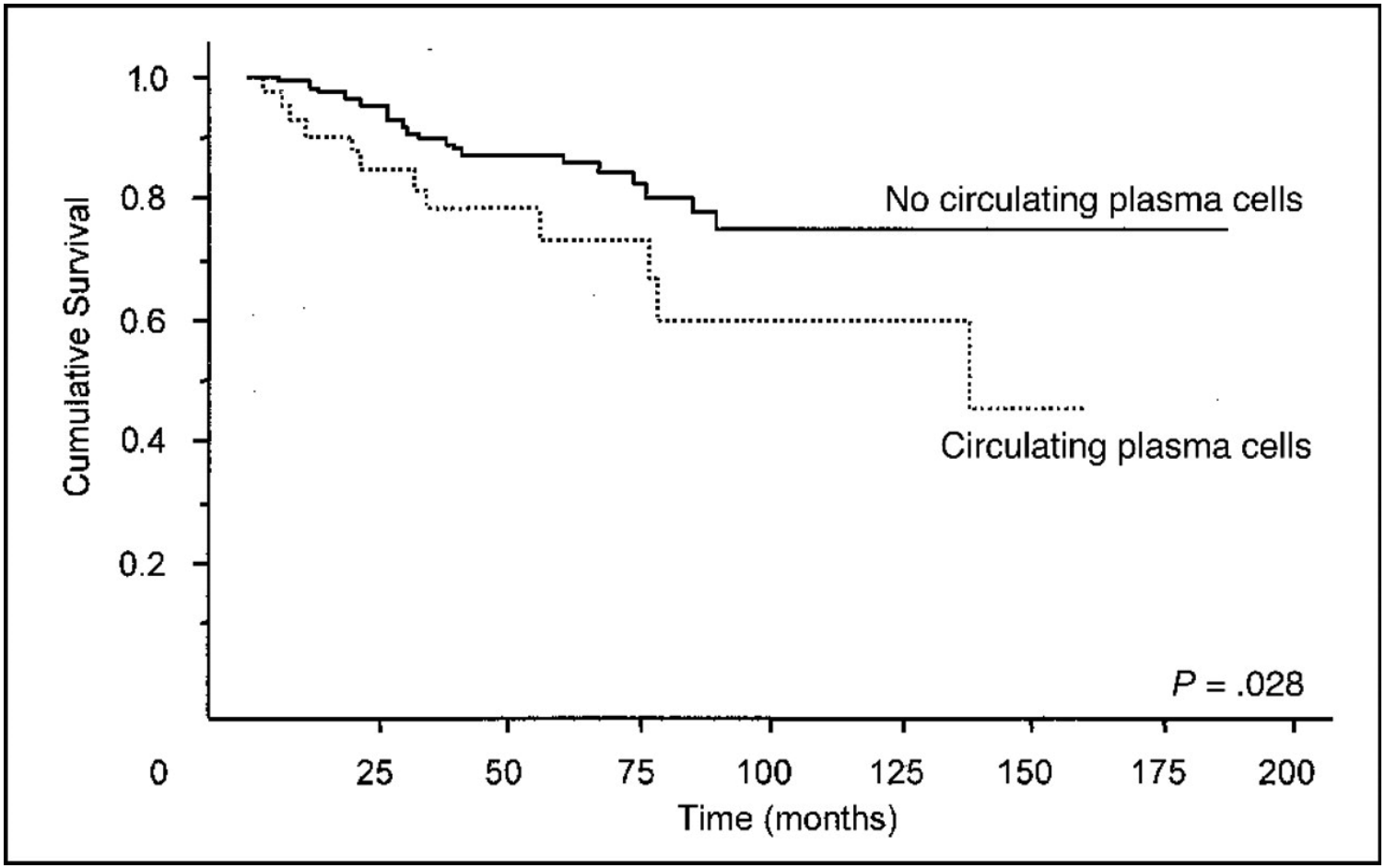
CIRCULATING PLASMA CELLS IN MGUS



Kumar, S. et al. J Clin Oncol; 23:5668-5674 2005

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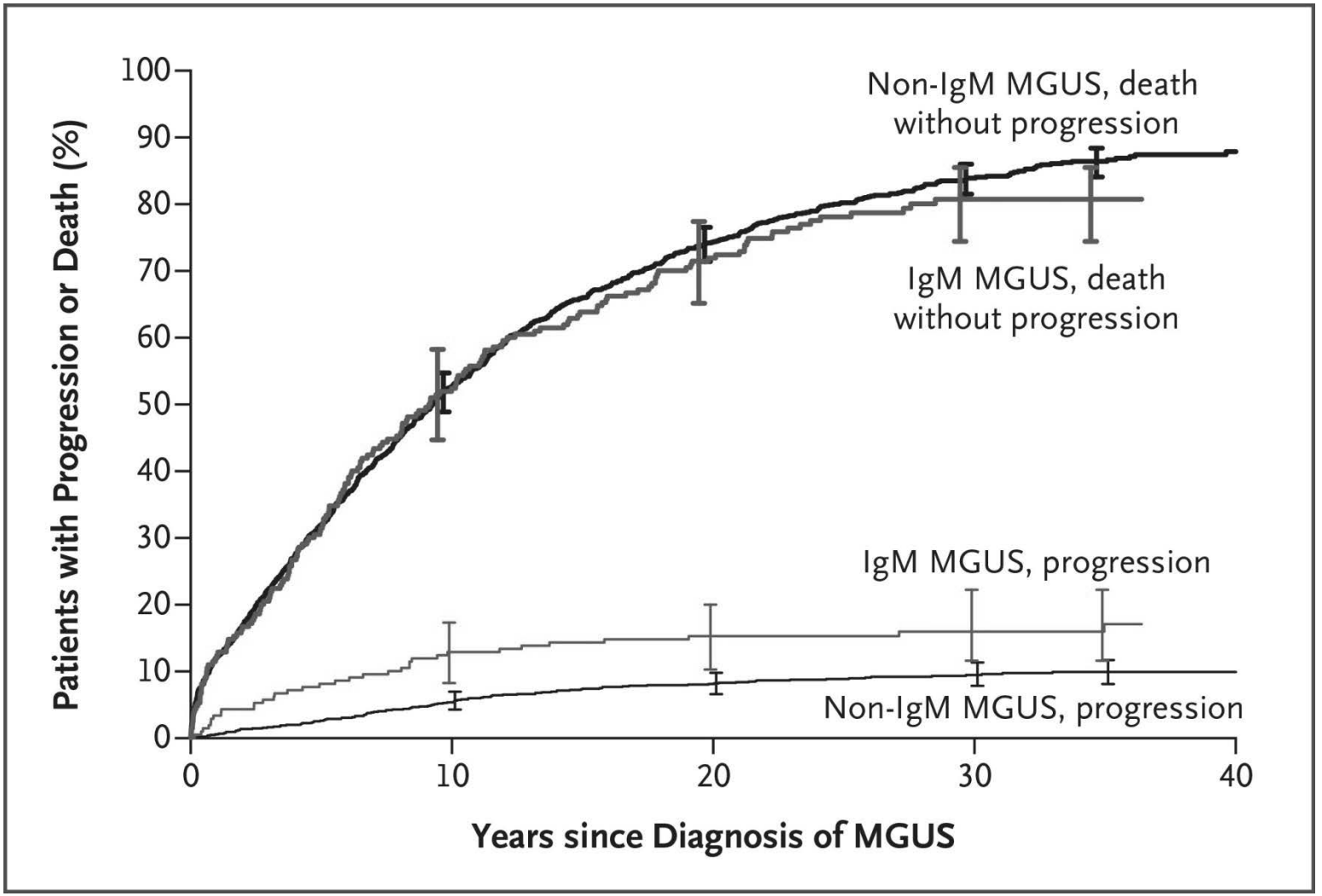
Risk of Progression of MGUS



Kyle RA et al. N Engl J Med 2018;378:241-249

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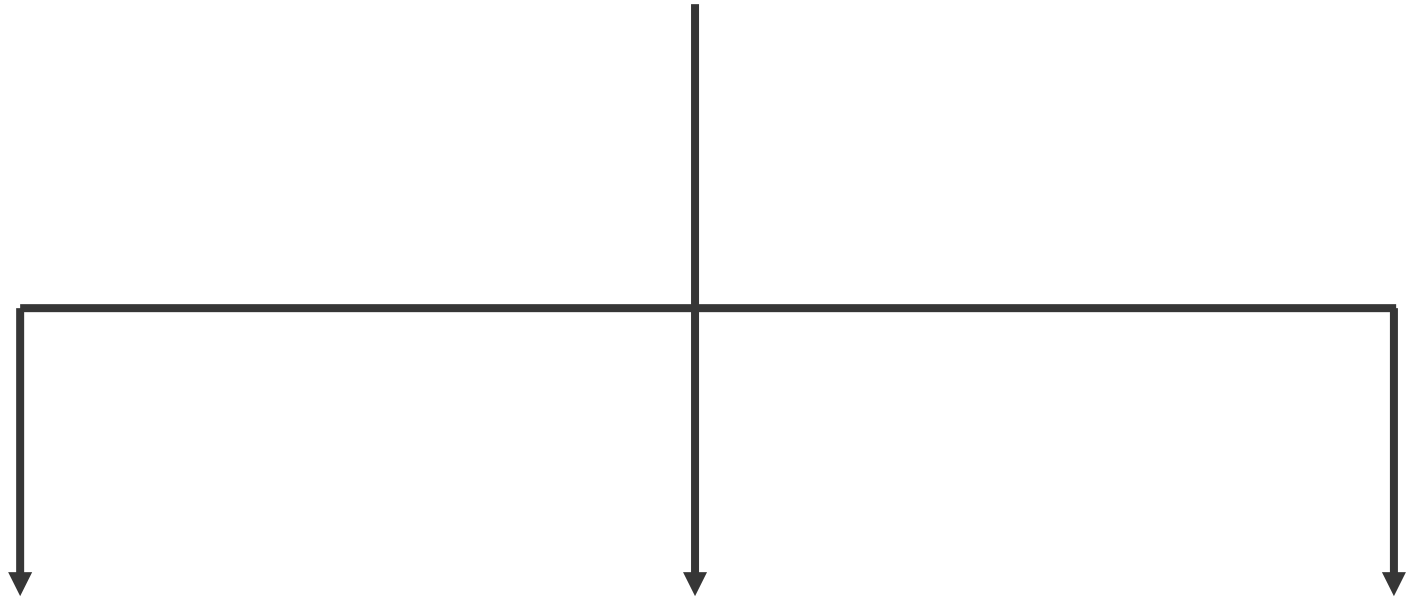
MGUS



Cancers
Myeloma
Macroglobulinemia
Plasmacytoma

Paraprotein
AL Amyloidosis
LCDD
Cryoglobulinemia

Associations
Neuropathy
Proliferative GN
Skin Disorders
Fractures

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SMM

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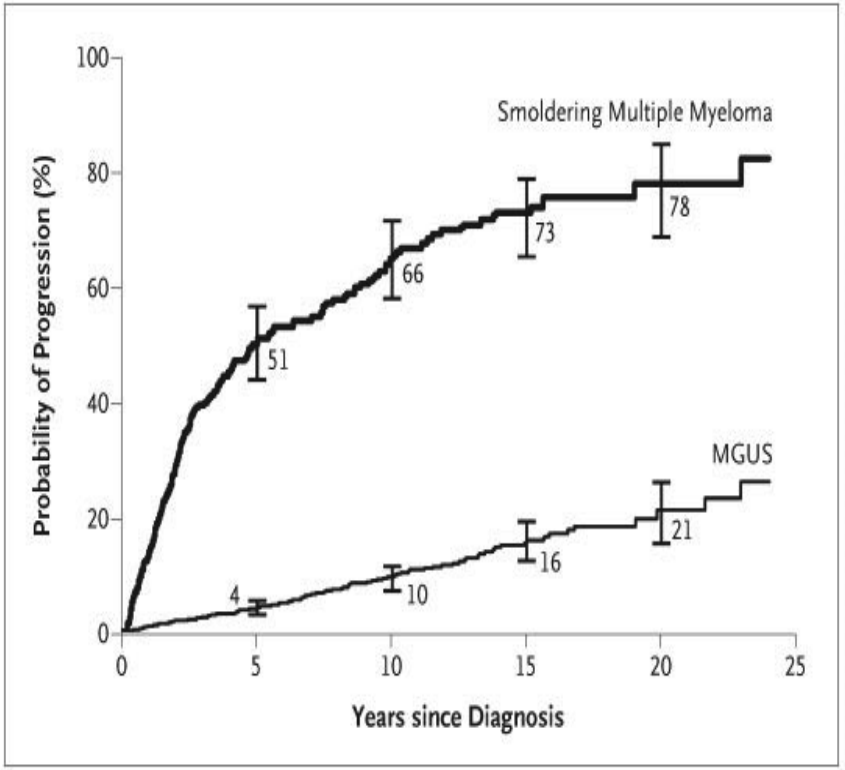
MEDICAL INTELLIGENCE ARCHIVE

Smoldering Multiple Myeloma

Robert A. Kyle, M.D., and Philip R. Greipp, M.D.

N Engl J Med 1980; 302:1347-1349 | June 12, 1980 | DOI: 10.1056/NEJM198006123022405



Kyle R et al. N Engl J Med 1980; 304:1347-48; Kyle RA, et al. N Engl J Med 2007;356:2582-2590

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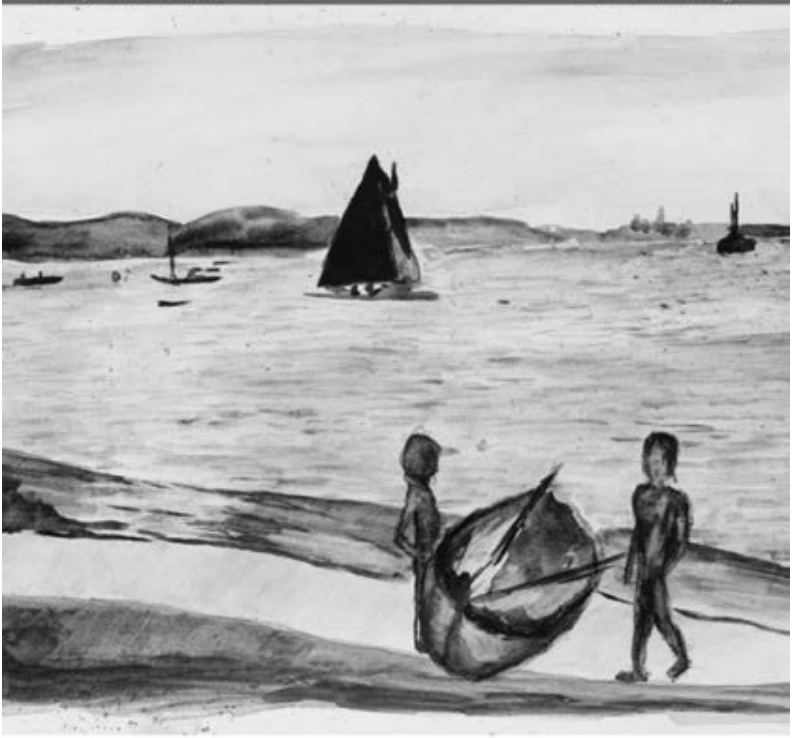
SMM Paradigm Shift

MGUS

Myeloma

THE LANCET Oncology

Volume 15 · Issue 12 · November 2014 www.thelancet.com/oncology



Review

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

This International Myeloma Working Group consensus updates the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcaemia, renal failure, anaemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be

Lancet Oncol 2014; 15: e538–48

See Online for a podcast interview with S Vincent Rajkumar

Division of Hematology, Mayo

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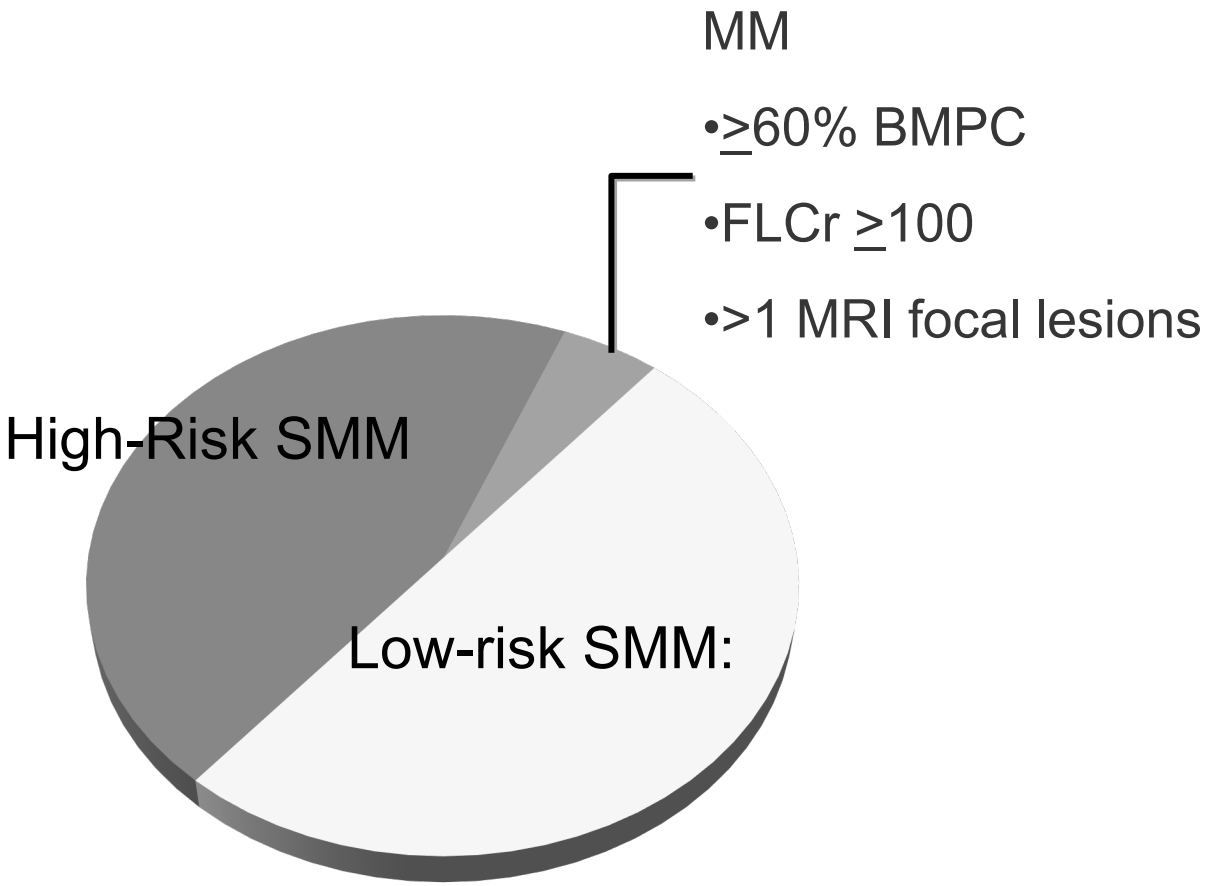
Smoldering Multiple Myeloma



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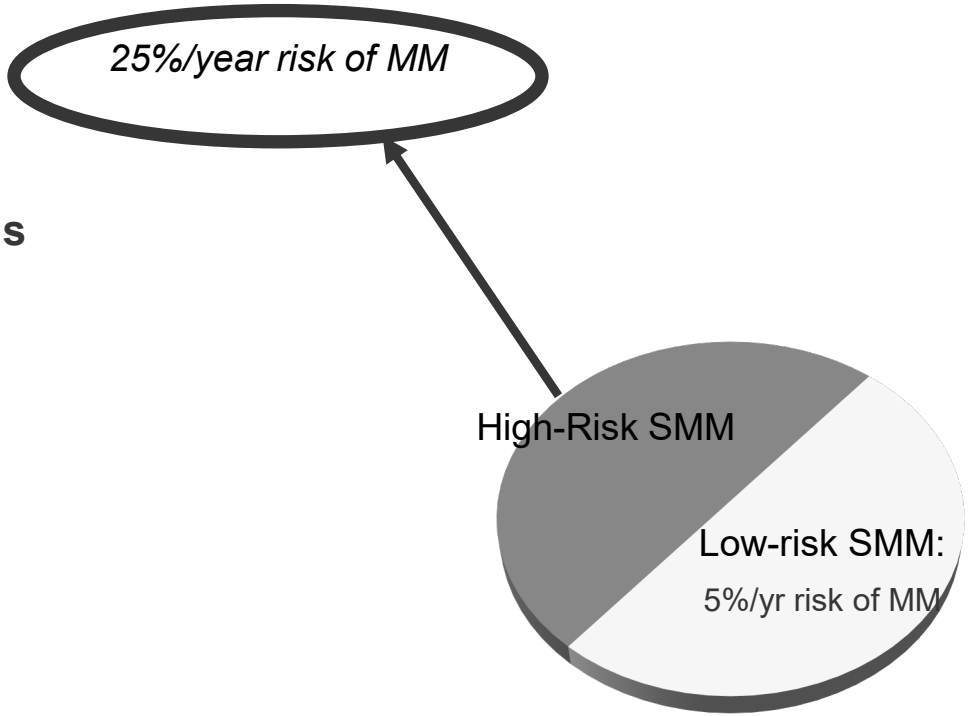
High Risk Smoldering Multiple Myeloma

≥10% PCs plus:

- **M protein ≥3 gm/dL**
- **Absence (<5%) of normal PCs by immunophenotyping plus Immunoparesis**
- **Abnormal FLC ratio 8-100**
- **Del(17p), t4;14, gain(1q21)**
- **IgA type**
- **Evolving pattern**
- **Increased circulating plasma cells**



Rajkumar SV, Landgren O, Mateos MV. Blood 2015

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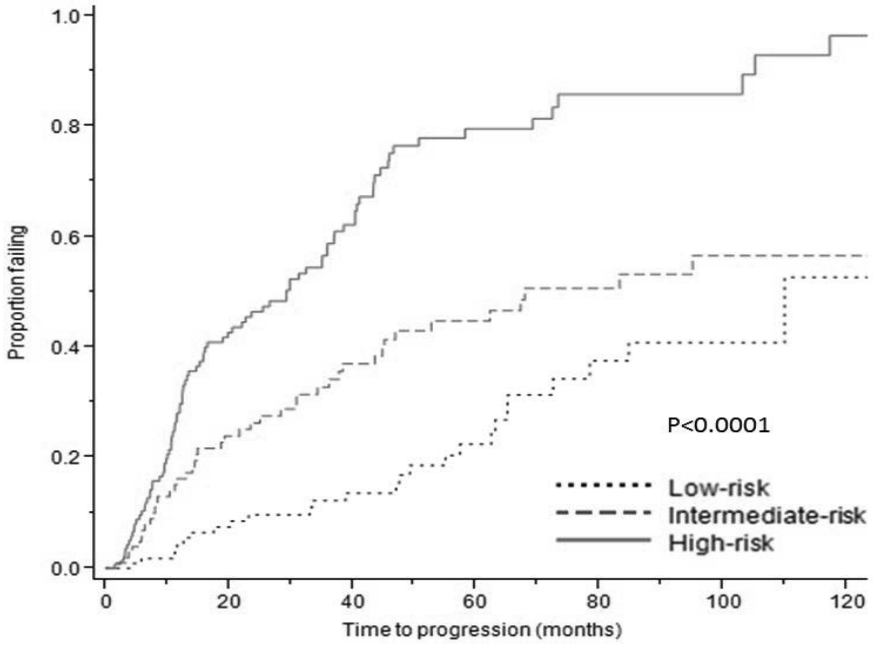
Mayo 2018 Risk Stratification (2-20-20)



Factors

- M Spike >2g/dL
- BMPC >20%
- FLC ratio >20

Stratification

Low-risk: 0
Intermediate-risk: 1
High-risk: >=2

Lakshman et al, BCJ, 2018

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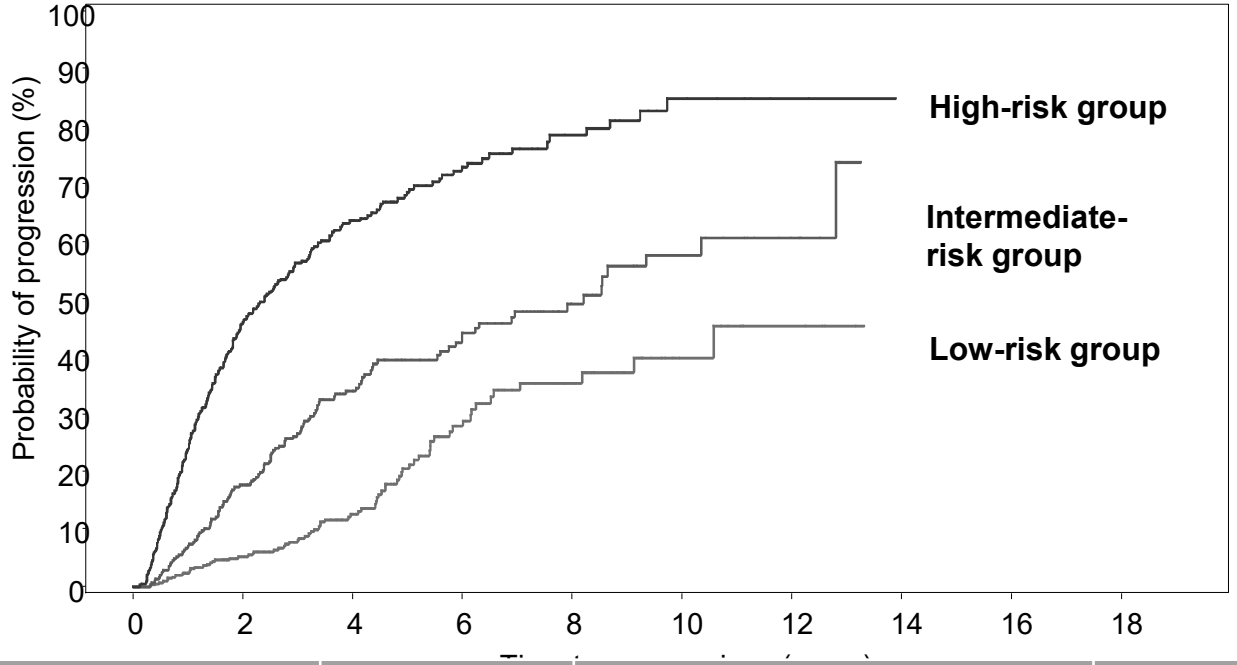
IMWG 2019 Risk Stratification of SMM (n=1151)



M Spike: >2g/dL
FLC Ratio: > 20
BMPC: > 20%

Risk Stratification Groups	Number of risk factors	Hazard Ratio (95% CI) Versus Low-risk group	Risk of Progression at 2 years	Number of patients
Low-risk group	0	Reference	5%	424 (37%)
Intermediate-risk group	1	2.25 (1.68 to 3.01)	17%	312 (27%)
High-risk group	2-3	5.63 (4.34 to 7.29)	46%	415 (36%)

San Miguel. ASCO 2019. Abstr 8000. Mateos Blood Cancer J. 2020;10:102.

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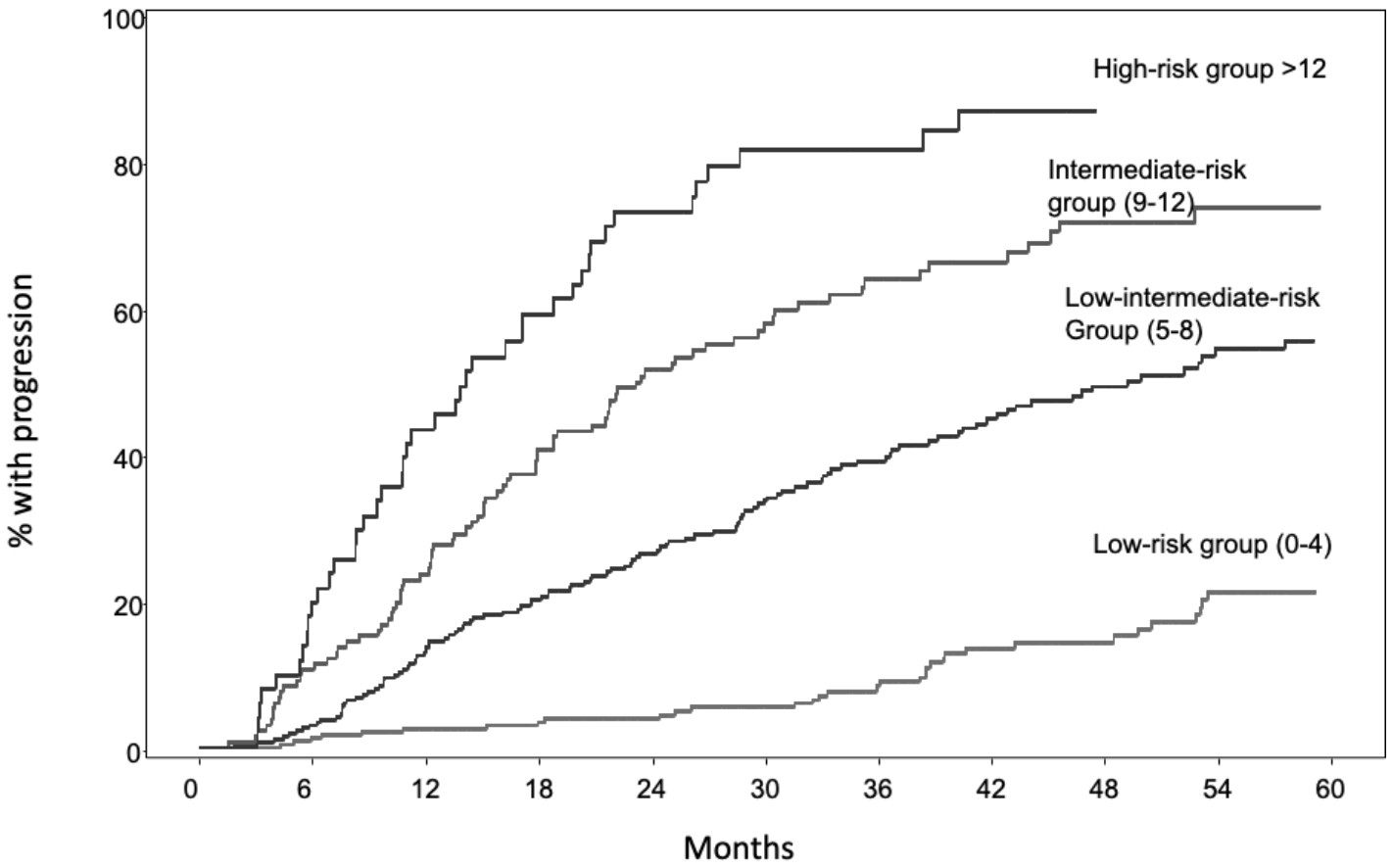
IMWG 2019 Risk Stratification of SMM

Risk Factor	Score
FLC Ratio	
0-10 (ref)	0
> 10-25	2
> 25-40	3
> 40	5
M protein (g/dL)	
0-1.5 (ref)	0
> 1.5-3	3
> 3	4
BMPC%	
0-15 (ref)	0
> 15-20	2
> 20-30	3
> 30-40	5
> 40	6
FISH abnormality	2



San Miguel. ASCO 2019. Abstr 8000. Mateos Blood Cancer J. 2020;10:102.

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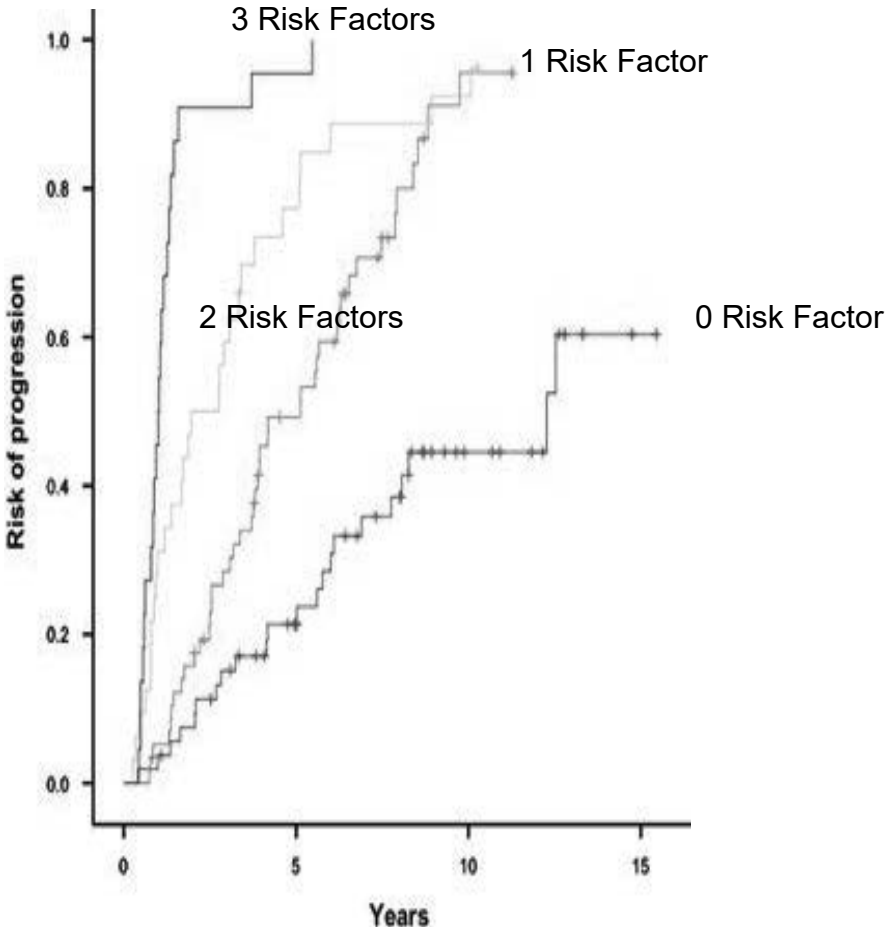
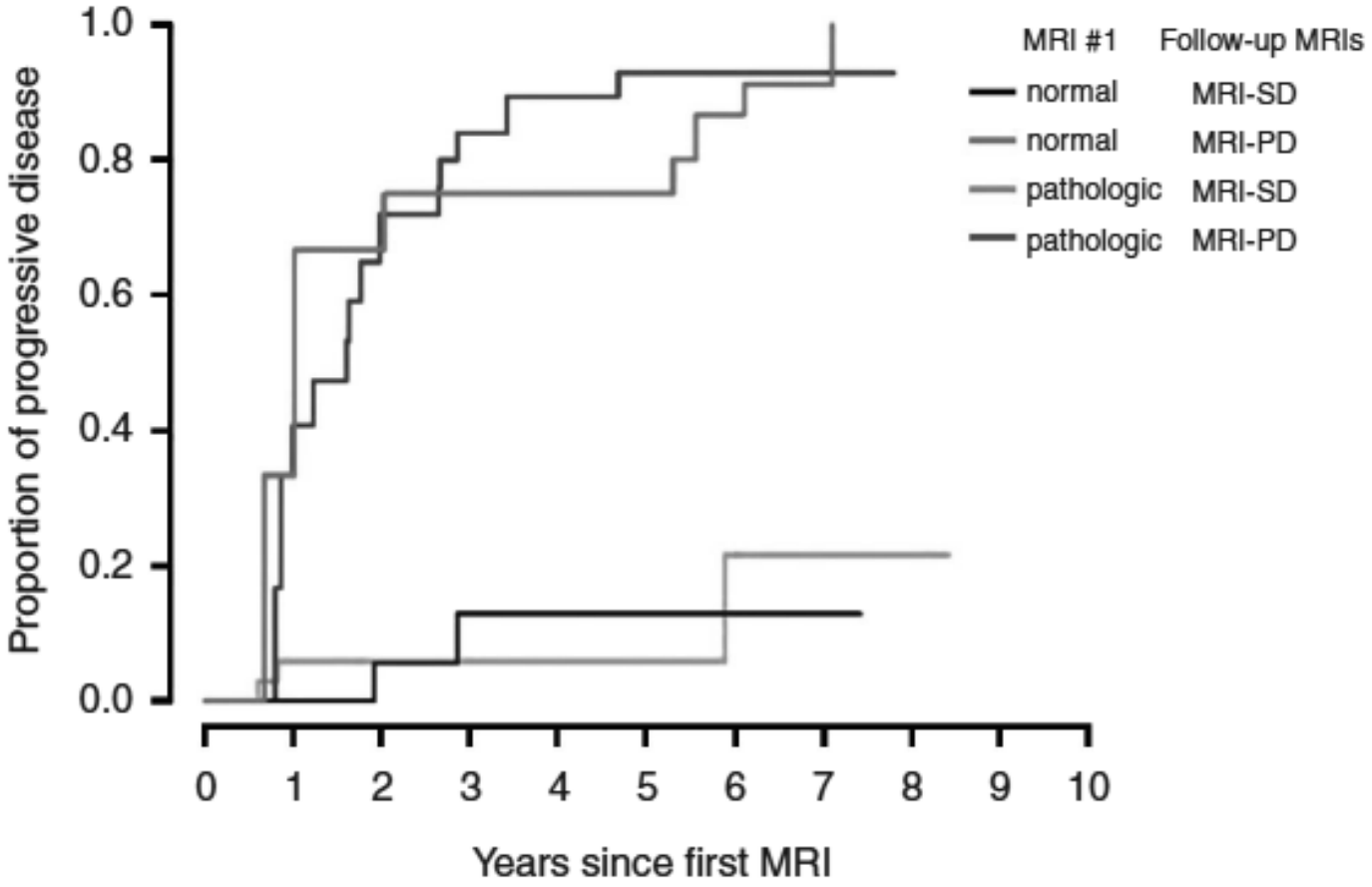
Evolving SMM



Risk factors: eMP, eHb and BMPC ⩾20%

Ravi P, et al. Blood Cancer J. 2016

Evolving MRI findings



Merz et al, Leukemia 2014

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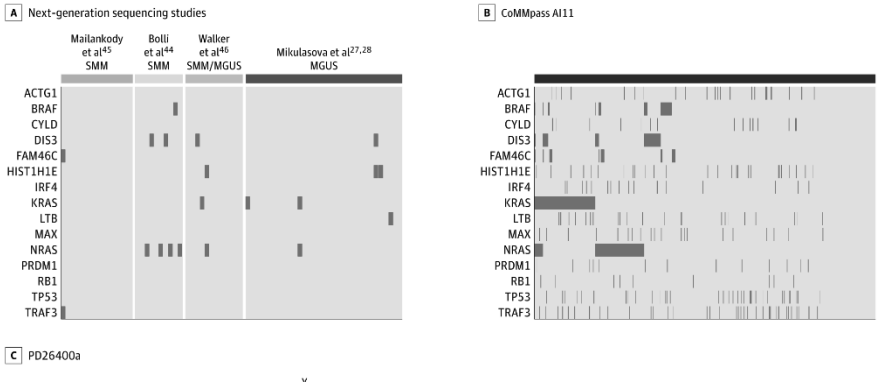
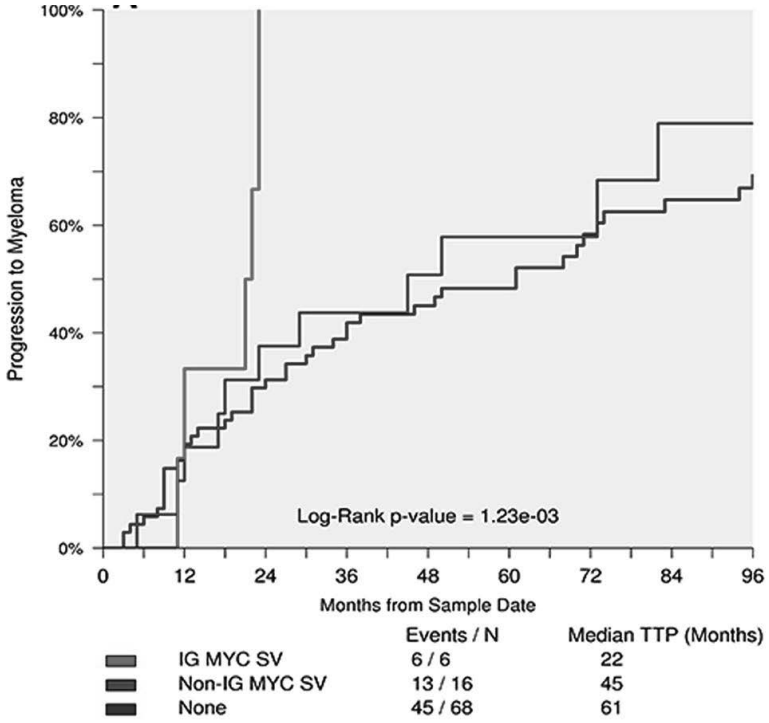
Future Directions





Maura F, et al. JAMA Oncol. 2020;6(3):425-432. doi:10.1001/jamaoncol.2019.4659

Misund K, et al. Leukemia volume 34, pages322–326 (2020)