# Modeling the risk of progression in smoldering multiple myeloma

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## Introduction

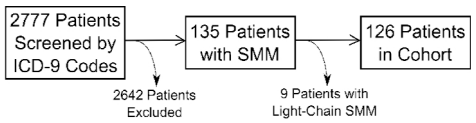
- Smoldering multiple myeloma (SMM) is a precursor state to multiple myeloma (MM) with a highly variable risk of progression to active MM
- Emerging data suggests there may be a role for early treatment in appropriately selected patients
- Identifying patients at risk of imminent progression to MM is critical for redefining MM requiring therapy and for designing clinical trials of early intervention
- Existing biomarkers and risk models have not been validated
- We sought to validate the Mayo Clinic risk models and biomarkers and to derive a novel risk model for an ethnically diverse SMM population seen at an urban academic medical center

## Objectives

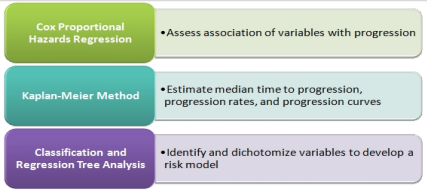
- To design a risk model that identifies patients with Ultra-High Risk SMM
- To validate an existing risk model for Smoldering Myeloma
- To identify biomarkers related to progression to Multiple Myeloma

## Patient Selection

- Electronic medical records queried for all outpatients seen within the University of Pennsylvania Health System with ICD-9 codes for multiple myeloma, monoclonal gammopathy, or plasma cell neoplasm
- Eligibility Criteria (based on 2003 IMWG consensus criteria for SMM):
  - M-protein ≥ 3 g/dL and/or BMPC ≥ 10%
  - No evidence of myeloma-related tissue impairment (Ca ≥11 mg/dL, Cr ≥2 mg/dL, Hgb <10 g/dL, or lytic lesions on skeletal survey)
  - Any patient receiving myeloma-directed chemotherapy was excluded




## Statistical Methods




## Patient Characteristics

| | | Number | % |
|---|---|---|---|
| Sex | Male | 69 | 54.8 |
| | Female | 57 | 45.2 |
| Race | Caucasian | 98 | 77.8 |
| | African-American | 24 | 19.0 |
| | Other | 4 | 3.2 |
| Isotype | IgG | 83 | 65.8 |
| | IgA | 31 | 24.6 |
| | IgM | 3 | 2.4 |
| | IgD | 1 | 0.8 |
| | BiClonal | 6 | 4.8 |
| Light-Chain | Kappa | 80 | 63.5 |
| | Lambda | 38 | 30.2 |
| Hypogammaglobulinemia | | 61 | 49.1 |
| Abnormal Cytogenetics | | 8 | 10.0 |
| FISH Abnormalities, n=59 | | 34 | 57.6 |
| | | Median | Range |
| Age | | 62 | 31 - 91 |
| Creatinine (mg/dL) | | 0.97 | 0.5-8.2 |
| M-Protein (g/dL) | | 1.8 | 0.01-5.2 |
| BMPC (%) | | 17.5 | 10-80 |
| sFLCR | | 8.6 | 1.0-2423.1 |
| Albumin (g/dL) | | 3.9 | 2.1-5.3 |
| β2-Microglobulin (mcg/mL) | | 2.1 | 1.0-25.7 |

Median Follow-up: 4 years

## CART Determined Factors

| | N | Median TTP (years) | 2-year Progression Free Rate ± SE (%) |
|---|---|---|---|
| BMPC <40% | 102 | 6.8 | 81 ± 4 |
| BMPC ≥40% | 19 | 0.4 | 25 ± 10 |
| sFLCR <50 | 102 | 8.4 | 76 ± 4 |
| sFLCR ≥50 | 16 | 1.0 | 34 ± 13 |
| Albumin >3.5 | 95 | 8.4 | 78 ± 4 |
| Albumin ≤3.5 | 27 | 1.8 | 48 ± 11 |

## Univariate Analyses

### a) Of continuous variables

| Variable | N | Hazard Ratio | 95% CI | Wald P-Value |
|---|---|---|---|---|
| Age | 126 | 1.00 | 0.98 – 1.02 | 0.99 |
| Creatinine | 124 | 0.43 | 0.14 – 1.19 | 0.10 |
| Albumin | 122 | 0.41 | 0.23 – 0.73 | 0.003 |
| β2-Microglobulin | 93 | 0.96 | 0.83 – 1.11 | 0.58 |
| M-protein (g/dL) | 126 | 1.70 | 1.30 – 2.21 | <0.001 |
| BMPC | 121 | 1.05 | 1.04 – 1.06 | <0.001 |
| sFLCR | 118 | 1.000 | 1.000 – 1.001 | 0.41 |

### b) Of dichotomous variables

| | Group | N | Median TTP (years) | Progression Free Rate at 2 years ± SE | HR | Wald P-Value |
|---|---|---|---|---|---|---|
| All Patients | | 126 | 6.8 | 72 ± 4 | | |
| Gender | Male | 69 | 5.6 | 73 ± 6 | 1.00 | 0.56 |
| | Female | 57 | 8.4 | 72 ± 6 | 0.85 | |
| Race | Caucasian | 98 | 5.6 | 71 ± 5 | 1.00 | 0.29 |
| | African-American | 24 | 10.4 | 76 ± 9 | 0.65 | |
| Hypogamma-globulinemia | Absent | 63 | 5.6 | 71 ± 6 | 1.00 | 0.74 |
| | Present | 61 | 6.8 | 72 ± 6 | 0.91 | |
| Cytogenetics | Normal | 70 | 4.8 | 69 ± 6 | 1.00 | 0.19 |
| | Abnormal | 8 | 0.7 | 38 ± 17 | 1.95 | |
| Hyperdiploidy | Absent | 45 | 4.0 | 62 ± 8 | 1.000 | 1.00 |
| | Present | 15 | 4.8 | 70 ± 8 | 1.001 | |
| M-Protein | < 3 g/dL | 98 | 8.4 | 80 ± 4 | 1.00 | 0.001 |
| | ≥ 3 g/dL | 28 | 1.8 | 47 ± 10 | 2.65 | |
| BMPC | < 60% | 115 | 6.8 | 76 ± 4 | 1.00 | <0.001 |
| | ≥ 60% | 6 | 0.1 | 0 | 15.42 | |
| sFLCR | < 8 | 56 | NR | 80 ± 6 | 1.00 | 0.045 |
| | ≥ 8 | 62 | 4.8 | 63 ± 7 | 1.84 | |
| | < 100 | 107 | 8.4 | 73 ± 5 | 1.00 | 0.009 |
| | ≥ 100 | 11 | 1.7 | 47 ± 17 | 2.99 | |

## Assessment of Risk Models

### a) Penn Risk Stratification Model

| Risk Group | N | Median TTP (years) | 2-year Progression Free Rate ± SE (%) | HR | 95% CI |
|---|---|---|---|---|---|
| Low | 73 | NR | 84 ± 4 | 1.00 | |
| Intermediate | 24 | 3.07 | 56 ± 12 | 3.24 | 1.55 – 6.75 |
| High | 14 | 0.35 | 19 ± 11 | 11.16 | 5.03 – 24.78 |

**Risk Factors:**
- Plasma Cells ≥40%
- sFLCR ≥50
- Albumin ≤3.5

*Low Risk* = 0 risk factors
*Intermediate Risk* = 1 risk factor
*High Risk* = ≥2 risk factors

### b) Mayo Clinic 2008 Model

| Risk Group | N | Median TTP (years) | 2-year Progression Free Rate ± SE (%) | HR | 95% CI |
|---|---|---|---|---|---|
| Low | 47 | NR | 83 ± 6 | 1.00 | |
| Intermediate | 54 | 5.6 | 71 ± 7 | 1.98 | 0.99 – 4.00 |
| High | 13 | 0.7 | 31 ± 13 | 4.59 | 1.92 – 11.01 |

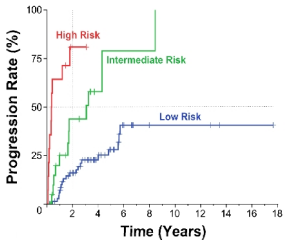
NR = Not Reached

**Risk Factors:**
- M-protein ≥3 g/dL
- Plasma Cells ≥10%
- sFLCR ≥8

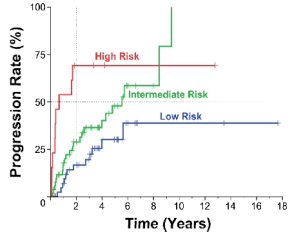
*Low Risk* = 1 risk factor
*Intermediate Risk* = 2 risk factors
*High Risk* = 3 risk factors

## Plots of Progression vs Time

**a) Penn Model**



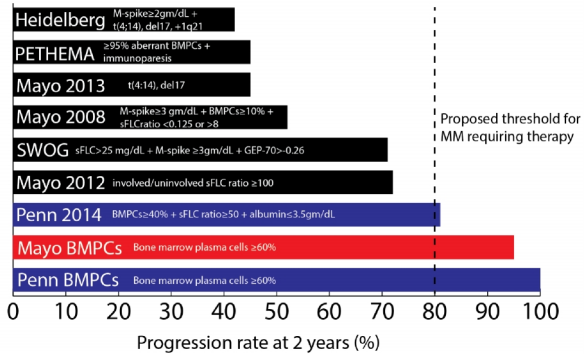

**b) Mayo Clinic 2008 Model**




## Conclusions

- Incorporating a depressed serum albumin, we have developed a novel risk stratification model that identifies ultra high-risk SMM
- All patients with BMPCs ≥60% developed active MM within 2 years
- We have validated the Mayo Clinic 2008 model in an ethnically diverse population
- These findings have implications for redefining SMM that requires therapy

### Comparison of High Risk SMM Models




## Disclosures

Disclosures: None

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