Mortality and Disease Progression in Systemic Mastocytosis: A Population-Based Cohort Study

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Introduction

- Systemic mastocytosis (SM) is a heterogeneous clonal mast cell disorder, typically driven by KIT D816V (~95%), and associated with substantial morbidity and mortality.
- Subtype classification (advanced vs non-advanced SM) is central to prognosis, yet most long-term outcome data come from referral-based cohorts rather than routine clinical practice.
- Disease progression from non-advanced to advanced SM represents a clinically critical transition with major implications for surveillance, treatment, and patient counseling.
- Population-based data describing long-term mortality and disease progression in real-world U.S. healthcare settings remain limited.

Objectives

- Quantify long-term all-cause mortality across advanced and non-advanced SM subtypes in a real-world healthcare system.
- Evaluate disease progression from non-advanced to advanced SM over 5- and 10-year horizons and identify key clinical predictors of progression.

Methods

- **Study design & setting:** Retrospective population-based cohort study conducted within Kaiser Permanente Southern California (KPSC), a large integrated healthcare system with comprehensive longitudinal electronic health records and complete mortality ascertainment.
- **Study population:** Adults aged ≥18 years with an electronic health record–documented diagnosis of SM between 2008 and 2024 were identified. The index date was defined as the earliest recorded SM diagnosis date, including diagnoses established outside KPSC when documented in the medical record. Patients were required to have active KPSC membership at the index date.
- **Subtype confirmation and classification:** All SM diagnoses and subtype assignments were manually confirmed by study physicians through detailed medical record review using WHO 2016 diagnostic criteria, including pathology, laboratory, and clinical documentation.[1]
  - Non-advanced SM: indolent SM (ISM) or smoldering SM (SSM)
  - Advanced SM: aggressive SM (ASM), SM with associated hematologic neoplasm (SM-AHN), or mast cell leukemia (MCL)
- **Outcomes:** All-cause mortality (National Death Index + internal KPSC mortality records) and progression from non-advanced to advanced SM during follow-up, based on physician-confirmed subtype reclassification.
- **Follow-up:** Follow-up began at the index date.
  - For mortality analyses, patients were followed until death or end of study (Nov. 30, 2025).
  - For progression analyses, patients were followed until progression to advanced SM, death, health plan disenrollment, or end of study (Nov 30, 2025), whichever occurred first.
- **Statistical analysis:**
  - Kaplan–Meier methods were used to estimate 5- and 10-year mortality and progression probabilities.
  - Absolute risk differences and restricted mean survival time were calculated to support clinical interpretation.
  - Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and identify risk factors. Candidate predictors included demographic characteristics and baseline clinical variables; final models retained variables that remained statistically significant.

Figure 1. Cohort Identification and Analysis Populations for the SM Study

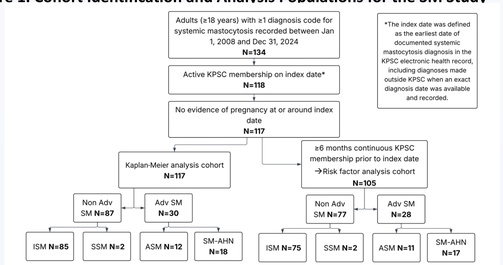


Table 1. Mortality Outcomes in AdvSM and Non-AdvSM at 5 and 10 Years

Horizon	Subtype	N	Deaths (≤τ)	Absolute risk at τ (95% CI)	Absolute risk differences (95% CI)	Months of life lost in SM, mean (95% CI)
5 years	Non-adv SM (ref)	87	7	9.6 (2.5 – 16.2)	Reference	Reference
	Adv SM	30	17	59.5 (36.2 – 74.3)	+49.8 (+30.2 to +69.5)	+23.9 (+14.2 to +33.7)
10 years	Non-adv SM (ref)	87	11	22.9 (7.9 – 35.5)	Reference	Reference
	Adv SM	30	20	75.7 (48.7 – 88.5)	+52.7 (+30.0 to +75.5)	+57.4 (+37.9 to 76.9)

Results

Study Population

- Among 134 identified SM patients, 117 met criteria for the mortality analysis and 105 for progression analyses.
- At baseline, 87 patients had non-advanced SM and 30 had advanced SM.
- Median follow-up was 4.0 years (AdvSM: 1.4; Non-AdvSM: 4.2)
- Patients with advanced SM were diagnosed at older ages (mean: 68 years) than those with non-advanced disease (mean: 55 years).
- The cohort was predominantly non-Hispanic White (63.8%), with Hispanic patients comprising 22.9%; men and women were approximately equally represented.

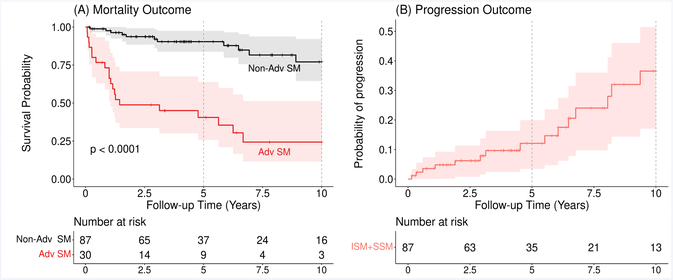
Mortality

- Overall mortality differed markedly by SM subtype (Figure 2A).
- Advanced SM was associated with substantially reduced survival compared with non-advanced SM.
- Crude HR: 6.74 (95% CI, 3.32–13.70); adjusted HR: 4.95 (95% CI, 2.35–10.45), adjusting for age and baseline comorbidity index.
- Absolute mortality risk diverged early and widened over time, with clear separation of survival curves by subtype at both 5 and 10 years.

Disease Progression from Non-advance to Advanced SM

- Among patients with non-advanced SM, 18 progressed to advanced SM during follow-up.
- Progression increased gradually over time (Figure 2B):
  - 5-year progression probability: 12.0% (95% CI, 3.4–19.9); 10-year progression probability: 36.5% (95% CI, 17.0–51.4)
- Older age was the only independent predictor of progression:
  - 5-year horizon: HR 1.12 per year increase in age (95% CI, 1.05–1.20); 10-year horizon: HR 1.08 per year (95% CI, 1.03–1.14)
- No additional clinical factors remained significant predictors of progression after adjustment.

Figure 2A. Kaplan–Meier Estimates of All-Cause Mortality in Advanced vs Non-Advanced SM
Figure 2B. Cumulative Probability of Progression to Advanced SM Among Patients With Non-Advanced Disease



10-year progression probability: 36.5%, indicating substantial long-term risk despite relatively slow early progression.

Key Findings

- Advanced SM was associated with a ~5-fold higher adjusted mortality risk compared with non-advanced disease.
- Mortality risk diverged early and continued to widen over long-term follow-up.
- Disease progression occurred gradually over time, with age as the dominant predictor of progression.
- Real-world population-based data demonstrate substantial heterogeneity in long-term outcomes across SM subtypes.

Conclusions

- SM subtype strongly determines long-term outcomes, with advanced SM associated with markedly higher mortality in routine clinical practice.
- Progression from non-advanced to advanced SM accumulated over time, with age as the dominant predictor, highlighting the importance of long-term surveillance in patients with non-advanced SM.
- Real-world population-based data demonstrate substantial heterogeneity in SM outcomes, emphasizing the importance of accurate subtype classification and longitudinal follow-up.
- Future research should evaluate whether targeted therapies can reduce progression and improve survival.

1. MASTering systemic mastocytosis: Lessons learned from a large patient cohort
Tse, Kevin Y. et al. Journal of Allergy and Clinical Immunology: Global, Volume 3, Issue 4.

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