

## Introduction

- Systemic mastocytosis (SM) is a clonal mast cell disease primarily driven by the activating KIT D816V mutation, resulting in abnormal mast cell accumulation in extracutaneous organs.
- SM spans a wide clinical spectrum, from indolent or smoldering disease to advanced subtypes (e.g., aggressive systemic mastocytosis [ASM], systemic mastocytosis with an associated hematologic neoplasm [SM-AHN], or mast cell leukemia [MCL]) that can be rapidly fatal.
- Due to disease rarity and heterogeneity, real-world long-term mortality risk remains uncertain, particularly outside specialized referral settings.
- Prior mortality benchmarking of SM has been conducted mainly in European registries and population-based cohorts, while comparable U.S. health system-based analyses are limited.
- Clinically interpretable mortality benchmarks require appropriate comparator populations, which have been less commonly incorporated in prior SM survival studies.

## Objectives

- Evaluate mortality separately for advanced SM (AdvSM) and non-advanced SM (Non-AdvSM) to reflect subtype-specific prognosis.
- Compare SM outcomes with two matched reference cohorts from the same health system to provide clinically interpretable benchmarks for routine U.S. practice.

## Methods

- Design & setting:** Retrospective cohort study using longitudinal EHR data from Kaiser Permanente Southern California (KPSC) with comprehensive mortality linkage.
- SM cohort and subtypes:** Adults (≥18 years) with an EHR-recorded SM diagnosis (2008–2024), required ≥6 (12 in sensitivity analysis) months continuous membership before diagnosis.
- SM confirmation & subtypes:** SM diagnosis and subtype assignments were manually confirmed by study physicians using WHO 2016 criteria based on pathology, laboratory, and clinical records.<sup>1</sup>
  - 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)
- Comparator cohorts:** no SM diagnosis; required ≥12 months continuous membership before cohort entry:
  - CSU-INC: incident, allergist-confirmed chronic spontaneous urticaria
  - SYM-INC: incident symptom-similar cohort with ≥2 SM-compatible symptoms on the same date (no CSU)
- Matching:** Comparators matched to each SM patient on age (±5 years), sex, and index date (±90 days).
- Outcome:** All-cause mortality, captured via National Death Index and internal KPSC sources; follow-up from index date until death, disenrollment, or end of study.
- Statistical analysis:**
  - Kaplan–Meier methods estimated 5- and 10-year survival, absolute risk differences, and restricted mean survival time.
  - Mortality comparisons used marginal Cox proportional hazards models with robust variance.
  - Adjusted Cox models controlled for demographic and baseline clinical confounders; age and baseline comorbidity index were retained in final models.

## Results

- Cohort identification:** We identified 107 patients with SM, including 80 with Non-AdvSM and 27 with AdvSM, matched to 535 CSU-INC and 749 SYM-INC comparators.
- Baseline profile:** Age and sex distributions were similar across SM and comparator cohorts by design. Within the SM cohort, AdvSM patients were older (mean age 68.3 vs 54.8 years) and more often male (70.4% vs 42.5%) than Non-AdvSM patients.
- Absolute mortality differences (Table 1):**
  - AdvSM showed marked excess mortality vs CSU-INC (+58.0% at 5 years; +78.7% at 10 years) and vs SYM-INC (+50.4% at 5 years; +61.7% at 10 years).
  - Non-AdvSM showed modest excess mortality vs CSU-INC (+5.0% at 5 years; +18.8% at 10 years), with only the 10-year difference statistically significant.
  - Non-AdvSM survival was similar to SYM-INC at both time horizons (no statistically significant differences).

**Table 1. Five- and Ten-Year Survival and Absolute Mortality Difference**

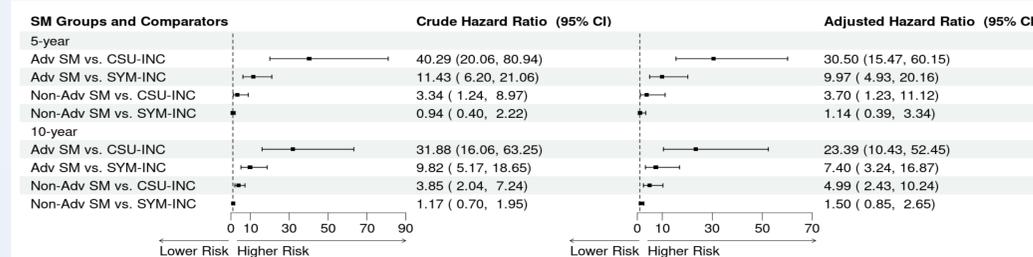
Comparison	5-year KM survival probability (95% CI)		
	SM	Comparator	Difference
Adv SM vs CSU-INC	38.6 (23.7–63.0)	96.6 (94.8 - 98.5)	+58.0 (+39.1 to +77.0)
Adv SM vs SYM-INC	38.6 (23.7–63.0)	89.0 (86.3 - 91.7)	+50.4 (+31.3 to +69.5)
Non-Adv SM vs CSU-INC	91.6 (85.4–98.3)	96.6 (94.8 - 98.5)	+5.0 (-1.7 to +11.7)
Non-Adv SM vs SYM-INC	91.6 (85.4–98.3)	89.0 (86.3 - 91.7)	-2.7 (-9.6 to +4.3)

Comparison	10-year KM survival probability (95% CI)		
	SM	Comparator	Difference
Adv SM vs CSU-INC	12.1 (2.4–60.6)	90.7 (86.8 - 94.9)	+78.7 (+58.8 to +98.6)
Adv SM vs SYM-INC	12.1 (2.4–60.6)	73.8 (68.6 - 79.4)	+61.7 (+41.5 to +82.0)
Non-Adv SM vs CSU-INC	71.9 (58.4–88.6)	90.7 (86.8 - 94.9)	+18.8 (+3.2 to +34.4)
Non-Adv SM vs SYM-INC	71.9 (58.4–88.6)	73.8 (68.6 - 79.4)	+1.9 (-14.1 to +17.9)

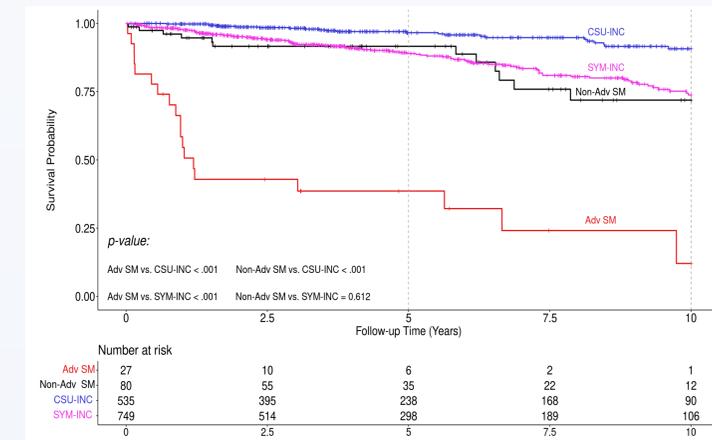
- Hazard ratios (Figure 2):** Adjusted Cox models showed markedly elevated mortality risk in AdvSM. In contrast, Non-AdvSM demonstrated a modest but statistically significant increase in mortality risk compared with CSU-INC, while showing little to no excess risk relative to SYM-INC.

**Figure 2. Crude and Adjusted Hazard Ratios for All-Cause Mortality**



- Sensitivity analysis:** Findings were consistent in sensitivity analyses (data not shown).

**Figure 1. Kaplan–Meier survival curves for AdvSM, Non-AdvSM, CSU-INC, and SYM-INC over 10 years of follow-up**



- Kaplan–Meier curves demonstrated marked separation in survival by SM subtype, with substantially worse survival in AdvSM.
- Differences between Non-AdvSM and comparator cohorts were smaller and varied by comparator, becoming more apparent with longer follow-up.

**5-year survival:** Non-AdvSM 91.6%, AdvSM 38.6%, CSU-INC 96.6%, SYM-INC 89.0%

**10-year survival:** Non-AdvSM 71.9%, AdvSM 12.1%, CSU-INC 90.7%, SYM-INC 73.8%

## Key Findings

- Real-world context vs prior literature:** In this U.S. health-system cohort, Non-AdvSM 10-year survival was 71.9%, which appears lower than survival reported in major registry/referral cohorts, where 10-year survival for indolent/smoldering SM is often >90%.
- Subtype-stratified prognosis:** Survival differed substantially by SM subtype, with AdvSM demonstrating markedly reduced 5- and 10-year survival compared with Non-AdvSM.
- Comparator benchmarking:** Non-AdvSM showed modest excess long-term mortality vs CSU-INC, whereas survival was similar to SYM-INC at both 5 and 10 years.

## Conclusions

- SM subtype remains a primary determinant of long-term survival and should be accurately classified in routine practice.
- Matched reference cohorts offer a practical framework for interpreting SM survival outcomes relative to comparable patient populations in routine clinical practice.
- Future work should examine the impact of targeted therapies and disease surveillance on survival across the SM spectrum.

1. Tse KY, et al. MASTering systemic mastocytosis: Lessons learned from a large patient cohort. J Allergy Clin Immunol Glob. 2024;3(4):100316.

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