Evaluation of Survival Among Patients With Indolent Systemic Mastocytosis: A Population-Level Retrospective Cohort Analysis Using Healthcare Claims Dataset

Sudipto Mukherjee[1], Douglas J. Cattie[2], Daniel Shaheen[2], Dakota Powell[2], Teresa Green[2]

[1]Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; [2]Blueprint Medicines Corporation, Cambridge, MA, USA

Presented at ASH 2023
San Diego, CA, USA

Background and Objective

Background

- Systemic mastocytosis (SM) is a rare, heterogenous, clonal mast cell disease driven by the KIT D816V mutation in up to 95% of cases[1-3]
- Indolent systemic mastocytosis (ISM) is the most common subtype, characterized by a more chronic clinical course associated with a significant symptom burden that may worsen over time, poor quality of life, and the potential for life-threatening anaphylaxis[4,5]
- Patients with more disease risk factors may demonstrate higher symptom burden and may have increased rates of disease progression and mortality[6]

Objective

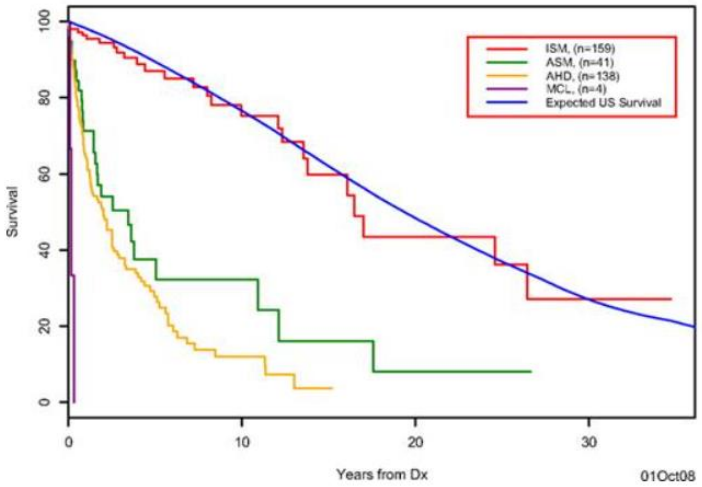
- The objective of this analysis was to evaluate overall survival (OS) in patients with ISM to build upon the existing literature and further establish the impact of ISM on survival

1. Valent P, et al. *Int J Mol Sci*. 2019;20(12):2976. 2. Shomali W and Gotlib J. *Hematology Am Soc Hematol Educ Program*. 2018;2018(1):127-36. 3. Kristensen T, et al. *J Mol Diagn.* 2011;13:180-8. 4. Cohen S, et al. *Br J Haematol.* 2014;166:521-8. 5. Magliacane D, et al. *Mediterr J Hematol Infect Dis*. 2014;8:65-74. 6. Sperr WR, et al. *Lancet Haematol*. 2019;6(12):e638-49.

New Evidence Suggests Diminished Survival in ISM

2009

Lim, Ken-Hong, et al. ***Blood*** 113.23 (2009): 5727-5736.



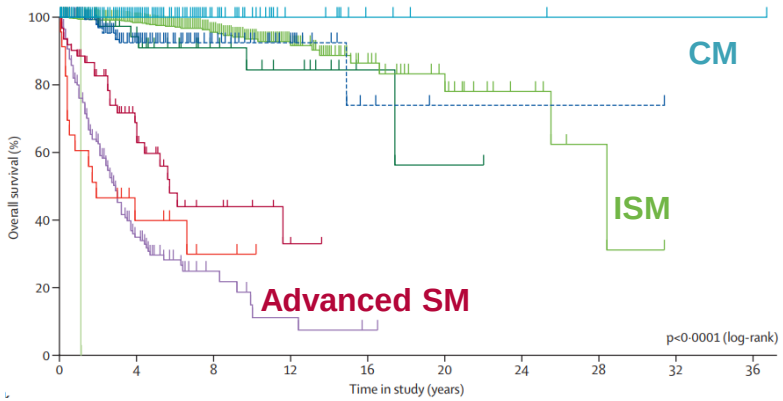
- Evaluated N = 159 patients with ISM
- Single-center study (Mayo Clinic)
- Median follow-up 1.7 years post-diagnosis

<u>Conclusion</u>:

Survival of ISM population not significantly different from expected US survival

2019

Sperr, Wolfgang R., et al. ***The Lancet Haematology*** 6.12 (2019): e638-e649.



- Evaluated N = 1,006 patients with ISM
- Multi-center study (ECNM registry)
- Median follow-up 3.4 years

<u>Conclusion</u>:

Survival of ISM patients was diminished versus cutaneous mastocytosis patients

2020

Kibsgaard, Line, et al. ***Int J Womens Dermatol*** 6.4 (2020): 294-300.

Mastocytosis	No.	Crude risk of CCI ≥ 1 OR (95% CI)	Adjusted risk of CCI ≥ 1 OR (95% CI)*	Adjusted risk of CCI ≥ 1 OR (95% CI)†
Mastocytosis overall	891	2.10 (1.80–2.45)	2.44 (2.06–2.90)	1.63 (1.35–1.97)
Cutaneous mastocytosis	489	1.26 (0.98–1.62)	1.50 (1.15–1.94)	1.57 (1.19–2.08)
Indolent systemic mastocytosis	377	3.51 (2.82–4.39)	3.47 (2.75–4.39)	1.83 (1.38–2.41)
Systemic mastocytosis	25	17.37 (7.24–41.69)	12.31 (4.89–30.99)	1.63 (0.63–4.19)

- Evaluated N = 393 patients with ISM
- National population-based cohort study, Danish National Health Registries
- ISM patient survival was compared to a matched non-ISM cohort
- Median follow-up 9 years

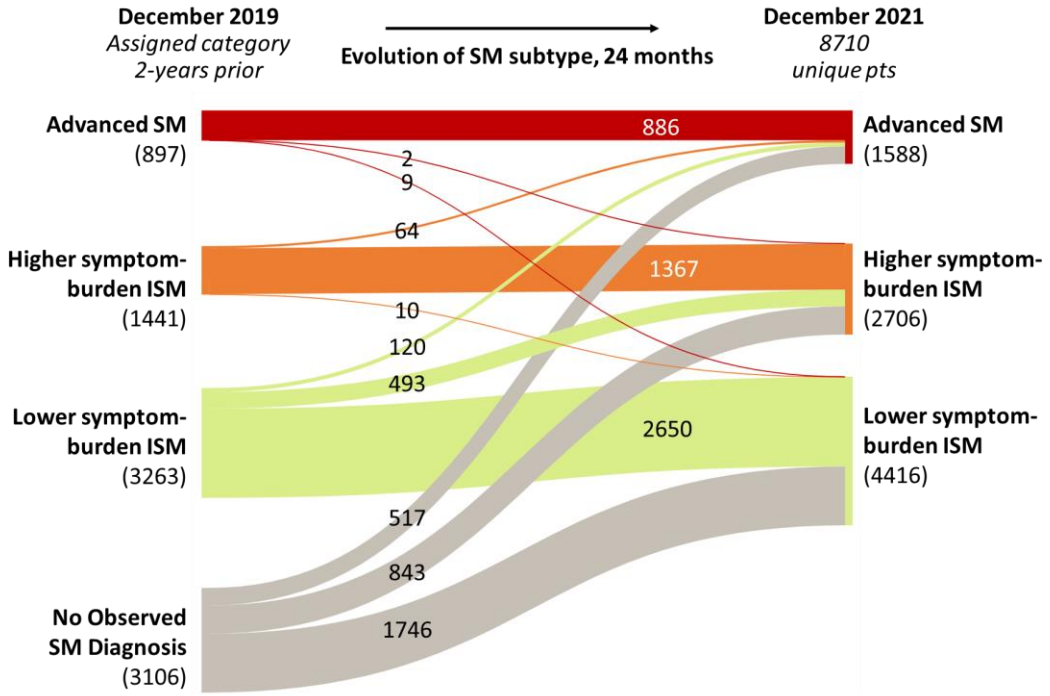
<u>Conclusion</u>:

Mortality was increased among ISM populations versus non-ISM patients, with hazard ratio of 1.53 – 2.59

AHD, systemic mastocytosis with associated hematologic disorders; ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; ECNM, European Competence Network on Mastocytosis; ISM, indolent systemic mastocytosis; MCL, mast cell leukemia; OS, overall survival; SM, systemic mastocytosis.

Previous Studies have Explored the Risk of Progression from ISM to Advanced SM

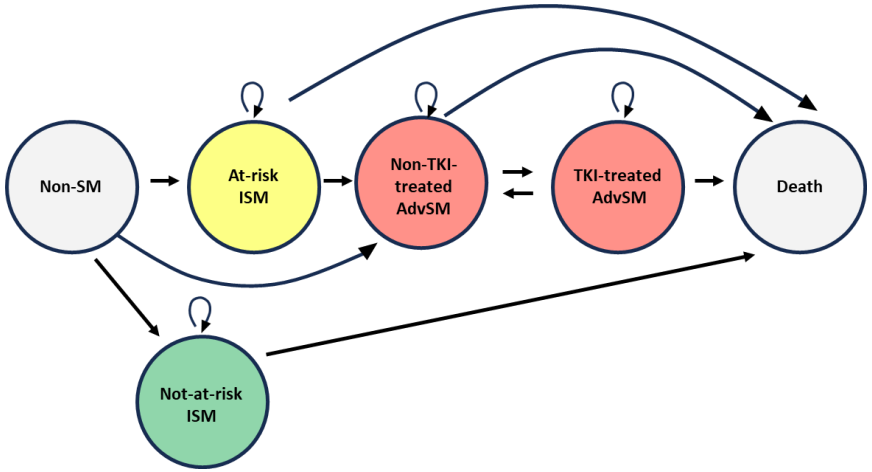
- In a two-year interval, **3.9%** of ISM patients were observed to progress from indolent SM to advanced SM



Mukherjee, Sudipto, et al. "Patterns of Disease Progression in Patients with Systemic Mastocytosis: A US Population-Level Analysis Using Health Claims-Based Dataset." ***ASH 2022**, manuscript in preparation.*

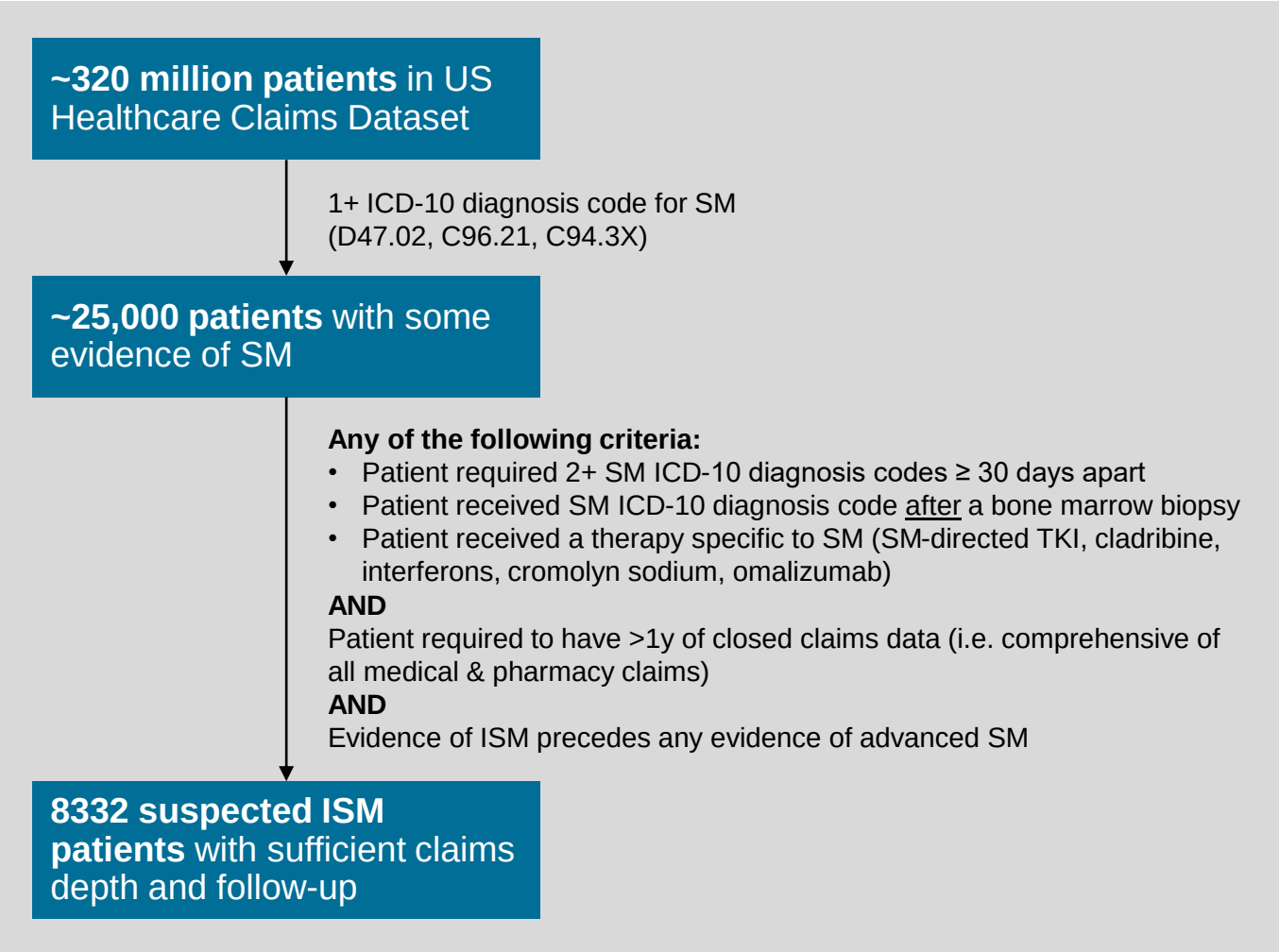
AdvSM, advanced SM; TKI, tyrosine kinase inhibitor.

- Using a discrete-time Markov modeling approach, modeled the **cumulative** risk of disease progression from ISM to Advanced SM across a patient's total disease course
- Model is based on empirical fixed-interval rates of survival and progression documented in literature
- Estimate cumulative risk of progression from indolent SM to advanced SM to be **18.0%** ±3.1% S.D



Mukherjee, Sudipto, et al. "A Model of Cumulative Risk of Disease Progression Among Patients with Indolent Systemic Mastocytosis ." ***ASH 2023**, abstract.*

Study Design and Methodology



Additional Methodological Detail:

- Study period: 2015 – 2022
- Analysis anchored to the first observed ICD-10 diagnosis code for SM
  - Progression to advanced SM was inferred if a patient generated a subsequent code specific to mast cell leukemia (MCL), aggressive SM, or an associated hematologic neoplasm (AHN)
- Mortality information available within claims dataset, and inferred if a patient did not generate any medical or pharmacy claims for 12 or more consecutive months
- Three independent non-SM control groups established through stratified sampling approach, matched by sex, age, CCI, payer status, and race/ethnicity of the ISM population

CCI, Charlson Comorbidity Index; ICD-10, International Classification of Diseases, Tenth Revision.

Patient Characteristics for ISM and Control Groups Well Matched

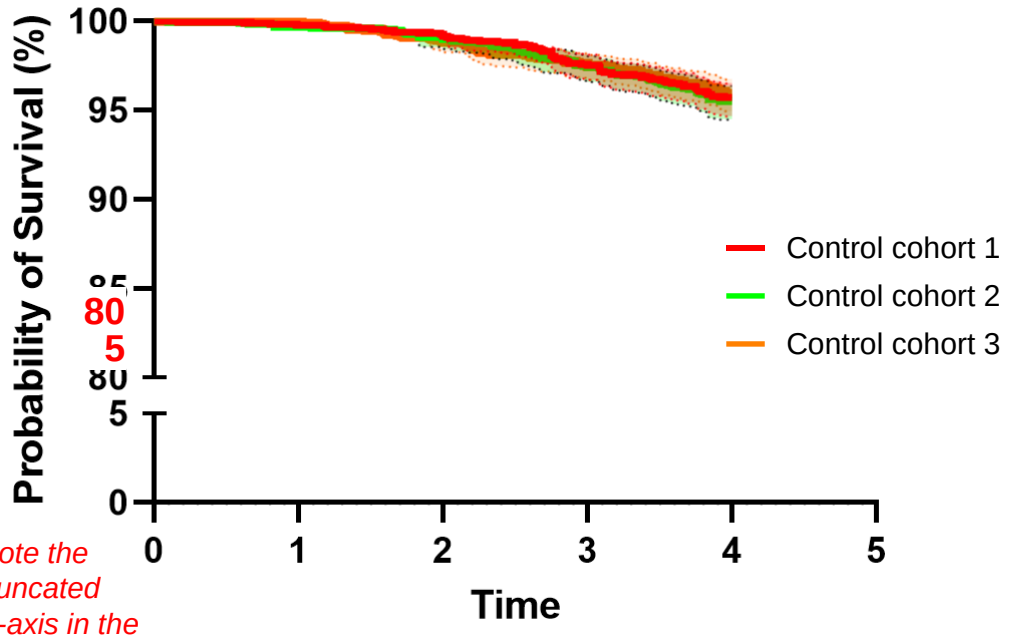
Parameter	Patients with ISM (N=8332)	Control cohort 1 (N=2000)	Control cohort 2 (N=2000)	Control cohort 3 (N=2000)
Sex, n (%)				
Male	2421 (29.1)	569 (28.5)	577 (28.9)	582 (29.1)
Female	5911 (70.9)	1431 (71.6)	1423 (71.2)	1418 (70.9)
Age in years, n (%)				
0–35	2314 (27.8)	559 (28.0)	547 (27.4)	550 (27.5)
36–48	2085 (25.0)	494 (24.7)	496 (24.8)	493 (24.7)
49–60	2016 (24.2)	488 (24.4)	483 (24.2)	486 (24.3)
61+	1917 (23.0)	459 (23.0)	474 (23.7)	471 (23.6)
CCI, n (%)				
0	1666 (20.0)	396 (19.8)	405 (20.3)	387 (19.4)
1	1592 (19.1)	381 (19.1)	380 (19.0)	385 (19.3)
2–3	2600 (31.2)	633 (31.7)	624 (31.2)	628 (31.4)
4+	2474 (29.7)	590 (29.5)	591 (29.6)	600 (30.0)
Payer, n (%)				
Commercial	6063 (72.8)	1455 (72.8)	1452 (72.6)	1459 (73.0)
Medicare	908 (10.9)	220 (11.0)	228 (11.4)	217 (10.9)
Medicare Advantage	485 (5.8)	113 (5.7)	107 (5.4)	114 (5.7)
Managed Medicaid	538 (6.5)	129 (6.5)	130 (6.5)	128 (6.4)
Other	338 (4.1)	83 (4.2)	83 (4.2)	82 (4.1)
Race/ethnicity, n (%)				
White, non-Hispanic or Latino	3613 (43.4)	869 (43.5)	874 (43.7)	865 (43.3)
Hispanic or Latino	387 (4.6)	95 (4.8)	90 (4.5)	95 (4.8)
Black or African American	226 (2.7)	53 (2.7)	52 (2.6)	55 (2.8)
Unknown/other	4106 (49.3)	983 (49.2)	984 (49.2)	985 (49.3)

**** Note: Race and ethnicity were matched between cohorts; however, this information was only available for approximately 50% of the patients***

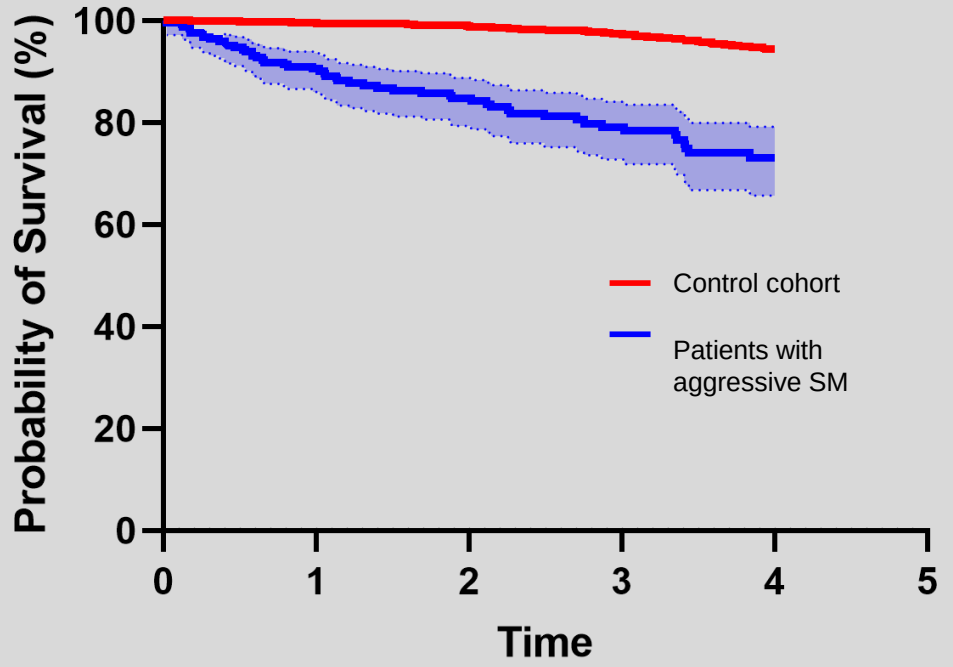
Data presented as n (%).
ISM, indolent systemic mastocytosis.

Overall Survival is Consistent Among Non-SM Control Cohorts

- Three independent samplings of non-SM control cohorts produced patient populations that were consistent in their survival (P = 0.7950)
- As all 3 cohorts had similar rates of survival, patients with ISM in this analysis were compared to control cohort 1



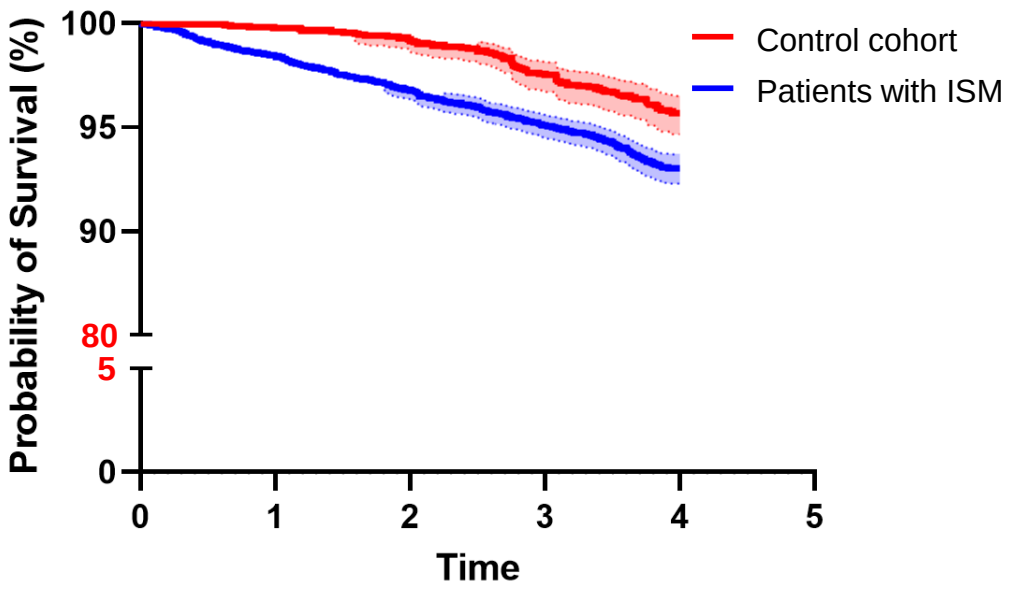
Note the truncated Y-axis in the indicated figures



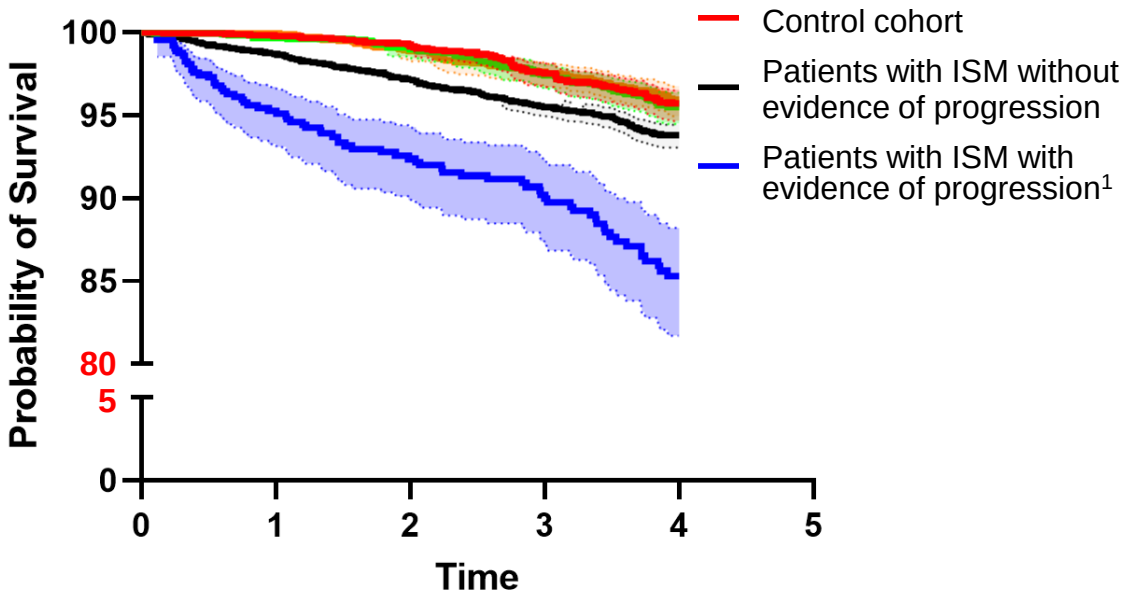
Note: To assess the face validity of this analytic approach, survival for patients with aggressive SM was compared to a control cohort, producing results in line with existing literature (P <0.0001, log-rank HR of 6.64, 95% CI 3.56 – 12.39)

ISM, indolent systemic mastocytosis; SM, systemic mastocytosis

Overall Survival in Patients With ISM is Diminished Compared to Matched Non-SM Patients



- Patients with ISM had a statistically significant difference in OS compared to the matched non-SM cohorts (*P* <0.0001*, with a log-rank HR of 1.70, 95% CI 1.39-2.10)

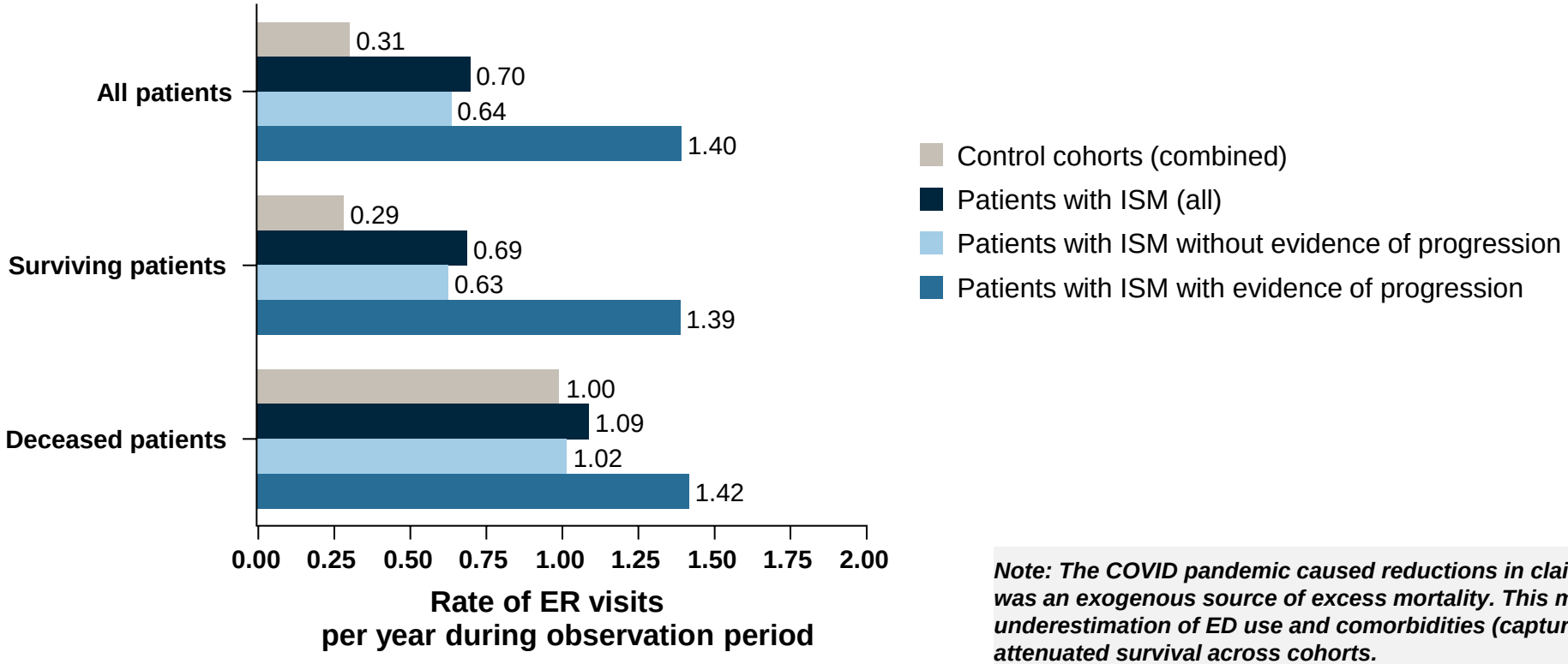


- Excess mortality was noted among ISM patients without evidence of disease progression compared to matched non-SM cohorts (P = 0.0005, with a log-rank HR of 1.53, 95% CI 1.23 – 1.90)
- Patients with evidence of progression to AdvSM had worse survival (P < 0.0001*, log-rank HR of 3.87, 95% CI 2.58 – 5.79)

*Nominal P-value
HR, hazard ratio.
[1] Progression to advanced SM was inferred based on a subsequent ICD-10 diagnosis code for aggressive SM, mast cell leukemia, or an associated hematologic malignancy

Health Resource Utilization Among ISM Patients Shows Disease Burden

- The ISM cohort presented to the ER 0.70 times per year, compared to 0.31 times per year for the combined non-ISM control cohorts, based on the sum of ER visits observed across the cumulative cohort observation period
- Patients with ISM who died during the study interval had the highest frequency of ER visits at a rate of 1.09 visits per year



Note: The COVID pandemic caused reductions in claims volume and was an exogenous source of excess mortality. This may result in an underestimation of ED use and comorbidities (captured in CCI) and attenuated survival across cohorts.

ER, emergency room.

Conclusions

- This is the first and largest population-level claims analysis of OS in the ISM population in the US
- The results of this analysis demonstrated a statistically significant decrease in survival among patients with ISM compared with matched non-SM cohorts (P <0.0001), consistent with emerging evidence from large national disease registries
- This decrease in survival was observed in both ISM patients who showed progression to AdvSM and those who did not. Notably patients with ISM visited the emergency department at twice the rate of control cohorts
- These data support emerging evidence that ISM comprises a wide phenotypic spectrum with certain patients being at a greater risk of progression to advanced disease and increased mortality, and who may benefit from earlier therapeutic intervention

Acute, severe symptoms of ISM, in addition to progression risk, may contribute to the excess mortality seen among patients with ISM and warrant focused research to identify specific patient characteristics or disease features that confer a higher risk of mortality

Acknowledgments

- Medical writing and editorial support were provided by Kimberly Dent-Ferguson, MBS, MPH, of Red Nucleus, and funded by Blueprint Medicines Corporation