Economic Burden of Advanced Systemic Mastocytosis: A Real-World Evaluation of Direct Healthcare Resource Utilization and Costs from a United States Payer Perspective

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Background

- Systemic mastocytosis (SM) is a rare mast cell neoplasm that results from clonal proliferation of abnormal mast cells in at least one extracutaneous organ/tissue.[1] Activating mutations in the KIT-gene (D816V) are almost always present in the malignant mast cells.[2]
- The World Health Organization (WHO) classifies SM into non-advanced SM or advanced SM (AdvSM), which includes aggressive SM (ASM), SM with associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL).[1,3]
- There are specific issues unique to AdvSM which need to be managed, including debilitating symptoms, organ damage and shortened survival.[4] As patients with AdvSM have different treatment history and level of care, understanding their healthcare burden is important to determine the unmet need. Limited evidence exists on the real-world economic burden of AdvSM.

OBJECTIVE: To estimate and compare rates of healthcare resource utilization (HCRU) and medical costs between patients with AdvSM and a matched cohort of patients without AdvSM in the United States (US).

Methods

STUDY DESIGN AND DATA SOURCE

- A retrospective cohort study with a 24-month observation period (12-months pre-and post-index) was conducted using the PharMetrics® Plus database from 01 Oct 2015 to 30 Sep 2019 (study period).
- Patients with AdvSM were identified from Oct 1, 2016 to Sep 30, 2018 (selection window). The index date was the date of the first observed SM diagnosis code.
- A 1% random sample of health plan claimants was extracted from the source dataset for forming a non-SM comparison cohort. A randomly selected pharmacy or medical claim was defined as the index date for these patients.

SAMPLE SELECTION

- A claims-based algorithm was used to identify newly diagnosed AdvSM patients (≥18 years old) using the following steps:

Step 1: Identification of overall SM sample

- Patients were identified with ≥1 medical claim in any position with any of the following ICD-10 CM codes: D47.02 **OR** C94.30 **OR** C94.31 **OR** C94.32 **OR** C96.21 during the selection window.

Step 2: Of step 1, AdvSM patients were identified

- Included patients who met eligibility criteria for MCL **OR** SM-AHN **OR** ASM any time during the 24-month study period (12-month baseline/pre-index period and 12-month follow-up/post-index period).
  - Patients with MCL were identified using ≥2 SM-specific ICD-10 codes of C94.30 OR C94.31 OR C94.32 OR ≥1 diagnosis code of D47.02 AND ≥1 code of C94.30 OR C94.31 OR C94.32
  - Patients with SM-AHN were identified with diagnosis codes for SM **AND** ≥1 diagnosis code of D46.X (Myelodysplastic syndrome [MDS]) OR C92.X (Acute myeloblastic leukemia [AML]) OR C93.X (Chronic myelomonocytic leukemia) OR D47.1 (Myeloproliferative neoplasms [MPN]) OR C94.6 (MDS/MPN) OR D45 (Polycythemia vera) OR D47.4 or D75.81 (Myelofibrosis) OR D47.3 (Essential [hemorrhagic] thrombocythemia) OR C95.10, C95.11, or C95.12 (Chronic eosinophilic leukemia [CEL])
  - Patients with ASM were identified using ≥1 diagnosis code of C96.21 **OR** presence of diagnosis code D47.02 **AND** ≥2 c-finding codes (including codes for evidence of organ failure, liver or spleen impairment, thrombocytopenia, neutropenia, and weight loss/malabsorption)
- Upon identification of AdvSM, the following eligibility criteria were applied:
  - Continuous health plan enrollment for 12-months preceding and following (including) the index date
  - No data quality issues (invalid year of birth, gender or health plan enrollment dates)
  - Without ≥1 diagnosis code for SM in the 12-month pre-index period

OUTCOMES

- Baseline demographic, clinical characteristics, and all-cause HCRU and direct medical costs were assessed in the 12-month pre-index period.
- Rates and frequency of HCRU and direct medical costs were examined over the 12-month post-index period (including index date).
  - HCRU categories (proportion and mean number) included pharmacy reported by prescription fills, outpatient including physician office visits, emergency room [ER] visits, lab/pathology tests, radiology exams, surgical services, and ancillary services use and inpatient visits.
  - All-cause total direct medical costs included outpatient pharmacy, outpatient medical (physician office visit, ER visit, lab/pathology, radiology, surgical and outpatient ancillary services), and inpatient costs.

STATISTICAL ANALYSIS

- To adjust for potential selection bias, AdvSM patients were direct matched (1:1) on age, gender, index year, and Charlson comorbidity index (CCI) score to non-SM controls.
- Differences in HCRU and costs during the 1-year prior to and following diagnosis were compared using McNemar's test for categorical variables and paired-t test or Wilcoxon-signed rank tests for continuous variables.
- A generalized estimating equation model (GEE) with log link/gamma distribution was used to estimate adjusted cost-ratio between cohorts.
- All costs were converted to 2019 USD using the medical component of the Consumer Price Index.

Conclusion

- This study showed that patients with AdvSM had significantly higher HCRU and medical costs during the 1-year prior to and following AdvSM diagnosis compared to matched patients without SM.
- Future research is needed to understand the role of treatments that could mitigate the economic burden among this population.

LIMITATIONS

- Despite efforts to control for potential selection bias with a matched cohort design, all group differences may not have been fully captured.
- Patients with SM-AHN may be under-represented in the current study with the eligibility requirement of both an AHN and SM diagnosis code.
- Given the observational, retrospective nature of the study, relationships should be considered associative rather than causal.

Results

STUDY SAMPLE

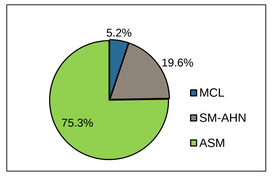
- A total of 97 AdvSM patients (mean±SD age 49±13 years, 70% female, mean±SD CCI 2.1±2.0) were identified and included in the analysis (**Table 1**).
- Prevalent baseline comorbidities included cancer (41%), hypertension (35%), and anxiety (29%) (**Table 1**).
- After direct matching, patients in the two cohorts were well-balanced on age, gender, index year, payer type, and CCI.

TABLE 1. BASELINE CHARACTERISTICS

Characteristics	Pre-Match			Post-Match		
	AdvSM (N=97)	Non-SM (N=110,362)	P-value	AdvSM (N=97)	Non-SM (N=97)	P-value
Age, Mean (SD)	49.0 (12.6)	43.4 (13.6)	<.0001	49.0 (12.6)	49.3 (12.0)	0.4675
Female (%)	70.1%	52.2%	0.0004	70.1%	70.1%	NA
Region (%)			0.0828			0.0015
Northeast	18.6%	18.4%		18.6%	17.5%	
Midwest	32.0%	27.8%		32.0%	23.7%	
South	30.9%	41.8%		30.9%	55.7%	
West	18.6%	12.1%		18.6%	3.1%	
Payer Type (%)			0.1301			0.9814
Commercial	56.7%	57.7%		56.7%	58.8%	
Self-insured	38.1%	40.3%		38.1%	37.1%	
Others	5.2%	2.1%		5.2%	5.2%	
Index Year (%)			<.0001			NA
2016	0.0%	13.9%		0.0%	0.0%	
2017	39.2%	48.3%		39.2%	39.2%	
2018	60.8%	37.8%		60.8%	60.8%	
CCI, Mean (SD)	2.1 (2.0)	0.4 (1.0)	<.0001	2.1 (2.0)	2.1 (2.0)	0.8745
Physician specialty (%)			<.0001			<.0001
Primary care physician	20.6%	16.9%		20.6%	18.6%	
Oncologist/Hematologist	12.4%	0.8%		12.4%	0.0%	
Allergist/Immunologist	6.2%	0.3%		6.2%	0.0%	
Other	60.8%	82.0%		60.8%	81.4%	
Comorbidities (%) *						
Cancer	41.2%	3.8%	<.0001	41.2%	15.5%	<.0001
Hypertension	35.1%	20.9%	0.0006	35.1%	41.2%	0.3035
Anxiety	28.9%	11.1%	<.0001	28.9%	23.7%	0.3532
Asthma	27.8%	4.7%	<.0001	27.8%	18.6%	0.0947
Depression	23.7%	8.0%	<.0001	23.7%	17.5%	0.2568
Tests of interest (%)						
Bone marrow biopsy	23.7%	0.1%	<.0001	23.7%	0.0%	NC
Serum Tryptase	61.9%	0.7%	<.0001	61.9%	1.0%	<.0001
Medications (%) *						
Corticosteroids	66.0%	29.9%	<.0001	66.0%	46.4%	0.0046
Antihistamines	39.2%	7.0%	<.0001	39.2%	18.6%	0.0006
Epinephrine injectors	38.1%	0.8%	<.0001	38.1%	1.0%	<.0001
Antileukotrienes	37.1%	3.1%	<.0001	37.1%	1.0%	<.0001
Montelukast	37.1%	3.1%	<.0001	37.1%	1.0%	<.0001

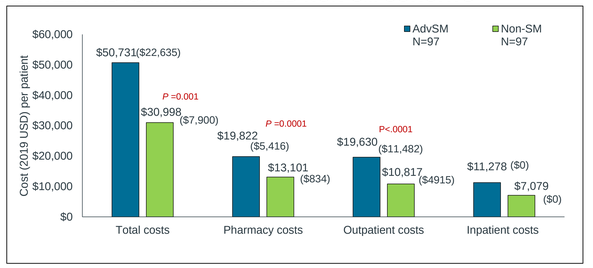
*Top 5 prevalent comorbidities and medications of interest have been presented; NA: P-values are not applicable because patients were direct matched on age group, gender, year of index, and CCI; NC: Could not be computed due to 0 cell size

FIGURE 1. DISTRIBUTION BY TYPE OF ADVSM



- The majority of AdvSM patients had ASM (75%) followed by SM-AHN (20%) and MCL (5%) (**Figure 1**).
- Median pre-index medical costs were significantly higher for AdvSM patients compared to matched non-SM comparator cohort (**Figure 2**).

FIGURE 2. MEAN (MEDIAN) PRE-INDEX MEDICAL COSTS BETWEEN ADVSM AND MATCHED NON-SM COHORTS

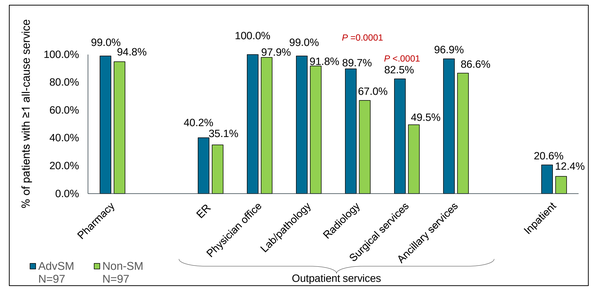


P-values are presented only for medians

OUTCOMES: POST-INDEX HCRU AND COSTS

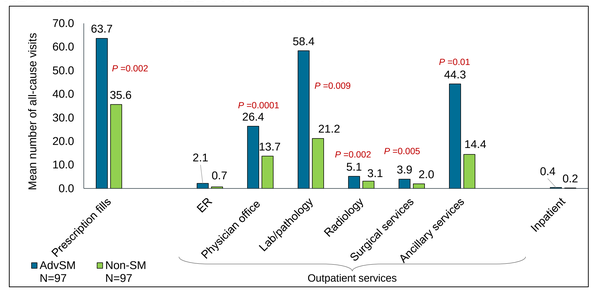
- Proportion of patients with utilization of outpatient medical services was higher in the AdvSM cohort as compared to the non-SM cohort over the 1-year follow-up (**Figure 3**).
  - Epinephrine prescription fills were observed in 36% of patients with AdvSM compared with 1% of non-SM controls.

FIGURE 3. PROPORTION OF PATIENTS WITH ALL-CAUSE HCRU BETWEEN ADVSM AND MATCHED NON-SM COHORTS



- Mean number of prescription fills and outpatient service utilization was significantly higher among AdvSM vs non-SM patients (**Figure 4**).

FIGURE 4. MEAN POST-INDEX ALL-CAUSE HCRU BETWEEN ADVSM AND MATCHED NON-SM COHORTS



- Mean [median] medical costs during the 1-year post-index period were also higher for AdvSM vs. non-SM patients (**Table 2**).
  - Pharmacy (38.2%) and outpatient costs (38.0%) accounted for majority of the follow-up costs among AdvSM patients.
  - Findings from GEE showed that patients with AdvSM had 2.1 times higher all-cause total costs as compared to patients without SM (adjusted cost ratio: 2.1; 95% CI: 1.43-3.07; *P*=0.0001).

TABLE 2. MEAN (MEDIAN) ALL-CAUSE MEDICAL COSTS BETWEEN ADVSM AND MATCHED NON-SM COHORTS

Medical costs	AdvSM (N=97)		Non-SM (N=97)		P-value (mean)	P-value (median)
	Mean	Median	Mean	Median		
Total	$69,133	$29,123	$24,065	$8,293	0.0004	<.0001
Pharmacy	$26,400	$4,300	$13,101	$871	0.0155	<.0001
ER	$3,938	$0	$809	$0	0.1710	0.0144
Physician office	$3,615	$2,534	$2,086	$1,011	0.0254	<.0001
Lab/Pathology	$3,276	$1,470	$600	$256	0.0007	<.0001
Radiology	$2,259	$1,081	$852	$296	0.0008	<.0001
Surgical	$3,571	$3,571	$1,246	$1,246	0.0053	0.0008
Ancillary services	$9,587	$2,185	$2,745	$516	0.0096	<.0001
Inpatient	$16,487	$0	$5,385	$0	0.0681	0.0059

ASM: Aggressive SM; CCI = Charlson Comorbidity Index; ER = emergency room; GEEs = generalized estimating equations; HCRU: healthcare resource utilization; MCL: Mast cell leukemia; SD = standard deviation; US = United States; SM: Systemic mastocytosis; SM-AHN: SM with associated hematological neoplasm

References: [1] Pardanani A. American journal of hematology. 2019 Mar, 94(3):363-77; [2] Grootens J et al. EBioMedicine. 2019 May 1. 43:150-8; [3] Arber DA, et al. Blood. 2016, 127:2391-2405; [4] Valent P et al. International journal of molecular sciences. 2019 Jan;20(12):2976.

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