Original Article

Patient-reported outcomes among patients with systemic mastocytosis in routine clinical practice: Results of the TouchStone SM Patient Survey

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BACKGROUND: Systemic mastocytosis (SM) is a rare clonal neoplasm driven by *KIT* D816V and other mutations. Data were collected from the patient perspective on disease burden and included an SM-specific symptom assessment tool. **METHODS:** US adults aged 18 years and older with a self-reported SM diagnosis completed an online TouchStone SM Patient Survey of 100 items, including the 12-item Short-Form Health Survey, the Indolent Systemic Mastocytosis Symptom Assessment Form, and the Work Productivity and Activity Impairment Questionnaire, as well as questions about SM diagnosis, the impact of SM on daily activities, work impairment, and health care use. The results were analyzed using descriptive statistics. **RESULTS:** Fifty-six individuals completed the survey (89% women; median age, 48 years; mean time since diagnosis, 6.7 years), reporting indolent SM (66%), aggressive SM (9%), smoldering SM (5%), and unknown SM subtype (18%). Over a 1-year recall, respondents reported seeking emergency care for anaphylaxis (30%) and taking three or more prescription medications (52%) for SM. Over one half of patients (54%) reduced their work hours because of SM, and 64% avoided leaving home because of symptoms. A majority of respondents (93%) had experienced ≥10 SM-related symptoms, noting that the *most bothersome* were anaphylactic episodes (18%), abdominal/stomach pain (16%), diarrhea/loose stools (13%), and fatigue (11%). Whereas an Indolent Systemic Mastocytosis Symptom Assessment Form-derived total symptom score of 28 is used to indicate moderate-to-severe symptoms, the mean total symptom score was 52.7. Mental and physical component summary scores from the 12-item Short-Form Health Survey were below population norms. **CONCLUSIONS:** Patients who were surveyed reported substantial symptom burden and unmet needs because of SM, as evidenced by seeking emergency care and reporting bothersome symptoms, poor quality of life, and reduced work hours and productivity. ***Cancer* 2022;128:3691-3699**.

LAY SUMMARY:

- The objective of this research was to understand the burden and unmet needs in the rare disease of systemic mastocytosis (SM) to guide future care.
- Fifty-six patients completed an online survey containing questions about their diagnosis, medications, health care use, quality of life, and SM symptoms.
- The results demonstrated that SM is associated with severe and burdensome symptoms, anaphylactic events, emergency department visits, use of multiple medications, reduced ability to work, and poor physical and psychological quality of life.
- These findings suggest the need for future advances to address unmet needs in patients affected by SM.

KEYWORDS: cross-sectional studies, disease burden, myeloid neoplasm, myeloproliferative neoplasm, patient-reported outcomes, systemic mastocytosis.

INTRODUCTION

Systemic mastocytosis (SM) is a rare hematopoietic disease associated with the uncontrolled proliferation of dysfunctional mast cells and is estimated to affect 32,000 adults in the United States.[1,2] Greater than 90% of SM cases are driven by activated *KIT* gene mutations, frequently at position D816.[3] SM is classified as a myeloid neoplasm with highly variable phenotypic expression and is subdivided into nonadvanced and advanced subtypes.[4] Nonadvanced SM is composed of indolent SM (ISM) and smoldering SM (SSM), whereas advanced SM (AdvSM) consists of aggressive SM, SM with an associated

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hematologic neoplasm, and mast cell leukemia (MCL).[5] In an analysis of the Danish National Health Registry, 82% of all SM cases were categorized as ISM.[2] Similar proportions of patients with ISM were reported in the European Competence Network on Mastocytosis, a registry that had >3000 enrolled patients across 25 centers in 12 countries as of 2018.[6]

Patients who have AdvSM have a decreased life span compared with those with nonadvanced SM, who have a normal life span,[1,5,7] but the disease burden is often substantial.[8,9] Patients with nonadvanced SM experience symptoms that negatively affect quality of life and diminish functional status, including a risk of life-threatening anaphylactic episodes.[8,9] Despite burdensome symptoms and care-seeking behavior, patients with SM report a substantial delay in diagnosis, with a median time of 7 years from symptom onset to a diagnosis of SM.[9] In patients who have nonadvanced subtypes, extensive delays (median, 9 years) between experiencing symptoms and receiving a diagnosis are reported compared with those who have AdvSM (median, 3 years).[9]

Patients with SM require consultation with multiple medical specialties, and referral to specialized centers adept at managing multiorgan dysfunction remains an important treatment paradigm.[10] Although improving the survival of patients with AdvSM is a crucial goal of existing management strategies, mitigating the burden of nonadvanced SM relies heavily on symptom-directed therapies.[10] Common medications used to relieve nonadvanced SM symptoms are antihistamines, mast cell stabilizers, leukotriene antagonists, and prostaglandins inhibitors.[3,11] Chemotherapies and tyrosine kinase inhibitors may be used in AdvSM, but these medications are associated with severe side effects, including infections, anemia, and low platelet counts.[12] Recently, omalizumab has been used to prevent anaphylactic episodes.[11]

Improving SM disease management and treatment necessitates an understanding of the holistic patient disease experience as well as treatment limitations and gaps. The objective of this study was to uncover unmet needs of patients with SM by querying their health care treatment patterns in addition to general health status, productivity, and SM-specific patient-reported outcomes.

MATERIALS AND METHODS

Recruitment and study population

Adults aged 18 years and older who self-reported a diagnosis of SM, lived in the United States, and were not participating in a clinical trial were eligible to enroll in the TouchStone SM Patient Survey study (the *TouchStone Survey*). Recruitment was conducted using the Mast Cell Connect Registry (MC Connect; ClinicalTrials.gov identifier NCT02620254),[13] a patient registry initiated in 2015 that is sponsored by Blueprint Medicines Corporation and advertised through The Mast Cell Disease Society, Inc., and specific providers to advance understanding of mastocytosis and its impact on patients.[9,13] The study was reviewed and approved by a central Institutional Review Board, and all patients provided informed consent.

Study instrument: The TouchStone SM Patient Survey

The TouchStone Survey was composed of 100 questions and included three validated instruments: the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF), the 12-item Short-Form Health Survey (SF-12), and the Work Productivity and Activity Impairment (WPAI) Questionnaire.[14–17] The ISM-SAF is a reliable and valid, 12-item questionnaire[16,17] that assesses relevant SM-specific symptoms identified by patients with ISM and SSM.[17]

Reported severity of bone pain, abdominal pain, nausea, spots on skin, itching, flushing, fatigue, dizziness, brain fog, headache and diarrhea generates a total symptom score (TSS) that carries prognostic significance.[16,17] The SF-12, WPAI, and ISM-SAF were combined with investigator-developed questions that were adapted from items used in a previous cross-sectional study[18,19] of patients with myeloproliferative neoplasms regarding symptoms and the type and frequency of health care use (27 questions); the impact of SM on daily functioning, emotional well-being, and quality of life (32 questions); and patient demographics (10 questions).

Special instructions and recall period

This survey was administered over 4 weeks during June and July 2020. The recall period was 4 weeks for the SF-12 and 2 weeks for the ISM-SAF. Because of the potential impact of the COVID-19 pandemic on patients' health care-seeking behaviors, recall period instructions were adapted to facilitate the capture of usual patterns of activity outside of the quarantine measures implemented during 2020. For example, survey respondents were instructed to recall health care use, work impairment, and WPAI metrics based on their experiences during a *typical 7-day period* before the onset of travel restrictions, which may have disrupted usual care and work behaviors. Patients were asked to consider typical patterns of care in the year before COVID-19 quarantine periods (during 2019) for the following items: use and storage of injectable epinephrine (e.g., EpiPen), use

of the emergency department because of anaphylaxis, and management of anaphylaxis at home.

Analysis and reporting

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc.). Health care use and burden were measured as continuous variables (e.g., the time from symptom onset to diagnosis, the number of physicians seen before receiving an SM diagnosis), and descriptive statistics were used to derive mean, median, standard deviation (SD), and confidence interval (CI) values. Categorical survey variables, such as employment status, SM subtype, type of physician seen, and frequency of visits, were reported as the number of respondents per category and proportion. Existing validated patient-reported outcome measures were scored using established algorithms.[14–16]

Scores for the SF-12 were derived according to the scoring algorithm, including the physical component score (PCS) and the mental component score (MCS), ranging from 0 (the lowest possible level of health) to 100 (the highest possible level of health).[14] All scores were assessed relative to national norms of 50.[14,20] Scores were then stratified by categorical variables of interest: employment (full-time, part-time, unemployed because of SM, unemployed not because of SM, or other), number of physician office visits (<7, 7–13, or ≥14 visits), primary specialty managing SM (allergist/immunologist, general practitioner, hematologist/oncologist, or other), frequency of injectable epinephrine use (zero or one time, two or more times), pain level (little-to-moderate pain or high pain), and type of SM-related care facility (academic hospital, community hospital, or others).

For the ISM-SAF, severity by individual symptom (on a scale from 0 [representing no symptoms] to 10 [representing severe symptoms]) and the TSS were calculated for each respondent.[16] The TSS is calculated to denote the overall severity of SM symptoms, with scores ≥28 suggesting moderate-to-severe SM symptoms.[16] Symptom severity scores, diarrhea frequency, and the TSS were analyzed as continuous variables, with measures of central tendency, SD, and 95% CIs computed for the entire sample and for the subgroup of patients who reported an ISM subtype.

The TouchStone Survey queried work impairment and changes in employment status (e.g., reduced hours, medical disability, early retirement) as a result of SM. In addition, items from the WPAI documented the impact on work hours (e.g., hours worked, hours missed because of SM, and hours missed for other reasons) and the extent to which SM affected work productivity and regular daily activities outside of work. The results were analyzed categorically and further stratified by two key categorical variables: frequency of injectable epinephrine use and perceived level of pain.

RESULTS

Demographics

In total, 56 patients completed the TouchStone Survey among 350 who were contacted through MC Connect, yielding a response rate of 16%. The median age of respondents was 48 years, and 89% of respondents were women. Among those surveyed, 43% received an initial diagnosis of SM from an allergist/immunologist, and 59% reported that a physician in this specialty was primarily responsible for their SM-related care. Patients reported an average of 5.6 years between the onset of symptoms and their diagnosis and that, in addition, a mean of 6.7 years had passed since they received an SM diagnosis at the time of survey completion. Full demographic details and reported comorbidities are presented in Table 1.

SM symptoms

Fifty-two respondents (93%) reported ≥10 SM-related symptoms and events in their lifetime. Respondents reported significant impacts of SM symptoms on daily life, with 64% ($n = 36$) noting that they avoided leaving their home because of SM and 66% ($n = 37$) noting that pain interfered with work. When asked about the *most bothersome* SM-related symptom ever experienced, 18% ($n = 10$) of patients reported anaphylactic episodes, 16% ($n = 9$) selected abdominal or stomach pain, 13% ($n = 7$) reported diarrhea, and 11% ($n = 6$) noted fatigue. All respondents reported at least six SM-related symptoms *ever experienced*, and the mean was 14.25 SM-related symptoms per patient. One half ($n = 28$) of respondents cited better quality of life as the primary goal for management and treatment (outside of a cure), and 23% ($n = 13$) noted desiring improvement of symptoms.

As captured in the ISM-SAF, patient-reported levels of symptom severity varied by type of symptom. Over a 2-week recall period, the mean score for fatigue had the highest reported severity (6.75), whereas spots on skin had the lowest reported severity (3.77). The mean severity of diarrhea was in the top five most severe symptoms; 89.3% ($n = 50$) of patients reported a frequency of one or more episodes of diarrhea in the past 2 weeks, and 14.3% ($n = 8$) reported 24 episodes of diarrhea. The mean ± SD number of diarrhea episodes was 8.92 ± 8.22. Overall, respondents had a mean TSS of 52.7, and the mean TSS for the

TABLE 1. Baseline Patient Demographic and Clinical Characteristics, $n = 56$

Variable	Mean ± SD or No. (%)
Age: Median [range], years	48 [20–76]
Women	50 (89.0)
Time from symptom onset to receiving physician diagnosis, years	5.6 ± 4.1
Time since initial SM diagnosis, years	6.7 ± 5.7
Comorbidities	
Hereditary α-tryptasemia	4 (7)
Postural orthostatic tachycardia	19 (34)
Ehlers–Danlos syndrome	17 (30)
Diabetes	6 (11)
High blood pressure	27 (48)
Osteopenia/osteoporosis	16 (29)
SM subtype	
ISM	37 (66)
ASM	5 (9)
SSM	3 (5)
SM-AHN	1 (2)
Unknown	10 (18)
No. of physicians seen for SM symptoms before receiving a diagnosis	5.8 ± 3.0
Type of physician who diagnosed SM	
Allergist/immunologist	24 (43)
Dermatologist	13 (23)
Hematologist/oncologist	12 (21)
Gastroenterologist	3 (5)
Other	4 (7)
No. of primary physicians who manage SM	
Allergist/immunologist	33 (59)
Hematologist/oncologist	12 (21)
General practitioner/PCP	9 (16)
Other	2 (4)
Setting of care for primary SM physician	
Academic hospital	18 (32)
Multispecialty group/HMO	16 (29)
Single specialty group	5 (9)
Solo practice	9 (16)
Community hospital	2 (4)
Other	4 (7)
Not sure	2 (4)

Abbreviations: ASM, aggressive systemic mastocytosis; HMO, health maintenance organization; ISM, indolent systemic mastocytosis; PCP, primary care physician; SD, standard deviation; SM, systemic mastocytosis; SM-AHN, systemic mastocytosis with an associated hematologic neoplasm; SSM, smoldering systemic mastocytosis.

subgroup of patients reporting nonadvanced SM ($n = 40$) was 52.4. Symptom severity scores and the TSS generated from the ISM-SAF are depicted in Table 2.

General health (SF-12) and burden of SM on daily functioning

We calculated a mean ± SD PCS score of 35.1 ± 12.50 and a mean ± SD MCS score of 37.8 ± 9.86, with median values of 33.9 (range, 13.9–61.2) and 37.9 (range, 19.7–55.9) for the PCS and the MCS, respectively. SF-12 component scores in the subgroup of patients reporting nonadvanced SM were similar to scores in the overall sample (mean PCS, 36.9 [median, 37.3]; mean MCS, 38.8 [median, 38.1]). Stratified analyses indicated that respondents who were unemployed because of SM had lower median SF-12 scores than the overall sample (PCS, 25.5; MCS, 32.9). Furthermore, respondents who required ≥14 physician office visits in the prior year and those who reported injectable epinephrine use at least twice had lower (worse) PCS and MCS than the overall study sample. Table 3 details the stratified SF-12 analyses.

TABLE 2. Systemic Mastocytosis Symptoms From the Indolent Systemic Mastocytosis Symptom Assessment Form, $n = 56$

Symptom queried	Mean ± SD severity score, 0–10 scale[a]	95% CI
Bone pain	4.05 ± 2.89	3.28–4.83
Abdominal pain	5.18 ± 3.10	4.35–6.01
Nausea	4.27 ± 3.31	3.38–5.15
Spots on skin	3.77 ± 3.27	2.89–4.64
Itching	4.43 ± 3.06	3.61–5.25
Flushing	5.07 ± 3.26	4.20–5.95
Fatigue	6.75 ± 2.91	5.97–7.53
Dizziness	4.11 ± 2.91	3.33–4.89
Brain fog	5.32 ± 3.32	4.43–6.21
Headache	4.75 ± 3.57	3.79–5.71
Diarrhea	4.96 ± 3.06	4.15–5.78
Total symptom score	52.66 ± 21.28	47.09–58.23

Abbreviations: CI, confidence interval; SD, standard deviation.
[a]Severity for each symptom queried is reported on a scale from 0 (no symptoms) to 10 (worst imaginable symptoms).

Work status and productivity

Approximately 54% of respondents reported *ever reducing* their hours at work, 27% reported *voluntarily* quitting their job because of SM, and 16% reported being terminated from their job as a result of SM. Patients who reported severe pain were more likely to note SM-related changes to employment status. For example, 100% of patients who reported early retirement because of SM also reported severe pain over the past 4 weeks. Greater use of injectable epinephrine (two or more uses) was not associated with greater work impairment. Table 4 details the frequency of reported work impairment and employment status.

Health care use

Respondents reported seeking consultation from a variety of physicians because of SM symptoms over a typical year. For all visit frequency categories, patients reported primary care and allergy/immunology as the most common physician visits. For patients who reported three or more physician's visits, the top specialties seen included primary care, allergy/immunology, and hematology/oncology. Details on physician visits are presented in Table 5.

TABLE 3. Median Physical and Mental Component Summary Scores From the 12-Item Short-Form Health Survey Stratified by Six Key Variables, *n* = 56

Variable	Median score (range)	
	PCS	MCS
Overall	33.9 (13.9–61.2)	37.9 (19.7–55.9)
Stratified by:		
Employment status		
Full time, *n* = 17	37.9 (22.8–60.4)	33.5 (22.0–51.7)
Part time, *n* = 9	33.5 (17.2–51.0)	37.8 (19.7–54.8)
Unemployed because of SM, *n* = 15	25.5 (14.6–-47.8)	32.9 (21.3–53.3)
Unemployed not because of SM, *n* = 6	45.1 (19.6–61.2)	49.4 (44.6–54.1)
Other, *n* = 9	39.7 (14.0–57.2)	41.0 (33.9–55.9)
No. of HCP visits in 1 year		
<7, *n* = 18	38.5 (18.2–61.2)	43.9 (33.1–55.9)
7–13, *n* = 22	37.1 (14.6–60.4)	39.0 (19.7–53.3)
≥14, *n* = 16	24.8 (14.0–40.2)	32.3 (21.3–51.5)
Primary disease manager		
Allergist/immunologist, *n* = 33	33.5 (17.2–61.2)	37.8 (19.7–54.1)
General practitioner, *n* = 9	34.1 (25.4–57.2)	34.1 (22.0–55.9)
Hematologist/oncologist, *n* = 12	36.6 (14.0–40.2)	38.5 (25.9–54.8)
Other, *n* = 2	16.4 (14.6–18.2)	43.2 (33.1–53.3)
No. of injectable epinephrine uses in 1 year		
0–1, *n* = 48	36.6 (13.9–61.2)	38.8 (21.3–56.0)
≥2, *n* = 8	25.3 (21.1–51.0)	28.8 (19.7–42.4)
Perceived pain in prior 4 weeks		
High pain, *n* = 26	25.6 (14.6–45.6)	33.5 (21.3–53.3)
Little to moderate pain, *n* = 30	40.0 (13.9–61.2)	40.0 (19.7–56.0)
Care setting		
Academic hospital, *n* = 18	39.4 (21.1–60.1)	40.0 (21.8–54.1)
Community hospital, *n* = 2	28.5 (27.1–30.0)	41.3 (38.8–44.1)
Other, *n* = 36	32.2 (14.0–61.2)	35.5 (19.7–55.9)

Abbreviations: HCP, health care provider; MCS, mental component score; PCS, physical component score; SM, systemic mastocytosis.

Study participants reported routinely using multiple medications to treat their SM symptoms. Over one half (52%; *n* = 29) of those surveyed indicated taking three or more prescription medications to manage their SM. In addition, 61% (*n* = 34) of respondents reported taking three or more over-the-counter (OTC) medications for SM symptoms. Notably, 88% (*n* = 49) of participants reported keeping injectable epinephrine on hand for emergency use in the event of an anaphylactic episode, and 77% (*n* = 43) reported storing injectable epinephrine in two or more different locations to anticipate possible use. Over a 1-year recall, 30% (*n* = 17) of patients reported at least one emergency department visit for anaphylaxis, and 63% (*n* = 35) chose to manage one or more anaphylactic episodes at home rather than seeking care in the emergency department. Patients who reported one or more annual anaphylactic episodes had higher (more severe) mean ISM-SAF skin domain scores compared with those who reported no episodes (14.4 vs. 10.4, respectively, $p = .03$). Patients who reported >12 anaphylactic episodes had a mean skin domain score of 17.3.

DISCUSSION

The TouchStone SM Patient Survey is the first real-world study in SM to capture patient perspectives on the holistic impact of SM considering quality of life, symptom burden, pain, daily functioning, use of medications, health care services by specialists, and work status. Respondents in this

TABLE 4. Work Impairment as a Result of Systemic Mastocytosis Stratified by ≥2 Injectable Epinephrine Uses and Severe Pain, *n* = 56

Work impairment[a]	No./total no. (%)		
	Patients overall	Injectable epinephrine use ≥2 times in 1 year	Severe pain in prior 4 weeks
Reduced hours at work	30 (54)	5/30 (17)	16/30 (53)
Voluntarily quit job	15 (27)	4/15 (27)	13/15 (87)
Taken early retirement	4 (7)	1/4 (25)	4/4 (100)
Gone on medical disability	18 (32)	4/18 (22)	12/18 (67)
Been terminated from job	9 (16)	3/9 (33)	6/9 (67)
No impact of disease on work	15 (27)	1/15 (7)	3/15 (20)

[a]Respondents reported impairment over a typical 7-day period before the COVID-19 pandemic.

TABLE 5. Patients Reporting Systemic Mastocytosis-Related Physician Office Visits Over 1 Year

No. of patient-reported visits	No./total no. (%)				
	Primary care	Allergy/immunology	Gastroenterology	Dermatology	Hematology/oncology
0	11/55 (20)	13/56 (23)	24/55 (44)	30/55 (55)	28/54 (52)
≥1	44/55 (80)	43/56 (77)	31/55 (56)	25/55 (45)	26/54 (48)
≥3	28/55 (51)	25/56 (45)	13/55 (24)	4/55 (7)	17/54 (31)
≥6	13/55 (24)	12/56 (21)	6/55 (11)	1/55 (2)	6/54 (11)
≥12	6/55 (11)	7/56 (13)	3/55 (5)	0/55 (0)	4/54 (7)

study are similar to other SM registry populations, composed of >70% who had nonadvanced disease reported as ISM and SSM subtypes. Survey responses were mainly from female participants, which is consistent with previous surveys[21–24] but not representative of the sex distribution in the incidence or prevalence of SM, which is 50% men.[8] As reported in prior literature,[9] our study confirmed long diagnostic delays despite multiple specialist visits (more than five physicians, on average) before diagnosis. Although less than one half of patients in this study received their diagnosis from an allergist/immunologist, the majority reported this specialist as primarily managing their SM care. There are few published rates of comorbidities in patients with SM; Compared with other studies of patients who have similar conditions, TouchStone respondents reported greater proportions of diabetes (11% vs. 2%–5%[2,22]) and lower proportions of hereditary α-tryptasemia (7% vs. 18%[25]).

Symptom burden was high among survey respondents, with patients experiencing an average of 14 SM-related symptoms in their lifetime—the most bothersome of which were reported to be anaphylaxis and abdominal pain, followed by diarrhea and fatigue. Nearly 90% of patients reported experiencing diarrhea in the past 2 weeks on the ISM-SAF, including approximately one in seven patients who reported 24 episodes. Across symptoms assessed in the ISM-SAF, *fatigue*, *brain fog*, and *abdominal pain* were associated with the highest mean severity scores, and these findings align with prior research indicating that fatigue is the most severe symptom of mastocytosis.[26] Only six respondents ranked fatigue/exhaustion as the *most bothersome* symptom, potentially reflecting how certain SM symptoms may be perceived as relatively manageable yet still are rated as severe. The mean reported ISM-SAF TSS (52.7) in this patient sample surpassed the 28-point threshold for moderate-to-severe disease,[16,27] further substantiating the high symptom burden despite high rates of polypharmacy and physician visits. Notably, even in the subset of patients reporting nonadvanced SM (ISM and SSM), the mean TSS indicated higher disease severity.

TouchStone respondents also reported health-related quality-of-life component scores that were lower (worse) than mean SF-12 scores in other conditions with high symptom burden,[28,29] as reported in Figure 1. On the basis of this comparison of reported SF-12 scores across various conditions, patients with SM reported average PCS scores most similar to scores in patients who have lung cancer[29] and average MCS scores most similar to scores in patients

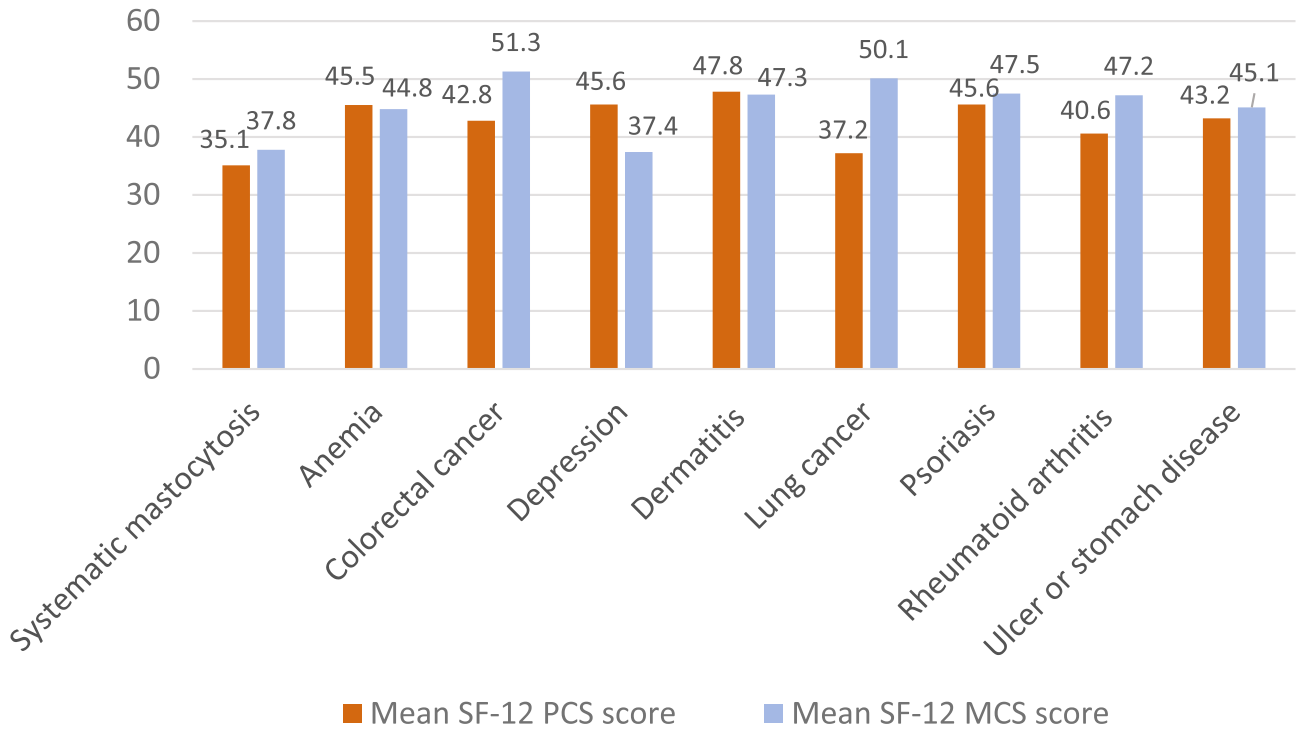

Figure 1. SF-12 mean mental component score and physical component score for patients in the TouchStone SM Patient Survey compared with values for other conditions[28,29] MCS indicates mental component score; PCS, physical component score; SF-12, 12-item Short-Form Health Survey; SM, systemic mastocytosis.

who have depression.[28] Comparing the quality of life of patients with SM versus that of patients with other conditions, particularly cancer, may be a poor comparison because of an imbalance of disease duration and expected survival. Similarly, heterogeneity in sample size, study design, and population differences (e.g., age, comorbid conditions) between our study and prior studies preclude direct comparisons. With these caveats, the relatively low MCS and PCS scores reported by participants in our study suggest that SM has a substantial negative impact on patients' health-related quality of life. In SM specifically, the median PCS and MCS scores among TouchStone Survey respondents were lower than scores previously reported in a study of patients with AdvSM,[30] which found median for PCS of 36.5 and a median for MCS of 45.3.

Relatively lower health status is consistent with the high health care use reported by patients in this study, including emergency department visits and anaphylactic episodes. Over a 1-year period, 30% of surveyed patients reported using injectable epinephrine at least once. These findings are consistent with an estimated 26%–44% incidence of anaphylaxis in patients with mast cell disorders reported elsewhere.[9] Fear of anaphylaxis and the related worry about requiring anaphylaxis treatment while traveling or performing activities has also been reported among patients with SM.[9] These types of concerns may help to explain why approximately 77% of patients in the TouchStone Survey reported storing injectable epinephrine in two or more different locations to anticipate possible use. It is important to note that the majority of patients (>88%) were prescribed epinephrine, indicating that health care providers understand the associated anaphylaxis risk in patients with SM and provide the appropriate treatment to protect patients.

Patients with SM have higher health service use and higher medical costs compared with matched controls in the US population.[31,32] In addition to high rates of physician office visits, TouchStone respondents confirmed high rates of polypharmacy (with more than one half of patients reporting three or more OTC medications and three or more prescription medications for SM), yet they still experienced persistent, bothersome symptoms. This polypharmacy rate is similar to that in other diseases (e.g., 68% reported by patients with rheumatoid arthritis).[33] Prior research documents patient fears around polypharmacy for symptom control, including concerns related to drug–drug interactions, anaphylaxis induced by multiple medications, and unwanted side effects.[9] Reducing the number and type of medications required to adequately manage SM is an important treatment goal.

Bothersome and poorly controlled SM symptoms may also affect patients' productivity. Over one half of TouchStone Survey respondents reported reduced work hours related to SM. Nearly one third of patients reported going on medical disability. More than one half of respondents indicated that pain significantly affected their daily functioning, including their ability to work. Notably, severe pain seems to be associated with a substantial impact on work status because more than one half (53%) of patients who reported reduced hours at work also reported severe pain. Furthermore, more than two thirds of patients who *voluntarily* quit their job, took early retirement, went on medical disability, or were terminated from their job also reported severe pain related to SM (Table 4). As reported above (see Results), survey responses about the impact of symptoms on daily life corroborated the impact of SM on work status. For example, a majority (64%) of patients reported avoiding leaving home because of their SM symptoms, and nearly two thirds (66%) noted that pain interfered with work. This was also observed in lower physical quality-of-life scores (across PCS and MCS) for patients reporting pain. Work impairment has been documented in patients with mast cell disorders.[34] For patients with SM, unpredictable onset of acute symptoms was a major contributor to qualifying for disability insurance coverage (among those transitioning away from the workforce), and loss of income affected patients' ability to manage their disease.[9] Our findings of reduced work hours and documented medical disability combined with polypharmacy may help to contextualize how and why patients with SM experience financial instability.

Limitations

Our sample size is smaller than some previous studies on the burden of mast cell disorders, which reported hundreds of patients,[22,34] although it is similar to another survey of 50 patients with myeloproliferative neoplasms.[21] The small sample and relatively low participation (16%) may be partially explained by recruitment from a disease registry as opposed to broader community approaches.[21,22,34,35] However, our response rate is consistent with other published surveys.[36] The TouchStone Survey was also subject to standard biases inherent to survey-based studies (i.e., question order effects, etc.). For instance, recruiting patients using email and social media may have attracted patients who were more likely to be engaged in internet-based communications and women,[23,24] as observed in prior patient surveys.[21,22,34] Patients with more severe disease manifestations may

also have been more likely to participate, affecting the generalizability of these findings to all patients with SM. In addition, patient-reported health care services may have been affected by recall bias, and the frequency of physician visits may reflect health care provider management rather than symptom-driven encounters. Although investigators sought to account for the possible impact of COVID-19 patient responses, overall findings nonetheless may have been affected. Finally, the survey relied on patient confirmation of SM disease, and each respondent's SM diagnosis was not otherwise verified.

CONCLUSIONS

The TouchStone SM Patient Survey documents a substantial burden of SM in a sample of patients with reported nonadvanced SM disease and is the first study to report real-world symptom burden using the validated ISM-SAF. Our results demonstrated high SM-related health resource use, including polypharmacy for symptom control, numerous visits to multiple specialists, and documented mean TSS scores, suggesting moderate-to-severe SM symptoms. Patients with SM participating in the TouchStone Survey reported impaired physical functioning and mental health, decreased work performance and productivity, difficulty completing daily activities, and overall poor quality of life, potentially reflecting the chronic nature of the disease. Persistent disability, poor functional status, and frequent anaphylaxis highlight a clear unmet need in this patient population. Future studies in a larger sample of patients with SM should continue to evaluate the substantial symptom burden and impact on quality of life.

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AUTHOR CONTRIBUTIONS

Ruben A. Mesa: Supervision (lead), conceptualization (equal), methodology (equal), writing–original draft (supporting), and writing–review and editing (equal). **Erin M. Sullivan:** Conceptualization (equal), methodology (equal), writing–original draft (lead), formal analysis (equal), and writing–review and editing (equal). **David Dubinski:** Project administration (lead), conceptualization (lead), methodology (equal), and writing–review and editing (equal). **Brittany Carroll:** Conceptualization (supporting), methodology (equal), visualization (lead), and writing–review and editing (equal). **Valerie M. Slee:** Conceptualization (supporting), formal analysis (supporting), writing–original draft (supporting), and writing–review and editing (equal). **Susan V. Jennings:** Conceptualization (supporting), methodology (equal), formal analysis (supporting), writing–original draft (supporting), and writing–review and editing (equal). **Celeste C. Finnerty:** Conceptualization (supporting), methodology (equal), formal analysis (supporting), writing–original draft (supporting), and writing–review and editing (equal). **Linda S. Bohannon:** Conceptualization (supporting), methodology (equal), writing–original draft (supporting), and writing–review and editing (equal). **Susan D. Mathias:** Conceptualization (supporting), methodology (equal), formal analysis (supporting), writing–original draft (supporting), and writing–review and editing (equal). **Betsy J. Lahue:** Conceptualization (supporting), methodology (supporting), formal analysis (lead), writing–original draft (lead), and writing–review and editing (lead). **Mariana C. Castells:** Conceptualization (supporting), methodology (equal), writing–original draft (supporting), and writing–review and editing (equal).

CONFLICTS OF INTEREST

Erin M. Sullivan, David Dubinski, and Brittany Carroll own stock/stock options as employees of Blueprint Medicines Corporation, which develops therapies to treat systemic mastocytosis. Rubin A. Mesa, Linda S. Bohannon, Susan D. Mathias, and Mariana C. Castells received nominal research compensation for their time as part of the TouchStone Survey research team. Linda Bohannon reports grants or contracts from Labcorp, Geron, Amgen, Merck, and Alkermes outside the submitted work. Betsy J. Lahue is employed by Alkemi LLC, a firm that receives consulting fees from Blueprint Medicines Corporation.

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REFERENCES

1. Vaes M, Benghiat FS, Hermine O. Targeted treatment options in mastocytosis. *Front Med (Lausanne)*. 2017;4:110.
2. Cohen SS, Skovbo S, Vestergaard H, et al. Epidemiology of systemic mastocytosis in Denmark. *Br J Haematol*. 2014;166(4):521-528.
3. Bose P, Verstovsek S. Avapritinib for systemic mastocytosis. *Expert Rev Hematol*. 2021;14(8):687-696.
4. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
5. Sperr WR, Kundi M, Alvarez-Twose I, et al. International prognostic scoring system for mastocytosis (IPSM): a retrospective cohort study. *Lancet Haematol*. 2019;6(12):e638-e649.
6. Valent P, Oude Elberink JNG, Gorska A, et al. Study Group of the European Competence Network on Mastocytosis (ECNM). The data registry of the European Competence Network on Mastocytosis (ECNM): set up, projects, and perspectives. *J Allergy Clin Immunol Pract*. 2019;7(1):81-87.
7. Lim KH, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood*. 2009;113(23):5727-5736.
8. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med*. 2015;373(2):163-172.
9. Jennings SV, Slee VM, Zack RM, et al. Patient perceptions in mast cell disorders. *Immunol Allergy Clin North Am*. 2018;38(3):505-525.
10. Pardanani A. Systemic mastocytosis in adults: 2021 update on diagnosis, risk stratification and management. *Am J Hematol*. 2021;96(4):508-525.
11. Castells M, Butterfield J. Mast cell activation syndrome and mastocytosis: initial treatment options and long-term management. *J Allergy Clin Immunol Pract*. 2019;7(4):1098-1106.
12. Piris-Villaespesa M, Alvarez-Twose I. Systemic mastocytosis: following the tyrosine kinase inhibition roadmap. *Front Pharmacol*. 2020;11:443.
13. Lee P, George TI, Shi H, et al. Systemic mastocytosis patient experience from Mast Cell Connect, the first patient-reported registry for mastocytosis [abstract]. *Blood*. 2016;128(22):4783.
14. Ware J, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220-233.
15. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4(5):353-365.

16. Padilla B, Shields AL, Taylor F, et al. Psychometric evaluation of the Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) in a phase 2 clinical study. *Orphanet J Rare Dis*. 2021;16(1):434.
17. Taylor F, Akin C, Lamoureux RE, et al. Development of symptom-focused outcome measures for advanced and indolent systemic mastocytosis: the AdvSM-SAF and ISM-SAF©. *Orphanet J Rare Dis*. 2021;16(1):414.
18. Mesa RA, Miller CB, Thyne M, et al. Differences in treatment goals and perception of symptom burden between patients with myeloproliferative neoplasms (MPNs) and hematologists/oncologists in the United States: findings from the MPN Landmark survey. *Cancer*. 2017;123(3):449-458.
19. Mesa R, Miller CB, Thyne M, et al. Myeloproliferative neoplasms (MPNs) have a significant impact on patients' overall health and productivity: the MPN Landmark survey. *BMC Cancer*. 2016;16:167.
20. Ware J, Kosinski M, Keller SD. SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales. 2nd ed. The Health Institute; 1995.
21. Chang CS, Chen CW, Chiang IJ, Ku FC, Lee YM, Siddiqui A. A cross-sectional study of patients and physicians on the impact of myeloproliferative neoplasms on patient health: the Landmark Survey from Taiwan. *J Patient Exp*. 2021;8:23743735211059053.
22. Pemmaraju N, Wilson NR, Clementi Doan T, et al. Myeloproliferative neoplasm questionnaire: assessing patient disease knowledge in the modern digital information era. *Leuk Lymphoma*. 2021;62(9):2253-2260. doi:10.1080/10428194.2021.1901096
23. Porter SR, Whitcomb ME. Non-response in student surveys: the role of demographics, engagement and personality. *Res High Educ*. 2005;46:127-152.
24. Kannan V, Wilkinson KE, Varghese M, et al. Count me in: using a patient portal to minimize implicit bias in clinical research recruitment. *J Am Med Inform Assoc*. 2019;26(8–9):703-713. doi:10.1093/jamia/ocz038
25. Chollet MB, Akin C. Hereditary alpha tryptasemia is not associated with specific clinical phenotypes. *J Allergy Clin Immunol*. 2022;149(2):728-735.e2. doi:10.1016/j.jaci.2021.06.017
26. van Anrooij B, Kluin-Nelemans JC, Safy M, Flokstra-de Blok BM, Oude Elberink JN. Patient-reported disease-specific quality-of-life and symptom severity in systemic mastocytosis. *Allergy*. 2016;71(11):1585-1593.
27. Akin C, Sullivan E, Roche M. Siebenhaar F. Utility of a validated disease-specific measure to assess symptomology in patients with indolent systemic mastocytosis (ISM). *J of Allergy Clin Immunol*. 2022;149(2):AB220. doi:10.1016/j.jaci.2021.12.720
28. Grozdev I, Kast D, Cao L, et al. Physical and mental impact of psoriasis severity as measured by the compact Short Form-12 Health Survey (SF-12) quality of life tool. *J Invest Dermatol*. 2012;132(4):1111-1116. doi:10.1038/jid.2011.427
29. Kenzik KM, Ganz PA, Martin MY, et al. How much do cancer-related symptoms contribute to health-related quality of life in lung and colorectal cancer patients? A report from the Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium. *Cancer*. 2015;121(16):2831-2839.
30. Hartmann K, Gotlib J, Akin C, et al. Midostaurin improves quality of life and mediator-related symptoms in advanced systemic mastocytosis. *J Allergy Clin Immunol*. 2020;146(2):356-366.e4.
31. Norregaard C, Shah D, Hull M, et al. Economic burden of advanced systemic mastocytosis: a real-world evaluation of direct healthcare resource utilization and costs from a United States payer perspective. Paper presented at: Association of Managed Care Pharmacy (AMCP) Meeting; April 12–16, 2021; Virtual.
32. Norregaard C, Hull M, Shah D, et al. Healthcare burden of patients newly diagnosed with moderate to severe non-advanced systemic mastocytosis using a real-world database of US health plan members. Paper presented at: Association of Managed Care Pharmacy (AMCP) Meeting; April 12–16, 2021; Virtual.
33. Gomides APM, Albuquerque CP, Santos ABV, et al. High levels of polypharmacy in rheumatoid arthritis—a challenge not covered by current management recommendations: data from a large real-life study. *J Pharm Pract*. 2021;34(3):365-371. doi:10.1177/0897190019869158
34. Jennings S, Russell N, Jennings B, et al. The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions. *J Allergy Clin Immunol Pract*. 2014;2(1):70-76.
35. Yu J, Paranagama D, Parasuraman S. Recruitment strategies and geographic representativeness for patient survey studies in rare diseases: experience from the Living with Myeloproliferative Neoplasms patient survey. *PLoS One*. 2020;15(12):e0243562. doi:10.1371/journal.pone.0243562
36. Booker QS, Austin JD, Balasubramanian BA. Survey strategies to increase participant response rates in primary care research studies. *Fam Pract*. 2021;38(5):699-702. doi:10.1093/fampra/cmab070