# Symptom burden in transplant ineligible patients with newly diagnosed multiple myeloma: a population-based cohort study

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Hira S Mian,[1] Gregory R Pond,[1] Tanya M Wildes,[2] Branavan Sivapathasundaram,[3] Jonathan Sussman,[1] Hsien Seow[1]

[1]Juravinski Cancer Center, Department of Oncology, McMaster University, Hamilton, ON; [2]Washington University School of Medicine, St. Louis, MO; and [3]McMaster University, Hamilton, ON

**Corresponding author:**
Hira S Mian
Email: hira.mian@medportal.ca

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Running head: Symptom burden in MM

Multiple myeloma (MM), a neoplasm characterized by the clonal proliferation of malignant plasma cells, is associated with major morbidity and mortality. The median age at diagnosis is 70 years, making MM a disease burden of older adults. While much progress has been made in the therapeutics for newly-diagnosed multiple myeloma (NDMM) patients including transplant ineligible patients, MM remains an incurable malignancy. Both the disease of MM itself, as well as the treatments initiated, likely impact patient quality of life and burden of symptoms. To date, there has been no large population study conducted in adults with NDMM, specifically transplant ineligible patients, examining the effect of symptom burden over time and associated factors.

In 2007, as part of an initiative to improve symptom management, routine prospective collection of a patient reported outcome, Edmonton Symptom Assessment System (ESAS) score, during all outpatient cancer clinic visits was initiated in Ontario, Canada. ESAS is a validated and reliable patient-reported outcome tool that is used to assess common cancer-associated symptoms.[1] It consists of nine symptoms including tiredness, impaired well-being, pain, drowsiness, loss of appetite, anxiety, shortness of breath, depression and nausea which are scored by the patients on a numeric rating scale from 0 (no symptoms) to 10 (worse possible symptoms). We conducted a longitudinal study of ESAS data in order to examine symptom trajectory and determine factors associated with moderate to severe symptoms in the first year following diagnosis among transplant ineligible adults with NDMM receiving treatment between 2007-2018.

Multiple administrative health care databases in the universal, single payer, publicly funded system in Ontario, Canada were linked using a unique encrypted patient identifier and analyzed at ICES (formerly known as the Institute for Clinical Evaluative Sciences). ICES is an

independent, non-profit research institute whose legal status allows it to collect and analyze health care and demographic data without consent for health system evaluation and improvement. The study was approved by the ethics committee of McMaster University and followed data confidentiality and privacy guidelines of ICES.

All adults (age ≥18) with a new diagnosis of MM (International Classification of Diseases for Oncology, 3rd Edition, histology code 9732) between Jan 2007-Dec 2018 were identified. Patient demographics (age, sex) were extracted. Baseline co-morbidities were recorded using the modified Charlson-Deyo Comorbidity Index (CCI) within one year prior to diagnosis date.[2] Socioeconomic status was determined using a validated modified Ontario Marginalization Index.[3] Myeloma related end-organ damage was defined as previously described by Fiala *et al.*[4] Treatment centre (non-teaching vs teaching) was defined as the centre where the patient first received MM treatment. Treatment receipt was defined as those patients that did not receive a transplant but did receive treatment with one or more of the following agents: oral cyclophosphamide/melphalan (often used in combination with steroids) or novel agents (thalidomide, lenalidomide or bortezomib often used in combination as thalidomide / melphalan / prednisone, lenalidomide/dexamethasone, bortezomib / melphalan / prednisone or cyclophosphamide / bortezomib / dexamethasone) within one year of diagnosis; the above anti-myeloma drugs encompass all funded cancer drugs available to patients during the study period.

Symptoms were assessed using ESAS score which consists of nine symptoms described previously. We considered ESAS scores of ≥ 4 (moderate or severe) symptoms as being clinically relevant as it has been previously shown to identify a clinically significant burden.[5] For the final cohort creation, only transplant ineligible patients who received MM treatment as

defined above and reported at least 1 ESAS in the 12 months following the date of diagnosis were included. All analyses were conducted using statistical analysis system (SAS version 9.4).

A total of 4610 transplant ineligible patients who received treatment for NDMM were identified, of which 2876 (62.3%) completed at least 1 ESAS assessment following diagnosis and were included in the final cohort. In this final cohort, a total of 27,701 unique ESAS assessments were captured. Patients recorded a median of 15 ESAS assessments in the first year [interquartile range (IQR) 9-29]. Detailed baseline characteristics of the cohort are shown in Table I.

Trajectory for moderate to severe symptoms in each month following diagnosis is shown in Figure 1. For most symptoms, a high proportion of the cohort reported moderate to severe symptoms at diagnosis ranging from tiredness (64%) and impaired well-being (60%) being among the most prevalent to nausea being the least prevalent (13%). Most symptoms decreased over the first year, with the largest decline happening in the first 3 months. One year following diagnosis, there continued to be a substantial burden of symptoms, with over 25% of the cohort reporting moderate-severe levels of each of the following symptoms: tiredness, impaired well-being, pain, drowsiness and loss of appetite. Additionally, whereas physical symptoms such as pain improved over time, psychosocial symptoms of anxiety/depression showed minimal improvement with generally flat scores.

The odds of reporting moderate to severe symptoms during the first year are listed in Table II with a higher odds ratio for a co-variate being 'worse' for each specified symptom. Increasing age was associated with a slightly lower burden of pain, depression and nausea with an odds ratio borderline at 0.98. Female sex had a 1.19 to 1.59 higher odds of reporting moderate to severe symptoms for all categories except shortness of breath. An urban geographic location

was associated with higher anxiety and nausea. Socioeconomic impact did not have an impact on most symptoms except for tiredness. Increased co-morbidity status did not show any clear correlation with increased symptoms. A more recent diagnosis year was associated with slightly lower odds of pain, loss of appetite and nausea. Receiving treatment at a non- teaching hospital was associated with higher odds of reporting pain and depression. Myeloma related end-organ damage, specifically bone disease, was associated with higher symptom burden; the effect size ranging from 1.52 to 2.65 times for impaired well-being and pain respectively.

In summary, our study demonstrates that transplant ineligible patients with NDMM experience substantial burden of symptoms following diagnosis. From a patient's perspective, knowledge of these symptoms and how they change over time may enhance communication regarding expected trajectory and informed shared decision-making. From the oncology team's perspective, understanding the considerable burden of symptoms both at diagnosis and over time may be an essential first step in incorporating multidisciplinary teams, with a specific focus on managing psychosocial symptoms, which are known to be often unaddressed by oncology teams.[6]

Several patient characteristics were identified in our study as being associated with an increased odds of experiencing high symptom burden. Although increasing age was associated with a slight decrease in symptom burden, given the minimal change in odds ratio, the clinical impact of this is unknown. Females compared to males had a higher symptom burden for nearly all recorded symptoms in our study similar to previous reported literature in oncology which also noted sex differences in symptom burden and quality of life.[7, 8] Additionally, although increased co-morbidities has been previously shown to be correlated with a higher symptoms burden, [9] we did not detect a statistically significant relationship in our retrospective study and future

prospective studies are needed for further investigation. Non-teaching hospital was associated with higher rates of pain and depression and although the exact reason cannot be determined from our data, clinical outcomes are known to be different among teaching versus non-teaching sites.[10] Lastly, while the majority of patients in our study were using novel drugs, these drugs were not associated with a decrease in symptom burden, suggesting that symptom management may require both effective anti-myeloma therapy as well as optimal supportive care services.

Comparison of our results to other transplant ineligible studies is limited due to the heterogenous populations included which encompasses newly-diagnosed, relapsed as well as palliative patients.[11, 12] Despite these differences, our study is consistent with the results of a systematic review which also showed that severe fatigue and pain were common symptoms, which reached a pooled prevalence of greater than 40% with anxiety/depression present in nearly 25% of the patients.[13]

A major strength of our study is that it is the largest, longitudinal study done on symptom burden among this patient group using patient reported outcomes. Our study utilizes real-world data with a focus on older adults with MM who are under-represented in clinical trials.[14] Our study has several limitations. Our administrative database does not contain myeloma-specific variables, such as stage, response, or frailty status, which may be associated with symptom burden. Additionally, we did not capture symptoms during specific lines of treatment which may also be important as shown in a recent prospective study where quality of life deteriorated with increasing line of treatment.[15] The myeloma defining 'CRAB' features may also be under reported or over reported compared to prospectively conducted studies[16] due to the limitations of diagnosis and billing codes in the administrative database. Similarly, retrospective collection of co-morbidities may have also led to underreporting as noted in previous studies.[17] ESAS scores

were only recorded during outpatient visits and potentially severe symptoms during hospital admission may have been missed in our study. While ESAS has been validated for general cancer symptoms, we were unable to capture symptoms specifically related to MM nor the impact of symptom burden on the disruption of functional and social activities of the patients or caregivers.

In conclusion, transplant ineligible patients with MM experience substantial burden of symptoms in the first year following diagnosis. Future prospective studies both in clinical trials and in real-world patients are needed to further evaluate factors associated with high symptom burden longitudinally while simultaneously evaluating interventional supportive care strategies to alleviate this burden.

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Table I: Characteristics of MM patients who reported at least one 1 ESAS score in first 12 months following diagnosis

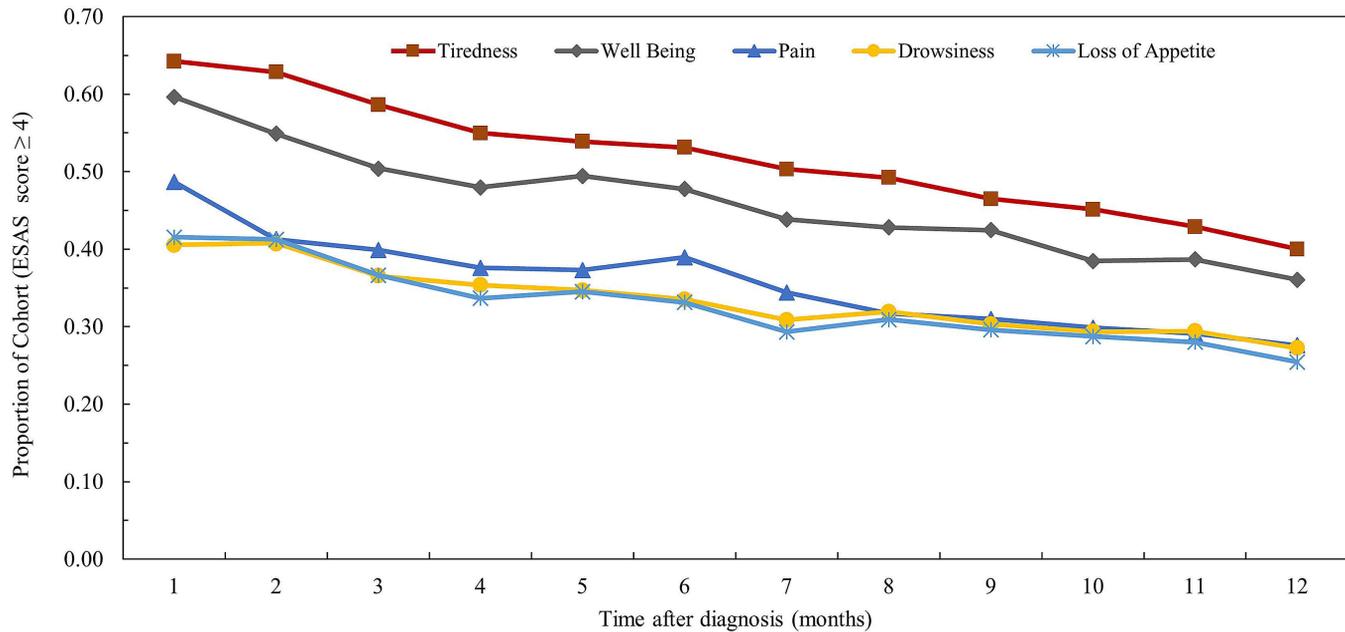| Characteristics | (N=2876) |
| --- | --- |
| Age, years (median, IQR) | 74 (70-80) |
| Male, n (%) | 1649 (57.3) |
| Geographic Region, n (%) | |
|   Urban | 2473 (86.0) |
|   Rural | 403(14.0) |
|  Socioeconomic status, poor, n (%) | 464 (16.1) |
| Charlson Co-morbidity Index, n (%) | |
|   ≤ 1 | 2478(86.2) |
|   ≥ 2 | 398 (13.8) |
| Year of Diagnosis, n (%) | |
|  2007-2012 | 953 (33.1) |
|  2013-2018 | 1923 (66.9) |
| Myeloma end organ damage*, n (%) | |
|   Anemia | 911 (31.7) |
|   Hypercalcemia | 130 (4.5) |
|   Bone disease | 304 (10.6) |
|   Renal failure | 752 (26.2) |
| Time from diagnosis to treatment, days (median, IQR) | 39 (20-87) |
| Time from diagnosis to first recorded ESAS score (median, IQR) | 35 (14-79) |
| Hospital type, n (%) | |
|   Teaching | 676 (23.5) |
|   Non-Teaching | 2200 (76.5) |
| Novel agents, n (%) | |
|   Proteasome inhibitor | 2146 (74.6) |
|   Immunomodulatory agent | 688 (23.9) |
| Patients alive at one year, n (%) | 2349 (81.7) |

IQR interquartile range
*Patient could have more than one 'CRAB' feature

Table II: The odds ratio of reporting moderate to severe Edmonton Symptoms Assessment System Score (ESAS ≥ 4) during the first year following diagnosis using multivariable logistic regression[#]

| | Tiredness | Well Being | Pain | Drowsiness | Loss of Appetite | Anxiety | Shortness of Breath | Depression | Nausea |
|---|---|---|---|---|---|---|---|---|---|
| **Age** **(per year increase)** | 1.01 (0.99-1.02) | 1.00 (0.99-1.02) | **0.98** **(0.98-0.99)** | 0.99 (0.99-1.01) | 1.00 (0.99-1.01) | 0.99 (0.98-1.00) | 1.00 (0.99-1.01) | **0.98** **(0.87-0.99)** | **0.98** **(0.97-0.99)** |
| **Sex** **(female vs male)** | **1.36** **(1.11-1.68)** | **1.35** **(1.12-1.63)** | **1.28** **(1.09-1.52)** | **1.19** **(1.02-1.39)** | **1.43** **(1.22-1.67)** | **1.59** **(1.35-1.85)** | 0.92 (0.79-1.06) | **1.32** **(1.12-1.52)** | **1.56** **(1.33-1.85)** |
| **Location** **(urban vs rural)** | 0.85 (0.63-1.15) | 0.99 (0.76-1.30) | 1.00 (0.79-1.27) | 0.96 (0.76-1.20) | 1.04 (0.83-1.32) | **1.29** **(1.05-1.61)** | 0.99 (0.79-1.22) | 1.06 (0.85-1.32) | **1.35** **(1.02-1.72)** |
| **Socioeconomic** **(poor vs non-poor)** | **1.31** **(1.01-1.69)** | 0.95 (0.74-1.22) | 0.93 (0.75-1.16) | 1.10 (0.89-1.36) | 0.92 (0.74-1.14) | 1.18 (0.96-1.45) | 1.15 (0.94-1.40) | 0.89 (0.72-1.09) | 1.06 (0.85-1.32) |
| **Charlson** **(≥ 2 vs ≤ 1)** | 1.20 (0.88-1.64) | 1.09 (0.83-1.44) | 1.02 (0.80-1.29) | 1.20 (0.95-1.51) | 1.02 (0.81-1.29) | 1.02 (0.82-1.28) | 1.10 (0.89-1.37) | 1.02 (0.81-1.27) | 1.07 (0.85-1.36) |
| **Diagnosis Year** **(per year increase)** | 0.98 (0.94-1.01) | 0.97 (0.94-1.01) | **0.96** **(0.93-0.99)** | 0.99 (0.96-1.02) | **0.92** **(0.89-0.95)** | 0.97 (0.95-1.00) | 0.99 (0.97-1.02) | 0.99 (0.87-1.02) | **0.95** **(0.92-0.98)** |
| **Anemia** **(yes vs no)** | 1.05 (0.84-1.31) | 1.05 (0.86-1.28) | 0.96 (0.81-1.14) | 1.00 (0.84-1.18) | 0.95 (0.80-1.13) | **1.23** **(1.05-1.45)** | **1.19** **(1.01-1.40)** | 1.11 (0.95-1.31) | 0.99 (0.83-1.18) |
| **Hypercalcemia** **(yes vs no)** | 1.86 (0.98-3.53) | 1.10 (0.68-1.78) | **1.64** **(1.06-2.54)** | 1.36 (0.90-2.04) | 1.25 (0.83-1.88) | 1.14 (0.79-1.66) | 1.10 (0.76-1.58) | 1.35 (0.94-1.96) | 1.18 (0.81-1.73) |
| **Bone Disease** **(yes vs no)** | 1.23 (0.87-1.73) | **1.52** **(1.10-2.12)** | **2.65** **(1.92-3.67)** | 1.29 (0.99-1.67) | **1.72** **(1.31-2.27)** | 1.07 (0.84-1.37) | 1.022 (0.80-1.30) | 1.22 (0.96-1.56) | 1.12 (0.87-1.45) |
| **Renal Disease** **(yes vs no)** | 1.26 (0.99-1.62) | **1.31** **(1.05-1.64)** | 0.85 (0.71-1.03) | 1.12 (0.93-1.35) | **1.36** **(1.13-1.65)** | 1.07 (0.89-1.27) | 1.09 (0.92-1.30) | 1.081 (0.91-1.29) | 1.07 (0.89-1.30) |
| **Hospital** **(Non-teaching vs teaching)** | 0.91 (0.72-1.17) | 1.09 (0.88-1.35) | **1.27** **(1.05-1.54)** | 0.93 (0.88-1.11) | 0.94 (0.78-1.14) | 1.11 (0.93-1.33) | 1.05 (0.88-1.27) | **1.23** **(1.03-1.47)** | 1.08 (0.88-1.30) |
| **Novel Drugs** **(yes vs no)** | 1.01 (0.73-1.39) | 0.96 (0.71-1.30) | 1.20 (0.93-1.55) | 0.94 (0.73-1.20) | 0.96 (0.75-1.25) | 0.99 (0.78-1.26) | 0.88 (0.69-1.11) | 0.95 (0.75-1.21) | 1.12 (0.87-1.45) |

[#]Note: Data are presented as Odds Ratio (95% Confidence Interval). A higher OR is 'worse' indicating that the covariate is associated with a higher odds of reporting moderate to severe symptom. Bold indicates statistically significant (P <0.05)

Figure 1: Proportion of cohort reporting moderate-to-severe Edmonton Symptom Assessment Scores (ESAS ≥ 4) for A) tiredness, well-being, pain, drowsiness and loss of appetite and B) anxiety, shortness of breath, depression and nausea by month following diagnosis

**A**



**B**