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Differences in Hospital, Emergency Room and Outpatient Visits Among Adults With and Without Monoclonal Gammopathy of Undetermined Significance

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Abstract

Introduction: This study evaluated the impact of receiving a monoclonal gammopathy of undetermined significance (MGUS) diagnosis on healthcare utilization from patients at a community-based multispecialty provider organization.

Methods: A cohort of patients with MGUS (n = 429) were matched on sex, age, and length of enrollment to a cohort of patients without MGUS (n = 1286). Healthcare utilization was assessed: 1-12 months before, 1 month before and after, and 1-12 months after diagnosis/index date. Multivariable conditional Poisson models compared change in utilization of each service in patients with and without MGUS.

Results: During the 2 months around diagnosis/index date, the rates of emergency room, hospital and outpatient visits were higher for patients with MGUS than patients without MGUS. In the year before MGUS diagnosis, the association was still elevated, although attenuated.

Conclusion: Understanding the care of MGUS patients is important given that multiple myeloma patients with a pre-existing MGUS diagnosis may have a better prognosis.

Keywords

monoclonal gammopathy of undetermined significance, multiple myeloma, emergency, hospitalization, outpatient

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Introduction

Multiple myeloma is the second most common hematologic malignancy in the US, with a 5-year survival of just 54%.[1] Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant plasma cell disorder preceding the development of multiple myeloma.[2] This premalignant condition is asymptomatic, and is typically diagnosed[3] incidentally through blood tests.[2,4,5] Patients with MGUS progress to multiple myeloma at a rate of approximately 1% annually,[6,7] yet despite the relatively low risk of progression, patients with

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MGUS undergo clinical follow up every 6-12 months for signs of disease progression.[8-10]

There are no population-based screening recommendations for MGUS detection, primarily due to a lack of treatment for MGUS and the relatively low probability of subsequent development of multiple myeloma.[6,7] However, patients may experience high levels of stress after a diagnosis of MGUS,[8-10] which could result in changes in healthcare services utilization.[11] Furthermore, anxiety associated with a precancerous diagnosis could cause someone to disengage completely with the healthcare system, or inversely, receive more frequent follow-up care to monitor the disease.[12] There are no standardized guidelines for MGUS surveillance, and as a result follow-up care for patients with MGUS is variable.[13] Also, in addition to the life-long risk of progression to multiple myeloma, MGUS has been found to be associated with a range of complications including renal impairment, osteoporosis, skeletal fracture, neuropathy and increased rates of infection, which may lead to higher healthcare utilization, particularly emergency department visits.[3,14] Previous studies have found that these complications in MGUS patients can be limited or avoided when identified and appropriately treated.[15]

This study used real-world electronic health data from patients seeking care at a large medical provider group in central Massachusetts to compare hospital, emergency room, and outpatient visits between a cohort of patients with MGUS and a matched cohort of patients without MGUS. We assessed the association between MGUS diagnosis and healthcare utilization across three-time frames: 1-12 months before diagnosis/index date, 1 month before and after diagnosis/index date, and 1-12 months after diagnosis/index date.

Methods

Study Design and Data Sources

We analyzed electronic health record (EHR) data, including cancer diagnoses, compiled from patients seeking care at a community-based multispecialty provider organization between 2007-2015. Additional data on cancer diagnoses (using International Classification of Diseases for Oncology, third Edition (ICD-O-3 (ICD-O-3) codes) were obtained from the Massachusetts Cancer Registry.[16] This study was approved by the Institutional Review Board of the University of Massachusetts Chan Medical School (IRB # H00009667). This is a secondary data analysis, and no informed consent was required. This study used a limited dataset. The reporting of this study conforms to STROBE guidelines.[17]

Patients With Monoclonal Gammopathy of Undetermined Significance

This analysis included 429 patients with MGUS who were identified through the application of an EHR-based algorithm to a large EHR-based database, previously detailed elsewhere.[18] Briefly, all patients with MGUS had at least two MGUS diagnosis codes within 12 months in their EHR between January 2007 and December 2015, plus at least one serum or urine protein electrophoresis test and 1 immunofixation test (identified by Common Procedural Terminology (CPT) codes), and at least one in-office visit with an oncologist within 90 days of MGUS diagnosis. Patients with a diagnosis of multiple myeloma at baseline (ICD-O-3 morphology code 9732) or within three months following MGUS diagnosis were excluded. In the original study, medical charts for a random sample of 252 selected cases were abstracted then adjudicated independently by two physicians, with 157 MGUS diagnoses confirmed. The positive predictive value of the algorithm was 76% (95% CI: 70%-82%).[18]

Patients Without Monoclonal Gammopathy of Undetermined Significance

For each patient with MGUS, three patients without MGUS were selected from the same patient population among individuals who actively sought care in the health system during the study period.[16] Patients without MGUS were matched to patients with MGUS by age (±2 years), sex, and length of enrollment in the health system (at least 12 months before and 6 months after index date). Patients without MGUS were assigned an index date based on MGUS cases' earliest MGUS diagnosis date. To be eligible for the present analysis, patients had to be actively seeking care in the healthcare system, defined as having at least one clinical encounter or laboratory test in the year before and the year after index date. After matching was completed, one patient without MGUS was excluded because lacked data indicating healthcare utilization during the study period.

Outcomes

We examined the total number of emergency room, hospital, and outpatient visits in the year before (1-12 months before), the months immediately adjacent to (one month before and after), and one year after (1-12 months after) MGUS diagnosis/index date. The one year period after a diagnosis of MGUS was selected since most guidelines recommend that people return for a follow-up visit within 6-12 months after diagnosis.[19-22] All emergency room, hospital and outpatient visits were identified from EHR data using CPT codes (Supplemental Table 1).

Statistical Analysis

Descriptive statistics were used to compare sociodemographic and clinical characteristics of patients according to MGUS status. Chi-square tests were also used to describe and compare characteristics of patients with or without MGUS diagnosis that had at least one emergency room, hospital, or outpatient visit.

Table 1. Sociodemographic and Clinical Characteristics of Patients According to Monoclonal Gammopathy of Undetermined Significance Status.

Characteristics at Diagnosis/Index Date	Patients with MGUS (n = 429)	Patients without MGUS (n = 1286)	*P*-Value[c]
Men, n (%)	217 (50.6)	650 (50.5)	.99
Age at Index Date (Mean ± SD), year	74.9 ± 10.4	74.8 ± 10.4	.84
Race, n (%)			
Non-Hispanic White	365 (97.6)	1042 (96.2)	.28
Non-Hispanic Black	6 (1.6)	19 (1.7)	
Other	3 (.8)	22 (2.0)	
Cancer diagnosis[a]			
Breast	8 (1.9)	34 (2.6)	.11
Prostate	9 (2.1)	22 (1.7)	
Blood[b]	3 (.7)	1 (.1)	
Other	12 (2.8)	51 (4.0)	
Charlson Comorbidity Index			
0	110 (25.6)	504 (39.2)	.0001
1	80 (18.6)	261 (20.3)	
2+	239 (40.5)	521 (40.5)	
Mean ± SD	2.3 ± 2.3	1.6 ± 1.9	.0001

May not total 100% due to rounding. Missing values for race (patients with (n = 55) and without (n = 203) MGUS).
[a]Presence of ICD-O-3 code in tumor registry data prior to MGUS diagnosis/index date.
[b]Leukemia, non-Hodgkin lymphoma.
[c]*p*-values from Chi-square or t-tests.

We also evaluated the influence of other covariates that are known to be associated with a MGUS diagnosis or healthcare utilization, including sex (male/female), age at diagnosis/index date (continuous), race/ethnicity (non-Hispanic White vs other race/ethnicities), history of cancer diagnosis at baseline (breast, prostate, blood, other) and Charlson comorbidity index at baseline (categories: 0, 1, ≥2; and continuous). We used conditional Poisson regression to analyze data from the matched cohorts.[23] Crude models and models adjusted for Charlson comorbidity index categories and race were used to evaluate the total count of each category of healthcare utilization services (emergency room, hospital, and outpatient visits) among patients with MGUS as compared with their matched cohort of patients without MGUS.[23] We considered adjusting for other variables, including BMI and history of cancer diagnosis, but did not include them in the final model because their inclusion did not change the point estimates by more than 10%. We performed a sensitivity analysis replicating the models described above among the 157 patients with validated MGUS diagnoses (Supplemental Tables 1-2), and compared those results to the larger group of 429 algorithm-identified MGUS cases.

Results

Sociodemographic and Clinical Characteristics

Slightly more than half of the study population was male (50.6%), with a mean age at diagnosis/index date of 75 years old. The majority were non-Hispanic White (96.9%). Patients with MGUS had a significantly higher Charlson comorbidity index (2.3) than patients without MGUS diagnosis at baseline (1.6; *P*-value=.0001) (Table 1).

Emergency Room Visits

A significantly higher percentage of patients with MGUS had at least one emergency room visit a year before (21.0% vs 10.3%; *P*-value < .05), one month before and after (6.3% vs 2.9%; *P*-value < .05) and a year after (23.3% vs 14.4%; *P*-value < .05) MGUS diagnosis date than patients without MGUS. Among those patients who had at least one emergency room visit, there was no statistically significant difference in the mean number of emergency room visits by MGUS status across all time periods (Table 2).

After adjusting for Charlson comorbidity index and race, patients with MGUS were 55% (Incidence Rate Ratio (IRR): 1.55; 95% Confidence Interval (CI): 1.24 to 1.94) more likely to have an emergency room visit than patients without MGUS diagnosis a year before diagnosis/index date. During the one month before/after the index date patients with MGUS were 74% (IRR: 1.74; 95% CI: 1.07 to 2.82) more likely to have an emergency room visit than patients without MGUS. Similar, yet slightly attenuated results were observed during the year after MGUS diagnosis/index date as patients with MGUS were 50% (IRR: 1.50; 95% CI: 1.24 to 1.82) more likely to have an emergency room visit than patients without MGUS (Table 3).

Table 2. Total Number of Participants with at Least 1 Visit (n) and Average Count of Services Per Person Among Patients with MGUS and Matched Patients Without MGUS.

	Patients with MGUS			Patients without MGUS[a]			*P*-Value
Healthcare Service	n (%)	Mean ± SD[b]	Median (25^{th}-75^{th} Percentile)	n (%)	Mean ± SD[b]	Median (25^{th}-75^{th} Percentile)	
1-12 months before diagnosis/index date[c]							
Emergency room visits	90 (21.0)	1.67 ± .97	1 (1-2)	133 (10.3)	1.68 ± 1.41	1 (1-2)	.92
Hospital visits	60 (14.0)	3.78 ± 3.11	3 (2-5)	64 (5.0)	3.33 ± 2.88	2 (2-3.5)	.40
Office or outpatient visits	226 (52.7)	9.02 ± 6.60	8 (4-12)	657 (51.1)	6.19 ± 4.57	5 (3-8)	<.05
One month before and after diagnosis/index date[c]							
Emergency room visits	27 (6.3)	1.33 ± 1.06	1 (1-1)	38 (2.9)	1.29 ± 1.10	1 (1-1)	.78
Hospital visits	20 (4.7)	2.70 ± 1.89	2 (1.5-3.5)	15 (1.2)	2.47 ± 1.12	2 (2-3)	.67
Office or outpatient visits	232 (54.1)	3.65 ± 2.10	3 (2-5)	419 (32.6)	1.89 ± 1.23	2 (1-2)	<.05
1-12 months after diagnosis/index date[c]							
Emergency room visits	100 (23.3)	1.85 ± 1.76	1 (1-2)	185 (14.4)	1.78 ± 1.85	1 (1-2)	.76
Hospital visits	58 (13.5)	4.14 ± 3.39	3 (2-6)	113 (8.8)	3.11 ± 2.30	2 (2-4)	<.05
Office or outpatient visit	267 (62.2)	9.87 ± 6.79	8 (5-13)	761 (59.2)	6.31 ± 5.07	5 (3-8)	<.05

[a]Participants were matched on age, sex and length of enrollment in the health system.
[b]The mean, standard deviation (SD), median, and 25^{th} – 75^{th} percentile reported is among those with at least 1 of those services.
[c]Time periods are not overlapping: 1 year before (1–12 months before), the months immediately adjacent to (1 month before and after), and 1 year after (1–12 months after) MGUS

Table 3. Magnitude of Change in Healthcare Utilization Among Patients with MGUS as Compared with their Matched Cohort of Patients without MGUS, Before, During and After MGUS Diagnosis/Index Date Using Conditional Poisson Regression.

	1-12 months before Diagnosis/Index date[b]		One month before and after Diagnosis/Index date[b]		1-12 months after Diagnosis/Index date[b]	
	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]
Healthcare Service	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Emergency room visits	2.01 (1.63-2.47)	1.55 (1.24-1.94)	2.20 (1.43-3.39)	1.74 (1.07-2.82)	1.68 (1.40-2.01)	1.50 (1.24-1.80)
Hospital visits	3.20 (2.65-3.85)	2.23 (1.78-2.79)	4.38 (2.88-6.65)	4.76 (2.80-8.09)	2.04 (1.73-2.41)	1.65 (1.38-1.97)
Office or outpatient visits	1.50 (1.42-1.58)	1.27 (1.20-1.34)	3.21 (2.91-3.53)	2.86 (2.59-3.17)	1.65 (1.57-1.73)	1.48 (1.41-1.55)

[a]Adjusted for Charlson comorbidity index and race, participants were matched on age, sex and length of enrollment in the health system (12 months before and 6 months after index date).
[b]Time periods are not overlapping: 1 year before (1-12 months before), the months immediately adjacent to (1 month before and after), and 1 year after (1-12 months after) MGUS diagnosis/index date.

Hospital Visits

A significantly higher percent of patients with MGUS had at least one hospital visit a year before (14.0% vs 5.0%; P-value < .05), one month before and after (4.7% vs 1.2%; *P*-value < .05) and a year after (13.5% vs 8.8%; *P*-value < .05) MGUS diagnosis date than patients without MGUS. Among patients who had at least one hospital visit during the year after MGUS diagnosis/index date, the mean number of hospital visits was slightly higher for those with MGUS than patients without MGUS (4.1 vs 3.1; *P*-value = .001). However, no difference in the mean number of hospital visits was observed by MGUS status before MGUS diagnosis/index date, and during the 2-month period around diagnosis/index date (Table 2).

After adjusting for Charlson comorbidity index and race, patients with MGUS were 2 times (95% CI: 1.81 to 2.83) more

likely to have a hospital visit than patients without MGUS in the year before diagnosis/index date. During the one month before/after index date, patients with MGUS were 5 times (95% CI: 2.78 to 7.87) more likely to have a hospital visit than patients without MGUS, while during the year after MGUS diagnosis/index date patients with MGUS were 67% (95% CI: 1.40 to 1.99) more likely to have a hospital visit than patients without MGUS (Table 3).

Office or Outpatient Visits

There were no statistically significant differences in the proportion of patients with and without MGUS who had at least one outpatient visit during the year before (52.7% vs 51.1%) and the year after (62.2% vs 59.2%) MGUS diagnosis/index date. However, more patients with MGUS had at least one outpatient visit within the one month before/after diagnosis/index date (54.1% vs 32.6%) than patients without MGUS. Among patients who had at least one outpatient visit during all periods evaluated, the mean number of outpatient visits was slightly higher for those with MGUS than patients without MGUS (Table 2).

After adjusting for Charlson comorbidity index and race, patients with MGUS were 27% (95% CI: 1.21 to 1.35) more likely to have an outpatient visit than patients without MGUS diagnosis one year before diagnosis/index date. During the one month before/after the index date, patients with MGUS were 3 times (95% CI: 2.59 to 3.17) more likely to have an outpatient visit than patients without MGUS, while during the year after MGUS diagnosis/index date patients with MGUS were 49% (95% CI: 1.42 to 1.57) more likely to have an outpatient visit than patients without MGUS (Table 3).

Sensitivity Analysis

When analyses were restricted to the 157 MGUS cases with diagnoses validated by chart review in an earlier study,[18] the conclusions were largely in line with the results observed in the larger group of 429 MGUS cases. No differences were found in sociodemographic characteristics among the patients identified with the algorithm and those validated by chart review (Supplemental Table 1). In addition, emergency, office or outpatient and hospital visits were similar between both groups during the three-time points (Supplemental Table 1).

Discussion

In this matched cohort study of patients seeking care at a large provider group in central Massachusetts, we found that patients with MGUS had higher rates of emergency room, hospital and outpatient visits one year before and after and during the 2-month period around MGUS diagnosis/index date than patients without MGUS. However, different patterns of utilization were observed within the different time intervals. Patients with MGUS had higher rates of hospital visits than patients without MGUS one year before, and during the period immediately around MGUS diagnosis. In addition, the proportion of emergency room and outpatient visits during the 2-month period around MGUS diagnosis/index date was higher among patients with MGUS than patients without MGUS.

A clear understanding of the care and surveillance of patients with MGUS is of clinical relevance given that multiple myeloma patients with a pre-existing MGUS diagnosis have been shown to have a better prognosis.[4,5,24] In addition, cancer patients may have better outcomes if they had greater utilization of primary care preceding their cancer diagnosis.[25,26] Yet, few studies evaluated the impact of an MGUS diagnosis on ER, hospital and outpatient visits. Previous population-based studies had found the prevalence of MGUS in emergency hospital admission to be higher than expected, potentially due the presence of common conditions associated with unplanned admission to hospital related to MGUS.[27] Also, previous studies found that MGUS patients experience excess morbidity and mortality, including visits related to nephrology and rheumatology, before and after MGUS diagnosis in a United Kingdom study.[28] Consequently, the elucidation of healthcare utilization patterns among MGUS patients may provide insight into how patients diagnosed with MGUS differ clinically from patients without this diagnosis, and provide the first step in determining the factors that may contribute to their observed improved prognosis following a multiple myeloma diagnosis.[29]

After adjusting for comorbidities and race, patients with MGUS in our population had higher rates of emergency room utilization, and more hospital and outpatient visits than patients without MGUS across all time periods. The higher rate of emergency room and hospital visits among patients with MGUS in comparison with patients without MGUS is most likely due to symptoms related to other health conditions, because MGUS is largely asymptomatic. However, in rare cases, patients could experience tingling, weakness or numbness related to the diseases process.[30] These observations could also explain why we observed an increase in utilization closer to MGUS diagnosis date, followed by a decrease during the year after diagnosis. Furthermore, the observed increase in outpatient visits after diagnosis among patients with MGUS found in multivariable models may include follow-up appointments related to MGUS; however, we were not able to identify the reasons for outpatient visits in the available data.

This study has several notable strengths including the use of a matched cohort study design with extensive longitudinal real-world EHR data to objectively evaluate healthcare utilization before and after MGUS diagnosis. We also acknowledge several limitations to this study. Since MGUS is almost always diagnosed incidentally, cases of MGUS were limited to those patients who sought medical care and may not be representative of patients with undetected MGUS. In

addition, MGUS diagnosis was confirmed in a random sample of our population by comprehensive EHR review, and thus some of our cases may have been false positives.[18] However, the consistency between our main results and the results of a sensitivity analysis limited to the 157 validated cases lends support to our findings, and suggests that potential misclassification did not greatly influence study findings. In addition, the study population was largely non-Hispanic White, and future studies should be conducted in more diverse populations. The use of electronic health data has several limitations including missing data on variables such as socioeconomic status and lifestyle factors potentially associated with healthcare utilization, as data are collected as part of medical care and not for research purposes. Within our database, we were unable to determine whether outpatient visits were specifically for MGUS follow up, which would have allowed us to further investigate MGUS-specific healthcare utilization. As a part of case and non-case inclusion criteria we required at least one interaction with healthcare systems during the study period to make sure patients were current users of the healthcare system. Due to this requirement, it is possible that we selected for patients that were more likely to seek care or had more interactions with the healthcare system than the entire patient population. However, we believe this step helped to ensure both the case and comparison groups were active patients of the provider group during the study period. In addition, although our EHR database does capture claims from care received outside the organization, we were not able to evaluate how completely outside care was captured, nor assess whether this differed between patients with MGUS and those without. As a result, it is possible that we missed some care that patients received outside of the community-based multispecialty provider organization, and thus underestimated care utilization.[31]

Conclusions

In conclusion, our findings suggest that patients with MGUS are more engaged with the healthcare system than patients without MGUS, particularly around the time of MGUS diagnosis. This pattern of care could be indicative of how patients arrive at an incidental MGUS diagnosis, since the condition itself is largely asymptomatic. In addition, quantifying the care and surveillance of patients with MGUS is of clinical relevance given that multiple myeloma patients with a pre-existing MGUS diagnosis have been shown to have a better prognosis, potentially due to an earlier multiple myeloma diagnosis.[4,5,24] However, future studies evaluating comorbid conditions related to MGUS diagnosis and follow-up are needed to understand reasons behind differences in healthcare utilization patterns incurred by these patients, including in larger and more diverse populations of patients with validated MGUS diagnoses.

Appendix

Abbreviations

CI	Confidence intervals
CPT	Current Procedural Terminology
EHR	Electronic Health Record
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
IRR	Incidence Rate Ratio
MGUS	Monoclonal Gammopathy of Undetermined Significance
UMMS	University of Massachusetts Medical School

Declaration of Conflicting Interests

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Ethical Approval

This study was approved by the Institutional Review Board of the University of Massachusetts Chan Medical School (IRB # H00009667). This is a secondary data analysis no informed consent was required by the patients.

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Supplemental Material

Supplemental material for this article is available online.

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