

Rising Prevalence of Central Nervous System Involvement in Multiple Myeloma: A 2012-2020 National Inpatient Sample (NIS) Analysis in the United States

Charles J. Mazof , Vishva Natarajan , Augustos Vrattos , Parth Shah , Frederick Lansigan , Jennifer Hong

PII: S2152-2650(25)04299-5  
DOI: <https://doi.org/10.1016/j.clml.2025.12.004>  
Reference: CLML 2743



To appear in: *Clinical Lymphoma, Myeloma and Leukemia*

Received date: Oct 21, 2025  
Revised date: Dec 1, 2025  
Accepted date: Dec 11, 2025

Please cite this article as: Charles J. Mazof , Vishva Natarajan , Augustos Vrattos , Parth Shah , Frederick Lansigan , Jennifer Hong , Rising Prevalence of Central Nervous System Involvement in Multiple Myeloma: A 2012-2020 National Inpatient Sample (NIS) Analysis in the United States, *Clinical Lymphoma, Myeloma and Leukemia* (2025), doi: <https://doi.org/10.1016/j.clml.2025.12.004>

This is a PDF of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability. This version will undergo additional copyediting, typesetting and review before it is published in its final form. As such, this version is no longer the Accepted Manuscript, but it is not yet the definitive Version of Record; we are providing this early version to give early visibility of the article. Please note that Elsevier's sharing policy for the Published Journal Article applies to this version, see: <https://www.elsevier.com/about/policies-and-standards/sharing#4-published-journal-article>. Please also note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

# Rising Prevalence of Central Nervous System Involvement in Multiple Myeloma: A 2012-2020 National Inpatient Sample (NIS) Analysis in the United States

Charles J. Mazof<sup>a</sup>, Vishva Natarajan<sup>a</sup>, Augustos Vrattos<sup>a</sup>, Parth Shah<sup>b</sup>, Frederick Lansigan<sup>b</sup>, Jennifer Hong<sup>a,c</sup>

<sup>a</sup>Geisel School of Medicine at Dartmouth, Hanover, NH, 03755

<sup>b</sup>Department of Medicine, Hematology Oncology Section, Dartmouth-Hitchcock Medical Center, Lebanon, NH, 03756

<sup>c</sup>Department of Surgery, Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH, 03756

## Contact Information:

Charles Mazof, BA: [charles.j.mazof.MED@dartmouth.edu](mailto:charles.j.mazof.MED@dartmouth.edu)

Vishva Natarajan, MS: [vishva.natarajan.MED@dartmouth.edu](mailto:vishva.natarajan.MED@dartmouth.edu)

Augustos Vrattos, BA: [augustinus.vrattos.23@dartmouth.edu](mailto:augustinus.vrattos.23@dartmouth.edu)

Parth Shah, MD: [parth.s.shah@hitchcock.org](mailto:parth.s.shah@hitchcock.org)

Frederick Lansigan, MD: [frederick.lansigan@hitchcock.org](mailto:frederick.lansigan@hitchcock.org)

\*Jennifer Hong, MD [Corresponding Author]: [jennifer.hong@hitchcock.org](mailto:jennifer.hong@hitchcock.org)

Keywords: central nervous system, extramedullary disease, multiple myeloma

## Abstract

**Background:** Central nervous system involvement in multiple myeloma (CNS-MM) is a rare but aggressive extramedullary manifestation occurring in approximately 1% of multiple myeloma (MM) patients. CNS-MM is associated with poor prognosis, with median survival ranging from two to seven months. Small studies have suggested that advances in MM treatment may be leading to increasing prevalence of CNS-MM; however, a comprehensive analysis of temporal trends is lacking. **Methods:** We conducted an epidemiological study of the 2012-2020 National Inpatient Sample, an all-payer database of US inpatient hospital admissions. Patients aged 18 and older with both MM and secondary CNS neoplasms were identified using ICD-9 and ICD-10 diagnosis codes. We then calculated weighted prevalence estimates and assessed them using regression analysis. **Results:** CNS-MM prevalence increased significantly, increasing by 166% from 2012 to 2020 ( $p < 0.001$ ). This increase outpaced the 29% rise in overall MM prevalence ( $p < 0.001$ ) during the same period. We observed no significant changes in mortality or discharge outcomes over time. Patients who were white ( $p < 0.05$ ) and had income over median ( $p < 0.01$ ) received more CNS-

targeting diagnostic or therapeutic care, but we found no evidence of improved inpatient survival due to these procedures ( $p=0.70$ ) after adjusting for disease severity. **Conclusion:** The prevalence of CNS-MM has grown to 2-3% of MM patients since 2020, with stable rates of mortality despite interventions. Further investigation is needed to explore underlying mechanisms of this growth and improve outcomes.

## 1. Introduction

Involvement of the central nervous system in multiple myeloma (CNS-MM) is an uncommon and aggressive extramedullary disease occurring in roughly 1% of patients with multiple myeloma (MM).<sup>1-7</sup> It has been reported that 76% of CNS-MM cases are from MM relapse while 24% are present at initial MM diagnosis.<sup>8</sup> The clinical manifestations of CNS-MM are diverse, with leptomeningeal myelomatosis, intraparenchymal masses, spinal lesions, and subdural masses currently reported in the literature.<sup>3,5,6,8-14</sup> Treatment of CNS-MM is challenging due to its varied clinical presentations and the lack of established treatment guidelines.<sup>9,15</sup> Additionally, there is added complexity due to recent developments in immunomodulatory agents, CAR-T cells, proteasome inhibitors, intrathecal (IT) chemotherapy, and radiation therapy.<sup>8,15-20</sup> Despite these advances, the prognosis for CNS-MM remains dismal, with a median overall survival (OS) as low as 2-7 months after diagnosis.<sup>4,7,8,11,15,16,21,22</sup>

Emerging evidence suggests that CNS-MM prevalence may be increasing, potentially driven by improvements in MM treatment that prolong OS and allow for secondary disease progression.<sup>2</sup> However, rigorous analysis of cross-sectional national level data assessing temporal trends of CNS-MM prevalence remain scarce. Most available data are derived from small cohorts, case reports, or retrospective analyses, underscoring the need for comprehensive studies that assess incidence trends and risk factors across larger, population-based datasets.

In this study, we leveraged the National Inpatient Sample (NIS) dataset from 2012 to 2020 to assess trends in CNS-MM prevalence across the U.S.<sup>23</sup> By examining nationwide inpatient hospitalizations, this analysis provides a more well-powered evaluation of CNS-MM prevalence, offering insights into its epidemiological trajectory and potential implications for clinical practice.

## 2. Methods

We conducted a cross-sectional study of the prevalence of comorbid multiple myeloma and secondary CNS neoplasm using the 2012–2020 National Inpatient Sample (NIS), the largest publicly available all-payer inpatient care database in the United States containing data on more than seven million hospital stays. These surveys are compiled by the Hospital Cost and Utilization Project (HUCP; [hcup.us.arhq.gov](http://hcup.us.arhq.gov)) and cover a representative sample of hospital discharges from each year. Surveys performed from 2012 onwards consisted of 20% of U.S. hospital discharges within their respective year. Each year, the databases included basic demographics (age, sex, race), insurance status, and International Classification of Diseases (ICD) diagnosis and procedure codes, providing a representative sample of national trends with a size ideal for evaluating rare diseases.

### 2.1 Inclusion Criteria

To identify patients with multiple myeloma and concurrent secondary malignant neoplasm in the central nervous system, ICD-9 and ICD-10 codes were used (Table S1). Because ICD-9 was retired in October 2015, the ICD-9 codes were used for records before October 2015, while ICD-10 codes were used for records obtained afterwards. We included all adults ( $\geq 18$  years of age) who had concurrent diagnosis for both MM and secondary CNS neoplasm in the 2012-2020 NIS datasets.

Due to imperfect and inconsistent diagnostic coding procedures across institutions, we also validated our identification of the CNS-MM study sample with additional ICD procedure codes for CNS imaging, biopsy, and intrathecal (IT) antineoplastic therapy (Table S1).

### 2.2 Statistical Approach

To determine the yearly prevalence of CNS-MM, we used NIS-provided discharge weights, strata, and cluster variables to generate nationally representative estimates of inpatient hospitalizations. After case identification with ICD-9 and ICD-10 codes, and CNS-MM cases were subcategorized by demographics. Prevalence rates were reported per 100,000 inpatient hospitalizations. ICD procedural codes were analyzed to assess treatment trends over time.

Stata scripts were used to acquire the subset of CNS-MM cases from the NIS. Regression analyses and figure generation were performed in R with `srvyr` and `tidyverse` packages.

### 3. Results

#### 3.1 Description of dataset

Over the nine-year period from 2012 to 2020, a total of 4,990 CNS-MM cases were recorded across the U.S., with annual case counts consistently below 1,000.

Table 1 characterizes the demographic distribution of CNS-MM patients, including age, sex, race, and insurance status. The mean age at diagnosis was 66.7 years, with 62.7% of cases occurring in white patients. Men accounted for a greater proportion of cases (57.5%) than women (42.5%). Regarding insurance coverage, Medicare was the most common primary payer, covering 62.5% of CNS-MM patients, followed by private insurance (23.5%) and Medicaid (9.9%). 4.1% of patients did not have insurance.

#### 3.2 Increased prevalence of CNS-MM

We next utilized survey weights for each year to calculate the annual prevalence of CNS-MM per 100,000 admissions. Doing so revealed a statistically significant ( $p < 0.001$ ) increase from 1.07 to 2.86 cases per 100,000 from 2012 to 2020 using a linear regression model, representing a 166% rise in prevalence over the nine-year period (Table 1, Figure 1). This increase in inpatient CNS-MM prevalence far outpaced the 29% rise in overall inpatient MM prevalence in the NIS dataset during the same timeframe (Figure 1,  $p < 0.001$ ), suggesting that the rising number of CNS-MM cases was not merely due to an increase in overall MM admissions, but rather due to a true increase in CNS involvement. Therefore, a growing proportion of inpatient MM patients presented with secondary CNS involvement in the last decade.

To validate identification of CNS-MM cases, we further individually considered year-to-year trends of relapsed MM cases (203.02, C90.02) and secondary CNS neoplasm (198.3, 198.4, C79.31, C79.32, C79.49). Relapsed MM rose by 160% over the same period, consistent with rising relapse burden (Figure 1). We then observed that there was a very low rise in reported secondary CNS neoplasm cases in the NIS dataset, which increased by 4.8% over the same time period (Figure S1). This suggests that the increasingly large numbers of patients who had concurrent ICD codes for secondary CNS neoplasm and MM most likely did indeed represent recurrent disease rather than spontaneous independent secondary malignancies.

#### 3.3 Outcome Measures

Given the increasing prevalence of CNS-MM beyond overall MM prevalence, we assessed key outcome measures to evaluate its clinical impact. Specifically, we examined mortality rates, disease severity, and discharge dispositions using NIS-defined strata to determine whether rising

CNS-MM cases correlated with worsening prognostic trends. Table 2 summarizes these outcome measures across the study years.

Despite the significantly increased prevalence of CNS-MM, we observed no significant change in mortality, severity, discharge rates, or lengths of stay over time (Table 2, Figures S2-4). Most CNS-MM patients fell into the “major” or “extreme severity” categories designated by the NIS within its publicly available data elements directory, highlighting the aggressive nature of the disease.<sup>24</sup> Most patients (85%) were discharged home, home with care, or transferred to long-term care facilities such as hospice or skilled nursing centers (Table 2).

### 3.4 Prognostic and Outcome Variables

We then compared CNS-MM with all MM cohorts to identify any factors that may predispose myeloma patients to aggressive disease, finding that income, sex, race, and geography did not differ significantly between the two groups when using a survey-weighted chi-squared test (Table S1, Table 3). However, significant differences were observed; CNS-MM involved younger patients and had higher mortality risk, greater severity, less favorable discharge dispositions, and longer stay-lengths (as defined by NIS survey categories) compared to the all-MM cohort (Table 3).

### 3.5 Diagnostic and Therapeutic Procedures

To understand trends in CNS-MM diagnosis and treatment, we examined all inpatient CNS-directed imaging and procedures in our NIS cohort and assessed patient and disease factors that were significantly associated with intervention (Table S1, S3). Although we identified low numbers of patients ( $n = 70$ ), we found trends suggesting that diagnostic procedures (imaging, biopsy, lumbar puncture) may be performed proportionately less often for women ( $p = 0.09$ ) and significantly less often for black patients (Figure 2,  $p < 0.05$ ). At the same time, patients with income above median received more diagnostic and therapeutic procedures (Figure 2,  $p < 0.01$ ).

Mortality outcomes were not significantly different ( $p = 0.70$ ) between those who did and did not receive diagnostic procedures, despite equivalent disease severity in patients who received diagnostic procedures compared to the overall CNS-MM cohort (Figure 2).

To estimate current clinical interventions in CNS-MM, we compiled the most common inpatient procedures performed on CNS-MM patients. Table S2 lists the top 20 such procedures from 2015–2020. There was a mix of supportive interventions such as blood transfusions and ventilation with CNS-targeting treatments including spinal chemotherapy and diagnostic spinal tap. Brain-targeting procedures were relatively uncommon compared to spinal procedures.

## 4. Discussion

Our analysis of CNS-MM prevalence from 2012–2020 revealed a 166% increase over eight years, far outpacing the 29% increase in overall MM discharges and the 8% increase in primary MM diagnoses reported in the SEER database over the same time period.<sup>25</sup> This result suggests a shift in MM disease course, with an increasing proportion of patients developing secondary CNS involvement. Given the poor prognosis of CNS-MM, the rise in national prevalence supports anecdotal accounts that in recent years MM patients are experiencing a greater likelihood of relapsing and progressing to a more aggressive disease course.<sup>4,22</sup> Furthermore, our results implicate the CNS as a potential reservoir for disease even after therapy-induced remission, which has been suggested in the literature.<sup>2,26–28</sup> Pre-2013 studies estimated CNS-MM at 1% of all MM cases; however, our results, after adjusting for population weights, suggest a current prevalence of 2–3% of all MM cases.<sup>1,3,5,29</sup>

We accounted for potential errors in our estimated CNS-MM prevalence by assessing trends in MM treatment and physician coding and diagnostic procedures over the same time periods. First, since we used independent ICD codes for MM and secondary CNS neoplasm to identify our patient cohort, MM patients with unrelated CNS neoplasms may have been included (Table S1). However, based on recent epidemiological data, around 0.06% of patients over 65 years old have CNS cancer, a vanishingly small number compared to the 1% of MM patients with CNS-MM.<sup>30</sup> Next, because the NIS tracks inpatient discharges and does not link episodes of care for the same patient, it is possible that a CNS-MM patient could be double-counted for any subsequent readmission. Some treatments for CNS-MM—such as high-dose methotrexate or combination chemotherapy—may require multiple inpatient admissions.<sup>15</sup> Likewise, allogeneic and autologous stem cell transplants (SCTs) can contribute to frequent readmissions, both during induction chemotherapy and because of post-transplant complications, particularly in the context of immunosuppression associated with allogeneic SCTs.<sup>31,32</sup> However, we found no evidence that any these treatments were being used more often over time (Table S3). Furthermore, readmissions related to chimeric antigen receptor T-cell (CAR-T) therapies are unlikely to contribute meaningfully to our findings, as the first FDA approval for CAR-T in MM occurred in 2021 after the end of our study period.<sup>17,33</sup> To rule out the possibility that our observed trends were due to changing physician billing/coding habits, we performed additional analyses to confirm that ICD coding rates did not significantly change during the study period ( $p = 0.60$ ). Finally, expanded access to MRI, cerebrospinal fluid (CSF) cytology, and next-generation sequencing (NGS) have increased detection capabilities and may be contributing to greater apparent prevalence due to more sensitive testing for CNS-MM rather than a true biological rise.<sup>10,34</sup> We saw no significant increases in the rates of diagnostic testing, including imaging (Table S3).

Given that CNS-MM cases have increased significantly in recent years, clinicians who treat CNS diseases, including neurologists, neurosurgeons and oncologists, should have an increased suspicion for CNS-MM when evaluating intracranial masses in patients with history of MM, as

the radiographic features of this disease can mimic more common intracranial pathology such as subdural hematomas.<sup>15,35</sup> Our findings underscore the need for further research into targeted surveillance, risk factors, and optimized treatment approaches for CNS-MM, and the underlying mechanisms for relapse in the CNS.

While our analysis cannot investigate the drivers of increased CNS-MM prevalence, it is likely that broad changes in primary MM therapy over the last decade have impacted the patterns of MM relapse. The introduction of immunomodulatory drugs, monoclonal antibodies, and proteasome inhibitors has significantly extended the overall survival (OS) in MM.<sup>15,17,18</sup> A longer survival may allow for disease progression into the immune-privileged CNS, behind the BBB, which presents a therapeutic challenge to current MM treatments.<sup>9,15</sup> This finding is supported by our observation that the rate of MM relapse has risen by 160% during the same period.

#### *Clinical Considerations for CNS-MM*

Despite the rising prevalence of CNS-MM, there is still a lack of standardized management guidelines.<sup>2,15</sup> NIS records of ICD procedure codes were somewhat sparse (see *Caveats and Limitations*), so we cautiously interpret our analysis of therapeutic data. We did not find evidence that inpatient CNS-specific diagnostic and therapeutic procedures (CNS imaging, biopsy, lumbar puncture, IT chemotherapy, immunotherapy radiation) improved mortality ( $n = 70$ ,  $p = 0.70$ ) compared to patients who did not receive procedures, after adjusting for disease severity. This could be explained by the moderate ability of several current systemic MM treatments to cross the BBB (lenalidomide, pomalidomide, dexamethasone).<sup>2,8,15</sup>

We also demonstrated socioeconomic inequities in CNS-MM treatment. Interestingly, we also observed that when procedures occurred, they were more likely to be on white patients ( $p < .05$ ) in the top income quartile ( $p < .01$ ). Men were also proportionally more likely to undergo procedure compared to women although this was not significant ( $p = 0.09$ ). Lastly, 4.1% of CNS-MM patients are uninsured, likely due to the younger ages in our cohort, as 8.6% of 45-64 year-olds are uninsured compared to 1.0% of people 65+.<sup>36</sup> Future studies should evaluate how to standardize therapies and minimize potential barriers of access to the most promising interventions.<sup>8,15</sup>

#### *Caveats and Limitations*

An important distinction to make is that our absolute values and prevalence rates almost certainly underestimate the true prevalence of both CNS-MM and MM. Most studies before 2020 estimated CNS-MM to be around 1% of all MM cases, while our approach suggests that there is a prevalence of 0.5% of all MM cases.<sup>1,2,3,28</sup> Furthermore, because the NIS only collects inpatient admissions data, it likely did not capture most MM cases, which are largely treated in outpatient settings. ICD codes, due to inconsistent practices across institutions, also provide an unreliable view of true

rates. We instead suggest that the true prevalence of CNS-MM at the end of our study period in 2020 may be 2-3% of all MM cases, based on NIS-provided population weights.

Our procedures analysis must also be interpreted with caution, as only about 50% of the dataset contained procedure codes. Absolute procedure rates are almost certainly underestimated. Because the NIS dataset only includes cross-sectional inpatient data, CNS-MM patients treated in an outpatient or palliative setting such as with oral venetoclax would be omitted. We were also unable to obtain precursory therapeutic data. However, relative and proportional comparisons across years and variables within the dataset are statistically sound, as confounding correlations between ICD-coding rates and sociodemographic variables appear unlikely and are minimized by survey weights.

### *Conclusions and Future Directions*

The prevalence of CNS-MM has increased significantly over time in the NIS dataset. As patients live longer with myeloma due to more effective therapies, clinicians should maintain higher suspicion for CNS involvement, particularly in the setting of new focal neurologic signs or symptoms. Given the higher mortality, greater disease severity, and longer hospital stays associated with CNS-MM, earlier recognition and diagnosis may help improve outcomes. Future studies should clarify the drivers of the observed increase in CNS-MM and define genetic and physiological risk factors for its development. Standardizing treatment approaches, ideally through prospective clinical trials or more systematic reporting of CNS events and therapies, is essential to identify the most effective regimens.

### *Clinical Practice Points*

- Prevalence of CNS involvement in extramedullary multiple myeloma increased 166% from 2012 to 2020.
- Greater suspicion for CNS involvement is appropriate for management of patients with relapsed multiple myeloma.

### **Authorship Statement**

**Charles Mazof:** Conceptualization, Data Curation, Formal Analysis, Methodology, Visualization, Writing – Original Draft, Writing – Review and Editing. **Vishva Natarajan:** Conceptualization, Methodology, Writing – Original Draft. **Augustos Vratos:** Formal Analysis, Methodology, Validation, Writing – Review and Editing. **Parth Shah:** Supervision, Writing – Review and Editing. **Frederick Lansigan:** Supervision, Writing – Review and Editing. **Jennifer Hong:** Conceptualization, Data Curation, Resources, Supervision, Writing – Review and Editing.

## Acknowledgements

We thank Beverly Allen and Lauren Sinks for coordinating this research and the Department of Neurosurgery at Dartmouth-Hitchcock Medical Center for its support of this work.

## Ethics Approval Statement

This research was reviewed by the Institutional Review Board (IRB) of Dartmouth-Hitchcock Medical Center and was determined to be Not Human Research in accordance with institutional and federal guidelines.

## Conflicts of Interest statement

No conflicts of interest declared.

## Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## References

1. Paludo J, Painuly U, Kumar S, et al. Myelomatous Involvement of the Central Nervous System. *Clin Lymphoma Myeloma Leuk*. 2016;16(11):644-654. doi:10.1016/j.clml.2016.08.010
2. Egan PA, Elder PT, Deighan WI, O'Connor SJM, Alexander HD. Multiple myeloma with central nervous system relapse. *Haematologica*. 2020;105(7):1780-1790. doi:10.3324/haematol.2020.248518
3. Schluterman KO, Fassas ABT, Van Hemert RL, Harik SI. Multiple Myeloma Invasion of the Central Nervous System. *Arch Neurol*. 2004;61(9):1423-1429. doi:10.1001/archneur.61.9.1423
4. Yamashita T, Takamatsu H, Kawamura K, et al. A nationwide survey on central nervous system multiple myeloma in Japan: analysis of prognostic and treatment factors that impact survival. *Br J Haematol*. 2021;195(2):217-229. doi:10.1111/bjh.17717
5. Fassas ABT, Muwalla F, Berryman T, et al. Myeloma of the central nervous system: association with high-risk chromosomal abnormalities, plasmablastic morphology and

- extramedullary manifestations. *British Journal of Haematology*. 2002;117(1):103-108. doi:10.1046/j.1365-2141.2002.03401.x
6. Ellington TD, Henley SJ, Wilson RJ, Wu M, Richardson LC. Trends in solitary plasmacytoma, extramedullary plasmacytoma, and plasma cell myeloma incidence and myeloma mortality by racial-ethnic group, United States 2003-2016. *Cancer Medicine*. 2021;10(1):386-395. doi:10.1002/cam4.3444
  7. Katodritou E, Dalampira D, Delimpasi S, et al. Central nervous system multiple myeloma: A real-world multi-institutional study of the Greek Myeloma Study Group. *Am J Hematol*. 2024;99(10):1897-1905. doi:10.1002/ajh.27425
  8. Chen CI, Masih-Khan E, Jiang H, et al. Central nervous system involvement with multiple myeloma: long term survival can be achieved with radiation, intrathecal chemotherapy, and immunomodulatory agents. *Br J Haematol*. 2013;162(4):483-488. doi:10.1111/bjh.12414
  9. Sammartano V, Cerase A, Venanzi V, et al. Central Nervous System Myeloma and Unusual Extramedullary Localizations: Real Life Practical Guidance. *Front Oncol*. 2022;12:934240. doi:10.3389/fonc.2022.934240
  10. Zhang L, Fang K, Ren H, Fan S, Wang J, Guan H. Comparison of the diagnostic significance of cerebrospinal fluid metagenomic next-generation sequencing copy number variation analysis and cytology in leptomeningeal malignancy. *BMC Neurol*. 2024;24(1):223. doi:10.1186/s12883-024-03655-7
  11. Bansal R, Rakshit S, Kumar S. Extramedullary disease in multiple myeloma. *Blood Cancer J*. 2021;11(9):161. doi:10.1038/s41408-021-00527-y
  12. Onodera K, Kurisu K, Takebayashi S, et al. Intracranial plasmacytoma arising from dura mater secondary to multiple myeloma and presenting with sudden lethal intracerebral hemorrhage: A case report and literature review. *Surg Neurol Int*. 2021;12:55. doi:10.25259/SNI\_693\_2020
  13. Varga G, Mikala G, Gopcsa L, et al. Multiple Myeloma of the Central Nervous System: 13 Cases and Review of the Literature. *J Oncol*. 2018;2018:3970169. doi:10.1155/2018/3970169
  14. Meinhardt AL, Sandifer CW, Dave M. Solitary Primary Intracranial Extramedullary Plasmacytoma With Lymph Node Metastasis. *Cureus*. 14(4):e23767. doi:10.7759/cureus.23767
  15. Touzeau C, Moreau P. How I treat extramedullary myeloma. *Blood*. 2016;127(8):971-976. doi:10.1182/blood-2015-07-635383
  16. Lee D, Kalff A, Low M, et al. Central nervous system multiple myeloma--potential roles for intrathecal therapy and measurement of cerebrospinal fluid light chains. *Br J Haematol*. 2013;162(3):371-375. doi:10.1111/bjh.12404

17. Abramson HN. Immunotherapy of Multiple Myeloma: Current Status as Prologue to the Future. *Int J Mol Sci.* 2023;24(21):15674. doi:10.3390/ijms242115674
18. Puertas B, González-Calle V, Sobejano-Fuertes E, et al. Novel Agents as Main Drivers for Continued Improvement in Survival in Multiple Myeloma. *Cancers (Basel).* 2023;15(5):1558. doi:10.3390/cancers15051558
19. Anderson KC. Progress and Paradigms in Multiple Myeloma. *Clin Cancer Res.* 2016;22(22):5419-5427. doi:10.1158/1078-0432.CCR-16-0625
20. Steinhardt MJ, Schaefer C, Leyboldt LB, et al. Activity of CAR-T cells and bispecific antibodies in multiple myeloma with extramedullary involvement. *Blood Cancer J.* 2025;15(1):126. doi:10.1038/s41408-025-01330-9
21. Nieuwenhuizen L, Biesma DH. Central nervous system myelomatosis: review of the literature. *Eur J Haematol.* 2008;80(1):1-9. doi:10.1111/j.1600-0609.2007.00956.x
22. Jurczynski A, Grzasko N, Gozzetti A, et al. Central nervous system involvement by multiple myeloma: A multi-institutional retrospective study of 172 patients in daily clinical practice. *American J Hematol.* 2016;91(6):575-580. doi:10.1002/ajh.24351
23. Healthcare Cost and Utilization Project (HCUP). HCUP National Inpatient Sample (NIS).
24. NIS description of data elements. <https://hcup-us.ahrq.gov/db/nation/nis/nisdde.jsp>
25. Myeloma - Cancer Stat Facts. SEER. Accessed November 27, 2025. <https://seer.cancer.gov/statfacts/html/mulmy.html>
26. Wirk B, Wingard JR, Moreb JS. Extramedullary disease in plasma cell myeloma: the iceberg phenomenon. *Bone Marrow Transplant.* 2013;48(1):10-18. doi:10.1038/bmt.2012.26
27. Ruiz-Heredia Y, Sanchez-Vega B, Barrio S, et al. Concurrent progressive multifocal leukoencephalopathy and central nervous system infiltration by multiple myeloma: A case report. *J Oncol Pharm Pract.* 2019;25(4):998-1002. doi:10.1177/1078155218769367
28. Varga C, Xie W, Laubach J, et al. Development of extramedullary myeloma in the era of novel agents: no evidence of increased risk with lenalidomide–bortezomib combinations. *British Journal of Haematology.* 2015;169(6):843-850. doi:10.1111/bjh.13382
29. Katodritou E, Terpos E, Kastritis E, et al. Lack of survival improvement with novel anti-myeloma agents for patients with multiple myeloma and central nervous system involvement: the Greek Myeloma Study Group experience. *Ann Hematol.* 2015;94(12):2033-2042. doi:10.1007/s00277-015-2484-y
30. Neff C, Price M, Cioffi G, et al. Complete prevalence of primary malignant and nonmalignant brain tumors in comparison to other cancers in the United States. *Cancer.* 2023;129(16):2514-2521. doi:10.1002/cncr.34837

31. Swan D, Hayden PJ, Eikema DJ, et al. Trends in autologous stem cell transplantation for newly diagnosed multiple myeloma: Changing demographics and outcomes in European Society for Blood and Marrow Transplantation centres from 1995 to 2019. *Br J Haematol.* 2022;197(1):82-96. doi:10.1111/bjh.18025
32. Li X, Wang W, Zhang X, Liang Y. Multiple myeloma with isolated central nervous system relapse after autologous stem cell transplantation: A case report and review of the literature. *Front Oncol.* 2022;12:1027585. doi:10.3389/fonc.2022.1027585
33. Mikkilineni L, Kochenderfer JN. CAR T cell therapies for patients with multiple myeloma. *Nat Rev Clin Oncol.* 2021;18(2):71-84. doi:10.1038/s41571-020-0427-6
34. Gu W, Rauschecker AM, Hsu E, et al. Detection of Neoplasms by Metagenomic Next-Generation Sequencing of Cerebrospinal Fluid. *JAMA Neurol.* 2021;78(11):1355-1366. doi:10.1001/jamaneurol.2021.3088
35. Prajsnar-Borak A, Balak N, Von Pein H, Glaser M, Boor S, Stadie A. Intracranial multiple myeloma may imitate subdural hemorrhage: How to overcome diagnostic limitations and avoid errors in treatment. *Neurol Neurochir Pol.* 2017;51(3):252-258. doi:10.1016/j.pjnns.2017.02.005
36. Keisler-Starkey K. Health Insurance Coverage in the United States: 2023. *US Census Bureau.* Published online September 2024.

**Table 1. Demographics of CNS-MM patients by year.** The mean is shown for age while weighted count is shown for all other variables. Percentages are of total yearly cases.

	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
Total	330	335	260	460	625	645	655	890	790	4990
Age (mean)	67.29	66.43	66.77	65.78	64.43	64.97	66.62	68.93	68.25	66.76
Sex										2120
Female	135 (41%)	155 (46%)	130 (50%)	175 (38%)	225 (36%)	265 (41%)	270 (41%)	405 (46%)	360 (46%)	2120 (43%)
Male	195 (59%)	180 (54%)	130 (50%)	285 (62%)	400 (64%)	380 (59%)	385 (59%)	485 (55%)	430 (54%)	2870 (57%)
Race										3130
White	265 (80%)	205 (61%)	175 (67%)	295 (64%)	395 (63%)	360 (56%)	370 (57%)	550 (62%)	515 (65%)	3130 (63%)
Black	50 (15%)	60 (18%)	40 (15%)	70 (15%)	135 (22%)	150 (23%)	160 (24%)	205 (23%)	165 (21%)	1035 (21%)
Hispanic	5 (1.5%)	35 (10%)	10 (3.8%)	50 (11%)	50 (8.0%)	80 (12%)	85 (13%)	90 (10%)	75 (10%)	480 (10%)
Asian	0 (0%)	10 (3.0%)	15 (5.8%)	15 (3.3%)	15 (2.4%)	15 (2.3%)	0 (0%)	20 (2.2%)	15 (1.9%)	105 (2.1%)
Native American	5 (1.5%)	5 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (0.8%)	0 (0%)	0 (0%)	15 (0.3%)

Other	0 (0%)	10 (3.0%)	15 (5.8%)	10 (2.2%)	5 (0.8%)	15 (2.3%)	35 (5.3%)	20 (2.2%)	5 (0.6%)	115 (2.3%)
Insurance										3115
Medicare	205 (62%)	220 (66%)	165 (64%)	300 (65%)	335 (54%)	390 (61%)	395 (60%)	610 (69%)	495 (63%)	495 (10%)
Medicaid	0 (0%)	35 (10%)	20 (7.7%)	25 (5%)	65 (10%)	105 (16%)	70 (11%)	95 (11%)	80 (10%)	495 (10%)
Private	100 (30%)	70 (21%)	65 (25%)	110 (24%)	180 (29%)	125 (19%)	170 (26%)	165 (19%)	185 (23%)	1170 (23%)
None	25 (7.6%)	10 (3.0%)	10 (3.8%)	25 (5.4%)	45 (7.2%)	25 (3.9%)	20 (3.1%)	20 (2.2%)	25 (3.2%)	205 (4.1%)

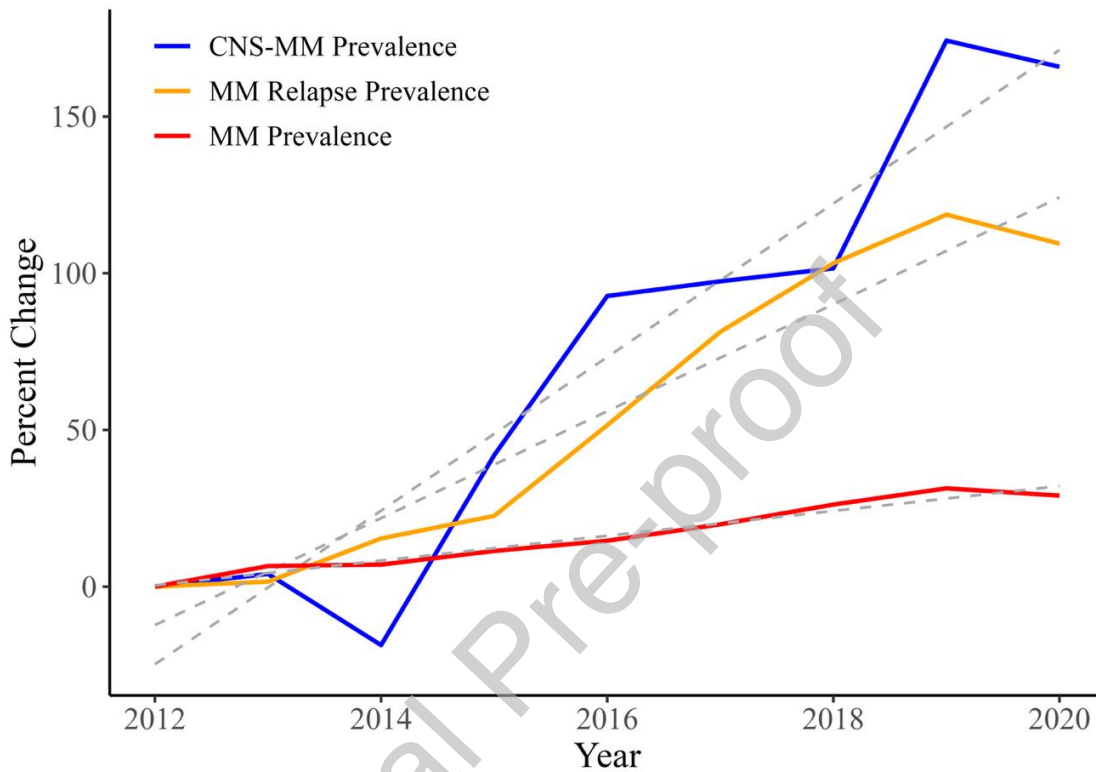
**Table 2. Dataset outcome measures by year.** The weighted count is shown for each variable. Mortality risk and severity levels are defined using the All Patient Refined Diagnosis Related Groups (APR-DRG) developed by 3M Health Information Systems. Percentages are of total yearly cases.

	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
Total	330	335	260	460	625	645	655	890	790	4990
Discharge Disposition										
Routine	85 (26%)	105 (31%)	85 (33%)	170 (37%)	185 (30%)	200 (31%)	180 (28%)	315 (35%)	210 (27%)	1535 (31%)
Short Term Facility	15 (4.5%)	15 (4.5%)	10 (3.8%)	20 (4.3%)	15 (2.4%)	15 (2.3%)	30 (4.6%)	40 (4.5%)	15 (1.9%)	175 (3.5%)
Long Term Facility	95 (29%)	75 (22%)	70 (27%)	130 (28%)	200 (32%)	200 (31%)	235 (36%)	230 (26%)	250 (32%)	1485 (30%)
Against Medical Advice	0 (0%)	0 (0%)	0 (0%)	5 (1.1%)	0 (0%)	0 (0%)	5 (0.8%)	15 (1.7%)	0 (0%)	25 (0.5%)
Home Care/Hospice	90 (27%)	100 (30%)	65 (25%)	90 (20%)	155 (25%)	155 (24%)	115 (18%)	220 (25%)	215 (27%)	1205 (24%)
Died	45 (14%)	40 (12%)	30 (12%)	45 (9.8%)	65 (10%)	75 (12%)	90 (14%)	70 (7.9%)	100 (13%)	560 (11%)
Mortality Risk										
Minor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (0.8%)	0 (0%)	10 (1.5%)	0 (0%)	5 (0.6%)	20 (0.4%)
Moderate	95 (29%)	60 (18%)	50 (19%)	45 (9.8%)	135 (22%)	105 (16%)	115 (18%)	160 (18%)	140 (18%)	905 (18%)
Major	165 (50%)	210 (63%)	160 (62%)	205 (45%)	335 (54%)	385 (60%)	335 (51%)	495 (56%)	400 (51%)	2690 (54%)
Extreme	70 (21%)	65 (19%)	50 (19%)	80 (17%)	150 (24%)	155 (24%)	195 (30%)	235 (26%)	245 (31%)	1245 (25%)
Severity										
Minor	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (0.8%)	20 (3.1%)	5 (0.8%)	15 (1.7%)	10 (1.3%)	55 (1.1%)
Moderate	45 (14%)	30 (9.0%)	20 (7.7%)	30 (6.5%)	85 (14%)	55 (8.5%)	80 (12%)	185 (21%)	125 (16%)	655 (13%)
Major	195 (59%)	225 (67%)	170 (65%)	195 (42%)	350 (56%)	335 (52%)	310 (47%)	455 (51%)	400 (51%)	2635 (53%)
Extreme	90 (27%)	80 (24%)	70 (27%)	105 (23%)	185 (30%)	235 (36%)	260 (40%)	235 (26%)	255 (32%)	1515 (30%)

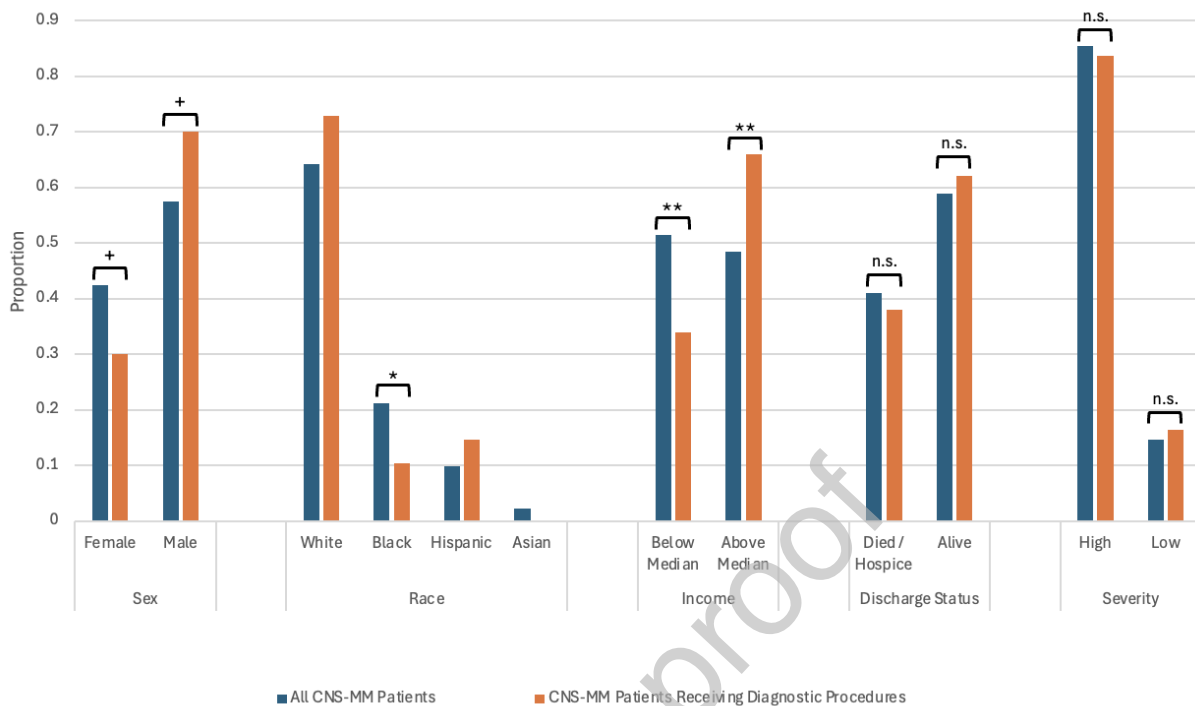
**Table 3: CNS-MM vs all MM Prognostic Factors and Outcomes.** Age and length of stay are expressed as means and statistically compared with Student's t-tests, while the remaining variables are expressed as percentages and statistically compared with chi-squared tests.

Variable	CNS-MM	MM	Statistical Test
Age (mean)	66.76	69.42	$t=7.39$ (df=1007, $p<.001$ )
Length of Stay (mean)	8.67	7.18	$t=-5.05$ (df=1004, $p<.001$ )
Sex			$\chi^2=1.91$ (df=1, $p=0.16$ )
Female	42.48%	44.73%	
Male	57.52%	55.24%	
Race			$\chi^2=4.86$ (df=5, $p=0.43$ )
White	62.73%	61.65%	
Black	20.74%	21.58%	
Hispanic	9.62%	7.90%	
Asian	2.10%	2.01%	
Native American	0.30%	0.38%	
Other Race	2.30%	2.76%	
Mortality Risk			$\chi^2=346.7$ (df=3, $p<.001$ )
Minor	0.40%	5.34%	
Moderate	18.14%	41.35%	
Major	53.91%	37.17%	
Extreme	24.95%	13.46%	
Loss of Function Risk			$\chi^2=102.0$ (df=3, $p<.001$ )
Minor	1.10%	3.13%	
Moderate	13.13%	23.47%	
Major	52.81%	49.75%	
Extreme	30.36%	20.96%	

**Figure 1: Changes in prevalence rates since 2012.** From 2012-2020, all MM prevalence increased 29%, significantly less than the 109% increase of MM relapses ( $p < .001$ ) and the 166% increase of CNS-MM ( $p < .001$ ). CNS-MM prevalence also increased significantly more than MM relapse prevalence ( $p < .05$ ).



**Figure 2: Characteristics of all CNS-MM Patients vs CNS-MM Patients with Diagnostic Procedures.** Black CNS-MM patients received proportionally fewer diagnostic procedures compared to other races ( $p < .05$ ). Wealthier patients receive proportionally more diagnostic procedures ( $p < .01$ ). Female patients may receive proportionally fewer procedures ( $p = 0.09$ ). Receiving diagnostic procedures was not associated with significantly higher or lower mortality or severity.



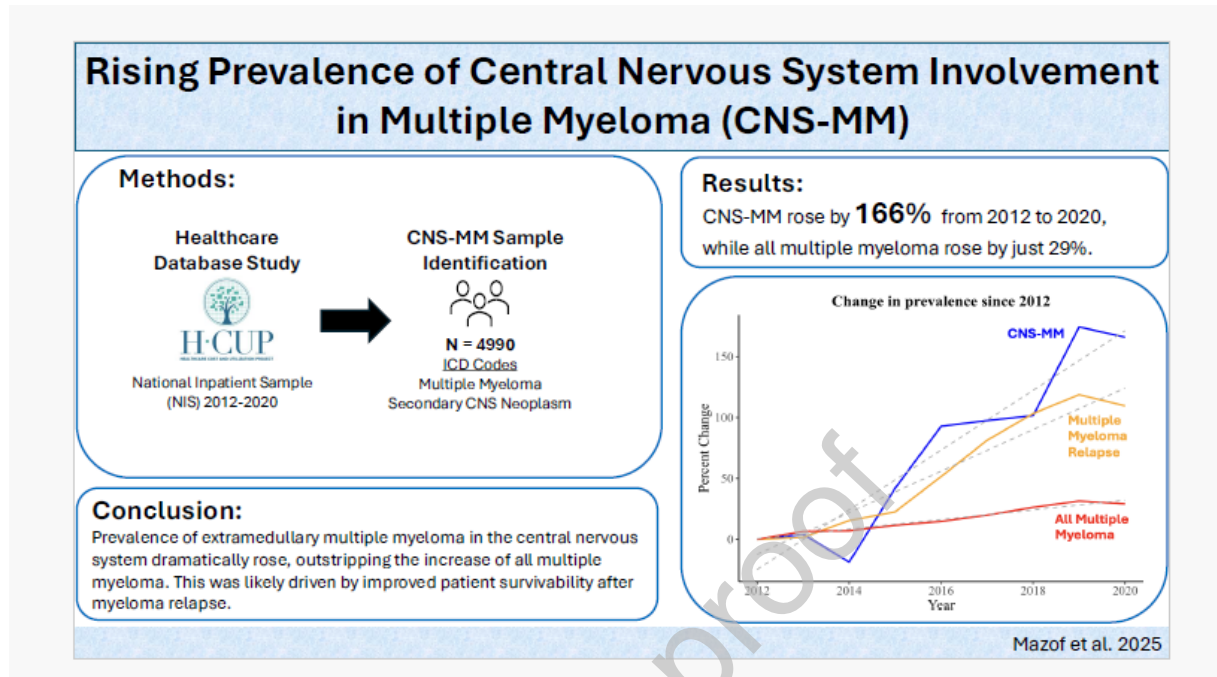
### MicroAbstract

In an analysis of the U.S. National Inpatient Sample (2012–2020), CNS involvement in multiple myeloma rose 166%, outpacing overall myeloma trends. CNS-targeting procedures were performed more often among patients who were white and had higher incomes but were not associated with a survival benefit.

### Clinical Practice Points

- Prevalence of CNS involvement in extramedullary multiple myeloma increased 166% from 2012 to 2020.
- Greater suspicion for CNS involvement is appropriate for management of patients with relapsed multiple myeloma.

## Graphical Abstract



Journal Pre-proof

## Supplemental Data

Table S1. ICD-9 and ICD-10 codes used.

Disease	ICD-9	ICD-10
Multiple Myeloma	203.00	C90.00
	203.01	C90.01
	203.02	C90.02
Secondary CNS Neoplasm	198.3	C79.32
	198.4	C79.31
		C79.49
Brain MRI	88.91	B030Y0Z
		B030YZZ
		B030ZZZ
Brain CT/X-ray	87.01-9 87.17	B02000Z
		B0200ZZ
		B02010Z
		B0201ZZ
		B020Y0Z
		B020YZZ
		B020ZZZ
Excision of Brain, Diagnostic	01.11 01.12 01.13 01.14 01.18	00B00ZX
		00B03ZX
		00B04ZX
		00B10ZX
		00B13ZX
		00B14ZX
		00B20ZX
		00B23ZX
		00B24ZX
		00B60ZX
		00B63ZX
		00B64ZX
		00B70ZX
		00B73ZX
		00B74ZX
		00B80ZX
		00B83ZX
00B84ZX		
00B90ZX		
00B93ZX		
00B94ZX		
00BA0ZX		

		00BA3ZX
		00BA4ZX
		00BB0ZX
		00BB3ZX
		00BB4ZX
		00BC0ZX
		00BC3ZX
		00BC4ZX
		00BD0ZX
		00BD3ZX
		00BD4ZX
Excision of Spine, Diagnostic	03.31	00BT0ZX
	03.32	00BT3ZX
	03.39	00BT4ZX
		00BW0ZX
		00BW3ZX
		00BW4ZX
		00BX0ZX
		00BX3ZX
		00BX4ZX
		00BY0ZX
		00BY3ZX
		00BY4ZX
		00JU3ZZ
		009U3ZZ
Injection of Antineoplastic into Brain		3E0Q004
		3E0Q005
		3E0Q00M
		3E0Q0HZ
		3E0Q304
		3E0Q305
		3E0Q30M
		3E0Q3HZ
		3E0Q704
		3E0Q705
		3E0Q70M
Injection of Antineoplastic into Spine	99.25	3E0R302
	99.28	3E0R303
		3E0R304
		3E0R305
		3E0R30M
		3E0R3HZ
		3E0S302

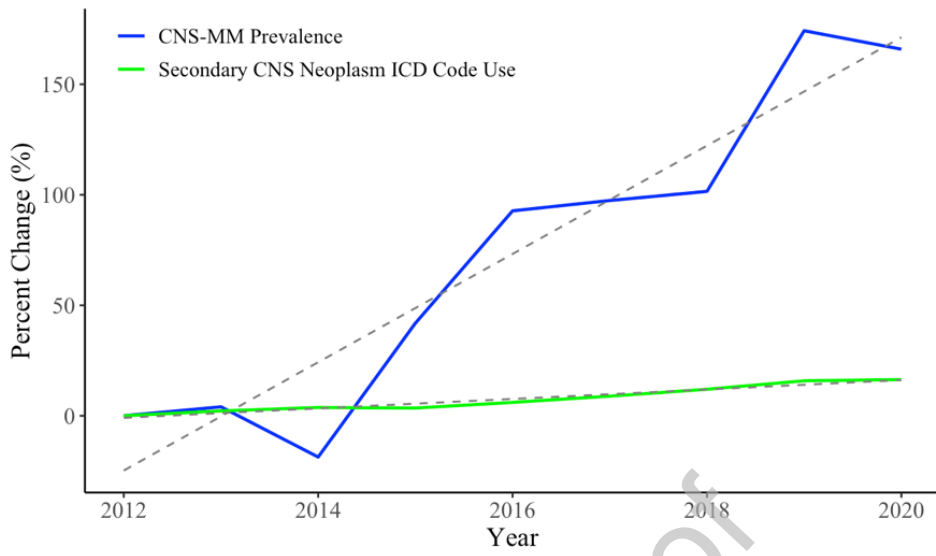
3E0S303  
 3E0S304  
 3E0S305  
 3E0S30M  
 3E0S3HZ

**Table S2.** Top 20 most common CNS-MM procedures over the years 2015–2020.

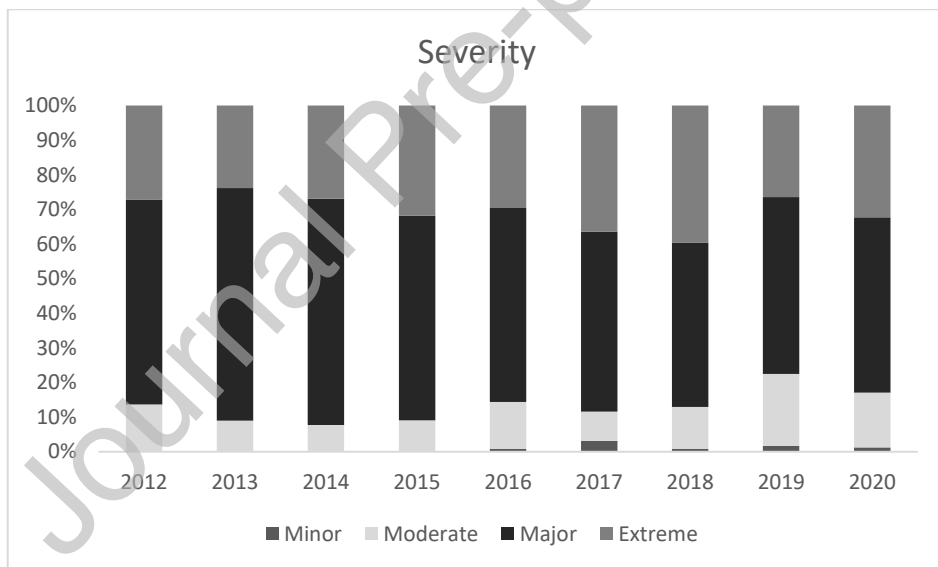
<b>Procedure Code</b>	<b>Description</b>	<b>Count</b>	<b>% of Total</b>
30233N1	Transfusion of Nonautologous RBCs, Percutaneous	525	21.88
02HV33Z	Insertion of Infusion Device into SVC, Percutaneous	310	12.92
009U3ZX	Drainage of Spinal Canal, Percutaneous Approach, Diagnostic	270	11.25
07DR3ZX	Extraction of Iliac Bone Marrow, Percutaneous, Diagnostic	265	11.04
30233R1	Transfusion of Nonautologous Platelets into Peripheral Vein	240	10
0BH17EZ	Insertion of Endotracheal Airway into Trachea, Natural or Artificial	200	8.33
5A1D70Z	Performance of Urinary Filtration, Prolonged Intermittent 6-18hrs	190	7.92
3E04305	Introduction of Other Antineoplastic into Central Vein	150	6.25
5A1955Z	Respiratory Ventilation, >96 Consecutive Hrs	115	4.79
5A1945Z	Respiratory Ventilation, 24-96 Hrs	110	4.58
3E0R305	Introduction of Other Antineoplastic into Spinal Canal, Percutaneous Approach	95	3.96
5A1935Z	Respiratory Ventilation, Less than 24 Consecutive Hours	85	3.54
00NX0ZZ	Release Thoracic Spinal Cord, Open Approach	80	3.33
0DH63UZ	Insertion of Feeding Device into Stomach, Percutaneous Approach	80	3.33
30243N1	Transfusion of Nonautologous Red Blood Cells into Central Vein, Percutaneous Approach	80	3.33
3E03305	Introduction of Other Antineoplastic into Peripheral Vein	70	2.92
B548ZZA	Ultrasonography of SVC, Guidance	70	2.92
8E09XBZ	Computer Assisted Procedure of Head and Neck Region	60	2.5
00BX0ZZ	Excision of Thoracic Spinal Cord, Open Approach	55	2.29
4A10X4Z	Monitoring of Central Nervous Electrical Activity, External Approach	55	2.29

**Table S3.** Selected demographics across MM, CNS-MM, and CNS procedures

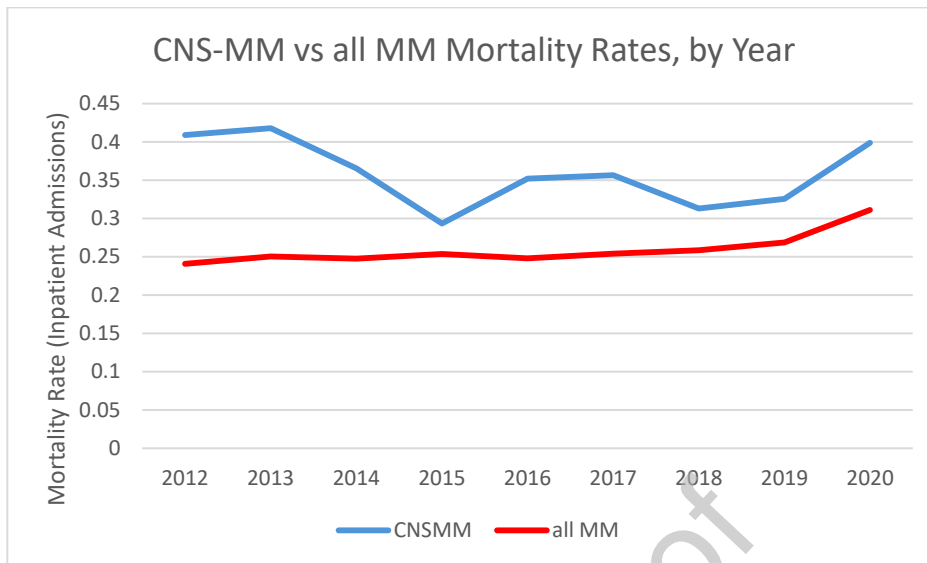
	<b>All MM</b>	<b>CNS-MM</b>	<b>CNS-MM with CNS procedures</b>	<b>CNS-MM with diagnostic CNS procedures</b>	<b>CNS-MM with IT chemotherapy</b>
Total	977,130	4,990	350	250	130
Age	67.42	66.76	64.32	65.46	60.71
Sex					
Female	437,060	2,120	140	75	70
Male	539,770	2,870	210	175	60
Race					
White	602,365	3,130	250	175	105
Black	210,865	1,035	35	25	10
Hispanic	77,150	480	45	35	10
Asian	19,665	105	5	0	5
Native American	3,705	15	0	0	0
Other	26,975	115	5	5	0
Income Quartile					
1st (Low)	259,855	1,425	60	45	20
2nd	236,205	1,100	60	40	25
3rd	235,935	1,230	120	105	25
4th (High)	228,785	1,150	110	60	60
Discharge Disposition					
Alive	717,020	3,195	240	170	95
Died/Hospice	253,980	1,765	110	80	35



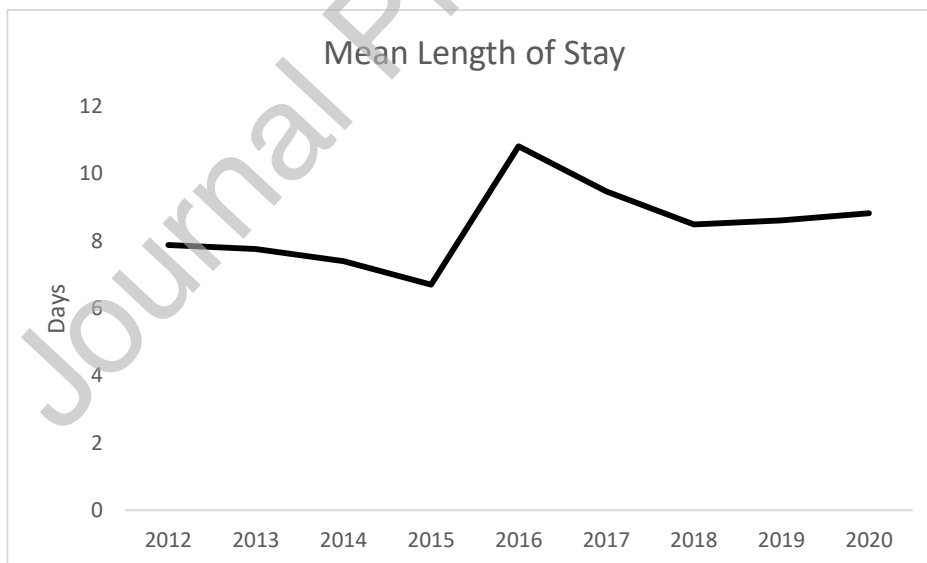
**Figure S1.** CNS-MM Prevalence vs Secondary CNS Neoplasm ICD Code Use.



**Figure S2.** Severity categories of the CNS-MM sample



**Figure S3.** CNS-MM and all MM Mortality Trends, By Year (Deaths + Hospice Discharge Outcomes). CNS-MM did not show a significant uptrend ( $p = 0.44$ ), while all MM had a small, but significant uptick in mortality rate ( $p = 0.013$ ).



**Figure S4.** CNS-MM Average Length of Inpatient Stay, By Year,  $F(1,996) = 1.32$ ,  $p=0.25$ .