Received: 20 August 2023 | Revised: 11 September 2023 | Accepted: 15 September 2023

DOI: 10.1002/jha2.798

eJHaem

British Society for Haematology

RESEARCH ARTICLE

Real-world utilization and healthcare costs for multiple myeloma: A retrospective analysis of patients in Singapore

Diana Beatriz Bayani[1] | **Yihao Clement Lin**[2] | **Melissa G. Ooi**[3] | **Allison Ching Yee Tso**[2] | **Hwee Lin Wee**[1,4]

[1]Saw Swee Hock School of Public Health, National University of Singapore, Singapore

[2]Department of Hematology, Tan Tock Seng Hospital, Singapore

[3]Department of Haematology-Oncology, National University Cancer Institute, Singapore

[4]Department of Pharmacy, National University of Singapore, Singapore

Correspondence
Diana Beatriz Bayani, Saw Swee Hock School of Public Health, National University of Singapore, Tahir Foundation Building, 12 Science Drive 2, Republic of Singapore, 117549; Department of Pharmacy, National University of Singaore.
Email: dbayani@u.nus.edu

Abstract

Multiple myeloma, a hematological malignancy, imposes a significant financial burden on healthcare systems. Health technology assessments (HTA) and economic evaluations play vital roles in reimbursement decisions and cost containment. This study aimed to explore healthcare utilization patterns and costs among myeloma patients in Singapore through a retrospective analysis of 605 patients treated at two cancer centers. Data encompassing demographics, treatment utilization, and billing were extracted from electronic records, and a cost analysis was performed from the perspective of the Singapore healthcare system. The results revealed common usage of immunomodulatory agents (52%) and proteasome inhibitors (37%), with bortezomib being the most frequently used targeted treatment. Treatment costs increased with disease progression, displaying variations depending on the therapeutic agent used. Notably, hospitalization costs due to adverse events were substantial, with pneumonia as the leading cause. This study highlights the high cost of myeloma therapy in Singapore, posing a financial burden for households. Findings may inform economic evaluations, evidence generation, reimbursement, and subsidy decisions. Leveraging real-world data from electronic records provides valuable insights into local healthcare utilization patterns. Future studies may explore integrating billing databases with clinical repositories for a more comprehensive analysis, and consider limitations such as incomplete clinical information and potential selection bias.

KEYWORDS
costs, multiple myeloma, real-world data, resource use, Singapore

1 | INTRODUCTION

Multiple myeloma is a hematological malignancy that arises from the proliferation of malignant plasma cells in the bone marrow. It predominantly affects elderly males, and had a global incidence of 1.78 per 100,000 people in 2020 [1]. Recent therapeutic advancements have significantly improved the prognosis of myeloma, transforming it from an incurable disease to a more treatable condition with longer survival rates [2]. Depending on the disease stage and patient status, treatment may involve chemotherapy, proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, steroid therapy, stem cell transplantation, and supportive care.

In Singapore, multiple myeloma is estimated to have an annual incidence of around 100 cases per year, although the exact prevalence remains unknown. Despite being a relatively uncommon form of blood cancer, multiple myeloma imposes a substantial financial burden on the healthcare system due to the high costs of therapy, the need for multiple drug regimens, and the frequent occurrence of relapses or disease progression [3]. As such, the use of generics and biosimilars has increased, together with other cost containment measures. Consequently, many countries, including Singapore employ explicit value assessments, such as health technology assessment (HTA) and economic evaluation to inform decisions surrounding reimbursement and financing [4]. These approaches prioritize coverage for cost-effective drugs, ensuring optimal value for payers, and managing budget impact through value-based pricing strategies.

While global clinical trials provide valuable insights into myeloma management, obtaining clinically relevant data specific to the Singaporean population can be challenging due to the limited representation of Asian patients in these trials. Therefore, it is essential for economic evaluations to consider the local context, accurately reflecting healthcare practices and treatment patterns. For example, certain drugs, while utilized as initial treatments in the United States or Europe, are relegated to later stages of treatment in Singapore. Moreover, some drugs may not even be accessible in Singapore. In addition to clinical data, cost localization is crucial due to significant variations in monetary values and purchasing power across different jurisdictions [5].

Localization and contextualization of costs and clinical data ensure that the assessments account for the unique characteristics of the local patient population, healthcare system, and treatment landscape. Real-world data (RWD) collected from electronic records, claims databases, and registries is increasingly used for this purpose as it provides more accurate and comprehensive information about costs and outcomes beyond controlled trial settings. RWD can be used to inform several aspects of an economic evaluation in myeloma, including but not limited to costs per cycle of treatment, choice of drugs/regimens used, duration of treatment, and number of treatment lines [6–8].

The integration of RWD in economic evaluation enhances the robustness, generalizability, and relevance of such assessments, empowering decision-makers to make well-informed, evidence-based choices regarding the value of health technologies. In this study, our objective is to provide valuable insights on healthcare utilization and costs of myeloma patients using real-world data, for the purpose of HTA in Singapore context.

2 | MATERIALS AND METHODS

2.1 | Data collection

We conducted a retrospective analysis of myeloma patients from two of three major public cancer centers in Singapore. The cohort consisted of all patients diagnosed between January 2018 and December 2020 to capture treatment patterns over a period of up to 2 years. We identified patients using the relevant diagnosis codes based on the International Classification of Diseases (ICD-10 code C90.0 for Multiple Myeloma and ICD-9-CM Diagnosis Code 203.0) [9] and the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT 20300/1) [10]. Detailed electronic records containing demographic data, visit type, diagnosis code, health service utilization, and billing data at the individual patient level were extracted from the hospitals until 2022. The analysis included only resident patients (Singaporeans and Permanent Residents) above 21 years of age and excluded foreign residents and medical tourists to avoid skewing the costs. The study received ethics approval from the Domain Specific Review Board (DSRB) of the National Healthcare Group in Singapore (DSRB Reference: 2021-00038).

2.2 | Classification of treatment lines and drug exposure

We classified patients into treatment lines based on their utilization history of myeloma drugs recorded in their billing records. Treatment lines were defined according to the International Myeloma Working Group (IMWG) protocol, where a line consists of one or more cycles of a single drug, a combination of drugs, or a planned sequence of regimens followed by stem cell transplantation [11]. We classified subsequent treatment lines and progression based on the IMWG criteria, which include treatment regimen discontinuation, unplanned addition of a new drug, or treatment switching.

Furthermore, we identified patients based on the specific drug class to which they were exposed, considering the numerous combinations of regimens and agents. The key drug classes of interest were proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, alkylating agents, and corticosteroids. Patients with a follow-up duration or treatment utilization record of less than 28 days were excluded from the analysis to ensure sufficient coverage of a treatment cycle.

2.3 | Cost analysis

We analyzed costs from the perspective of the Singapore healthcare system, encompassing the total expenses reflected in patients' accounts, regardless of the payer and government subsidies received. These charges included direct medical costs for drugs, diagnostics, procedures, and the use of hospital facilities for outpatient and inpatient care, such as chair time for chemotherapy services and hospitalization for adverse events, as well as professional fees. Costs were expressed in Singapore Dollars (SGD), using 2022 values where 1 SGD equals 0.75 United States Dollars (USD) based on prevailing exchange rates.

For the utilization of myeloma treatments, we summarized costs into mean monthly costs based on the actual duration of treatment for each patient, incorporating both outpatient administration and initial inpatient administration as necessary. In addition, the costs were reported as monthly costs or equivalent to one treatment cycle, allowing for consistent reporting for use in an economic model with a

TABLE 1 Patients' characteristics.

	Total (%) $n = 605$
Sex	
Male	333 (55)
Female	272 (45)
Survival status	
Alive	376 (62)
Ethnicity	
Chinese	507 (67.3)
Malay	101 (16.7)
Indian	48 (7.9)
Others	49 (8.1)

1-month cycle length. Hospitalizations due to adverse events resulting from treatments were identified based on the primary treatment diagnoses according to the relevant ICD and SNOMED codes. We summarized the costs based on the total cost for each patient's actual length of stay.

3 | RESULTS

A total of 605 patients were included in the analysis, meeting the predefined inclusion criteria. The demographic characteristics of the patients are summarized in Table 1. When examining the distribution by drug class, a significant proportion of patients (52%) received treatment with immunomodulatory agents, primarily thalidomide and lenalidomide. Proteasome inhibitors were administered to 37% of patients, while monoclonal antibodies were used in 11% of cases. Analyzing individual drugs, bortezomib was the most commonly prescribed targeted treatment, used by 31% of patients, followed by thalidomide, cyclophosphamide, and lenalidomide (27.6%, 26.6%, and 21.5%, respectively). Dexamethasone, a form of steroid, often used in combination with targeted agents, was administered to more than half of the patients (see Table 2).

The analysis revealed an increasing trend in mean monthly treatment costs as the disease progressed, as indicated by the costs per treatment line in Table 3. The mean monthly cost for patients in the first-line treatment was $5,798.44, increasing by at least 30% for each subsequent line of therapy, due to the cost of the newer agents used, as well as the availability of generic alternatives for older drugs such as lenalidomide and bortezomib commonly used in the first line. Notably, these costs exhibited significant variability, as demonstrated by the reported standard deviation within each category. When comparing two drugs of interest, daratumumab-based regimens were found to be notably more expensive than bortezomib-based regimens, primarily due to the unit cost difference between a vial of daratumumab and bortezomib. However, when comparing post-progression treatment costs, bortezomib-based regimens incurred higher costs compared to subsequent treatment regimens following first-line daratumumab use.

TABLE 2 Utilization of drugs by class.

Drugs (% of users)	
Proteasome inhibitors	224 (37)
Bortezomib	188 (31.8)
Ixazomib	19 (3.13)
Carfilzomib	17 (2.81)
Immunomodulatory agents (IMId)	315 (52)
Thalidomide	167 (27.6)
Lenalidomide	130 (21.5)
Pomalidomide	18 (2.98)
Monoclonal antibody	70 (11.57)
Daratumumab	66 (10.91)
Elotuzumab	4 (0.66)
Cyclophosphamide	161 (26.6)
Dexamethasone	310 (51)

TABLE 3 Mean monthly costs (in Singapore dollars [SG$]).

	Mean	SD
By treatment line		
First line	5,798.44	12,047.15
Second line	7,478.93	9,192.31
Third line	11,185.32	12,667.36
Fourth line	14,663.74	13,741.30
By the main agent		
Daratumumab-based regimen (all lines)	6,134.23	3,249.42
Bortezomib-based (all lines)	1,934.74	1,670.97
Post-progression by the main agent		
Post-progression with bortezomib treatments	4,228.36	3,457.11
Post-progression with daratumumab treatment	1,661.70	1,281.51

It is important to note that the reported treatment costs exclude drug administration, disease management, and laboratory costs, which average S$184 and S$152.64 per treatment session, respectively. Drug administration expenses encompass preparatory charges for infusion bags, adapters, syringes, IV setup and insertion, IV fluids, and treatment monitoring. Disease management and laboratory testing per treatment cycle include laboratory fees full blood count, renal and liver panel, serum-free light chain, and serum paraprotein band determination, necessary for monitoring disease progression based on IMWG criteria [12].

Patients also incurred substantial hospitalization costs resulting from treatment-related adverse events. Pneumonia was the leading cause of hospital admission among those receiving myeloma treatment, with an average length of stay (LOS) of 11 days and an associated cost of S$13,760. Neutropenia followed closely, with an average LOS of 10 days and a mean cost of S$13,266 per event. Anemia had an average

TABLE 4 Hospitalization costs.

Primary diagnosis	*N* (%)	Mean cost per hospitalization in SGD (SD)	Mean length of stay per hospitalization in SGD (SD)
Neutropenia	48	13,266.31 (24,724.54)	9.79 (11.65)
Anemia	18	2,567.50 (2,669.66)	1.94 (2.79)
Pneumonia	107	13,760.94 (23,305.64)	11.15 (14.98)
Diarrhea	31	4,403.23 (4,527.49)	4.87 (4.63)

LOS of 2 days and a cost of S$2,567. Further details can be found in Table 4. All costs are reported on a per-hospitalization episode basis.

4 | DISCUSSION

This study presents a comprehensive analysis of the costs associated with managing multiple myeloma, including treatment-related expenses and hospitalization due to adverse events. The results demonstrate the predominant utilization patterns and the corresponding cost variations based on the treatment line and choice of therapeutic agent. Currently, the average monthly cost of multiple myeloma therapy exceeds the national median monthly income in Singapore [13], highlighting the financial burden for most households. The cost estimates generated from this study can serve as valuable inputs for economic evaluations of different therapies for multiple myeloma, particularly as new drugs are introduced to the market. Real-world data collected locally, such as electronic medical records, provide important context for economic models and can inform reimbursement and subsidy decisions, ultimately improving access to treatments.

The utilization patterns observed in this study align with the recommendations outlined in the Singapore Myeloma Study Group Guidelines for managing multiple myeloma patients [14]. These guidelines predominantly advocate for proteasome inhibitor-based therapies, as they offer superior response rates and improved survival outcomes, alongside the use of thalidomide, melphalan, lenalidomide, and cyclophosphamide [14]. In comparison to cost estimates from other countries, the monthly cost per patient for therapy medications alone in Singapore is higher than those reported in China [15], The Netherlands [16], and Germany [17], but considerably lower than the costs in the United States [18, 19], which are nearly double. Several factors contribute to these variations. Treatment practices differ between countries, and the therapeutic landscape evolves rapidly. In Singapore, older agents like thalidomide and cyclophosphamide are still commonly used, while international myeloma guidelines [20, 21] have increasingly recommended the use of lenalidomide. Patient characteristics may also vary, leading to different drug class requirements. Additionally, financing and pricing mechanisms differ across countries. For instance, in Singapore, confidential pricing schemes and patient access programs further reduce costs for patients [22]. In contrast, the costs and duration of hospitalization resulting from adverse events were similar to those reported in other countries.

This study used a large dataset comprising patients from two major cancer centers in Singapore, providing robust cost and utilization data. Unlike many studies that rely on sampling, we extracted data from all relevant patients, enabling us to leverage real-world data that accurately reflects resource utilization in the local context. This dataset is valuable for informing modeling studies that have a similar scope in terms of population and treatments considered. As HTA becomes increasingly prominent in Singapore, this study contributes to evidence generation, particularly in cases where local data is limited and clinical trials lack representation of Asian patients.

However, the study has certain limitations. First, relying solely on electronic records may not offer a complete picture of patients' utilization and cost patterns, as crucial clinical information often exists in unstructured formats. This limitation constrained our ability to conduct a detailed analysis of factors influencing utilization, such as disease severity and transplant eligibility. Other confounding factors that may bias outcomes were not investigated, as they were beyond the study's scope. Moreover, the current subsidy framework and treatment availability also impact patients' monthly costs, number of treatment lines, and choice of drugs in the regimen. Therefore, actual therapy demand and costs may be influenced by various factors not reflected in patients' medical and billing records.

Second, using real-world data presents data quality challenges, as the completeness and accuracy of data collection, extraction, and analysis are dependent on the available data. While the datasets used in this study were generally comprehensive, some sociodemographic variables were missing, and it is possible that certain services or drugs were not captured in the patient's statement of account. Furthermore, the data source only provided utilization and billing information, lacking other relevant clinical endpoints such as survival and treatment response.

Third, the approved period for data extraction was relatively short, limiting our ability to capture a complete picture of disease progression until patient death for most individuals. As the majority of patients were still alive, we had limited information on later treatment lines and accurate survival data. This raises the possibility of underestimating costs, especially for subsequent treatment stages not covered during the follow-up period, which typically entail higher expenses. However, it is worth noting that the introduction of generic equivalents such as bortezomib since 2022 [23] has led to a decrease in the unit prices of targeted agents. This reduction is anticipated to lower both the prices and overall treatment costs, regardless of the chosen regimen or treatment line. It's important to consider both of these limitations when using these estimates in an economic evaluation.

Fourth, while clear selection criteria were established for patient inclusion, there is a potential for selection bias resulting from data extraction using solely diagnosis codes, which may include coding errors. This bias is dependent on the coding practices of nurses or attending physicians, which may not fully capture the patient's

situation. Many patients were coded as having newly diagnosed myeloma despite having undergone two or more lines of therapy.

Lastly, although data was collected from two major cancer centers in Singapore, it may not be representative of the entire myeloma cohort in the country, as there are patients who seek treatment at other tertiary cancer centers or private hospitals that were not included in this study.

5 | CONCLUSION

In conclusion, despite the limitations of this study, the analysis of healthcare utilization and costs offers valuable insights to complement the clinical data from randomized controlled trials and real-world data obtained from registries. This is particularly important for localizing cost-effectiveness studies and comparing the utilization patterns of Singaporean patients with those in other settings. While our findings may not be directly applicable to other countries, they can serve as valuable inputs for health economists conducting modeling and HTAs related to myeloma treatments. Additionally, these findings have the potential to inform subsidy and financing decisions in this high-cost treatment area. Future research should explore the integration of real-world data sources, such as billing databases, with clinical databases and registries to enable a more comprehensive analysis of multiple myeloma management and outcomes.

AUTHOR CONTRIBUTIONS

Diana Beatriz Bayani and Hwee Lin Wee conceptualized the study while Melissa G. Ooi, Yihao Clement Lin, and Allison Ching Yee Tso provided inputs. Yihao Clement Lin, Melissa G. Ooi, and Allison Ching Yee Tso assisted with data acquisition and management. Diana Beatriz Bayani analyzed the data and consulted with Hwee Lin Wee, Melissa G. Ooi, and Allison Ching Yee Tso on the results and presentation of findings. Diana Beatriz Bayani drafted the manuscript and all authors reviewed, edited, and approved the final manuscript.

ACKNOWLEDGMENTS

We would like to extend our appreciation to the National University of Singapore for granting a Research Scholarship to DB Bayani, enabling the completion of this study as part of their PhD program. The rest of the authors received no support for the research, authorship, and publication of this article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

FUNDING INFORMATION

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ETHICS STATEMENT

The study received ethics approval from the Domain Specific Review Board (DSRB) of the National Healthcare Group in Singapore (DSRB Reference: 2021-00038).

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

DATA AVAILABILITY STATEMENT

Due to the sensitive nature of the research, the institutional data owners did not give consent for their data to be publicly shared. As a result, supporting data are unavailable.

ORCID

Diana Beatriz Bayani https://orcid.org/0000-0002-0042-8547
Melissa G. Ooi https://orcid.org/0000-0002-7392-0655
Allison Ching Yee Tso https://orcid.org/0000-0003-3943-7229
Hwee Lin Wee https://orcid.org/0000-0002-7150-1801

REFERENCES

1. Huang J, Chan SC, Lok V, Zhang L, Lucero-Prisno DE, 3rd, Xu W, et al. The epidemiological landscape of multiple myeloma: a global cancer registry estimate of disease burden, risk factors, and temporal trends. Lancet Haematol. 2022;9(9):e670–77.
2. Mateos M-V, Nooka AK, Larson SM. Moving toward a cure for myeloma. Am Soc Clin Oncol Educ Book. 2022;42:643–54.
3. Rajkumar SV. Value and cost of myeloma therapy. Am Soc Clin Oncol Educ Book. 2018;38:662–66.
4. Pearce F, Lin L, Teo E, Ng K, Khoo D. Health technology assessment and its use in drug policies: Singapore. Value Health Reg Issue. 2019;18:176–83.
5. García-Mochón L, Rovira Forns J, Espin J. Cost transferability problems in economic evaluation as a framework for an European health care and social costs database. Cost Effect Res Alloc. 2021;19(1):43.
6. Lou J, Kc S, Toh KY, Dabak S, Adler A, Ahn J, et al. Real-world data for health technology assessment for reimbursement decisions in Asia: current landscape and a way forward. Int J Technol Assess Health Care. 2020;36(5):474–80.
7. Kc S, Lin LW, Bayani DBS, Zemlyanska Y, Adler A, Ahn J, et al. What, where, and how to collect real-world data and generate real-world evidence to support drug reimbursement decision-making in Asia: a reflection into the past and a way forward. Int J Health Policy Manag. 2023;12(Issue 1):1–9.
8. Kang J, Cairns J. "Don't Think Twice, It's All Right": Using additional data to reduce uncertainty regarding oncologic drugs provided through managed access agreements in England. PharmacoEconomics Open. 2022;7(1):77-91.
9. World Health O. ICD-10: International statistical classification of diseases and related health problems: Tenth revision. 2nd ed. Geneva: World Health Organization; 2004.
10. El-Sappagh S, Franda F, Farman A, Kwak K-S. SNOMED CT standard ontology based on the ontology for general medical science. BMC Med Inf Decis Making. 2018;76(18):1–19.
11. Rajkumar SV, Richardson P, San Miguel JF. Guidelines for determination of the number of prior lines of therapy in multiple myeloma. Blood. 2015;126(7):921–22.
12. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the international myeloma workshop consensus panel 1. Blood. 2011;117(18):4691–95.

13. Mo M. Median gross monthly income from work (Including employer CPF Contributions) of full-time employed residents. 2023. https://stats.mom.gov.sg/Pages/Income-Summary-Table.aspx
14. Mel de S, Chen Y, Gopalakrishnan SK, Ooi M, Teo C, Tan D, et al. The Singapore myeloma study group consensus guidelines for the management of patients with multiple myeloma. Singapore Med J. 2017;58(2):55–71.
15. Zhou X, Xia J, Mao J, Cheng F, Qian X, Guo H. Real-world outcome and healthcare costs of relapsed or refractory multiple myeloma: a retrospective analysis from the Chinese experience. Hematology 2016;21(5):280–86.
16. Blommestein HM, Verelst SG, Zagorska A, Stevanovic J, Engstrom A, Sonneveld P, et al. Real-world evidence on healthcare resource use and associated cost with multiple myeloma in the Netherlands. Value Health. 2016;19(7):A751.
17. Kocaata Z, Wilke T, Fischer F, Welte R, Einsele H. Healthcare resource utilization and cost of patients with multiple myeloma in Germany: a retrospective claims data analysis. PharmacoEconomics Open. 2022;6(4):619–28.
18. Madduri D, Hagiwara M, Parikh K, Pelletier C, Delea TE, Kee A, et al. Real-world treatment patterns, healthcare use and costs in triple-class exposed relapsed and refractory multiple myeloma patients in the USA. Future Oncol. 2021;17(5):503–15.
19. Gupta N, Tai M-H, Kaila S, Thompson-Leduc P, Ghelerter I, Kurteva S, et al. Real-world healthcare resource utilization and costs among patients with multiple myeloma in the United States. J Clin Oncol. 2022;40(16_suppl):e18811.
20. Kumar SK, Callander NS, Adekola K, Anderson L, Baljevic M, Campagnaro E, et al. Multiple myeloma, version 3.2021, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2020;18(12):1685–717.
21. Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-upĀ. Ann Oncol. 2021;32(3):309–22.
22. Agency for Care Effectiveness. Procedures and guidelines for company submissions to the Agency for Care Effectiveness for funding consideration. 2022.
23. Health Sciences Authority. Listing of approvals and post-registration actions. 2023. https://www.hsa.gov.sg/therapeutic-products/approvals-and-post-reg-actions

How to cite this article: Bayani DB, Lin YC, Ooi MG, Tso ACY, Wee HL. Real-world utilization and healthcare costs for multiple myeloma: A retrospective analysis of patients in Singapore. eJHaem. 2023;4:1013–1018. https://doi.org/10.1002/jha2.798