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Economic Evaluation

An Economic Model to Establish the Costs Associated With Routes to Presentation for Patients With Multiple Myeloma in the UK

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ABSTRACT

Objectives: Patients with myeloma often face significant diagnostic delay, with up to one-third of UK patients diagnosed after an emergency presentation (EP). Compared with other routes, patients presenting as an emergency have more advanced disease, increased complications, and poorer prognosis.

Methods: An economic model was developed using a decision-tree framework and lifetime time horizon to estimate costs related to different presentation routes (EP, general practitioner [GP] 2-week wait, GP urgent, GP routine, and consultant to consultant) for UK patients diagnosed as having myeloma. After diagnosis, patients received one of 3 first-line management options (observation, active treatment, or end-of-life care). Inputs were derived from UK health technology assessments and targeted literature reviews, or based on authors' clinical experience where data were unavailable. Active treatment, complication, and end-of-life care costs were included.

Results: The average per-patient cost of treating myeloma (across all routes) was estimated at £146 261. The average per-patient cost associated with EP (£152 677) was the highest; differences were minimal compared with GP 2-week wait (£149 631) and consultant to consultant (£147 237). GP urgent (£140 025) and GP routine (£130 212) were associated with marginally lower costs. Complication (£42 252) and end-of-life care (£11 273) costs were numerically higher for EP than other routes (£25 021-£38 170 and £9772-£10 458, respectively).

Conclusions: An economic benefit may be associated with earlier diagnosis, gained via reduced complication and end-of-life care costs. Strategies to expedite myeloma diagnosis and minimize EPs have the potential to improve patient outcomes and may result in long-term savings that could offset any upfront costs associated with their implementation.

Keywords: diagnostic delay, health economics, multiple myeloma, myeloma.

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Introduction

Multiple myeloma represents a significant global health burden, with increasing incidence year on year.[1,2] In the UK specifically, approximately 6000 individuals have been diagnosed as having myeloma and approximately 24 000 live with the disease.[3,4] These patients often face considerable delays to detection and diagnosis, particularly at the primary care level, with up to one-third of patients diagnosed after emergency presentation (EP).[5] This can partly be explained by the relatively low incidence of myeloma compared with other cancers but may also result from patients presenting with vague symptoms that overlap with other common illnesses.[3,6] Musculoskeletal issues, pain, and fatigue, common in patients diagnosed as having myeloma, may also be attributed to the aging process; therefore, patients may delay seeking advice from their general practitioner (GP).[6-8] Many patients have multiple GP appointments and are referred to a range of medical disciplines before a correct diagnosis is reached.

Survival rates vary considerably between different routes of presentation, with poorer outcomes often attributed to delayed diagnosis.[9] In particular, patients with myeloma who are diagnosed after EP have a considerably poorer prognosis than those diagnosed via other routes, such as GP routine referral or GP suspected cancer referral with a maximum 2-week wait (GP TWW).[9] Data reported by the National Cancer Intelligence Network showed a 1-year relative survival rate of 62% for EPs compared with 88% for GP referrals and 89% for the GP TWW route.[5] Furthermore, patients diagnosed via EP are likely to present with complications indicative of end-organ damage, such as hypercalcemia, renal insufficiency, anemia, and bone disease (known as CRAB complications).[9] Therefore, it was hypothesized that delays to diagnosis result not only in poorer survival and

quality of life outcomes but in a higher economic burden as a result of increased resource use.

There is a strong clinical argument for ensuring that delays to myeloma detection and diagnoses are minimized. Reduced incidence of EPs would likely reduce disease burden and complications, improving patients' quality and length of life.[10] Nevertheless, we are unaware of any research that addresses the costs associated with such delays and the economic impact of different routes to diagnosis. Thus, we evaluated the economic costs associated with different routes of presentation for patients newly diagnosed as having myeloma in the UK. The methodology applied, although specified for the UK healthcare system, may be adopted for future studies analyzing diagnostic routes in other country-specific healthcare systems.

Methods

Model Structure

A decision-tree model framework was adopted, informed by the routes of presentation categorized by Howell et al[9] (2017), to estimate the costs associated with routes of presentation for patients newly diagnosed as having myeloma in the UK (Fig. 1). The modeled routes included EP, GP TWW, GP urgent, GP routine, and consultant to consultant referral (Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.01.001) and estimated costs over a lifetime time horizon given the incurable nature of the disease. Throughout model development, the authors' significant clinical experience of treating patients with multiple myeloma within the UK National Health Service (NHS) was used to validate both the modeling approach and the model inputs.

After diagnosis, patients were modeled to receive one of 3 first-line management options (active treatment with antimyeloma drugs [hereinafter active treatment], observation, or end-of-life care), which determined the subsequent treatment pathway. The proportion of patients in each first-line management cohort by referral route are presented in Table 1.[9] Patients received observation because they were assumed to have a diagnosis of smoldering myeloma, which could progress to active myeloma, requiring active treatment.[11] In the absence of available data, active treatment was modeled identically for patients receiving active treatment at diagnosis or after an initial period of observation.

The model used an NHS and a personal social service perspective. Inputs, such as probabilities and treatment duration, were based on the National Institute for Health and Care Excellence (NICE) technology appraisals and targeted literature reviews, or based on authors' clinical experience where data were unavailable. Cost inputs (relating to treatment, complications, and end-of-life care) were informed by the British National Formulary, electronic market information tool, and NHS reference costs 2019-2020.[12-14]

Observation

Patients receiving observation as first-line management only incurred costs associated with monitoring until active treatment was initiated on progression to active myeloma. Howell et al[9] (2017) collected data from patients diagnosed between July 1, 2012, and December 31, 2013. To reflect the possibility that some higher-risk patients diagnosed as having smoldering myeloma may receive treatment, in line with changes in practice such as the introduction of the SLiM diagnostic criteria (bone marrow plasma cells ≥60%, light chain ratio of ≥100 in the serum, magnetic resonance imaging with >1 focal lesion) for myeloma in 2014, 10% of those reported to receive observation by Howell et al[9] (2017) were instead modeled to receive active treatment after diagnosis, in line with the authors' clinical experience.

Active Treatment

The active treatment pathway was based on NICE guidance in 2019, the time of study conception; however, costs were updated to reflect the most recent cost year for which data had been published. The treatment pathway included stem cell transplant (SCT), chemotherapy, and targeted treatments. Treatments recommended in the UK differ according to eligibility for SCT; therefore, patients modeled to receive active treatment were categorized by SCT eligibility, which determined subsequent treatments. The probability of being eligible for SCT was based on unpublished data from the same data set reported by Howell et al[9] (2017), adjusted to match 2017 estimates of SCT eligibility from the British Society of Blood and Marrow Transplantation.[15]

The model accounted for several possible treatment options at 3 successive stages (first, second, and subsequent lines [3+]) of the active treatment pathway. Not all patients received multiple lines of treatment; a proportion were modeled to proceed directly to end-of-life care after each treatment line.

The proportion of patients modeled to receive first, second, and subsequent lines of treatments are presented in Appendix Table 2a and b in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.01.001. The proportion of patients proceeding to each line of therapy, the duration of treatment, and treatment-free intervals were based on real-world data reported by Yong et al[16] (2016). The frequencies of laboratory tests were based on NICE technology appraisals and then applied for the duration of treatment or treatment-free intervals.[16]

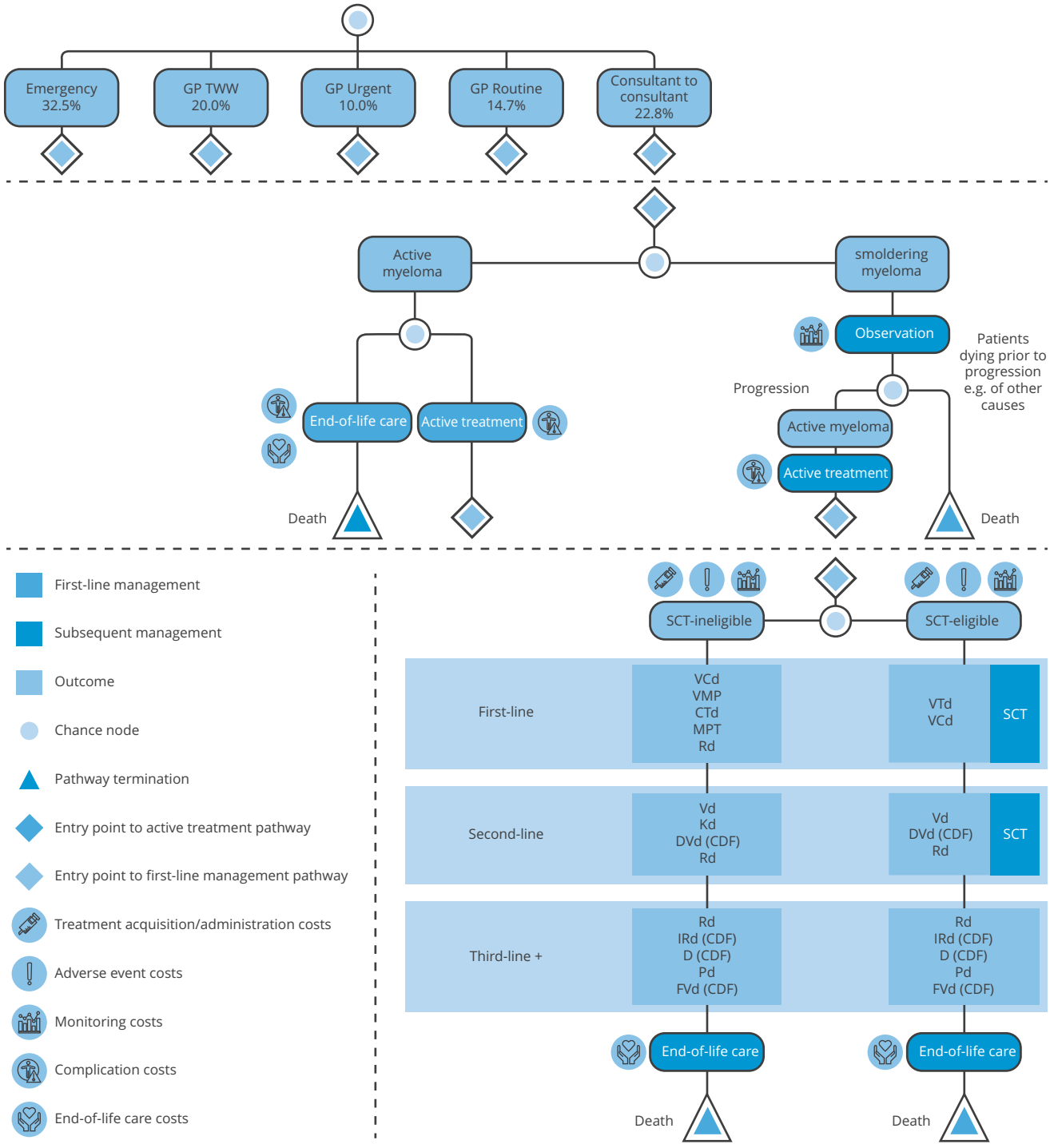
A patient population with mean body surface area of 1.73 m^2 and mean weight of 71.5 kg was used to determine antimyeloma drug costs (Appendix Table 3a in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.01.001), as per the NICE appraisal of lenalidomide plus dexamethasone.[17] Costs for SCT, derived from the NICE appraisal of bortezomib, were applied to the proportion of patients receiving SCT.[18] The model also included costs associated with administration of first-, second-, and subsequent-line treatments and those attributed to treatment-related adverse events (AEs) that represented a significant cost burden (Appendix Tables 3b and 4 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.01.001).

End-of-Life Care

Prior to death, all patients with myeloma were assumed to receive end-of-life care to manage symptoms and relieve pain. End-of-life care was modeled to be provided in a hospital, hospice, nursing home, or at home; the probabilities of patients dying in each setting differed according to first-line management, based on Howell et al[19] (2013).

For patients receiving observation or active treatment as first-line management, the probability of receiving end-of-life care in different settings was assumed to approximately equate to published probabilities for all patients with myeloma.[19] For those receiving end-of-life care as first-line management, shorter life expectancy was assumed after diagnosis to reflect advanced disease or presence of a comorbidity. These patients had an increased probability of dying in a hospital.[19] A weighted average cost across settings, adjusted for the reported probabilities, was applied to patients receiving end-of-life care. The probabilities and duration for which the cost was applied in the model are presented in

Figure 1. Structure of the decision-tree model used in this analysis, along with the proportion of patients presenting via each route. Routes to diagnosis in the UK were those published by Howell et al[9] (2017) for patients diagnosed from July 1, 2012, to December 31, 2013. First- and second-line treatment for SCT-eligible patients includes SCT and induction/maintenance treatments.



CDF indicates Cancer Drugs Fund; CTd, cyclophosphamide, thalidomide, and dexamethasone; D, daratumumab monotherapy; DVd, daratumumab, bortezomib, and dexamethasone; FVd, panobinostat, bortezomib, and dexamethasone; GP, general practitioner; GP TWW, GP suspected cancer referral with a maximum 2-week wait; IRd, ixazomib, lenalidomide, and dexamethasone; Kd, carfilzomib and dexamethasone; MPT, thalidomide, melphalan, and prednisone; Pd, pomalidomide and dexamethasone; Rd, lenalidomide and dexamethasone; SCT, stem cell transplant; VCd, bortezomib, cyclophosphamide, and dexamethasone; Vd, bortezomib and dexamethasone; VMP, bortezomib, melphalan, and prednisone; VTd, bortezomib, thalidomide, and dexamethasone.

Table 1. Proportion of patients estimated to receive each of the 3 first-line management options and the SCT eligibility of those receiving active treatment.

Referral route	First-line management (Howell et al[9] (2017) + expert clinical opinion)			Howell et al[9] (2017) adjusted based on BSBMT	
	Active treatment	Observation	End-of-life care	SCT eligible	SCT ineligible
Emergency	0.7823	0.0726	0.1452	0.3919	0.6081
GP TWW	0.6263	0.3079	0.0658	0.5141	0.4859
GP urgent	0.6143	0.2786	0.1071	0.4089	0.5911
GP routine	0.4786	0.4500	0.0714	0.2669	0.7331
Consultant to consultant	0.6220	0.3293	0.0488	0.3919	0.6081

BSBMT indicates British Society of Blood and Marrow Transplantation; GP, general practitioner; GP TWW, GP suspected cancer referral with a maximum 2-week wait; SCT, stem cell transplant.

Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.01.001.[20,21]

Complications

A diagnosis of myeloma often follows one or more of the clinical presentations summarized by the CRAB criteria. The model accounted for these to capture elevated costs and resource use associated with managing these complications. The probabilities of patients experiencing CRAB features according to route of presentation were based on those reported for the whole patient cohort by Howell et al[9] (2017), validated by authors' clinical experience. It was assumed that the probability of experiencing complications after observation was independent of the original presentation route.

Additional healthcare costs were applied to patients presenting with CRAB complications; a summary of treatment costs and resource use associated with each of these is presented in Appendix Table 6 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.01.001.

Sensitivity Analyses

Sensitivity analyses were conducted to address elements of uncertainty in the model and to explore the robustness of results. A deterministic sensitivity analysis (DSA) was used to identify drivers of uncertainty in the results by varying parameters individually (±20%). The DSA tested the sensitivity of the costs per route, calculated assuming that 1 patient presents via each route.

A probabilistic sensitivity analysis was also conducted, comprising 1000 probabilistic simulations. Inputs were randomly sampled from relevant probability distributions to assess the combined uncertainty in parameters on the costs per route.[22]

Results

For a patient diagnosed as having myeloma in the UK, the undiscounted lifetime cost of treating myeloma was estimated to be £146 261 averaged across all referral routes. £99 505 was associated with antimyeloma treatment costs (acquisition, administration, monitoring, and AE costs), £36 237 constituted costs of managing complications, and £10 520 was attributed to end-of-life care. For the incident UK population of patients newly diagnosed as having myeloma (N = 6000), the model estimated total lifetime undiscounted direct costs of £878 million; £298 million was associated with EPs.[3]

The costs for each route of presentation (total and disaggregated), assuming 1 patient presents via each, are presented in Appendix Table 7 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.01.001. Although EP was associated with the highest total costs (£152 677), differences were minimal compared with GP TWW (£149 631) and consultant to consultant routes (£147 237). However, total costs were marginally lower for GP urgent (£140 025) and GP routine routes (£130 212).

Costs associated with antimyeloma treatment, complications, end-of-life care, and total costs disaggregated by first-line management are highlighted in Figure 2A-D. Antimyeloma treatment costs were similar across routes, whereas complication and end-of-life care costs were considerably higher for EP (£53 525) than for other routes (£34 793-£48 446). Figure 2D shows that antimyeloma treatment at diagnosis comprised 93.2% of the costs associated with EP, versus 64.1% to 78.3% for other routes. Antimyeloma treatment costs for patients who received initial observation, but progressed to active disease and received active treatment, comprised only 4.8% of total antimyeloma treatment costs for EP; for other routes, this was 20.1% to 34.9% and was highest for the GP routine route.

Sensitivity Analyses

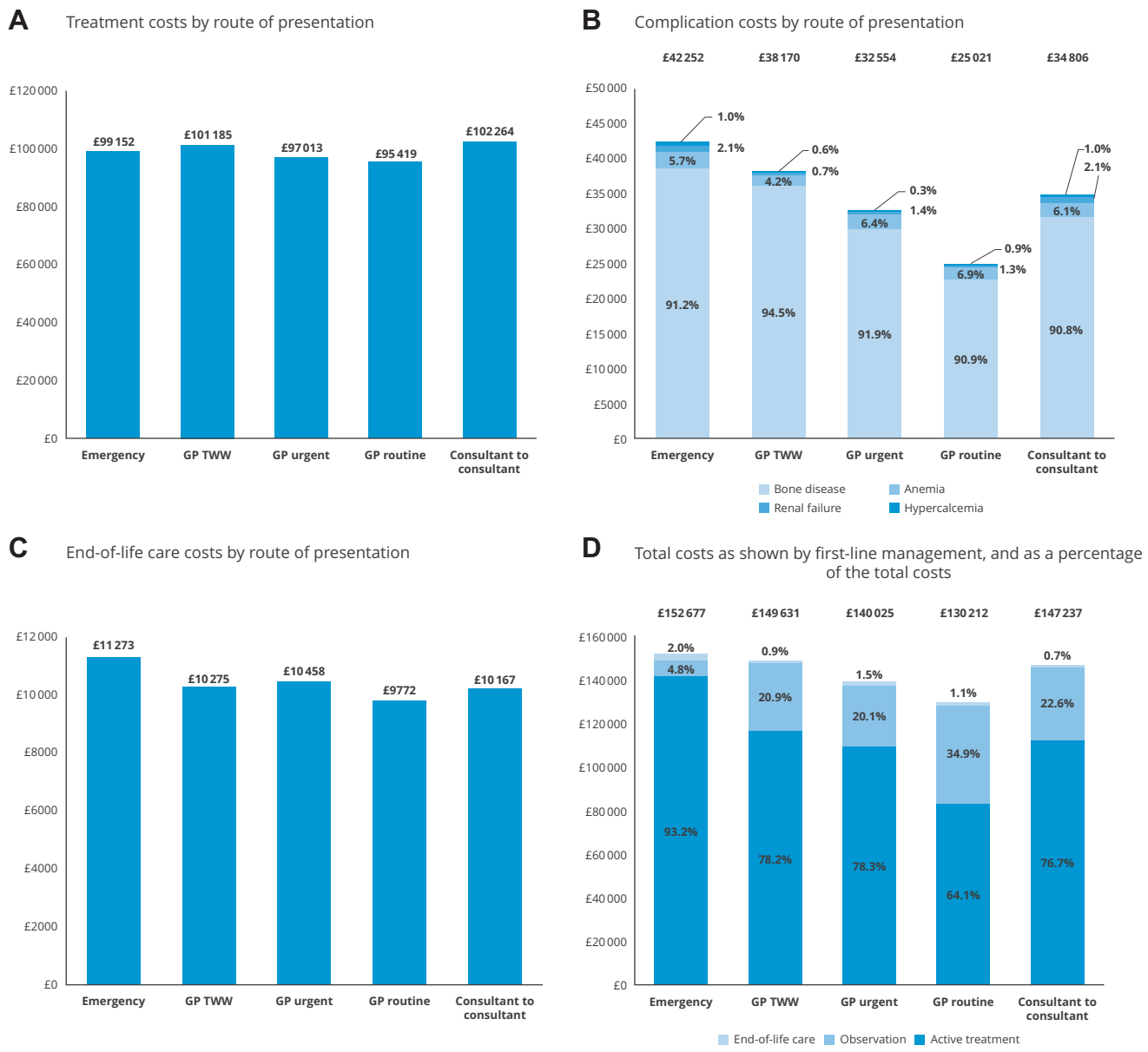
The DSA results are presented in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.01.001; patient weight was the most influential parameter for all routes, apart from GP routine. For the GP routine route, the proportion of patients progressing from smoldering to active myeloma was found to have the largest influence on the expected cost per route. This parameter was one of the most influential for all other routes, apart from EP. Across all routes, the proportion of patients reaching second-line therapy (for both SCT-eligible and SCT-ineligible patients) affected model outcomes.

The probabilistic sensitivity analysis results (based on costs per route, calculated assuming 1 patient presents via each route) are presented in Appendix Figure 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2023.01.001. The order of routes from the most to least costly was consistent with the base case analysis.

Discussion

This study demonstrated that, although total treatment costs were similar across all routes, there may be an economic benefit associated with earlier diagnosis of myeloma, gained through reduction in complication and end-of-life care costs. A difference of £18 732 per patient was estimated for combined complication and end-of-life care costs between EP and GP routine routes. Complication costs were the highest for patients diagnosed via EP,

Figure 2. Treatment (A), complication (B), end-of-life care (C), and total (D) costs for each presentation route (assuming 1 patient presents via each route). Complication costs are disaggregated by type of complication. Total costs are shown disaggregated by first-line management. Percentages shown may not sum to 100% because of rounding.



GP indicates general practitioner; GP TWW, GP suspected cancer referral with a maximum 2-week wait.

which is associated with more advanced disease, increased complications, and poorer prognosis and survival compared with patients presenting via other routes. These data likely reflect a higher patient symptomatic burden and consequent poorer quality of life compared with other routes.

It is known that patients presenting as an emergency have poorer prognosis and shorter survival time (Howell et al[9] [2017]). However, available overall survival data are reported from diagnosis, not from initiation of active treatment, so any impact of reduced survival on active treatment costs could not be robustly accounted for in the model. Should patients diagnosed via EP incur similar overall costs as the other routes but over a shorter period of time, it is likely that the monthly/annual costs would be much higher for the EP route.

To the best of our knowledge, this is the first economic analysis to systematically quantify the costs associated with patients newly diagnosed as having myeloma in the UK, considering the entire treatment pathway from diagnosis to death. To the best of our knowledge, the use of routes of presentation to quantify the impact of delays to diagnosis has not been adopted elsewhere and offers a unique insight into the potential economic benefit associated with earlier diagnosis. Other studies have investigated the lifetime costs associated with myeloma care and reported mixed results; average per-patient lifetime costs of Canadian $119 107 and $184 495 have been estimated for Canada and the United States, respectively.[23,24] A key difference between these studies and our analysis was their use of a net cost method whereby the cost incurred by a matched control without myeloma was

subtracted from the cost incurred by a patient with myeloma. Furthermore, it is unclear as to the level of detail with which these studies considered the costs associated with complications and AEs, which may drive differences in reported costs. Another important consideration is the different cost years used, with the Canadian estimate based on data from 1997 to 2007 and the United States estimate adjusted to 2016.

Despite similar per-patient lifetime costs reported for the UK and the United States, the focus on phase-specific costs of myeloma (prediagnosis, initial, continuous, and terminal care) represents a further key difference to our study.[24] Additionally, the Canadian study reported lower costs and did not capture those associated with community service agencies nor private healthcare plans.[23] A difference in country-specific treatment pathways may have also contributed to the variation between the 3 reported lifetime costs.

Interestingly, de Oliveira et al[24] (2016) outlined the prevalence of 21 types of cancer among 349 092 patients; myeloma was the third least prevalent but incurred the second highest costs. In addition, myeloma has been shown to have a longer delay in diagnosis than many other types of cancer.[25] The findings presented here demonstrate that delays may be associated with increased costs and highlight the large economic burden associated with myeloma treatment. The results, disaggregated into the cost categories, go some way to identifying where reductions could be made. In particular, earlier diagnosis at the precursor stage, possibly through targeted screening, may represent an opportunity to reduce the costs incurred through complications, with the additional benefit of improving patient quality and length of life.

The results of our study also aligned with UK National Audit Office predictions on cancer care costs in 2021, stating cancer service costs to be £13 billion. Thus, at 2.0% of new cancer cases, this approximately equates to a £265 million annual cost associated with UK patients with myeloma.[3,26] This compares well with the total lifetime cost for myeloma of £878 million estimated from the model for the incident myeloma population in the UK (N = 6000).

A key strength of the model is the high granularity with which it describes the entire treatment pathway for UK patients with myeloma, accounting for a large number of events and their associated costs. The model comprehensively explores the factors that may drive differences in costs between routes of presentation. Additionally, the model structure, data sources, and inputs were selected to closely align with clinical guidelines (European Society for Medical Oncology guidelines and NICE guidance) and deemed to be reflective of UK practice at the time of study conception based on the authors' clinical experience of treating patients with multiple myeloma within the UK NHS. Where possible, model inputs were based on UK-specific data sources identified via targeted literature reviews and validated by clinical experts with extensive experience treating patients with myeloma within the NHS. In particular, the characteristics of patients presenting via each route, determining subsequent treatment pathways and representing key drivers of cost differences, were based on the study by Howell et al[9] (2017). These data were derived from a large patient cohort (N = 441) from the Haematological Malignancy Research Network, treated within the NHS. Given that clinical guidelines are applied across the UK, this cohort can be considered broadly applicable to the wider UK population. A limitation of these data is that they are based on patients diagnosed in 2012-2013 in a limited region of the UK; as such, changes in clinical guidelines over time and geographical differences may affect applicability to current UK practice. Additionally, inputs were based on the subgroups of patients diagnosed via each route, further reducing patient numbers and introducing some uncertainty. Modeling the rapidly evolving active treatment pathway for myeloma remains a challenge, with the modeled pathway based on NICE guidance at the time of study conception. Where necessary, model inputs were based directly on the authors' clinical experience to ensure that the model was reflective of current practice.

Although the inputs and results presented here are specific to the UK healthcare system, the novel application of a decision-tree framework based on routes of presentation to quantify the economic impact of delays to diagnosis may be of interest to other healthcare systems and the model can be adjusted for country-specific data inputs. The adoption and application of this methodology to other healthcare systems may help to demonstrate the wider economic impact associated with delayed diagnosis of myeloma.

A limitation of the model is the lack of data pertaining to the effect of receiving observation as first-line management on subsequent treatment regimens, such as treatment duration, necessitating a simplifying assumption. Therefore, we modeled active treatment identically for patients who received active treatment at diagnosis and after a period of observation (after an initial diagnosis of smoldering myeloma). Therefore, total antimyeloma treatment costs were similar across routes of presentation, despite differences in patient characteristics between routes of presentation and resulting differences in the proportions of patients receiving active treatment at diagnosis or after observation. Should an initial period of observation affect subsequent active treatment, total antimyeloma treatment costs may differ between EP and other routes, with costs potentially reduced should observation positively affect subsequent treatment outcomes. This is particularly pertinent given that active treatment at diagnosis comprised the greatest proportion of the total antimyeloma treatment costs for EP, whereas other routes had larger proportions of antimyeloma treatment costs associated with patients initially undergoing observation.

In addition, no published data were available to directly inform the probability of patients reaching each line of therapy conditional on SCT eligibility or route of presentation. Therefore, it was assumed that the proportion of patients reaching second or subsequent lines (3+) of therapy, mean durations of treatment, and treatment-free intervals were identical for all patients receiving active treatment (regardless of route of presentation or SCT eligibility). These limitations could be mitigated through collection of individual patient data from a source such as a comprehensive cancer or myeloma registry such as the Haematological Malignancy Research Network. Finally, some of the data sources used to inform key model inputs were published several years before study conception; nevertheless, these were deemed to be relevant to UK clinical practice and were the most relevant sources identified from the literature searches used. More recent real-world evidence would be beneficial to enable updates to this approach and account for changes in clinical practice and outcomes for patients with myeloma.

In summary, this model comprehensively explores the factors that may drive differences in economic costs between routes of presentation for UK patients with myeloma. The results suggest a potential economic benefit associated with earlier diagnosis through reduced complication and end-of-life care costs. Strategies to expedite myeloma diagnosis and minimize EPs not only have the potential to improve patient outcomes as suggested by Howell et al[9] (2017) but may also result in long-term cost savings that could offset any upfront costs associated with their implementation. The model captures differences in the distribution of treatment costs across different parts of the decision-tree

framework, but the impact of initial observation on subsequent active treatment remains a key data gap. Addressing remaining data gaps through further data collection would strengthen our understanding of the economic impact of delays to diagnosis for UK patients with myeloma.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2023.01.001.

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Drafting of the manuscript: Porteous, Gibson, Eddowes, Drayson, Pratt, Bowcock, Willis, Parkin, Renwick, Laketic-Ljubojevic, Howell, Smith, Stern
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