The Economic Burden of Multiple Myeloma. Definition of a Model for Forecasting Patients' Costs

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ABSTRACT

Background: The aim of this study was to evaluate healthcare costs in a single-centre population of patients with multiple myeloma (MM), in an attempt to develop a model for forecasting costs.
Methods: A cohort of 387 MM patients, diagnosed at Policlinico San Matteo (Pavia, Italy), between 2002 and 2014, was analysed grouping patients into those eligible (n=223) or not eligible (n=164) for transplantation. After descriptive statistics, the benchmark model - Ordinary Least Squares - and different variations of the Generalized Linear Model were adopted.
Results: The average total cost per patient was around €28,500 for patients not eligible for transplantation and around €87,000 for the eligible ones. The difference in marginal costs for transplant-eligible patients was probably due to higher costs for hospitalisation and the costs of the transplant procedure itself. The analysis highlighted four determinants useful for building a model to forecast expenditure: age, bortezomib use, lenalidomide use, and number of lines of therapies. The two most important determinants of expenditure were use of the novel agents and the total number of lines of therapy, which reflects a higher number of doses and a greater need for accesses to hospital.
Conclusion: In conclusion, using a Generalized Linear Model, we identified four determinants in our cohort which were useful for building a model to predict expenditure for MM patients. Although the analysis was performed in a particular setting in a single hospital, the model could be applied to any scenario of patients..

Key words: Myeloma, Health, Expenditures, GLM.

INTRODUCTION

Multiple myeloma (MM) is a plasma cell neoplasm with a complex clinical picture characterized by anaemia, infections, renal impairment and bone destruction. According to the Italian Association of Cancer Registries [1], the incidence of MM and its mortality rate were stable in Italy during the period 1999-2016: around 5,700 new cases were estimated for 2016 while the prevalence is expected to increase because of better survival.

The outcome of patients with MM changed markedly in the past decade thanks to the introduction of novel therapies, including immune-modifying drugs (thalidomide and lenalidomide) and proteasome inhibitors such as bortezomib [2]. A further improvement was observed after approval of the use of pomalidomide, the latest immune-modifying drug, the monoclonal antibodies daratumumab and elotuzumab, and the new-generation proteasome inhibitors carfilzomib and ixazomib. In addition, the new trend is to combine these drugs in order to deepen the response, with the aim of achieving long-term control of the disease [3].

Consequently, both the progression-free survival and the overall survival of MM patients have improved, not only for young patients but also for elderly ones [4]. On the other hand, these unprecedented results in the treatment of MM have raised concern about the high costs of the drugs and their affordability, which is compounded by several factors, such as the multidrug combinations, the new approach of continuous therapy and the prolonged survival of patients [5-10]. In spite of the importance of this problem, very few studies have been performed on a real-world approach to the care of patients, considering the total cost for patients instead of merely drug costs.

The aim of this study was to evaluate healthcare costs and outcome in a single-centre population of MM patients in an attempt to develop cost forecasts for this disease.

METHODS

In this retrospective, observational study, after local ethics committee approval and having obtained patients' written consent, data were retrieved from the hospital discharge records and medical charts of MM patients. For this study we considered a cohort of 855 patients with MM newly diagnosed in the period between 2002 and 2014 (under observation until 2015) at San Matteo Policlinico Hospital (Pavia, Italy). Of these, only 387 patients, who received at least one line of therapy and for whom direct healthcare costs were available were included in the study. The sample consisted of 223 patients treated with an autologous stem cell transplant (57.6% of the sample) and 164 ineligible for transplant (42.3% of the sample).

The diagnosis of symptomatic MM was made according to the 2003 International Myeloma Working Group guidelines [11]. Data regarding the patients' characteristics, therapies and survival were retrieved. Overall survival was measured from the onset of treatment until death from any cause or last follow-up. The Kaplan-Meier product limit method was used to estimate survival curves and the comparison of survival curves between groups of patients was tested via the log-rank test.

In the analysis we identified the dependent variable as the expenditure for patients, which included the costs of drugs, admission to emergency departments, hospital and intensive care units, laboratory and diagnostic tests and procedures. Costs were calculated from the diagnosis of MM until death, end of follow-up or end of the study. The costs of hospitalisation were calculated in euros based on diagnosis-related groups, obtaining the average cost per-patient-per-month (PPPM) according to homogenous groups of patients. Cost PPPM was calculated as the mean cost for the entire disease history of patients divided by the number of months of follow-up, while the cost PPPM of the first year was calculated as the mean cost relative to the first year of follow-up divided by twelve months.

Diagnoses and procedures were coded using the International Classification of Diseases 9th revision, Clinical Modification system (ICD-9-CM, 2007) and their costs, together with all the costs of outpatient services (physician visits, laboratory and radiology day hospital services) were calculated according to regional tariffs, while drug costs were those in the official price list.

We first performed descriptive statistics. The median and interquartile range were calculated for quantitative variables. Qualitative variables were described as absolute and relative percentages of each category. The CRAB variable was defined as the presence of at least one among hyperCalcaemia (calcaemia >11.5 mg/dl), Renal failure (creatinine >2 mg/ml), Anaemia (haemoglobin <10 g/dL) and Bone disease. Concerning response to the first line of therapy, a binary variable was generated on the basis of Very Good Partial Response (VGPR) [12], with patients categorized as having VGPR and better or less than a VGPR. International Staging System scores were also categorized into two groups: 1-2 vs 3 [13]. For extramedullary disease, a value of 1 was assigned if present and 0 if absent. Differences between two groups of patients (eligible for transplant vs not eligible for transplant) were tested by Fisher's exact test (for qualitative variables) and by the Mann-Whitney test for independent data (for quantitative variables).

The cost function showed a linear relationship between the total monthly cost for each patient, the patient's demographic and clinical characteristics (i.e. sex, age at the time of diagnosis, presence of extramedullary disease, presence of CRAB and response to the first line of therapy), the drugs administered and the procedures applied (i.e. doses of lenalidomide, bortezomib, chemotherapy drugs and corticosteroids, total number of lines of therapy,

number of accesses to emergency departments, and days of therapy and hospitalisation). The *'Year Trend'*, taking into account that patients were observed over a period of time, helps to evaluate the variation of costs across the years. The total healthcare expenditure per patient, used as the dependent variable in the cost regression models, was measured in euros (€).

Since some of the independent variables may be strongly correlated and may generate a problem of multicollinearity, each model was tested for multicollinearity with "Variance Inflation Factors (VIF)". The cost function was estimated through a multivariate Ordinary Least Squares (OLS) regression model which assumes a linear relationship between costs and their determinants and that healthcare costs are normally distributed [14]. It is well known, however, that healthcare costs are not normally distributed (i.e. they are skewed with an asymmetric distribution of errors) and so the OLS model may produce estimations with inaccurate standard errors and confidence intervals [14]. Although a potential solution to the problem of skewness in the residuals is to use a linear regression model for the log of healthcare costs [15], in the current study we chose to adopt a Generalized Linear Model (GLM) for the following reasons: it is estimated on the untransformed scale, so retransformation is not needed (differently from the log model) and predictions allow for heteroskedasticity through the choice of the distributional family [15-17]. The most commonly used link functions, which relate the conditional mean to the covariates, for healthcare costs are the identity – where covariates act additively on the mean, so that the interpretation of coefficients is the same as linear regression – and the log link – where covariates act multiplicatively on the mean [15, 18, 19]. Our modelling framework compared several combinations of families, which have the role of relating the variance function to the mean, and the link-function most commonly used in practice to model healthcare costs: Gamma-Identity, Gamma-Log, Gaussian-Identity, Gaussian-Log and iGaussian-Log. To balance the statistical fit of the model we used the Akaike Information Criterion (AIC) [20] and the Link-test to understand whether the 'link' used in the GLM is appropriate [21]. In the link test, the dependent variable was regressed on the predicted values and their squares. If the model is specified correctly, the squares of the predicted values have no power. The lower the AIC test is, the better the model.

All estimations were made using STATA 14.

RESULTS

Clinical data and healthcare costs were available for 387 of the 855 patients. Table 1 shows a comparison of the clinical and cost characteristics of the transplant-eligible patients with respect to those not eligible for transplantation. The median age was 57 years for transplant-eligible patients and 70 for not eligible patients (p<0.001). The median total cost per patient was around €28,500 for patients not eligible for transplantation and around €87,000 for the eligible patients (p<0.001). The median overall survival of the two groups (Figure 1), eligible or not for transplantation, was 10.1 and 4.6 years,

TABLE 1. Characteristics of patients.

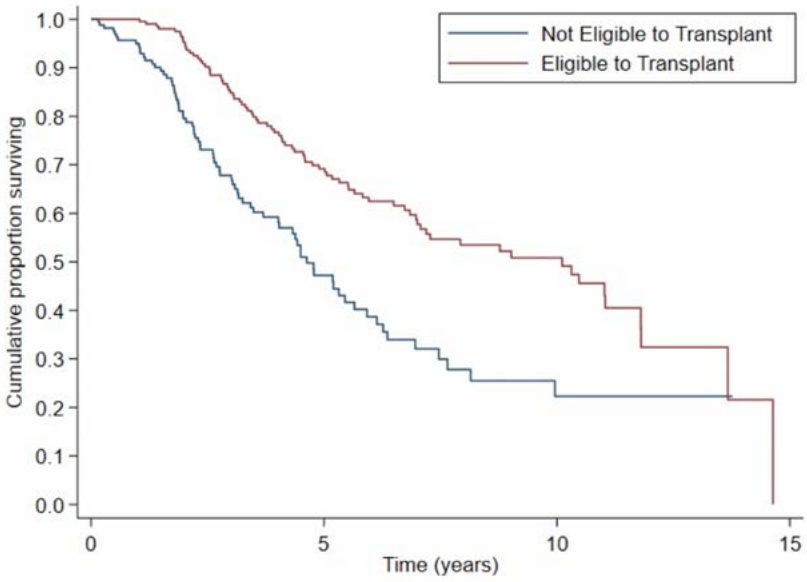
	TOTAL (387)	NOT ELIGIBLE FOR TRANSPLANT (164)	ELIGIBLE FOR TRANSPLANT (223)	P-VALUE
Age (years), median (IQR)	61 (28 – 87)	70 (30 – 87)	57 (28 – 69)	<0.001
Sex, n (%)				0.680
Male	209 (54 %)	91 (55%)	118 (53%)	
Female	209 (54 %)	91 (55%)	118 (53%)	
CRAB, n (%)				0.024
Absent	84 (22%)	45 (27%)	39 (17%)	
At least one present	303 (78%)	119 (73%)	184 (83%)	
Creatinine, n (%)				0.401
≤2 mg/ml	320/360 (89%)	137/157 (87%)	183/203 (90%)	
>2 mg/ml	40/360 (11%)	20/157 (13%)	20/203 (10%)	
ISS, n (%)				0.024
1-2	77/305 (25%)	26/138 (19%)	51/167 (34%)	
3	228/305 (75%)	112/138 (81%)	116/167 (69%)	

TABLE 1. Characteristics of patients.

	TOTAL (387)	NOT ELIGIBLE FOR TRANSPLANT (164)	ELIGIBLE FOR TRANSPLANT (223)	P-VALUE
EMD, n (%)				0.261
Absent	296/380 (78%)	122/163 (76%)	174/217 (80%)	
Present	84/380 (22%)	41/163 (25%)	43/217 (20%)	
Response to first line of therapy, n (%)				<0.001
<VGPR	188 (49%)	118 (72%)	70 (31%)	
≥VGPR	199 (51%)	46 (28%)	153 (69%)	
Total number of lines of therapy, n (%)				0.133
≤3	322 (83%)	142 (87%)	180 (81%)	
>3	65 (17%)	22 (13%)	43 (19%)	
Number of Emergency Department accesses, median (IQR)	0 (0-6)	0 (0-15)	0 (0-4)	0.353
Duration of hospitalization (days), median (IQR)	30 (13-69)	11 (0-47)	40 (25-89)	<0.001
Total number of days of therapy, median (IQR)	422 (268-683)	364 (188-653)	459 (289-719)	<0.001
Total cost per patient (euros), median (IQR)	62,176	28,449	86,979	<0.001
Median overall survival (years)	6.8	4.6	10.1	<0.001

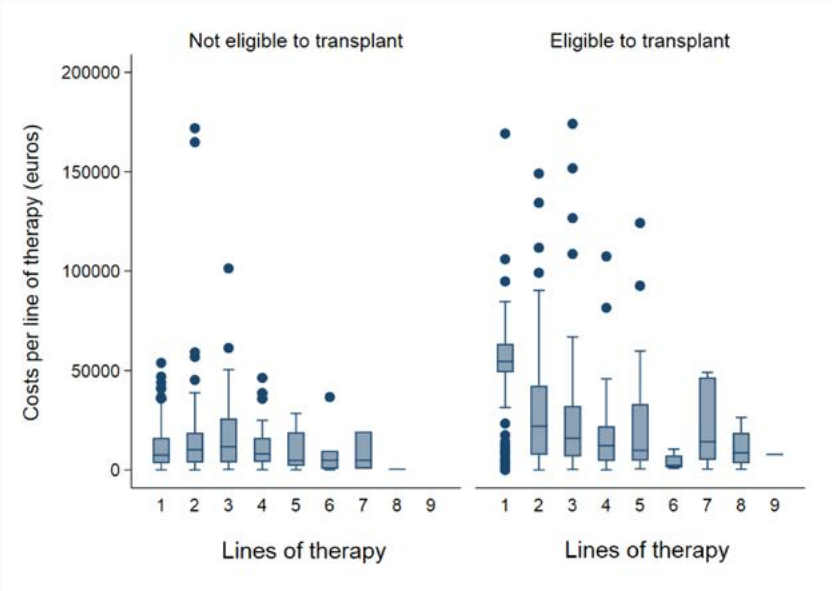
Note: CRAB: Calcium-Renal failure-Anaemia-Bone lesions; ISS International Staging System; EMD: Extramedullary Disease; VGPR: Very Good Partial Response, IQR: interquartile range.

FIGURE 1. Survival curves of patients eligible to transplant and patients not eligible to transplant.



respectively. So, on average, the per year expenditure was €8,614 for patients eligible for transplantation and €6,195 for those not eligible. No significant differences were observed between the two groups apart from a slightly higher incidence of advanced International Staging System stages in patients not eligible for transplantation

FIGURE 2. Survival curves of patients eligible to transplant and patients not eligible to transplant.



than in those eligible (81% vs 69%; p=0.024), a higher percentage of CRAB in transplant-eligible patients (83% vs 73%; p=0.024) and a higher percentage of good responses in transplant-eligible patients (≥VGPR; 69% vs 28%; p<0.001).

The median duration of hospitalisation was 11 days for patients not eligible for transplantation and 40 for the eligible ones (p<0.001), due to the duration of hospitalisation for the transplant. The median total number of days of therapy was 364 days for patients who were not candidates for transplantation and 459 days for transplant-eligible patients (p<0.001).

Although, using the VIF test, the number of line of therapies was strongly correlated with bortezomib, lenalidomide and chemotherapy dosages, due to its important role, this variable was not discarded from the analysis. By contrast, since the number of days of hospitalisation and the duration of therapy were found to be strongly correlated with many other variables, with a correlation of more than 40% in many cases, these two variables were not considered during the model estimation. Extramedullary disease was not included in the model because of missing values and the low frequency at onset.

Figure 2 shows the trend of costs over the years of follow-up. For patients ineligible for transplantation, there was not a significant trend (Kendall's score=1547 with p=0.439), whereas for transplant-eligible patients there was a decreasing trend with increasing line of therapy (Kendall's score= -40295 with p<0.001).

Table 2 presents the results for the GLM regression model with different combinations of families and link-functions. For the sake of brevity, although all combinations were tested (i.e. Gamma-Identity, Gamma-Log, Gaussian-Identity, Gaussian-Log and iGaussian-Log), the only two models presented are the Gaussian-Identity, which has the same meaning as the benchmark OLS model, and the model that best fits the data (Gamma-Identity GLM). In the Gamma family and Identity link-function, the AIC was among the lowest and, especially, the link-test was not significant, demonstrating that the model was correctly specified. As shown in Table 2, gender does not affect the costs while age is inversely correlated with costs, that is, as age increases, costs decrease.

When this model was applied in the two groups through the Gamma-Identity model, one year more implies a reduction of €627 of costs for transplant-eligible patients and of €262 for those not eligible.

As expected, bortezomib and lenalidomide represented not only two of the most influential variables in total expenditure per patient, but they were also, in all cases, statistically significant. Applying Gamma-Identity and/or Gaussian-Identity models, in which the link-test was not significant, yielded the same results, confirming the role of these drugs in determining total expenditure.

In the case of bortezomib the marginal increment per dose was €754 in transplant-eligible patients and €696 in patients not eligible for transplantation according to the Gamma-Identity GLM. In the case of lenalidomide, an additional month of therapy with this drug increased costs by €5257 in patients eligible for transplantation and by €4780 in those not eligible. The CRAB variable was not significant in any model. The incremental cost per patient in relation to the number of lines administered showed wide variability. The impact of one line more of treatment varied between €9272 for transplant-eligible patients and €3568 for not eligible ones. The Gamma-Log confirmed the results obtained

TABLE 2. Comparison of results between Gamma-Identity and Gaussian-Identity (OLS model).

A.	GAMMA – IDENTITY					
	Autologous Transplant			Patients Not Eligible for Transplant		
	Coefficient	Std.Err.		Coefficient	Std.Err.	
Age	-627.359	257.551	*	-262.081	56.833	***
Sex	-3586.071	3288.607		671.990	1659.165	
Bortezomib	754.026	256.453	***	695.719	56.890	***
Lenalidomide	5257.386	621.952	***	4780.280	449.6937	***
Chemotherapy	715.259	465.065		245.914	80.744	**
CRAB	993.757	465.065		2601.540	1825.310	
Total n. of therapy lines	9271.942	3208.261	**	3568.612	1089.514	**
Year Trend	1833.387	659.494	**	-55.499	176.653	
N. of accesses to ED	197.975	173.076		232.376	56.792	***
Response to first line of therapy	-5284.918	3780.194		510.299	1447.036	
AIC	24.554			21.864		
LINK-TEST	0.588			0.576		

B.	GAUSSIAN – IDENTITY (OLS MODEL)					
	Autologous Transplant			Patients Not Eligible for Transplant		
	Coefficient	Std.Err.		Coefficient	Std.Err.	
Age	-1200.133	377.299	**	-545.322	112.577	***
Sex	-2833.023	4781.363		-140.782	1678.090	
Bortezomib	1016.124	256.190	***	697.892	59.616	***
Lenalidomide	6061.276	446.409	***	5678.452	219.281	***
Chemotherapy	269.587	321.821		152.243	119.593	
CRAB	1030.824	7121.852		480.071	1655.828	
Total n. of therapy lines	5839.690	2581.321	*	2455.454	1078.243	*
Year trend	1472.629	554.707	**	-730.104	275.637	**
N. of accesses to ED	159.816	178.692		164.422	65.706	**
Response to first line of therapy	-6552.568	5480.999		1735.965	2003.488	
AIC	23.654			21.505		
LINK-TEST	0.550			0.630		

Note: Std. Err.M standard error; CRAB: Calcium, Renal failure, Anaemia, Bone lesions; ED: Emergency Department; AIC; Aikake Information Criterion . *** indicates p<0.001, ** indicates p<0.05 and * indicates p<0.1.

with the Gamma-Identity GLM and the Gaussian-Log those obtained with the OLS model. The strong impact of this variable can be interpreted as being due to the fact that administering more lines of therapy implies higher dosages, more hospitalisation and greater costs for the structure.

In most of the models, only patients undergoing autologous transplantation had a significant coefficient for the Year Trend variable. The overall conclusion might be only at a general level: the marginal costs of patients who are eligible for transplantation increase over time due to the hospitalisation costs and expenditure for the transplant procedure itself. Since the number of emergency accesses observed in both groups of patients was low, the impact of this variable on total cost per patient was low in all the models (i.e. nearly €200 of marginal increment). Response to the first line of therapy was not significant in any of the models investigated.

DISCUSSION

The aim of the present study was to analyse the costs related to patients affected by MM, highlighting the weights of the cost determinants. The medical records of 855 MM patients treated at the Policlinico San Matteo from 2002 to 2014 were reviewed. The final sample consisted overall of 387 subjects who were then divided into those eligible or not eligible for transplantation. No significant differences emerged between the two groups. Only the possibility of obtaining a good response (≥VGPR), as expected, was higher in patients who underwent an autologous transplant (p=0.001).

The particularity of this study with respect to the literature in the field of sustainability in myeloma patients is that, differently from almost all the other studies published [10, 22-24], we had the possibility of matching administrative and clinical data, registered at onset, in order to identify any variable that could have a weight in the costs. The idea regarding clinical aspects was that an aggressive presentation could negatively influence the expenditure or, on the contrary, that its negative impact could be overcome by the efficiency of novel agents. The second novelty of this work [22] was that the costs were analysed through the application of a more complex model, the GLM, which has been shown to be the most appropriate for economic analyses in the field of healthcare [15-17].

Chemotherapy did not play a key role probably because it is usually adopted in very advanced phases of disease and for short periods. The CRAB variable was not significant in any model since the high efficacy of new drugs reduces the negative impact of a greater disease burden by shortening the period of being symptomatic. Likewise, the response to the first line of therapy was not significant in any of the models investigated. This was probably because although new drugs are more effective in producing responses of good quality, prolonging the good control of disease and symptoms, this advantage is not able to outweigh the economic burden of the novel agents. This is in line with previous studies on the economic burden of transplantation in MM. For example, Corso *et al.* [5] demonstrated that autologous transplantation provided a significant prolongation of survival compared to that obtained with conventional chemotherapy but that the costs for patients undergoing this procedure remained very high even with a long-term analysis, probably because the advantages were not able to outweigh the cost of the procedure.

The total cost per patient was, on average, around €28,500 for patients not eligible for transplantation and around €87,000 for patients who were eligible for this procedure. This is coherent with literature. Corso *et al.* [6] investigated costs for patients in the Region of Lombardy who received a diagnosis of MM in the period between 2003 and 2009. They found that people treated with stem cell transplantation incurred average costs of €125,202, while the average expenditure for subjects treated with chemotherapy was €38,443. In the period between 2001 and 2006, before the introduction of bortezomib and lenalidomide, De Portu *et al.* [23] conducted a retrospective, longitudinal study on the incidence of and costs for MM in two cohorts of residents (≤70 years and >70 years old) in Regions of north-eastern Italy. The total estimated costs per patient were €76,630 and €22,892€ for younger and older patients, respectively [23]. This means that, as expected, the expenditure for younger patients was significantly higher than that for older ones because it included transplant costs. However, when we matched total costs for patients eligible or not with their overall survival, which was 10.1 and 4.6 years, respectively, the per year expenditure was around €8,614 and €6,195, respectively, and thus not very different. This is probably because older patients, like younger ones, are being ever more frequently treated with novel agents, increasing the total costs.

The analysis of this cohort through the GLM identified four determinants useful for building a model to forecast expenditure for MM patients: age, bortezomib use, lenalidomide use, and number of lines of therapy. Age had a positive influence on the burden of expenditure. The explanation of this observation is different in the two groups: in younger patients the observed reduction of costs along the years is related to the impact of the cost of transplantation in the first year, whereas for the patients not eligible for transplantation the lower costs are related to the fact that, not benefiting from transplantation, these patients tend to be treated for shorter periods than younger patients. In line with previous literature, bortezomib and lenalidomide were shown to be the most influential variables in total expenditure per patient [22, 24]. Differently from Teitelbaum *et al.* [22], who focused only on the claim-based burden of new drugs, our study considered direct costs from the database of a single hospital.

The strong impact of the total number of lines of therapy can be attributed to the fact that administering more lines implies higher dosages, more days of hospitalisation and greater costs for the structure. The overall conclusion relative to the *Year Trend* might be only at a general level: the marginal costs for patients who are eligible for transplantation increase over time because of hospitalisation costs and costs of the transplant procedure itself. The limitation of this work, as in the case of that by Teitelbaum *et al.* [22], is the retrospective approach which results in problems of generalisation and missing values with loss of information. This research could progess with the development of a predictive model based on future forecasts.

In conclusion, the impact of novel agents on the total expenditure for patients affected by onco-haematological diseases has been widely demonstrated. However, it is

probably time to change our approach to the problem of sustainability, moving from a descriptive approach to a predictive one. This means not just observing how much we have spent or determineing the cost-effectiveness of adopting new strategies in haematology but deciding how much we are prepared to spend to improve the outcome of our patients andtrying to forecast the expenditure in order to allocate the resources better. To the best of our knowledge, this is the first study to tackle the problem in this way. Using a GLM, we identified four determinants in our cohort, described above, which were useful in building a model to forecast expenditure for MM patients. Although, the analysis was performed in a particular setting in a single hospital, the model could be applied to any scenario, enabling a prediction of the expenditure for a particular population of patients.

Conflict of Interest

None of the authors, except Prof. Luca Arcaini, has anything to disclose regarding financial, professional or personal relationships which could potentially bias this work. Prof. Arcaini reports that he receives personal fees from Celgene, Janssen-Cilag, and Roche, and grants and personal fees from Gilead Sciences and Verastem, not related to the submitted work.

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