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A Tentative Staging of Multiple Myeloma by Utilizing Respective Coefficients of Prognostic Factors

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Abstract

Introduction: Multiple myeloma is a heterogeneous disease with different survival times among patients. Accurate prediction of prognosis in multiple myeloma is essential, as patients with a shorter survival time may require early bone marrow transplantation (BMT) and more advanced chemotherapy as a part of their first-line treatment. In the present study, a parameter, depicted by gamma (γ) symbol, was utilized to categorize patients into different stages. Gamma value is equal to the summation of each prognostic factor multiplied by its corresponding beta coefficient. This parameter has been previously studied for the staging of some malignancies, such as "Nottingham Prognostic Index" for breast cancer and "Prognostic Score" for parotid carcinoma.

Methods: One hundred forty-three cases were randomly divided into two groups. Beta coefficients for prognostic factors, including creatinine, calcium, and albumin, were obtained from multivariate Cox analysis in the first group. In this group, a staging system based on patients' gamma parameters was defined followed by the evaluation of the accuracy of this staging system in the second group.

Results: The staging system that developed from the first group was suitable for the prediction of outcomes in the second group. The patients of the second group were divided into approximately equal numbers in each stage comprising 29, 24, and 18 cases in stage 1, 2, and 3, respectively. In this group, the median overall survival (OS) values for patients in each stage were 92, 57, and 22 months, respectively, with log-rank = 0.002.

Conclusions: The proposed method demonstrated promising results for myeloma prognostication. The authors believe this approach would increase the strength and validity of staging of multiple myeloma.

INTRODUCTION

Multiple myeloma (MM) is considered to be the second most common hematologic cancer [1]. Different staging systems have been proposed for risk stratification of MM. However, current staging systems have limitations and therefore are in the process of developing. A suitable staging system should consist of a reliable method of prognosis prediction based on widely obtained, reproducible parameters, and segregate patients into roughly equal groups [2]. The proposed staging method of this study fulfills these criteria.

One major problem in current staging systems is the different number of cases in each stage, especially in revised international staging system (R-ISS) [3, 4]. Furthermore, main prognostic factors in MM consist of continuous variables that are generally grouped as a single prognostic parameter. For instance, in a group of cases where albumin concentrations are less than 3.5 g/dL, different albumin values that are classified under the same group, i.e., albumin < 3.5 g/dL group may be related to different prognosis.

According to Bradburn et al. [5], one simple and possibly underused quantity for a given risk group is gamma value that is derived from the proportional

Cox model.

$$\gamma = B1X1 + B2X2 + \ldots.. + BpXp \quad (1)$$

Gamma in Equation 1 is equal to the sum of prognostic parameters multiplied by their beta coefficients (B). Beta coefficient is a simple parameter that is reported in multivariate Cox analysis.

The present article tentatively assessed a different approach to prognostic factors that could improve myeloma staging systems. In this study, the given cases were randomly divided into two groups. The staging was defined based on gamma parameters derived from the first group of cases. The defined stage was then applied to the second group to evaluate its ability for risk stratification. This approach has been utilized for the staging of some malignancies, such as "Nottingham Prognostic Index" [6, 7, 8] for breast cancer and "Prognostic Score" [9, 10] for parotid carcinoma. The present study examined this staging method in our patients with multiple myeloma.

METHODS

The present study included 143 consecutive cases that were diagnosed and treated as MM in 501 AJA hospital during 1998 until 2016 and had available hemoglobin, platelet, serum albumin, calcium, and creatinine levels. These parameters had prognostic and diagnostic significance in MM [11, 12, 13, 14, and 15]. In multivariate Cox analysis of these five parameters, corrected calcium (mg/dL), serum albumin (g/dL), and creatinine (mg/dL) significantly influenced the overall survival (OS) in all cases and therefore were selected for staging. The OS was defined as the time elapsed from the start of the first-line treatment to death from any cause. It is worth mentioning that creatinine (DSS [11], MWJ [12]), corrected serum calcium (DSS [11], MWJ [12]), and serum albumin (ISS [13], R-ISS [3]) have previously been used in staging systems.

According to age (>65 years) and gender, patients were randomly divided into two groups. Group one included 72 cases, of which 21, 23, 18, and ten patients were males younger than 65 years, males older than 65 years, females younger than 65 years, and females older than 65, respectively. Group two consisted of 71 cases including 21, 22, 18, and 10 cases in each of the above subgroups, respectively. In the first group, beta coefficients of creatinine, calcium, and albumin in multivariate Cox analysis were measured, and as explained later, patients' gamma values were calculated. The patients in the first group were categorized into three stages by considering the obtained values of gamma. The accuracy of this staging for prognosis prediction was then tested in the second group by the Kaplan–Meier analysis.

RESULTS

In group one, multivariate Cox analysis of corrected calcium, creatinine, and albumin was performed. The beta coefficients for corrected calcium, creatinine, and serum albumin were 0.162, 0.197, and − 0.364, respectively (Table 1). Gamma value based on these parameters was defined as follows:

$$\text{Gamma} = (\text{corrected\_calcium} \times 0.162) + (\text{creatinine} \times 0.197) + (\text{albumin} \times -0.364). \quad (2)$$

Gamma values for group one were calculated based on Equation 2 for each patient. Three subgroups were defined as stage 1, 2, and 3 by considering percentile 33, 66, and 100% in gamma values in group one (Table 2). This resulted in a uniform distribution of 24 patients in each subgroup.

Equation 2, which was derived from the first group, was then applied for calculating gamma values for the second group. The second group was categorized into three stages in the same manner as group one.

In the first group, the Kaplan–Meier analysis showed significant differences between the three stages, with log-rank < 0.001 (Figure. 1a). The median OS values were 88, 45, and ten months for stage 1, 2, and 3, respectively.

Table 1: Univariate and Multivariate Cox Analysis of Prognostic Factors in the First Group.

Parameters	Univariate Analysis			Multivariate Analysis		
	Specific Coefficient (B)	Confidence Interval 95%	P Value	Specific Coefficient (B)	Confidence Interval 95%	P Value
Creatinine	0.196	0.087–0.305	<0.001	0.197	0.080–0.314	0.001
Corrected calcium	0.216	0.072–0.360	0.003	0.162	0.006–0.319	0.042
Albumin	–0.418	(–0.826)-(0.010)	0.045	–0.364	(–0.814)-(+0.087)	0.114

Table 2: Staging System Derived from the Data of the First Group

Stages	Median OS (Number of Cases) in each Stage of the First Group	Median OS (Number of Cases) in each Stage of the Second Group
Stage 1: Gamma Values Less than 0.58	88 Months (24)	92 Months (29)
Stage 2: Gamma Values Between 0.58 to	45 Months (24)	57 Months (24)
Stage 3: Gamma Values More than 0.94	10 Months (24)	22 Months (18)

Gamma Value =Corrected Calcium (mg/dL)*0.162+Creatinine (mg/dL) *0.197+Albumin (g/dL) *–0.364

DISCUSSION

The proposed method has following advantages over the current multiple myeloma staging systems:

This approach utilizes prognostic factors as well as their corresponding weights to construct an index for staging. According to Simon and Altman [16], categorizing patients by prognostic index is a preferable method [17].

It accommodates continuous variables as well as discrete ones. Current staging systems define cut-offs for continuous prognostic factors. Therefore, all variables in a certain range will be classified under one group, despite the fact that there could be huge differences between the prognoses for values in that range. In contrast to these staging systems, the proposed method does not consider cut-offs; it rather takes into account the effect of continuity of each factor by considering it in gamma equation. As main prognostic parameters in MM are continuous, the approach presented in the current study is reliable.

This approach categorizes the patients into groups with an equal number of cases in comparison with current methods, particularly R-ISS [3, 4].

While independent prognostic factors, such as albumin, B2M, LDH, and cytogenetic parameters, are well-known, the existing approaches for myeloma staging should be developed to propose a precise staging system that can predict prognosis as well as segregate cases into roughly equal groups. Although the proposed approach would reduce simplicity of staging, it will enhance the strength of staging and also eliminate the above-mentioned limitations. Staging by gamma value is strengthened by rigorous statistical science to optimize prognostication by a group of risk factors [5]. This approach has been utilized previously for other cancers, such as breast cancer [6, 7, 8] and parotid carcinoma [9, 10]. Moreover, the current approach displayed promising results for myeloma staging in the tentative study performed. The authors would, therefore, like to invite other research groups to evaluate this approach as a possible method for developing myeloma staging systems.

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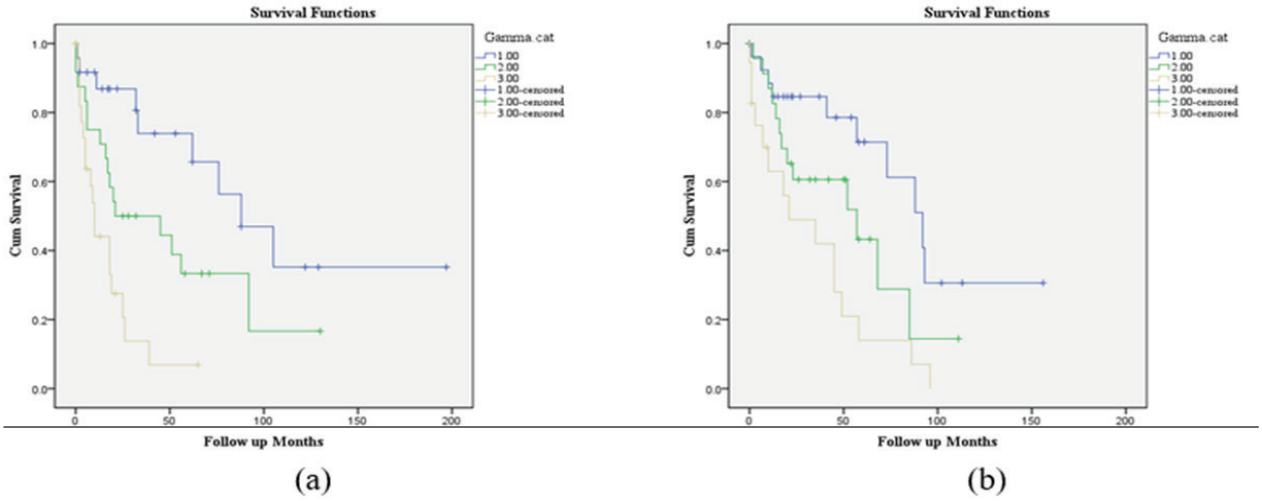

Figure 1: a) Staging MM Cases by Gamma Values in the First Group of Cases. b) Staging MM Cases by Gamma Values (Derived from the First Group) in the Second Group of Cases.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ETHICS APPROVAL

Not applicable.

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