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Short Research Communication

Multiple Myeloma Index for Risk of Infection

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Abstract

Based on our earlier research into the main characteristics and risk factors for infections in hospitalized patients with multiple myeloma, we created the numerical Multiple Myeloma Index for Risk of Infection (MMIRI) to predict infection in myeloma patients. The included factors that could influence the pathogenesis and incidence of infections were sex, performance status, Durie Salmon stage of disease, International Staging System, serum creatinine level, immune paresis, neutropenia, serum ferritin level, the presence of any catheters, disease duration, stable/progressive disease, and type of therapy. For each of these parameters, the strength of association with infection was statistically estimated and specific number of points was assigned to each of these parameters, proportional to the strength of the association. When designing the MMIRI, we included only those parameters that we determined were pathophysiologically associated with the infection. After further statistical analysis, we identified an optimal cutoff score of 6 or above as indicating a significant risk for infection, with a sensitivity of 93.2% and specificity of 80.2%. The scoring system in the retrospective receiver operating characteristic analysis showed an area under the curve of 0.918. The potential value of the MMIRI is the possibility of identifying those patients who would benefit from the prophylactic administration of antibiotics and other anti-infective measures while minimizing the contribution to antibiotic resistance related to the overuse of these drugs. As far as we know, this index represents the first attempt to create such an instrument for predicting the occurrence of infections in myeloma patients.

Introduction

The intrinsic immune dysfunction in combination with therapy-related immunosuppression leads to an increased risk for infections, which is a hallmark of multiple myeloma (MM) and major cause of mortality [1-5]. Furthermore, the infection itself can pathogenetically contribute to the progression of MM through different mechanisms, such as robust production of promyeloma cytokines (e.g., interleukin-6) and activation of Toll-like receptors on malignant plasma cells [6-10]. Today, with the advent of several new and effective antimyeloma drugs and increased overall survival, preventing death from infections becomes paramount. We tried to create the numerical Multiple Myeloma Index for Risk of Infection (MMIRI) to predict infection in myeloma patients and help identify patients who have a higher risk for developing infections.

Materials and Methods

To develop the index, we used our earlier research into the main characteristics and risk factors for infections in hospitalized patients with MM [11]: we took retrospective data from hospital medical documentation for 240 cases of hospitalized patients with MM (120 males and 120 females; average age of 69, range of 41-89 years) who were diagnosed or treated in our Department from January 2008 to December 2010. Because the majority of patients were hospitalized more than once, the total number of our

cases was larger than the number of patients included in this study (37 males and 35 females, respectively). Only patients who were not treated with autologous or allogeneic hematopoietic stem cell transplant were included. The diagnosis was established according to International Myeloma Working Group criteria [12]. The great majority of patients in this study had IgG, IgA, or a light-chain myeloma; however, one patient with IgD and one with nonsecretory myeloma were also included [11]. Our patients were treated fairly uniformly at the time of this study: vincristine, doxorubicin, and dexamethasone and oral melphalan and prednisone regimens were mostly used as induction therapy (according to patient age and eligibility for high-dose therapy), with thalidomide-based protocols as second-line therapy and bortezomib-based protocols as third- or next-line therapy. In some patients, monotherapy with dexamethasone was used as a front-line therapy, as well as for postinduction [11]. The study was approved by the Medical School of Rijeka Ethics Committee.

The criteria for infection used in our study were increased body temperature above the normal range (37 °C) or isolation of a microbial agent in patients who also had concomitant clinical symptoms and/or humoral signs of infection (leukocytosis, neutrophilia, marked "left shift," or increased C-reactive protein in comparison with a baseline value) [11]. The included factors that could influence the pathogenesis and incidence of infections were sex, performance status [13], Durie Salmon stage of disease [14], International Staging System [15], serum creatinine level (normal or increased), immune paresis defined qualitatively (decreased serum concentration of any polyclonal Ig class), neutropenia (defined as blood neutrophil count of $\leq 2\times10^9$/L), serum ferritin level (normal; moderately increased; extremely increased), the presence of any catheters, disease duration, stable/progressive disease, and type of therapy. The number of cases, age, sex, and duration of disease for MM patients with and without infections are presented in Table 1. The characteristics of tested parameters are shown in Table 2 [11].

For each of these parameters, the strength of association with infection was statistically estimated. When designing the MMIRI, we included only those parameters that we determined were pathophysiologically associated with the infection. A specific number of points was assigned to each of these parameters, proportional to the strength of the statistical association. Statistical association between nominal variables was measured by Cramer's V coefficient, whereby a minimum coefficient value of 0.15 was required. For the scoring system, the coefficient values were divided by a minimum value and rounded to the nearest integer. The cutoff value of the scoring system was determined by optimization of sensitivity and specificity based on the Youden index together with classical receiver operating characteristic analysis.

Table 1. Main cases characteristics

	With infections	Without infections	Total
Number of cases	43	197	240
Age, median (range)	65 (41–89)	69 (41–86)	69 (41–89)
Sex (male/female), n	9/34	111/86	120/120
Disease duration (months), median (range)	26 (1–121)	7 (1–150)	8 (1–150)

Table 2. Characteristics of tested parameters

Tested Parameters		Number of Cases	Group without Infections	Group with Infections
Sex	Male	120	111	9
	Female	120	86	34
ECOG performance status	0	16	16	0
	1	88	85	3
	2	70	60	10
	3	45	30	15
	4	20	5	15
Durie-Salmon stage of disease	1A	6	5	1
	2A	51	47	4
	2B	1	0	1
	3A	106	89	17
	3B	59	40	19
International Staging System	1	54	44	10
	2	57	50	7
	3	98	81	17
Serum creatinine level	≤100 mmol/L (f); ≤120 mmol/L (m) (normal value)	133	117	16
	>100≤175 mmol/L (f); >120≤175 mmol/L (m)	52	41	11
	>175 mmol/l (f, m)	49	35	14
Immuneparesis	Yes	184	148	36
	No	46	40	6
	No	160	138	22
Neutropenia	1.01-2x10^9/L	55	44	11
	0.51-1x10^9/L	14	8	6
	<0.5x10^9/L	3	1	2
Serum ferritin level	≤120 µg/L (f); ≤300 µg/L (m)	51	46	5
	>120≤240 µg/L (f); > 300≤600 µg/L (m)	19	16	3
	>240 µg/L (f); >600 µg/L (m)	32	18	14
Types of therapy	Without therapy	39	32	7
	VAD	76	71	5
	MP	13	11	2
	Thalidomide-based	20	17	3
	Dexamethasone	55	48	7
	Bortezomib-based	28	14	14
	Others	5	1	4
Presence of any catheters	Without catheters	190	179	11
	UC	32	22	10
	CVC	2	2	0
	UC, CVC, ITC	2	0	2
	CVC, ITC	1	1	0
	UC, CVC	8	0	8

f: female, m: male; VAD: vincristine, doxorubicin, dexamethasone, MP: oral melphalan and prednisone, UC: urinary catheter, CVC: central venous catheter, ITC: intrathoracic catheter

Results

We provide the relevant parameters associated with infections in the statistical analysis and the corresponding number of points assigned in the MMIRI in Table 3. Some other parameters, such as immune paresis and the International Staging System, showed no association with infections, and the parameters of sex and type of therapy were excluded from further analysis based on our determination that they were not useful. With these adjustments, we identified an optimal cutoff score of 6 or above as indicating a significant risk for infection, with a sensitivity of 93.2% and specificity of 80.2%. The scoring system in the retrospective receiver operating characteristic analysis showed an area under the curve of 0.918 ($p<0.0001$; Figure 1).

Table 3. Parameters associated with infections included in the MMIRI point system with corresponding points assigned for each parameter

Parameter	Cramer V coefficient	Points
Longer duration of disease (>8 months)	0.2326	2
Durie Salmon Clinical Stage 3B	0.1975	1
ECOG0 and 1	-0.2935	-2
ECOG2	-0.0671	0
ECOG3	0.1862	1
ECOG4	0.4416	3
Presence of catheter	0.6539	5
Elevated creatinine value	0.1545	1
Moderately elevated ferritin value: >120 to ≤240 µg/L (f) >300 to ≤600 µg/L (m)	0.3012	2
Extremely elevated ferritin value: >240 µg/L (f) >600 µg/L (m)	0.3834	3
Neutropenia	0.1418	1
Progressive disease	0.3206	2

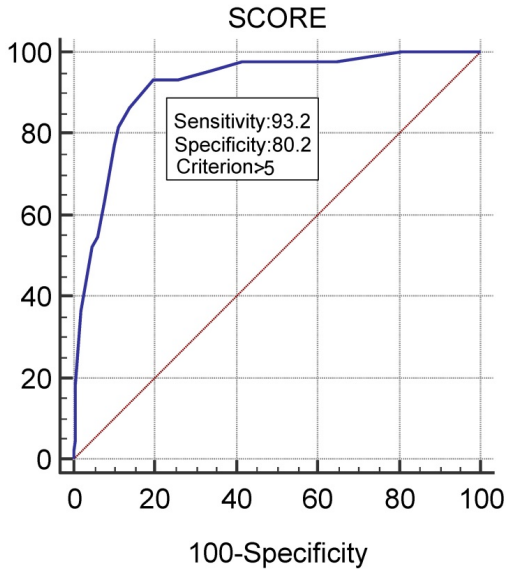

Figure 1. Testing of MMIRI by determining its sensitivity and specificity

Discussion

The proposed index was created based on retrospective data from our specific hospital environment. As noted, the parameter of sex was excluded from further analysis; based on our findings, its association with infections in our sample was indirect because of its link with the other infection-relevant factors already incorporated into the MMIRI (e.g., the women included in our research more often had a certain kind of catheter). The parameter of type of therapy was also excluded because some regimens used at the time of our study are now obsolete, and the type and sequence of drugs and regimens used today are somewhat different. So far, it is well known that some therapies may be associated with the occurrence of infections (e.g. herpes zoster in patients treated with proteasome inhibitors or high-dose dexamethasone, for which effective antiviral prophylaxis is mandatory). Some recent papers show a possible association of some novel drugs with infection [16-25]. Thus, a possible causative link between certain drugs and infection occurrence must be investigated in further clinical studies, and the results can be incorporated into a subsequent modification of the proposed index.

Because transplanted patients were excluded, this index can be applied only to those patients who are not in the process of hematopoietic stem cell transplant or just post transplantation. Nevertheless, we believe that this index has great potential to help identify patients who have a higher risk for developing infections and to improve outcomes for myeloma patients. According to the present results, the patients with score of 6 or above are candidates for mandatory antimicrobial prophylaxis, which is the main message of this research. MMIRI and the total score can facilitate decision making about the timing of antimicrobial prophylaxis and other anti-infective measures (e.g., immunoglobulin, granulocyte growth factors). This index was created based on retrospective data, and our next step is to test it prospectively with a larger group of patients treated with currently used anti-myeloma drugs and regimens.

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Competing Interests

The authors have declared that no competing interest exists.

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