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ORIGINAL PAPER

Short or Long Survival in Multiple Myeloma. A Simple Method for Determining the Prognosis

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Abstract Finding prognostic factors in multiple myeloma is a real challenge. Several attempts might be found in the literature for that purpose but the results are not satisfactory. Therefore, in the current retorpective study authors analyzed the potential prognostic value of some laboratory data in 104 patients with multiple myeloma. They found the albumin and M-component ratio being lower than 1 and the initial WBC $<4{,}5\times10^9$/l correlated strongly with poor prognosis. In addition the low albumin level was not related to albuminuria and that the low WBC was not linked to bone marrow infiltration rate or to antineutrophil antibody formation. On the basis of their experiences authors created an AMWBC score containing A/M and WBC at diagnosis found to be in good correlation to prognosis. Further studies involving more patients are needed to verify the real prognostic value of AMWBC score in multiple myeloma treated with new targeted therapies.

Keywords Prognostic factors · Multiple myeloma · AMWBC score

Introduction

The prognosis of a disease is determined by the disease characteristics and the therapy applied. Multiple myeloma (MM) is still not a curable disease. The melphalan and prednisolone (MP) therapy induces a 3-year median survival and the combination chemotherapies such as VAD, VCMP and M2 protocols lead to better response but have no survival benefit. The autologous stem cell transplantation therapy (ASCT) achieved a 5-year survival rate of 50% [1]. There is a significant variation in the survival of patients with myeloma as approximately 3% of patients live longer than 10 years, and 50% of patients pass away in the first 2 years from diagnosis [2]. Number of prognostic factors have been identified as having importance in the pretreatment evaluation of patients with MM. The Durie-Salmon staging system (DSS) for multiple myeloma has proven to be an effective system of patients' stratification for clinical trial research [3]. However, some of the criteria are not applicable in the general, everyday routine work, like the plasma cell labeling index (PCLI) [4]. Authors assumed that a staging scheme based on common laboratory measurements could provide a simple alternative to DSS.

Methods

In this retrospective study records of all 114 consecutive patients in whom multiple myeloma was diagnosed at Semmelweis University 3rd Department of Internal Medicine from 1981 to 1996 were reviewed. Among them104 patients had the first initial data available for analysis. Male and female ratio was 62/42, mean age was 63 years (range: 36–90 years). The isotype distribution was as follows IgG: 67, IgA: 28, IgM: 3 and light chain myeloma: 6. The therapy for MM patients mainly consisted of the combination of melphalan (M) and prednisone (P) with or without cyclophosphamide (C) and vincristine (V), carmustine and adriamycin, like in the MP, VMCP, M2 and the VAD protocols. Routine laboratory

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checkup included urine and serum protein electrophoresis studies and total blood counts. Karyotype analysis was not available in all cases therefore these data were not sufficient for statistical analysis.

The plasma cell infiltration rate was determined on the basis of bone marrow aspiration cytology and/or cristal bone biopsy specimen analysis. The differential count of the aspirate was based on the calculation of a minimum of 1,000 nucleated cells. Student's T-test was used for analyzing significance of differences between groups of patients selected according to different degree of bone marrow infiltration rate, initial WBC, immunoglobulin isotype and survival time, the level of serum albumin and urin albumin and stadium according to Durie and Salmon staging system [3]. The correlation was computed through minimum sum of squares method, significance was tested with F-test. Based on A/M and WBC parameters at diagnosis a so-called AMWBC score has been introduced and correlated to survival. Explanation for the missing seven patients (114−7=97) shown on Table 2: 6 of them were light chain myeloma and 1 had been lost from follow up.

The determination of anti-neutrophil antibodies by an ELISA method took place in 30 patients presenting with low WBC [5].

Results

Our results show that those patients who had Albumin and M-proteint (A/M) ratio below 1 at diagnosis lived significantly (p=0,00048) shorter (mean: 1,5 years) in comparison to those having A/M above 1 (mean: 3 years) (Fig. 1). The low albumin level was not at all the consequence of albumin loss in the urine as it was confirmed by the determination of 48 patients' urine albumin level in a 24 h collected sample (Fig. 2).

According to the initial WBC- estimating the cutoff value at $4{,}5\times10^9$/l- patients presented with WBC below $4{,}5\times10^9$/l lived

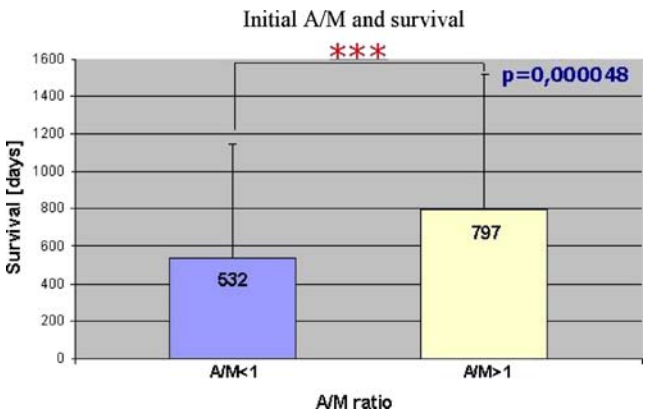


Fig. 1 Initial A/M and survival

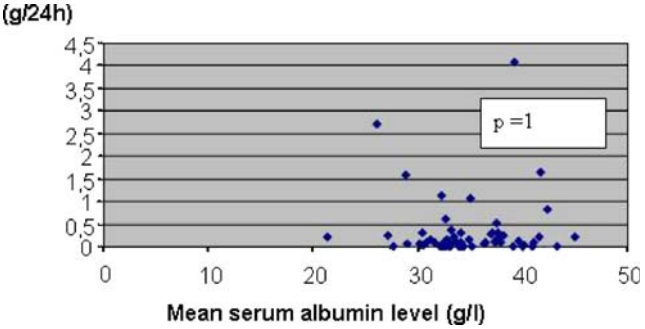


Fig. 2 Mean albumin excretion

significantly (p=0,016) shorter (mean survival: 24,2 months) in comparison to those having WBC >$4{,}5\times10^9$/l (mean survival: 41, 7 months). Interestingly in our cohort the initial WBC was independent from the bone marrow infiltration rate (Fig. 3).

In all other respects our data were comparable to previous findings like that type IgG is more favourable than other subtypes concerning life expectancy and that patients stadium type III/B lived shorter (26,6 months) than those in stadium I/A (43 mo) (p=0,11) (Figs. 4 and 5).

Patients with poor outcome who were refractory to therapy had been proven to have A/M ratio <1 from the begining and in the whole course of their disease (Fig. 6). Those patients of favourable outcome and who were good responders started with A/M >1 and also maintained it almost until the end of their life (Fig. 7).

In the sera of 30 myeloma patients presenting with low WBC count, antineutrophil antibody tests were carried out, but they did not show any real positivity (data not shown). Comparative statistical analysis of A/M and the stadium III (DSS) at 2 years concerning specificity, sensitivity, the positive predictive value and negative predictive value were as follows: in the case of A/M<1: 87%−60%− 86%− and 62% respectively and in the DSS: 60%−90%−90% and 60%. These results mean that the A/M score has stronger predictive value at the critical cutoff level of 2 year survival, when 50% of the patients have died already.

Including our data in a socalled AMWBC score system it becomes clear that the prognostic significance of the parameters examined separately in this comprehensive form might be more pronounced (Tables 1 and 2).

Discussion

The current retrospective analysis of simple laboratory data of 114 patients with multiple myeloma resulted in two major observations from the aspect of the survival times. Both the decreased ratio of albumin/M component concentrations and the decrease in the WBC were signs of poor

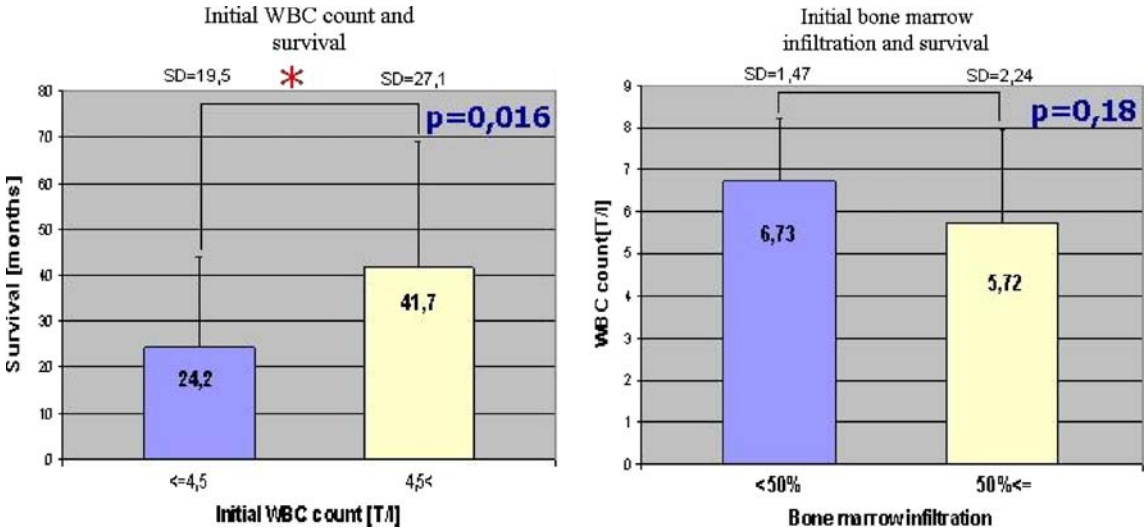


Fig. 3 Initial WBC count and survival—Initial bone marrow infiltration and survival

prognosis. The diminution of A/M ratio can take place in two ways; the decrease in the serum level of albumin and the increase in the concentration of the monoclonal protein component. Both these trends of changes can be clearly explained by the pathomechanism of the disease itself.

The so-called myeloma cytochin, IL-6 is a proinflammatory cytochin that decreases the synthesis of albumin and increases that of CRP in hepatocytes. The age associated rise in IL-6 has been linked to lymphoproliferative disorders, like MM [6]. There is a long list of studies attempting to predict outcome with the combination of independent variables, like plasmoblastic morphology, PCLI, β2microglobulin (β2M) level, serum albumin and cytogenetics [7, 8]. These and other earlier studies failed to identify patients with the shortest survival, especially those who live less than 2 years, for whom therefore innovative therapeutic approaches would be resonable.

Serum M-protein concentration generally reflects myeloma cell mass, and serial measurements are used to determine the effect of chemotherapy in MM patients. Jacobson et al. came to the conclusion that β-2- microglobulin (β2M) and albumin in combination are the most predictive variables with prognostic importance in MM [9]. Bladé et al. found that the blood urea and serum albumin were significant in determining prognosis in MM [10]. There was a study similar to our's where prognosis was determined with applying the ratio of the M-

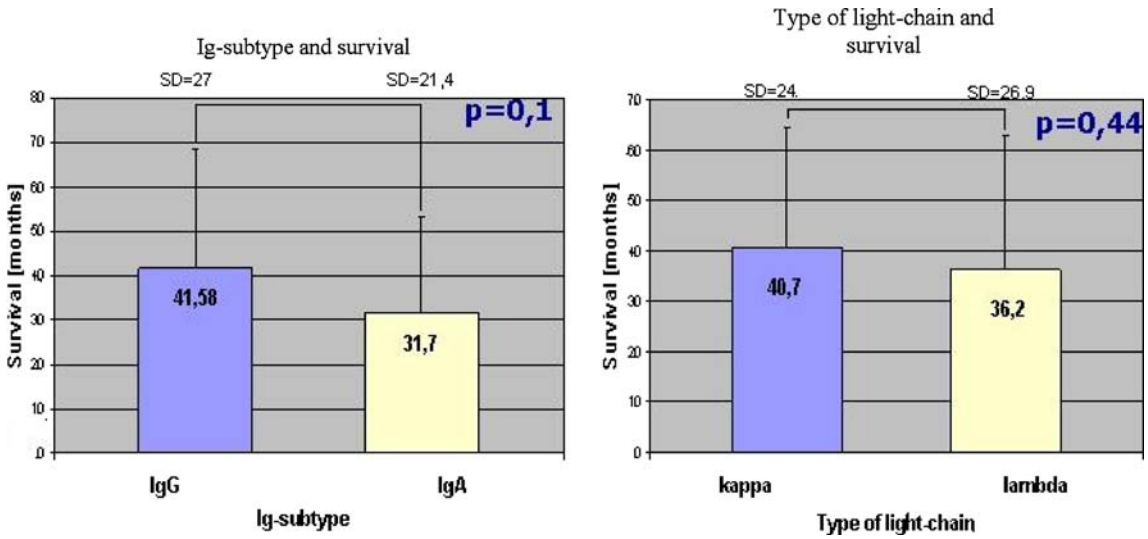


Fig. 4 Ig subtype and survival—Type of light chain and survival

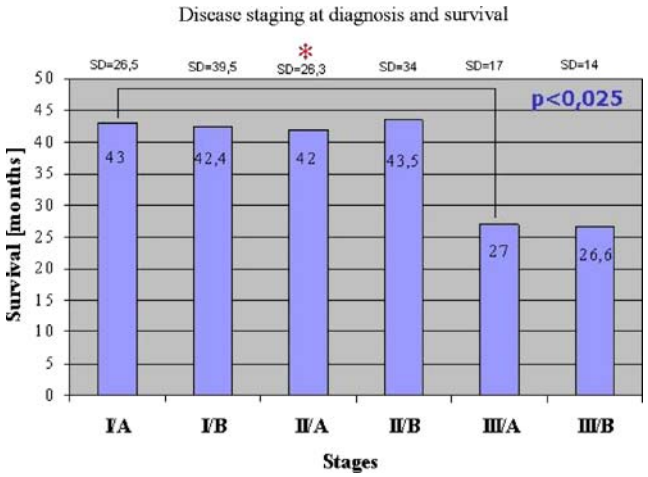


Fig. 5 Disease staging at diagnosis and survival

component concentration to the plasma cell infiltration rate in the bone marrow. The determination of the bone marrow infiltration rate by means of a 2 mc long iliac crest bone marrow specimen makes this attempt problematic [11].

Kyle et al. in a review of 1,027 patients noticed that 20% of them have low WBC. Moreover they found that bone marrow infiltration rate does not have any impact on survival and that thrombocytopenia is of prognostic significance [12]. However, the observed cytopenia not related to bone marrowe infiltartion remained unexplained.

The latest SWOG study on more than 10,000 patients came to the conclusion that β2M and albumin in combination are the most predictive variables with prognostic importance in MM. However what β2M elevation really means in the process other than renal impairement is still unsettled [13].

According to our results A/M was found to be stronger prognostic factor regarding specificity, especially at the critical 2 years, than the DSS. A/M is reflecting directly the dual effects of the so-called myeloma cytochin IL-6 inducing monoclonal protein producing plasma cell proliferation in the bone marrow and inhibiting albumin production in the liver at the same time. We confirmed that the low albumin level was

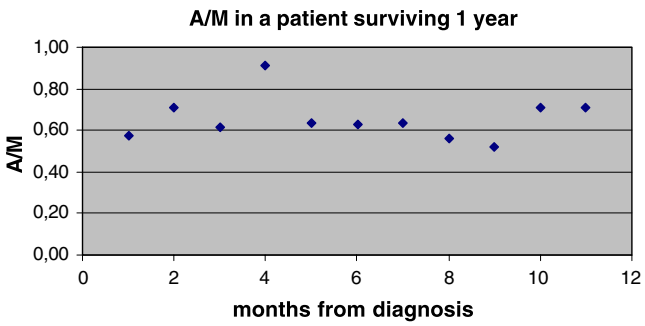


Fig. 6 A/M in a patient surviving 1 year

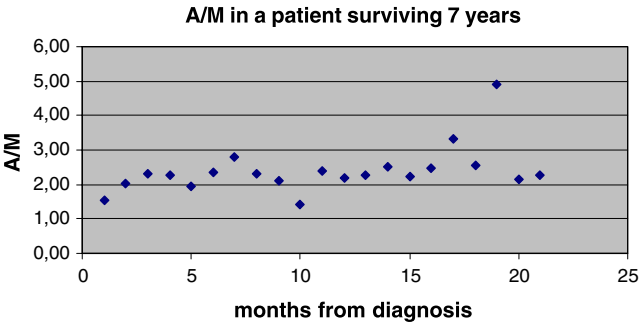


Fig. 7 A/M in a patients surviving 7 years

not related to albuminuria. Based on earlier studies it is well known that albuminuria develop only late in the course of the disease as a consequence of amyloid formation in the kidney.

The suprising findig that in the background of the low WBC count—which is another prognostic factor for poor outcome—the role of plasma cell expansion and antineutrophil antibody formation can also be excluded, but might be explained by coexistent dysplastic hemopoiesis in the bone marrow. As a matter of fact, there are several reports on such cases in the literature [14, 15].

Thus, the AMWBC score comprising these two routine laboratory parameters, the ratio of A/M and the initial WBC count, seems to be able to reflect the actual severity of the disease in a multiple myeloma patient and to prognose survival time.

A/M below 1 and WBC below 4, 5×10^9/l sufficiently well determine the group of MM patients at presentation who at high risk and who should be addressed, therefore more aggressive or alternative therapy than that our patients had.

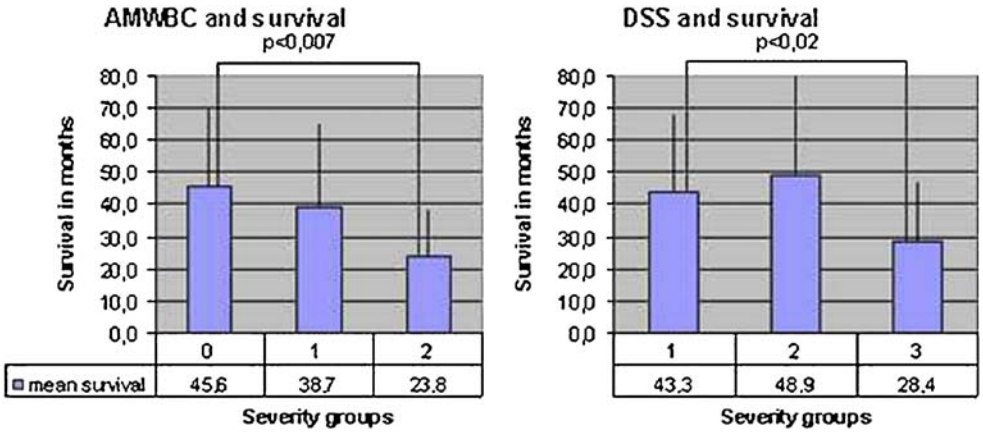
As the disease prognosis is partly determined by the therapy applied, further studies are needed to decide whether AMWBC score will or will not be applicable for this purpose when new therapeutical modalities are used other than those listed above. Preliminary reports are promising in this respect as studies on thalidomide therapy found serum albumin the best parameter distinguishing the group of long-term responders [16, 17].

Table 1 AMWBC prognostic score index calculation

Score	0	1
WBC	$\geq 4.5 \times 10^6$/l	$<4.5 \times 10^6$/l
A/M	≥1	<1

WBC< 4.5=1 score; WBC≥4.5=0 score, A/M≥1=0 score, A/M<1= 1 score, Patient having A/M≥1 and WBC≥4.5×106/l, the AMWBC= 0, Patient having A/M<1 and WBC<4.5×106/l, the AMWBC=2, Patient having either of factors 1, the AMWBC=1
0 score= good; 1 score= intermedier; 2 score= poor

Table 2 AMWBC and survival—DSS and survival



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