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# PROGNOSTIC IMPLICATIONS OF ENDOTHELIAL ACTIVATION AND STRESS INDEX (EASIX) IN MULTIPLE MYELOMA PATIENTS.

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**ABSTRACT:**

**Background**: Multiple myeloma (MM) is a B-cell malignant neoplasm. The Endothelial Activation and Stress Index (EASIX) is easily produced with common laboratory indicators ([creatinine× LDH]/platelets). The purpose of this study was to determine whether EASIX score could be a novel prognostic marker for MM patients and its implications on the outcome of the disease.

**Subjects & methods**: Forty MM patients were involved in the study in addition to 40 normal individuals as controls. Initially after diagnosis, the International Staging System (ISS) was evaluated, and EASIX score was calculated. Bortezomib, cyclophosphamide, and dexamethasone (VCD) were administered to each patient. The treatment response was evaluated, and the progression-free survival (PFS) was calculated using the Kaplan-Meier survival analysis.

**Results**: EASIX score in MM patients was significantly higher than in controls; the optimal cutoff value of EASIX was determined at 3.5 by a ROC curve. According to the ISS, patients with high EASIX score at initial diagnosis were at a more advanced stage of disease. Based on EASIX Kaplan-Meier survival analysis, patients with higher scores had PFS times that were significantly shorter than those with a lower scores (9.813 vs. 11.542 months).

**Conclusion**: EASIX score could be effective in predicting survival in MM patients.

**Keywords**: Multiple myeloma, EASIX, prognosis, ISS, VCD

## 1. INTRODUCTION

Multiple myeloma (MM) is a B-cell malignant neoplasm defined by an increase in the number of terminally differentiated plasma cells in the bone marrow, along with the production of an excess of monoclonal immunoglobulins (1).These malignant plasma cells lead to bone damage and cause bone marrow failure, as well as other MM-related adverse events such as hypercalcemia, renal disease, and infections. (2)

Several studies have defined prognostic factors that can predict disease heterogeneity and its impact on survival as the International Staging System (ISS) of multiple myeloma. It is classified into three stages based on the combination of β2-microglobulin and serum albumin. The worst outcome is ISS stage III. (3) Other prognostic markers, including cytogenetics and FISH, as well as gene expression profiling, were used to categorize MM patients. However, these tests can be quite costly as well as the difficulties of using invasive methods. Furthermore, the complexity and absence of standardization among these markers can result in unreliable results. (4).

In spite of the technologies that are now available, it is still challenging to anticipate each patient's prognosis. As a consequence of the development of numerous novel drugs for MM treatment, the effectiveness of combination therapies significantly improved, along with their overall survival (OS).(5) Unfortunately, methods for stratifying MM patients have not run with the advancement of this therapeutic profile. . As a result, creating more efficient techniques for monitoring and following up with these patients is getting more and more crucial. (6)

The interaction of MM cells with the bone marrow microenvironment is critical to the pathogenesis of MM. It is currently evident that the microenvironment of MM is primarily composed of inflammatory cells, which are the main cytokine sources and can also mediate immune suppression in MM patients. (7) The Endothelial Activation and Stress Index (EASIX), a biomarker associated with malfunction of the endothelium, that may be easily produced with common laboratory indicators ([creatinine× LDH]/platelets) ,was recently introduced by a German and US collaboration (8). Following an allogeneic stem cell transplant, acute graft-versus-host disease can be accurately predicted by this factor (9). Additionally, it has recently been proposed that EASIX could be used to predict survival in patients with and without hematological malignancies who had COVID-19. (10)

The components of EASIX- serum creatinine, LDH and platelet count- are


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renowned indicators of MM prognosis (11). The aim of this study was to ascertain if EASIX score might be a novel prognostic marker for patients with multiple myeloma in addition to investigating its prognostic implications on the outcome of the disease.

**Subjects & Methods**

The study included forty MM patients who were presented to the Hematology outpatient clinic or admitted to the Hematology Department of the Medical Research Institute (MRI). The IMWG diagnostic criteria for symptomatic MM were used to make the diagnosis. (12) As controls, forty normal, healthy participants of concordant age and gender were involved. This study was approved by the Medical Research Institute's (MRI) ethical committee and informed consents were given by both patients and controls. All patients were subjected to: entire medical history, comprehensive clinical assessment, complete blood count (CBC) (13), bone marrow examination (14), laboratory analysis: creatinine (15), lactate dehydrogenase (LDH) (16), Beta-2 microglobulin (β2M),calcium, albumin (17), electrophoresis of serum protein and immunofixation (18) and radiographic analysis to assess osteolytic bone lesions (19). During the initial diagnosis, ISS (12) and EASIX score were evaluated. The formula used to determine the EASIX score was -LDH (U/L) × Creatinine (mg/dL) / platelet count ($10^9$ /L) (20).Patients were excluded if they had known cardiac disease or underwent PET-CT in the last three months.

As induction therapy, all patients in the study were given six cycles (28-day cycle) of bortezomib-based protocol (VCd): (21) Bortezomib (Velcade): subcutaneously 1.3 mg/$m^2$; Cyclophosphamide: orally 300 mg/$m^2$; Dexamethasone: orally 40 mg on days one, eight, fifteen, and twenty-two. After six cycles of chemotherapy, patients were reassessed in view of their clinical examination, laboratory investigations, radiological assessment, and treatment response. For a period of 12 months all patients were monitored.

**Statistical analysis:**

SPSS 23.0 for Windows was utilized to analyze the data (SPSS Inc., Chicago, USA). Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Chi-square and Fisher Exact tests were used to analyze qualitative data while quantitative data were tested by Student t-test and Mann Whitney test. Spearman coefficient correlation co-efficient (r) tests were used for the correlation between EASIX score and different parameters. The level of significance was set at $p \leq 0.05$.

The receiver operating characteristic (ROC) curve was used to establish the optimal cutoff of EASIX for survival outcomes. Kaplan-Meier Estimate was used to analyze pertinent survival endpoints, such as progression-free survival (PFS).

**Results:**

**Patient's characteristics:**

IgG was the predominant MM type (52.5%), and light chain disease affected 7.5 % of patients. In terms of ISS staging, 12.5% were categorized as ISS I, 70 % as ISS II, and 17.5% as ISS III. Lytic bone lesions were present in 65 % of patients. Table 1 illustrates a comparison between MM patients and the control group with regards to different parameters.

**Table 1: Comparison between MM patients and the control group with regards to different parameters**

| | **Patients (n = 40)** | **Control (n = 40)** | **p-value** |
|---|---|---|---|
| **Age (years)** | | | |
| Mean ± SD. | 55.6 ± 6.2 | 55.4 ± 8.4 | 0.892 |
| **Sex** | | | |
| Male | 23 (57.5%) | 20 (50%) | 0.501 |
| Female | 17 (42.5%) | 20 (50%) | |
| **Hb (g/dl)** | | | |
| Mean ± SD. | 9.2 ± 1.6 | 13.0 ± 0.8 | <0.001* |
| Median (Min. – Max.) | 8.9 (6.5 – 12.8) | 13.0 (12.0 – 14.1) | |
| **WBC count ($\times 10^3/\mu L$)** | | | |
| Mean ± SD. | 10.1 ± 5.6 | 7.3 ± 1.3 | 0.047* |
| Median (Min. – Max.) | 8.3 (3.0 – 24.1) | 7.1 (5.0 – 10.0) | |
| **Platelet count ($\times 10^9/L$)** | | | |
| Mean ± SD. | 287.3 ± 69.7 | 305.0 ± 69.7 | 0.260 |
| Median (Min. – Max.) | 298.5 (169.0 – 400.0) | 326.5 (179.0 – 389.0) | |
| **Calcium (mg/dl)** | | | |
| Mean ± SD. | 10.7 ± 1.1 | 9.5 ± 0.4 | <0.001* |
| Median (Min. – Max.) | 11.1 (9.0 – 12.7) | 9.5 (9.0 – 10.0) | |
| **Creatinine (mg/dl)** | | | |
| Mean ± SD. | 2.3 ± 1.0 | 0.7 ± 0.2 | <0.001* |

| | | | |
|---|---|---|---|
| Median (Min. – Max.) | 2.4 (0.6 – 4.5) | 0.7 (0.4 – 1.1) | |
| **LDH (U/L)** | | | |
| Mean ± SD. | 387.6 ± 172.4 | 291.1 ± 35.6 | 0.001* |
| Median (Min. – Max.) | 304.5 (211.0 – 962.0) | 289.0 (240.0 – 353.0) | |
| **CRP (mg/L)** | | | |
| Mean ± SD. | 15.5 ± 11.1 | 1.9 ± 0.9 | <0.001* |
| Median (Min. – Max.) | 12.5 (2.3 – 44.8) | 1.6 (0.7 – 3.6) | |
| **β2M (mg/L)** | | | |
| Mean ± SD. | 5.1 ± 2.8 | 1.0 ± 0.2 | <0.001* |
| Median (Min. – Max.) | 4.7 (0.9 – 11.5) | 1.0 (0.7 – 1.2) | |

*: Statistically significant at $p \leq 0.05$
SD: Standard deviation

**EASIX score:**
At diagnosis, EASIX score was computed in all patients and in controls. When compared to the control group, it was significantly greater in MM patients, with a median of 3.1 (0.5-11.0) as opposed to 0.7 (0.4-1.1) ($p < 0.001$) (Table 2). There were positive correlations between EASIX and age, calcium, CRP and bone marrow aspiration plasma cell percentage at diagnosis. Also, a negative correlation was found between EASIX and time of progression of the disease. On the other hand, there was no significant correlation found with ISS, hemoglobin, WBCs count, and beta-2 microglobulin. (Table 3)

**Table 2: Comparison of EASIX score between MM patients and controls**

| EASIX | Patients (n = 40) | Control (n = 40) | p-value |
|---|---|---|---|
| Mean ± SD. | 3.4 ± 2.5 | 0.7 ± 0.2 | <0.001* |
| Median (Min. – Max.) | 3.1 (0.5 – 11.0) | 0.7 (0.4 – 1.1) | |

**Table 3: Correlation between EASIX score and different parameters for patients group**

| Patients (n = 40) | EASIX score | |
|---|---|---|
| | $r_s$ | p-value |
| **Age (years)** | 0.389* | 0.013* |
| **ISS staging** | 0.278 | 0.083 |
| **Hb (g/dl)** | -0.263 | 0.102 |
| **WBC count (×103/µL)** | 0.176 | 0.276 |
| **Calcium (mg/dl)** | 0.422* | 0.007* |
| **CRP (mg/L)** | 0.432* | 0.005* |
| **β2M (mg/L)** | 0.237 | 0.141 |
| **BMA plasma %at diagnosis** | 0.369* | 0.019* |
| **Time of progression (months)** | -0.317* | 0.046* |

$r_s$: Spearman coefficient *: Statistically significant at $p \leq 0.05$

The impact of EASIX on prognosis was analyzed using the ISS. EASIX's ideal cutoff value was established at 3.5 by a receiver operating characteristic (ROC) curve to evaluate EASIX's prognostic accuracy in MM patients. Thus, we can distinguish between MM patients with high risk (ISS- III) and those with low risk (ISS- I and II). In addition, 85.71% was the sensitivity, 69.7% was the specificity, PPV was 37.5%, and NPV was 95.8%. The AUC was determined to be 0.740 (Figure 1) (Table 4).

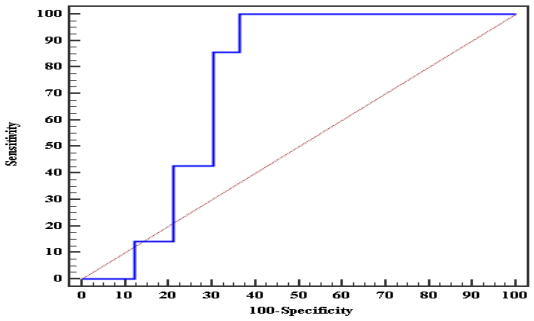


**Figure 1: ROC curve to determine the prognostic performance of EASIX**

**Table 4: Prognostic performance of EASIX in MM patien**

| | AUC | p-value | 95% CI | Cut off | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|---|
| **EASIX** | 0.740* | 0.048* | 0.594 – 0.886 | >3.50 | 85.71 | 69.7 | 37.5 | 95.8 |

AUC: Area under a Curve CI: Confidence Intervals
NPV: Negative predictive value PPV: Positive predictive value
*: Statistically significant at $p \leq 0.05$

Sixteen patients (40%) were classified as high EASIX (>3.5), and 24 (60%) were classified as low EASIX (≤3.5). Tables 5a and 5b show differences in the clinical baseline traits between patients in the high EASIX group and low EASIX group. Patients with a high EASIX score were older than those with a low score, however, the difference was not statistically significant (p = 0.279). Patients in the high EASIX group had more unfavorable risk factors such as hypercalcemia, high WBCs& CRP, and low platelets. According to the ISS, patients with high EASIX at diagnosis had a more advanced stage of disease than patients with low EASIX. Patients with high EASIX scores (after induction &at the end of follow-up) had a lower complete remission (CR 25%), high progression of the disease (PD 25%), and shorter time to progression (9.8 ± 3.0 months) than those with low EASIX score (CR 33.3% after induction and 41.7% at the end of follow up), (PD 8.3%), and time to progression (11.5 ± 1.6 months).

**Table 5a: Relationship between EASIX score and different parameters for the patient group**

| **Patients (n = 40)** | **EASIX score** | | **p-value** |
|---|---|---|---|
| | **Low (≤3.5) (n = 24)** | **High (>3.5) (n = 16)** | |
| **Age (years)** | | | |
| ≤60 | 22 (91.7%) | 12 (75.0%) | 0.195 |
| >60 | 2 (8.3%) | 4 (25.0%) | |
| Mean ± SD. | 54.8 ± 6.4 | 56.9 ± 5.8 | 0.279 |
| **Hb (g/dl)** | | | |
| <10 | 17 (70.8%) | 15 (93.8%) | 0.114 |
| >10 | 7 (29.2%) | 1 (6.3%) | |
| Mean ± SD. | 9.6 ± 1.7 | 8.7 ± 1.3 | 0.095 |
| Median (Min.– Max.) | 9.3 (7.4 – 12.8) | 8.6 (6.5 – 12.5) | |
| **WBC count ($\times 10^3/\mu L$)** | | | |
| Mean ± SD. | 8.8 ± 5.2 | 12.2 ± 5.8 | 0.033* |
| Median (Min. – Max.) | 7.4 (3.0 – 24.1) | 10.1 (5.5 – 22.3) | |
| **Platelet count ($\times 10^9/L$)** | | | |
| Mean ± SD. | 317.2 ± 57.1 | 242.5 ± 63.8 | <0.001* |
| Median (Min. – Max.) | 322.0 (190.0 – 400.0) | 228.0 (169.0 – 386.0) | |
| **Calcium (mg/dl)** | | | |
| <11 | 14 (58.3%) | 4 (25.0%) | 0.038* |
| ≥11 | 10 (41.7%) | 12 (75.0%) | |
| Mean ± SD. | 10.5 ± 1.0 | 11.1 ± 1.2 | 0.061 |
| Median (Min. – Max.) | 10.2 (9.0 – 12.0) | 11.4 (9.1 – 12.7) | |
| **CRP (mg/L)** | | | |
| Mean ± SD. | 12.3 ± 9.0 | 20.4 ± 12.4 | 0.024* |
| Median (Min. – Max.) | 9.9 (2.3 – 34.5) | 18.3 (3.9 – 44.8) | |
| **β2M (mg/L)** | | | |
| <3.5 | 8 (33.3%) | 4 (25.0%) | 0.729 |
| >3.5 | 16 (66.7%) | 12 (75.0%) | |
| Mean ± SD. | 4.7 ± 2.8 | 5.7 ± 2.6 | 0.171 |
| Median (Min. – Max.) | 4.1 (0.9 – 11.5) | 5.1 (2.5 – 10.5) | |

SD: Standard deviation *: Statistically significant at $p \leq 0.05$

**Table 5b: Relation between EASIX score and different parameters for patients group**

| Patients (n = 40) | EASIX score | | p-value |
|---|---|---|---|
| | Low (≤3.5) (n = 24) | High (>3.5) (n = 16) | |
| **ISS staging** | | | |
| I | 4 (16.7%) | 1 (6.3%) | 0.026* |
| II | 19 (79.2%) | 9 (56.3%) | |
| III | 1 (4.2%) | 6 (37.5%) | |
| **Response after induction** | | | |
| CR | 8 (33.3%) | 4 (25.0%) | 0.408 |
| VGPR/PR | 14 (58.3%) | 8 (50.0%) | |
| PD | 2 (8.3%) | 4 (25.0%) | |
| **Response at end of follow up** | | | |
| CR | 10 (41.7%) | 4 (25.0%) | 0.136 |
| VGPR/PR | 12 (50.0%) | 6 (37.5%) | |
| PD | 2 (8.3%) | 4 (25.0%) | |
| Relapse | 0 (0.0%) | 2 (12.5%) | |
| **BMA plasma cells (%) before treatment** | | | |
| Mean ± SD. | 55.6 ± 17.0 | 63.5 ± 15.6 | 0.945 |
| Median (Min. – Max.) | 51.0 (29.0 – 81.0) | 64.5 (26.0 – 92.0) | |
| **Time to progression (months)** | | | |
| Mean ± SD. | 11.5 ± 1.6 | 9.8 ± 3.0 | 0.157 |
| Median (Min. – Max.) | 12.0 (6.0 – 12.0) | 12.0 (4.0 – 12.0) | |

SD: Standard deviation *: Statistically significant at $p \leq 0.05$

**Survival analysis**

The Kaplan-Meier curve for EASIX was used to determine progression-free survival (PFS). It has been shown that patients with a high EASIX score have a significantly shorter PFS duration compared to those with a low score (9.813 vs. 11.542 months) (Figure 2) (Table 6).

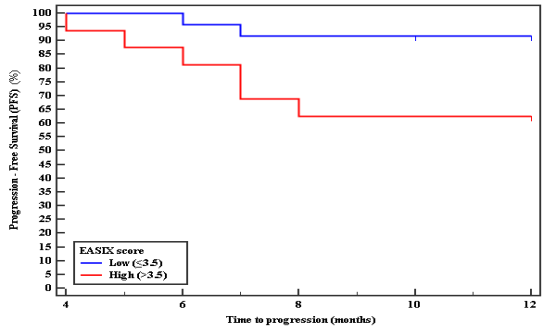


**Figure 2: Kaplan-Meier survival curve for progression-free survival (PFS) according to EASIX score**

**Table 6: The PFS with EASIX as assessed by the Kaplan-Meier survival curve**

| EASIX score | Mean | % | Log rank | |
|---|---|---|---|---|
| | | | $\chi^2$ | p-value |
| Low (≤3.5) | 11.542 | 91.7% | 5.196* | 0.023* |
| High (>3.5) | 9.813 | 62.5 | | |

$\chi^2$: Chi square test

**Discussion**

Multiple myeloma is triggered by the uncontrolled expansion of neoplastic plasma cells. Despite the availability of improved and novel biomarkers for predicting MM patients' overall prognosis, currently, there is insufficient data to use predictive markers to assess initial MM treatment, intensify therapy for high-risk MM, or switch to an entirely alternative therapeutic strategy. (22)

Even though MM is incurable, new therapies have significantly improved the median overall survival over time. However, even among patients with the same genetic background, there is a significant difference in outcome, with survival ranging from a few months to more than ten years. (22) However, developing more accurate and rapid methods

for characterizing MM patients and predicting their outcomes remains a major challenge. (23)

Serum creatinine, Platelet counts, and LDH can all be used to calculate the EASIX score. These three EASIX characteristics have been identified as MM prognostic factors. In patients with MM who received effective novel treatments like thalidomide, lenalidomide, or bortezomib, elevated serum LDH levels are linked to progressive disease and worse survival outcomes (24, 25). At the time of diagnosis of MM, renal insufficiency was also linked to an advanced disease stage, significant tumor burden, greater hazard of treatment-related side effects, and early death (26, 27). Recently registered analysis revealed that patients with renal insufficiency still exhibited poorer survival outcomes in comparison to those with adequate renal function, despite the development of novel, efficient medicines which improve renal function and decrease early mortality (28). It's uncertain how platelet levels in MM affect prognosis. Regardless of the degree of bone marrow plasmacytic infiltration, cytokines including megakaryocyte growth factors, which are connected to MM pathogenesis, are probably going to have an effect on platelet production (29). Additionally, patients with MM who at diagnosis had a low platelet count typically have a poor prognosis. (11).Our study demonstrates that EASIX score was significantly higher in patients with MM compared to control group and showed a correlation with age, calcium, CRP, plasma cell percentage in bone marrow aspiration before treatment, and time to progression of the disease in MM patients. In addition, high EASIX score patients have more opposing clinical traits, including hypercalcemia, high CRP, and a significantly higher proportion of ISS III compared to low EASIX patients, and this demonstrates that the EASIX score exhibits the aggressiveness and tumor load. Our results were in accordance to some extent with those of Song et al. (11) who stated that patients with MM, having high EASIX score at diagnosis, had a progressive stage of disease based on the ISS and unfavorable risk factors for instance anemia, low performance score, hypercalcemia, high-risk chromosomal abnormalities, and renal insufficiency (11). On the other hand, Thanhakun et al.(30 ) concluded that diffuse large B-cell lymphoma patients with a high EASIX score have a significantly larger percentage of patients with poor performance status, bulky disease and advanced stage, and present with higher-risk conditions as evaluated by the International Prognostic Index. Subsequently, we believed that EASIX, which includes these three characteristics, could be effective in predicting survival in MM.

Based on our results of the Kaplan-Meier curve for EASIX, patients with a high EASIX score have a significantly shorter PFS time than those with a low score. Song et al. (11) reported that MM patients with a high EASIX in each group of ISS exhibited significantly poorer overall survival (OS) compared to those with a low EASIX. Also, they mentioned that one of their study limitations was that they lacked information on progression-free survival (PFS). Furthermore, they recommended an analysis of the relationship between EASIX and PFS because it could potentially enhance EASIX's prognostic significance. Also, Gu JS et al. (31) reported that the group with high-EASIX had inferior recurrence-free survival and overall survival than the group with low-EASIX in upper tract urothelial carcinoma patients. Moreover, Park S. et al. (32) stated that the one-year OS and PFS rates of patients with diffuse large B-cell lymphoma were inferior in the high-EASIX patients compared to the low-EASIX patients.

Endothelial dysfunction and angiogenesis play a substantial contribution to the development of MM and may also be predictive of prognosis. Endothelial cells in MM differ from resting endothelial cells in their expression of cell adhesion molecules, cytokine receptors, and growth factors. These elements are assigned to angiogenesis, which is necessary for tumor invasion, development, and metastasis (33). Angiopeietin-2, a marker of angiogenesis, is elevated in MM and linked to disease progression and short survival (34). As an endothelial dysfunction-related measure that is independent of other prognostic variables, EASIX may therefore be crucial for the prognostic classification of MM. To the best of our knowledge, this study is the first to evaluate the prognostic value of EASIX in patients with MM in Egypt in the context of progression-free survival.

**Conclusion**

In conclusion, our study suggests that patients with high EASIX score at the time of diagnosis should be carefully evaluated because they are significantly more likely to experience disease progression and short progression-free survival. Therefore, EASIX score may identify, at the time of diagnosis, patients at high risk of developing disease progression and can be considered as an independent prognostic factor of an unfavorable survival outcome.

**Recommendations**

Determination of EASIX score in patients with MM at diagnosis is likely recommended to guide the treatment decision.

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