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The relationship between endothelial activation and stress index with survival and early mortality in acute myeloid leukemia

Akut miyeloid lösemide endotel aktivasyonu ve stres indeksi ile sağkalım ve erken mortalitenin ilişkisi

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ABSTRACT

Aim: The Endothelial Activation and Stress Index (EASIX) score is used as a marker of endothelial damage and used to predict acute graft-versus-host disease and sinusoidal obstruction syndrome. We wanted to evaluate the effects of EASIX, modified EASIX (mEASIX) and sepsis modified EASIX (sEASIX) on early mortality and overall survival (OS) in patients with acute myeloid leukemia.

Materials and Methods: We reviewed patients diagnosed and followed up with Acute Myeloid Leukemia (AML) in our Hematology Department, retrospectively. Patients between 18 -70 years of age and who were administered 7+3 (7 days cytarabine, and 3 days anthracycline) chemotherapy protocol (except acute promyelocytic leukemia) were included. EASIX, mEASIX and sEASIX scores of the patients, both at the time of diagnosis and at the end of the 4th week, were calculated.

Results: Seventy-five patients were included in the study. The mean age was 49.05 (19-68) years and 41% were alive. EASIX and mEASIX scores measured both at the time of diagnosis and at the end of induction therapy were found to be significantly associated with early mortality (p=0.01, p<0.01) and OS (p<0.01, p<0.01).

Conclusion: There is no specific scoring system or marker that we can use practically in the clinic to show early mortality in these patients who receive intensive treatment in AML. Of course, there are many factors that can affect mortality in this period. However, based on the current results, we think that EASIX, mEASIX and sEASIX scores can be used with other prognostic factors to predict early mortality and survival.

Keywords: Endothelial dysfunction, acute myeloid leukemia, early mortality

ÖZ

Amaç: *Endotelyal Aktivasyon ve Stres İndeksi (EASIX) skoru, endotel hasarının bir belirteci olarak ve akut greft-versus-host hastalığı ile sinüzoidal obstrüksiyon sendromunu öngörmek için kullanılır. Bu çalışmada, EASIX, modifiye EASIX (mEASIX) ve sepsis modifiye EASIX (sEASIX) skorlarının akut miyeloid lösemi hastalarında erken mortalite ve genel sağkalım (OS) üzerindeki etkilerini değerlendirmek amaçlanmıştır.*

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Gereç ve Yöntem: *Gereç ve Yöntem: Hematoloji kliniğimizde Akut Miyeloid Lösemi (AML) tanısı konulan ve takibi yapılan hastaları retrospektif olarak inceledik. Çalışmaya 18-70 yaş aralığında, 7+3 (7 gün sitarabin ve 3 gün antrasiklin) kemoterapi protokolü uygulanan (akut promiyelositik lösemi hariç) hastalar dahil edildi. Hastaların tanı anında ve dördüncü haftanın sonundaki EASIX, mEASIX ve sEASIX skorları hesaplandı.*

Bulgular: *Çalışmaya 75 hasta dahil edildi. Ortalama yaş 49,05 (19-68) yıldı ve %41'i hayattaydı. Hem tanı anında hem de indüksiyon tedavisinin sonunda ölçülen EASIX ve mEASIX skorlarının erken mortalite (p=0,01, p<0,01) ve OS (p<0,01, p<0,01) ile anlamlı şekilde ilişkili olduğu bulundu.*

Sonuç: *AML'de yoğun tedavi gören bu hastalarda erken mortaliteyi göstermek için klinikte pratik olarak kullanabileceğimiz spesifik bir skorlama sistemi veya belirteç bulunmamaktadır. Elbette, bu dönemde mortaliteyi etkileyebilecek birçok faktör bulunmaktadır. Ancak, mevcut sonuçlara dayanarak, EASIX, mEASIX ve sEASIX skorlarının erken mortalite ve sağkalımı öngörmek için diğer prognostik faktörlerle birlikte kullanılabileceğini düşünüyoruz.*

Anahtar Sözcükler: *Endotel disfonksiyonu, akut miyeloid lösemi, erken mortalite*

INTRODUCTION

The Endothelial Activation and Stress Index (EASIX) score (lactate dehydrogenase [LDH; U/L] X creatinine [mg/dL]/platelet [10^9 cells/L]) has emerged as a marker of endothelial damage. It is used to predict acute graft-versus-host disease and sinusoidal obstruction syndrome (SOS). There are articles in the literature that it can predict the risk of mortality in Myelodysplastic Syndrome (MDS), Multiple Myeloma (MM), and COVID-19 infection due to its relationship with endothelial damage and the parameters used (1,2,3). Since the post-CAR-T cytokine release syndrome relationship between C-reactive protein (Crp), LDH and thrombocytopenia is known from previous studies, it is recommended that the modified EASIX (mEASIX) scoring be used as a predictor in CAR-T treatments (4).

In acute myeloid leukemia (AML) patients, survival is increasing with new definitions and treatment managements created by clarifying genetic diversity. However, causes such as hyperleukocytosis, bleeding and sepsis, which have an important role in early mortality and are directly related to endothelial dysfunction, continue to be important problems.

We hypothesized that EASIX, mEASIX and sepsis modified EASIX (sEASIX) scores may be meaningful in terms of predicting complications due to endothelial dysfunction in the acute period in AML, to reveal early mortality and overall survival (OS). In addition, considering that Prothrombin time (PT) and albumin values are also associated with endothelial damage. For these reasons, we wanted to evaluate the effects of these two values together with EASIX, mEASIX and sEASIX scores.

MATERIALS AND METHODS

Definition of Scoring Systems and Patient Selection

We reviewed patients diagnosed and followed up with AML in our Hematology Department, retrospectively. In order to obtain a more homogeneous group in terms of treatment and follow-up, patients over the age of 18 and under the age of 70 who underwent 7+3 (7 days of cytarabine, and 3 days of an anthracycline) chemotherapy protocol were included in the study. Acute promyelocytic leukemia (APL) and seconder AML were excluded from the study because of different treatment and follow-up strategies. EASIX (LDHxcreatinine/platelet), mEASIX (LDHxCrp/platelet) scores of the patients at the time of diagnosis (Ea0, mEa0) and at the end of remission induction treatment (at week 4; Ea1, mEa1) were calculated. In addition, we made the sEASIX score by adding PT and albumin values to the EASIX score to evaluate the effects of PT and albumin values on endothelial damage. We evaluated the sEASIX score similarly as sEa0 and sEa1.

Mortality within the first 6 months (considering the duration of remission induction and consolidation treatments) was considered as early mortality. Survival and early mortality rates of the patients were compared with all scores.

The study was conducted in accordance with the Declaration of Helsinki, Ethical Principles for Medical Research. This study was approved by Trakya University Faculty of Medicine Ethical Committee (TÜTF-BAEK2022/312).

Statistical Analysis

Statistical analysis was performed using IBM SPSS v26 software. Numerical variables were expressed as median and range. Categorical variables were expressed with count and frequency. Comparison of numerical variables were performed with non-parametric tests (Mann-Whitney) and categorical variables were analyzed with chi-square test. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off values of the quantitative metabolic parameters for OS.

RESULTS

The study included 75 patients, 39 (52%) were female. The mean age at diagnosis was 49.05 (19-68) years and the mean age was 50.53 (19-71). It was observed that 41% of the patients were alive (Table-1). EASIX, mEASIX and sEASIX scores of the patients, both at the time of diagnosis and at the end of the 4th week, were calculated. In all scorings, the median value was determined both at diagnosis and at the end of the 4th week of treatment. Cut-of values were calculated for all groups using ROC analysis (Table-2). Each scoring was divided into 2 groups, considering that values above this value would be associated with poor prognosis and values below would be associated with good prognosis.

It was observed that the OS was statistically lower in patients with high scores in all three scorings at the time of diagnosis (Ea01: p=0.021, mEa0: p=0.004 and sEa0: p=0.028) (Figures-1, 2 and 3). Similarly, at the end of the 4th week of treatment, all 3 scorings were statistically significant with the OS (Ea1: p=0.017, mEa1: p=0.029 and sEa1: p=0.028) (Figures-4, 5 and 6).

It was determined that 17 (22.7%) patients died within 6 months after the diagnosis. Considering the relationship between endothelial damage and early mortality, we found that high scores were statistically associated with early mortality in the evaluation of all three scores at the time of diagnosis (Ea0: p=0.01, mEa0: p<0.01 and sEa0: p=0.003). In the same way, when evaluated at the end of the 4th week of treatment, it was seen that the high scores of all 3 assessments were statistically significantly associated with early mortality (Ea1: p=0.005, mEa1: p<0.01 and sEa1: p=0.004) (Table-3).

Table- 1. Characteristic features of patients

No		75
Age	mean	50.53 (19-71)
Age at diagnosis	mean	49.05 (19-68)
Gender		Male 36 – 48% Female 39 – 52%
The average follow-up		24 months
Early mortality (EM)	No-%	24 – 32%
ECOG* perf. score 3-4	No-%	14 – 19% 9 patients in EM group
Survival	Mortality No-%	Ex - 44 patients - 59% Alive- 31 patients – 41%
	infection-related mortality	32 - 73% 11 – 46% patients in EM group
Genetic analyze #	PCR – No	NPM1 – 10 FLT3 – 3 NPM1 + FLT3 – 2 t(8,21) – 3 inv16 - 3
	NGS**	ASXL1 -3 TET2 -2 NRAS -2 SF3B1 -2 RUNX -1

* ECOG: Eastern Cooperative Oncology Group
** NGS: Next generation sequencing
# There are results for a limited number of patients due to access to this examination at that time.

Table-2. ROC analysis of scores

Roc Curve	AUC (95%)	Cutt of	p	Sensitivity %	Specificity %
EASIX*	0,65 (0,531-0,779)	0,0215	**0,023**	41	13
mEASIX**	0,69 (0,581-0,817)	0,0313	**0,003**	68	29
sEASIX***	0,66 (0,542-0,788)	0,0866	**0,015**	43	13
EASIX1	0,60 (0,472-0,736)	0,0061	0,13	57	36
mEASIX1	0,68 (0,558-0,809)	0,0027	**0,008**	96	61
sEASIX1	0,66 (0,527-0,788)	0,0124	**0,022**	93	61

* EASIX: The Endothelial Activation and Stress Index score
** mEASIX: modified Endothelial Activation and Stress Index score
*** sEASIX: sepsis modified Endothelial Activation and Stress Index score

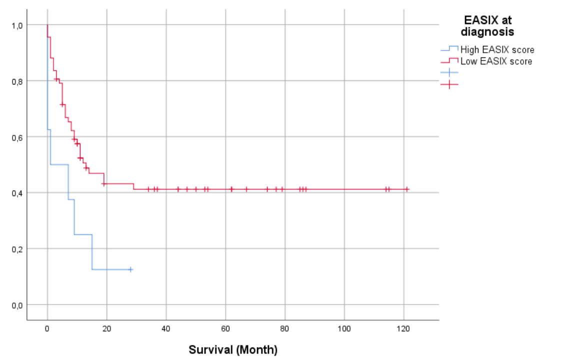

Figure- 1. EASIX risk score at the time of diagnosis and overall survival.

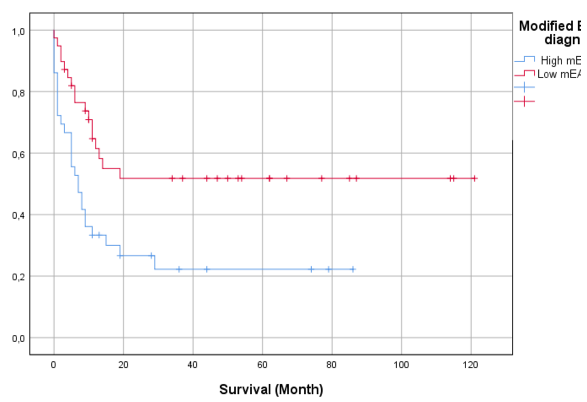

Figure-2. mEASIX risk score at the time of diagnosis and overall survival.

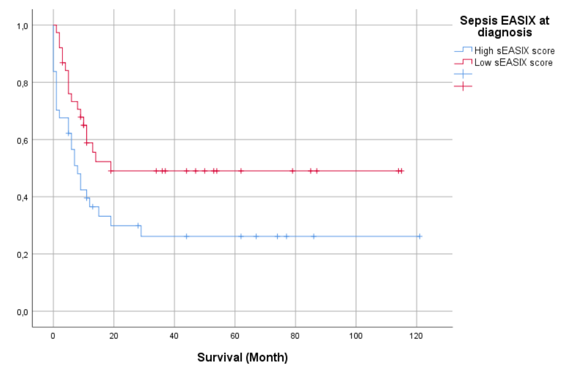

Figure-3. sEASIX risk score at the time of diagnosis and overall survival.

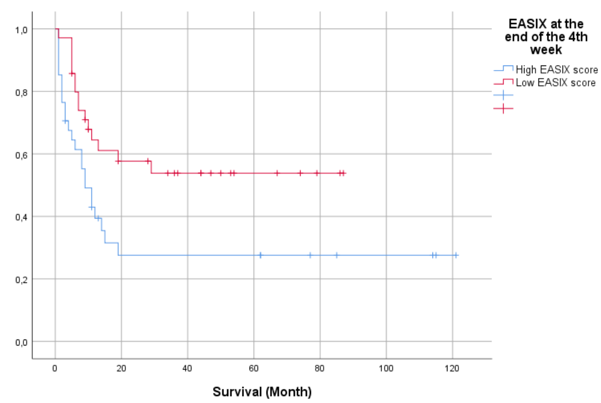

Figure-4. EASIX risk score at the end of the 4th week and overall survival.

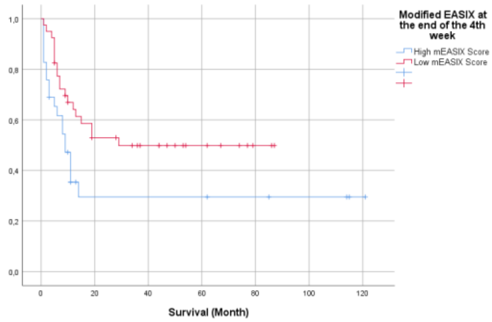

Figure-5. mEASIX risk score at the end of the 4th week and overall survival.

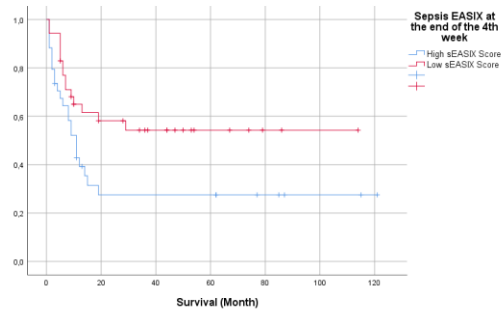

Figure-6. sEASIX risk score at the end of the 4th week and overall survival.

DISCUSSION

Treatment induction therapy is an intensive treatment regimen in eligible patients with AML (except AML M3), which has genetic heterogeneity. Today, with the identification of targeted molecules and their addition to intensive therapy in accordance with genetic heterogeneity, treatment response increases, and survival increases with better supportive treatments and patient care. However, even if survival increases, early mortality remains important. For this reason, the management of infections and cytopenia's are the most important step of treatment management.

Endothelial dysfunction has an important role among the causes of mortality in patients with AML. Sepsis, SOS, graft-versus-host-disease, transplant-associated microangiopathy are among the causes of mortality due to endothelial dysfunction (5). Although many biomarkers are suggested as a predictor, LDH, platelet, Crp, creatinine, ferritin, and fibrinogen are values that can be used practically in the clinic for endothelial dysfunction. For this reason, the EASIX score consisting of LDH, platelets and creatinine is often recommended to predict the clinical manifestation of SOS due to endothelial dysfunction. In a similar manner, in patients with allogeneic stem cell transplantation, the EASIX score, unrelated to SOS, was found to be associated with increased non-relapse mortality and decreased survival. This association was found to be related to endothelial dysfunction (6). Also, it has been evaluated together with angiopoietin-2 in low-risk MDS patients in the literature and has been shown to be associated with survival (3). For a similar reason, it has been shown that the mEASIX score may be meaningful to show cytokine release after CAR-T treatment (4).

The importance of endothelial dysfunction in sepsis, which is an important cause of mortality in the follow-up of AML, is known. Many laboratory evaluations may indirectly indicate endothelial dysfunction. Albumin takes an important place in these markers. The role of albumin in cadherin phosphorylation and formation of endothelial barriers is essential (7,8). On the other hand, the relationship between vascular endothelium and coagulation is well known. The most frequently used example of this in clinical use is the PT, which is also included in the ISTH scoring in disseminated intravascular coagulation (DIC) (9).

We found that the EASIX and Crp-mEASIX scores measured both at the time of diagnosis and at the end of the induction treatment (on the 28th day) were associated with mortality in the first 6 months. When we added albumin and PT to this scoring (sEASIX), the result was similar. Of course, there is no specific scoring system or marker that we can use practically in the clinic to show early mortality in these patients who receive intensive treatment in AML. However, in line with these results, we think that the evaluation of EASIX, mEASIX and sEASIX scores at the time of diagnosis and at the 4th week of treatment can be a prognostic evaluation method in terms of early mortality and survival in patients. Its practical calculation will also facilitate its use in the clinic. It can be a scoring that can be easily used in the follow-up of patients together with other prognostic factors. The most important limitations of the study are that it is a single center and retrospective study. In addition, there is no multivariate analysis with molecular results, which is an important prognostic marker. There is a need for a study to be conducted with other prognostic markers in larger patient groups. At the time, there was a limitation on access to genetic analyses for both next generation sequencing and FLT3. This resulted in the availability of results for a limited number of patients. This was another important limitation in the study.

CONCLUSION

AML is a heterogeneous disease group and is evaluated with multiple prognostic markers. However, access to all prognostic factors and working conditions are not optimal in all centers and it may take time to reach the results. Although mortality is decreasing with current treatments in the light of molecular targeted therapies, infection maintains its importance in early mortality. We think that EASIX, mEASIX and sEASIX scoring are practical and associated with early mortality and survival in our study, so they can be used together with other factors in the evaluation of early mortality and survival in these patients.

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Conflict of interest: The author declared no conflict of interest.

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