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Prognostic Value of Neutrophil to Lymphocyte Ratio in Acute Myeloid Leukemia

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Abstract

Objective: Acute myeloid leukemia (AML) is a heterogeneous, hematologic malignancy at which short survival may be seen. Our study aims to evaluate the effect of the neutrophil-to-lymphocyte ratio (NLR) on the course of the disease, response to therapy, and overall survival (OS). Materials and Methods: A total of 124 patients followed-up with the diagnosis of AML from 2016 to 2019 were retrospectively examined. Results: 69 of the cases (55.6%) were men and 55 (44.3%) were women. The average age at the time of diagnosis was 53.44 ± 30.3 years old. We determined the NLR as median 0.46 (0.16 - 1.1). In AML, 69 patients were responsive to the induction regimen (57.9%) while 46 patients were unresponsive (37.8%). 5 patients died before completing the regimen. D-dimer was found to be higher and fibrinogen was found to be lower in the responsive group. Lower OS was observed in cases of >60 years of age, male gender, non-APL AML, high NLR, and recurrence at diagnosis. Recurrences were detected in 23 patients (18.5%) and the median time to the recurrence was 416 (236 - 639) days. Fibrinogen level and the bone marrow blast ratio at the time of application were determined to be associated with recurrence. The median follow-up time was 856 (143 - 1276) days. Final condition analysis reveals that 74 patients (59.6%) are alive. Conclusion: We determined in our study that the NLR is effective on survival. Medical literature on this subject is scanty and prospective studies with large patient groups are needed.

Keywords

Acute Myeloid Leukemia, Neutrophil to Lymphocyte Ratio, Prognosis, Survival

1. Introduction

AML is a heterogeneous hematologic malignancy and may result in a short OS for reasons like infection, bleeding, leukocytosis if untreated [1] [2]. Many factors related to the patient and the tumor has been associated with a poor prognosis for AML [3] [4] [5] [6] [7]. The neutrophil-to-lymphocyte ratio is a beneficial prognostic marker in infectious diseases, inflammatory, emergency surgical conditions, and post-operative complications. [8] [9] [10] [11] It can also be a mortality marker in cardiovascular events [12] [13]. It was previously mentioned that a high NLR ratio is beneficial in demonstrating prognosis in some solid tumors and hematologic malignancies like lymphoma and multiple myeloma. With high NLR, low OS and disease free survival in breast cancer; in gastric cancer, a correlation was found with both advanced stage and low progression-free survival (PFS) and OS. NLR ≥ 6.0 in Hodgkin lymphoma, one of the hematological malignancies, was associated with low PFS, and poor OS and PFS in multiple myeloma. [14] [15] [16] [17]. However, its importance in acute leukemias is not clear.

The study aims to investigate the effects of cell count and clotting tests at the time of initial admission before being diagnosed with AML, and whether NLR has an impact on prognosis.

2. Materials and Methods

The data of 104 patients with AML who were treated in the Medical Adult Hematology Clinic between 2015 and 2019 were retrospectively analyzed.The effects of demographic andclinical data on overall survival (OS) and progression-free survival (PFS) were investigated. The descriptive statistics related tonumerical variables were presented as mean standard deviation or median. Nominal variables selected as frequency (percentage), Numerical variable with a t-test. Categorical variables were evaluated with aChi-square test. The Cox regression method was used to find the variables related toOS and PFS. For drawing survival curves, Kaplan Meier method was used. Analyses were made with SAS University Edition 9.4 program. $P<.05$ was accepted as significant. The ethical approval was obtained from the ethics committee (decision date: 05.02.2021 and no. 2021/3085).

3. Results

63 of the cases (60.5%) were men and 41 (39.4%) were women. Of the 104 cases, 47 had AML with repetitive genetic abnormalities, 7 had neoplasia withmyelodysplasia, 3 had myeloid neoplasia related tothe therapy, 1 had sarcoma, and 46 had the AML which could not be specified as otherwise. 3 of our patients had extramedullary involvement. The average age and parametres at the time of diagnosis are summarized (**Table 1**).

53 patients were responsive (myeloblast < 5% in bone marrow) to the induction regimen (62.3%) while 27 patients were unresponsive (31.7%). Five patients

Table 1. Laboratory parameters at the time of application.

Laboratory parameter	*mean ± sd*	*median (Q1 - Q3)*
Hemoglobin (g/dL)	9.0 ± 2.1	8.9 (7.4 - 10.4)
Leukocyte (/mcL)	43.123 ± 63.357	8.600 (2.600 - 62.250)
Neutrophil (/μL)	8.078 ± 19.468	1.150 (390 - 5.400)
Lymphocyte (/μL)	7.890 ± 15.203	3.500 (1.300 - 8.400)
Monocyte (/μL)	26.516 ± 43.831	2.800 (400 - 35.200)
NLR	1.19 ± 2.29	0.48 (0.14 - 1.32)
Platelet (/mm³)	81.818 ± 102.349	56.500 (28.500 - 94.000)
MPV	9.8 ± 2.1	10.0 (8.6 - 11.5)
D-dimer (ng/mL)	6.05 ± 7.51	1.6 (0.9 - 11)
INR	1.2 ± 0.18	1.2 (1.1 - 1.3)
aPTT (sn)	28.2 ± 3.6	28 (26 - 30)
Fibrinogen (mg/dL)	382 ± 159	380 (260 - 485)
Blast (%)	61.6 ± 25.1	70 (35 - 80)
Follow-up Time (days)	549 ± 478	436 (122 - 883)

died before completing the regimen. The median follow-up time was 436 (122 - 883) days. It was found that leucocyte (WBC), neutrophil, lymphocyte, monocyte counts, hemoglobin (Hb) level, platelet (PLT), MPV, INR, aPTT, NLR, fibrinogen and the biopsy blast count were not associated with the response to therapy. Median D-dimer was found lower in the unresponsive group 3.6 ± 1.0 ng/mL than in the responsive group 7.1 ± 1.1 ng/mL ($P = 0.02$).

Recurrences were detected in 21 patients (20.1%) and the median time to the recurrence was 315 (208 - 483) days. The values of WBC > 30.000/mcL [$P = 0.02$, HR: 0.25 (0.07 - 0.84)], D-dimer level [$P = 0.03$, HR: 1.219 (1.040 - 1.493)] and age at the time of application were determined to be associated with recurrence. But no relationship between recurrences and the facts that Hb count was <10 g/dL, PLT < 20.000 mm³ and biopsy blast ratio was >30%.

It wasdetermined that OS was strongly associated with the NLR [$P = 0.0002$ HR: 1.149 (1.038 - 1.242)]. OS was median 559 (164 - 953) days in the patients with NLR < 1.32 and 138 (33 - 359) days in the ones with the ratio ≥1.32 (Figure 1). In addition, being over 60 years old [$P = 0.0002$ HR: 0.343 (0.193 - 0.605)] neutrophil count [$P = 0.02$ HR: 1.012 (1.000 - 1.021)], INR [$P = 0.01$ HR: 1.254 (1.045 - 01.495)], fibrinogen [$P = 0.03$ HR: 1.023 (1.001 - 1.044)] and OS were found to be related. Final condition analysis reveals that 49 patients (47.1%) are alive (Figure 2).

4. Discussion

Most of the AML cases are observed at >60 years of age and more frequently in men [18] [19] [20] [21]. 33.6% of our patients were >60 years old and the disease

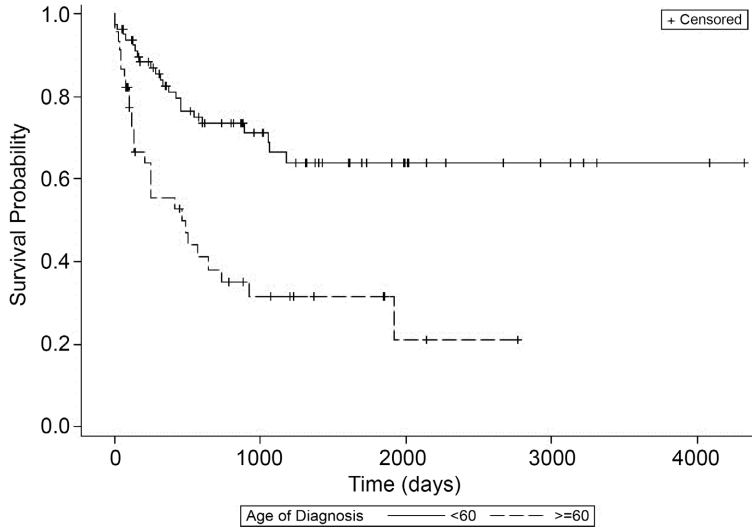

Figure 1. Overall survival curves by age.

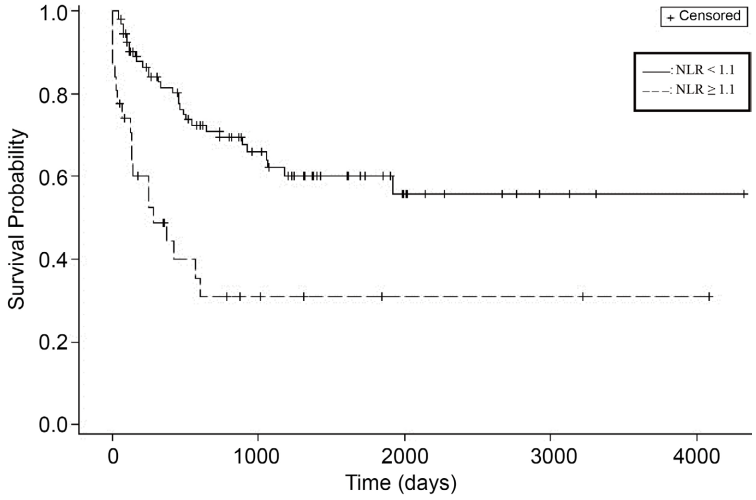

Figure 2. Overall survival curves by NLR.

was more frequent in men. In our study, OS was lower in older age and male gender, which was consistent with the literature.

The incidence of secondary AML increases with aging and has poorer prognosis than de novo AML [22]. Preexisting myelodysplastic or myeloproliferative disorders are observed in 24% - 40% of AML cases [23] [24] [25] [26] [27]. The secondary AML rate was found as 10.5% in our study. The reason for less rate of secondary AML could be the lesser old population and racial differences.

AML is usually noticed with whole blood count and peripheral smear test results [28]. Pancytopeniais usually present and hyperleukocytosis (>100.000/mm^3) is detected at 10% of cases at diagnosis [29]. 15.3% of the cases had hyperleukocytosis and 34.6% had pancytopeniain our study. Bertoli *et al.* determined that leukocyte count is not an effective factor in the complete response in their study [30]. The values of WBC ≥ 100.000/mm^3 and PLT ≤20.000 /mm^3 were defined as

bad prognostic factors in another study [31]. WBC, Hb, and PLT values were not associated with the response to therapy and OS in our study.

Arber *et al.* classified the blast ratio as <30% and ≥30% and they did not find any difference for OS in their study [32]. Davutoğlu *et al.* did not find an association between the bone marrow blast ratio and OS in their study [33]. Recurrences in 20.1% of patients were determined in our study and we did not find an association between the blast ratio and both the response to therapy and the OS-similarly to the results of the latter study.

The NLR was studied in diffuse B-cell lymphoma, Hodgkin lymphoma, and multiple myeloma to assess the prognosis and its effect was confirmed [34]. However, this ratio has not been evaluated on a large-scalefor acute leukemia. Mushtaq et alincluded 63 relapsed/refractory AML patients in their study. They found that this ratio was associated with the OS and response to therapy and it was 3.2 months for the patients with NLR ≥ 3, 9.2 months for the ones with NLR < 3 [35]. In our study, it was detected for about 4.6 months while OS NLR was ≥1.32, and about 18.6 months was <1.32. Supports the interaction between the tumor microenvironment and the immunological response of the host.

5. Conclusion

We recommend considering the NLR as it can predict OS and also, as it's a non-invasive and routine test. Also, we think that more studies are needed on this subject, as there is a limited number of studies evaluating NLR in AML patients.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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