

Elevated erythrocyte sedimentation rate is associated with metastatic disease and worse survival in patients with cutaneous malignant melanoma

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Abstract. Elevated erythrocyte sedimentation rate (ESR) is common in cancer patients and it may affect survival. However, its clinical role and prognostic significance remain unknown in melanoma patients. The objective of the present study was to determine the clinical significance of the ESR levels in cutaneous melanoma patients. A total of 139 cutaneous melanoma patients were enrolled in this study and were retrospectively investigated. The median age of the patients was 52 years (range, 16-88 years). The median ESR was 22 mm/h (range, 2-122 mm/h). Significant differences in ESR were found to be associated with sex, histology, blood hemoglobin level, lactate dehydrogenase (LDH) and metastatic disease. Female patients ($P=0.006$) and those with nodular histology ($P=0.005$), low hemoglobin concentration ($P<0.001$), higher LDH levels ($P=0.003$) and metastatic disease ($P<0.001$) were more likely to have elevated ESR levels. However, ESR was not found to be significantly associated with age, site of lesion, or pathological indicators, including Clark's level of invasion, Breslow's depth, mitotic rate, ulceration, vertical growth phase, tumor-infiltrating lymphocytes, regression, neurotropism, lymphovascular invasion and BRAF (V600E) mutation ($P>0.05$). ESR was also not associated with lymph node involvement ($P=0.188$) or responsiveness to chemotherapy ($P=0.390$). However, ESR was found to be significantly associated with outcome; patients with increased ESR had worse survival compared with those with normal values (hazard ratio=2.033; 95% confidence interval: 1.156-3.577; $P=0.012$). In conclusion, elevated ESR was found to be associated with metastatic disease and

was also found to be a prognostic factor adversely affecting survival in patients with cutaneous melanoma.

Introduction

It has been demonstrated that there is an association between chronic inflammation and carcinogenesis (1), and that subclinical or even undetectable inflammation may be as significant as chronic inflammation in increased cancer risk, cancer development and progression (1). Chronic inflammation may promote excessive cell proliferation and activate a cascade of cellular events, promoting tumor cell growth (2). Furthermore, tumor progression *per se* may also stimulate host immune response and inflammation.

Erythrocyte sedimentation rate (ESR) is the most widely used laboratory test for evaluating the inflammatory status in clinical practice, including infection, autoimmune and malignant diseases (3). Elevated ESR is frequently encountered in patients with cancer. The outcome in various malignancies depends on the type of the underlying disorder, the stage and duration of the disease, and the regimen and intensity of the antitumor treatment. In addition, an elevated ESR level has also been identified as a prognostic factor adversely affecting survival in cancer patients (2-8). A number of studies indicated that an increased ESR level is associated with worse survival; patients with higher ESR values in various malignancies, including colorectal cancer (2), renal cell cancer (4), head and neck cancer (5), soft tissue sarcoma (6), breast cancer (7), glioma (8) and prostate cancer (9), had a shorter survival compared with those with normal ESR levels.

Although there have been sufficient data on other types of tumors, to the best of our knowledge, the prognostic value of ESR in melanoma patients has not been adequately investigated (10,11) and the significance of elevated ESR levels in melanoma patients has not been fully elucidated. However, increased ESR levels have been identified as an adverse prognostic factor for survival in melanoma patients as a secondary finding when different parameters were investigated in our previously published trials (12-15).

In the present study, the ESR levels were evaluated in cutaneous melanoma patients, and the associations with disease prognosis and various known clinical variables were determined.

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Patients and methods

Patients. A total of 139 adult patients with histologically confirmed cutaneous melanoma in whom ESR was determined were included in the present analysis and were retrospectively investigated. The patient records were retrieved from the cancer registry of the Institute of Oncology, University of Istanbul (Istanbul, Turkey) for review of the clinicopathological factors and patient survival. The patients were treated and followed-up according to standard international guidelines, such as National Comprehensive Cancer Network (<https://www.nccn.org/patients/guidelines/melanoma/>) and European Society for Medical Oncology (<http://www.esmo.org/Guidelines/Melanoma>) guidelines.

The ESR values of the patients were determined at first admission by the standard Westergren method (16,17). The study protocol was reviewed and approved by the local Ethics Committee.

Statistical analysis. Comparisons between clinicopathological characteristics and ESR values were performed using the Mann-Whitney U test, independent samples t-test and logistic regression test. Receiver operating characteristic curves were used to define the cut-off value of ESR levels for survival analysis. Kaplan-Meier analysis was used for estimation of patient survival and differences in outcomes were assessed using log-rank statistics. A P-value of ≤ 0.05 was considered to indicate statistically significant differences.

Results

Patient characteristics. A total of 139 cutaneous melanoma patients were enrolled in the present study. The median age of the patients was 52 years (range, 16-88 years). The demographic and clinicopathological characteristics are summarized in Table I. The median value of ESR values of the patients was 22 mm/h (range, 2-122 mm/h). Significant differences in ESR were only found in association with sex, histology, blood hemoglobin level, lactate dehydrogenase (LDH) levels and metastatic disease (Table I). Female patients ($P=0.006$) and those with nodular histology ($P=0.005$), low hemoglobin concentration ($P<0.001$), higher LDH levels ($P=0.003$) and metastatic disease ($P<0.001$) were more likely to have elevated ESR values. However, the ESR levels were not found to be significantly associated with age, site of lesion, or pathological indicators such as Clark's level of invasion, Breslow's depth, mitotic rate, ulceration, vertical growth phase, tumor-infiltrating lymphocytes, regression, neurotropism, lymphovascular invasion and BRAF (V600E) mutation ($P>0.05$). ESR was also not associated with lymph node involvement ($P=0.188$) or responsiveness to chemotherapy ($P=0.390$).

Effect of elevated ESR on survival. When survival analyses of possible clinicopathological variables affecting outcome were performed, nodular histology ($P=0.043$), high mitotic rate ($P=0.004$), presence of ulceration ($P=0.034$), presence of lymphovascular invasion ($P<0.001$), increased serum LDH level ($P<0.001$), lymph node involvement ($P=0.005$), multiple node involvement ($P=0.010$), distant metastasis ($P<0.001$) and

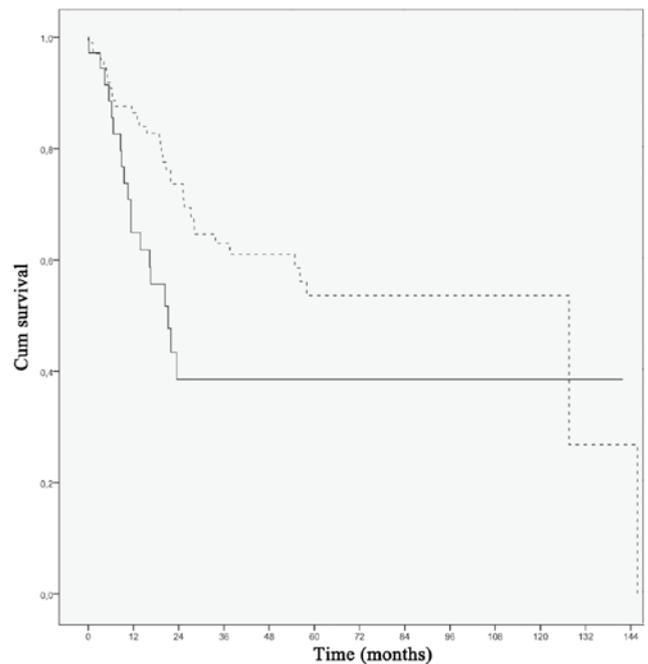


Figure 1. Overall survival curves in melanoma patients according to ESR (<35 vs. ≥ 35 mm/h; $P=0.012$). Dotted line, <35 mm/h; straight line, ≥ 35 mm/h. ESR, erythrocyte sedimentation rate.

failure to respond to chemotherapy ($P=0.002$) were found to be poor prognostic factors for overall survival (Table II). ESR was found to be significantly associated with outcome, with patients with elevated ESR exhibiting worse survival compared with those with normal ESR values ($P=0.012$) (Table II, Fig. 1).

Discussion

The aim of the present study was to evaluate the prognostic value of ESR elevation focusing specifically on cutaneous melanoma patients. The study analyzed 139 melanoma patients, including all disease stages, which, to the best of our knowledge, is the largest population-based sample size from a single institution to date.

At the time of the analysis, to our knowledge, only a limited number of studies had focused on the prognostic value of the ESR level in cutaneous melanoma patients (10,11). In the Norwegian Radium Hospital, 177 metastatic melanoma patients treated with various chemotherapy regimens were included in a regression analysis of prognostic factors (10). Multivariate analysis identified ESR >15 mm/h as a significant prognostic factor indicating short survival with a low probability of surviving for 3 months, whereas patients with normal ESR values had a median survival of 11.5 months, with 94% surviving for 3 months. In another study, 71 patients with metastatic disease were included (11). The serum ESR levels were significantly elevated in patients with progressive disease. On logistic regression analysis, ESR was found to be of low specificity.

The present study revealed that an elevated ESR level was associated with metastatic disease, but not lymph node involvement. ESR level at diagnosis was a prognostic factor

Table I. Patient/disease characteristics and correlations between ESR and various clinicopathological variables.

Variables	n	ESR (mm/h), median (range)	HR (95% CI)	P-value
No. of patients	139	22 (2-122)		
Age (years)			1.001 (0.985-1.018)	0.162
<50	64	20.5 (2-122)		
≥50	75	23 (3-83)		
Sex			1.017 (0.999-1.035)	0.006
Male	87	19 (2-122)		
Female	52	30 (5-83)		
Site of lesion			1.005 (0.984-1.026)	0.652
Axial	69	22 (3-70)		
Extremities	58	19.5 (2-83)		
Histopathology			0.978 (0.953-1.003)	0.005
Nodular	24	27 (10-70)		
Others	74	19.5 (2-83)		
Clark's level			1.012 (0.979-1.047)	0.280
I-III	19	16 (3-63)		
IV-V	83	21 (5-83)		
Breslow's thickness, mm			1.016 (0.981-1.051)	0.398
<2	20	18.5 (3-62)		
≥2	85	21 (3-83)		
Mitotic rate, n/mm ²			1.011 (0.986-1.036)	0.387
≤3	47	20 (3-83)		
>3	50	21 (7-83)		
Ulceration			1.028 (0.999-1.059)	0.115
Absent	38	20 (3-52)		
Present	62	22 (3-83)		
Neurotropism			1.013 (0.953-1.075)	0.690
Absent	58	20.5 (3-83)		
Present	3	25 (22-40)		
Vertical growth phase			0.999 (0.925-1.079)	0.988
Absent	3	15 (10-42)		
Present	60	20 (3-83)		
Lymphovascular invasion			1.026 (0.994-1.060)	0.107
Absent	72	19.5 (3-66)		
Present	15	26 (5-83)		
Tumor-infiltrating lymphocytes			1.008 (0.978-1.039)	0.599
Absent	23	16 (3-83)		
Present	70	21.5 (3-83)		
Regression			1.012 (0.987-1.039)	0.350
Absent	61	20 (3-66)		
Present	28	21 (7-83)		
BRAF (V600E) mutation			0.972 (0.931-1.015)	0.171
Negative	12	27 (7-96)		
Positive	15	22 (6-63)		
Hemoglobin level			0.953 (0.931-0.975)	<0.001
Low	36	35.5 (10-122)		
Normal	98	18 (2-83)		
Serum lactate dehydrogenase			1.033 (1.012-1.055)	0.003
Normal	109	21 (2-83)		
High	24	34 (11-122)		

Table I. Continued.

Variables	n	ESR (mm/h), median (range)	HR (95% CI)	P-value
Lymph node metastasis			1.023 (0.994-1.054)	0.188
No	35	18 (2-52)		
Yes	68	22 (5-83)		
No. of lymph node metastasis			1.028 (0.996-1.060)	0.078
1	37	21 (5-51)		
≥2	30	22 (5-83)		
Metastatic stage (M1)			1.044 (1.022-1.066)	<0.001
No	99	18 (2-75)		
Yes	40	31.5 (2-122)		
Stage of metastatic disease			0.989 (0.965-1.014)	0.401
M1a-b	14	37 (15-96)		
M1c	26	31.5 (2-122)		
Response to chemotherapy			0.987 (0.959-1.016)	0.390
No	20	38 (15-122)		
Yes	14	31.5 (6-83)		

ESR, erythrocyte sedimentation rate; HR, hazard ratio; CI, confidence interval.

Table II. Analysis of variables in association with overall survival.

Variables	HR (95% CI)	P-value
Age	1.037 (0.607-1.772)	0.893
Sex	0.677 (0.377-1.215)	0.191
Site of lesion	0.608 (0.332-1.115)	0.104
Histology	0.457 (0.211-0.993)	0.043
Clark's level	2.054 (0.717-5.881)	0.171
Breslow's thickness	1.824 (0.702-4.743)	0.211
Ulceration	2.362 (1.045-5.341)	0.034
Mitotic rate	2.972 (1.354-6.523)	0.004
Neurotropism	2.430 (0.314-18.77)	0.379
Vertical growth phase	22.06 (0.001-48851)	0.356
Lymphovascular invasion	5.681 (2.432-13.27)	<0.001
Tumor-infiltrating lymphocytes	0.886 (0.383-2.049)	0.776
Regression	0.892 (0.370-2.146)	0.798
BRAF (V600E) mutation	1.037 (0.397-2.709)	0.940
Hemoglobin level	0.903 (0.492-1.657)	0.740
Serum lactate dehydrogenase	3.844 (2.104-7.020)	<0.001
Lymph node metastasis	4.002 (1.396-11.47)	0.005
No. of lymph node metastases	2.729 (1.233-6.044)	0.010
Metastatic disease	8.299 (4.717-14.60)	<0.001
Stage of metastatic disease	1.384 (0.647-2.964)	0.398
Response to chemotherapy	0.268 (0.110-0.651)	0.002
Erythrocyte sedimentation rate	2.033 (1.156-3.577)	0.012

HR, hazard ratio; CI, confidence interval.

for survival in melanoma patients and it was associated with other poor prognostic factors. A number of previously reported trials suggested that increased ESR values at presentation may adversely affect prognosis in patients with various types of cancer (2,4-9). Our findings were in agreement with the results reported by these studies. A limited number of our previously performed trials, which included small sample sizes (<100 patients), were focused specifically on melanoma and yielded similar confirmative results (12-15). The P-values in those studies were significantly low, namely P<0.001 (12,14), P=0.001 (13) and P=0.002 (15).

The association of systemic inflammation and patient survival may have implications for immune modulation in melanoma. The correlation of inflammatory status with metastatic disease suggests that melanoma with metastasis may be more immunogenic, thus inducing a more prominent inflammatory response. ESR, as a widely used laboratory test for evaluating the inflammatory status in clinical practice was found to be significantly associated with survival in melanoma patients, suggesting an important role of inflammation in melanoma progression. Inflammatory cells have been suggested to promote carcinogenesis, possibly by augmenting DNA damage, promoting tumor cell proliferation, and stimulating angiogenesis and metastasis.

In conclusion, elevated ESR was found to be associated with metastasis and it predicts worse survival in cutaneous melanoma patients. Therefore, ESR may be a prognostic risk factor and be correlated with other powerful prognostic variables. Despite its relatively low sensitivity and specificity in monitoring disease activity, the ESR assessment is a widely used, cost-effective and simple test, which may be a viable alternative to novel, more expensive methods in the prognostication of cutaneous melanoma patients. The present study was limited by its retrospective design and relatively

small number of included patients. A prospective study of a larger patient sample is required to confirm the results of the present study.

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