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Association Between Uveal Melanoma and Allostatic Load

HAARISUDHAN SURESHKUMAR[1], ABHIJITH EATHARA[1], AVISEK DATTA[2], REEM ALAHMADI[3], RYAN H. NGUYEN[4] and MICHAEL J. HEIFERMAN[1]

[1]*Department of Ophthalmology and Visual Sciences, University of Illinois College of Medicine, Chicago, IL, U.S.A.;*
[2]*Department of Epidemiology and Biostatistics, University of Illinois School of Public Health, Chicago, IL, U.S.A.;*
[3]*Vitreoretinal Division, King Khaled Eye Specialist Hospital, Riyadh, Kingdom of Saudi Arabia;*
[4]*Department of Medicine, University of Illinois College of Medicine, Chicago, IL, U.S.A.*

Abstract. *Background/Aim: Allostatic load (AL) is a measure of chronic stress that is associated with worse cancer outcomes. The purpose of this retrospective cohort study was to investigate the relationship between AL and uveal melanoma (UM) clinical features. Patients and Methods: AL score was calculated as a composite of ten biomarkers in 111 patients with UM from the University of Illinois Hospital. One point was assigned to an AL score for each biomarker based on predetermined cutoff values. Linear and logistic regression analyses evaluated the relationship between AL score and several tumor clinical characteristics. Results: High AL score had a significant relationship with extraocular extension (p=0.015). There was also a significant difference in mean blood glucose levels between the different tumor size groups (p=0.029). Higher AL scores also had a trend of being associated with a smaller tumor size (p=0.069). Conclusion: AL score was significantly associated with the presence of extraocular extension for uveal melanoma, while the smallest tumor size group was associated with the highest blood glucose level. No other significant correlations were found between AL and other clinical features of UM. The relationship between AL score and extraocular extension warrants further investigation. Additional research is needed to evaluate socioeconomic factors and their effect on the relationship between chronic stress and the clinical features of UM.*

Melanoma is a common type of cancer comprised of malignant melanocytes that occur in a variety of anatomical locations, including the skin, eyes, and mucosa. The eye is the third most common site of melanoma, with an incidence of approximately 83% in the uvea, 5% in the conjunctiva, and 10% in other sites (1). Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, with a mean incidence rate of 5.1 cases per million per year in the United States (2). Despite its rarity, UM is a disease of considerable interest due to its poor prognosis, with a disease- specific mortality rate of over 50% in UM cases (3). Due to this mortality rate and tendency to metastasize, early identification and treatment is important to improve the prognosis for patients with UM (3).

A variety of factors influence the prognosis and clinical presentation of UM. The genetic mutations associated with UM have been well characterized and correlate with distinct prognostic profiles (4). Independent of these genetic profiles, over-expression of preferentially expressed antigens in melanoma has been associated with a worse prognosis of UM (5). Moreover, the presence of clinical risk factors, such as the largest basal diameter and tumor thickness, suggests that genetic mutations only play a partial role in determining the prognosis of UM. Thus, it is important to consider the role of novel risk factors to improve the prognostication of UM.

Another factor that may play an important role in determining the clinical presentation of UM is chronic stress. Chronic stress can be described as persistent mental and physical strain that can lead to modification of normal physiology with potentially harmful effects on the human body (6). With regards to cancer, chronic stress has been found to promote mechanisms of tumor progression, such as angiogenesis, metastatic dissemination, and resistance against antitumor therapies (7, 8). Moreover, chronic stress can result in biological dysfunction contributing to the disruption of allostasis, which describes the body's physiological ability to adapt to external stressors. The cumulative deterioration caused by chronic stress and the disruption of allostasis can be measured with a set of biological markers known as allostatic load (AL) (9, 10).

Several studies have demonstrated a significant correlation between a high AL and worse cancer outcomes. Xing *et al.* investigated AL markers (lipid profiles, BP, and others) before

Correspondence to: Michael Heiferman, 1855 West Taylor Street, M/C 648, Chicago, IL 60612, U.S.A. Tel: +1 3129963937, e-mail: mheif@uic.edu

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and after an individual received their breast cancer diagnosis to determine whether high AL had a correlation with the presence of poorly differentiated and larger breast cancers among black women (11). They found that an elevated pre-diagnostic AL was associated with a poorer breast cancer prognosis. Similarly, recent studies by Wang *et al*. and Guan *et al*. found that high AL was associated with a higher risk of breast cancer (12, 13). Obeng-Gyasi *et al*. identified a similar correlation in patients with non-small cell lung cancer, associating a high AL with a poor prognosis (10). Furthermore, Acheampong *et al*., using an AL measure called Multi-Systemic Biological Risk (MSBR), identified a correlation between a high MSBR and a high cancer mortality rate (14). AL is an emerging biomarker in cancer outcomes and has been shown to correlate with a worse prognosis in multiple types of cancer.

There have been no studies examining the association between AL and clinical features of UM. Thus, in the present study, we sought to evaluate the correlation between AL and the clinical features of UM in the patient population of the University of Illinois Hospital. Specifically, we hypothesized that a high AL correlates with poorer presenting features of UM.

Patients and Methods

Data source and inclusion/exclusion criteria. The Institutional Review Board approval (STUDY2021-1481) for this study was obtained from the University of Illinois Chicago. Patients that were diagnosed with UM from 2010 to 2023 at the University of Illinois Hospital were selected for a retrospective chart review. Patients that were 21 years or older who met our inclusion criteria based on diagnostic codes for UM had metabolic panel and vitals recorded within six months of their diagnosis. Patients missing one or more values necessary in calculating the AL score were removed from our analysis. All recorded data were stored in a HIPAA compliant RedCAP file (Vanderbilt University, Nashville, TN, USA).

Measures. In this retrospective chart review, the following demographic variables were recorded: age at diagnosis, race, ethnicity, sex, date of birth, zip code, and past medical history. High AL was measured using the following components and their corresponding cutoffs as described previously: (I) systolic blood pressure ≥140 mmHg, (II) diastolic blood pressure ≥90 mmHg, (III) heart rate ≥90 bpm, (IV) body mass index ≥30 kg2/m, (V) glucose ≥110, (VI) aspartate aminotransferase (AST) ≥40, (VII) alanine aminotransferase (ALT) ≥40, (VIII) alkaline phosphatase ≥101, (IX) creatinine >1.3, (X) albumin <3 g/dl (10, 15, 16). Using these cutoffs, each parameter was dichotomized as a 1, if high AL was indicated, and a 0 if not. Each parameter assigned a 1 was then summed to yield an AL score. In our subsequent analysis, patients received one point towards the AL score for each biomarker that fell in the most pathologic quartile as described previously (17-19). For systolic blood pressure, diastolic blood pressure, heart rate, glucose, AST, ALT, alkaline phosphatase, and creatinine, patients who fell in the highest quartile for a given biomarker were assigned a 1. For BMI, patients who fell in the lowest and highest quartile were assigned a 1. Lastly, for albumin, patients in the lowest quartile were assigned a 1. Each parameter assigned a 1 was then summed to yield an AL score for each patient. Lastly, tumors were categorized as small, medium, or large according to previously described size classifications utilized in the Collaborative Ocular Melanoma Study (COMS) (20).

Statistical analysis. Demographics and biomarker characteristics were assessed with counts and percentages for categorical variables, as well as means and standard deviations for continuous variables. We used the median AL score of our study sample as a cutoff to determine the "Low" and "High" AL categories, as previously described in other studies (11). Linear regression analyses were performed for any continuous outcome of interest using categorical AL as our predictor. Similarly, logistic regression analyses were performed for binary outcomes of interest using categorical AL as our predictor. Relative risk with 95%CI was assessed for linear regression analyses, while odds ratios with 95%CI were used for logistic regression analyses. *p*-Values less than 0.05 were considered statistically significant. Lastly, an ANOVA was used to identify significant differences in mean AL score among tumor sizes. All results for analyses were generated using R software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of the study sample. A total of 111 patients were selected for our study based on our inclusion criteria. A summary table of select socioeconomic and clinicopathologic characteristics of all study participants is shown in Table I. The average age at which this study sample was diagnosed was 61.6 years old. In terms of UM tumor clinicopathology, among the overall study sample, most patients (53.7%) were diagnosed with AJCC Stage 2 cancer. Moreover, the average tumor thickness and largest basal diameter of our study was 5.87 mm and 11.30 mm, respectively (Table I).

Association between AL score and tumor clinical features. Table II depicts the distribution of the various biomarkers contributing to AL score and AL score itself based on this study's sample. A total of 35 (31.5%) patients from our study sample were found to have a high AL score. The mean AL score for our study sample was 1.98 with a standard deviation of 1.40 (Table II).

Figure 1A depicts the linear and logistic regression analyses between AL score and different tumor clinical features through our secondary analysis using cutoffs to determine AL score. As seen from this figure, the relationship between AL score and extraocular extension was found to be significant (*p*-value=0.015) (Figure 1A).

Figure 1B depicts the linear and logistic regression analyses between AL score and different tumor clinical features with calculated confidence intervals and *p*-values. AL score was calculated by using the quartile method as previously described. Linear regression analyses between AL score and largest basal diameter, along with tumor thickness, was conducted. Furthermore, logistic regression analyses were conducted between the different AJCC stages, local recurrence, extraocular extension, and AL score (Figure 1B).

Table I. *Select characteristics of the study sample. SD: Standard deviation.*

	Study population (N=111)
Age at diagnosis (years)	
Mean (SD)	61.5 (15.6)
Sex	
Male	53 (47.7%)
Female	58 (52.3%)
Race (n=102)	
Non-white	28 (27.5%)
White	74 (73.5%)
Ethnicity (n=100)	
Non-Hispanic	92 (92.0%)
Hispanic	8 (8.0%)
Tumor stage (n=89)	
Stage 1	20 (22.5%)
Stage 2	45 (50.6%)
Stage 3	7 (7.9%)
Stage 4	17 (19.1%)
Tumor thickness	
Mean (SD)	5.93 (3.55)
Basal diameter	
Mean (SD)	10.70 (3.84)

Table II. *Distribution of study sample for allostatic load (AL) and AL biomarkers. AST: Aspartate aminotransferase; ALT: alanine aminotransferase.*

	Study population (N=111)
Biomarkers: Mean (SD)	
Allostatic score	1.98 (1.40)
Systolic blood pressure	134.15 (24.82)
Diastolic blood pressure	77.60 (11.39)
Heart rate	81.17 (20.22)
Body mass index	28.96 (9.23)
Glucose	117.71 (53.17)
AST	31.18 (69.18)
ALT	29.69 (46.60)
Alkaline phosphatase	99.11 (107.74)
Creatinine	1.00 (0.68)
Albumin	3.97 (0.66)
High biomarkers	N (%)
High allostatic score	35 (31.5%)
Systolic blood pressure ≥140 mmHg	40 (36.0%)
Diastolic blood pressure ≥90 mmHg	14 (12.6%)
Heart rate ≥90 bpm	21 (18.9%)
Body mass index ≥30 kg/m^2	37 (33.3%)
Glucose ≥110 mg/dl	42 (37.8%)
AST ≥40	7 (6.3%)
ALT ≥40	15 (13.5%)
Alkaline phosphatase ≥101	24 (21.6%)
Creatinine >1.3	9 (8.1%)
Albumin <3	9 (8.1%)

Lastly, Table III depicts the results of an ANOVA comparing the AL score means between different tumor size groups, as designated by the size classifications previously described in the COMS trial (20). As shown, mean glucose levels varied significantly across tumor size groups (p-value=0.029), with the small group having the highest mean glucose level (Table III).

Discussion

Recently, emerging evidence has demonstrated that the presence of a higher AL is significantly correlated with a worse tumor presentation for multiple types of cancer. To our knowledge, this retrospective study is the first to examine the correlation between biomarkers of physiological dysregulation (AL) and the clinical features of UM.

In our study, we used the surrogate endpoints of largest basal diameter, tumor thickness, AJCC stage, local recurrence, and extraocular extension for tumor presentation. Interestingly, the results of our study contrast the results of other studies investigating the relationship between AL score and clinical features of other types of cancer. For example, our results indicate there is no significant relationship between AL score and tumor thickness or largest basal diameter. On the other hand, Xing *et al*. and Parente *et al*. noted a significant relationship between AL score and breast tumor size (11, 15). However, in contrast to breast cancer where screening is part of national guidelines, UM is typically discovered incidentally through regular eye exams or upon acute ocular symptoms. Moreover, unlike the study by Xing *et al*., our study found no significant relationship between AL score and tumor staging. Lastly, although found to be insignificant, the relationships between AL score and local recurrence demonstrate weak correlations. It should be noted that our study may be potentially underpowered to detect the significance of these correlations.

Our primary analysis in which cutoffs were used to determine AL score is a well-accepted method of AL score analysis that has been commonly utilized in previous literature (10). This analysis yielded that AL score has a significant relationship with extraocular extension, indicating that a high AL may play a role in the pathophysiology of extraocular extension. Given that extraocular extension is a significant indicator of a poorer prognosis of UM, AL and its relationship to the presence of extraocular extension should be further investigated to understand the role of allostatic disruption on the pathogenesis of extraocular extension of UM (3, 21, 22). Our secondary analysis, which used the quartile methodology, has also been established in AL and cancer outcomes research. Given the variability of measuring AL and the lack of a gold standard for AL in cancer research, the discrepancy between the two findings further supports the need for validating the optimal AL measurement methodology.

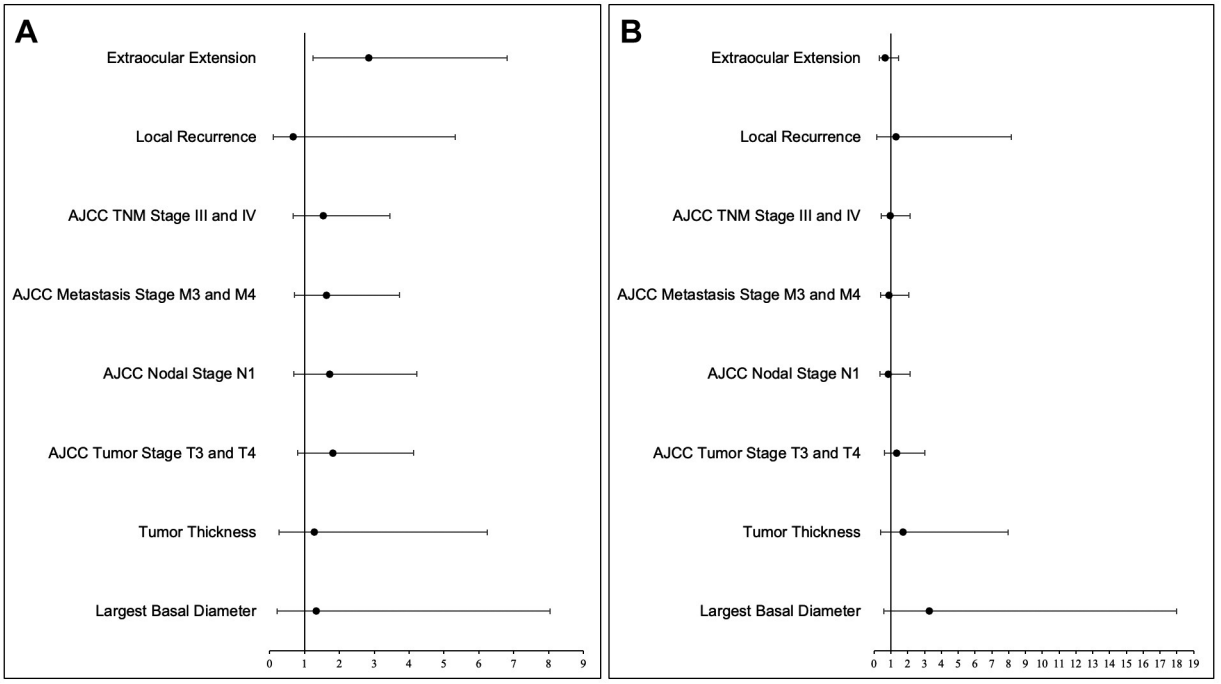

Figure 1. *Forest plot of linear and logistic regression analysis with odds ratio and 95% confidence interval for A) allostatic load score cutoff method and B) Quartile method. AJCC: American Joint Committee on Cancer.*

Table III. *ANOVA for significant differences in biomarker means.*

	Tumor size			
	Small (n=15)	Medium (n=57)	Large (n=21)	*p*-Value
Biomarkers: Mean (SD)				
Allostatic score (Cutoff method)	2.00 (1.46)	2.02 (1.43)	1.95 (1.28)	0.905
Allostatic score (Quartile method)	3.67 (1.18)	2.74 (1.45)	3.05 (1.32)	0.069
Systolic BP	133.40 (21.85)	133.30 (26.75)	138.43 (22.25)	0.715
Diastolic BP	77.80 (13.75)	78.19 (11.07)	80.38 (11.35)	0.728
Heart rate	82.40 (13.09)	81.51 (22.06)	76.00 (15.50)	0.499
Body mass index	27.74 (4.96)	30.03 (11.04)	28.76 97.95)	0.681
Glucose	151.93 (108.42)	109.58 (25.87)	126.95 (60.53)	**0.029**
AST	21.67 (7.30)	36.40 (93.87)	24.48 (18.38)	0.708
ALT	24.67 (19.48)	34.04 (63.28)	25.81 (13.38)	0.724
Alkaline phosphatase	84.73 (38.95)	87.39 (64.31)	116.005 (130.98)	0.353
Creatinine	0.90 (0.22)	1.00 (0.70)	0.90 (0.22)	0.743
Albumin	4.12 (0.65)	4.03 (0.52)	4.11 (0.75)	0.808

BP: Blood pressure; AST: aspartate aminotransferase; ALT: alanine aminotransferase. Statistically significant *p*-values are shown in bold.

A subsequent analysis on comparing the AL score and biomarker means between different tumor sizes was conducted. These tumor sizes were grouped into categories based on size classifications as previously described by the COMS trial (20). There was a trend (*p*-value=0.069) in the differences between AL score (quartile method) means between tumor size groups, with the smallest tumor size having the highest mean AL score. We hypothesize that patients who suffer from chronic diseases are more likely to visit their primary care physician and have early detection of melanocytic choroidal tumors. Moreover, among all the biomarkers, the mean glucose was significantly different

(p-value=0.029) across the different tumor size groups, with the smallest tumor size group having the highest mean glucose level. We hypothesize that patients with a high glucose level are more likely to get a comprehensive diabetic screening, leading to early detection of UM.

Furthermore, it should be noted that ALT and AST were included as biomarkers for AL in this study. Although AST and ALT are biomarkers that are not typically included in AL scores, these markers were included in our study because they are routinely included at our institution for systemic surveillance. The liver is a common site of metastasis for UM, as 2% of patients typically have metastasis at the time of diagnosis, and there is evidence of a connection between liver enzymes and stress (23).

Understanding how AL relates to the clinical features of UM is important to understand as it provides contextual information for how AL may relate to prognosis. Several studies have elucidated a connection between AL and prognosis of other cancers. For example, Chen *et al*. found that high AL correlates with a higher mortality rate in breast cancers (24). Similarly, Yang *et al*. found that high AL correlated with a higher all-cancer mortality among older cancer survivors (25). Thus, further research is warranted to understand how AL may relate to the prognosis of UM.

Due to the retrospective design of this study, it cannot be determined whether AL score (and its subcomponents) predisposed the study participants to UM or were a result of disease burden. Thus, further research must be conducted to evaluate AL score before and after diagnosis to determine the nature of the relationship between AL score and UM. Additionally, many of the patients included in this study were diagnosed in the past five years. As a result, the correlations established in this study are not accurate in determining long-term clinical features of UM when evaluating factors like tumor metastasis, given that the average time from diagnosis to metastasis is 27 months (26). Lastly, other commonly used biomarkers in the AL literature (such as lipid panels, C-reactive protein, or HbA1c) were excluded from our study as these factors were not routinely collected in the course of care for our patients. Future studies of AL in UM may evaluate these additional markers to evaluate their relationship with UM clinical presentation.

Conclusion

Our findings contributed important knowledge regarding how AL score and specific AL biomarkers are associated with different tumor clinical features. Additional research to explore socioeconomic information and its impact on the relationship between AL and UM could add additional granularity to the findings of this study. Lastly, further research is warranted to understand how AL correlates with prognosis and disease mortality in UM.

Conflicts of Interest

The Authors declare no potential conflicts of interest in relation to this study.

Authors' Contributions

M.H. conceived the presented idea. A.E, H.S., and A.D. acquired data, conducted data analysis, and drafted the manuscript. R.A., R.N., and M.H. interpreted the data and revised the manuscript. All Authors reviewed the final manuscript and approved it for final submission.

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