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Research Article

Association Between Preoperative Albumin-to-Globulin Ratio (AGR) and Recurrence-Free Survival in High-Risk Resected Cutaneous Melanoma

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Abstract

Objectives: Recurrence risk varies among patients with resected stage II–III cutaneous melanoma. We evaluated whether preoperative albumin-to-globulin ratio (AGR) is associated with recurrence-free survival (RFS) in this high-risk population.

Methods: This retrospective cohort included 190 patients with stage II–III cutaneous melanoma after curative-intent resection. Preoperative AGR was calculated from serum albumin and total protein values within one month before surgery. Receiver operating characteristic (ROC) analysis identified a cohort-specific AGR cut-off for recurrence prediction. RFS was estimated by Kaplan–Meier analysis, compared with the log-rank test, and factors associated with recurrence were evaluated using Cox proportional hazards regression.

Results: During a median follow-up of 68.2 months, recurrence occurred in 64 patients (33.7%). The ROC-derived AGR cut-off was 1.22, with an area under the curve of 0.69, sensitivity of 68%, and specificity of 66%. Patients with low AGR had significantly shorter RFS than those with high AGR (64.4 vs. 117.7 months, p<0.001). In multivariate analysis, low AGR remained independently associated with increased risk of relapse or death (2.66, 95% CI: 1.48–4.79, p=0.001).

Conclusion: Preoperative low AGR was independently associated with poorer RFS and may support recurrence risk assessment in high-risk resected melanoma.

Keywords: Albumin-to-globulin ratio, cutaneous melanoma, recurrence-free survival

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The burden of cutaneous melanoma is increasing worldwide. Approximately 325,000 new cases and 57,000 deaths were estimated in 2020, and epidemiologic projections suggest a further rise in annual diagnoses by 2040.[1] Although modern adjuvant therapies have improved postoperative management, stage II–III cutaneous melanoma still carries a substantial risk of recurrence after surgery.[2–4] The 8th edition of the American Joint Committee on Can-

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cer (AJCC) staging system provides important prognostic guidance; however, patients within the same stage may still experience different outcomes, highlighting the need for additional biomarkers.[5]

In recent years, increasing attention has been given to host-related factors that may influence melanoma progression. Melanoma progression and clinical outcomes may be influenced not only by tumor-related features but also by host-related conditions, including nutritional status, metabolic alterations, immune competence, and systemic inflammation.[6–8] In this setting, routine laboratory-derived blood biomarkers are attractive for risk assessment because they are inexpensive and widely available in clinical practice.[6,8] For this reason, peripheral blood–based inflammatory and immunonutritional markers have been evaluated in melanoma as practical surrogates of systemic host condition, particularly in advanced-stage disease and immune checkpoint inhibitor (ICI)-treated cohorts.[7,9–11] Collectively, these findings suggest that host-related biological features may provide prognostic information beyond anatomical staging alone.

The albumin-to-globulin ratio (AGR) is a simple serum-based parameter calculated from routinely measured albumin and globulin levels. Serum albumin is influenced by both nutritional status and systemic inflammatory activity, as reduced albumin levels may reflect inflammation-related catabolism in addition to inadequate nutrition.[12] In addition, chronic immune activation and systemic inflammation may lead to an increase in the globulin fraction.[13.] Therefore, AGR may represent an integrated measure of host nutritional reserve and systemic inflammatory burden, and its association with adverse outcomes across several solid tumors supports its role as a broad host-derived prognostic marker rather than a tumor-specific index.[14–17] Nevertheless, its prognostic relevance remains insufficiently defined in patients with resected high-risk stage II–III cutaneous melanoma. Given that recurrence after curative-intent surgery in this population may be shaped by both tumor-related factors and the systemic host environment, we evaluated the prognostic significance of preoperative AGR and its incremental prognostic value beyond disease stage and Breslow thickness.

Methods

Study Design and Patient Population

This retrospective cohort included patients with high-risk stage II–III cutaneous melanoma who underwent curative-intent resection and were treated or followed at the two participating centers between January 2010 and January 2026. Eligible patients had evaluable preoperative laboratory data and key clinicopathological variables. Case ascertainment was performed by reviewing institutional electronic records, pathology archives, and oncology follow-up files. The recorded variables included age, sex, primary tumor location, tumor stage, Breslow thickness, ulceration status, mitotic rate, Clark level, adjuvant therapy status, recurrence status, date of recurrence, and date of last follow-up. Primary tumor location was classified as extremity, trunk, or head and neck. Mitotic rate was recorded as mitoses/mm^2. Adjuvant therapy was documented as present or absent according to whether systemic treatment was administered after curative surgery.

Patients were included if they fulfilled the following criteria: age ≥18 years, histologically confirmed cutaneous melanoma, stage IIB–III disease after curative-intent resection, absence of distant metastasis at baseline, available pretreatment serum albumin and total protein values for AGR calculation, and sufficient follow-up data for recurrence assessment. Patients were excluded if they had stage I or stage IV disease, mucosal or ocular melanoma, melanoma of unknown primary origin, incomplete resection or residual macroscopic disease, unavailable baseline laboratory data, missing recurrence or follow-up information, or any clinical condition that could substantially affect serum albumin or globulin levels, such as active infection, severe inflammatory disease, advanced liver dysfunction, nephrotic syndrome, or another active malignancy.

For each patient, preoperative albumin and total protein values obtained within one month before curative-intent surgery were extracted from routine laboratory data. These biochemical measurements were part of standard preoperative clinical assessment and were performed using comparable institutional laboratory procedures. Serum globulin was derived by subtracting albumin from total protein, and AGR was calculated by dividing serum albumin by the estimated globulin value.

Ethical approval was granted by the Dokuz Eylül University Non-Interventional Research Ethics Committee (no: 2026/19-27, date: 18.05.2026). The study followed the principles of the Declaration of Helsinki, and informed consent was waived owing to its retrospective design and use of anonymized data.

Statistical Analysis

Numerical variables were reported as median and interquartile range, and categorical variables were summarized as counts and percentages. Low- and high-AGR groups were compared using the Mann–Whitney U test for numerical variables and either the chi-square or Fisher's exact test for categorical variables, depending on data distribution. Recurrence-free survival (RFS) was analyzed as a time-to-event endpoint, beginning at the date of curative-intent

surgery and ending at melanoma recurrence or death, whichever occurred first. Patients who were alive and recurrence-free were censored at the date of last follow-up. The reverse Kaplan–Meier approach was applied to calculate the median follow-up time for the cohort.

The AGR threshold associated with recurrence was identified using receiver operating characteristic curve (ROC) analysis, and the discriminatory performance of this cut-off was described by the area under the curve (AUC), sensitivity, and specificity. To further evaluate the added prognostic contribution of AGR, additional ROC analyses were conducted using Cox regression-derived linear predictors. A clinicopathological model including stage and Breslow thickness was compared with an extended model incorporating AGR in addition to these variables. Because both ROC curves were derived from the same patients, the AUCs were compared using DeLong's test for two correlated ROC curves, and the 95% confidence interval for the difference in AUC was calculated. A stratified bootstrap comparison with 2,000 resamples was performed as a sensitivity analysis. Because conventional ROC analysis based on binary recurrence status does not account for censoring or event timing, incremental prognostic value was additionally assessed using a likelihood ratio test comparing the nested Cox models, Harrell's C-index with a paired comparison of the between-model difference, and inverse-probability-of-censoring-weighted time-dependent AUCs at 12, 24, 36, and 60 months. Integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) were also evaluated at 36 and 60 months. A sensitivity analysis was performed with AGR modeled as a continuous variable. These analyses were conducted using R version 4.5.2 with the pROC, survival, timeROC, and survIDINRI packages.

RFS was estimated using the Kaplan–Meier method according to AGR status in the overall cohort and in stage II and stage III subgroups, and survival curves were compared using the log-rank test. Graphical presentation of the Kaplan–Meier analyses was performed using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Associations between baseline variables, including AGR status, and RFS were assessed using univariable and multivariable Cox proportional hazards models. Candidate covariates for the multivariable Cox regression model were identified using a purposeful-selection approach. A liberal threshold of $p \leq 0.200$ in univariable analysis was used for initial screening to avoid prematurely excluding potentially relevant variables. Clinically relevant variables and potential confounders were also considered irrespective of their univariable statistical significance. Selected variables were entered simultaneously into the multivariable model, and no automated stepwise selection procedure was applied. To preserve the information contained in AGR as a continuous measure and to address the limitations associated with dichotomization, AGR was standardized and evaluated in a separate multivariable Cox regression model. Hazard ratios (HRs) were expressed per 1-standard-deviation increase in AGR. Multicollinearity was assessed separately for each multivariable model using tolerance and variance inflation factor (VIF) values. The ROC-derived cut-off was retained only for exploratory categorical analyses and Kaplan–Meier visualization and was not considered a validated clinical threshold. Effect estimates were expressed as HRs and corresponding 95% confidence intervals (CIs). Statistical analyses were conducted using SPSS version 27.0 (IBM Corp., Armonk, NY, USA), and statistical significance was defined as a two-sided p value below 0.05.

Results

Baseline characteristics according to AGR status are summarized in Table 1. In the overall cohort, the median age was 58 years, and 105 patients (55.3%) were male. Tumor localization was most commonly the extremity (41.1%), followed by the trunk (33.2%) and head and neck region (25.7%). Stage II disease was present in 100 patients (52.6%), whereas 90 patients (47.4%) had stage III disease. The median Breslow thickness was 2.7 mm, and ulceration was present in 91 patients (47.9%). Most patients had Clark level IV–V disease (80.5%), and 81 patients (42.6%) received adjuvant therapy. As shown in Figure 1, ROC curve analysis identified a cohort-derived AGR threshold of 1.22 for exploratory recurrence-risk stratification. AGR showed moderate discriminatory ability, with an AUC of 0.69 (95% CI: 0.62–0.77, $p<0.001$). At this cut-off value, the sensitivity and specificity were 68% and 66%, respectively.

When patients were stratified according to this AGR cut-off, 106 patients (55.8%) were classified as having high AGR and 84 patients (44.2%) as having low AGR. Age, sex, tumor location, ulceration status, mitotic rate, Clark level, and receipt of adjuvant therapy were comparable between the AGR groups. However, patients with low AGR had a significantly higher proportion of stage II disease compared with those with high AGR (63.1% vs. 44.3%, $p=0.010$). In addition, Breslow thickness was significantly greater in the low AGR group than in the high AGR group (median 3.4 mm vs. 2.3 mm, $p=0.009$).

Survival Outcomes

During a median follow-up duration of 68.2 months (95% CI: 56.4–80.0), 64 RFS events occurred, all of which were recurrences; no deaths occurred without a preceding recurrence. Among patients with stage II disease, recurrence was

Table 1. Clinicopathological and demographic characteristics of the study cohort according to preoperative AGR status

Characteristics	All patients (n=190)	High AGR (n=106, 55.8%)	Low AGR (n=84, 44.2%)	p
Age, years (IQR)	58 (46-67)	57 (44-68)	58 (46-66)	0.739
Sex				0.865
Male	105 (55.3%)	58 (54.7%)	47 (56%)	
Female	85 (44.7%)	48 (45.3%)	37 (44%)	
Tumor location				0.405
Extremity	78 (41.1%)	45 (42.5%)	33 (39.3%)	
Trunk	63 (33.2%)	31 (29.2%)	32 (38.1%)	
Head and neck	49 (25.7%)	30 (28.3%)	19 (22.6%)	
Tumor stage				0.010
II	100 (52.6%)	47 (44.3%)	53 (63.1%)	
III	90 (47.4%)	59 (55.7%)	31 (36.9%)	
Breslow thickness, mm (IQR)	2.7 (1.2-5.5)	2.3 (0.9-4.3)	3.4 (1.5-6.7)	0.009
Ulceration				0.605
No	99 (52.1%)	57 (53.8%)	42 (50%)	
Yes	91 (47.9%)	49 (46.2%)	42 (50%)	
Mitotic rate, mitoses/mm^2 (IQR)	5 (2-12)	4 (2-12)	6 (3-12)	0.130
Clark				0.215
II–III	37 (19.5%)	24 (22.6%)	13 (15.5%)	
IV–V	153 (80.5%)	82 (77.4%)	71 (84.5%)	
Adjuvant therapy				0.216
No	109 (57.4%)	65 (61.3%)	44 (52.4%)	
Yes	81 (42.6%)	41 (38.7%)	40 (47.6%)	

AGR: Albumin-to-globulin ratio; IQR: Interquartile range.

observed in 27 patients (27.0%). In the stage III subgroup, recurrence occurred in 37 patients (41.1%). In the overall cohort, patients with low AGR showed significantly shorter RFS than those with high AGR on Kaplan–Meier analysis.

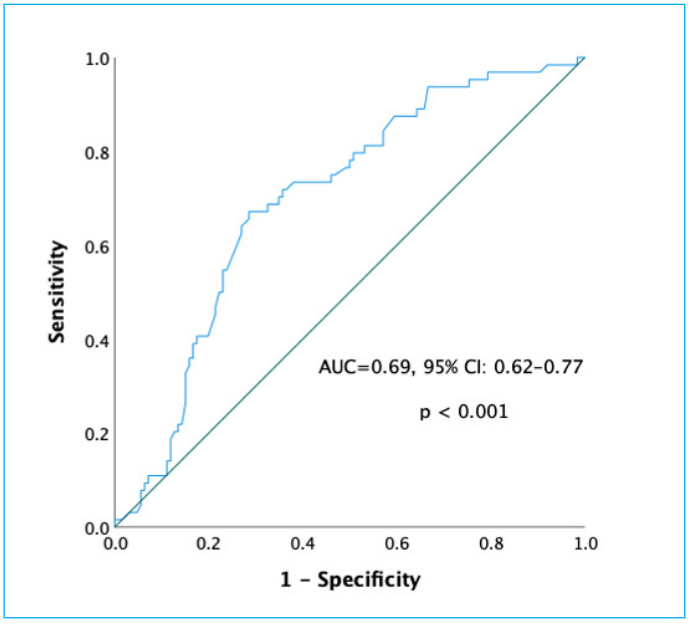

Figure 1. ROC curve analysis of preoperative AGR for recurrence prediction. AGR: Albumin-to-globulin ratio; AUC: Area under the curve; CI: Confidence interval; ROC: Receiver operating characteristic.

The median RFS was 64.4 months (95% CI 49.0–79.8) in the low AGR group compared with 117.7 months (95% CI 71.3–164.2) in the high AGR (p<0.001, Fig. 2a). When stratified by disease stage, patients with low AGR continued to show shorter RFS within both stage II and stage III subgroups. In the stage II subgroup, median RFS was 81.8 months in the low-AGR group (95% CI: 68.6–94.9) and 117.7 months in the high-AGR group, for which the 95% CI could not be estimated because of censoring (p<0.001, Fig. 2b). In patients with stage III disease, median RFS was 49.5 months (95% CI 29.1–69.9) in the low AGR group and 83.8 months (95% CI 72.1–95.5) in the high AGR group (p=0.002, Fig. 2c).

As shown in Table 2, stage III disease was associated with shorter RFS than stage II disease in the univariable Cox regression analysis (HR: 2.16, 95% CI: 1.30–3.58, p=0.003). Greater Breslow thickness (HR per 1-mm increase: 1.16, 95% CI: 1.10–1.21, p<0.001), a higher mitotic rate (HR per 1 mitosis/mm^2 increase: 1.02, 95% CI: 1.00–1.05, p=0.045), absence of adjuvant therapy (HR: 2.85, 95% CI: 1.70–4.77, p<0.001), and low AGR (HR: 2.76, 95% CI: 1.62–4.71, p<0.001) were also associated with shorter RFS, whereas age and sex were not statistically significant. In the multivariable model, stage III disease (HR: 2.01, 95% CI: 1.10–3.68, p=0.022), greater Breslow thickness (HR per 1 mm increase: 1.09, 95% CI: 1.03–1.16, p=0.001), and low AGR (HR: 2.66, 95% CI:

Table 2. Univariable and multivariable Cox regression analyses for RFS

	Univariable		Multivariable	
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age, years	1.00 (0.98–1.01)	0.831	NA	NA
Sex (male vs female)	1.17 (0.70–1.95)	0.537	NA	NA
Stage (III vs II)	2.16 (1.30–3.58)	0.003	2.01 (1.10–3.68)	0.022
Mitotic rate	1.02 (1.00–1.05)	0.045	1.00 (0.96–1.03)	1.000
Breslow thickness	1.16 (1.10–1.21)	<0.001	1.09 (1.03–1.16)	0.001
Adjuvant therapy (no vs yes)	2.85 (1.70–4.77)	<0.001	1.33 (0.72–2.48)	0.355
AGR (low vs high)	2.76 (1.62–4.71)	<0.001	2.66 (1.48–4.79)	0.001

AGR: Albumin-to-globulin ratio; CI: Confidence interval; HR: Hazard ratio; NA: Not applicable; RFS: Recurrence-free survival.

1.48–4.79, p=0.001) remained significantly associated with shorter RFS. Mitotic rate and adjuvant therapy status were not statistically significant after adjustment.

When AGR was evaluated as a standardized continuous variable in the multivariable Cox regression model, each 1-standard-deviation increase in preoperative AGR was associated with a lower hazard of recurrence or death (adjusted HR: 0.58, 95% CI: 0.43–0.80; p<0.001). Stage III disease (HR: 1.89, 95% CI: 1.05–3.39; p=0.033) and greater Breslow thickness (HR per 1-mm increase: 1.11, 95% CI: 1.05–1.17; p<0.001) were also independently associated with shorter RFS. Mitotic rate (HR: 1.00, 95% CI: 0.97–1.04; p=0.853) and adjuvant therapy status (HR: 1.26, 95% CI: 0.68–2.34; p=0.456) were not significantly associated with RFS.

Multicollinearity diagnostics showed no evidence of problematic collinearity in either multivariable model. In the model including AGR as a categorical variable, the VIF values were 1.317 for Breslow thickness, 1.232 for tumor stage, 1.363 for adjuvant therapy, 1.189 for mitotic rate, and 1.111 for AGR status. In the model including AGR as a standardized continuous variable, the corresponding VIF values were 1.297 for Breslow thickness, 1.194 for tumor stage, 1.366 for adjuvant therapy, 1.189 for mitotic rate, and 1.069 for standardized AGR.

As shown in Figure 3 and Table 3, ROC analyses based on Cox regression-derived linear predictors were performed to evaluate the incremental discriminatory value of AGR beyond a clinicopathological model based on disease stage and Breslow thickness. Model 1, which included disease stage and Breslow thickness, demonstrated an AUC of 0.762 (95% CI: 0.690–0.834). Model 2, which additionally incorporated AGR, demonstrated a numerically higher AUC

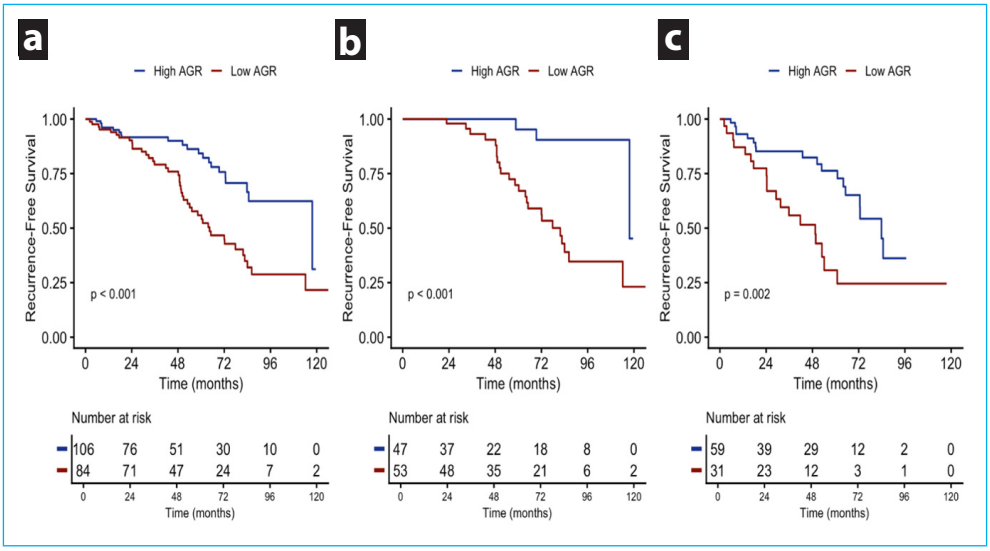

Figure 2. Kaplan–Meier curves for RFS according to preoperative AGR status in the overall cohort **(a)**, stage II subgroup **(b)**, and stage III subgroup **(c)**. AGR: Albumin-to-globulin ratio; RFS: Recurrence-free survival.

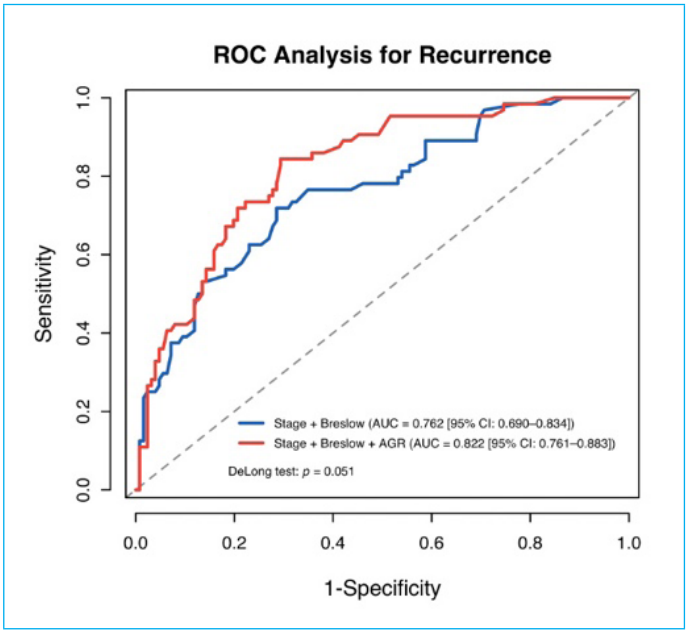

Figure 3. Comparison of ROC curves for the clinicopathological model and the extended model including AGR. Model 1 included disease stage and Breslow thickness, whereas Model 2 additionally included categorical AGR status. AGR: Albumin-to-globulin ratio: AUC: Area under the curve; CI: Confidence interval; ROC: Receiver operating characteristic.

of 0.822 (95% CI: 0.761–0.883). However, the difference between the two correlated ROC curves did not reach statistical significance (ΔAUC: 0.060, 95% CI: −0.0001 to 0.120; DeLong Z=1.956, p=0.051). A stratified bootstrap comparison yielded a concordant result (p=0.051).

The increase in Harrell's C-index was also not statistically significant (0.764 to 0.790; ΔC: 0.027, 95% CI: −0.025 to 0.078; p=0.316), and none of the time-dependent AUC comparisons at 12, 24, 36, or 60 months remained statistically significant after adjustment for multiple landmark comparisons. At 36 months, continuous NRI was statistically significant (0.258, 95% CI: 0.010–0.421; p=0.040), whereas IDI was not (0.036, 95% CI: −0.005 to 0.113; p=0.108). At 60 months, both IDI (0.070, 95% CI: 0.009–0.159; p=0.018) and continuous NRI (0.286, 95% CI: 0.070–0.456; p=0.020) suggested modest reclassification improvement. When AGR was modeled as a continuous variable, the difference in AUC was smaller and remained non-significant (ΔAUC: 0.041; p=0.153). In contrast, the addition of AGR significantly improved overall model fit in the nested Cox model comparison (likelihood ratio χ^2=13.36, 1 df; p<0.001). The complete results of the additional discrimination, reclassification, model-fit, and sensitivity analyses are presented in Supplementary Table S1.

Discussion

In this retrospective cohort of patients with high-risk resected cutaneous melanoma, low preoperative AGR was associated with an unfavorable recurrence pattern and shorter RFS. Importantly, this association persisted after adjustment for selected clinicopathological variables**,** suggesting that AGR may reflect a component of recurrence risk that is not fully captured by conventional tumor-related parameters alone. Notably, although the low-AGR group included a higher proportion of stage II disease, low AGR remained independently associated with shorter RFS after adjustment for stage and other clinicopathological variables, supporting its potential prognostic relevance beyond anatomical staging. Taken together, these findings indicate that AGR may serve as a simple, inexpensive, and readily available host-related biomarker for refining recurrence risk assessment in patients with resected stage II–III melanoma.

Incorporating AGR into the clinicopathological model increased the AUC from 0.762 to 0.822; however, this difference did not reach statistical significance according to DeLong's test. Similarly, neither the Harrell C-index comparison nor the censoring-adjusted time-dependent AUC analyses demonstrated a statistically significant improvement in discrimination. Some IDI and NRI estimates reached statistical significance; however, these reclassification findings should be considered exploratory because they were not accompanied by significant improvements in the C-index or time-dependent AUC analyses and should not be interpreted as establishing incremental prognostic or discriminatory performance of AGR. Although the addition of AGR significantly improved model fit and AGR remained independently associated with RFS, the present

Table 3. Comparison of discriminatory performance between the clinicopathological and extended models

Model	AUC (95% CI)	Sensitivity, %	Specificity, %	Comparison with Model 1
Model 1	0.762 (0.690-0.834)	72	71	Reference
Model 2	0.822 (0.761-0.883)	84	71	ΔAUC=0.060 (95% CI: -0.0001 to 0.120); DeLong p=0.051

Model 1 included disease stage and Breslow thickness. Model 2 additionally included categorical AGR status. The AUCs were calculated from Cox regression-derived linear predictors and compared using DeLong's test for two correlated ROC curves. AGR: Albumin-to-globulin ratio; AUC: Area under the curve; CI: Confidence interval.

findings do not establish that AGR improves the discriminatory performance of a model based on disease stage and Breslow thickness. Given the limited number of recurrence events, the borderline DeLong result should be regarded as hypothesis-generating. AGR is therefore best interpreted as an independent prognostic marker whose incremental contribution to risk discrimination requires confirmation in larger, externally validated cohorts.

From a clinical perspective, AGR should not be interpreted as a stand-alone determinant of adjuvant treatment or postoperative surveillance. Rather, if externally validated, it may serve as an adjunctive host-related marker alongside established clinicopathological factors such as disease stage and Breslow thickness. A low preoperative AGR could potentially support more individualized discussions regarding recurrence risk, identify patients who may benefit from closer clinical assessment or enrollment in prospective risk-stratification studies, and prompt evaluation of potentially relevant inflammatory or nutritional abnormalities. However, the present retrospective study was not designed to determine whether AGR-guided treatment or surveillance strategies improve outcomes. Therefore, no modification of adjuvant therapy or follow-up intensity can currently be recommended on the basis of AGR alone.

Across different surgically treated solid tumors, reduced preoperative AGR has been associated with aggressive clinicopathological features, greater recurrence risk, and inferior survival, suggesting its potential value as a host-derived prognostic marker.[18–22] Several recent studies have examined AGR alongside inflammatory and immunonutritional markers, with findings suggesting that the albumin–globulin balance may provide complementary prognostic insight in addition to established clinicopathological factors.[23–25] Unlike other solid tumors, evidence regarding the prognostic role of AGR in melanoma remains scarce, particularly in patients with preoperatively assessed, resected stage II–III disease. Nevertheless, emerging melanoma evidence suggests that inflammatory and immunonutritional biomarkers, including albumin-related indices, may have prognostic relevance, particularly among patients with advanced disease or those treated with ICIs.[9–11] Taken together, these observations collectively provide a rationale for investigating preoperative AGR as a clinically practical host-derived prognostic biomarker in patients undergoing resection for high-risk stage II–III cutaneous melanoma.

Several inflammation- and nutrition-based indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), prognostic nutritional index (PNI), and Glasgow Prognostic Score (GPS), have also been investigated as prognostic biomarkers in solid tumors and melanoma.[7,8,26] The present study did not directly compare AGR with these indices and therefore cannot establish that AGR provides superior prognostic performance. Its potential value should instead be interpreted as complementary to the clinicopathological variables evaluated in the present study. Although the addition of AGR to a model including disease stage and Breslow thickness resulted in a numerically higher AUC, head-to-head studies are required to determine whether AGR provides incremental prognostic information beyond other routinely available inflammatory and nutritional biomarkers.

The biological link between AGR and melanoma recurrence is likely multifactorial, involving cancer-related inflammation and impaired host metabolic reserve. Rather than serving solely as a nutritional marker, serum albumin is a multifunctional protein involved in maintaining oncotic pressure, antioxidant activity, regulation of inflammation, and ligand transport.[27] During systemic inflammation, albumin may be reduced by cytokine-driven mechanisms and may also undergo functional changes associated with oxidative stress and endothelial dysfunction.[28] Accordingly, lower albumin levels may represent a host phenotype associated with systemic inflammation, reduced physiological reserve, and metabolic stress. However, the globulin component includes acute-phase reactants, complement proteins, and immunoglobulins, all of which may increase in response to chronic immune stimulation.[13] Chronic inflammation contributes to cancer progression through mechanisms involving tumor growth, angiogenesis, immune evasion, and metastasis.[13] Therefore, low AGR may serve as an indicator of an adverse systemic inflammatory phenotype, reflecting both reduced albumin-mediated protection and increased globulin-related immune activation. In melanoma, this concept is particularly applicable because progression depends heavily on the balance between host immune surveillance and tumor immune escape. Chronic inflammation may generate a tumor-permissive microenvironment that promotes melanoma recurrence by enhancing angiogenesis, extracellular matrix remodeling, and recruitment of immunosuppressive myeloid cells.[29–31] In melanoma, immune escape and metastatic progression are closely interconnected processes, and tumor microenvironmental signals may weaken cytotoxic immune surveillance while supporting the persistence and outgrowth of residual micrometastatic disease after surgery.[32] Accordingly, AGR may not directly mediate melanoma recurrence but may serve as an accessible surrogate of the systemic inflammatory–nutritional context that influences host vulnerability and postoperative recurrence risk.

Adjuvant treatment should also be interpreted in the context of the long study period. Adjuvant management of resected melanoma changed substantially between 2010 and 2026, particularly following the introduction of anti-programmed cell death protein 1 therapies and BRAF/MEK-targeted therapy.[2–4] Therefore, patients treated during different calendar periods may have differed with respect to treatment availability, treatment efficacy, eligibility criteria, and postoperative surveillance practices. Because detailed and consistently recorded regimen-level information was not available across the entire retrospective cohort, adjuvant treatment was analyzed as a binary variable. This classification could not fully capture treatment heterogeneity and may have resulted in residual confounding related to treatment type and treatment era. Accordingly, the observed associations should be interpreted in the context of evolving standards of postoperative melanoma care.

The present findings should be interpreted in light of several methodological limitations. First, as this was a retrospective analysis, selection bias cannot be excluded, and the association between AGR and recurrence should not be interpreted as causal. Although eligibility was based on prespecified criteria, residual confounding cannot be ruled out, as comorbidities, occult inflammatory states, nutritional condition, medication use, and perioperative factors may have influenced serum albumin or globulin concentrations. Second, AGR was assessed using a single preoperative laboratory measurement. Therefore, dynamic changes in AGR during follow-up, after surgery, or during adjuvant therapy could not be evaluated. Serial assessment of AGR may provide additional prognostic information and should be investigated in future studies. Third, although laboratory measurements were performed using comparable standardized routine biochemical methods across the participating centers, minor inter-laboratory variability cannot be completely excluded. Fourth, the AGR cut-off value was derived from the present cohort using ROC analysis. This approach is practical for exploratory prognostic evaluation, but it may increase the risk of cohort-specific optimization. Therefore, the proposed cut-off requires external validation in independent melanoma cohorts before routine clinical application. Fifth, the number of recurrence events was relatively limited, particularly in subgroup analyses, which may have reduced the statistical power and restricted the number of variables that could be reliably included in multivariable models. Although AGR was independently associated with RFS, the study had limited statistical power to establish incremental discriminatory value. Detailed AJCC substages and nodal characteristics, including sentinel lymph node status and nodal tumor burden, are established prognostic factors; however, the numbers of patients and recurrence events within the individual categories were insufficient for reliable category-specific modeling. Therefore, disease stage was analyzed using the broader stage II versus stage III classification to minimize sparse-data bias, unstable effect estimates, and model overfitting. AGR remained independently associated with RFS; nevertheless, the study had limited statistical power to establish incremental discriminatory value. The difference in AUC between the clinicopathological and extended models was of borderline statistical significance, whereas the Harrell C-index and censoring-adjusted time-dependent AUCs did not differ significantly between the models. In addition, because conventional ROC analysis based on binary recurrence status does not account for censoring or the timing of recurrence, its findings should be interpreted alongside the time-to-event discrimination analyses. Overall survival was not analyzed because the number of death events was insufficient for a reliable time-to-event analysis; therefore, the prognostic findings of the present study are limited to RFS. Sixth, some potentially relevant prognostic factors, including molecular features such as BRAF mutation status, detailed comorbidity burden, performance status, body mass index, C-reactive protein, and lactate dehydrogenase, were not uniformly available and therefore could not be fully incorporated into the analyses**.** In addition, direct head-to-head comparisons between AGR and established inflammation- and nutrition-based indices such as NLR, PLR, LMR, SII, PNI, and GPS could not be performed, and the present findings should not be interpreted as demonstrating the superiority of AGR over these biomarkers. Finally, the limited number of participating centers may restrict the external validity of our findings, particularly for broader melanoma populations and contemporary cohorts treated with standardized modern adjuvant therapy.

Conclusion

Preoperative AGR was independently associated with RFS in patients with resected stage II–III cutaneous melanoma. Although AGR may provide complementary prognostic information beyond disease stage and Breslow thickness, the present findings do not support its use as a stand-alone determinant of adjuvant treatment or surveillance intensity. Its potential role is currently limited to adjunctive risk assessment and hypothesis generation. Prospective multicenter studies with external validation are required to determine whether incorporating AGR into postoperative risk models can meaningfully improve clinical decision-making and patient outcomes.

Disclosures

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (no: 2026/19-27, date: 18.05.2026).

Informed Consent: Informed consent was waived by the ethics committee because of the retrospective design of the study and the analysis of anonymized data.

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Supplementary Table S1. Additional analyses of the incremental prognostic contribution of AGR beyond disease stage and Breslow thickness

Analysis	Time point	Model 1	Model 2	Difference / incremental estimate (95% CI)	p
Conventional AUC (DeLong comparison)	Overall	0.762 (0.690-0.834)	0.822 (0.761-0.883)	Delta AUC = 0.060 (-0.0001 to 0.120)	0.051
Stratified bootstrap AUC comparison	Overall	0.762	0.822	Delta AUC = 0.060	0.051
Harrell's C-index	Overall	0.764 (SE 0.030)	0.790 (SE 0.030)	Delta C = 0.027 (-0.025 to 0.078)	0.316
Likelihood ratio test (nested Cox models)	Overall	Reference	Extended model	chi-square = 13.36 (1 df)	<0.001
Time-dependent AUC	12 months	0.847 (SE 0.043)	0.768 (SE 0.076)	-0.079	0.258
Time-dependent AUC	24 months	0.818 (SE 0.050)	0.761 (SE 0.054)	-0.057	0.555
Time-dependent AUC	36 months	0.773 (SE 0.046)	0.808 (SE 0.040)	0.034	0.780
Time-dependent AUC	60 months	0.735 (SE 0.047)	0.809 (SE 0.042)	0.074	0.138
Integrated discrimination improvement	36 months	-	-	0.036 (-0.005 to 0.113)	0.108
Continuous net reclassification improvement	36 months	-	-	0.258 (0.010 to 0.421)	0.040
Integrated discrimination improvement	60 months	-	-	0.070 (0.009 to 0.159)	0.018
Continuous net reclassification improvement	60 months	-	-	0.286 (0.070 to 0.456)	0.020
AUC with continuous AGR (sensitivity analysis)	Overall	0.762 (0.690-0.834)	0.803 (0.739-0.867)	Delta AUC = 0.041 (-0.015 to 0.097)	0.153

Model 1 included disease stage and Breslow thickness. Model 2 additionally included categorical AGR status, except in the sensitivity analysis, in which AGR was modeled as a standardized continuous variable. Time-dependent AUC p values were adjusted for comparisons across four prespecified landmarks; the unadjusted p value for the 60-month comparison was 0.043. Confidence intervals for IDI and NRI were obtained using perturbation resampling. AGR: Albumin-to-globulin ratio; AUC: Area under the curve; CI: Confidence interval; IDI: Integrated discrimination improvement; NRI: Net reclassification improvement; SE: Standard error.