



Increased Serum Vitamin D and Decreased Serum Cholesterol Are Associated with Development of Squamous Cell Carcinoma in Actinic Keratosis Patients: A Retrospective Machine-Learning Analysis of the All of Us Database

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Introduction

Actinic keratosis (AK) is a common pre-malignant skin lesion with a 10% transformation rate to squamous cell carcinoma (SCC). Due to potential local SCC spread and metastasis, early risk stratification for AK patients is desired [1] While the relationship between ultraviolet exposure and AK progression is well established, other risk factors are understudied. Hence, we utilized a machine-learning analysis on patient-level data to identify demographic and laboratory value risk factors for AK patients who developed SCC.

Methods

We performed a retrospective machine-learning analysis of the All of Us database using SNOMED codes 201101007 to

identify AK cases and 254651007, 403892001, 285307007, 423284006 to identify cutaneous SCC cases. The complete machine-learning analysis methodology is detailed in Supplemental File 1.

Results

We included a total of 9,915 and 202 AK patients without SCC and with SCC, respectively. Demographics are detailed in Table S1. With Random Forest, SCC risk was not affected by patient demographics. Relevant significant features from highest to lowest permutation included serum cholesterol, 25-hydroxyvitamin D3, urea nitrogen (BUN), cobalamin, creatinine (Cr), body mass index (BMI), and albumin (Figure 1A). The Shapley Plot showed increased risk of SCC with increasing levels of serum 25-hydroxyvitamin D3,



Figure 1. Random Forest and Shapley Plots depicting the contribution of individual features in AK progression to squamous cell carcinoma (SCC). (A) Random Forest Plot ranking individual features ranked based on permutation values. (B) Representative Shapley Plot depicting the effect of individual feature value variance on the risk of AK progression to SCC with their respective SHAP values. Higher and lower SHAP values indicate higher and lower risk for SCC, respectively.

BUN, cobalamin, and Cr and decreasing levels of serum cholesterol, BMI, and albumin. There was decreased risk of SCC with increasing levels of serum cholesterol, BMI, and albumin and decreasing levels of serum 25-hydroxyvitamin D3,

BUN, cobalamin, and Cr (Figure 1B). The average area under the ROC curve (AUC) score on a 5-fold cross-validation was 0.66 (SD = 0.04) (Figure S1). Feature Gini-impurity values are shown in Figure S2.

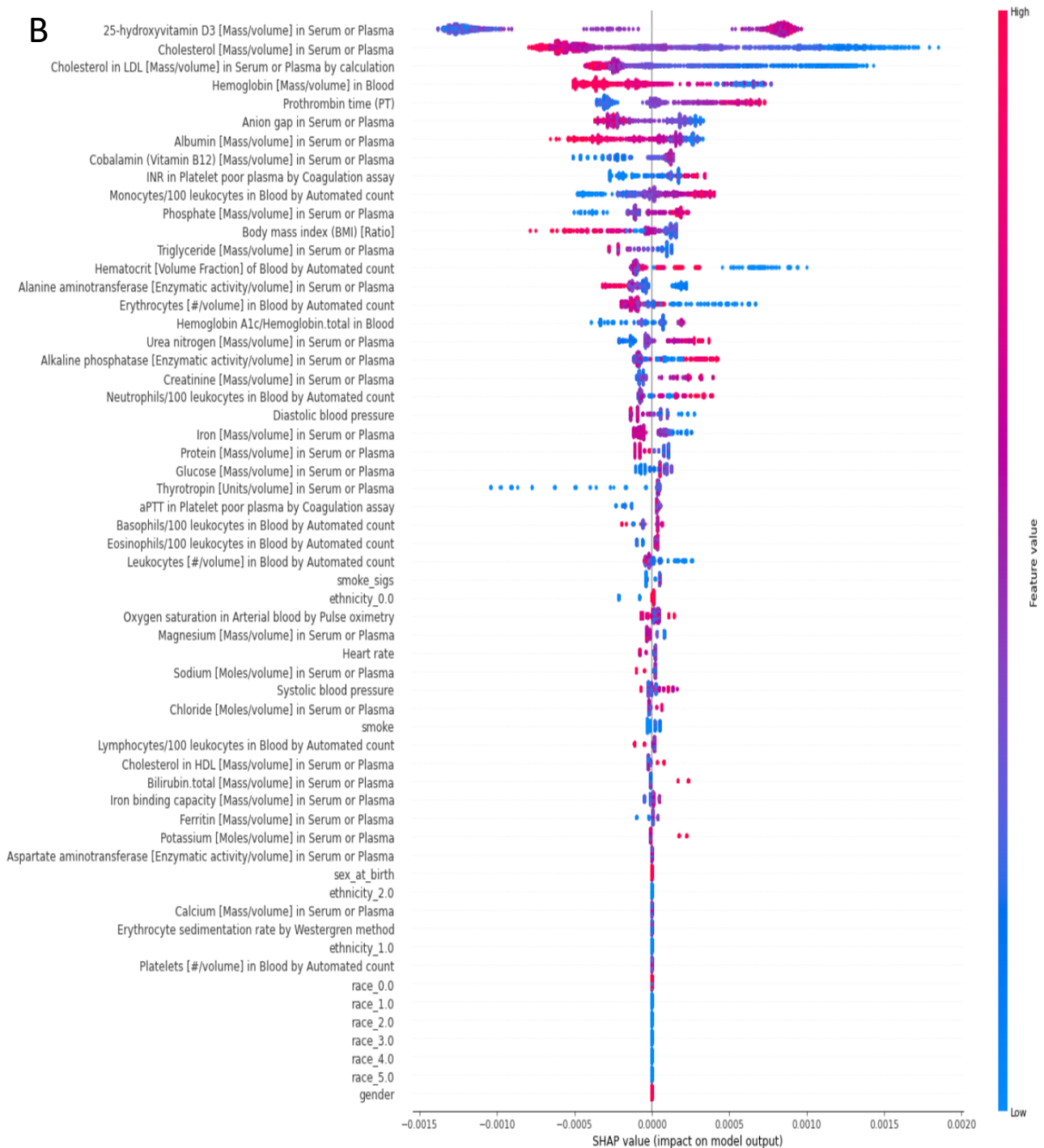


Figure 1. (Continued)

Discussion

We found that decreased serum cholesterol and 25-hydroxyvitamin D3, but not patient demographics, were associated with increased risk of developing SCC in AK patients. Notably, in an *in vitro* metabolic gene expression analysis of lymphomas, malignant cells exploited cholesterol uptake to foster tumor growth, and *in vitro* studies are exploring antibody-mediated blockade of cholesterol

uptake in tumor cells as treatment for cholesterol-dependent cancers [2]. Our finding of increased SCC risk with higher 25-hydroxyvitamin D3 levels may serve as a proxy for increased sunlight exposure, a well-documented risk factor for SCC development in AK patients [3].

Additional associated SCC risk factors include increased cobalamin levels and decreased albumin levels. Similarly, in a retrospective study of 427 Japanese patients, higher dietary intake of vitamin B12 was associated with increased risk

(HR: 2.82; $P=0.009$) of esophageal SCC [4]. Additionally, in a retrospective study of 100,122 cancer patients, hypoalbuminemia was associated with increased risk (OR: 1.29; 95% CI: 1.12–1.49) for non-melanoma skin cancers [5].

Limitations include retrospective design, AUC score <0.75, and lack of external validation.

Conclusion

In sum, this investigation found that demographics did not predict development of SCC in patients with AK. Serum cholesterol and vitamin D levels merit further study as early identifiers of SCC development in AK patients and potential therapeutic targets. Increased cobalamin levels and decreased albumin levels may increase SCC risk in AK patients. This multifactorial risk assessment may provide a patient-oriented approach to risk stratification and preventative care for AK patients and improve clinical outcomes.

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