

# The Association Between C-reactive Protein/Albumin Ratio with the Stages of Malnutrition Defined by GLIM Criteria in Older Inpatient

## Yaşlı Yatan Hastalarda C-reaktif Protein/Albümin Oranının GLIM Kriterlerine göre Tanımlanan Malnütrisyon Evreleri ile İlişkisi

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### Abstract

**Objective:** This study aimed to determine the relationship between the C-reactive protein (CRP)/albumin ratio (CAR) and malnutrition, and its stages as defined by the global leadership initiative on malnutrition (GLIM) criteria. Additionally, it sought to establish CAR cut-off points to predict malnutrition and its stages.

**Methods:** The study included patients aged  $\geq 60$  years hospitalised at the clinic of internal medicine between June 2021 and May 2022. Serum CRP and albumin levels were measured within the first 24 hours of hospitalization. CAR was calculated as CRP (mg/L) divided by albumin (g/dL). Malnutrition and its stages were assessed using the GLIM criteria. ROC curve analysis was performed to identify CAR cut-off values for predicting stage 1 and stage 2 malnutrition.

**Results:** A total of 127 patients (46.5% male; median age 73) were included. Stage 1 malnutrition was present in 26% of cases and stage 2 in 23.6% of cases. Median CAR was 1.8 (0.07-50.4) in well-nourished patients, 6.8 (0.08-135.2) in patients with stage 1 malnutrition, and 9.8 (0.08-86.4) in patients with stage 2 malnutrition ( $p=0.014$ ). CAR demonstrated an area under the curve (AUC) of 0.649 [95% confidence interval (CI): 0.552-0.747,  $p=0.004$ ] for total malnutrition and an AUC of 0.669 (95% CI: 0.542-0.796,  $p=0.009$ ) for stage 2. The CAR cut-off value for stage 2 malnutrition was determined as  $\geq 8.4$  (sensitivity: 53.3% and specificity: 79.7%).

**Conclusion:** CAR is associated with the diagnosis and staging of malnutrition according to GLIM criteria. It serves as a practical tool for assessing malnutrition risk, particularly for stage 2 malnutrition.

**Keywords:** Malnutrition, GLIM criteria, C-reactive protein/albumin ratio



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## Öz

**Amaç:** Bu çalışma, C-reaktif protein (CRP)/albümin oranının (CAR) malnütrisyon ve malnütrisyon üzerine küresel liderlik girişimi (GLIM) kriterlerine göre belirlenen evreleri ile ilişkisini belirlemeyi amaçlamıştır. Ayrıca, CAR'ın malnütrisyon ve evrelerini öngörmedeki kesme noktalarını belirlemek hedeflenmiştir.

**Yöntem:** Çalışmaya, Haziran 2021-Mayıs 2022 tarihleri arasında iç hastalıkları kliniğine başvuran ve yaşları  $\geq 60$  olan hastalar dahil edildi. Hastaneye yatışın ilk 24 saati içinde serum CRP ve albümin düzeyleri ölçüldü. Malnütrisyon ve evreleri GLIM kriterlerine göre değerlendirildi. CAR'ın evre 1 ve evre 2 malnütrisyonu öngörmedeki kesme noktalarını belirlemek için ROC eğrisi analizi yapıldı.

**Bulgular:** Çalışmaya toplam 127 hasta (erkek %46,5; medyan yaş 73) dahil edildi. Hastaların %26'sında evre 1, %23,6'sında evre 2 malnütrisyon saptandı. Medyan CAR değerleri normal beslenenlerde 1,8 (0,07-50,4), evre 1 malnütrisyon grubunda 6,8 (0,08-135,2), evre 2 grubunda ise 9,8 (0,08-86,4) idi ( $p=0,014$ ). CAR'ın total malnütrisyon için eğri altında kalan alan (EAA): 0,649 [%95 güven aralığı (GA): 0,552-0,747;  $p=0,004$ ] ve evre 2 malnütrisyon için EAA: 0,669 (%95 GA 0,542-0,796;  $p=0,009$ ) olarak bulundu. Evre 2 malnütrisyon için CAR kesme noktası  $\geq 8,4$  (duyarlılık: %53,3 ve özgüllük: %79,7) olarak bulundu.

**Sonuç:** CAR, GLIM kriterlerine göre malnütrisyonun tanı ve evrelemesiyle ilişkilidir. Özellikle evre 2 malnütrisyon açısından pratik bir belirteç olarak kullanılabilir.

**Anahtar Kelimeler:** Malnütrisyon, GLIM kriterleri, C-reaktif protein/albümin oranı

## Introduction

Malnutrition is a common and substantial health problem. Its prevalence varies from 20% up to 50% according to patient characteristics, the care setting, and the diagnostic criteria used<sup>(1-4)</sup>. This variability makes it difficult to harmonize study results because there is no broadly accepted gold standard for assessing nutritional status. Delays in diagnosis and treatment may further increase health expenditures, morbidity, and mortality. Simplified, globally accepted, and easy-to-apply tests are needed.

Several malnutrition screening and assessment tools have been created and validated for specific populations, such as for older individuals, community-dwelling people or hospitalized patients<sup>(5-8)</sup>. In 2019, the global leadership initiative on malnutrition (GLIM) criteria were introduced to promote a consistent approach to diagnosing malnutrition worldwide. These criteria also aimed to reduce delays in initiating appropriate interventions<sup>(5)</sup>. In this two-step approach, patients at risk are first identified using one of the validated screening tools. Following the first step, the diagnosis and degree of malnutrition are determined. For the diagnosis, involuntary weight loss, low body mass index (BMI), and decreased muscle mass are phenotypic criteria, and poor dietary intake or absorption and inflammation are etiological criteria. Diagnosing malnutrition according to the GLIM criteria requires the identification of at least one phenotypic and one etiologic criterion. The severity of malnutrition is classified into two stages: moderate (stage 1) and severe undernutrition (stage 2), based on phenotypic criteria<sup>(5)</sup>.

Since inflammation is one of the etiological criteria in the GLIM framework, laboratory markers such as C-reactive protein (CRP), albumin, and prealbumin are recommended as supportive indicators<sup>(5)</sup>. CRP is secreted in response to pro-inflammatory cytokines during inflammatory and infectious processes. Its levels can also be elevated in the presence of trauma, tissue injury, and cardiovascular diseases<sup>(9)</sup>. Albumin is a negative acute-phase protein. It decreases during inflammation and is frequently used in the diagnosis of malnutrition<sup>(10)</sup>. The CRP/albumin ratio (CAR) is obtained by dividing CRP by the albumin level. The literature indicates that CAR is a prognostic indicator of disease severity or activity in various rheumatologic diseases and in patients with coronavirus disease-2019 and Crohn's disease. It also predicts morbidity and mortality in critical conditions such as sepsis, septic shock, and malignant diseases<sup>(11-17)</sup>. Research has demonstrated its value as an independent predictor of overall mortality and amputation in patients undergoing endovascular surgery for peripheral arterial disease<sup>(18)</sup>. In a study conducted in cancer patients (solid or hematological neoplasms), CAR and length of hospital stay were significantly higher in patients diagnosed with malnutrition using GLIM criteria whereas; BMI and albumin values were significantly lower<sup>(19)</sup>. Another study in cancer patients assessed the predictive value of adding inflammatory markers such as the inflammatory burden index, CRP, neutrophil-to-lymphocyte ratio, and albumin to the GLIM criteria for diagnosing malnutrition. The modified criteria showed better predictive capacity for both short- and long-term prognosis, with CRP being identified as a valuable indicator of malnutrition severity in short-term outcomes<sup>(20)</sup>.

The GLIM is widely used for the diagnosis of malnutrition. However, it includes many variables that create difficulties in its application. As inflammation is included in the GLIM criteria and CAR has been shown to be a prognostic indicator in many diseases, the use of CAR might be practical for indicating nutritional risk. Currently, no studies have investigated the correlation between CAR and GLIM-defined malnutrition stages in older patients. Consequently, we designed the study to determine the relationship between CAR and malnutrition, and between CAR and the stages of malnutrition using GLIM criteria, as well as to establish the cut-off points of CAR for predicting malnutrition and its stages.

## Materials and Methods

In this retrospective study, sociodemographic, clinical, and laboratory data were collected from patient records, including age, sex, education level, living situation, income status, comorbidities, number of medications, length of hospital stay, BMI, grip strength (GS), CRP, and albumin levels.

### Study Population

Patients aged 60 years and older who were hospitalized in the Internal Medicine Department of Ege University Hospital between June 2021 and May 2022 were retrospectively included in the study. Patients with missing anthropometric measurements, GS values, laboratory data, or GLIM evaluations were excluded.

The study was approved by the Ege University Medical Research Ethics Committee, İzmir, Türkiye (approval no: 22-12T/50, date: 06.12.2022). For this type of retrospective study formal consent is not required.

### Anthropometric Measurements

BMI was calculated as weight (kg) divided by height squared ( $m^2$ ).

### GLIM Criteria

The GLIM criteria necessitate a two-step approach<sup>(5)</sup>. First, patients at risk of malnutrition are identified through validated screening tools; second, the diagnosis and degree of malnutrition are determined. Malnutrition according to GLIM required  $\geq 1$  phenotypic criterion (weight loss, low BMI, or reduced muscle mass) plus  $\geq 1$  etiologic criterion (reduced intake/absorption or inflammation). Inflammation may be associated with acute illness or injury, or with chronic

disease. Severe inflammation related to acute illness or injury can be caused by major infection, burn or trauma. Chronic inflammation linked to various conditions, such as chronic obstructive pulmonary disease (COPD), malignant disease, chronic kidney disease, and other disorders involving persistent or recurring inflammation, can be assessed using CRP as a supplementary laboratory indicator<sup>(5)</sup>.

Malnutrition was staged as follows: stage 1 (moderate) if weight loss was 5–10% within 6 months or 10–20% beyond 6 months, BMI  $< 20 \text{ kg/m}^2$  if  $< 70$  years or  $< 22 \text{ kg/m}^2$  if  $\geq 70$  years, or reduced muscle mass; stage 2 (severe) if weight loss was  $> 10\%$  within 6 months or  $> 20\%$  beyond 6 months, BMI  $< 18.5 \text{ kg/m}^2$  if  $< 70$  years or  $< 20 \text{ kg/m}^2$  if  $\geq 70$  years, or markedly reduced muscle mass. As muscle mass measurements were not available in our study, malnutrition staging was conducted based on the remaining GLIM criteria.

### Muscle Strength Assessment

Handgrip strength was measured using a Takei dynamometer (Takei T.K.K. 5401 digital dynamometer, Takei Scientific Instruments Co. Ltd, Tokyo, Japan). Measurements were performed with a validated protocol<sup>(21)</sup>.

### Laboratory Measurements

Serum CRP and albumin values were retrieved from the measurements taken within the first 24 hours after hospitalization. CAR was calculated as CRP (mg/L) divided by albumin (g/dL).

### Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 25.0 for Windows (SPSS Inc., Chicago, IL, USA). To evaluate the distribution of the data, the Kolmogorov-Smirnov test was applied. Normally distributed variables were shown as mean  $\pm$  standard deviations and non-normally distributed variables were shown as medians (minimum-maximum values). Categorical variables were expressed as counts and percentages. Chi-square, Mann-Whitney U, or t-tests were used to assess differences between the two groups, when appropriate. Comparisons among three groups were performed using Kruskal-Wallis analysis, followed by adjacent post-hoc tests. P-values with Bonferroni corrections were used for post-hoc analysis. The area under the (AUC) receiver operating characteristic (ROC) curve was computed to evaluate and compare the predictive capabilities of CAR, CRP, and albumin in identifying malnutrition and its stages. An AUC value greater than 0.8

suggests strong diagnostic accuracy, while values between 0.6 and 0.8 indicate moderate accuracy, and values below 0.6 reflect limited diagnostic performance<sup>(22)</sup>. ROC curves were also constructed to determine CAR threshold values for predicting malnutrition stages according to the GLIM criteria. Optimal cut-off values were determined using the Youden index.

For correlation analysis, Pearson correlation was applied to normally distributed data, while Spearman correlation was applied to non-normally distributed data. A p-value of less than 0.05 was considered statistically significant.

## Results

Of 127 patients, 46.5% were male, with a median age of 73. Table 1 provides the demographic and clinical characteristics of the study population, categorized by their nutritional status.

According to the GLIM criteria, 50.4% of patients were classified as well-nourished, 26% had stage 1 malnutrition,

and 23.6% had stage 2 malnutrition. CRP, albumin, and CAR values differed significantly among the three groups ( $p=0.019$ ,  $p=0.04$ , and  $p=0.014$ , respectively). Post-hoc analysis showed that CRP and CAR were significantly higher, and albumin was significantly lower, in stage 2 malnutrition compared with the well-nourished group ( $p=0.042$ ,  $p=0.034$ , and  $p=0.005$ , respectively). No significant differences were found between stage 1 and the well-nourished group ( $p=0.104$ ,  $p=0.157$ , and  $p=0.081$ ).

CAR showed a strong positive correlation with CRP ( $r=0.929$ ,  $p<0.001$ ) and a strong negative correlation with albumin ( $r=-0.633$ ,  $p<0.001$ ). In addition, CAR demonstrated a moderate positive correlation with length of hospital stay ( $r=0.520$ ,  $p<0.001$ ) and a moderate negative correlation with handgrip strength ( $r=-0.307$ ,  $p=0.020$ ). Other correlations were weaker and are presented in Supplementary Table 1.

The AUC values of CRP, albumin, and CAR for predicting malnutrition (stage 1+2) according to GLIM criteria were 0.644 [95% confidence interval (CI): 0.546-0.742,  $p=0.005$ ],

**Table 1. The characteristics of the study population according to nutritional status**

Variables	Total population (n=127)	Well nourished (n=64)	Stage 1 malnutrition (n=33)	Stage 2 malnutrition (n=30)	Total malnutrition (n=63)	p-value <sup>a</sup>	p-value <sup>b</sup>
Age (years)	73 (60-95)	69.5 (60-90)	72 (60-95)	76 (60-91)	73.7±9*	0.142	0.79
Gender, male (%)	46.5	42.2	45.5	56.7	50.8	0.331	0.419
The number of comorbidities	4 (0-11)	4 (0-11)	4 (1-9)	3 (0-9)	4 (0-9)	0.485	0.725
The number of medications	7 (0-19)	7 (0-19)	6 (1-11)	7 (0-11)	6 (0-11)	<b>0.048</b>	0.136
Duration of hospital stay (day)	8 (1-56)	7 (1-41)	12 (1-56)	9 (2-55)	10 (1-56)	<b>0.012</b>	0.059
Muscle strength (kg)	20.5±8.5*	21.4±8.5*	21 (7.1-37.2)	16 (1-39.6)	19.2±8.7*	0.151*	0.059
Body mass index (kg/m <sup>2</sup> )	27±6.26*	30.4±5.4*	23.6 (15-37)	22.9 (14-36)	23.5±5*	<b>&lt;0.001*</b>	<b>&lt;0.001</b>
Calf circumference (cm)	34 (23-49)	36 (25-48)	33 (26-41)	31 (23-49)	32±4.6*	<b>&lt;0.001</b>	<b>&lt;0.001</b>
CRP	11 (0.3-305)	5.6 (0.3-126)	25 (0.3-305)	26.9 (0.3-190)	25 (0.3-305)	<b>0.005</b>	<b>0.019</b>
Albumin	3.5 (1.2-4.7)	3.7 (1.2-4.7)	3.4 (1.3-4.5)	3.1 (1.9-4.7)	3.2 (1.2-4.7)	<b>0.002</b>	<b>0.004</b>
CAR	3.2 (0.07-135.2)	1.8 (0.07-50.4)	6.8 (0.08-135.2)	9.8 (0.08-86.4)	8.8 (0.08-135.2)	<b>0.004</b>	<b>0.014</b>

Total malnutrition: stage 1 malnutrition+stage 2 malnutrition according to GLIM

<sup>a</sup>: p-values between well-nourished and total malnutrition, <sup>b</sup>: p-values between well-nourished, stage 1, and stage 2 malnutrition, \*: Normally distributed variables were shown as mean ± SD, \*\*: Independent sample t-test was used, CRP: C-reactive protein, CAR: C-reactive protein to albumin ratio, GLIM: Global leadership initiative on malnutrition, SD: Standard deviation

0.660 (95% CI: 0.564-0.755,  $p=0.002$ ), and 0.649 (95% CI: 0.552-0.747,  $p=0.004$ ) (Figure 1). For stage 2 malnutrition, the AUCs were 0.669 for CAR (95% CI: 0.542-0.796,  $p=0.009$ ) and 0.662 for CRP (95% CI: 0.534-0.790,  $p=0.012$ ) (Figure 2).

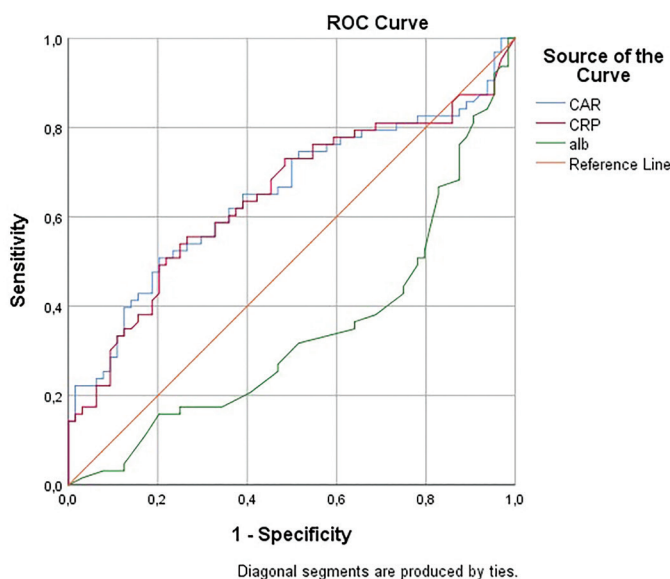
Optimal CAR thresholds determined by Youden index were  $\geq 8.29$  for overall malnutrition and  $\geq 8.40$  for stage 2 malnutrition. For overall malnutrition, the cut-off of  $\geq 8.29$  yielded a sensitivity of 50.0% and a specificity of 79.7%, with positive predictive value (PPV) 70.8% and negative predictive value (NPV) 61.8%. For stage 2 malnutrition, the cut-off of  $\geq 8.40$  provided a sensitivity of 53.3% and a specificity of 79.7%, with PPV 44.8% and NPV 84.7%.

## Discussion

In this study, we investigated the association between CAR and malnutrition (including stages defined by the GLIM criteria) in hospitalized older adults. Our results showed that CAR values were significantly higher in patients with stage 2

malnutrition than in well-nourished individuals. However, no significant difference was observed between well-nourished patients and those with stage 1 malnutrition, or between patients with stage 1 and stage 2 malnutrition. The optimal CAR cut-off of  $\geq 8.40$  demonstrated moderate diagnostic accuracy for stage 2 malnutrition, with a sensitivity of 53.3% and specificity of 79.7%, yielding a relatively low PPV (44.8%) but a higher NPV (84.7%). These findings suggest that CAR may be more useful for ruling out severe malnutrition than for confirming its presence.

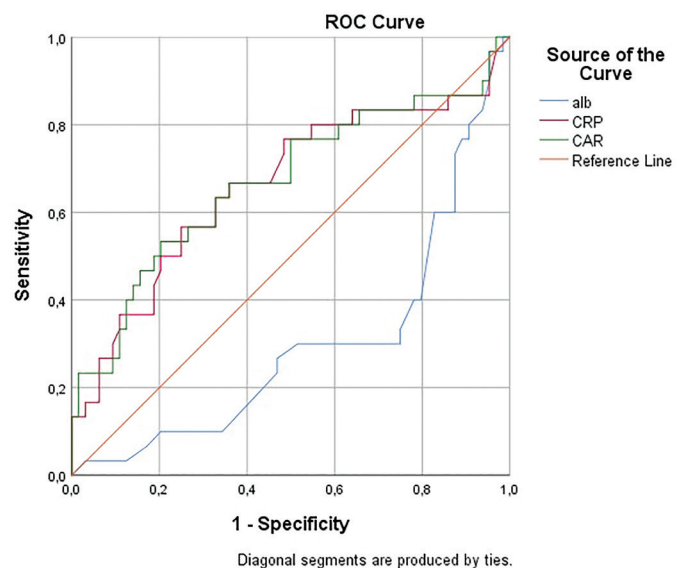
Our results align with previous studies highlighting the role of systemic inflammation in malnutrition pathogenesis and diagnosis<sup>(5,20)</sup>. CRP is a well-established biomarker of inflammation, while albumin reflects both nutritional status and inflammatory burden<sup>(14)</sup>. Eckart et al.<sup>(23)</sup> demonstrated that elevated CRP combined with hypoalbuminemia increased malnutrition risk during acute illness. In our study of hospitalized patients aged over 60 years, those



**Figure 1.** ROC curves of CRP, albumin, and CAR for predicting overall malnutrition (stage 1+stage 2) according to GLIM criteria

Optimal CAR threshold (Youden's J):  $\geq 8.29$ ; CAR=CRP (mg/L)/albumin (g/dL). AUC=0.649 (95% CI: 0.552-0.747); sensitivity 50.0%, specificity 79.7%, PPV=70.8%, NPV=61.8%

ROC: Receiver operating characteristic, CAR: C-reactive protein to albumin ratio, CRP: C-reactive protein, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value



**Figure 2.** ROC curve of CAR and CRP for predicting stage 2 malnutrition according to GLIM criteria

Optimal CAR threshold (Youden's J):  $\geq 8.40$ ; CAR=CRP (mg/L)/albumin (g/dL). AUC=0.669 (95% CI: 0.542-0.796); sensitivity 53.3%, specificity 79.7%, PPV=44.8%, NPV=84.7%

ROC: Receiver operating characteristic, CAR: C-reactive protein to albumin ratio, CRP: C-reactive protein, AUC: Area under the curve, CI: Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value

with malnutrition according to GLIM criteria had higher CRP, lower albumin, and higher CAR. A higher CAR ratio was observed as the stage of malnutrition increased. Since CAR is mathematically derived from CRP and albumin, the observed correlations largely reflect a mechanistic relationship. They should not be interpreted as independent biological associations. Our findings extend the evidence by demonstrating that CAR may not only be a prognostic marker but also serve as a supportive indicator for severe malnutrition as defined by GLIM.

The pathophysiological link between CAR and malnutrition is biologically plausible. Inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor- $\alpha$  suppress appetite, promote proteolysis, and reduce albumin synthesis, contributing to muscle wasting and weight loss<sup>(24)</sup>. In our study, despite a difference in BMI between well-nourished participants and those with stage 1 and stage 2 malnutrition, there was no difference in GS. Malnutrition can impair immune responses, perpetuating chronic inflammation and creating a vicious cycle<sup>(25)</sup>. In our study, there was no difference in the number of chronic diseases between the groups, but the inflammatory burden caused by the disease may differ between groups, and inflammatory responses may change depending on inflammaging.

CAR has been shown to predict adverse outcomes in sepsis, malignancies, and critical illness<sup>(13,17)</sup>. In older adults, high CAR has been associated with longer hospital stays and higher mortality<sup>(26,27)</sup>. Kaplan et al.<sup>(12)</sup> found a CAR exceeding 16.28 was identified as a significant predictor of mortality, demonstrating 92.1% sensitivity and 58.0% specificity. In line with these findings, our study showed that the duration of hospitalization was significantly longer in patients with malnutrition than in those without, and that CAR was positively correlated with length of hospital stay. Taken together, these findings reinforce the clinical importance of CAR as both a nutritional and a prognostic marker.

In 393 patients with COPD, CAR values were significantly higher in those with an nutritional risk screening (NRS)-2002 score  $\geq 3$ , indicating a higher risk of malnutrition. A cut-off value of 3.26 predicted nutritional risk<sup>(28)</sup>. In that study, patients with NRS-2002  $\geq 3$  also had significantly lower albumin and higher CRP levels. Moreover, among 234 emergency department patients, higher CAR was again associated with malnutrition risk according to NRS-2002<sup>(29)</sup>. Nutritional status was assessed using the mini nutritional assessment in 155 elderly outpatients after excluding those with CRP  $>10$ . A CAR threshold of  $\geq 0.86$  (CRP in mg/L,

albumin in g/dL) predicted malnutrition (sensitivity 48.4%, specificity 71.7%)<sup>(30)</sup>. In our study, CAR cut-off values were considerably higher. This difference may be attributable to variations in study populations and exclusion criteria, particularly the exclusion of patients with CRP  $>10$  mg/L.

From a clinical perspective, our results suggest that CAR could complement existing screening tools, particularly when rapid assessment is needed. A low CAR ( $<8.40$ ) may reliably exclude severe malnutrition, potentially reducing unnecessary investigations. However, given the modest PPV, positive results should always be followed by a comprehensive nutritional assessment, including anthropometric and functional measures such as GS. Compared with the conventional application of GLIM, CAR measurement is simple, inexpensive, and widely available, thereby increasing its practical value in resource-limited settings.

### Study Limitations

Our study has several strengths. To our knowledge, it is the first study to evaluate the association between CAR and GLIM-defined malnutrition stages in older hospitalized patients. Additionally, we determined specific cut-off values that may be clinically applicable. Nonetheless, limitations must be acknowledged. The retrospective design precludes causal inference, and the single-center sample limits generalizability. Furthermore, we relied on a single baseline measurement of CRP and albumin, which may not reflect dynamic changes during hospitalization. The sample size was modest, which may have limited the statistical power to detect differences between stage 1 patients and well-nourished patients.

Future research should aim to validate these findings in larger, prospective, multicenter cohorts. Longitudinal studies assessing dynamic changes in CAR may provide insights into CAR's role in monitoring nutritional interventions and predicting outcomes. Moreover, integrating CAR with other inflammatory markers (e.g., neutrophil-to-lymphocyte ratio, IL-6) could enhance diagnostic performance.

### Conclusion

In conclusion, CAR is associated with malnutrition severity according to the GLIM criteria and may be particularly useful for identifying and especially ruling out patients at risk of severe malnutrition. While its diagnostic accuracy is moderate, its simplicity and availability make it a promising tool in the nutritional assessment of older hospitalized patients.

## Ethics

**Ethics Committee Approval:** The study was approved by the Ege University Medical Research Ethics Committee, İzmir, Türkiye (approval no: 22-12T/50, date: 06.12.2022).

**Informed Consent:** For this type of retrospective study formal consent is not required.

## Footnotes

### Authorship Contributions

Surgical and Medical Practises: N.S.G., Concept: N.S.G., S.Ç., S.S., Design: N.S.G., S.Ç., S.S., Data Collection or Processing: N.S.G., Analysis or Interpretation: N.S.G., S.Ç., S.S., Literature Search: N.S.G., F.E., Writing: N.S.G., S.S., F.E.

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