# A Practical and Applicable New Index as an Indicator of Inflammation in the Diagnosis of Erectile Dysfunction: C-reactive Protein-to-Albumin Ratio

**Mesut Cilli[1], Kemal Turker Ulutas[2]**
[1]Department of Urology, Reyhanlı State Hospital, Ministry of Health, Hatay, Turkey; [2]Department of Biochemistry, Reyhanlı State Hospital, Ministry of Health, Hatay, Turkey

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**Abstract:** Current evidence suggests that the significant underlying pathophysiological mechanism in erectile dysfunction (ED) is endothelial dysfunction. It is clinically essential to monitor ED because inflammatory processes lead to dysfunctional endothelium and the progression of atherosclerosis. The current retrospective analysis assessed the registers of 90 patients with ED complaints (ED group) and 78 healthy people without ED complaints (control group) who were being managed at the urology units of the surgical outpatient clinic. The international index of erectile function-5 (IIEF-5) evaluated the ED. C-reactive protein (CRP)/albumin ratio (CAR) value was determined by manually dividing serum CRP value by the albumin value in patients whose CRP value was between 0 and 5 mg/l. The average CAR was 0.45 ± 0.37 (ED group) versus 0.22 ± 0.1 in the control group (p=0.0001). IIEF-5 results were negatively correlated with CAR values (r=−0.299; p=0.0001). The strongest cut-off of CAR for predicting ED was 0.025, with 81.8% sensitivity and 75% specificity (p=0.0001). The ED group showed higher levels of CAR and CRP than the control group. CAR can be used as a practical, easy-to-calculate, and cost-effective index in diagnosing ED patients.

**Mailing Address:** Mesut Cilli, MD., Department of Urology, Reyhanlı State Hospital, Ministry of Health, Yenisehir, 222 St., PB: 31500, Reyhanlı, Hatay, Turkey; Phone: +90 (533) 454 38 60; e-mail: drmesutcilli@hotmail.com

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## Introduction

Erectile dysfunction (ED) denotes that a person cannot provide full penile erection or maintain it for fulfilling sexual intercourse (Sooriyamoorthy and Leslie, 2022). ED was generally considered a psychogenic disorder in the past; however, it is now known that more than 80% of the cases have an organic etiology (Yafi et al., 2016). The causes of ED can be multifactorial. However, vascular causes are among the top pathogenic factors because the penis has a significant vascular bed. The primary pathophysiological mechanism underlying vasculogenic ED is endothelial dysfunction (Vlachopoulos et al., 2008).

Acute phase reactants (APR) are inflammatory indicators that show substantial variations in serum levels in cases of infection, trauma, inflammatory diseases, and malignancy. The most important positive APR is C-reactive protein (CRP); the most significant negative APR is albumin.

Endothelial cells, which constitute the inner lining of penile arteries, regulate the vascular tone and penile blood flow according to stimuli. Nitric oxide (NO) released from endothelial cells is a vital neuromodulator for the standard induction and maintenance of erections. With the effect of NO, relaxation occurs in the corpus cavernosum and penile vascular smooth muscle. Thus, there is an increase in blood flow from the systemic circulation to the penis. In vasculogenic ED, nitric NO production from endothelial cells is reduced; thus, endothelial cells' regulatory role is inhibited. Inflammatory processes result in endothelial dysfunction and the progression of atherosclerosis (Devaraj et al., 2004; Bisoendial et al., 2007). Because endothelial dysfunction also causes atherosclerosis, the concomitance of ED and systemic atherosclerosis is common (Vlachopoulos et al., 2008). Therefore, CRP – one of the inflammatory markers – may help determine the prognosis of ED and cardiovascular diseases and monitor the treatment (Li et al., 2019; Rencuzogullari et al., 2019). Another molecule also synthesized by the liver, albumin can preserve the microvasculature and lower the rise in vascular permeability by its anti-inflammatory, antioxidant, and anti-apoptotic effects (Vincent et al., 2014). In the literature, low serum albumin levels have been accepted as a biomarker for predicting situations like acute coronary syndrome, heart failure, kidney failure, and stroke (Chien et al., 2017). These two molecules are actively involved in diagnosing and following vascular pathologies. Considering that the incidence of cardiovascular diseases is high among patients with ED, these two molecules can be used as early indicators of ED (Zhao et al., 2019). The current research evaluates the diagnostic effectiveness of albumin and CRP, which are considered inflammation markers in ED, and a new index, CRP/albumin ratio (CAR), among patients with ED.

## Material and Methods

*Study design*

This cross-sectional retrospective research was carried out by evaluating registers of healthy individuals and patients with ED complaints who were being managed at

the urology units of the surgical outpatient clinic between July 2019 and May 2022. Ninety participants with ED complaints and 78 healthy participants without ED complaints who met the eligibility criteria were enrolled.

*Participation criteria*

The current study included sexually active and married patients aged between 40 and 70 and with the international index of erectile function-5 (IIEF-5) of less than 22 score. Individuals having a psychiatric disorder, history of penile or pelvic trauma or surgery, congestive cardiac condition, endocrine disruption other than diabetes, chronic liver/kidney disease, current inflammation and/or antibiotic drug use, patients with CRP > 10 mg/l, history of neurological disorders, high prostate-specific antigen (PSA) levels suggesting the need for prostate biopsy, urogenital system cancer, those using drugs that cause iatrogenic ED, and individuals below 34 years old or over 72 years old were excluded. As part of routine care, a comprehensive physical examination was performed for each patient presenting to the urology outpatient clinic, and a detailed anamnesis was taken from all patients and recorded. Height, weight, and waist circumference measurements were obtained for each patient and body mass index (BMI) ($kg/m^2$).

In the present study, a history of previous surgery, medication use, and smoking and alcohol use were recorded for each participant. A fasting sample was collected from each participant between 8 and 10 a.m. Fasting blood glucose, glycosylated hemoglobin (HbA1c), complete blood count, sedimentation, CRP, vitamin-B12, vitamin D, folate, prolactin, follicle-stimulating hormone, luteinizing hormone, total testosterone, oestradiol, insulin, thyroids, total PSA and free PSA levels were measured. Albumin levels ranged from 35 to 55 g/l, and CRP was between 0 and 5 mg/l. CAR value was estimated by dividing CRP by albumin. HbA1c level of ≥ 6.5 or currently on pharmacological treatment for diabetes defined diabetes mellitus (DM). Dyslipidaemia was described as having fasting blood cholesterol ≥ 200, high-density lipoprotein (HDL) < 40 mg/dl, and low-density lipoprotein (LDL) ≥ 130 mg/dl or being currently on pharmacological treatment for dyslipidaemia.

The IIEF-5 form with a list of five questions was used in the current study. Each question is scored from 1 to 5 in this form, with 5 being the best response. A summary score of 5–7 points indicate severe ED, 8–11 points indicate moderate ED, 12–16 points indicate moderate-mild ED, 17–21 points indicate mild ED, and 22–25 points indicate no ED.

*Statistical analysis*

Power calculation was carried out with G-Power 3.05 program for Windows. A sample of a reference study was considered for the power analysis. When the data about patient and control groups were measured, the investigation had a power level of 83 percent (post hoc power analysis). The Kolmogorov-Smirnov method determined the normality. The variance was analysed using the Mann-Whitney U

and independent *t*-test. Pearson's chi-squared test compared categorical variables, whereas Spearman's correlation investigated the correlations. Descriptive statistics were reported using mean and standard deviation for numerical data and frequency and proportion for the categorical data. A p-value below 0.05 was identified as the criterion for significance. SPSS v24.0 (IBM Co., Ohio, USA) was utilized for the analysis.

## Results

The study included 168 men, 90 sexually active, and 78 healthy controls. The characteristics of the study participants did not differ significantly in their age, weight, height, and body mass index (p>0.05). In addition, of the study subjects did not differ in smoking (p=0.344), alcohol abuse (p=0.103), and comorbid diseases such as elevated blood pressure and coronary-artery disease (p=0.156 and p=0.099). Patients with similar demographic data were selected, while others were excluded from the study.

Mean serum CRP concentrations were more significant in the patient group (3.41 ± 1.98 mg/l) compared to the control group (1.61 ± 1.05 mg/l) (p=0.001). As seen in Figure 1, the CAR was 0.45 ± 0.37 in the patients and 0.22 ± 0.1 in the control (p=0.0001). The albumin levels were reduced in the ED group (39.4 ± 15.3 g/l) than those in the control group (45.5 ± 3.6 g/l) (p=0.008). In addition, the groups did not differ in laboratory parameters (p>0.05). Pearson correlation revealed that IIEF-5 was not correlated with albumin (p=0.133) but indicated a negative correlation with CRP (r=−0.335; p=0.0001) and CAR (r=−0.299; p=0.0001). As seen in Figure 2, the cut-off of CAR for predicting ED was 0.025, which had a sensitivity of 81.8% and a specificity of 75% (ROC

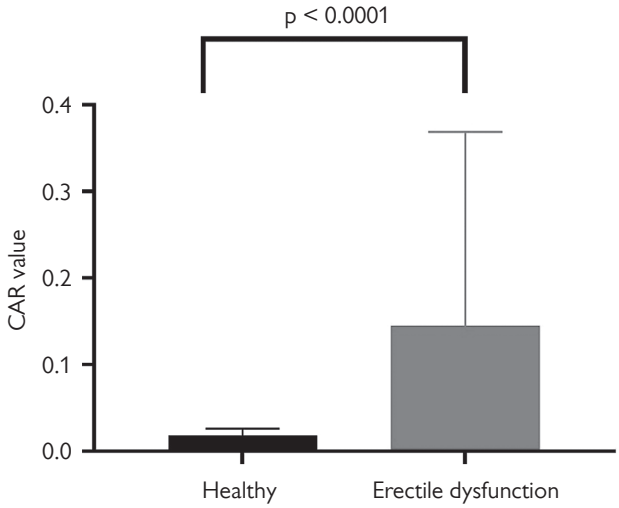


*Figure 1 – C-reactive protein/albumin ratio (CAR) for comparison of groups.*

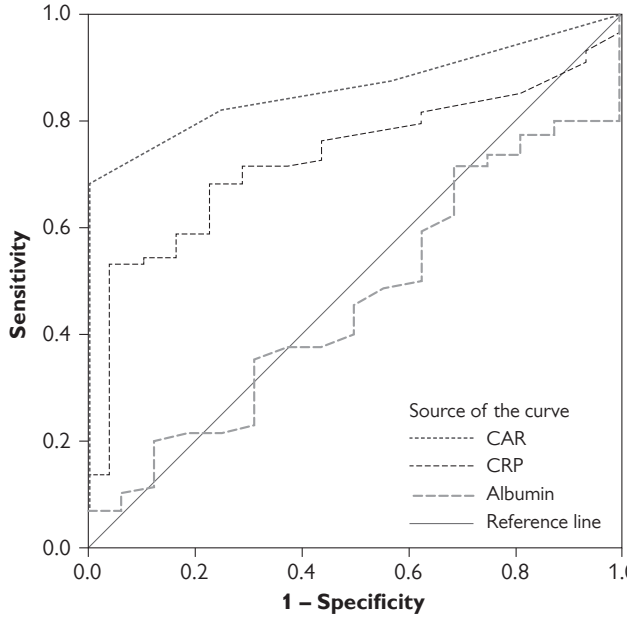


*Figure 2 – The receiver operating characteristic (ROC) curve of C-reactive protein/albumin ratio (CAR) for predicting erectile dysfunction.*

[receiver operating characteristic]: 0.862, 95% CI [confidence interval]: 0.801–0.923, p=0.0001). While CRP had a substantial potential for diagnosing ED in the ROC curve, the same was not valid for albumin (Table 1).

## Discussion

It is necessary to distinguish whether the etiology of ED is primarily a psychological or an organic cause. Although the etiology of ED may include various factors, diagnostic tools are crucial for these patients (Sooriyamoorthy and Leslie, 2022). In this term, CAR can be used as a practical device due to its easy-to-calculate and cost-effective index in diagnosing ED.

For elderly patients, the leading cause of ED is organic diseases due to the vascular failure of penile arteries and veins caused by atherosclerosis (Stuckey et al., 2007). Vascular inflammation mediates a crucial function in the continuation

**Table 1 – The ROC analysis for predicting erectile dysfunction**

| Variables | AUC | SE | P-value | 95% CI | |
|---|---|---|---|---|---|
| | | | | lower | upper |
| CAR | 0.862 | 0.031 | 0.0001 | 0.801 | 0.923 |
| CRP | 0.729 | 0.043 | 0.0001 | 0.644 | 0.814 |
| ALB | 0.459 | 0.050 | 0.4280 | 0.361 | 0.557 |

CRP – C-reactive protein; CAR – CRP/albumin ratio; ALB – albumin; AUC – area under curve; CI – confidence interval; SE – standard error; ROC – receiver operating characteristic

and manifestation of atherosclerosis and endothelial dysfunction (Devaraj et al., 2004; Bisoendial et al., 2007; Vlachopoulos et al., 2008). It has been shown that atherosclerosis is not caused by passive vascular damage induced by the penetration of lipids but by an aggressive inflammatory mechanism (Guay, 2007). Inflammatory diseases play a role in initiating and developing atherosclerosis and cause a stable atherosclerotic plaque to become an unstable lesion (Ross, 1993). ED shares the same modifiable risk factors as cardiovascular risk factors, including hypertension, diabetes, dyslipidemia, smoking, obesity, metabolic syndrome, sedentary lifestyle (Sangiorgi et al., 2021).

Albumin is the most common protein in the plasma of mammals, which is synthesized only by the liver at a rate of 9–14 g per day in healthy persons (Vincent et al., 2014; Czub et al., 2018). Albumin has begun to be used to evaluate the mortality and morbidity of some diseases. The most critical negative acute phase reactant is albumin, and serum albumin levels decrease in the presence of chronic inflammatory conditions (Gulhar et al., 2022). Hypoalbuminemia is a robust prognostic marker in many disease states and in several processes. Apart from the usual prognostic markers in patients with cardiovascular disease, low serum albumin has independently emerged as a robust prognostic parameter in these patients (Arques, 2020). Previous studies found a correlation between hypoalbuminemia and ED in chronic viral liver diseases and in patients undergoing haemodialysis and continuous peritoneal dialysis (Toda et al., 2005; Martín-Díaz et al., 2006; Kim et al., 2015; Costa et al., 2018; Kusumawardhani et al., 2021). Few studies in the literature compare ED patients without chronic liver disease or chronic renal failure with healthy patients (Demir and Barlas, 2021; Balta and Mikhailidis, 2022). A positive correlation was found between hypoalbuminemia and ED in a study conducted on individuals with chronic kidney disease. This study showed that subjects with albumin lower than 3.5 g/dl had a higher frequency of ED (Costa et al., 2018). Another study conducted on subjects with chronic viral liver disease found a correlation between IIEF-5 scores and serum albumin levels; albumin was defined as an independent predictor of ED (Toda et al., 2005). In subjects undertaking continuous ambulatory peritoneal dialysis, the risk of experiencing sexual dysfunction, after adjusting for age, was 9.3 times higher in subjects having an albumin of $< 3.5$ g/dl compared with patients with an albumin level of 3.5–5 g/dl (Kusumawardhani et al., 2021). In a study conducted among individuals having liver disease due to chronic hepatitis B, serum albumin level was $4.1 \pm 0.5$ g/dl in patients with ED and $4.4 \pm 0.3$ g/dl in patients without ED. High albumin lowered the risk of ED occurrence (Kim et al., 2015). Demir and Barlas (2021) performed a comparative analysis of individuals with ED versus those who do not have ED and showed that albumin levels were considerably lower among individuals having ED versus the control group. However, the difference between the groups did not reach statistical significance (Demir and Barlas, 2021). In our study, mean albumin values were significantly lower in the ED group ($39.4 \pm 15.3$ g/l) compared to the control group ($45.5 \pm 3.6$ g/l) ($p=0.008$).

Pearson correlation analysis also showed that IIEF-5 scores were not correlated with albumin levels.

CRP is an APR synthesized by the liver following the release of proinflammatory cytokines, like IL-6, and activates the complement system by binding to the surface of tissue debris and bacteria, which induces phagocytosis. It is used as a sensitive marker to monitor the temporality of inflammatory conditions. Because it is an inflammatory component of atherosclerosis, CRP can be used to assess cardiovascular risk when analysed using more sensitive assays – high-sensitivity CRP (hs-CRP) tests – for measuring deficient CRP concentrations (Moutachakkir et al., 2017; Herwald and Egesten, 2021). CRP, a marker of fibrinolytic activity and atherosclerosis, is a known predictor for myocardial infarction and stroke in healthy individuals. Some studies have shown that CRP and hs-CRP can be valuable inflammatory markers for assessing ED risk (Zambon et al., 2010; Elzanaty et al., 2016; Shigehara et al., 2016; Li et al., 2019). In the study conducted by Demir and Barlas (2021) comparing individuals with ED and healthy subjects, the CRP was higher in those with ED than in control. Higher CRP levels were related to a higher risk of ED, and a close association was also found between CRP levels and IIEF (Demir and Barlas, 2021). In the present study, serum CRP was also markedly higher in the patient than in the control with a negative correlation of IIEF-5.

There is still a need for non-invasive parameters that can be easily measured, simple to use, inexpensive and can suggest a prognosis. CAR has recently been put into use, and an increasing number of studies are being conducted on it. It has been used as a prognostic and mortality indicator for cardiovascular diseases, gastric, pancreatic, and hepatocellular malignancies, diabetes mellitus, patients with sepsis, and patients hospitalized in intensive care (Saito et al., 2018; Rencuzogullari et al., 2019). Limited studies are available investigating CAR and ED interplay (Demir and Barlas, 2021; Balta and Mikhailidis, 2022). Demir and Barlas (2021) revealed that CAR was significantly greater in individuals with ED compared to the controls; higher CAR values were observed to be related to a higher ED risk. The IIEF-5 results were negatively correlated with the CAR levels, i.e., as the ED worsened, CAR values also increased. In Demir and Barlas (2021) study, the serum CRP level optimal for diagnosing ED was ≥ 2.70 mg/l (sensitivity – 53.5%; specificity – 61.7%). In contrast, the optimal value of CAR for ED detection was ≥ 0.55 (sensitivity – 56.6%; specificity – 59.6%) (Demir and Barlas, 2021). In the present study, the optimal cut-off value of CAR for predicting ED was 0.025 (sensitivity – 81.8%; specificity – 75%). These findings indicate that the CAR can strongly detect ED occurrence easily and non-expensively.

Some limitations require consideration for the current research, although our strong side includes having a relatively large population-based sample. The retrospective design of the study limits the follow-up and long-term outputs. We could not remove the effects of unknown or unassessed confounders and did not classify the type of ED (i.e., vasculogenic or psychologic), which could be sources of

bias. The results apply to specific settings of Turkey and should not be generalizable to other countries or ethnic groups.

## Conclusion

CAR strongly increased in the ED. These results show that by determining CAR values, inflammatory markers can be used to assess the occurrence and determine the ED level of severity ED. Further studies with larger sample sizes should further explore the relation between albumin, CRP, CAR, and ED.

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