

*Aktuelne teme /
Current topics*

ALBUMIN TO GLOBULIN RATIO AS A
BIOMARKER IN MALIGNANT DISEASE; A
CLINICAL SIGNIFICANCE AND
PRACTICAL APPLICATION

ALBUMIN-GLOBULIN ODNOS KAO
BIOMARKER U MALIGNIM BOLESTIMA;
KLINIČKI ZNAČAJ I PRAKTIČNA PRIMENA

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Key words

albumin to globulin ratio, biomarker,
prognostic marker

Ključne reči

albumin/globulin odnos, biomarker,
prognostički marker

Abstract

Introduction: The prognostic markers for human cancers are numerous, mostly are expensive or cannot be obtained before treatments. Albumin and globulin are two major components of human serum and they have been concerned as noninvasive prognostic factors in various malignancies. Serum biochemical parameter-the pretreatment albumin to globulin ratio (AGR) has been commonly considered to be a reliable biomarker.

Topic: The discovery of biological markers, which can predict the risk of metastasis and mortality to assist with clinical decision-making, is still a major topic. Recent studies have shown that albumin to globulin ratio is widely used as a prognostic biomarker in diverse cancers. Reference value for AGR is usually between 1,0 and 1,8 in a healthy population. A low AGR indicate increased production of globulins or insufficient synthesis of albumin in patients with cancer. A decreased albumin level and an increased globulin level are part of chronic inflammation which support tumor development. Albumin and globulin have a strong impact on inflammation and immunity of host.

Conclusion: Diverse researches analyzed the clinical significance of pretreatment AGR and its potential contribution to the prognosis of cancer. Results indicated that a low AGR was associated with adverse clinical outcome and poor survival. AGR is considered to be an optimal prognostic marker than the single serum albumin or globulin levels.

INTRODUCTION

Cancer is a global health issue and one of the most significant leading cause of death worldwide⁽¹⁾. Growing cancer incidence and mortality rate require development of appropriate biomarkers with diagnostic, prognostic and predictive values. Nowadays, the prognostic markers for human cancers are numerous, but majority of them have some lim-

iting factors (cost of particular test, low sensitivity and specificity...) or are not available before treatment⁽²⁾. The clinical outcomes of patients with cancer exposed to similar treatment are various⁽³⁾. Thus, the focus of clinicians is on a searching of biomarkers to guide treatment decisions. Prognostic biomarkers enable the monitoring of the therapy, tumor staging and determination of potential malignancy,

including the prognosis of remission (4). The research challenge in oncology is to find biomarkers which are noninvasive, inexpensive, feasible, safe, and easy to measure with good disposition to access outcome of treatment.

Total serum protein is one of the most widely used parameter in laboratory findings(5). Better laboratory test that examines main fractions of serum proteins and their concentration is electrophoresis. The protein electrophoresis test is used to separate proteins in the blood based on their electrical charge and size. This method is used to identify and measure the presence of pathological proteins, the absence of normal proteins and to detect various protein electrophoresis patterns associated with certain conditions and diseases. Arne Wilhelm Kaurin Tiselius was a Swedish biochemist who won the Nobel Prize in 1948 for discovery of protein electrophoresis(6).

Albumin and globulin are two major constituents of human serum. In some studies they are highlighted as non-invasive prognostic factors in various malignancies. Furthermore, these components play a key role in immunity and inflammation, which are closely associated with tumor response. Albumin is also an objective parameter that reflects nutritional status of patients with cancer(7). Entirely, the pretreatment albumin to globulin ratio (AGR) has been commonly considered to be a credible prognostic biomarker for outcome prediction (overall survival, recurrence rate, risk stratification)(8).

Role and importance of biomarkers

The term biomarker is frequently used in modern medical literature. The significance and purpose of biomarkers in biomedical sciences is still a matter of great importance. Appropriate diagnosis, staging and treatment of cancer are essential for all patients. Laboratory analyses of blood are most widespread diagnostic procedure and biomarkers are used to classify patients into certain categories. In general terms, biomarker is any parameter that can be used as a measurable indicator of pathophysiological state of an organism(9)

Cancer biomarkers can be used in screening, differential diagnosis and clinical staging of cancer. Moreover these markers can be applied to determine tumor size and metastasis, to access response to treatment, to evaluate the risk of tumor recurrence through monitoring(10). Some of them are good prognostic indicators of tumor progression. Without taking into account the nature of tumor, application of biomarker must correlate well with proven improvements in patient outcomes. Prognostic markers are specific and they represent a measurable parameter which give information about the overall patient survival, outcomes and recurrence rate without regard to therapy(11). On the other hand, main focus of predictive biomarker is on the effect of certain therapy models(12). A great number of biomarkers with prognostic value have also been recognized and applied to the treatment of cancer. Despite that, most of them are unaffordable or can not be used before treatments. For this reason, identifying new and easily accessible prognostic markers are still necessary(7). Hence, the detection of potential biomarkers in oncology, which can predict the risk of metastasis and mortality to assist with clinical decision-making, is still a

core issue. Recent studies have shown that albumin to globulin ratio is widely used as a prognostic biomarker in diverse types of cancers.

Serum albumin, globulin and albumin to globulin ratio (AGR)

Total serum protein content give some information regarding a patient's general status; more clinically useful data are obtained from fractionating the total protein. The normal serum protein level is 60 to 80 g/L. Albumin constitutes nearly 60% of total serum protein (concentration varies between 35 and 50g/L in healthy population), and the rest is the total globulin concentration (13). The albumin/globulin ratio is the parameter which represents the amount of albumin in the serum divided by the globulins. This ratio is widely used to access and identify causes of change in total serum protein(14). Reference range for AGR is usually between 1,0 and 1,8 in a healthy population. The AGR may change whenever the any fraction of serum protein alterate (increase or decrease). A low AGR mean overproduction of globulin or underproduction of albumin in patients with cancer. The decrease in albumin level may be also associated with decreased production in liver or increased loss by kidneys. Increased globulins may be directly related to chronic inflammation, infection and tumor(15).

Albumin is synthesized in the liver and it is involved in many functions: maintain colloid osmotic pressure in intravascular space, helps balance blood pH, serves in the transport of bilirubin, hormones, metals, vitamins and drugs(13). The globulin fraction comprises of hundreds of serum proteins including carrier proteins (cortisol binding protein), enzymes, complement, and immunoglobulins. Majority of them are produced in the liver, but the immunoglobulins are product of activated plasma cells. Globulins are divided into four groups by electrophoresis (α_1 , α_2 , β and γ - fraction of globulin). Any increase or decrease in the globulin fraction should be accessed by serum electrophoresis (the pattern should be visually examined for abnormalities in certain area). A variety of clinical studies examined low albumin level as a prognostic marker in human cancers, including lung cancer, breast cancer, gastrointestinal cancer, lymphoma, endometrial cancer, adrenal cancer(16).

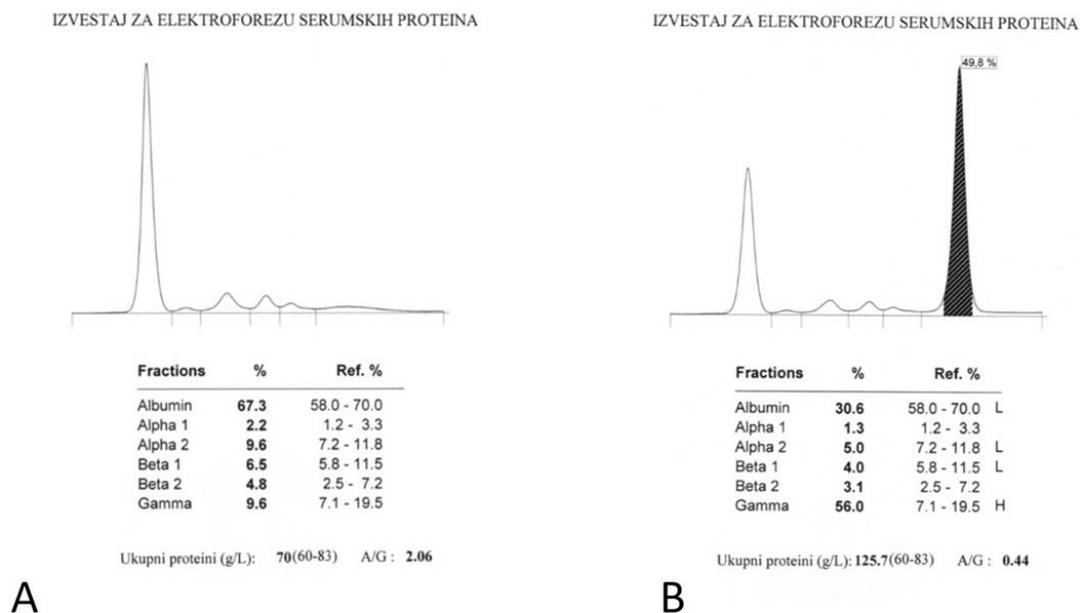
Relationship between AGR, immunity, inflammation and cancer

A chronic inflammation is closely associated with decreased albumin level and increased globulin level. Additionally, various studies confirm relationship between chronic inflammation and development of cancer(17). Systemic inflammation causes an increase in the levels of diverse proinflammatory cytokines and they are responsible for changes in the cancer microenvironment. Synthesis of albumin in liver could be suppressed as a result of activated proinflammatory cytokines interleukin 1, interleukin 6 and tumor necrotic factor α . High production of cytokines which regulate inflammatory response correlate with tumor promotion and progression. Consequently decreased AGR is accompanying state at the stage of tumor progression. Inflammatory reaction is associated with the tumor prolifer-

ation, invasion, metastasis, and resistance to treatment (18). In the basic of chronic oxidative stress is inflammation and this process is closely associated with production of oxygen free radicals. Albumin also plays an important role in an antioxidant processes suppressing the growth of cancer cell lines and stabilizing cell growth and DNA replication (13,19). Cancer related inflammatory reaction has a remarkable impact on hypoalbuminemia(17), which is in large part assigned to the cytokine-induced suppression of albumin synthesis and its increased degradation (7). Numerous researches have found direct connection between inflammation and poor prognosis in different types of tumors(8,15). Furthermore, maintenance of systemic inflammatory response has been noted to contribute poorer outcome in patients. Inflammatory cytokines interleukin (IL)-1 and IL-6 are often marked as factors responsible for carcinogenesis by increasing the proliferation, metastasis, and immune escape of tumor cells(20). These findings support chronic inflammation is associated with poor overall survival (OS) in patients with different malignant tumors(8). Some acute-phase reactants among which are C-reactive protein, complement C3, fibrinogen, ceruloplasmin, serum amyloid A belongs to the fraction of globulins. These mediators are produced in a state of acute and chronic inflammation, thus increased level of globulin indicate existence of continuous systemic inflammation(21).

Lung cancer is still leading cause of cancer related death globally. These patients with a low pretreatment AGR are more likely to have poor prognosis than patients with a normal or high AGR(20). One meta-analysis study suggested that AGR is useful in risk assessment and design of certain treatment strategies in lung cancer. As a result, group of patients with low AGR should be treated more proactively and followed up regularly (20). Pretreatment albumin-to-globulin ratio could reflect both malnutrition and systemic inflammation in cancer patients (3). The AGR as a more

appropriate and accurate prognostic marker for progression of malignant disease than serum albumin or globulin alone (1,8,20). Decreased albumin is closely associated with malnutrition and suppressed anti-oxidant activity but increased globulins indicate intensity of inflammatory response which lead to severe stage of disease (1). Indeed, malnutrition decreases capacity for treatment tolerance and causes immunosuppressed condition in cancer patients (3). Albumin and globulin together in one parameter could emphasize progression of malignant process and point out on the course of disease. AGR is more specific than albumin levels only (because their values can be interfered by many limiting factors such as liver insufficiency, stress, hypervolemia and hypovolemia, ...) (8). A number of studies indicated that the AGR can predict the OS of cancer patients. Recent studies have reported that AGR has been used to predict outcome in various types of solid as well as hematological malignancies, including breast cancer, colorectal cancer, lung cancer, nasopharyngeal carcinoma, and natural killer/T-cell lymphoma (NKTCL)(7). Some clinical parameters are used to evaluate systemic inflammation status, including white blood cell count, neutrophil-lymphocyte ratio and CRP, and these markers have also been reported to have an important impact on the prognosis of cancer patients. The impact of AGR on the prognosis of tumor has been carefully analyzed in numerous trials. Relationship between AGR, lymph node metastasis (LNM) and overall survival were comprehensively evaluated in one meta analysis performed in China. Results indicated that low AGR was significantly associated with poor OS and significant increase in LNM (1). Patients with low AGR have had higher tumor stage and grade, larger tumor size, higher rate of lymph node metastasis and recurrence (22). It is interesting to note that low AGR in general healthy screened population (retrospective cohort study) was also identified as risk factor for increased all-cause mortality, cancer incidence and mortality rate (23). Numerous arti-



Slika 1. A, Serum protein electrophoresis, regular findings. B, Decreased albumin, increased globulin, low AGR.

cles perform meta-analysis to confirm significance of AGR and prognostic nutrition index(PNI) as prognostic biomarkers for digestive system cancers, glioma, lung cancer, breast, hepatocellular and pancreatic carcinoma (20,22,24,25). Entirely, low AGR is independent prognostic factor which indicate poor prognosis for patient with different types of cancer (7,8)

Conclusion

Cancer remains an immense health issue and the occurrence rate of cancer is increasing due to aging and growth of world population as well as increased prevalence of cancer risk factors. Up to now, the prognostic markers for human

cancers are essential for risk assessment, overall patient survival, outcomes and recurrence rate without regard to therapy. Numerous studies demonstrated the clinical significance of pretreatment AGR and its potential contribution to the prognosis of cancer. Results indicated that a low AGR was associated with adverse clinical characteristics and poor survival. AGR is considered to be an optimal prognostic marker than the single serum albumin or globulin levels. Pretreatment AGR is a biomarker that is easy-to-perform with both clinical and economic benefits for predicting OS in various cancers.

Sažetak

Uvod: Za procenu ishoda lečenja tumora koriste se brojni prognostički biomarkeri. Nedostatak većine markera je što se ne mogu primeniti pre započetog lečenja ili što zbog svoje vrednosti predstavljaju značajan trošak za zdravstveni sistem. Albumini i globulini su glavne komponente serumskih proteina i razmatrani su kao neinvazivni prognostički faktori u brojnim malignitetima. Biohemijski parametar- albumin globulin odnos (AGR) se smatra pouzdanim biomarkerom. **Tema:** Jedna od vodećih tema je otkrivanje relevantnih biomarkera koji mogu predvideti rizik od metastaza i mortaliteta prilikom odabira odgovarajućih terapijskih protokola. Nedavno su studije pokazale da se albumin/globulin odnos koristio kao prognostički biomarker kod pacijenata sa različitim vrstama tumora. Kod zdravih osoba AGR odnos se nalazi u rasponu od 1,0 do 1,8. Nizak AGR može biti odraz prekomerne produkcije globulina ili smanjene sinteze albumina kod pacijenata obolelih od kancera. Obe pojave reflektuju hroničnu inflamaciju koja pogoduje progresiji tumora, težim oblicima bolesti, lošijoj prognozi i kraćem vremenu preživljavanja. Albumini i globulini igraju značajnu ulogu u imunitetu i inflamatornim procesima koji su usko povezani sa nastankom i razvojem tumora u organizmu. **Zaključak:** U okviru različitih istraživanja prikazan je klinički značaj AGR pre započetog terapijskog protokola u vidu potencijnog doprinosa prognozi različitih vrsta tumora. Rezultati su ukazivali da je nizak AGR povezan sa lošijom kliničkom slikom i slabijim ukupnim preživljavanjem. U odnosu na pojedinačne vrednosti albumina ili globulina, AGR kao prognostički biomarker se smatra boljim pokazateljem dugoročne prognoze kod obolelih od malignih bolesti.

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■ The paper was received / Rad primljen: 18.02.2021.
Accepted / Rad prihvaćen: 08.03.2021.