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(RESEARCH ARTICLE)

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Hospitalised patients' albumin-globulin ratio may predict negative clinical outcomes

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Abstract

Aims: This research assesses the predictive capability of the ratio of serum albumin levels (ALB) to globulins levels (GLB), known as the AGR, and to determine whether this ratio may be used to anticipate adverse clinical outcomes in these patients.

Methods: This observational study was conducted at the Prince Rahid bin Al-Hussein Military Hospital in Irbid governorate to analyze medical and surgical adult patients. The study aimed to explore the prognostic performances of the assessed albumin to globulin ratio (AGR) against composited negative clinical outcomes, including a decline in creatinine clearance, liver function indices, systemic inflammatory response syndromes, sepsis, longer hospital stays, and death. Factors investigated included patients' demographics, biochemical and complete blood count laboratory results, and subjective reported data. The study focused on evaluating the AGR as an independent variable for predicting adverse clinical outcomes. The optimal threshold for the tested prognosticator of interest (AGR) was determined, and patients were divided into two groups with lower AGR than the cutoff point. A chi square test was conducted to represent the comparative distribution rates between the investigated variables.

Results: A study involving 302 patients found that 51.66% were assigned to Group I, characterized by a lower albumin to globulin ratio (AGR) below the optimal cutoff point of 0.795, and the remaining patients were classified into Group II with an AGR above 0.795. The Pearson correlation coefficient for composite outcomes of interest (cOI) was moderately high in the negative direction for the higher AGR group compared to the lower AGR group. The age distribution was evenly distributed between the lower and higher AGR groups. A binary logistic regression model was created to show the relationship between AGR and the likelihood of adverse clinical outcomes. The prognosticator AGR was evaluated to be 0.928±0.015, with a p-value of less than 0.001, indicating statistical significance. The optimal threshold for the study was 0.795, with a sensitivity of 87.8% and a specificity of 85.23%.

Conclusion: Our study found that maintaining an albumin to globulin ratio below 0.795 can have positive effects on hospitalised patients, both medically and surgically admitted, by predicting adverse clinical outcomes.

Keywords: Albumin to globulin ratio; Adverse clinical impacts; Medical and surgical patients; Predictive utility; Composited negative outcomes of interest

1. Introduction

Serum is the clear part of blood that contains two main types of proteins: albumin proteins, making up 50% of serum protein and reflecting colloidal and nutritional status, and globulin proteins, which indicate immune function and the severity of inflammation. An AG R test measures the ratio of albumins to globulins, providing insights into your

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nutritional status and immune function. The usual AGR range is greater than 1, typically falling between 1 and 2. The text quantifies two main categories: albumin, which prevents blood vessel leakage, and globulins, which help in defending against infections and transporting nutrients in the body [1-3].

Albumin (ALB) is a negative acute-phase reactant, and a decrease in its leve.ls is a critical factor for long-term survival in different clinical scenarios. It is a robust indicator of a negative outcome in the majority of diseases. A low AGR result is associated with a range of diseases affecting organs, particularly liver and kidney dysfunctions, non-infectious and infectious systemic inflammatory syndromes, autoimmune diseases, as well as potential issues such as malnutrition, specific cancers, and type 2 diabetes. Research indicates a correlation between a low A/G ratio and chronic kidney disease, as well as potential links between a low A/G ratio and poorer health outcomes in specific cancer types. **4-6**

A high AGR value could suggest either increased albumin production by the liver or falsely elevated albumin levels caused by hemoconcentration. Hemoconcentration and decreased albumin levels, known as Hypoalbuminemia, are commonly observed in clinical scenarios, like in instances of diarrhoea and severe dehydration. Elevated AGR values, particularly exceeding 2, may suggest reduced globulin levels, which are often observed in individuals with antibody deficiencies, indicating a weakened immune system. Severe conditions can cause a decrease in globulin levels and albumin levels, leading to a slight reduction in the Albumin to Globulin Ratio (AGR) compared to other abnormal conditions. **7-8**

The total protein test quantifies the collective concentration of all proteins in the bloodstream, emphasising albumin (A) and globulin (G). Typically, evaluating total proteins and albumin levels in comprehensive metabolic panels or liver panels is crucial for determining globulin levels. Subtracting albumin levels from total protein levels to calculate the AGR is a valuable method for diagnosing, screening, and monitoring various health conditions. Diagnosis occurs post-symptom manifestation, whereas screening involves preemptive tests for health issues before symptoms arise. Panel tests, such as total protein, may be included in regular checkups for individuals at increased risk of liver or kidney disease to identify issues at an early stage. **9-10**

Monitoring is utilised to track a condition's progression over time or in reaction to treatment. Repeat tests at regular intervals may be conducted to measure total protein and albumin levels in individuals with known liver or kidney issues or those taking medications that impact these organs. Typically, total protein and albumin tests are conducted in medical offices without requiring patients to follow any specific instructions. If they undergo a panel test with more measurements than total protein, they might be instructed to fast for 8 to 12 hours. **11-12** This study aimed to examine the relationship between evaluated AGR prognosticator and clinical outcomes in our Jordanian medically and surgically admitted hospitalised patients.

2. Material and Methods

An observational study was conducted at the Prince Rahid bin Al-Hussein Military Hospital in Irbid governorate to analyse medical and surgical adult patients. Under the registration number of 8_3/2024, our institutional review board committee approved this study to be conducted on 19 February 2024. Owing to its retrospective nature, the applied studied patients' consent forms was waived and their collected data were retrieved primarily from our institutional electronic medical reporting system (Hakeem) in adjunctive to other supplementary sources of paper based documented notes. Adult admitted patients, either medically or surgically, whose baseline kidney, liver, hemodynamic, and systemic immune inflammatory statuses were stable were included in this study.

As previously mentioned, this study primarily aimed to explore the prognostic performances of the assessed albumin to globulin ratio (AGR) against a composited negative clinical outcome. These composited outcomes of interest (cOI) include a decline in creatinine clearance, impairment in liver function indices, indications of systemic inflammatory response syndromes, evidence of sepsis, longer hospital stays than anticipated, and death from any cause. Other factors that were investigated include, but are not limited to, patients' demographics, biochemical and complete blood count laboratory results, and subjective reported data.

Firstly, the study focused on evaluating the AGR as an independent variable for predicting the positivity of occurrence the adverse clinical outcomes (the positive state and assigned as 1) rather than non-occurring (the negative state and was assigned as 0) via conducting a binary logistic regression. Once the abstracted coefficient that were necessary for constructing the binary regressional association model and evaluating the significance of variability in determining the outcome of interest, a sequential statistical analysis of receiver operating characteristic (ROC) testing accompanied with sensitivity analysis for expressing the predictive utility of AGR against positivity of cOI by illustration the area under the ROC (AUROC±SEM) and for exploring the optimal operative point in addition to the other sensitivity indices results.

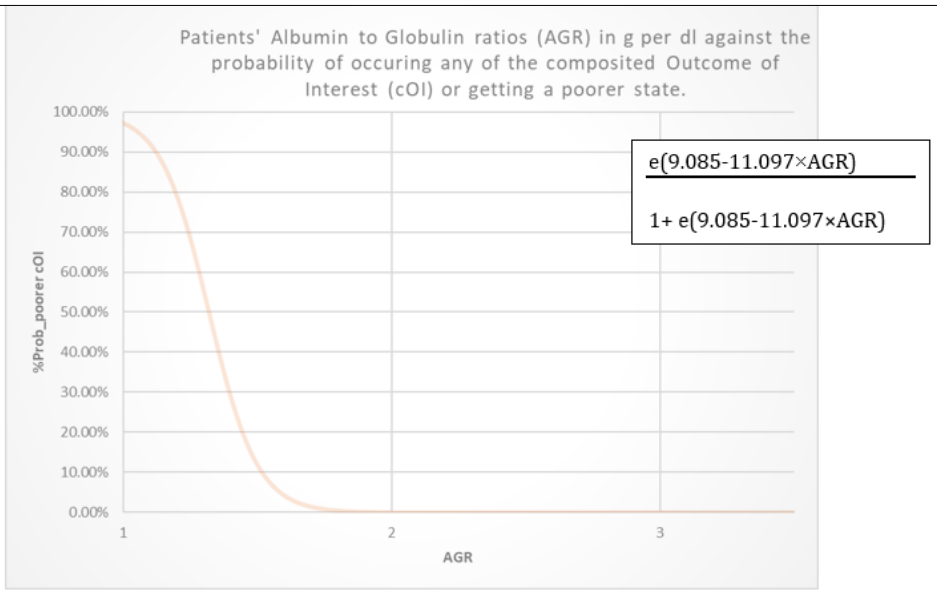
These sensitivity indices results including primarily the true positive rate (sensitivity), true negative rate (specificity), positive and negative predictive values, youden's index, and accuracy index.

After knowing the optimal threshold for our tested prognosticator of interest (AGR) in which the higher value above this threshold revealed a superior outcome of interest (the negative state of cOI) and oppositely the lower values than this patients' specific exploring cutoff point revealed a inferior outcome of interest (the positive state of cOI). Accordingly, all eligible tested patients were dichotomized into two major groups; Group I with a lower AGR than cutoff point and Group II with a higher AGR than cutoff point. Consequently, a chi square test was conducted to represent the comparative distribution rates between the investigated variables across the Group I-II. Additionally, we abstracted the odd ratios to express the unadjusted associations, the pearson correlation to express the correlation value with its standard error of value (R±SEV), and the chi square static significance (χ^2).

Microsoft Office LTSC Professional Plus 2021 Excel was utilised to collect and organise patients' data. IBM SPSS Statistics version 25 was used for statistical analysis and summarising the results of the study. This study utilised a significance level of 0.05.

3. Results

Out of 302 eligible patients, 51.66% (156 patients) were assigned to Group I, characterised by a lower albumin to globulin ratio (AGR) below the optimal cutoff point of 0.795. The remaining patients were categorised into Group II with an AGR above 0.795. The Pearson correlation coefficient for the composite outcomes of interest (cOI) was significantly moderately high in the negative direction [-0.729±0.039, χ 2=160.276, p<0.001] for the higher AGR group (Group II or better cOI) compared to the lower AGR group (Group I or poorer cOI). The unadjusted risk estimate was 0.025 (95% CI; 0.013-0.048) with distribution rates of poorer cOI of 134 (85.9%) in the lower AGR group and 19 (13.0%) in the higher AGR group.

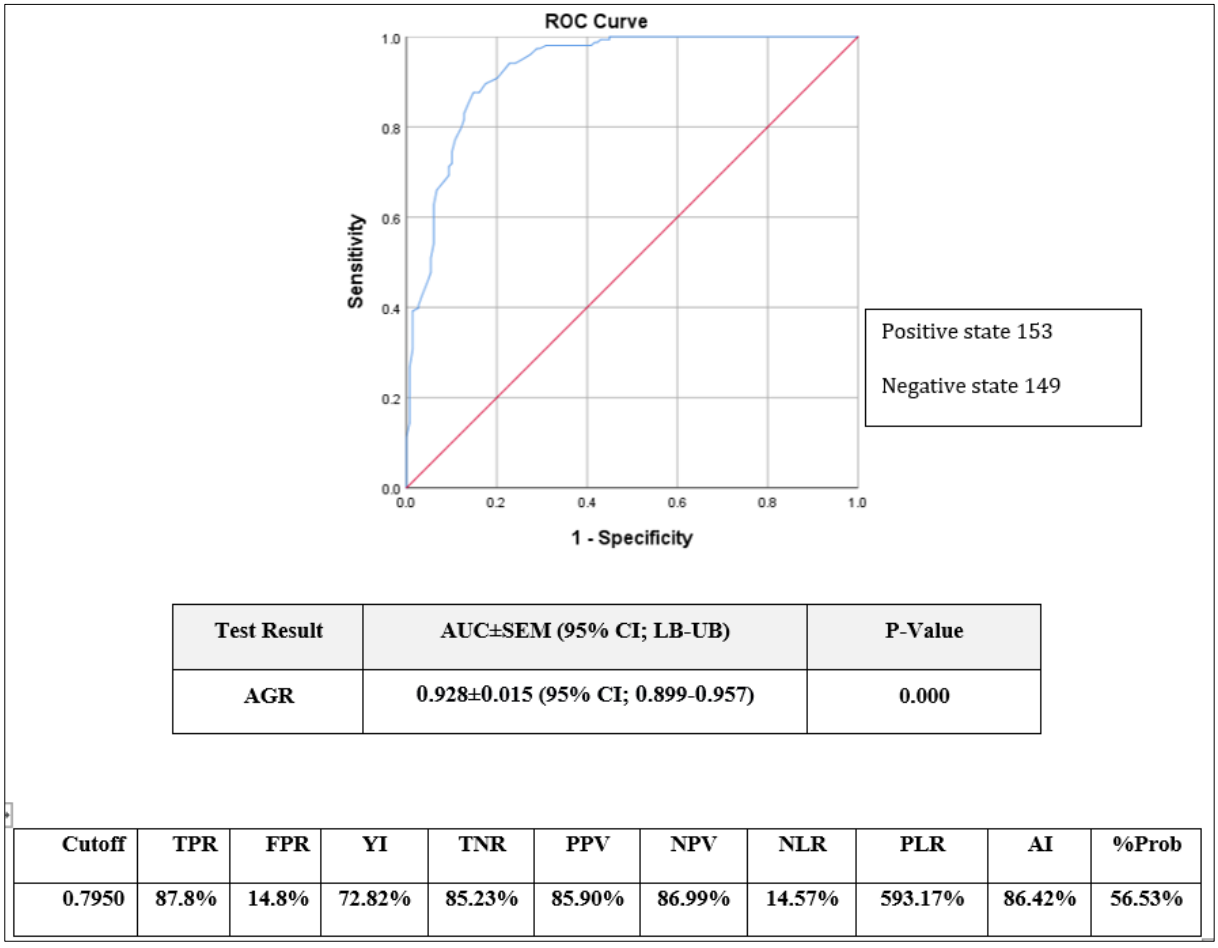


	B±S.E.M	Exp(B)	P-Value	χ 2 (df)	VR	%Cases
AGR	-11.097±1.419	0.000 (95% CI; 0.000-0.000)	0.000	χ 2 (8) 8.062 0.427	51.6%-68.8%	86.1%
Constant	9.085±1.116	8820.427	0.000			

Figure 1 Binary logistic regression analysis was performed on patients who experienced at least one of the specified outcomes, labelled as 1, and patients who did not experience any of the outcomes, labelled as 0. The study examined the albumin to globulin ratio (AGR) as a predictor for the likelihood of positive or negative results. The coefficients needed to create the binary logistic regression model were obtained

The gender distribution rates in the AGR-based binary cohorts were not statistically significant, with an approximately equal allocation of the two genders in Group I-II. The ages of the tested patients were evenly distributed between the lower and higher AGR groups, showing no significant difference. Albumin and globulin levels showed significantly different distributions between Group I and Group II. There was a moderate positive correlation (0.668 ± 0.042, X2 = 134.783, p-value < 0.001) for albumin and a moderately strong negative correlation (0.729 ± 0.039, X2 = 160.471, p-value < 0.001) for globulin. The odds ratios for the albumin and globulin variables of the tested patients were 29.880 (95% CI; 15.39-58.03) and 0.024 (95% CI; 0.012-0.046), respectively. The distribution rates of the tested variables in Group I-II are detailed in **Table 1**.

A binary logistic regression model was created to show the relationship between AGR and the likelihood of adverse clinical outcomes. The formula used was e^(9.085-11.097×AGR) / 1+e^(9.085-11.097×AGR), with a variability range of 51.6% to 68.8%. Around 86.1% of cases can be assessed using this model for patients with similar circumstances to those in the study. **Figure 1** below fully depicts the binary logistic regression model with its abstracted coefficients and other parameters of interest.



Test Result	AUC±SEM (95% CI; LB-UB)	P-Value
AGR	0.928±0.015 (95% CI; 0.899-0.957)	0.000

Cutoff	TPR	FPR	YI	TNR	PPV	NPV	NLR	PLR	AI	%Prob
0.7950	87.8%	14.8%	72.82%	85.23%	85.90%	86.99%	14.57%	593.17%	86.42%	56.53%

Figure 2 An ROC analysis was performed on the prognostic factor of interest in this study, the albumin to globulin ratio (AGR), to determine its predictive value for positive and negative outcomes of interest (cOI). The performance of the utility was quantified as the area under the ROC curve along with its standard error of the mean (AUROC±SEM). A sensitivity analysis was conducted to determine the optimal operating thresholds for AGR, along with other sensitivity indices such as TPR, TNR, PPV, NPV, NLR, PLR, YI, and AI

The performance of our prognosticator AGR was evaluated to be 0.928±0.015 (95% CI; 0.899-0.957), with a p-value of less than 0.001, indicating statistical significance. 153 patients were identified as positive in the ROC test. There were 149 patients classified as negative (labelled as 0) in the ROC test. 16 cases were classified as missing cases. The study set the optimal threshold at 0.795, with a sensitivity of 87.8% and a specificity of 85.23%. The probability of at least one of the composite outcomes of interest occurring in the studied patients during the admission period at the abstracted optimal threshold was determined to be 56.53%. The ROC analysis results, along with the corresponding sensitivity indices, are fully displayed in **Figure 2**.

Table 1 The comparative distribution rates of the tested variables across Group I-II

	Lower AGR Group I (AGR<0.795) (156, 51.66%)	**Higher AGR Group II (AGR≥0.795) (146, 48.34%)**	**Total (302, 100%)**	**R ρ**	**OD**	**χ 2 p-Value**
cOI						
Better cOI	22 (14.1%)	127 (87.0%)	149 (49.3%)	-0.729±0.039*	0.025 (95% CI; 0.013-0.048)	160.276 0.000
Poorer cOI	134 (85.9%)	19 (13.0%)	153 (50.7%)			
Gender						
Female	75 (48.1%)	73 (50.0%)	148 (49.0%)	-0.019±0.058	0.926 (95% CI; 0.589-1.454)	0.112 0.738
Male	81 (51.9%)	73 (50.0%)	154 (51.0%)			
Age (Years)						
<60	55 (35.3%)	37 (25.3%)	92 (30.5%)	+0.108±0.057	1.604 (95% CI; 0.976-2.637)	3.499 0.061
≥60	101 (64.7%)	109 (74.7%)	210 (69.5%)			
H. Albumin (g/day)						
<18.5	117 (75.0%)	54 (37.0%)	171 (56.6%)	+0.383±0.053	5.111 (95% CI; 3.118-8.378)	44.371 0.000
>=18.5	39 (25.0%)	92 (63.0%)	131 (43.4%)			
Globulin (g/dl)						
<3.04	16 (10.3%)	121 (82.9%)		-0.729±0.039	0.024 (95% CI; 0.012-0.046)	160.471 0.000
≥3.04	140 (89.7%)	25 (17.1%)				
ALB (g/dl)						
<2.585	142 (91.0%)	37 (25.3%)	179 (59.3%)	+0.668± 0.042	29.880 (955 CI; 15.39-58.03)	134.783 0.000
≥2.585	14 (9.0%)	109 (74.7%)	123 (40.7%)			

A chi-square test was performed to compare the variables between Group I and Group II. The results were presented as distribution rates, including both numbers and percentages. Unadjusted odds ratios were also recorded to represent the associations. The Pearson correlations were displayed along with their standard error values (R±SEVs), as well as the Chi statistic for significance (X2) along with the significance level. Group I consist of patients with albumin to globulin ratios (AGR) below the cutoff point of 0.795, while Group II consists of patients with AGR values equal to or higher than 0.795.

4. Discussion

This study aimed to investigate the prognostic utility of an innovative abstracted biochemical ratio, albumin to globulin ratio (AGR), in both medically and surgically admitted hospitalised patients. This straightforward and accessible ratio

is derived from two commonly requested biochemical tests included in comprehensive biochemical or liver panels. Due to the frequent use and cost-effectiveness of the components of our tested AGR, including total protein and albumin levels, we studied its effectiveness in predicting adverse clinical outcomes such as acute kidney or liver injury, non-infectious or infectious systemic inflammatory syndromes, hemodynamic disturbances, organ failures, and patient mortality.

In contrast to our study, Gremese E et al.'s 2023 narrative review examined the prognostic value of low serum albumin levels in hospitalised patients. The review covered emergency medicine, cardiovascular disease, COVID-19, nephrology, cancer, and autoimmune rheumatic diseases. The study found that blood ALB is a good tool for hospitalised patients' treatment efficacy and long-term monitoring. [13]

Zhou X et al. created the 2023 CRP-to-albumin nomogram. The concordance index, receiver operating characteristic, and calibration curve predict sepsis patients' in-hospital death in this nomogram. Kaplan-Meier curves and subgroup analysis assessed the model's risks. AUC was 0.881 in the training set and 0.801 in the validation set on the ROC curve. K-M curves showed higher in-hospital mortality in high CAR patients. Sepsis survival is accurately predicted by CAR-based model. [14]

Chen J et al. examined 196 advanced NSCLC patients treated with anlotinib from June 2018 to June 2021 in 2023. The exposure was a baseline serum albumin-to-globulin ratio (AGR) of serum total protein minus albumin. From anlotinib treatment start to death or last follow-up, OS was measured. The study used linear regression to examine AGR-OS relationships. Adjusting for confounders, the AGR-OS relationship was non-linear with an inflection point of 1.24. Hazard ratio and CI: 13.05 [0.52 to 327.64]. In advanced NSCLC patients who received anlotinib, AGR level was an independent protective factor for OS. [15]

Wang et al. examined acute and chronic periprosthetic infection biomarkers like serum globulin and albumin/globulin. A January 2016–March 2021 retrospective study examined 162 periprosthetic infections and aseptic loosening patients. Those with acute, chronic, and aseptic loosening were examined. AUC determined globulin and albumin/globulin diagnostic value. Acute and chronic periprosthetic infection patients had higher CRP, ESR, d-dimer, globulin, PLT, and PMR than aseptic loosening patients. For CRP, albumin/globulin, ESR, and globulin, the optimal cutoff, AUC, sensitivity, and specificity were 8.3 mg/L, 0.903, 78.57%, 88.68%, 1.31, 0.899, 91.07%, and Albumin/globulin exceeds ESR and CRP. AGR and GLB were tested for PJI in orthopaedic surgery by Dong M et al. The 182 patients were divided into 61 knee and 121 hip groups. Receiver operating characteristic curves diagnosed AGR, GLB, and inflammatory markers (ESR and CRP). AGR, GLB, ESR, and CRP had high knee (94.7% and 87.0%) and hip (84.6% and 75.8%) sensitivity and specificity. In the knee group, "AGR or ESR" and "AGR and GLB" had 99.6% and 98.9% sensitivity and specificity. The best PJI indicators were AGR, GLB, CRP, and ESR. [16-17]

Our study found that the AGR at the optimal threshold of 0.795 had high predictive performance, with an AUROC±SEM of 0.928±0.015 (95% CI; 0.899-0.957) and comparable sensitivity and specificity values of 87.8% and 85.23%, respectively. Positive and negative predictive values were 85.90% and 86.99%, respectively. This study had limitations and drawbacks. Our study's observational, retrospective design, small sample size, and single-center were drawbacks. This study examined an innovative, simple, and affordable tool that wasn't used in clinical practice despite its emerging evidence of reasonable predictive performance for outcomes of interest and may add an additional evidence step to strengthen its role in screening, disagnosis, and monitoring.

5. Conclusion

Our study found that maintaining an albumin to globulin ratio below 0.795 can have positive effects on hospitalised patients, both medically and surgically admitted, by predicting adverse clinical outcomes.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest in this manuscript

Statement of ethical approval

There is no animal/human subject involvement in this manuscript

Statement of informed consent

Owing to the retrospective design of this study, the informed consent form was waived.

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