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An elevated gamma gap as diagnostic tool for acute systemic inflammatory response syndromes in Hospitalized patients

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Abstract

Aims: This study aimed to investigate the predictive value of the Gamma Gap in relation to the probability of cOI positivity. Our secondary objectives aimed to determine the optimal threshold in the Jordanian tested cohort, beyond which negative adverse outcomes would significantly rise. We aimed to assess the sensitivity and specificity of the Gamma gap and compare it with similar previous studies and other related sensitivity indices.

Methods: An observational study was conducted at Prince Rahid bin Al-Hussein Military Hospital to analyze adult medical and surgical patients. The study aimed to examine the prognostic abilities of the evaluated Gamma Gap compared to a combined negative clinical outcome. The study included adult admitted patients with stable baseline renal, liver, hemodynamic, and systemic immune-inflammatory statuses. The study used binary logistic regression to examine the Gamma Gap as an independent variable for predicting adverse clinical outcomes. A sequential statistical analysis of receiver operating characteristic (ROC) testing and sensitivity analysis was conducted to express the predictive utility of the Gamma Gap against the positivity of adverse clinical outcomes. The study also identified the ideal cutoff point for the Gamma Gap, with a value above it indicating a worse outcome and a value below it indicating a better outcome.

Results: A study involving 302 eligible patients was conducted to determine the optimal cutoff point for composite outcomes of interest (cOI). The study found that the higher Gamma Gap group had a stronger positive Pearson correlation coefficient than the lower Gamma Gap group. The unadjusted risk estimate was 29.75 (95% CI; 15.78-56.09). The two genders were distributed equally across the groups, with no statistically significant gender distribution rates. Albumin and albumin to globulin ratio levels showed significantly different distributions between the groups. The ages of the tested patients were insignificantly distributed between the groups. A binary logistic regression model was developed to evaluate 83.4% of cases. The prognosticator Gamma Gap performed as expected, with a p-value of less than 0.001 and an evaluation of 0.902±0.018.

Conclusion: According to our research, hospitalised patients may benefit from keeping their Gamma Gap below 3.04, and this subtracted biochemical tool can be extremely useful in predicting unfavourable clinical outcomes as well as in the screening, diagnosis, and follow-up of both medically and surgically admitted patients.

Keywords: Gamma gap; Protein gap; Clinical significance of inflammatory diseases; Infectious and non-infectious inflammatory syndromes; Diagnostic tools

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1. Introduction

The gamma gap, which is the disparity between serum total protein and albumin levels, may prompt testing for chronic infections or monoclonal gammopathy, even though there is no evidence to support this clinical threshold. An elevated gamma gap of 4 g/dL is not a sensitive indicator for HIV, HCV, or MGUS but demonstrates high specificity for these conditions. An increased gap may warrant additional testing for HIV and HCV, but does not warrant electrophoresis without more clinical information.

The study emphasises the significance of factoring in the gamma gap when diagnosing different metabolic disorders like HIV and MGUS. Researchers can enhance their understanding of the potential effects of different factors on the overall health outcomes of individuals with certain conditions by modifying the gamma gap for each condition. A gamma gap of 4 g/dL has shown high specificity for HIV and HCV, which can be helpful in raising the post-test probability of having these conditions. A threshold of 4 g/dL was not effective for detecting HIV and HCV, which limited its ability to exclude these conditions.

Multiple myeloma (MM) is an untreatable cancer defined by mature plasma cells and represents 1.3% of all cancers and 15% of blood cancers. It is essential to monitor disease burden and treatment response in patients with MM because M-spike production is linked to the overall tumour burden. Serum protein electrophoresis (SPEP) and immunofixation are the preferred methods for measuring M-spike, but they usually take several days to provide results in most facilities. These tests are generally requested before starting treatment and at each following treatment cycle.

There is a need for a validated, affordable, same-day, point-of-care assessment for disease and response, especially in regions with limited resources and access to healthcare. The correlation between gamma gap and mortality rate in elderly patients with coronary artery disease (CAD) has not been extensively researched, and the underlying mechanisms remain unclear. Elevated gamma gap in older patients with CAD leads to higher rates of heart failure and mortality, likely caused by systemic inflammation and immune dysfunction, which play a role in atherosclerosis development. An elevated gamma gap can be caused by elevated globulin levels or decreased albumin levels, both of which are risk factors for all-cause mortality.

The discovery of a combined effect of low BMI and high gamma gap on the risk of heart failure and mortality is new and requires more research. Low BMI and high gamma gap could indicate chronic malnutrition and inflammation, resulting in an increased risk of negative outcomes. Another mechanism could clarify the connection between BMI and gamma gap, as the high quantity of activated macrophages in adipose tissue boosts globulin breakdown.

This study aimed to investigate the predictive value of the Gamma Gap in relation to the probability of cOI positivity. Our secondary objectives aimed to determine the optimal threshold in the Jordanian tested cohort, beyond which negative adverse outcomes would significantly rise. We aimed to assess the sensitivity and specificity of the Gamma gap and compare it with similar previous studies and other related sensitivity indices.

2. Material and Methods

In order to analyse adult medical and surgical patients, an observational study was carried out at the Prince Rahid bin Al-Hussein Military Hospital in the Irbid governorate. Our institutional review board committee gave its approval for this study to be carried out on February 19, 2024, under registration number 26_3/2024. The applied studied patients' consent forms were waived due to the study's retrospective nature, and the majority of the data were obtained from our institution's electronic medical reporting system (Hakeem), supplemented by additional sources of paper-based documented notes. This study included adult admitted patients with stable baseline renal, liver, hemodynamic, and systemic immune-inflammatory statuses, either medically or surgically. As stated earlier, the main objective of this investigation was to examine the prognostic abilities of the evaluated Gamma Gap in comparison to a combined negative clinical outcome. A decrease in creatinine clearance, abnormalities in liver function indices, signs of sepsis, prolonged hospital stays beyond expectations, and death from any cause are among the composited outcomes of interest (cOI). The demographics of the patients, the results of laboratory tests for biochemistry and complete blood counts, and subjectively reported data are just a few of the additional variables that were looked into.

First, using binary logistic regression, the study examined the Gamma Gap as an independent variable for predicting the positivity of occurrence of adverse clinical outcomes (the positive state, assigned as 1) as opposed to non-occurring (the negative state, assigned as 0). A sequential statistical analysis of receiver operating characteristic (ROC) testing and sensitivity analysis was conducted after the abstracted coefficients that were required to construct the binary

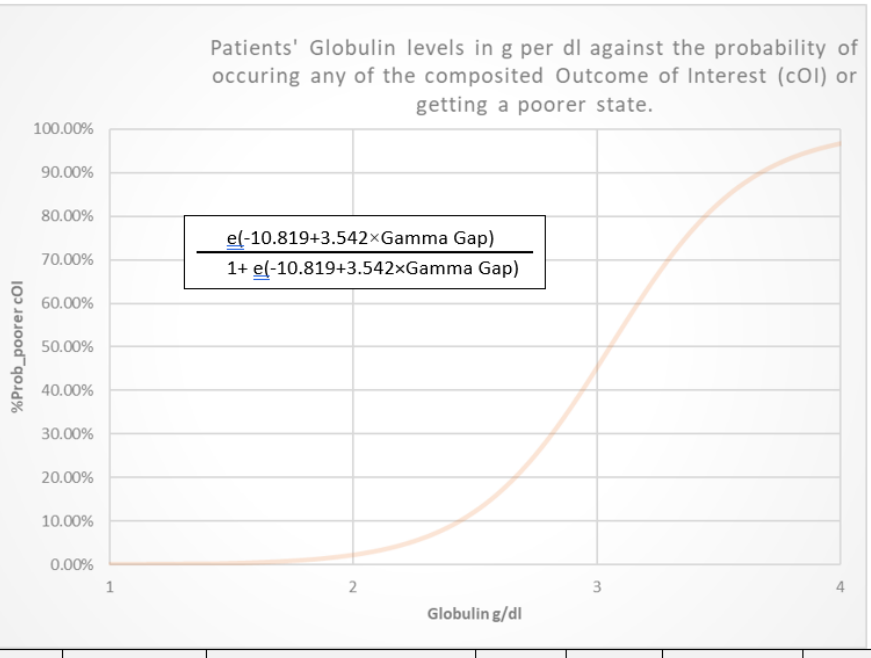
regressional association model and assess the significance of variability in determining the outcome of interest were obtained. This allowed for the expression of the predictive utility of Gamma Gap against positivity of cOI by illustrating the area under the ROC (AUROC±SEM) and for the exploration of the optimal operative point in addition to the results of the other sensitivity indices. The true positive rate (sensitivity), true negative rate (specificity), positive and negative predictive values, Youden's index, and accuracy index are the main outcomes of these sensitivity indices.

Knowing the ideal cutoff point for our tested prognosticator of interest (the Gamma Gap), where a value above it indicated a worse outcome of interest (the positive state of cOI), and a value below this patient's particular exploring cutoff point indicated a better outcome of interest (the negative state of cOI), was the next step. Consequently, a dichotomy was applied to all eligible patients who underwent testing: Group I had a Gamma Gap that was lower than the cutoff point, while Group II had a higher Gamma Gap than the cutoff point. In order to illustrate the comparative distribution rates between the studied variables throughout Group I–II, a chi square test was performed. Furthermore, we abstracted the chi square static significance (χ 2), the pearson correlation to express the correlation value with its standard error of value (R±SEV), and the odd ratios to express the unadjusted associations.

Patient data was gathered and arranged using Microsoft Office LTSC Professional Plus 2021 Excel. The study's results were compiled and statistical analysis was performed using IBM SPSS Statistics version 25. The significance level used in this investigation was 0.05.

3. Results

137 patients, or 45.36% of the 302 eligible patients, were placed in Group I, which was distinguished by a lower Gamma Gap below the 3.04 optimal cutoff point.

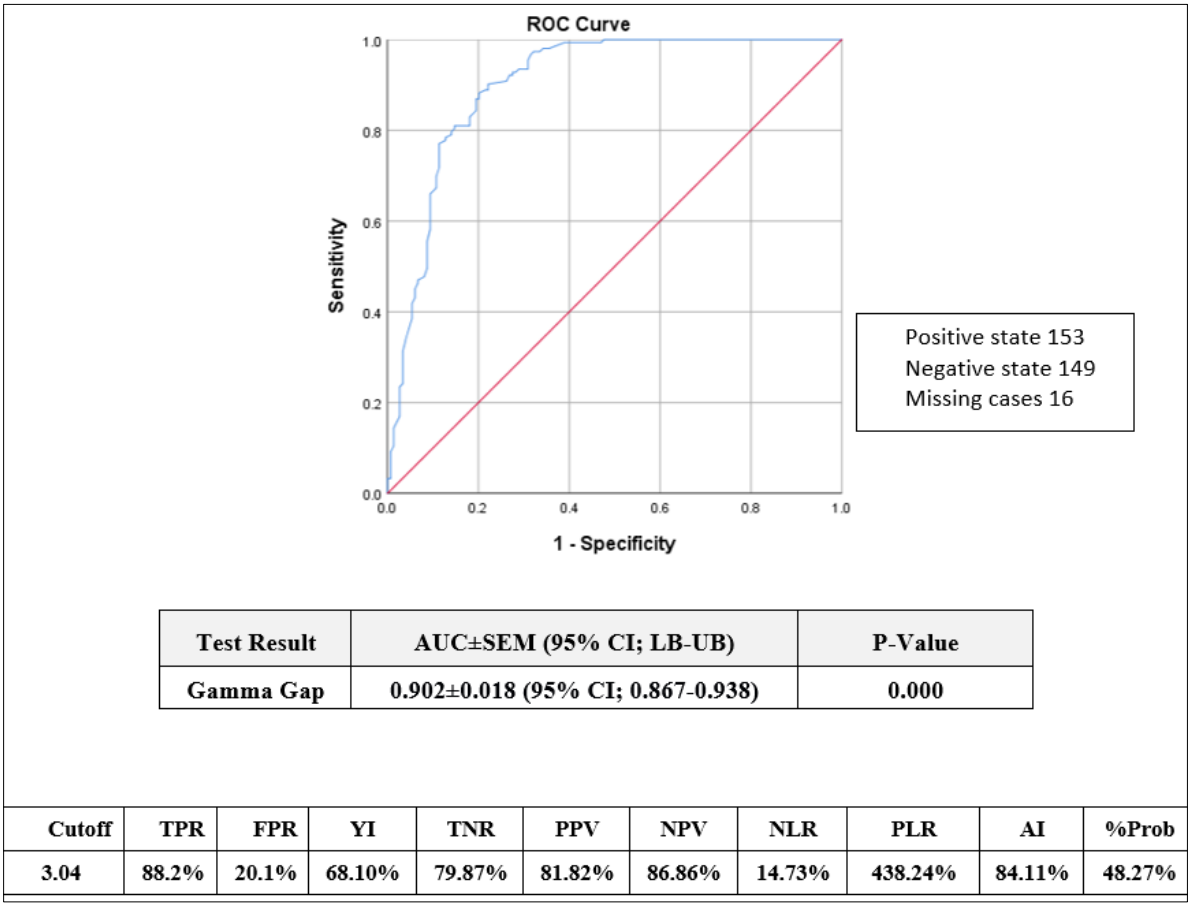


	B±S.E.M	Exp(B)	P-Value	χ 2 (df)	VR	%Cases
Gamma Gap	3.542±0.401	34.526 (95% CI; 15.75-75.7)	0.000	χ 2 (8) 21.006 0.007	46.1%-61.5%	83.4%
Constant	-10.819±1.259	0.000	0.000			

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 Gamma Gap or as known as Protein Gap as a predictor for the likelihood of positive or negative results. The coefficients needed to create the binary logistic regression model were obtained

Group II was assigned to the remaining patients based on a higher Gamma Gap of ≥3.04. For the composite outcomes of interest (cOI), the higher Gamma group (Group II or inferior cOI) had a significantly stronger positive Pearson correlation coefficient [+0.684±0.042, χ 2=141.250, p<0.001] than the lower Gamma Gap group (Group I or superior cOI). With distribution rates of poorer cOI of 135 (81.8%) in the higher Gamma Gap group (Group II) compared to 18 (13.1%) in the lower Gamma Gap group (Group I), the unadjusted risk estimate was 29.75 (95% CI; 15.78-56.09).

The two genders were distributed roughly equally across Groups I–II in the Gamma-based binary cohorts, with no statistically significant gender distribution rates. Albumin and the other derived prognosticating tool, albumin to globulin ratio (AGR) levels, showed significantly different distributions between Group I and Group II. The ages of the tested patients, as a dichotomized level, were also insignificantly distributed between the lower and higher Gamma Gap groups (Group I-II). For albumin (-0.449±0.052, X2 = 61.008, p-value < 0.001) and AGR (-0.729±0.039, X2 = 160.471, p-value < 0.001), both showed a significantly negative correlation. For the albumin and AGR variables of the patients who were tested, the odds ratios were, respectively, 0.140 (95% CI; 0.084-0.234) and 0.024 (95% CI; 0.012-0.046). **Table 1** provides specifics regarding the distribution rates of the tested variables in Groups I–II.



Test Result	AUC±SEM (95% CI; LB-UB)	P-Value
Gamma Gap	0.902±0.018 (95% CI; 0.867-0.938)	0.000

Cutoff	TPR	FPR	YI	TNR	PPV	NPV	NLR	PLR	AI	%Prob
3.04	88.2%	20.1%	68.10%	79.87%	81.82%	86.86%	14.73%	438.24%	84.11%	48.27%

Figure 2 An ROC analysis was performed on the prognostic factor of interest in this study, the Gama or Protein Gap, 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 association between the Gamma Gap and the probability of unfavourable clinical outcomes was demonstrated by the development of a binary logistic regression model. The formula with a variability range of 46.1%-61.5% was e^(-10.819+3.542×Gamma Gap)/ 1+e^(-10.819+3.542×Gamma Gap). This model can be used to evaluate 83.4% of cases for patients whose circumstances are comparable to those in the study. The binary logistic regression model, along with its abstracted coefficients and other relevant parameters, is fully shown in **Figure 1** above.

Our prognosticator Gamma Gap performed as expected, with a p-value of less than 0.001, indicating statistical significance, and an evaluation of 0.902±0.018 (95% CI; 0.867-0.938). The ROC test revealed that 153 patients were

positive. In the ROC test, 149 patients were categorised as negative, or assigned the number 0. It was determined that 16 cases were missing. With a sensitivity of 88.2% and a specificity of 79.87%, the study determined that 3.04 was the ideal threshold. 48.27% was found to be the probability that at least one of the composite outcomes of interest would occur in the patients under study during the admission period at the abstracted optimal threshold. **Figure 2** fully displays the results of the ROC analysis along with the corresponding sensitivity indices.

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

	Lower Gamma Group I (G<3.04) (137, 45.36%)	**Higher Gamma Group II (G≥3.04) (165, 54.64%)**	**Total (302, 100%)**	**R ρ**	**OD**	**χ 2 p-Value**
cOI						
Better cOI	119 (86.9%)	30 (18.2%)	149 (49.3%)	+0.684±0.042	29.75 (95% CI; 15.78-56.09)	(1) 141.250 0.000
Poorer cOI	18 (13.1%)	135 (81.8%)	153 (50.7%)			
Gender						
Female	66 (48.2%)	82 (49.7%)	148 (49.0%)	-0.015±0.058	0.941 (95% CI; 0.598-1.480)	(1) 0.069 0.792
Male	71 (51.8%)	83 (50.3%)	154 (51.0%)			
Age (Years)						
<60	38 (27.7%)	54 (32.7%)	92 (30.5%)	-0.054±0.057	0.789 (95% CI; 0.481-1.295)	(1) 0.880 0.348
≥60	99 (72.3%)	111 (67.3%)	210 (69.5%)			
AGR						
<0.795	16 (11.7%)	140 (84.8%)	156 (51.7%)	-0.729±0.039	0.024 (95% CI; 0.012-0.046)	(1) 160.471 0.000
>=0.795	121 (88.3%)	25 (15.2%)	146 (48.3%)			
ALB (g/dl)						
<2.585	48 (35.0%)	131 (79.4%)	179 (59.3%)	-0.449±0.052	0.140 (95% CI; 0.084-0.234)	(1) 61.008 0.000
≥2.585	89 (65.0%)	34 (20.6%)	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 Gamma Gap below the cutoff point of 3.04, while Group II consists of patients with Gamma Gap values equal to or higher than 3.04.

4. Discussion

The objective of this research was to examine the predictive value of a novel subtracted biochemical test, known as the Protein Gap, Gamma Gao, or globulin level, in hospitalised patients who had been admitted for medical or surgical reasons. This simple and easily comprehensible ratio is obtained from two frequently asked biochemical tests found in full biochemical or liver panels. We investigated the efficacy of our tested Gamma Gap in predicting unfavourable clinical outcomes, such as acute kidney or liver injury, non-infectious or infectious systemic inflammatory syndromes,

hemodynamic disturbances, organ failures, and patient mortality, because its components—total protein and albumin levels—are widely used and reasonably priced.

Based on the availability of testing for HIV, hepatitis C, and monoclonal gammopathy of unknown significance (MGUS), gamma gaps were found in three subpopulations in a study that used the National Health and Nutrition Examination Survey (NHANES) 1999-2014. Participants with these diseases had mean gamma gaps of 3.4–3.8 g/dL; higher gamma gaps are associated with higher likelihood ratios, sensitivity, and specificity. The purpose of the study was to look into the connection between gamma gap and levels of AST, ALT, MGUS, HIV, and a comprehensive metabolic panel. For HIV and MGUS, the gamma gap showed the highest AUC, whereas for hepatitis C, the highest AUC was seen in AST and ALT. The gamma gap for HCV showed an AUC of 0.74, and a high gamma gap of 4.0 g/dL indicated a 97.8% specificity. The AUC of the gamma gap for MGUS was 0.64, and at the elevated gamma gap threshold of 4 g/dL, the sensitivity and specificity for MGUS were 15.4% and 95.4%, respectively. The study emphasises how crucial it is to take the gamma gap into account when diagnosing different metabolic disorders, like MGUS and HIV, and how more investigation is required to find the best course of action for treating MGUS and other related conditions.

The association between the gamma gap (GG) and treatment response as determined by M-spike and disease burden was examined through a retrospective chart review. Patients who satisfied specific requirements were included in the study, which was approved by the Duke University Medical Centre. These included pathologic confirmation of the multiple myeloma diagnosis, evaluation at the Duke MM clinic between 2000 and 2013, current or finished treatment for MM, and availability of both a SPEP and a CMP (including albumin and total protein). The research findings indicate a strong correlation between the gamma gap (GG) and M-spike at the onset, during, and conclusion of treatment. This implies that GG measurement may offer a quick and low-cost way to assess clinical response in multiple myeloma (MM) patients. The study does have certain limitations, though, such as being a retrospective chart review conducted at a single centre, not including patients with nonsecretory myeloma or light chain disease, only using GG in the absence of M-spike and quantitative Ig levels, and not replacing existing testing.

The gamma gap and its role in renal diseases, specifically in chronic kidney disease (CKD), were the subject of a prospective cohort analysis involving one hundred patients with chronic kidney disease (CHP). The findings demonstrated that positive regression coefficients for both CRP and γ-gap were linked to lower survival times and higher hazards. Although in the opposite direction, albumin likewise showed negative regression coefficients linked to higher hazard and shorter survival times. The study emphasises how crucial it is to take into account the gamma gap and its function in renal diseases, especially in patients with chronic kidney disease (CKD). It offers insightful information about how these variables might affect patients with CHPs' overall survival. Regardless of nutritional status, inflammation is a significant predictor of low serum albumin levels in dialysis patients. Serum CRP and albumin levels are predictive of death from all causes, and higher in-hospital mortality is linked to severe hypoalbuminemia.

According to our research, the Gamma Gap demonstrated strong predictive performance at the ideal threshold of 3.04, with an AUROC±SEM of 0.902±0.018 (95% CI; 0.867-0.938) and a comparatively higher sensitivity (88.2%) in comparison to specificity values of 79.87%. 81.82% and 86.86%, respectively, were the positive and negative predictive values. There were issues and restrictions with this study. The small sample size, single-center setup, and retrospective, observational design of our study were limitations. This study looked at a novel, easy-to-use, and reasonably priced tool that wasn't being used in clinical settings despite growing evidence of its ability to predict outcomes of interest reasonably well. It may also add another evidence step to support its utility in monitoring, screening, and diagnosis.

5. Conclusion

According to our research, hospitalised patients may benefit from keeping their Gamma Gap below 3.04, and this subtracted biochemical tool can be extremely useful in predicting unfavourable clinical outcomes as well as in the screening, diagnosis, and follow-up of both medically and surgically admitted patients.

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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