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# Unveiling the Prognostic Significance of Immature Granulocytes and Nucleated Red Blood Cells in Geriatric Pneumonia Severity and Mortality Outcomes

## Geriatrik Pnömoni Ciddiyeti ve Mortalite Sonuçlarında İmmatür Granülositler ve Çekirdekli Eritrositlerin Prognostik Önemi

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## Abstract

**Aim**: The progression of pneumonia in the senior-age population can be catastrophic. Biomarkers capable of assessing the severity of pneumonia play a pivotal role in prognosis. We conducted an evaluation of the kinetics of immature granulocytes (IG) and nucleated red blood cells (NRBC) as potential indicators of the severity of geriatric pneumonia.

**Material and Method**: In this retrospective cross-sectional study, patients diagnosed with pneumonia were categorized using two prominent severity scoring systems, CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, age >65) and PSI (Pneumonia severity index). Additionally, the patients' discharge status and infection process markers were noted.

**Results**: A total of 80 patients were included in the evaluation, with a mean age of 72.23±7.26. Excluding the mortality rate of 49% when including oncology patients, the overall mortality rate was 26%. The deceased patients had longer hospitalization durations, higher CURB-65 and PSI category classifications, and elevated NRBC results. In CURB-65-based categorization, there was an increase only in NRBC levels associated with disease severity, whereas, in PSI-based categorization, the increase is in both NRBC and IG levels. No statistical difference was observed in NRBC and IG levels when excluding oncology patients from the analysis.

**Conclusion**: In geriatric pneumonia cases, the dynamics of NRBC appear to be more crucial in indicating disease severity compared to IG. However, this opportunity seems to be missed or compromised in patients with oncological comorbidities.

**Keywords**: CURB-65, Immature granulocyte, Nucleated red blood cell, Pneumonia severity index.

## Öz

**Amaç**: Yaşlı nüfusta pnömoninin seyri katastrofik olabilir. Pnömoninin ciddiyetini değerlendirebilen biyobelirteçler, prognozda önemli rol oynamaktadırlar. Bu çalışmada, geriatrik pnömoninin ciddiyetinin potansiyel göstergeleri olarak, immatür granülositlerin (İG) ve çekirdekli eritrositlerin (ÇE) kinetikleri değerlendirilmiştir.

**Gereç ve Yöntem**: Bu retrospektif ve kesitsel çalışmada, pnömoni tanısı konan hastalar, CURB-65 (Konfüzyon, Üre, Solunum sayısı, Kan basıncı, yaş >65) ve PSI (Pnömoni ciddiyet endeksi) olmak üzere iki önde gelen ciddiyet skorlama sistemine göre kategorize edilmiştir. Ayrıca, hastaların taburculuk durumu ve enfeksiyon süreci belirteçleri kaydedilmiştir.

**Bulgular**: Toplamda 80 hasta değerlendirmeye dahil edilmiştir ve yaş ortalamaları 72.23±7.26'dır. Onkoloji hastaları dahil edildiğinde %49 olan mortalite oranı, hariç tutulduklarında %26 idi. Ölen hastaların hastanede yatış süreleri daha uzundu, CURB-65 ve PSI kategori dereceleri daha yüksek sınıftaydı ve ÇE seviyeleri yükselmişti. CURB-65 tabanlı kategorizasyonda, hastalık şiddeti ile sadece ÇE düzeyinde artış gözlenirken, PSI tabanlı kategorizasyonda hem ÇE hem de İG düzeylerinde artış mevcuttu. Onkoloji hastaları analizden çıkarıldığında ÇE ve İG düzeylerinde istatistiksel fark gözlenmedi.

**Sonuç**: Geriatrik pnömoni vakalarında, ÇE'nin dinamiklerinin, İG'ye kıyasla hastalık şiddetini belirtmede daha hayati olduğu görünmektedir. Ancak, onkolojik komorbiditesi olan hastalarda bu fırsatın zayıfladığı ya da kaybolduğu görülmektedir.

**Anahtar Kelimeler**: CURB-65, Çekirdekli eritrosit, İmmatür granülosit, Pnömoni ciddiyet endeksi

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## INTRODUCTION

Pneumonia is widely acknowledged as a profound global health concern, primarily attributed to bacterial, fungal, or viral infections. Its ramifications, particularly in vulnerable populations, including the elderly, immunocompromised individuals, and those afflicted with underlying chronic ailments, render it a pressing matter necessitating intensive care interventions.[1] Prominently in these senior-age groups, the imperative for early diagnosis, judicious administration of antimicrobial agents, and comprehensive adjunctive measures cannot be overstated, as these pivotal interventions constitute the cornerstone in mitigating the incidence of pneumonia-associated complications and mortality rates.[2,3]

The severity of pneumonia is evaluated based on the patient's clinical symptoms, physical examination findings, and radiological outcomes.[4] Several scoring systems are available to assess pneumonia severity. One such system is the Pulmonary Severity Index (PSI), which calculates a score based on several parameters, including the patient's clinical findings, laboratory test results, and demographic factors.[5,6] Another prominent scoring system is the CURB-65 (Confusion, Urea, Respiratory rate, Blood pressure, age 65 and over) score, which predicts the severity of pneumonia by considering the patient's age, level of consciousness, urea level, respiratory rate, and blood pressure.[7,8]

In addition to clinical assessment, laboratory and imaging modalities are utilized minimally to confirm or provide supportive evidence for diagnosing pneumonia in patients. Besides the established markers such as C-reactive protein (CRP) and procalcitonin, novel parameters, including immature granulocytes (IG) and nucleated red blood cells (NRBC), have gained prominence as reliable indicators for predicting the severity of infection in pneumonia cases.[9] These parameters are commonly employed in the evaluation of pneumonia.

In the scientific literature, a wealth of studies elucidating the relationship between pneumonia severity indices and mortality outcomes exists. Within the scope of our investigation, our primary objective was to meticulously assess the dynamic alterations in immature granulocytes (IG) and nucleated red blood cells (NRBC), revered as indicators of heightened infection severity, across two preeminent and disparate severity index stratifications. Subsequently, we intended to discern the profound implications of these hematological changes on mortality rates, thereby contributing to the expanding body of knowledge on geriatric pneumonia management.

## MATERIAL AND METHOD

This study, conducted with a retrospective cohort design, obtained the approval of the Ethical Committee of Necmettin Erbakan University Meram Faculty of Medicine on July 10, 2019, (2019/1973), and the study hereby asserts its adherence to the principles outlined in the Helsinki Declaration.

The samples were created by scanning the discharge epicrisis of patients treated for pneumonia in the Internal Medicine clinic in the year 2019, prior to the pandemic. CURB-65 and PSI scores of the patients were calculated from the discharge epicrisis and nurse observation charts. Patients transferred from other services, voluntarily discharged during treatment, <65 years of age, and those with inconsistencies between CURB-65 and PSI scores were excluded from the study. The presence of comorbidities was not used as an exclusion criterion; nevertheless, comorbidities were additionally noted. Routine complete blood counts and primary biochemical test results of the patients at admission were retrospectively obtained from the hospital's digital system. The discharge status of the patients was recorded as death or survival. And concurrent demographic characteristics were noted. The patients categorized based on CURB-65 and PSI scores were compared with their available data.

Statistical analysis: The data in our study were analyzed using GraphPad Prism version 8 and IBM SPSS Statistics version 24. The data distributions were assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests for normality. Accordingly, independent t-tests were employed for non-categorical paired data analysis for non-skewed data, and one-way ANOVA with Bonferroni correction was used for multiple data analysis. In cases where the data did not follow a normal distribution, the Mann-Whitney U test was utilized for paired data evaluation, and the Kruskal-Wallis test was preferred for assessment among multiple groups. Non-parametric tests were chosen for subgroup analysis due to the reduced number of groups. The chi-square test was applied to compare groups, while Fisher's exact test was preferred for small-sample groups. A significance level of 0.05 was considered for rejecting the null hypothesis (H0) in all analyses.

## RESULTS

A retrospective evaluation was conducted on a cohort of 107 patient files, from which exclusion criteria were applied, resulting in a final sample of 80 patients for the study. The mean age of the overall population was 72.23±7.26. Of the total, 36 patients were female (45%), and 32 (40%) had a cancer diagnosis.

In the study, which observed 27 patient deaths, the overall mortality rate was determined to be 49%. Notably, when cancer patients were excluded from the analysis, the mortality rate was reevaluated to 26%. The average duration of hospitalization was 11.72±4.01. No statistically significant differences were observed in terms of gender concerning length of hospital stay and age ($p > 0.05$). The demographic and laboratory characteristics of the patients, categorized based on both CURB-65 and PSI, are provided in **Table 1**.

**Table 1. Patient characteristics based on pneumonia severity**

| | CURB-65* | | | | PSI† | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Low (n=16) | Moderate (n=20) | High (n=44) | p value | Low (n=6) | Moderate (n=5) | High (n=20) | Very High (n=49) | p value |
| Age, year | 67.68±3.19 | 75.05±8.06 | 72.61±7.28 | 0.006* | 68.33±3.82 | 67.4±2.5 | 71.6±6.62 | 73.46±7.83 | 0.116 |
| Gender, F/M, n (%) | 7(44)/9(56) | 11(55)/9(45) | 18(41)/26(59) | 0.572 | 3(50)/3(50) | 0(0)/5(100) | 13(65)/7(35) | 20(41)/29(59) | 0.052 |
| Hospitalization day | 7.56±1.15 | 10.95±2.13 | 13.59±4.09 | 0.001* | 7.73±1.36 | 8.6±0.54 | 10.05±2.76 | 13.26±4.02 | 0.001* |
| Cancer, n (%) | 3 (19) | 7 (35) | 22 (50) | 0.080 | 0 (0) | 0 (0) | 7 (35) | 25 (51) | 0.018* |
| Mortality, (%) | 0 | 33 | 95 | 0.001* | 0 | 0 | 25 | 85 | 0.017* |
| CRP‡, mg/L | 48 (43-115) | 147 (95-253) | 122 (90-250) | 0.001* | 45 (42-51) | 52 (44-303) | 135 (78-228) | 122 (93-240) | 0.003* |
| Procalcitonin, µg/L | 1.3 (0.3-4.1) | 0.7 (0.4-1.9) | 2 (0.7-44.2) | 0.039* | 1.2 (0.07-1.4) | 3.6 (0.5-4) | 0.8 (0.6-9.3) | 1.9 (0.5-15) | 0.392 |
| WBC§, 103/uL | 11 (9.4-12.7) | 13.7 (8.5-17) | 14 (8.9-18.8) | 0.398 | 11.6 (10-12) | 18.5 (16.7-21) | 10.2 (8.5-15) | 13.5 (8.7-17) | 0.087 |
| IG¶, 103/uL | 0.13(0.04-0.4) | 0.2 (0.08-0.3) | 0.2 (0.08-0.4) | 0.456 | 0.05 (0.01-0.1) | 0.14 (0.13-0.2) | 0.33 (0.1-0.4) | 0.2 (0.08-0.4) | 0.031* |
| NRBC**, 105/uL | 0 (0-0.7) | 0.5 (0-4) | 1 (0-8) | 0.013* | 0 (0-0.2) | 0 (0-0.5) | 1 (10-17) | 1 (0-7) | 0.046* |

The data are expressed in mean and standard deviation or median and percentiles. The p-values were calculated by comparing subgroups based on disease severity. The Fisher's exact test and the Kruskal-Wallis test were utilized for the calculations. *, Confusion-Urea-Respiratory rate-Blood pressure-age 65 and over score; †,Pneumonia severity index; ‡,C-Reactive protein; §, White blood cell; ¶,Immature granulocyte; **,Nucleated red blood cell.

Significant statistical differences were observed between deceased patients and survivors with respect to variables including length of hospital stay (p=0.001, η2=0.174), CURB-65 (p=0.001, η2=0.212) and PSI scores (p=0.001, η2=0.195), and NRBC counts (p=0.001, η2=0.038) (**Figure 1**). Deceased patients exhibited a significantly prolonged duration of hospitalization, elevated CURB-65 and PSI scores, and NRBC counts approximately twofold higher than the survivors.

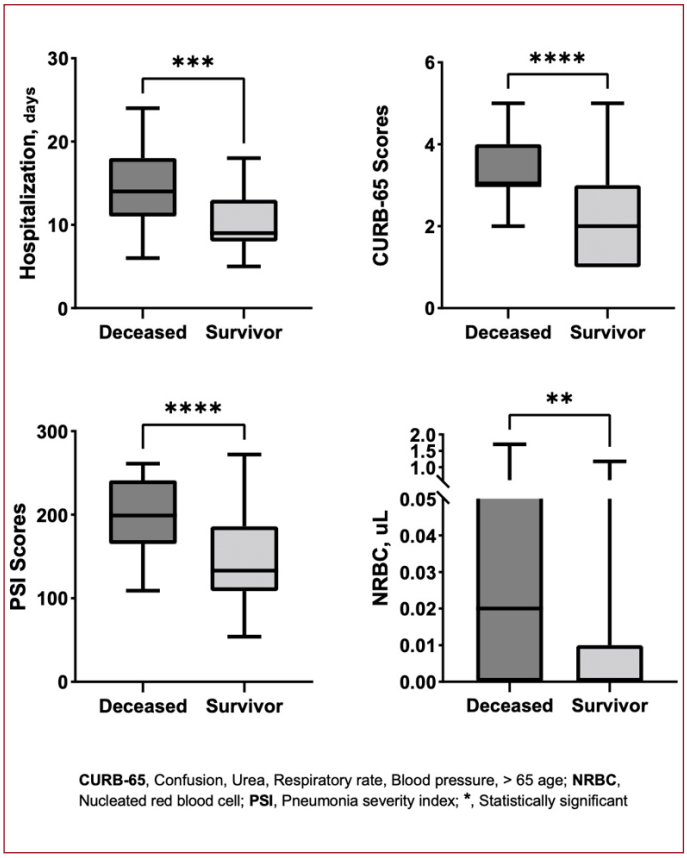


**Figure 1.** Differential parameters between survivors and non-survivors: a comparative analysis.

Among patients with an increased NRBC count, a statistically significant rise in CURB-65 score was detected (p=0.045). While a similar trend was observed in the PSI index, the difference did not reach the threshold of statistical significance (p=0.056).

When patients were evaluated based on the severity of the disease, comparisons of three subgroups using CURB-65 revealed significant age differences (p=0.006, $\varepsilon^2$=0.148), duration of hospitalization (p=0.001, $\varepsilon^2$=0.310), CRP levels (p=0.001, $\varepsilon^2$=0.179), procalcitonin levels (p=0.039, $\varepsilon^2$=0.057), and NRBC counts (p=0.013, $\varepsilon^2$=0.077) (**Figure 2a**).

Furthermore, when comparing four subgroups based on PSI, statistically significant differences were observed among the groups in terms of hospitalization duration (p=0.001, $\varepsilon^2$=0.207), CRP levels (p=0.003, $\varepsilon^2$=0.111), IG levels (p=0.031, $\varepsilon^2$=0.061), and NRBC counts (p=0.046, $\varepsilon^2$=0.054) (**Figure 2b**).

An additional assessment was carried out, excluding cancer patients and disregarding their prognostic impact. When cancer patients were excluded from the analysis, the statistically significant results for parameters hospitalization time (p=0.005, η2=0.158) and procalcitonin levels (p=0.047, η2=0.083), observed in the previous evaluation between deceased and survivors, continued to demonstrate statistical significance. However, when considering both the CURB-65 and PSI scores, there was no statistically significant correlation observed with either IG or NRBC (p > 0.05).

In the analysis of our patients, investigating the influence of IG and NRBC on pneumonia mortality, we found that NRBC exhibited a more significant effect (**Figure 3a**). However, this effect was not observed in cases of pneumonia among oncology patients (**Figure 3b**).

The following were noteworthy among the multiple correlations identified: NRBC demonstrated a moderate positive correlation with mortality (p=0.008, r=0.376). The duration of hospitalization displayed a significantly positive correlation with CURB-65 (p=0.001, r=0.790) and PSI (p=0.001, r=0.701) scores and a moderate correlation with NRBC (p=0.024, r=0.326) and mortality (p=0.005, r=0.399).

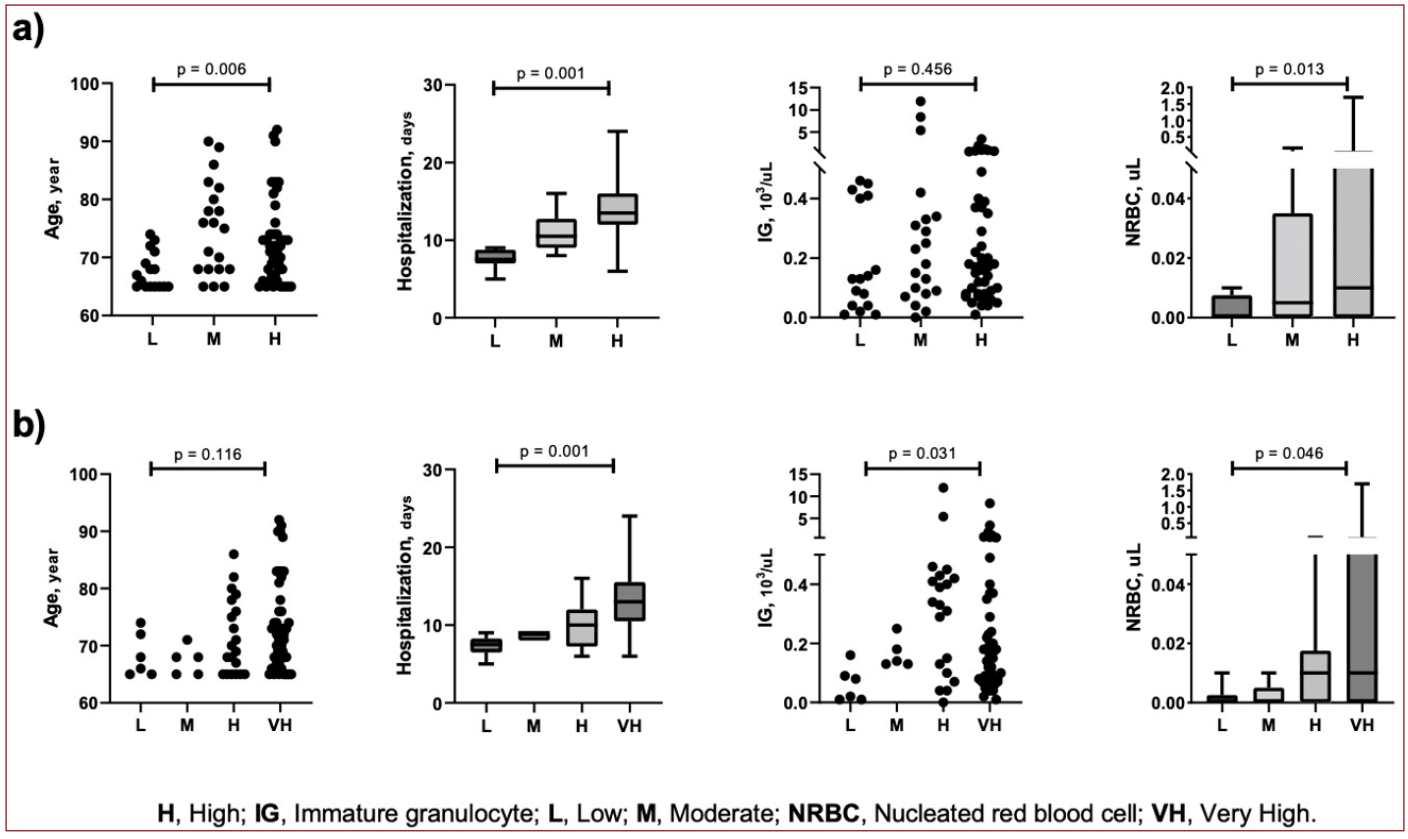


**Figure 2.** Comparison of Key Parameters Among Different Pneumonia Severity Indices, **a)** CURB-65, **b)** PSI.

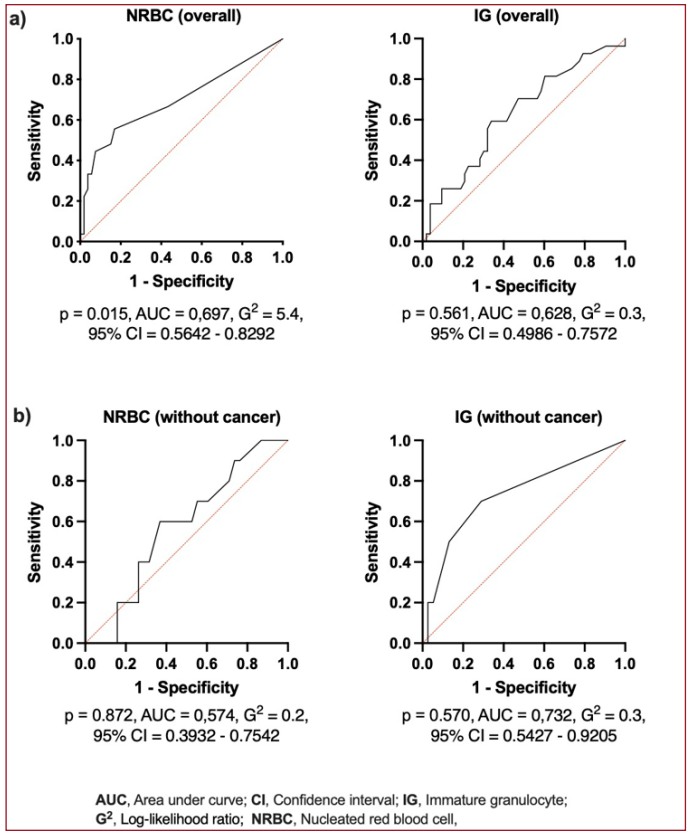


**Figure 3.** Impact of IG and NRBC results on mortality in a) All patients and b) Excluding oncology patients.

## DISCUSSION

Our present study was primarily aimed at assessing the variations of IG and NRBC about disease severity graded according to two different pneumonia scoring indices in geriatric pneumonia. Based on our investigation, which centered on two severity indices showing comparable grading, NRBC variability emerged as a more prominent factor compared to IG, alongside well-established infection markers. This finding persisted in favor of NRBC, even beyond conditions that introduce an unfavorable bias to prognosis, such as cancer. Elevated NRBC values were directly associated with higher mortality rates.

In the realm of infectious diseases, it is well-established that the aging process engenders a propensity for attenuated immune responses.[10] Notably, advanced age manifests as a state wherein the human immune system exhibits compromised efficacy in mounting robust defenses against a diverse array of pathogens.[11] Alongside the currently established biomarkers that forecast the trajectory of infections, the inclusion of nearly validated novel biomarkers will offer valuable support in informing therapeutic adjustments for these types of infections. Within this context, it is crucial to acknowledge the abundance of scientific literature and ongoing research that has extensively explored the relationship between IG and NRBC. Numerous studies have provided substantial support and scientific evidence regarding

the association of IG and NRBC on infectious diseases. Within our investigation, we identified alterations in the context of pneumonia severity that were attributed to IG, albeit to a lesser extent than NRBC. Importantly, these modifications were observed in patients without a cancer diagnosis.

Hereby, in relation to the exclusions made for oncology patients in our study, which are prominently discussed in our manuscript, it is necessary to acknowledge the direct association of the oncological condition or treatment process with immunity, which may lead to an elevated pneumonia severity score.[12-14] Thus, the parameters we selected for evaluation aimed to better represent real-life situations, considering the higher likelihood of detecting oncological comorbidities in our study population within the specified age group.

Studies examining IG have encompassed a wide range of infectious scenarios within the literature. A consistent observation that has emerged is the applicability of IG as an indicator for evaluating the severity of sepsis and infectious diseases.[14-16] In a similar vein, our investigation revealed that IG exhibited an adequate level of effectiveness in reflecting disease severity among our patient cohorts classified according to disease severity determined by the PSI.

Research studies examining the correlation between NRBC and infection/sepsis in the literature seem to exhibit a relatively superficial nature.[17-19] In light of this, our assessments of NRBC have demonstrated sufficient efficacy in reflecting disease severity and even mortality, regardless of factors such as oncological comorbidities that notably compromise immune function or being part of the geriatric population.

The most probable limitation of the study, despite the robustness of both severity indices, was the categorical difference between CURB-65 (3 categories) and PSI (4 categories). This discrepancy had the potential to adversely affect statistical calculations due to the need for group adjustments within the patient cohorts. Nevertheless, as both indices classified patients in the severe category, there was no numerical misrepresentation concerning prognostic estimations.

## CONCLUSION

Our study assessed the variations of IG and NRBC in geriatric pneumonia across varying levels of severity. NRBC was deemed more consequential than IG as an indicator of disease severity and mortality. Based on our results, elevated NRBC levels, irrespective of an oncological background, may be considered a risk factor for mortality in seniors with pneumonia.

## ETHICAL DECLARATIONS

**Ethics Committee Approval**: This study, conducted with a retrospective cohort design, obtained the approval of the Ethical Committee of Necmettin Erbakan University Meram Faculty of Medicine on July 10, 2019, (2019/1973)

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process**: Externally peer-reviewed.

**Conflict of Interest Statement**: The authors have no conflicts of interest to declare.

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**Author Contributions**: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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