(RESEARCH ARTICLE)

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Serial neutrophils count as a stratifying tool for early follicular tonsilitis remission

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Abstract

Background/Aim: This study examines the correlation between sequential serum neutrophil levels and the overall improvement status or reduction rate of intravenous antibiotic administration. This study seeks to identify a cost-effective and easily accessible biomarker that can accurately predict the need for hospitalisation in patients with acute tonsillitis who are receiving intravenous broad-spectrum antibiotics. The goal is to determine the patients' suitability for early discontinuation of intravenous antibiotics and discharge.

Methods: This study was conducted at the King Hussein Medical Centre in Jordan, focusing on patients with severe acute tonsillitis who did not respond to oral antibiotics. Data was collected from the electronic medical record system (Hakeem) from January 2018 to May 2021. The study classified serial serum neutrophil measurements during the first week of hospital admission into four categories. The levels were compared between the non-penicillin Cohort (Group I) and penicillin Cohort (Group II) using an Independent-T Test. The outcomes of interest included a drop in neutrophil counts exceeding 50%, a decrease in the use of intravenous antibiotics in favor of oral antibiotics, and early eligibility for discharge. The study also examined serial neutrophil counts over the tested days and compared to the outcomes of positive and negative states using receiver operating curve analyses. The optimal cutoff operating point for each ROC curve was determined by selecting the highest Youden's index of each prognosticator day level. The analysis of all results was conducted using SPSS version 20 with a significance level set at p-value <0.05.

Results: This study analyzed 1638 adult and elderly patients admitted to KHMC, RMS, Amman, Jordan between January 2018 and May 2021. The average age was 51.88±16.22 years, with patients dependent on intravenous penicillin being slightly older. The distribution of males and females was significant, with males making up 2.55 times the number of females. The odds ratio for positive outcomes was 4.12, with a high rate of poor outcomes in 1318 out of all eligible patients. A total of 994 (60.7%) medical patients were treated with intravenous administration, while 644 (39.3%) surgical patients were scheduled for a tonsillectomy procedure. The risk estimate for patients admitted from medical wards compared to surgical wards was an odds ratio of 0.562. The study also provided sensitivity analysis for the four tested serial neutrophil prognosticators at different day levels.

Conclusion: The study supports the use of Somatic Nucleated Cell (SNC) as a reliable measure for evaluating EFR in cases of catarrhal acute tonsillitis. The maximum SNC count in Group one was 11,269 cells per cubic millimeter. Acute streptococcal infection often exhibits an ESR higher than 40, but this may be concealed by other complications. The SNC test has advantages like simplicity, quickness, and cost-effectiveness, but lacks specificity. Monitoring SNC and EFR fluctuations can initiate treatment cessation, preventing relapse and severe complications during recovery.

Keywords: Ear, Nose, Throat; Neutrophils Counts; Severe Acute Tonsilitis; Serial Measurement,

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1. Introduction

Serial neutrophil counts, which indicate the changes in infection over time in a specific tissue area, can be useful in evaluating the effectiveness of specific antimicrobial treatments. We have utilised sequential neutrophil counts in the peripheral blood as a non-invasive measure of neutrophil movement at the affected site in individuals with recent-onset tonsillitis, where the infection is often limited to the tonsils. Serial neutrophil counts have also been obtained from patients diagnosed with recent-onset tonsillitis who were not administered any antibiotics, as well as from individuals without any medical condition serving as controls. [1-6]

Another facet of the cellular response to infection has been investigated by measuring the chemotactic activity of neutrophils in the peripheral blood. Serum neutrophils, a prominent type of white blood cells, are essential for various physiological defence and immune-related functions. These functions include attacking pathogens and releasing substances such as cytokines and chemotactic agents. Although modern therapies have made significant progress, the rates of illness and the emergence of resistance continue to be high, especially for infections acquired in hospitals. Acute stress conditions, as observed in this study on acute tonsillitis and other medical, trauma, and surgical-related illnesses, can lead to a substantial increase in white blood cells, specifically neutrophils and monocytes. Conversely, these conditions can also result in a significant decrease in levels of albumin and lymphocytes. [7-12]

Positive acute phase reactants, such as c-reactive protein (CRP), have intricate pathophysiological processes that result in stress-induced leukocytosis, with or without clinically significant hypoalbuminemia. Measuring neutrophil levels in a sequential manner, particularly after the onset of stress-related illness, is a useful independent risk factor for evaluating the mechanism of acute infections. It can also serve as a prognostic indicator for early recovery, allowing for timely adjustments in intravenous antibiotic treatment, or for early deterioration, necessitating an increase in intravenous antibiotic administration. Gonzales et al conducted a study on the clinical and immunological alterations associated with bacterial tonsillitis in adult patients. The study proposed the establishment of a staging system for severe tonsillitis, which would be determined by evaluating the number of neutrophils in the peripheral blood. RPCT was performed on patients diagnosed with either uncomplicated or minimally complicated bacterial tonsillitis. These patients were subjected to a neutrophil count and sore throat score on days 1, 2, 3, 4, and 7. The findings demonstrated a notable association between the alteration in neutrophil count and the successful treatment of tonsillitis. Due to its unique proposal for grading the severity of tonsillitis and its precise evaluation of neutrophil count, this study became an appealing model for indirectly assessing the severity of NF through consecutive neutrophil counts. [13-18]

Extensive research has been published on the subject of NF. Research has demonstrated a paradoxical relationship between the way a disease presents clinically and how it progresses. Colmenero et al discovered that there was no discernible distinction in the clinical severity between chronic and non-chronic necrotizing fasciitis (NF). In addition, Frazee et al demonstrated that the laboratory values and LRINEC score were not able to accurately predict the severity of the clinical condition. They found that patients with an LRINEC score below six should not be automatically classified as having a non-severe infection. This is because this group of patients had similar clinical symptoms, required similar surgical treatment, and had a lower likelihood of needing an amputation compared to those with a score of six or higher. The inconclusive results have not been able to solve the clinical and academic problem of distinguishing the severity of the disease. It is recommended that a new standard for assessing the severity of NF should be evaluated. [19-25]

This study examines the correlation between sequential serum neutrophil levels and the overall improvement status or reduction rate of intravenous antibiotic administration. This study seeks to identify a cost-effective and easily accessible biomarker that can accurately predict the need for hospitalisation in patients with acute tonsillitis who are receiving intravenous broad-spectrum antibiotics. The goal is to determine the patients' suitability for early discontinuation of intravenous antibiotics and discharge.

2. Methodology

This study was conducted retrospectively at the King Hussein Medical Centre (KHMC), a multi-disciplinary tertiary referral medical centre in Jordan, operated by the Royal Medical Services (RMS) Hospitals. Data on admitted patients with severe acute tonsillitis who did not respond to oral antibiotics were retrospectively collected from our electronic medical record system (Hakeem) for a period of 2 years and 5 months, from January 2018 to May 2021. This study excluded hospitably ill patients under the age of 18 who were admitted for reasons other than the primary reason being studied. It also excluded patients who received intravenous antibiotics of third generation cephalosporins before admission, had a length of stay (LOS) less than 2 days, had missing or incomplete data for the variables being studied, and did not have at least 3 measured serum neutrophil levels during the first week of admission.

The serial serum neutrophils measurements taken during the first week of hospital admission were classified into four categories: the level at admission, the level on the second to third day, the level on the fourth to fifth day, and the level on the sixth to seventh day. The levels were compared between the non-penicillin Cohort (Group I) and penicillin Cohort (Group II) using an Independent-T Test. Non-penicillin depend cohort (Cohort I) included patients whose intravenous antibiotics were mostly either third generation cephalosporins or intravenous lincosamides antibiotics. While in the penicillin cohort (Cohort II_ included primarily the intravenous cryst penicillin or Penicillin G.

Additional parametric data were also utilised to conduct an Independent T-Test, which presented the values of the analysed variables in the two penicillin groups as Mean±SD. The differences between these groups were expressed as Mean±SEM. The variables of patients affected by acute tonsillitis who met the eligibility criteria were analysed using a One-Sample T-Test and expressed as the mean value plus or minus the standard deviation. The comparative non-parametric dichotomous data were quantified as numbers (percentages) using the Chi Square Test. The risk estimates were also analysed using this test and expressed as odds ratios (OD).

The investigated outcomes of interest included a drop in neutrophil counts exceeding 50%, a decrease in the use of intravenous antibiotics in favour of oral antibiotics, and early eligibility for discharge. The positive condition of these combined desired results was found to have a decrease of less than 50% within three days of administering antibiotics or in cases where attempts to reduce the dosage were unsuccessful or early discharge was not achieved. This positive state was identified as 1 in the SPSS analysis. On the other hand, the focus is on the negative result of a decrease in neutrophil counts by more than 50% within the initial 3 days of administering intravenous antibiotics, or any related indicators such as early reduction in intravenous antibiotics or early discharge planning.

The serial neutrophil counts were examined over the tested days and compared to the outcomes of positive and negative states using receiver operating curve analyses. A Receiver Operating Characteristic (ROC) curve was generated to assess the predictive accuracy of serum neutrophil levels at admission, on the 2nd-3rd day, on the 4th-5th day, and on the 6th-7th day. The AUROC values of the 4 tested serial neutrophils prognosticator day levels were compared using the proposed Delong method. The results were expressed as AUC (95% CI; Range). The optimal cutoff operating point for each ROC curve was determined by selecting the highest Youden's index of each prognosticator day level, based on the stratified serial neutrophils level. This study also reported the results of sensitivity analysis for other four tested serial neutrophils prognosticators, including sensitivities, specificities, accuracies, positive and negative predictive values, and negative likelihood ratios. The analysis of all results was conducted using SPSS version 20 (Statistical Package for the Social Sciences, Chicago, IL, U.S.A.), with a significance level set at p-value <0.05.

3. Results

Out of the 2155 adult and elderly patients admitted to various departments at KHMC, RMS, Amman, Jordan between January 2018 and May 2021, a total of 1638 patients were included in this study, while 517 patients who did not meet the eligibility criteria were excluded. The average age of the entire study group was 51.88±16.22 years. The group of patients dependent on intravenous penicillin were slightly older than the group not dependent on penicillin (53.14±15.97 years versus 46.70±16.21 years, respectively, p>0.05). In the study, there was a significant difference in the distribution of males and females. Males made up approximately 2.55 times the number of females, with 1177 males (71.9%) compared to 461 females (28.1%) (p<0.05). Among the males, 46.3% (148 men) were in the non-penicillin cohort, while 53.8% (172 women) were in the penicillin cohort. On the other hand, 78.1% (1029 men) were in the penicillin cohort, while 21.9% (289 women) were in the non-penicillin cohort. The odds ratio (OD) for the positive outcome of interest, comparing females to males, was 4.12 (95% confidence interval [CI]: 3.21-5.34). A high rate of poor outcomes was observed in 1318 out of all eligible patients included in the study, resulting in an overall incidence of 80.46%.

A total of 994 (60.7%) medical patients were treated with intravenous administration, while 644 (39.3%) surgical patients were scheduled for a tonsillectomy procedure. Within the non-penicillin cohort, 158 (49.4%) were medical patients and 162 (50.6%) were surgical patients. In the penicillin cohort, there were 836 (63.4%) medical patients and 482 (36.6%) surgical patients. The risk estimate for patients admitted from medical wards compared to surgical wards was odds ratio (OR) of 0.562 (95% confidence interval [CI]: 0.440-0.719). The Fig 1 provides a comprehensive representation of the area under the ROC curves (AUROC) for the four tested serial neutrophils prognosticator day levels. The serum neutrophil levels on the 2nd to 3rd day of admission (referred to as the 2nd-3rd day neutrophil levels) have the highest AUROC (Area Under the Receiver Operating Characteristic) with an Area±SEM (Standard Error of the Mean) of 0.87±0.01 (95% Confidence Interval; Range: 0.85-0.89).

Table 1 Comparative variables and analyse outcome data between Cohort I (non-penicillin dependent cohort) and Cohort II (penicillin depend cohort).

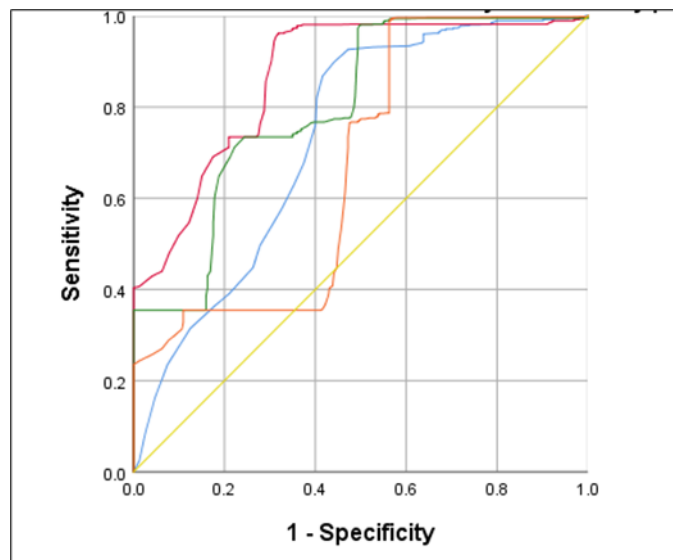| Variables		Total (N=1638)	Survivors (N=320, 19.54 %) Mean±SD	Non-Survivors (N=1318, 80.46%) Mean±SD	Mean Difference ±SEM	P-Value
Age (Yrs)		51.88±16.22	46.70±16.21	53.14±15.97	-6.44±0.99	0.105
Gender	F	461 (28.1%)	172 (53.8%)	289 (21.9%)	OD (F/M) 4.12 (95% CI; 3.21-5.34)	0.000*
	M	1177 (71.9%)	148 (46.3%)	1029 (78.1%)		
	M: F ratio	2.55: 1	0.86:1	3.56: 1		
Ward	Med	994 (60.7%)	158 (49.4%)	836 (63.4%)	OD (Med/Sur) 0.562 (95%CI; 0.440-0.719)	0.000*
	Sur	644 (39.3%)	162 (50.6%)	482 (36.6%)		

Figure 1 Receiver operating characteristic curve analysisd for the serial neutrophils counts at admission, 2nd and 3rd days, between 4th and 5th days, and between 6th and 7th days.

Table 2 The sensitivities, specificities, positive and negative predictive values, Youden and accuracy indices, and the negative likelihood ratios for the 4 tested 28-day poorer outcomes' prognosticators day levels.

Prognostic Indicator		TPR	FPR	YI	TNR	PPV	NPV	NLR	AI
Neutrophils counts	At admission	89.8%	44.1%	45.7%	55.9%	89.4%	57.1%	18.3%	83.2%
	2nd -3rd day	96.2%	31.9	64.3%	68.1%	92.6%	81.3%	5.6%	90.7%
	4th-5th day	71.2%	22.2%	49.0%	77.8%	92.9%	39.6%	37.0%	72.5%
	6th-7th day	99.3%	56.6%	42.7%	43.4%	87.8%	93.8%	1.6%	88.4%
TPR: True positive rate (sensitivity). FPR: False positive rate. YI: Youden index. TNR: True negative ratio (specificity).		PPV: Positive predictive value. NPV: Negative predictive value. NLR: Negative likelihood ratio. AI: Accuracy index.							

This is followed by the neutrophil levels on the 4th-5th day (0.80±0.01 (95% CI; 0.77-0.83)), the neutrophil levels at admission (0.73±0.02 (95% CI; 0.69-0.77)), and lastly, the neutrophil levels on the 6th-7th day (0.67±0.02 (95% CI; 0.64-0.71)). Table 2 presents the results of sensitivity analysis for the four prognosticators at different day levels. The table includes measures such as sensitivity (true positive rate), specificity (true negative rate), Youden index, positive predictive value, negative predictive value, negative likelihood ratio, and accuracy index. These measures were calculated for the four serial neutrophil levels that were tested.

4. Discussion

The present study consists of two outcome cohorts: Cohort I, which includes patients with non-penicillin dependent acute tonsillitis, and Cohort II, which includes patients with penicillin dependent acute tonsillitis. These patients were admitted and either scheduled for tonsillectomy or planned for intravenous antibiotic treatment. This study is unique because it directly compares the prognostic performance of the same prognosticator at different time intervals. The goal is to determine the best lag time-dependent operating cut-off serum neutrophil level that is associated with the most optimal clinical outcomes. Enable us to promptly identify clinically unacceptable outcomes, diagnose early in certain situations, and forecast overall poor outcomes, thus contributing to negative impacts in relation to the dynamic and flexible levels of neutrophils throughout the day. [26-31]

Our study found that the group of patients who received penicillin are more likely to have higher levels of neutrophils at the beginning and throughout the study, compared to the group of patients who did not receive penicillin (Cohort I). There are certain clinically significant factors that likely have prognostic value for early differentiation between different conditions. The sensitivity analysis indices for these factors may vary depending on other related factors and confounding variables. These factors are separate from the acute physiological abnormalities in patients. In the current era of limited medical resources and shrinking medical teams, it is important to ensure optimal resource allocation and efficient implementation of management protocols. Based on these observations, we have determined that a fluctuation in the number of neutrophils indicates a shift in the immune effectiveness of a specific patient at that particular moment. The most common reason is a change in the concentration of the agent causing the problem or a change in the way the host and parasite interact. [32-41]

Regarding EFT, it can indicate the initiation or occurrence of a particular immune response to the pathogens responsible for the condition. Three patients experienced complete resolution of EFT following a double-blind trial of oral flucloxacillin. These individuals exhibited a consistent decrease in neutrophil count over the course of the 5-day observation period. In the two cases where there had been a previous change in the pattern, remission was sustained without the occurrence of new symptoms. This is in contrast to the typical progression of the disease and the resulting treatment outcomes in the rest of the patients. In this study, we show that measuring the neutrophil count on days 3 and 5 after being diagnosed with EFT can accurately identify certain groups of patients who have varying probabilities of achieving remission within the next 4 weeks. This measurement is both sensitive and specific, making it a reliable marker for predicting patient outcomes. [42-51]

These findings have significant clinical and pathophysiological implications for erythroid tonsillitis. The author previously observed that the ingestion of a sharp foreign object caused acute follicular tonsillitis on the left side, resulting in a painful, persistent, red, filmy swelling of the left vocal cord, also known as "Quincke's disease". The tonsillitis and laryngeal lesion had resolved three days after the cause was removed. It was discovered that a comparable series of occurrences was linked to an increase in neutrophil count surpassing 6 G/l, followed by a subsequent decrease to below 2 G/l. However, two patients (Nos. 5 and 6) had a recurrence of their tonsillitis even though their neutrophil count dropped below 2 G/l. Both individuals had been continuously exposed to the causative agent: A at his place of work and B in a persistently overcrowded living arrangement. This study is constrained by its retrospective design. A more extensive, multicenter, and prospective study is required to account for various confounding factors and elucidate the causal relationships between the prognostic indicators and unfavourable outcomes being examined. Although there are limitations, our conclusions may provide additional value to the current rapidly changing and contentious pieces of evidence, particularly in cohorts of critically ill individuals. [52-58]

5. Conclusion

To summarise, this study has supported the use of SNC as a reliable measure for evaluating EFR in cases of catarrhal acute tonsillitis. The maximum SNC (Somatic Nucleated Cell) count in Group one was 11,269 cells per cubic millimeter. A study examining acute B-haemolytic streptococcal, acute tonsillitis, acute on chronic tonsillitis, and acute viral tonsillitis found that the average cell counts per cubic millimeter were 7, 13, 6, and 4,500, respectively, for each clinical

group. The figures demonstrate the challenging nature of distinguishing between various etiological types. However, Acute streptococcal infection often exhibits an erythrocyte sedimentation rate (ESR) higher than 40. It is important to note that this elevation in ESR may be concealed by other complications leading to high ESR levels. The study found that the maximum ESR was 75. As a result, the SNC test has several advantages, including its simplicity, quickness, and the fact that it does not require sedation. Additionally, it is easy to administer and produces consistent results. Although ESR is cost-effective and easily replicable, it lacks the ability to provide a definitive diagnosis. CRP is a useful tool, although it lacks specificity. Testing for elevated SNC aims to identify a clear connection between increased neutrophil count and bacterial infections, as well as the duration of the infection. By monitoring the fluctuations of SNC and EFR, treatment cessation can be initiated based on SNC levels. This approach can help prevent relapse and the emergence of severe complications during the recovery phase of bacterial tonsillitis. Adopting this treatment method could result in resource and cost savings, as well as enhancing patient care and preventing the development of complications. In order to validate the association between SNC and infection, a larger-scale study is required, which should include repeated testing for specific bacteria and/or viral cultures.

Compliance with ethical standards

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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