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Evaluation of Combination Models Predicting Long-term Hospitalization and Complication Occurrence in Deep Neck Infection

ABSTRACT

Background: The purpose of this retrospective study is to identify independent factors and their combinations that could predict complications and long-term hospitalization in deep neck infection (DNI) patients.

Methods: We analyzed data from 169 patients that were hospitalized from 2012 to 2022 due to deep neck infections. In addition to evaluating patient characteristics, we identified independent significant variables and their combinations that could predict complication occurrence and/or long-term hospitalization using multivariate analysis.

Results: According to the multivariate backward procedure, while only presence of comorbidity and neutrophil to lymphocyte rate (NLR) were found to be independent significant risk factors of complication ($P = .011$ and $P = .020$, respectively), site of origin (non-odontogenic), need for both medical and surgical treatment, C-reactive protein (CRP) and NLR were found to be significant risk factors predicting long-term hospitalization ($P < 0.001$, $P < 0.001$, $P = 0.037$ and $P = 0.008$, respectively). The discriminatory power of a combination of 3 variables (presence of comorbidity, NLR, and white blood leukocyte count) for the occurrence of DNI complications yielded an AUC (ROC) of 0.764. The discriminatory power of a combination of 4 variables (non-odontogenic origin, need for both surgical and medical treatment, CRP, and NLR) to identify DNIs requiring prolonged hospital stay yielded an AUC (ROC) of 0.900.

Conclusion: The final models obtained by the combination of variables for both complications and long-term hospitalization are promising for prognostic purposes.

Keywords: Deep neck infection, multivariate analysis, prognostic factor, neutrophil-to-lymphocyte rate

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INTRODUCTION

Bacterial infections that affect the deep neck cavities and originate in the upper respiratory-digestive system are referred to as deep neck infections (DNIs). Deep neck infections can originate from various sources, with the teeth, pharyngo-tonsillar tissue, and salivary glands being the most common.[1] Since the implementation of antibiotics, the incidence of DNI has decreased significantly compared to previous periods.[2]

In general, DNIs are polymicrobial. *Streptococcus* spp., *Peptostreptococcus* spp., *Staphylococcus aureus*, and anaerobes are the most frequently cultivated microorganisms in DNI.[3] Immunosuppression and diabetes are 2 of the most significant risk factors.[4] The primary symptoms include neck swelling, odynophagia, dysphagia, fever, and trismus.[5]

Respiratory obstruction, bacterial endocarditis, mediastinitis, suppurative jugular vein thrombophlebitis, carotid artery erosion, and septic shock are life-threatening complications.[2,6] Given the critical nature of the complications mentioned above, clinicians must possess the ability to anticipate their occurrence. As a result, a comprehensive examination of numerous factors has been suggested to ascertain their degree of prognostic significance.[7]

Patients admitted to our clinic as a result of DNI were retrospectively screened for this study. The objective of this research endeavor was to examine the attributes of the participants and to identify independent variables and their combinations that might serve as predictors of prolonged hospitalization and complications.

MATERIAL AND METHODS

Ethical Consideration

The study was authorized by the Non-Invasive Clinical Research Ethics Committee of the Cukurova University Faculty of Medicine (approval no: 116, date: 5.11.2021) and was carried out in accordance with the principles outlined in the Declaration of Helsinki. The patients' informed consent was not acquired because our investigation was retrospective.

Patients and Treatment Approach

Every patient record treated for DNI at the Cukurova University Faculty of Medicine Department of Otolaryngology between 2012 and 2022 was reviewed in this retrospective analysis. Patients under 18 years of age, those with peritonsillar abscesses, superficial infections, infections brought on by external (traumatic or surgical) neck injuries, and infections resulting from head and neck cancers were excluded from the study. The study comprised 169 DNI patients who satisfied the eligibility requirements. The study analyzed and recorded various demographic characteristics and clinical and laboratory variables of the patients. These variables included age, sex, presence of comorbid disease, origin of infection, identification status of the origin of infection, treatment modality, length of hospital stay, complication status, and results of bacterial cultures. Additionally, the study documented the blood levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and neutrophil-to- lymphocyte rate (NLR). The baseline was the laboratory results at the time of hospital admission.

All patients underwent routine otolaryngological examination, upper aero-digestive system endoscopy, blood tests, and contrast-enhanced computerized tomography (CT) upon admission. Intravenous antibiotics were administered to all patients. The same antibiotherapy (ampicillin—sulbactam intravenous 2 g every 6 hours) was given to all patients at the first admission. After the results of the culture-antibiogram of the patients, the infectious diseases clinic was consulted and the treatments were modified for the patients who needed a change in treatment. Surgical drainage was applied when encapsulated, hypodense abscess formation was observed in the contrast-enhanced CT of the patient, or when there was involvement in areas that may predispose to serious complications such as prevertebral and carotid space involvement, or when there were complications at the time of admission. Apart from these, surgical treatment was planned when there was no regression in clinical and laboratory findings despite parenteral antibiotic therapy.

The complication assessment covered potentially fatal consequences. This criterion excluded such conditions as skin fistulization and necrosis, as well as airway stenosis that did not need surgical treatment. Life-threatening DNI complications included necrotic fasciitis, mediastinitis, pleural empyema, septic shock, bacterial endocarditis, jugular vein thrombophlebitis, and tracheotomy-required airway constriction. Surgical drainage procedures included incisional neck drainage, intraoral and oropharyngeal drainage, neck exploration and debridement, tooth extraction, surgical excision, tracheotomy, thoracotomy, thoracoscopy, and thoracic tube application.

Statistical Analysis

Numerical values and percentages were used to represent categorical data, whereas the mean, standard deviation, and, in certain circumstances, the median and minimum—maximum values were used to characterize continuous variables. The categorical variables were compared between the groups using the Chi-square test. The Shapiro—Wilk test was used to confirm the distribution of continuous variables was normal. Depending on whether the statistical assumptions were satisfied, either the Student's *t*-test or the Mann—Whitney *U* test was used to compare continuous variables between 2 groups.

A stepwise backward logistic regression analysis was used to identify the major determinants of study outcomes, including complications and long-term hospitalization. The inflammation biomarkers (WBC, CRP, ESR, and NLR) were classified based on their median values (below median vs. above median) and were subsequently included in a logistic regression analysis. The logistic regression analysis included variables from the univariate analysis that were deemed statistically significant at a significance level of $P < .25$. These variables included age, comorbidities, treatment modalities, and inflammation biomarkers for complications. The research also took into account treatment methods, gender, place of origin, and inflammatory biomarkers related to long-term hospitalization. The odds ratios and related 95% CIs were supplied by the research. Receiver operator characteristic (ROC) curve analysis and associated performance diagnostics, such as area under the curve (AUC), sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, were used to assess the predictive ability of the models. The software program (IBM SPSS Corp.; Armonk, NY, USA) Version 20.0 was used to perform the analysis. At a significance level of 0.05, the tests were considered statistically significant.

MAIN POINTS

- Effective care of deep neck infection necessitates strict control of diabetes.
- The presence of non-odontogenic factors is a risk factor that negatively affects the prognosis.
- The neutrophillymphocyte rate is an independent predictor of complications and hospitalization.
- These models demonstrated significant efficacy in identifying individuals with an unfavorable prognosis.

RESULTS

Clinical and Laboratory Features

The demographic and clinical characteristics of the study population and statistical comparison between groups are presented in Table 1. There were 90 (53.3%) male and 79 (46.7%) female patients, resulting in a male-to-female ratio of 1.14 : 1. The mean age was 35.3 ± 19.6 years (median age 33.0 years). The median length of hospitalization length was 8 days. Hospitalization length for more than 8 days was determined as long-term hospitalization, while 8 days or less was considered short-term

Table 1. Demographic and Clinical Characteristics of the Study Population According to Study Outcomes

	Complication			Hospitalization		
	No (n = 149)	Yes (n = 20)	*P*	≤8 days (n = 86)	>8 days (n = 83)	*P*
Age (years)	31.0 (18.0-79.0)	49.5 (18.0-69.0)	**.008**	29.0 (18.0-72.0)	35.0 (18.0-79.0)	.545
Gender, n (%)			.943			.241
Male	80 (88.9)	10 (11.1)		42 (46.7)	48 (53.3)	
Female	69 (87.3)	10 (12.7)		44 (55.7)	35 (44.3)	
Hospitalization (days)	8.0 (2.0-23.0)	12.5 (3.0-30.0)	**.045**	–	–	–
Complication, n (%)						
No	–	–	–	78 (52.3)	71 (47.7)	.424
Yes				8 (40.0)	12 (60.0)	
Site of origin, n (%)						
Unknown	34 (82.9)	7 (17.1)	.268	21 (51.2)	20 (48.8)	.961
Diagnosed	115 (89.8)	13 (10.2)		65 (50.8)	63 (49.2)	
Site of origin, n (%)						
Non-odontogenic	39 (86.7)	6 (13.3)	.569	10 (22.2)	35 (77.8)	**<.001**
Odontogenic	76 (91.6)	7 (8.4)		55 (66.3)	28 (33.7)	
Comorbidities, n (%)						
No	115 (92.0)	10 (8.0)	**.020**	64 (51.2)	61 (48.8)	.891
Yes	34 (77.3)	10 (22.7)		22 (50.0)	22 (50.0)	
Treatment modalities, n (%)						
Only medical	57 (95.0)	3 (5.0)	.073	51 (85.0)	9 (15.0)	**<.001**
Medical + surgical drainage	92 (84.4)	17 (15.6)		35 (32.1)	74 (67.9)	
Bacterial culture, n (%)						
Negative	71 (87.7)	10 (12.3)	>.999	42 (51.9)	39 (48.1)	.810
Positive	78 (88.6)	10 (11.4)		44 (50.0)	44 (50.0)	
Inflammation biomarkers						
CRP (mg/L)	39.2 (0.1-427.0)	119.5 (0.4-475.0)	**.005**	21.3 (0.1-224.0)	86.0 (0.8-475.0)	**<.001**
ESR (mm/h)	42.0 (2.0-115.0)	52.0 (8.0-98.0)	.062	35.6 ± 19.7	52.5 ± 24.8	**<.001**
WBC (cells × 10^9 L)	11.6 (2.9-39.1)	13.8 (5.2-34.3)	**.035**	10.8 (5.2-32.8)	12.9 (2.9-39.1)	**.006**
NLR	4.9 (0.7-62.8)	9.0 (2.3-36.0)	**<.001**	3.6 (0.7-30.3)	7.2 (1.6-62.8)	**<.001**

Values in bold indicate statistical significance.

hospitalization. Of the 169 patients, 86 were classified as short-term hospitalized, whereas 83 of them were long-term hospitalized. The most prevalent comorbidities included diabetes mellitus (33 cases), cardiovascular disease (28), and chronical pulmonary disease (8), while 125 patients (73.9%) did not have any associated systemic diseases.

The source of the DNI was determined in 128 out of the 169 cases (75.7%). Of the 169 instances of DNI, odontogenic origins accounted for 83 cases or 49.1%. Afterward, there were infections that started in the pharyngo-tonsillar structures (28 cases; 16.5%), salivary glands (9 cases; 5.3%), neck cysts (4 cases; 2.3%), cervical lymph nodes (2 cases), hypopharynx (1 case), and thyroid gland (1 case). The source of infection could not be identified in 41 individuals, accounting for 24.2% of the total cases, despite extensive testing.

Bacterial culture results were available for 89 out of 109 patients who underwent surgical treatment. The most frequently isolated bacterial strains were *Streptococcus viridans* group (26 cases), Gram-positive anaerobic cocci (14 cases), *Staphylococcus epidermidis* (7 cases), *Staphylococcus aureus* (5 cases), *Pseudomonas aeruginosa* (4 cases), *Klebsiella pneumoniae* (3 cases), and polymicrobial growth (10 cases). There was no bacterial growth in 20 cases.

Life-threatening complications related to DNI were determined in 20 patients in our study. Among these, necrotizing fasciitis was the most common occurring in 9 cases. Mediastinitis occurred in 5 cases, suppurative jugular vein thrombophlebitis in 3 cases, bacterial endocarditis in 2 cases, and pleural empyema in 1 case. All complications were managed successfully, and none of the patients died owing to these complications.

All 5 patients who developed mediastinitis had their neck abscess drained, and 3 of them had thoracoscopies and thorax tube placements by thoracic surgeons. Patients with jugular vein thrombophlebitis underwent drainage of the neck abscess and continued therapy with anticoagulants and antibiotics. Not 1 patient had a surgery such as a jugular vein ligation or resection. Three individuals had tracheotomies because of significant stenosis in their upper respiratory tracts. These patients were already presenting with complications. Nine participants in our trial had multiple surgical procedures. Five of them had multiple debridement procedures due to necrotizing fasciitis. The remaining 4 patients had thoracoscopy and thoracic tube placement.

Inflammation biomarkers were classified (below median—above median) according to the median values. The median of CRP was 47.0 mg/L, the median of WBC was 11.8 cells × 10^9 L, the median of NLR was 5.5, and the median of ESR was 42.0 mm/h.

Table 2. Univariate and Multivariate Logistic Regression Analysis for the Prediction of Study Outcomes

	Complication				Long-term Hospitalization			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	1.03 (1.01-1.06)	.013			1.00 (0.99-1.02)	.579		
Gender	0.86 (0.34-2.19)	.756			0.69 (0.38-1.27)	.242		
Comorbidities (presence)	3.38 (1.30-8.80)	.013	4.27 (1.39-13.11)	.011	1.05 (0.53-2.08)	.891		
Site of origin (non-odontogenic)	1.67 (0.52-5.31)	.385			6.87 (2.97-15.88)	<.001	9.09 (2.79-29.41)	<.001
Treatment modalities (medical + surgical)	3.51 (0.98-12.51)	.053			11.98 (5.31-27.06)	<.001	9.80 (2.9-32.8)	<.001
CRP (>47.0 mg/L)	2.56 (0.93-7.03)	.067			5.67 (2.92-10.98)	<.001	2.84 (1.06-7.58)	.037
WBC (>11.8 cells × 10^9 L)	3.16 (1.08-9.22)	.035	3.17 (0.89-11.23)	.073	1.78 (0.96-3.27)	.065		
NLR (>5.5)	6.18 (1.73-22.12)	.005	5.04 (1.29-19.74)	.020	7.95 (3.99-15.84)	<.001	3.95 (1.44-10.86)	.008
ESR (>42.0 mm/h)	1.46 (0.56-3.78)	.435			3.09 (1.64-5.81)	<.001		
Nagelkerke R^2			0.209				0.585	
Hosmer and Lemeshow test statistic			4.18	.523			4.57	.712

CRP, C-reactive protein, ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte rate; OR, odds ratio; WBC, white blood cell count.

Logistic Regression Models: Complication Occurrence and Long-term Hospitalization

A logistic regression analysis was performed to identify possible risk variables for complications and prolonged hospitalizations. Only comorbidities and greater NLR levels were shown to be independent significant risk variables of complication by the multivariate backward approach (Table 2).

Regarding extended hospital stays, the backward logistic regression analysis revealed that non-odontogenic sites of origin, the need for both medical and surgical care, elevated CRP and NLR levels, and the need for both types of therapy were significant risk factors for long-term hospital stays (Table 2).

Performance of Models

We created a 3-variable model including comorbidity, NLR, and WBC levels to predict the likelihood of complications. Figure 1 shows that the model's discrimination performance was strong, with an AUC of 0.764 (95% CI: 0.648-0.880, $P < .001$) in predicting complications.

We created a 4-variable model that takes into account the location of origin, treatment methods, CRP, and NLR levels in order to predict long-term hospitalization. The model's AUC for predicting prolonged hospital stays was 0.900 (95% CI: 0.847-0.953, $P <$ .001), as shown in Figure 2.

DISCUSSION

As in the past, these infections remain dangerous and potentially fatal, even though the frequency of DNI and the incidence of complications have dropped with the widespread use of advanced diagnostic methods and antibiotic therapy. In order to lessen the likelihood of fatal and morbid disorders that could arise as a result of DNI, it is crucial to identify independent and relevant criteria that will inform us about the prognosis.

Measuring the predictability of the variables considered in long-term hospitalization and complication occurrence appears to be the best strategy for assessing the prognostic predictability of DNI. Our study's strengths included consecutive case series, well-defined exclusion criteria, and uniform patient treatment using the same protocol.

Patients who presented with complications had a substantially increased risk of prolonged hospitalization ($P = .045$) (Table 1). This is a naturally occurring consequence. It follows that the occurrence of these circumstances, which are common in the course of complications such as tracheotomy, thoracic tube insertion, and multiple surgical procedures, would

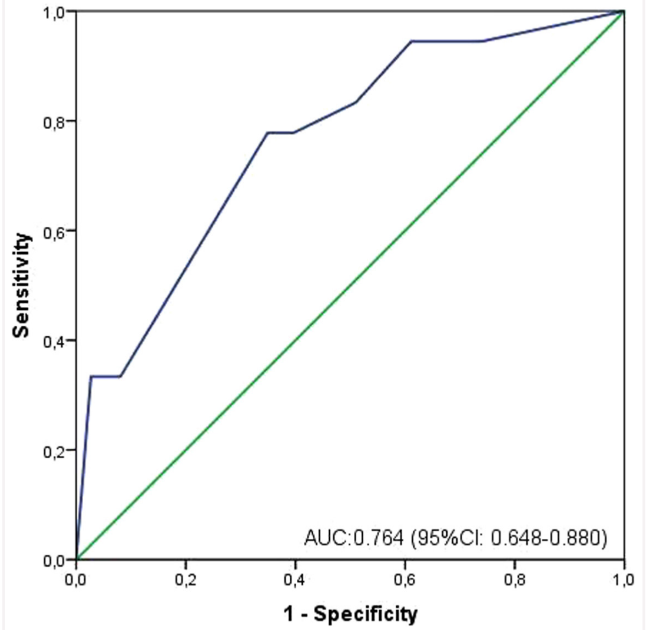

Figure 1. Receiver-operating characteristic curve of model for predicting complication occurrence.

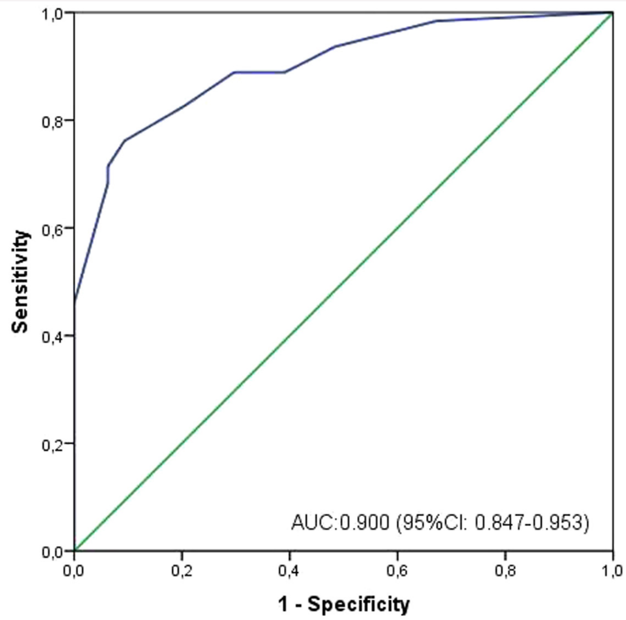

Figure 2. Receiver-operating characteristic curve of model for predicting long-term hospitalization.

inherently increase the likelihood of an extended hospital stay. Consequently, apart from the parameters that were assessed in our research, certain indicators of this nature were omitted from the evaluation.

In the study by Lin et al, diabetes mellitus—which is commonly documented in DNI patients—was found to be a risk factor for infection-related morbidity.[8] Additionally, in their multivariate analysis, Boscolo-Rizzo et al[9] found that diabetes mellitus elevated the probability of complications (OR 5.43, 95% CI: 2.55-11.53). Our study's findings demonstrated that one of the independent factors influencing the likelihood of complications is the existence of comorbidity, particularly diabetes mellitus (OR = 4.27, 95% CI: 1.39-13.11). Long-term diabetics may develop peripheral vascular disorder, which could reduce tissue oxygenation and put them at risk for anaerobic infection.[10] Furthermore, the hyperglycemic condition in diabetic individuals results in leukocyte and macrophage dysfunctions.[11] Besides, DNI patients who also have concomitant pulmonary disease are more likely to experience respiratory tract problems. Therefore, managing comorbid disease optimally is essential in the management of DNI.

Considering the cases of DNI with identified origin, the odontogenic origin constitutes the majority, while pharyngo-tonsillar origin is in second place. In our series, patients with identified pharyngo-tonsillar origin account for 62.2% of the cases of non-odontogenic origin. We observed more oral intake disorders and respiratory problems in DNI cases originating from this region. In the DNI analysis of Staffieri et al, they determined that those who needed surgical treatment (OR 4.66, 95% CI: 2.53-8.59) and/or patients of non-odontogenic origin (OR 1.88, 95% CI: 1.01-3.53) were at risk for long-term hospitalization.[7] As a result of our analysis, we obtained evidence confirming these findings (OR = 9.09, 95% CI: 2.79-29.41) for non-odontogenic site of origin (OR = 9.80, 95% CI: 2.09-32.8) for need for surgical treatment. Although other studies in the literature have not revealed such results, we consider that these patients are at risk for poor prognosis.[9,12] Early surgical intervention and aggressive medical treatment should not be hesitated for these patients. Early nutrition and airway support must be provided. Tracheotomy should be considered if airway support is required.

We assumed that high-risk DNI cases could be better determined by considering multiple variables. Thus, we designed combinations from significant and independent variables, which we found with our multivariate analysis, and evaluated the discrimination power and model goodness of fit of these combinations. In the study by Marioni et al, separate panels were created for 2 different determinants, and their discriminatory powers have been calculated.[13] Whereas, the area under the ROC curve was 0.7929 for long-term hospitalization, this value was 0.6701 for complications. Accordingly, an acceptable discriminant power was acquired for long-term hospitalization, but not sufficient discriminatory power for complications.[13] Our panels were designed by combining different markers, different from those suggested in that study, and according to the analysis's findings, the combinations we identified outperformed the other study in terms of discriminatory power. Thus, in the Hosmer and Lemeshow scales,[14] the combination designed for complication occurrence showed quite acceptable discriminatory power, while the combination for long-term hospitalization showed excellent discriminatory power. The combination model created with more than one variable gives a new dimension to the prognostic evaluation of DNI. These models have the potential to be a reliable option for early detection of high-risk patients for poor prognosis.

The process of DNI involves the complex relationship and interdependence of various clinical variables that contribute to prognosis. Previous investigations have not definitively established that any of the clinical factors examined had a distinct and substantial prognostic function. Consequently, our attention was directed toward the notion that a combination of various variables, as opposed to a solitary independent variable, can yield enhanced predictive capabilities. The resulting combination models, because of their potency and effectiveness, represent one of the most optimal choices known to us for predicting the prognosis of DNI. These findings will provide insights for future investigations with larger sample sizes. Nevertheless, our study had several limitations. The DNI prognosis does not take into account challenging factors such as geographical and ethnic variations, limited availability of microbiological culture in non-surgically treated patients, variations in antibiotic effectiveness, and disparities in surgical techniques. We were unable to retrieve the retrospective CT data of several individuals included in our investigation. Consequently, the statistical evaluation did not incorporate CT data. Additional limitations of the study encompassed its focus solely on a single institution and the retrospective nature of data collection. Moreover, while we adhered to our standardized treatment protocol for patients, it is unavoidable that there may be variations among clinicians due to individual differences.

Deep neck infection, despite advancements in detection and treatment, remains a collection of diseases with unpredictable progression and results. While there is no definitive independent variable that can accurately predict prognosis, the use of combination models may offer a viable approach for predicting long-term hospitalization and complications. These combination models, due to their ability to differentiate, have the potential to be one of the most effective choices we know of for predicting the outcome of DNI. The findings of this study will pave the way for more extensive research on this subject in the future.

Ethics Committee Approval: The study was approved by the Cukurova University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (approval no: 116, date: 5.11.2021).

Informed Consent: N/A.

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