Can biochemical biomarkers predict mortality in percutaneous dilatational tracheostomies?

Biyokimyasal biyobelirteçler perkütan dilatasyonel trakeostomilerde mortaliteyi tahmin edebilir mi?

Öz: Bu retrospektif çalışmanın amacı, prognozun ölümü olabileceğini perkütan dilatasyonel trakeostomi (PDT) uygulanan hastalarda mortaliteyi öngörmek için biyokimyasal parametrelerin biyobelirteç olarak kullanılabileceğini araştırmaktır.


Bulgular: Yıguna bakıldığında gün sayıları (p<0.006), prooperatif nötrofil sayıları (p<0.041) ve postoperatif NLR (p=0.041) açısından grupta anlamlı bir fark bulundu. Hayatta Kalanlar grubundaki hastaların prognozun öncesi ve sonrası parametrelerinde lenfosit sayıları (p<0.001), ortalama trombosit hacmi (MPV) (p=0.002) ve PLR (p<0.001) değerleri arasında fark saptandı. ROC eğrisi analizi, 6,91 kesme noktasında 68,7% hassasiyet ve 60,0% özgüllük gösteren PDT sonrası NLR değerinin mortalite riskini tahmin etmede prognozun öncesi ve sonrası parametrelerinde lenfosit sayıları (p<0.006), prooperatif nötrofil sayıları (p<0.041) ve postoperatif NLR (p=0.041) açısından grupta anlamlı bir fark bulundu. Hayatta Kalanlar grubundaki hastaların prognozun öncesi ve sonrası parametrelerinde lenfosit sayıları (p<0.001), ortalama trombosit hacmi (MPV) (p=0.002) ve PLR (p<0.001) değerleri arasında fark saptandı. ROC eğrisi analizi, 6,91 kesme noktasında sadece %68,7 hassasiyet ve 60,0% özgüllük gösteren PDT sonrası NLR değerinin, ölümle sonuçlanacak bir prognozun spesifik ve hassas bir biopsyomik belirleyici olarak kullanılabileceğini göstermiştir.

Sonuç: Bu pilot çalışmanın bir sonucu olarak, PDT sonrası ölçülen NLR seviyesinin PDT uygulanan hastalar için mortalite riskini tahmin etmede prognozun öncesi ve sonrası parametrelerinde lenfosit sayıları (p<0.006), prooperatif nötrofil sayıları (p<0.041) ve postoperatif NLR (p=0.041) açısından grupta anlamlı bir fark bulundu.
INTRODUCTION

Bedside percutaneous dilatational tracheostomy (PDT) is a procedure that many physicians perform in intensive care units. Besides producing lesser complications than surgical tracheostomy, this method also significantly reduces operating room and hospital costs (1,2). Among the advantages the procedure offers are that it is more easily performed, requires a smaller incision, and results in less tissue trauma, leading to lower rates of infection. The procedure is comfortable for the patient and because secretions and airway resistance are reduced, it allows early weaning from a mechanical ventilator. This in turn provides the opportunity for early mobilization and physiotherapy (3,4).

Ciaglia introduced the method in 1985, using a blunt-ended dilator. PDT was later modified by Griggs, who performed the procedure using guidewire dilating forceps 5. In addition to the advantages of PDT mentioned in the literature, there are also references related to PDT complications. It has been demonstrated that complications are generally minor but that 2%-20% of cases develop life-threatening complications (hemorrhage, hypoxia, puncture of the endotracheal tube cuff or extubation) (5-7). In this context, it is seen that although the benefits and risks of percutaneous dilatational tracheostomy (PDT) have been reported in many studies, there is a scarcity of research on the positive and negative effects of the procedure on patient mortality. Furthermore, a review of the literature reveals that there are no studies that have explored the relationship between mortality and biomedical parameters in the monitoring of patients undergoing PDT, nor any that have tested the possibility of using biomarkers in predicting mortality prior to the procedure.

The aim of this retrospective study was to explore the possibility of using biochemical parameters as biomarkers in predicting mortality in patients undergoing PDT where the prognosis may be fatal.

MATERIAL AND METHOD

The Patients

Patients treated in the Intensive Care Unit over the period July 1, 2016-April 30, 2018 and who underwent PDT using the Griggs technique were included in the study. This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of local Ethics Committee (Permission granted 06.06.2018, Decision No. 2018.06.08). The procedure was applied to patients who had no hemostatic disorder (platelet count of >50,000 mm3, activated partial thromboplastin and prothrombin time values less than 1.5 times the control value), with normal tracheal and neck structures (no goiter, past neck surgery, or soft tissue infection in the neck). Patients who did not meet these criteria and children (<16 years) were excluded.

Patient data were accessed via a simultaneous scan of the hospital database and the intensive care unit records. The patients’ age, gender, body mass index (BMI), admittance diagnosis, day of PDT (the day of intubation), weaning rates, early complications, days in intensive care, mortality rates and discharge status were recorded. Additionally, the patients’ blood hemoglobin, leukocyte, neutrophil, lymphocyte, platelet, eosinophil, basophil values, neutrophil-to-lymphocyte ratios (NLR) and platelet-to-lymphocyte ratios (PLR) 1 day prior to and 1 day following the PDT procedure were assessed.

The Patients were Grouped as Follows

- The SURVIVOR group (those who underwent PDT and were discharged from the hospital after treatment, n=20)
- The NON-SURVIVOR group (patients who underwent PDT but died at the hospital after treatment, n=67)

Surgical Procedure

PDT was performed on the patients using the Griggs technique. In addition to the standard monitoring of the patients, who were under orotracheal intubation and supported with a mechanical ventilator, invasive arterial pressure monitoring was performed, together with the administration of 2 mg/kg propofol (Propofol 1%, Fresenius), intravenous (IV), 1 µg/kg fentanyl (Fentanyl, Abbott) (IV) and 0.5 mg/kg rocuronium bromide (Esmeron, Organon) (IV). During the procedure, pressure or volume-controlled ventilation was applied and FiO2 was raised to 100%. After sedation and muscle relaxation, the patient’s head was extended while in the supine position with cushions beneath the shoulders. After the donning of a sterile gown and gloves, the region was wiped with an antiseptic solution and covered with a surgical drape with a hole. A bedside assistant standing at the head of the patient pulled down the cuff of the endotracheal tube and the cuff was inflated such that it would remain immediately below the vocal cords. After the donning of a sterile gown and gloves, the region was wiped with an antiseptic solution and covered with a surgical drape with a hole. A bedside assistant standing at the head of the patient pulled down the cuff of the endotracheal tube and the cuff was inflated such that it would remain immediately below the vocal cords. Then, using a 14G-tipped intravenous cannula after drawing in 4 ml normal saline, aspiration was performed through the first and second or second and third tracheal cartilage, and entry was made into the tracheal lumen. When the air was aspirated into the injector, the needle was separated from the injector, a guidewire was passed through into the tracheal lumen, and the cannula was drawn back. Local anesthesia in the amount of 4 ml
containing 2% Prilocaine (Citanest, AstraZeneca) was administered bilaterally into 1 cm around the wire. An 8-10 mm transverse incision was made with a scalpel. The expansion was achieved with an 8F dilator. The skin and trachea were stretched with forceps and a tracheostomy cannula (Percutaneous tracheostomy kit, Portex) of an inner diameter of 7 or 8 mm. was inserted through the guidewire. The cuff of the tracheostomy cannula was inflated to listen to respiratory sounds and after verifying that the cannula had been properly inserted, the endotracheal tube was removed. The area surrounding the tracheostomy tube was cleaned and then a sterile sponge was wrapped around it, the tracheostomy tube being fixed to the neck with a tie. X-rays of the lung were taken following the procedure. Complications occurring during and after the procedure (minor bleeding, surgical bleeding, subcutaneous emphysema, pneumothorax, wound infection and mortality) were recorded. Bleeding from the sponges wrapped around the stoma that did not stop in a short time and/or blood oozing from the tracheostomy tube with aspiration was considered minor bleeding. Bleeding from the stoma and/or trachea with aspiration despite the pressure dressing was defined as surgical bleeding.

Biochemical Analysis
The venous blood samples taken from the patients were analyzed and the study results were obtained from this analysis. A hematology analyzer (Mindray BC-6800, Shenzen, China) was used to obtain counts for blood hemoglobin levels (reference range: 10-18 g/dL), leukocytes (reference range: 4400-11,300/uL), neutrophils (reference range: 1100-9600/uL), lymphocytes (reference range: 500-6000/uL), monocytes (reference range: 100-1400/uL), eosinophils (reference range 0-1000/uL), basophils (reference range: 0-300/uL) and platelets (reference range: 150,000-500,000/uL).

Statistical Analysis
A power analysis package program (Gpower 3.1) was used for the study results and it was determined that the number of patients taken into the study constituted a suitable sample size. The Mann-Whitney U test was employed to compare the groups in terms of nonparametric data (p<0.05). The differences between the groups in terms of parametric data were explored with the Independent Samples t test (p<0.05). The Wilcoxon Signed Ranks test was used to determine the differences between the patients' blood count values before and after PDT (p<0.05). Spearman's rho Correlation test was used to identify the correlations between parameters (p<0.05). The ROC-Curve test was employed to determine the independent variables that could predict patients' early-stage prognosis, which would help in the decision on what type of treatment method would be used (surgical/conservative treatment) (p<0.05).

RESULTS
A total of 87 patients were included in the study. Of these patients, 53 (60.9%) were men and 34 (39.1%) were women; their mean age was 66.27±18.68 years. The patients’ mean BMI was 27.51±4.10. The mean duration of the patients’ intubation prior to PDT was 12.27±8.39 days. It was noted that 67 (77.0%) of the patients died at the hospital during treatment and 20 (23.0%) were discharged following treatment. Complications developed in a total of 6 (6.9%) during the PDT procedure in 2 patients in the form of minor bleeding, desaturation occurred in 2 patients, 1 patient developed subcutaneous emphysema, and 1 patient suffered esophageal perforation. A correlation could not be found between PDT and mortality (Table 1).

### Table 1. General characteristics of all the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD/Median (min-max)/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGE</strong></td>
<td>69 (11-92)</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>78 (50.00-96.00)</td>
</tr>
<tr>
<td><strong>HEIGHT</strong></td>
<td>168.50±8.86</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>27.51±4.10</td>
</tr>
<tr>
<td><strong>GENDER</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>53 (%60.9)</td>
</tr>
<tr>
<td>Female</td>
<td>34 (39.1%)</td>
</tr>
<tr>
<td><strong>COMPLICATION</strong></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>81 (93.1%)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Desaturation</td>
<td>2 (2.3%)</td>
</tr>
<tr>
<td>Subcutaneous emphysema</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Esophageal perforation</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td><strong>OUTCOME</strong></td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>20 (23.0%)</td>
</tr>
<tr>
<td>Death</td>
<td>67 (77.0%)</td>
</tr>
</tbody>
</table>

In the comparison of the NONSURVIVOR and SURVIVOR groups, no differences were observed in terms of age, diagnosis, gender, weight, height, BMI, day of PDT, or complications. On the other hand, significant statistical differences were found between the two groups in terms of days in intensive care (Z=-2.751, p=0.006), preoperative neutrophil count (Z=-2.048, p=0.041) and postoperative NLR (Z=-2.048, p=0.041). It was seen that in the NONSURVIVOR group, patients had been in the hospital for a longer period and their NLR values after the procedure were higher. It was however observed that there were no differences between the groups in terms of the other laboratory parameters (Table 2).

When the blood values of the patients in the SURVIVOR group before and after PDT were compared, it was noted that there were no statistical differences between the measured parameters (Table 3).
Differences were seen in the pre- and postoperative blood parameters of the patients in the NONSURVIVOR group in terms of lymphocyte count \( (Z=-3.859, p<0.001) \), MPV \( (Z=-3.098, p=0.002) \) and PLR \( (Z=-3.623, p<0.001) \) values. In this group, it was observed that the patients' lymphocyte count had risen postoperatively but that MPV and PLO values had fallen (Table 4).

The results of the correlation analysis of the data belonging to all of the patients revealed a positive correlation between the prognosis and the neutrophil count \( (r=0.221, p=0.040) \) and between the prognosis and post-PDT NLR \( (r=0.221, p=0.040) \), but a negative correlation between the prognosis and the time in intensive care \( (r=-0.300, p=0.005) \). Thus it was considered that prior to PDT, a high neutrophil count or a high NLR could point to a possible high risk of mortality. Furthermore, it was hypothesized that the mortality rate could decrease in cases where the patient's stay in the hospital was prolonged, ROC curve analysis showed that only the post-PDT NLR value, indicating 68.7% sensitivity and 60.0% specificity over the 6.91 cut-off point, could be a specific and sensitive biomedical marker and predictor of a prognosis that would end in mortality (Table 5, Figure 1).
The PDT procedure implemented during a patient’s treatment under intensive care facilitates weaning from a mechanical ventilator thanks to decreased pulmonary dead spaces, secretions and airway resistance, thus significantly reducing the risk of developing a hospital infection (5,8-10). At the same time, the capability of performing the procedure at bedside eliminates the need to transfer unstable and critical patients from the intensive care unit to the operating room (5,9,11,12). Moreover, it is known that PDT can produce serious, even life-threatening complications. Because of this, studies have been conducted about the use of various different PDT procedures in an effort to reduce risks (6). In a study by Kornblith et al. (13), the authors reported that PDT was performed 8.9±0.2 days after the patient’s presentation and that in addition, patients were connected to a ventilator for 9.7±0.4 days, that total time of ventilation was 21±0.6 days, time in the ICU being 29±0.6 days, time hospitalized, 35±0.8 days, and that the PDT-related complication rate was around 1.4%. The researchers reported further that the general mortality rate of the patients was 12% but that PDT-related mortality did not occur (13). Additionally, Karimpour et al. (6) revealed in their study that while the average duration of intubation of patients prior to PTD was 12 days, the success rate of weaning their patients from the ventilator in the first two weeks after the tracheostomy was 66.5%. The authors recorded a 16.7% rate of general perioperative and early complications, pointing out that most of these complications were minor and rapid recovery was achieved. On the other hand, 22.8% of patients died due to illness-related complications, with one patient expiring during the procedure (6). The literature refers generally to minor PDT-related complications, also indicating that sometimes 2%-20% of patients experience life-threatening complications such a major hemorrhage, hypoxia, accidental puncture of the ETT cuff (1.6%-6.6%), tracheal extubation (1.1%-3.3%), or airway obstruction (5,7). It has also been reported that subcutaneous emphysema and pneumothorax can develop in some patients (6,8,14). On the other hand, some studies have shown that complications are significantly reduced when PDT is performed by expert clinicians (15).

In our study, the number of pre-PDT intubation days was 12.27±8.39, which is consistent with the literature. Although there was 1 case (1.1%) of subcutaneous emphysema in our study and 1 case (1.1%) of esophageal perforation, there was no incident of pneumothorax. In 77% of the patients, death occurred as a result of existing illness and only 6 (6.9%) suffered minor complications. No incident of death was seen due to major complications or as a result of the procedure.
Previous studies demonstrated that neutrophil-to-lymphocyte ratios (NLR) and platelet-to-lymphocyte ratios (PLR) could be useful parameters for predicting prognosis and mortality in various diseases (16-18). Our aim in the study was to contribute to the literature by setting forth the relationship between mortality rates and the biochemical laboratory values we included in our investigation and to explore possible parameters that could be predictive of patient mortality. Toward this objective, when we compared the blood count results obtained from the patients before and after the PDT procedure, we found that the preoperative neutrophil and postoperative NLR results of patients who died at the hospital were significantly higher than those of patients who had been discharged from the hospital. Furthermore, when the parameters of the non-survivors measured before and after PDT were compared, it was observed that there had been a rise in neutrophil and lymphocyte counts and a decrease in MPV. It was seen that there was no significant change in the blood parameters of the discharged patients. On the other hand, in the correlation analysis, a positive correlation was observed between the patients’ prognosis and their neutrophil count prior to PDT and between the prognosis and the NLR obtained after the PDT procedure. It was considered that in cases where the neutrophil count was high prior to the procedure or where the NLR had increased after the procedure, the mortality rate was likely to rise in these patients. The ROC-Curve analysis performed to explore this consideration indicated that when the NLR obtained post-PDT was higher than 6.91, predictivity for a prognosis that would end in mortality could be made at 68.7% sensitivity and 60.0% specificity. As a result, it was proposed that NLR values obtained following the PDT procedure could be a specific and sensitive prognostic biomarker in predicting patient mortality. It was argued in our study that the statistically significant rise in the neutrophil and lymphocyte counts of the patients on the day following the day of the procedure could have been a secondary effect of the PDT. However, it was noted that the NLR values of these patients had not changed after the procedure and that on the contrary, their PLR values had fallen. It was considered that this fall could be a result of the increase in the lymphocyte count and the unchanged platelet count. On the other hand, although the postoperative NLR had not changed, the correlation analysis pointed to a positive correlation between the patient’s prognosis and their NLR values. The ROC-Curve test then performed showed that if NLR was greater than 6.31, the possibility and risk of death could increase for these patients. It was thought therefore that a fatal prognosis could stem from the increase in the neutrophil count or an increase in the lymphocyte count or from both and that the cause of the mortality risk for these patients was secondary to developing inflammatory reactions. Indeed, it was seen that 1 day after the procedure, the results of the blood tests showed that a procedure-related cellular inflammatory response had developed. It was however considered that this response would be more pronounced in patients who were given a fatal prognosis. In light of these findings, it was argued that a high postoperative neutrophil and/or a low lymphocyte count could be predictive of an increase in NLR and in this case, this would indicate a high risk of mortality for these patients. In addition to these hypotheses, it was further observed that the hospital stays of the patients who died at the hospital were statistically and significantly shorter than the patients who had been discharged. It was considered that the inflammatory response developing after the procedure may have acted as a factor in this and could have had an adverse effect on the patient’s treatment process. In fact, it had been discovered that the preoperative neutrophil counts of the patients in the mortality group had been high. This suggested that the PDT procedure performed had an additional inflammatory effect on the existing inflammation, one to which the patients in this condition had difficulty responding to, all of this having a secondary influence in shortening their lives.

Limitations
There are various limitations to be noted in this study. The first is that although the blood counts of the patients were examined, no serum biochemical laboratory parameters were included in the study. Secondly, the patient population consisted of patients suffering from different illnesses and the impact of these diseases on mortality was not examined. However, patients are stable in terms of additional diseases immediately before and after the tracheostomy procedure. Thirdly, the blood oxygenation rates of the patients for the patients before, during and after the procedure were not taken into account. On the other hand, despite all these limitations, it can be said that the results obtained from the research are interesting and original and for this reason, the study is a pioneering work that will likely form the foundation for more advanced research on the subject.

CONCLUSION
The result of this pilot study was the emergence of an argument to be made for the fact that postoperative NLR levels of patients undergoing percutaneous tracheostomy may be used as a prognostic biomarker in predicting the risk of mortality.
ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Clinical Researchs Ethics Committee (Permission granted 06.06.2018 Decision No. 206.06.08).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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.

REFERENCES