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Relationship Between Driving Pressure Measured During First 24 Hours and Mortality in Pediatric Critical Care Patients

Pediatrik Yoğun Bakım Hastalarında İlk 24 Saatte Ölçülen Sürüş Basıncı ile Mortalite Arasındaki İlişki

ABSTRACT *Objective:* Respiratory failure is one of the most common causes of mortality in pediatric intensive care unit (PICU) patients. Adult and a small number of pediatric studies have also associated driving pressure with mortality in ARDS patients, but studies showing the relationship between driving pressure and mortality in patients without ARDS are inconsistent and limited. This study aimed to determine whether driving pressure was associated with mortality in pediatric patients diagnosed as pediatric ARDS (pARDS) and non-pARDS who received mechanical ventilation support due to respiratory failure.

Materials and Methods: Mechanically ventilated patients were recorded if the foreseen ventilation duration was more than 24 hours. Driving pressure and other ventilator parameters of patients in the pARDS and non-pARDS groups were compared with their 30-day mortality.

Results: A total of 116 children were included in our study. 34 patients were classified in pARDS group, whereas 82 patients werein non-PARDS group. All patients'first day of mechanical ventilation parameters [ΔP (p<0,001), PIP (p<0,001), Pplat (p<0,001), Pmean (p=0,008), Cstat (p<0,001), Cstat/IBW (p<0,001), FiO2 (p=0,001)] werefound to be associated with hospital mortality. Driving pressure and other ventilator parameters associated with mortality in the univariate analysis were further evaluated by logistic regression analysis and driving pressure was determined as the most associated ventilator parameter with mortality (OR=1,51, 95% Cl 1.24 to 1.82, p = <0.001). We assessed independently the relationship between ΔP and mortality in patients non-pARDS and pARDS and we found ΔP was related to mortality in both patients (OR=1,59, 95% Cl 1.06 to 2.36, p <0.022) and non-ARDS patients (OR=1,47, 95% Cl 1.09 to 1.98, p <0.010). We identified a driving pressure cut-off value of 14,5 cmH2O for all patient groups.

Conclusion: Driving pressure was significantly associated with an increased risk of mortality among mechanically ventilated both pARDS and non-pARDS patients.

Keywords: Driving pressure, pediatric intensive care unit, mortality, pediatric acute respiratory distress syndrome

ÖZ *Amaç:* Solunum yetmezliği, çocuk yoğun bakım ünitesi (ÇYBÜ) hastalarında en sık ölüm nedenlerinden biridir. Yetişkin ve az sayıda pediatrik çalışma da ARDS hastalarında sürüş baskısı ile mortaliteyi ilişkilendirmiştir, ancak ARDS'si olmayan hastalarda sürüş basıncı ile mortalite arasındaki ilişkiyi gösteren çalışmalar tutarsız ve sınırlıdır. Bu çalışmada solunum yetmezliği nedeniyle mekanik ventilasyon desteği alan pediatrik ARDS (pARDS) ve non-pARDS tanılı pediatrik hastalarda sürüş basıncının mortalite ile ilişkisinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Öngörülen ventilasyon süresi 24 saatten fazla mekanik ventilasyon uygulanan hastalar kaydedildi. pARDS ve non-PARDS gruplarındaki hastaların sürüş basıncı ve diğer ventilatör parametreleri 30 günlük mortaliteleri ile karşılaştırıldı.

Bulgular: Çalışmamıza toplam 116 çocuk dahil edildi. 34 hasta pARDS grubunda sınıflandırılırken, 82 hasta PARDS dışı gruptaydı. Tüm hastaların mekanik ventilasyonun ilk günü parametreleri [ΔP (p<0,001), PIP (p<0,001), Pplat (p<0,001), Pmean (p=0,008), Cstat (p<0,001), Cstat/IBW (p<0,001), FiO2 (p=0,001)] hastane mortalitesi ile ilişkili bulunmuştur. Tek değişkenli analizde mortalite ile

ilişkilendirilen sürüş basıncı ve diğer ventilatör parametreleri, lojistik regresyon analizi ile ayrıca değerlendirildi ve sürüş basıncı, mortalite ile en ilişkili ventilatör parametresi olarak belirlendi (OR=1,51, %95 GA 1,24 - 1,82, p = < 0,001). pARDS ve pARDS olmayan hastalarda ΔP ile mortalite arasındaki ilişkiyi bağımsız olarak değerlendirdik ve ΔP'nin hem PARDS hastalarında (OR=1,59, %95 GA 1,06 - 2,36, p <0,022) hem de non-PARDS hastalarda mortalite ile ilişkili olduğunu bulduk. (OR=1,47, %95 GA 1,09 - 1,98, p <0,010). Tüm hasta grupları için 14,5 cmH2O'luk bir sürüş basıncı kesme değeri belirledik. *Sonuç:* Sürüş basıncı, mekanik olarak ventile edilen hem pARDS hem de pARDS olmayan hastalarda artan mortalite riski ile anlamlı şekilde ilişkiliydi. **Anahtar Kelimeler:** Sürüş basıncı, pediatrik yoğun bakım ünitesi, mortalite, pediatrik akut solunum sıkıntısı sendromu

Introduction

Respiratory failure is one of the most common causes of both hospitalization and mortality in patients in the pediatric intensive care unit (PICU). Although positive pressure mechanical ventilation is a life-saving treatment, it has been shown to have risks of morbidity and mortality due to complications. Although there is a consensus on mechanical ventilation in adult patients, this knowledge should be reflected with concrete data to the pediatric population (1,2,3,4). Mechanical ventilation with high tidal volumes may damage the lung through alveolar overdistension (volutrauma and barotrauma) and by causing the release of inflammatory cytokines (biotrauma) into the systemic circulation (5.6). Recently, it has been recommended to target driving pressure (ΔP) in patients with ARDS to achieve better results with the administration of optimal mechanical ventilation (7,8,9,10). ΔP is calculated as the difference between Plateau pressure (Pplat) and positive end-expiratory pressure (PEEP) and is determined by the ratio of the tidal volume to the compliance of the respiratory system ($\Delta P =$ Pplat –PEEP). ΔP estimates how much mechanical strain (dynamic strain) the tidal volume causes in the lung. It is a non-invasive and simple method and can be easily calculated at the bedside (10,11,12). In many studies, higher ΔP was associated with mortality in adult ARDS patients; non-ARDS patients' studies showing the relationship between driving pressure and mortality are few, but contradictory results have come out (13,14,15,16,17,18).

This study aimed to determine whether ΔP was associated with mortality in pediatric patients diagnosed as pARDS and non-pARDS who received mechanical ventilation support due to respiratory failure.

Materials and Methods

This is a single-center, prospective, observational study of patients admitted to the pediatric intensive care unit (PICU). The study protocol was approved by the local ethics committee (protocol no: 2019-344). In our study, patients who received invasive mechanical ventilation support due to respiratory failure in the pediatric intensive care unit older than 1 month and younger than 18 years were included in the study between March 2018 and April 2020. Patients receiving ventilation through a tracheostomy cannula at any time during the first 24 hours of ventilation, and patients who were extubated or died during the first 24 hours were excluded.

Mechanically ventilated patients were included in the study analysis if they had a ventilation duration of at least 24 hours. We divided the patients into two groups by calculating the oxygenation index (OI): [mean airway pressure (MAP) fraction of inspired oxygen (FiO2)]/ partial pressure of oxygen in arterial blood (PaO2) -100) used in the classification of PALICC, including ARDS and non-ARDS. PARDS definition was also identified based on the PALICC criteria (3). Data were prospectively recorded on day 1 including patient demographics, ventilator settings (VT, VT / ideal body weight (IBW), respiratory rate (RR), peak inspiratory *pressure* (PIP), plateau pressure (Pplat), mean airway pressure (Pmean), minute volume (VE), end-expiratory pressure (PEEP), static compliance (Cstat), fraction of inspired oxygen FiO2, inspiratory time (IT), expiratory time (ET) and we calculated oxygenation index (OI), cstat (VT/ ΔP), partial pressure of oxygen in arterial blood (PaO2) /FiO2, driving pressure (ΔP) , the pediatric index of mortality (PRISM) III scores and pediatric sequential organ failure assessment (pSOFA) scores.

All patients were ventilated with pressure control (PCV) mode during the hospitalization. All mechanical ventilator data were recorded 2 times in 24 hours. To measure the driving pressure of patients, Pplat was measured in the mechanical ventilator every 12 hours using an inspiratory hold maneuver. The average Pplat was calculated using the mean of 2 measurements within 24 hours. Then, the total PEEP was measured by expiratory hold maneuver. The average total PEEP was calculated using the mean of 2 measurements within 24 hours and ΔP was calculated with the Pplat-PEEP formula. Neuromuscular blocking agents

were applied to all patients before measurements. Patients were followed for 30 days until hospital discharge. We used ΔP compared to other mechanic ventilator parameters, between survivors and nonsurvivors at day 30. Besides, ΔP and other parameters of patients in the ARDS and non-ARDS groups were compared with their 30-day mortality.

Statistical Analysis

Primarily, we evaluated the relationship between ΔP and mortality in patients with ARDS and non-ARDS. Our second target was to evaluate the relationship between mortality and ΔP and other mechanical ventilator parameters. Driving pressure and other lung dynamics; according to the type and distribution of the data was compared with chisquare, Wilcoxon, Independent-T-test or Mann-Whitney-U test, and p <0.05 was considered statistically significant. The strength of the association between the two variables was measured using the correlation coefficient. We used Pearson correlation to the parametric variable and Spearman correlation to the nonparametric variable to detect covariances before logistic regression analysis. We evaluated the variables with Spearman's correlation analysis to detect covariances before logistic regression analysis. Parameters found significant with mortality in univariate analyses were evaluated by Logistic Regression analysis. (odds ratio [OR] and 95 % confidence intervals [CI]) Model fit was assessed using Hosmer-Lemeshow statistics. For the multivariable analysis, we identified covariates that may be associated with mortality. VT /IBW, PaO2, OI, FiO2, PRISM III score, Days of ventilation, and pSOFA score were not collinear with ΔP . We did not include Pplat, PIP, or Pmean in logistic regression models containing ΔP given concerns for collinearity Individual covariates included age, gender, PRISM III score, PaO2, OI, FiO2, Days of ventilation, and pSOFA score were not collinear with ΔP . We created 3 other modeling analyses for Pplat, PIP, and Pmean, because of collinearity with driving pressure. We evaluated this model to determine the best parameter related to 30-day mortality in whole patients under mechanical ventilation support due to respiratory failure. ΔP cut-off values in our study were categorized and mortality was estimated by a receiver operating characteristic (ROC) (19,20). We performed all statistical analyses using IBM SPSS Statistics for Windows version 22 (Armonk, NY) for analysis.

Results

Between March 2018 and April 2020, 263 patients received invasive mechanical ventilation support in our pediatric intensive care unit. 144 patients who did not meet the inclusion criteria were excluded from the study. A total of 116 children were included in our study. Median mechanical ventilation duration was 7 days (IQR, 9-14 days). Sepsis (31.8%) was the most common reason for patients' need for mechanical ventilation. followed by lower respiratory tract infection (28.4%). 34 patients were classified in the pARDS group, whereas 82 patients were in the non-pARDS group. Patients with pARDS or non-pARDS had no statistically significant pSOFA values (p-value:0,063), however, patients with pARDS had higher PRISM III scores (p-value < 0.001) than non-pARDS patients (P<0.010). Characteristics were reported in (Table I).

Seventeen patients had mild pARDS, 9 had moderate and 8 had severe pARDS. There were no differences in admission diagnosis and mortality at day 30 between the ARDS subgroups. There were 93 survivors and 23 nonsurvivors at 30 days. The comparison between survivors and non-survivors at day 30 is shown in (Table II).

All patients' mechanical ventilation parameters on the first day were [ΔP (p<0,001), PIP (p<0,001), Pplat (p<0,001), Pmean (p=0,008), Cstat (p<0,001), Cstat/IBW (p<0,001), FiO2 (p=0,001)] associated with hospital mortality. OI, PaO2, and days of ventilation were also associated with 30-day mortality in all patients (p<0,001, p=0,008, p=0,010, respectively). There was no significant association between VT/IBW (p=0,292), IT (p=0,986), ET (p=0,551), PEEP (p<0,221), RR (p=0,862), and 30-day mortality in all patients

Our aim in the primary regression model was to determine the effect of ΔP on 30-day mortality in all patients and the mechanical ventilator parameter most associated with 30-day mortality. Secondarily we aimed to determine the association of ΔP with 30-day mortality in patients with ARDS and non-ARDS. As the collinearity between ΔP , PIP, Pplat, and Pmean was statistically significant, a logistic regression model was constructed for each of these variables (Table III). ΔP was most associated with 30-day mortality (OR=1.51, 95% Cl 1.24 to 1.82, p = <0.001). Pmean was not associated with 30-day mortality in all patients. (OR=1.31, 95% Cl 0.98 to 1.73, p = 0.062). we conducted separately to determine the relationship between ΔP and mortality in patients non-ARDS and ARDS, we found ΔP related to

Table 1. Demographic and clinical characteristics with pARDS and non-pARDS patients						
Characteristic	pARDS patients (n=34)	Non-pARDS patients (n=82)	p-value			
Age (months)	15.6 (9-35)	13,5 (7-24.4)	0.117			
Female gender, n (%)	17.0 (50%)	34,0 (41.5%)	0.401			
Days of ventilation	13.1 (8.6-17.0)	8.5 (6.3-12.1)	0.010			
Admission diagnosis, n (%) Sepsis Pneumonia Neurological diseases Cardiological diseases Hematologic diseases Post-surgery Immun deficiency	12 (32.4%) 25 (30.5%) 10 (29.5%) 23 (28.1%) 9 (26.5%) 25 (30.5%) 1 (2.9%) 3 (3.7%) 1 (2.9%) 2 (2.4%) 1 (2.9%) 2 (2.4%) 1 (2.9%) 2 (2.4%)					
30-day mortality, (n) %	8 (23.5%)	15 (18.2%)	<0.001			
pARDS n (%) Mild pARDS n (%) Moderate pARDS n (%) Severe pARDS n (%)	17 (50.0%) 9 (26.5%) 8 (23.5%)					

Parametric data are presented as means	1 standard deviation or non-parametric data presented as median (first and third quartiles)

Table 2. Mechanical ventilator parameters and clinical findings of all patients according to hospital mortality						
Variable	Survivors at day 30 (n=93)	Non-survivors at day 30 (n=23)	p-value			
VT (mL)	71.9 (51.3-108.5)	82.0 (61.5-120.9)	0.180			
VT/IBW (mL/kg)	7.0 (6.0-8.1)	6.5 (5.0-9.0)	0.292			
VE (L/min)	2.8 (2.1-4.1)	2.3 (1.7-3.8)	0.117			
RR (bpm)	34.0 (34.0-40.0)	35.0 (30-42)	0.862			
PIP (cm H ₂ O)	23.6 (19.5-26)	29.0 (25.0-34.0)	<0.001			
P _{plat} (cm H ₂ O)	21.0 (19.0-25.0)	28.0 (24.033.0)	<0.001			
PEEP (cm H ₂ O)	7.0 (6.0-9.0)	7.0 (6.0-7.0)	0.221			
$\Delta P (cm H_2O)$	16.0 (13.0-18.0)	23.0 (19.0-26.0)	<0.001			
P _{mean} (cm H ₂ O)	11.7 (10.3-13.6)	13.1 (12.2-18.2)	0.008			
C _{stat} (mL/cmH ₂ O)	5.7 (3.5-8.1)	2.8 (2.0-5.7)	<0.001			
C _{stat} /IBW (mL/cmH ₂ O/kg)	0.4 (0.3-0.6)	0.3 (0.2-0.4)	<0.001			
IT (s)	0.6 (0.5-0.7)	0.6 (0.5-0.9)	0.986			
ET (s)	1.1 (0.9-1.3)	1.1 (0.8-1.2)	0.551			
FiO ₂ (%)	35.0 (30.0-44.0)	40.0 (40.0-60.0)	0.001			
OI	3.3 (2.5-3.7)	4.8 (3.2-12.1)	<0.001			
PaCO ₂ (mmHg)	48.0 (±6.7)	50.3 (±7.6)	0.225			
PaO ₂ . (mmHg)	122.3 (±26.4)	100.7 (±28.7)	0.008			
Days of ventilation	10.5 (7.0-13.5)	8.0 (7.0-15.0)	0.010			
PRISM III score	5.0 (2.3-8.8)	7.3 (2.0-10.0)	<0.001			
pSOFA score	5.0 (4.0-7.0)	6.0 (5.0-9.0)	0.063			

Parametric data are presented as mean±1 standard deviation or non-parametric data presented as median (first and third quartiles),V₁⁻ Tidal volume, V₁/IBW: Tidal volume/ ideal body weight, RR: Respiratory rate, *PIP: Peak* inspiratory *pressure*, P_{pat}: Plateau pressure, P_{mea}: Mean airway pressure, V_E. Minute volume, PEEP: Positive end-expiratory pressure, C_{stat}: Static compliance, FiO₂: fraction of inspired oxygen IT: *Inspiratory time*, ET: *Expiratory time*, OI: Oxygenation index, ΔP: Driving pressure, C_{stat}: Static compliance, FiO₂: Fraction of mortality scores, MV: Mechanical ventilator, PaO₂: Partial pressure of oxygen mortality in both patients groups (OR=1,59, 95% CI 1.06 to 2.36, p <0.022) and non-ARDS patients (OR=1,47, 95%) CI 1.09 to 1.98, p <0.010) (Table IV). After evaluating the relationship between inspiratory airway pressures (ΔP , PIP, Pmean, Pplat) with 30-day mortality by logistic regression analysis, we also compared these 4 parameters with ROC analysis for ΔP area under the curve was 0.838 (95% Cl, 0,738-0,939, p <0.001), Pplat 0.770 (95% Cl, 0,662-0,878, p <0.001), PIP 0,762 (95% CI, 0,648-0,876, p <0.001) and Pmean 0,678 (95% CI, 0,558-0,798, p =0.008). When assessing the risk of death at each level of ΔP . We defined the cut-off value related to mortality of our study as 17 cmH2O in pARDS patients, 13 cmH2O in non-ards patients, and 14,5 cmH2O in all patients. We found the overall mortality rate to be 10,2 times higher for patients with ΔP greater than 14,5 cm H2O compared to patients whose ΔP was equal to below 14,5 cm H2O (OR=10,2, 95% CI 1.37 to 70,75, p <0.001).

Discussion

Mechanical ventilation is one of the most common indications for admission to a pediatric intensive care unit (PICU), with up to 64% of admitted children requiring mechanical ventilation (21,22). Driving pressure (Δ P), which is calculated as end-inspiratory plateau pressure (PEEP) and is equivalent to the ratio between the VT and compliance of the respiratory system, can reduce mortality in children who

received mechanical ventilator support due to respiratory failure. ΔP is a non-invasive and simple method and can be easily calculated at the bedside.

Recent data in the adult ARDS population have shown that the ΔP is most related to mortality (10,23). In our study, we have shown that the ΔP on day 1 was associated with hospital mortality in pARDS patients. PALICC has not yet recommended ΔP targeting in pARDS patients. The relationship between ΔP and mortality in patients with ARDS has been demonstrated. However, this relationship is not clear in patients without ARDS. Serpa Neto et al in their meta-analysis study; revealed that it caused higher postoperative lung complications with higher ΔP during general anesthesia (24). In two previous studies, ΔP was found to be unrelated to mortality in patients without ARDS (14,18). We have also shown that the ΔP on day 1 was associated with 30-day mortality in non-pARDS patients among mechanical ventilation support due to respiratory failure. We applied mechanical ventilation to the patients in our study group without determining a low tidal volume or ΔP target. Therefore, we think that ΔP increases mortality in patients diagnosed as non-ARDS as it will have higher inspiratory airway pressures in this group. Nowadays, regarding the importance of driving pressure and survival, many studies are being conducted (25,26,27,28,29). Many studies of ARDS revealed associations between VT and mortality in children (8,25,26). We did not observe a significant association between VT and mortality in pARDS and non-pARDS patients. This might explain why we found

Table 3. Multivariable logistic regression model at hospital mortality for ΔP , PIP, P_{plat} and P_{mean}											
Model 1			Model 2			Model 3			Model 4		
Variable	e OR (95% CI)	p-value	Variable	OR (95% CI) p	-value	Variable	OR (95% Cl) p	-value	Variable	OR (95% Cl) p	value
Age	1.01 (0.98-1.03)	0.304	Age	1.01(0.99-1.03)	0.313	Age	1.01 (0.98-1.03)	0.304	Age	1.00 (0.98-1.02)	0.494
Gender	0.16 (0.03-0.73)	0.018	Gender	0.28(0.06-0.85)	0.028	Gender	0.24 (0.86-1.06)	0.030	Gender	0.39 (0.12-1.22) 0.018
OI	0.68 (0.51-0.91)	0.011	ОІ	0.69 (0.52-0.92)	0.011	ОІ	0.68 (0.51-0.90)	0.008	ОІ	0.62 (0.42-0.91)	0.014
PaO ₂	0.98 (0.95-1.01)	0.302	PaO ₂	0.98 (0.95-1.01)	0.214	PaO ₂	0.98 (0.95-1.00)	0.182	PaO ₂	0.97 (0.94-1.00)	0.093
FiO2	1.13 (1.01-1.27)	0.032	FiO ₂	1.15 (1.03-1.28)	0.010	FiO ₂	1.15 (1.03-1.28)	0.011	FiO ₂	1.20 (1.07-1.35)	0.001
PRISM II	0.90 (0.77-1.05)	0.194	PRISM III	0.87 (0.76-1.01)	0.085	PRISM III	0.87 (0.76-1.01)	0.086	PRISM III	0.89 (0.77-1.03)	0.126
Day (MV) 0.90 (0.76-1.06)	0.901	Day (MV) 0.91 (0.78-1.05)	0.910	Day (MV) 0.90 (0.78-1.04)	0.184	Day (MV)	0.93 (0.82-1.05)	0.273
ΔΡ	1.51 (1.24-1.82)	<0.001	PIP	1.26 (1.10-1.44)	0.028	P _{plato} 1.	29 (1.12-1.50)	0.001	P _{mean} 1.	31 (0.98-1.73)	0.062
OR: Odd ratio, CI: Confidence interval, FiQ: Fraction of inspired oxygen OI: Oxygenation index, ΔP : Driving pressure, <i>PIP: Peak</i> inspiratory <i>pressure</i> , P _{plat} : Plateau pressure, P _{mean} : Mean airway pressure, <i>PRISM III</i> score: The pediatric index of mortality scores, MV: Mechanical ventilator, PaO,: Partial pressure of oxygen											

mortality in pARDS patients was associated with driving pressure and compliance.

Recent data in the adult ARDS population have shown that driving pressure is more closely related to mortality than inspiratory airway pressures (10,23). A few pediatric studies also revealed a linear association between mortality and peak inspiratory pressure (PIP) and Pplat (8,25). We found that patients with high inspiratory airway pressures (PIP, Pplat, Pmean, Δ P) were associated with 30-day mortality in our study.

In 4 different multivariate regression modeling, we found the strongest parameter with mortality as ΔP A 1-SD increment in ΔP (approximately 7 cmH2O) was associated with

a %51 increase in the risk of death (10). The cut-off points of ΔP varied, ranging from 13 to 21 cmH2O (10,27,28). We defined the cut-off value of our study as 17 cmH2O in ARDS patients, 13 cmH2O in non-ards patients, and 14,5 cmH2O in all patients.

Our work has several strengths. It is one of the few prospective studies investigating the association of ΔP with mortality in both patients with pARDS and those without pARDS. ΔP and other mechanical ventilator parameters were measured using holding maneuvers without patient effort and with detailed data.

Our study has limitations, Firstly; We did not analyze the mechanical ventilator settings except for the first 24 hours, and therefore, there may be changes in mechanical ventilator pressures in the following days depending on the patient's lung dynamics. Another limitation is that the single-center study can generate limited data.

Conclusion

In our prospective observational single-center study, driving pressure was found to be significantly associated with an increased risk of mortality among mechanically ventilated both pARDS and non-pARDS patients. Future prospective randomized multi-center clinical trials are needed to determine a protocol targeting ΔP that can be developed and define optimum cutoff values.

Ethics

Ethics Committee Approval: The study was conducted by the ethical standards stated in the 'Declaration of Helsinki'. The University of Health Sciences Turkey, Dr. Behçet Uz

Children's Diseases and Surgery Training and Research Hospital Clinical Research Ethics Committee approved the study (decision no: 2020/07-02, date: 07.05.2020).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.A., S.T., Concept: E.S., U.K., H.A., Design: E.S., G.C., M.Ç., H.A., Data Collection and Process: G.A., S.T., Ö.S.S., Analysis or Interpretation: M.Ç., P.H., F.S., Literature Search: E.S., P.H., Ö.S.S., U.K., Writing: E.S., G.C., U.K.

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