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Original Article

Comparison of The Effects of Epidural Analgesia and Conventional Analgesia on Survival in Patients Undergoing Gynecological Oncological Surgery: A retrospective analysis

Jinekolojik Onkolojik Operasyon Geçiren Hastalarda Epidural Analjezi ile Geleneksel Analjezinin Sağkalım Üzerine Etkileri Karşılaştırılması: Retrospektif Bir Analiz

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Abstract

Purpose: We aimed to determine whether mortality due to gynecologic cancer differs in patients who received epidural analgesia versus conventional analgesia. Additionally, we aimed to investigate which analgesia approach results in a better prognosis for gynecologic cancer.

Materials and Methods: Patients who underwent surgery for a gynecologic malignancy were divided into two study groups based on the type of analgesia used: the Epidural Analgesia Group (n=120) and the Conventional Analgesia Group (n=88). All data were retrospectively collected from patient case charts. Variables recorded included patients' age, body mass index (BMI), presence of comorbid diseases, duration of anesthesia, amount of blood transfusion. During surgery, duration of hospital stay, duration of intensive care unit stay, presence of postoperative infection, and type of postoperative treatment.

Results: Survival after surgery tended to be higher in patients who received conventional analgesia (81 out of 88 patients) compared to those who received epidural analgesia (102 out of 120 patients), although this difference was not statistically significant (p=0.123). After controlling for all other factors, the coefficient for blood transfusion was -0.192 with a p- value of 0.007, indicating that a lower amount of blood transfusion was associated with increased survival. Similarly, the coefficient for the presence of comorbid diseases was -0.163 with a p-value of 0.022, suggesting that fewer comorbidities contributed to better survival post-surgery. Conventional analgesia showed higher survival rates (coefficient=0.163,p=0.022) compared to epidural analgesia. None of the other variables showed a significant correlation with survival.

Conclusion: This study is among the pioneering research efforts to explore the impact of analgesia methods on the prognosis of patients with non-metastatic gynecologic cancer. A lower amount of blood transfusion during surgery and fewer comorbid diseases contribute to improved survival rates.

Keywords: analgesia; epidural; prognosis

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Öz

Amaç: Epidural analjezi ve geleneksel analjezi uygulanan hastalarda jinekolojik kansere bağlı mortalitenin farklı olup olmadığını belirlemeyi ve ikinci olarak hangi analjezi yaklaşımının jinekolojik kanser prognozunda daha iyi olduğunu araştırmayı amaçladık.

Gereç ve Yöntem: Jinekolojik malignite nedeniyle ameliyat edilen hastalar kullanılan analjezi tipine göre iki çalışma grubuna ayrıldı: Epidural analjezi grubu (n=120) ve geleneksel analjezi grubu (n=88). Tüm veriler geriye dönük olarak hasta çizelgelerinden toplandı. Hastaların yaşı, vücut kitle indeksi (BKİ), ek hastalık varlığı, anestezi süresi, ameliyat sırasında yapılan kan transfüzyon miktarı, hastanede kalış süresi, yoğun bakımda kalış süresi, ameliyat sonrası enfeksiyon varlığı ve ameliyat sonrası tedavi şekli kaydedildi.

Bulgular: Cerrahi sonrası sağkalım geleneksel analjezi uygulanan hastalarda (88 hastanın 81'i), epidural analjeziye (120 hastanın 102'si) göre istatistiksel olarak fark olmaksızın daha yüksek olma eğilimindeydi (p=0.123). Diğer tüm faktörler kontrol edildikten sonra kan transfüzyonunun katsayısı -0,192 ve p değeri 0,007, komorbid hastalık varlığı katsayısı -0,163 ve p 0,022 değerine sahipti. Daha az miktarda kan transfüzyonu ve daha az eşlik eden hastalık, ameliyat sonrası hayatta kalma oranının artmasına katkıda bulunur. Geleneksel analjezi, epidural analjeziye göre daha yüksek sağkalım (katsayı=0,163, p=0,022) gösterdi. Diğer değişkenler hayatta kalma ile anlamlı bir korelasyon göstermedi.

Sonuç: Bu çalışma, analjezi yönteminin metastatik olmayan jinekolojik kanserli hastaların prognozuna etkisini araştıran önde gelen çalışmalardan biridir. Ameliyat sırasında daha az kan transfüzyonu yapılması ve eşlik eden hastalıkların daha az olması sağkalımın artmasına katkıda bulunur.

Anahtar Kelimeler: analjezi; epidural; prognoz

1. Introduction

Gynecologic cancers account for 12-15% of cancers in women (1). These cancers are most commonly diagnosed during the postmenopausal period, with 21% occurring during the reproductive period (1,2). Cervical cancer is more prevalent in sexually active women, whereas endometrial cancer is more frequent in sexually inactive women and during the postmenopausal period. Gynecologic cancers refer to malignant tumors originating from female genital organs. Among gynecologic cancers, cancers of the uterine corpus, cervix, and ovaries constitute the majority. According to American literature, cancers of the uterine corpus rank first (51%) among gynecologic malignancies, followed by ovarian cancer (26%) and cervical cancer (15%) (2). In European literature, cancers of the uterine corpus rank 6th among all cancers in women but remain the most common among gynecologic cancers. Worldwide, cervical cancer is the most frequent gynecologic cancer (3). According to data from Turkey, the estimated annual number of diagnosed cases is 844 for cervical cancer and 1477 for endometrial cancer (4).

The primary determinant of prognosis, recurrence, and survival is the surgical stage of the tumor. In addition to this, factors such as histological type, myometrial invasion, grade, patient age, genetic structure, concurrent tumors, and additional pathologies may affect prognosis (5). Several reports suggest that anesthetic methods may also influence prognosis (6-9). Although these findings are preliminary, several meta-analyses have supported this assertion. Regional anesthesia is believed to reduce surgery-induced stress and opioid use, leading many to argue that it lowers the risk of cancer recurrence (6).

We aimed to investigate whether mortality from gynecologic cancer differs between patients receiving conventional analgesia and those receiving epidural analgesia. Therefore, this retrospective study was conducted to determine which analgesic approach yields better prognosis for gynecologic cancer.

2. Methods

Study Design: The study was conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board (KAEK No: 107, Date: 11/05/2022). Our study included patients who underwent gynecological oncological surgery in a single center at the tertiary level Kanuni Sultan Süleyman Training and Research Hospital between 2015 and 2017. Written informed consent was obtained from all subjects. This is a comparative study involving 208 patients who underwent surgery for gynecologic malignancy. Patients were divided into two study groups based on the type of analgesia used: Epidural analgesia group (EA Group) (n=120) and conventional analgesia group (CA Group) (n=88).

Patient Selection Criteria: Patients with American Society of Anesthesiologists (ASA) physical status I–III, aged between 20 and 80 years, and scheduled for gynecological oncological surgery were included in the study. Patients with coagulopathy,

drug allergies, ASA IV status, and those undergoing laparoscopic surgery were excluded.

Anesthesia and Analgesia Protocol: All patients received general anesthesia. An epidural catheter was placed at the lumbar 2-3 or 3-4 interspace before induction of general anesthesia. The position and function of the epidural catheters were confirmed with a test dose of 2-3 ml of 2% lidocaine.No complications developed in the patients who received epidural analgesia; only those whose epidural catheter did not work were excluded from the study.

General anesthesia induction was performed using the following medications: Dormicum 0.15 mg/kg (Midazolam, 50 mg/10 ml, Deva Holding, Istanbul, Turkey), Propofol 1.5–2 mg/kg (Propofol 200 mg/20 ml, Sandoz, Switzerland), Talinat 1–2 µg/kg (Fentanyl 0.5 mg/10 ml, Vem Pharmaceutical Industry, Istanbul, Turkey), and Esmeron 0.6 mg/kg (Rocuronium Bromide 50 mg/5 ml, Merck Sharp Dohme, USA). Maintenance of general anesthesia was continued with Sevorane (Sevoflurane, Abbott, Istanbul, Turkey), Ultiva (Remifentanil 2 mg, VLD Medical Products, Istanbul, Turkey), and a mixture of oxygen and air.

Patients in the conventional analgesia group received Contramal (Tramadol HCl 100 mg, Abdi Ibrahim, Istanbul, Turkey), Deksalgin (Dexketoprofen 50 mg/2 ml, Nobel, Istanbul, Turkey), and Parol (Paracetamol 10 mg/ml, Atabay, Istanbul, Turkey) 15 minutes before the end of general anesthesia. Patient-controlled epidural analgesia (PCEA) was initiated half an hour before the end of surgery. The PCEA protocol was as follows: Marcaine 0.5% 100 mg (Bupivacaine 5 mg/flacon, AstraZeneca, Kirklareli, Turkey) mixed with Talinat 200 micrograms in 100 ml of isotonic saline. The lockout interval was set at 30 minutes, and the infusion rate was 2 ml/hour. PCEA was continued for 3 days. Additional analgesics, such as opioids or paracetamol, were administered as needed.

Outcome Parameters: All data were retrospectively collected from patient case charts. Patient age, body mass index (BMI), presence of comorbid diseases, duration of anesthesia, amount of blood transfusion during surgery, duration of hospital stay, duration of intensive care unit stay, presence of postoperative infection, and type of postoperative treatment (chemotherapy vs. radiotherapy/brachytherapy) were recorded.

Statistical Analyses: Data were analyzed using IBM Statistical Package for Social Sciences v20 (SPSS Inc., Chicago, IL, USA). Normal distribution of quantitative data was assessed using the Kolmogorov-Smirnov test. Parametric tests were applied to normally distributed data, while non-parametric tests were used for data with questionable normal distribution. Independent-samples t-test and Mann-Whitney U-test were used to compare independent groups. Distribution of categorical variables in both groups was compared using the Pearson chi-square test. Partial correlation tests were used to calculate correlation coefficients. Logistic regression was performed to identify risk factors for overall survival. Data are presented as mean ± standard deviation (SD) or median (interquartile range), as appropriate. Statistical significance was defined as $p \leq 0.05$.

3. Results

Demographic Data: Demographic characteristics are presented in Table 1. No significant differences were observed between the groups except for anesthesia duration, amount of blood transfusion during surgery, and receipt of postoperative radiotherapy/brachytherapy treatment. Anesthesia duration was significantly longer in the epidural analgesia (EA) Group compared to the conventional analgesia (CA) Group (217.2 ± 83.9 vs. 168.5 ± 62.53 minutes, $p < 0.001$). The amount of blood transfusion during surgery was higher in the EA Group than in the CA Group, although this difference was not statistically significant ($p = 0.063$). A total of 26 patients in the EA Group and 9 patients in the CA Group received radiotherapy/brachytherapy treatment ($p = 0.029$).

Outcome: Survival assessment was performed for 3 years after the operation. Survival tended to be higher in patients who received conventional analgesia (81 out of 88 patients) compared to those who received epidural analgesia (102 out of 120 patients). Survival rates were 92.05% for conventional analgesia and 85% for epidural analgesia. However, there was no statistically significant difference ($p = 0.123$) (Table 2)

Logistic regression analysis for survival: All variables were included in logistic regression analysis for survival (Figure 1, Figure 2). The odds ratio for blood transfusion was 0.872 ($p = 0.044$). A lower amount of blood transfusion during surgery was identified as the primary factor contributing to increased survival following surgery (Table 3).

To accurately assess the relationship between two variables, we eliminated the influence of other variables using partial correlation analysis. Table 4 presents the results: after controlling for all other factors, blood transfusion had a coefficient of -0.192 and a p-value of 0.007, while the presence of comorbid diseases had a coefficient of -0.163 and a p-value of 0.022. A lower amount of blood transfusion and fewer comorbid diseases were found to contribute to increased survival following surgery.

Conventional analgesia showed higher survival (coefficient = 0.163, $p = 0.022$) compared to epidural analgesia. Other variables did not show a significant correlation with survival.

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Table 1. Demographic data				
		Epidural (n=120)	**Conventional (n=88)**	***p* Value**
Age (years) *mean±SD*		57.5±16.88	53.4±14.62	0.068
BMI (kg/m^2) *median (IQR)*		28.13 (4.1)	28.68 (5.2)	0.064
Comorbid diseases	Hypertension *(n)*	29	11	0.335
	Diabetes mellitus *(n)*	2	3	
	Congestive heart failure *(n)*	4	1	
	Asthma *(n)*	3	3	
Anesthesia time (minutes) *mean±SD*		217.2±83.9	168.5±62.53	<0.001
Hospital stay (days) *median (IQR)*		8.0 (7.0)	7.5 (5.0)	0.196
ICU: Intensive care unit stay (days) *median (IQR)*		0.0 (1.0)	0.0 (1.0)	0.639
Blood transfusion (units) median (IQR)		0.0 (4.0)	0.0 (2.0)	0.063
Postoperative infection	Wound site infection *(n)*	11	4	0.655
	Urinary tract infection *(n)*	2	2	
	Pulmonary infection *(n)*	7	4	
Postoperative treatment	Chemotherapy *(n)*	34	16	0.091
	Radiotherapy/Brachytherapy *(n)*	26	9	0.029
BMI: Body mass index; SD: Standard deviation; IQR: Interquartile range				

Table 2. Comparison of overall survival according to analgesia type			
	Epidural (n=120)	**Conventional (n=88)**	***p* Value**
Survival (n)	102	81	0.123
Dead (n)	18	7	
Total (n)	120	88	

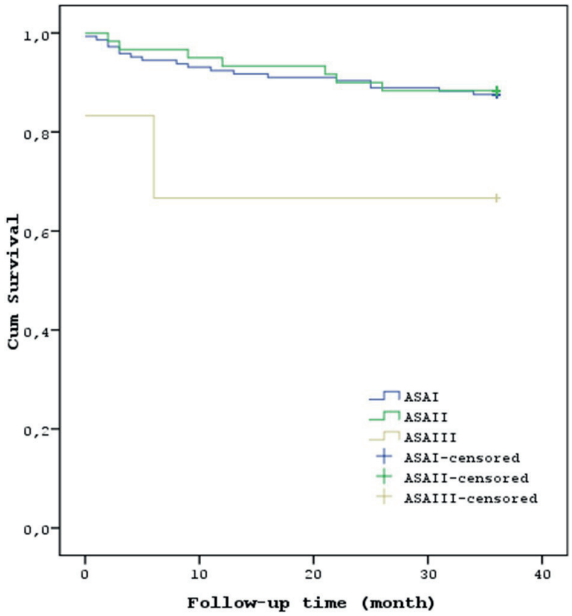

Figure 1. The ROC analysis for ASA score

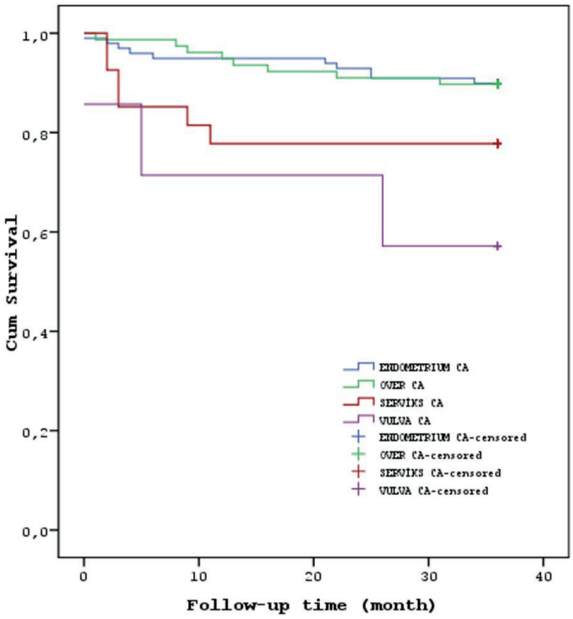

Figure 2. The ROC analysis for gynecological cancers

Table 3. Logistic regression analysis for overall survival			
		Odds ratio	***p* Value**
Age (years)		0.979	0.282
Weight (kg)		1.025	0.197
Height (cm)	Hypertension	0.966	0.251
Comorbid diseases	Diabetes mellitus	5.129	0.210
	Congestive heart failure	5.681	0.211
	Asthma	1.616	0.999
		3.848	0.439
Analgesia type (epidural / conventional)		0.759	0.638
Anesthesia time (minutes)		0.999	0.671
Hospital stay (days)		0.980	0.077
Intensive care unit stay (days)		0.845	0.409
Blood transfusion (units)		0.872	0.044
Postoperative infection	Wound site infection	1.083	0.937
	Urinary tract infection	0.668	0.723
	Pulmonary infection	5.190	0.999
Postoperative treatment	Chemotherapy	1.526	0.449
	Radiotherapy/Brachytherapy	1.516	0.496

Table 4. Partial correlation analysis with overall survival				
		Control variables	**coefficient**	***p* Value**
Age (yr)		All other variables	-0.030	0.680
Weight (kg)			-0.085	0.235
Height (cm)			-0.022	0.755
Comorbid diseases			-0.163	0.022
Analgesia type (epidural / conventional)			0.163	0.022
Anesthesia time (minutes)			-0.115	0.108
Hospital stay (days)			-0.134	0.060
Intensive care unit stay (days)			-0.077	0.279
Blood transfusion (units)			-0.192	0.007
Postoperative infection			-0.001	0.990
Postoperative treatment	Chemotherapy		0.114	0.109
	Radiotherapy/Brachytherapy		0.076	0.289

Diagnosis rates of patients: 46.9% Endometrial CA, 37.0% Ovarian CA, 12.8% Cervical CA, and 3.3% Vulvar CA. Epidural/ Traditional analgesia types: 51.5%/48.5% in patients with Endometrial CA, 60.3%/39.7% in patients with Ovarian CA, 70.4%/29.6% in patients with Cervical CA, and 57.1%/42.9% in patients with Vulvar CA. There was no statistically significant difference in analgesia types across diagnoses (p = 0.303) (Table 5).

Tablo 5. The relationship between cancer type and analgesia type							
Diagnosis	**Total**		**Type of analgesia**				
			Epidural		**Conventional**		
	n	**%**	**n**	**%**	**n**	**%**	**P**
Endometrial CA	99	46,9	51	51,5	48	48,5	0,303
Ovarian CA	78	37,0	47	60,3	31	39,7	
Cervical CA	27	12,8	19	70,4	8	29,6	
Vulvar CA	7	3,3	4	57,1	3	42,9	
Total	211	100	121	57,3	90	42,7	

Tablo 6. The relationship between cancer type and preoperative and postoperative hemoglobin values					
	PRE-OP HBG		**POST-OP HBG**		
	Mean ± SD	**Min-Max (Median)**	**Mean ± SD**	**Min-Max (Median)**	**P**
Total	11,5±1,9	6,9-16,5 (11,6)	10,6±1,6	7,2-16,4 (10,6)	<0,001
Diagnosis					
Endometrial CA	11,5±2,0	6,9-15,6 (11,9)	10,7±1,7	7,3-16,4 (10,9)	<0,001
Ovarian CA	11,6±1,9	7,7-16,5 (11,7)	10,6±1,5	7,2-14,1 (10,6)	<0,001
Cervical CA	10,9±2,0	7,4-14,6 (11,0)	10,2±1,6	7,3-14,6 (10,6)	0,011
Vulvar CA	12,1±1,4	10,5-14,1 (11,8)	10,8	8,5-12,5 (10,8)	0,063
p	0,369		0,424		

Tablo 7. Survival rate according to ASA score and the relationship between cancer type and mortality		
	3 year survival %(SE)	**Log Rank p**
Overall	87.2% (2.3	
ASA		
ASA I	87.6% (2.7%)	0.197
ASA II	88.3% (4.1%)	
ASA III	66.7% (19.2%)	
Cancer Type		
ENDOMETRIAL CA	89.9% (3%)	0.013
OVARIAN CA	89.7% (3.4%)	
CERVICAL CA	77.8% (8%)	
VULVAR CA	57.1% (18.7%)	

Tablo 8. The survival rate of gynecological cancers			
	ENDOMETRIAL CA	**OVARIAN CA**	**CERVICAL CA**
	Log Rank p	**Log Rank p**	**Log Rank p**
OVARIAN CA	0,975		
CERVICAL CA	0,076	0,089	
VULVAR CA	0,005	0,006	0,274

The decrease in post-operative hemoglobin levels in patients was found to be statistically significant ($p < 0.001$). Among the diagnoses, the decrease in hemoglobin levels was statistically significant in Endometrial CA ($p < 0.001$), Ovarian CA ($p < 0.001$), and Cervical CA ($p = 0.011$), but not statistically significant in Vulvar CA ($p = 0.063$). There was no statistically significant difference in preoperative and postoperative hemoglobin levels among diagnoses ($p = 0.369$, $p = 0.424$) (Table 6)

The survival rate according to ASA score and the relationship between cancer type and mortality are shown in Table 7. A statistically significant difference was found in survival rates across cancer types (p=0.013). The survival rate of vulvar CA was found to be lower than endometrial and ovarian CA (p=0.005 p=0.006) (Table 8).

4. Discussion

In the present study, we aimed to determine whether mortality due to gynecologic cancer differs in patients who received conventional versus epidural analgesia. We found that a lower amount of blood transfusion during surgery and fewer comorbid diseases contribute to increased survival. Furthermore, contrary to recent literature, we observed that conventional analgesia showed higher survival rates compared to epidural analgesia.

The relationship between surgery and anesthetic-induced immunosuppression and cancer recurrence remains unresolved. Surgery and anesthesia stimulate the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), causing immunosuppression through several tumor-derived soluble factors. Local anesthetics such as lidocaine increase natural killer (NK) cell activity. Anesthetics such as propofol and locoregional anesthesia, which decrease surgery-induced neuroendocrine responses by suppressing the HPA axis and SNS, may result in less immunosuppression and lower recurrence rates for certain types of cancer compared to volatile anesthetics and opioids (10).

Perioperative anesthesia and analgesia exacerbate immunosuppression in immunocompromised cancer patients. NK cells are critical components of anti-tumor immunity. Propofol anesthesia combined with postoperative ketorolac analgesia demonstrated a favorable impact on immune function by preserving NK cell cytotoxicity (NKCC) compared to sevoflurane anesthesia and postoperative fentanyl analgesia in patients undergoing breast cancer surgery (11).

The effects of anesthesia in patients undergoing thyroid cancer surgery are still not well understood. Propofol anesthesia was associated with lower recurrence rates, but not mortality, following surgery for papillary thyroid carcinoma compared to desflurane anesthesia (12).

Many studies have been conducted on the association between cancer recurrence and general anesthesia. Cummings et al., in a large cohort study of 42,151 patients, reported that five-year survival is higher (adjusted hazard ratio = 0.91, $p < 0.001$) in patients who undergo epidural analgesia for colectomy (6). De Oliveira et al. concluded that epidural anesthesia for ovarian cancer surgery decreases the requirement for volatile agents and extends recurrence-free time (7). Lin et al. reported that epidural anesthesia during surgery and postoperative epidural analgesia decrease the mortality rate of ovarian serous adenocarcinoma (8). In that study, the general anesthesia group had a hazard ratio of 1.214 ($p = 0.043$) compared to the epidural group. Partial correlation tests showed that regional anesthesia increases 5-year survival.

In an experimental study on mice conducted by Wada et al., the authors suggested that spinal anesthesia with administration of sevoflurane is more effective in suppressing postoperative tumors and preventing infection. The interferon-gamma to IL-4 ratio demonstrated an increase in the spinal anesthesia group, and this increase in postoperative IL-4 was found to be statistically significant (13).

However, there are other reports which claim that regional anesthesia or analgesia has no effect on a cancer patient's prognosis. Hsiang-Ling Wu et al. did not find a significant association between epidural analgesia and risk of recurrence, all-cause mortality, or cancer-specific mortality in patients with rectal cancer undergoing tumour resection (14). Roiss et al. concluded that the oncological outcomes of 4,772 patients after radical prostatectomy were not affected by the adjunctive use of spinal anesthesia (15). A study by Chang WK et al did not support a definitive association between EA and cancer recurrence or overall survival (OS) after surgical resection in patients with primary hepatocellular carcinoma (HCC) (16).

In the present study, after controlling for all other factors, blood transfusion had a coefficient of -0.192 and a p-value of 0.007, while the presence of comorbid diseases had a coefficient of -0.163 and a p-value of 0.022. A lower amount of blood transfusion and fewer comorbid diseases contribute to increased survival following surgery. Conventional analgesia showed higher survival rates (coefficient = 0.163, $p = 0.022$) compared to epidural analgesia. Other variables showed no significant correlation with survival.

The limitations of our study include its retrospective design, small sample size, single-center study, unrecorded variables such as genetic profiles, and a smaller number of patients receiving conventional analgesia compared to those receiving epidural analgesia. Tumor staging is also critical factors that significantly influence the long-term prognosis of cancer patients.However, since the disease stages of the patients cannot be accessed in the pathology reports, the inability to evaluate the relationship between staging and survival is a limitation of our study.

5. Conclusion

This study is among the leading investigations into the effect of analgesia methods on the prognosis of patients with non-metastatic gynecologic cancer. Partial correlation analysis shows that a lower amount of blood transfusion during surgery and fewer comorbid diseases contribute to increased survival. Conventional analgesia demonstrated higher survival rates compared to epidural analgesia.

Author contribution

Study conception and design: NA and NT; data collection: NA and NT; analysis and interpretation of results: NA and NT; draft manuscript preparation: NA and NT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the İstanbul S.B.U. Kanuni Sultan Süleyman Training and Research Hospital (Protocol no. 107/11.05.2022).

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Conflict of interest

The authors declare that there is no conflict of interest.

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