ATATURK
UNIVERSITY
PUBLICATIONS

Trends *in* Surgical Sciences

Formerly: Atatürk University Faculty of Medicine Journal of Surgical Medical Sciences
Official journal of Atatürk University Faculty of Medicine

Volume 4 • Issue 1 • April 2025

EISSN 3062-3308
https://dergipark.org.tr/en/pub/tss

Trends *in* Surgical Sciences

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Güncel Başlık (2025-...)
Trends in Surgical Sciences
EISSN: 3062-3308

Önceki Başlık (2022-2024)
Atatürk University Faculty of Medicine Journal of Surgical Medical Sciences / Atatürk Üniversitesi Tıp Fakültesi Cerrahi Bilimler Dergisi
EISSN: 2822-3519

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Trends *in* Surgical Sciences

About

Trends in Surgical Sciences is a peer reviewed, open access, online-only journal published by the published by Atatürk University.

Trends in Surgical Sciences is published triannual in Turkish and English in April, August, and December.

Journal History

As of 2025, the journal has changed its title to Trends in Surgical Sciences.

Current Title (2025-...)

Trends in Surgical Sciences
EISSN: 3062-3308

Previous Title (2022-2024)

Atatürk University Faculty of Medicine Journal of Surgical Medical Sciences / Atatürk Üniversitesi Tıp Fakültesi Cerrahi Bilimler Dergisi
EISSN: 2822-3519

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Trends in Surgical Sciences publishes clinical and basic research articles, reviews, rare case reports, and letters to the editors.

The target audience of the journal includes academicians, clinical researchers, medical/health professionals, students, and related professional and academic bodies and institutions.

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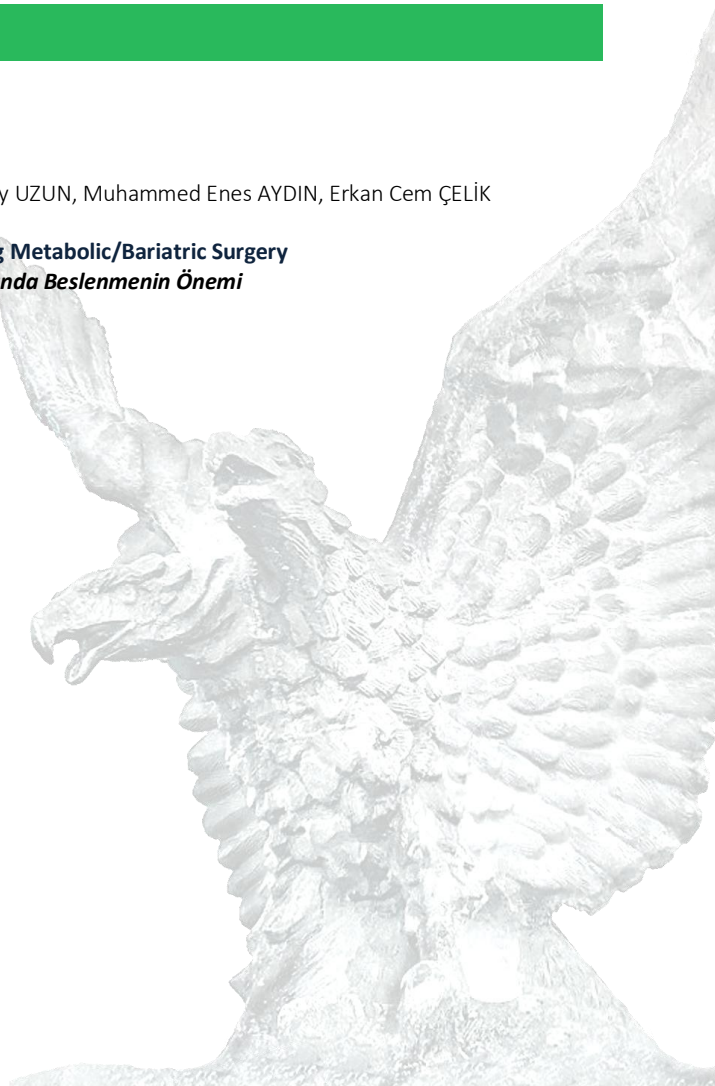

Trends *in* Surgical Sciences

EDİTÖRDEN

Saygıdeğer Meslektaşlarım,

Atatürk Üniversitesi Cerrahi Bilimler Dergisi, artık ***Trends in Surgical Sciences*** adıyla yayımlanıyor! Bu yeni isim, cerrahi bilimlerdeki en güncel araştırma ve gelişmeleri uluslararası düzeyde paylaşma hedefimizi daha güçlü bir şekilde yansıtacaktır.

Bilimsel keşiflerin ve tıbbî gelişmelerin hızla ilerlediği bir dönemde, her yeni çalışma, sağlık alanında daha iyi hizmet sunabilmek adına bir adım daha atılmasını sağlıyor. Bu sayımızda, tıbbın çeşitli alanlarında önemli katkılar sağlayan yedi kıymetli çalışmayı sizlerle paylaşmanın gururunu yaşıyoruz:

- Spinal anestezi ile yapılan sezaryenlerde hemodinamik etkilere dair yeni bulgular,
- Mikroorganizmaların antibiyotiklere karşı dirençlerini inceleyen çalışmalar,
- Çocukların görme sağlığını iyileştirmeye yönelik programların etkinliği,
- Meme kanserinin prognostik izlenebilirliği,
- Cerrahi süreçlerde anksiyete yönetimi üzerine yapılan derinlemesine araştırmalar,
- Rotem rehberliğinde kanama yönetimi üzerine literatürdeki güncel yaklaşımları ele alan kapsamlı bir derleme,
- Metabolik/Bariatrik cerrahi öncesinde ve sonrasında beslenmenin önemini vurgulayan, dikkat çekici bir çalışma.

Bu yolculukta, öncelikle her adımda rehberlik eden değerli editör arkadaşım Doç. Dr. Erkan Cem Çelik'e, bizlere profesyonel destek sunan Sayın Gökhan Çimen'e ve A.Ü. Bilimsel Araştırmalar Dergi Koordinatörü Doç. Dr. Yasin Topaloğlu'na, editöryel kurulumuza ve tüm hakemlerimize katkılarından dolayı en içten teşekkürlerimi sunarım.

Bu sayımızın, bilimsel düşüncenin gücüne inanan herkes için faydalı ve ilham verici olmasını temenni eder, araştırmaların sağlık alanında daha nice ilerlemelere vesile olmasını dilerim.

Saygılarımla,
Doç. Dr. Sevilay Özmen
Baş Editör

Trends *in* Surgical Sciences

EDITORIAL

Dear Colleagues,

We are pleased to announce that the Atatürk University Journal of Surgical Sciences is now being published under its new name: Trends in Surgical Sciences. This change reflects our commitment to sharing the latest research and advancements in surgical sciences on an international platform with greater strength and clarity.

In an era marked by rapid scientific discoveries and medical advancements, each new study represents a meaningful step toward improving healthcare services. In this issue, we are proud to present seven valuable studies that contribute significantly to various fields of medicine:

- New findings on hemodynamic effects in cesarean sections performed under spinal anesthesia,
- Research exploring the resistance of microorganisms to antibiotics,
  Evaluations of the effectiveness of programs aimed at improving children's visual health,
  Investigations into the prognostic traceability of breast cancer,
  In-depth studies on anxiety management during surgical procedures,
  A comprehensive review of current literature on bleeding management guided by ROTEM,
  A compelling study highlighting the importance of nutrition before and after metabolic/bariatric surgery.

On this journey, I would like to extend my heartfelt thanks to my esteemed editorial colleague, Assoc. Prof. Dr. Erkan Cem Çelik, for his continuous guidance, to Mr. Gökhan Çimen for his professional support, and to Assoc. Prof. Dr. Yasin Topaloğlu, the Coordinator of the Scientific Research Journals at Atatürk University. I also express my sincere gratitude to our editorial board and all our reviewers for their valuable contributions.

We hope this issue will be both beneficial and inspiring for all who believe in the power of scientific thought, and that the published research will continue to contribute to further progress in the field of healthcare.

Sincerely,
Assoc. Prof. Dr. Sevilay Özmen
Editor in Chief

ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article *Araştırma Makalesi* DOI: 10.61745/tss.1671431

Effects of Norepinephrine-Ephedrine Combination on Maternal Hemodynamics in Cesarean Sections Performed Under Spinal Anesthesia

Spinal Anestezi ile Yapılan Sezaryenlerde Norepinefrinin-Efedrin Kombinasyonunun Maternal Hemodinami Üzerine Etkileri

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ABSTRACT

Objective: The frequency of maternal hypotension after spinal anesthesia in Caesarean section (CS) may be as high as 90%. The aim of this study was to investigate the effect of the use of the combination of ephedrine and norepinephrine on maternal hemodynamics, neonatal APGAR and acidosis in CS delivery under spinal anesthesia.

Methods: This prospective, randomized, double-blind study included pregnant patients aged 18 - 45 years, evaluated as ASA class I-II for surgery, who underwent elective CS under spinal anesthesia. The clinical and laboratory findings, umbilical blood gases, maternal blood pressure and heart rate were also analyzed. The patients were randomly separated into 3 groups: Ephedrine (E), Ephedrine+Norepinephrine (EN), and Norepinephrine (N).

Results: Umbilical cord venous blood pH and HCO_3 was lower in Group EN than the other groups. APGAR score was lower in Group E. Heart rate in Groups EN and N decreased up to the middle of surgery, then was slightly elevated until the end of surgery. Heart rate persistently decreased in Group E from the beginning to the end of the surgery. SBP decreased significantly at the end of the surgery compared to basal levels in Group EN and N, and did not decrease significantly in Group E.

Conclusion: These findings suggest that the addition of norepinephrine to ephedrine might increase the risk of fetal acidosis and affect the APGAR score. The longer duration of action and the higher number of bolus of ephedrine might be associated with a lesser decrease in maternal blood pressure after the middle of the surgery.

Keywords: Post-spinal hypotension, vasopressor, norepinephrine, ephedrine, caesarean section

ÖZ

Amaç: Spinal anestezi sonrası sezaryen doğumlarda (CS) maternal hipotansiyon sıklığı %90'a kadar çıkabilmektedir. Bu çalışmanın amacı, spinal anestezi altında gerçekleştirilen sezaryen doğumlarda epinefrin ve norepinefrin kombinasyonunun maternal hemodinami, yenidoğan APGAR skorları ve asidoz üzerindeki etkilerini araştırmaktır.

Yöntem: Bu prospektif, randomize, çift kör çalışma; spinal anestezi altında elektif sezaryen geçiren, cerrahi için ASA sınıf I-II olarak değerlendirilen 18-45 yaş arasındaki gebeleri içermektedir. Klinik ve laboratuvar bulguları, umbilikal kan gazları, maternal kan basıncı ve kalp atış hızı analiz edilmiştir. Hastalar rastgele üç gruba ayrılmıştır: Epinefrin (E), Epinefrin+Norepinefrin (EN) ve Norepinefrin (N) grupları.

Bulgular: Umbilikal kord venöz kan pH ve HCO_3 seviyeleri EN grubunda diğer gruplara göre daha düşük bulunmuştur. APGAR skoru, E grubunda daha düşük saptanmıştır. EN ve N gruplarında kalp hızı ameliyatın ortasına kadar azalmış, ardından ameliyat sonuna

Received/ Geliş Tarihi	08.01.2025
Revision request/Revizyon Talebi	03.02.2025
Son Revizyon/Last Revision	04.02.2025
Accepted/Kabul Tarihi	17.02.2025
Publication Date/Yayın Tarihi	08.04.2025

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Cite this article: Soyalp C, Yüzkat N, Kurt N, Gülhaş N. Effects of Norepinephrine-Ephedrine Combination on Maternal Hemodynamics in Cesarean Sections Performed Under Spinal Anesthesia. *Trends Surg Sci*. 2025;4(1):1-10.

kadar hafif bir artış göstermiştir. E grubunda kalp hızı ameliyatın başından sonuna kadar sürekli azalma göstermiştir. EN ve N gruplarında sistolik kan basıncı (SKB), ameliyat sonunda başlangıç seviyelerine kıyasla anlamlı olarak azalmış, E grubunda ise anlamlı bir azalma gözlenmemiştir.

Sonuç: Bu bulgular, epinefrine norepinefrin eklenmesinin fetal asidoz riskini artırabileceğini ve APGAR skorunu etkileyebileceğini göstermektedir. Epinefrinin daha uzun etkili olması ve daha fazla bolus uygulanması, ameliyatın ortasından itibaren maternal kan basıncındaki azalmanın daha az olmasına katkıda bulunabilir.

Anahtar Kelimeler: Post-spinal hipotansiyon, vazopressör, norepinefrin, efedrin, sezaryen

INTRODUCTION

Caesarean section (CS) is a commonly used route of delivery for pregnant patients with some compelling indications and the rates of CS are increasing in patients with these indications. Anesthesiologists have a responsibility to take immediate care of the patient's safety and ensure optimal conditions during surgery. However, in CS procedures, the anesthetic given to the mother also affects the fetus. Hence, the safety and stability of the fetus becomes important in addition to that of the mother. The choice of the anesthesia method and anesthetic agent to be used is of great importance during CS.[1]

Anesthesia-related complications are the leading cause of maternal morbidity and mortality in CS with the most common reason in those applied with general anesthesia being failure of intubation and pulmonary aspiration of gastric content.[2] As a result of maternal mortality during general anesthesia, regional anesthesia has been increasingly used during CS.[3] The leading cause of mortality in regional anesthesia is due to the higher level of neural block and local anesthetic toxicity.[4] Following the introduction of regional anesthesia, the rates of anesthesia-related maternal mortality in CS procedures have decreased.[5]

There are several advantages of regional anesthesia such as a lower risk of aspiration with protection of airway reflexes and spontaneous respiration, lower risk of neonatal resuscitation, earlier initiation of breast-feeding, better postoperative analgesia, *less* postoperative vomiting, and early recovery of gastrointestinal motility.[6]

However, there are also some risks of this procedures. Bradycardia due to a higher level of block, decreased venous return and systemic vascular resistance due to medical sympathectomy may cause the development of maternal hypotension during surgery.[7] The frequency of maternal hypotension after spinal anesthesia may be as high as 90%. Nausea, vomiting, spinal cord ischemia, fetal acidosis and a lower APGAR score may also be observed after spinal anesthesia. Fetal acidosis and a lower APGAR score may result from compromised uteroplacental blood flow.

Therefore, it is important that maternal hypotension isavoided and the maternal hemodynamic status should be stabilized in pregnant patients during spinal anesthesia.[8] To prevent maternal hypotension as much as possible, preoperative and intraoperative intravenous crystalloid infusion, and vasoactive substances have been used. Several vasoactive medications such as norepinephrine, ephedrine, or phenylephrine have been examined in previous studies. However, there are few studies regarding the use of norepinephrine in obstetric patients. To the best of our knowledge, the effect of the combination of ephedrine and norepinephrine on maternal and fetal hemodynamics during Cesarean delivery under spinal anesthesia is not known and has not been studied to date. The aim of this study was to investigate the effect of the use of ephedrine and norepinephrine combined and alone on maternal hemodynamic parameters, neonatal APGAR and blood gas parameters in CS delivery under spinal anesthesia.

METHODS

The study was approved by the Van Yüzüncü Yıl University Local Institutional Ethics Committee with an approval number of June 6, 2018 decision no: 08, and was initiated after it was recorded with the clinical trial number of NTC03672071. Written informed consent was obtained from all subjects. The study included pregnant patients aged between 18 and 45 years, evaluated as ASA class II for surgery, who underwent elective CS under spinal anesthesia. The study was designed as a prospective, randomized, double-blinded study. Patients for whom elective CS was initiated under spinal anesthesia and was then changed to general anesthesia were excluded. Patients were also excluded if they were ASA class III or IV, had a twin or multiple pregnancy, if emergency CS was performed, and those who were hemodynamically unstable, had cardiac or pulmonary disorders, placenta previa, placental detachment, intrauterine fetal death, syndromic fetus, intrauterine growth retardation, preeclampsia, or a known history of allergy to ephedrine and/or norepinephrine. The newborn infants who were intubated in the postpartum period for any reason were also excluded. The physical

Table 1. Demographic data,nause-vomiting,irrability and headache

	E	EN	N	*P*
	(n=33)	(n=29)	(n=28)	
Age (years)	30.48±6.09	29.21±5.29	30.18±6.28	,681
Height (cm)	160 (150 / 176)	162 (151 / 180)	160 (155 / 170)	,602
Weight (kg)	80 (60 / 120)	80 (60 / 100)	71 (55 / 90)	.066
BMI	30.07 (23.44 / 44.08)	29.38 (20.76 / 35.16)	27.34 (19.84 / 35.16)	.111
Gravida	2 (1 / 8)	4 (1 / 8)	3 (1 / 6)	.245
Duration of surgery (mins)	38 (22 / 68)	36 (28 / 60)	34 (20 / 56) [AB]	**.047**
Number of drug boluses given n (%)				
I	12 (36.4)	14 (48.3)	14 (50.0)	.170
II	7 (21.2)	6 (20.7)	10 (35.7)	
III	14 (42.4)	9 (31.0)	4 (14.3)	
ASA score				
I	14 (42.4)	11 (37.9)	24 (85.7) [AB]	**<.001**
II	19 (57.6) [C]	18 (62.1) [C]	4 (14.3)	
Nausea-vomiting				
Absent	25 (75.8)	23 (79.3)	22 (78.6)	.949
Present	8 (24.2)	6 (20.7)	6 (21.4)	
Irritability				
Absent	32 (97.0)	28 (96.6)	24 (85.7)	.238
Present	1 (3.0)	1 (3.4)	4 (14.3)	
Headache				
Absent	26 (78.8)	25 (86.2)	27 (96.4)	.138
Present	7 (21.2)	4 (13.8)	1 (3.6)	

Datas were expressed as a mean±SD, number and percentage. OneWay ANOVA (RobustStatistic:Brown-Forsythe), Kruskal Wallis Test(Monte Carlo), Post Hoc Test : Dunn's Test, Fisher Freeman Halton (Monte Carlo), Pearson Chi Square Test(Monte Carlo); Post Hoc Test: Benjamini-Hochberg correction, [A] Significant for ephedrine group, [B] Significant for norepinephrine + ephedrine group, [C] Significant for norepinephrine group

examination and clinical findings, and laboratory parameters of the patients were evaluated, recorded and analyzed. Fetal blood gas analyses were recorded. Blood pressure and heart rate parameters of the patients were analyzed and compared. All patients were evaluated 30 minutes preoperatively. A large venous line was opened and 10 mL/kg crystalloid fluid was given to all patients intravenously in the preoperative evaluation room. The patients were monitored, and the hemodynamic parameters of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and oxygen saturation (SpO_2) were recorded preoperatively.

A total of 97 patients were initially evaluated and 7 were excluded from the study as they did not meet the criteria. Thus 90 patients were included and analyzed in the study. The patients were randomly separated into 3 groups according to the vasoactive agents applied during surgery, as the Ephedrine (E) group, theEphedrine+Norepinephrine (EN) group, and the Norepinephrine (N) group.

Spinal Anesthesia: Asepsis and antisepsis were first provided, then by palpating the L3-L4 spinal space, a Quincke injector was inserted into this space. A fixed dose of 12.5 mg 0.5% isobaric bupivacaine was injected into the subarachnoid space via the injector guide after cerebrospinal fluid drainage was seen. The spinal injector was withdrawn, and a pressured medical dressing was applied. The patient was positionedon the surgical table which was tilted 15˚ to the left. Continuous nasal oxygen of 2L/min was given to the patient via a nasal cannula. The level of dermatome was checked by hot-coldtest then when the block level arrive T4 surgery was initiated. All surgigal procedures were performed by same surgen.

Table 2. Blood gas values and APGAR score

	E (n=33)	EN (n=29)	N (n=28)	*P*
Venous				
pH	7.38 (6.96 / 7.49)	7.32 (6.9 / 7.44) [AC]	7.41 (6.51 / 7.54)	**.002**
PCO2	37.1 (9.3 / 70)	34.7 (7.1 / 49)	35.3 (21.6 / 92.7)	.528
PO2	15.4 (3.4 / 97.8)	16.25 (3.6 / 102.3)	17.85 (9 / 99.1)	.325
HCO3	20.8 (-4.1 / 27.1)	15.8 (1.9 / 23.1) [AC]	21.9 (1.8 / 36.4)	**.001**
BE	-1.7 (-27.9 / 23.8)	-11.6 (-29.9 / 2.5) [AC]	-1.95 (-23.6 / 9.5)	**.002**
Arterial				
Ph	7.4 (6.97 / 7.49)	7.32 (6.98 / 7.58)	7.42 (6.96 / 7.61) [B]	**.037**
PCO2	32.9 (7 / 51)	32.4 (6 / 52.5)	31.75 (9.3 / 48.2)	.707
PO2	21.8 (5.9 / 101)	18 (10.4 / 108.3)	26.75 (12.2 / 108.5)	.258
HCO3	20.8 (6.1 / 29.4)	16.5 (5.4 / 27.5)	21.75 (5 / 29.3)	.052
BE	-2.9 (-28.2 / 7.6)	-10.2 (-29.5 / 4.5)	-2.2 (-29.4 / 8.1)	.056
APGAR score				
1 min	7 (5 / 8) [BC]	8 (7 / 8)	8 (5 / 8)	**<.001**
5 mins	8 (6 / 9) [BC]	9 (8 / 9)	9 (7 / 9)	**.001**
(5-1) mins	1 (1 / 3)	1 (1 / 1)	1 (1 / 2)	.173
P (intragroups)	**<.001**	**<.001**	**<.001**	

Datas were expressed as a mean±SD, number and percentage. Kruskal Wallis Test(Monte Carlo), Post Hoc Test: Dunn's Test, Wilcoxon Signed Ranks Test(Monte Carlo),

[A] Significant for ephedrine group, [B] Significant for norephedrine + ephedrine group, [C] Significant for norephedrine group

Hemodynamic parameters were recorded every 2 minutes during surgery using non-invasive methods. To maintain cerebral perfusion pressure when MBP began to decline by > 20% compared to the baseline level, an intravenous bolus of 5 mg ephedrine was given to the E group, 5 mcg norepinephrine to the N group, and 5 mg ephedrine + 2.5 mcg norepinephrine to the EN group. The number of bolus ofvasoactive agents used in all groups, side effects such as nausea, vomiting, irritability and headache, APGAR at 1st and 5th minutes, blood gas parameters in cord blood, and duration of surgery were recorded and analyzed. The drugs used in the study were obtained as norepinephrine bitartrate, 1 mg/ml (Levophed®, Hospira, Inc., Lake Forest, IL, USA), and ephedrine sulfate, 50 mg/ml (Ephedrine Sulfate®, Akorn, Inc., India).

The patients were randomly separated into the 3 groups using the closed envelope method, and the study was designed as a double-blinded,randomize dstudy. The drugs used in the study were prepared by a physician not involved in any other part of the study. This physician held the code for randomization and group allocation.

Statistical Analysis

Data obtained in the study were analysed statistically using SPSS 25.0(IBM Corporation, Armonk, NY, USA) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological statistics) software. The conformity of the univariate data to normal distribution was evaluated using the Shapiro-Wilk test, and homogeneity of variance was evaluated with theLevene test. The conformity of the multivariate data to normal distribution was evaluated using the Mardia; (Dornik and Hansenomnibus) test, and homogeneity of variance was evaluated with theBox'm test. When comparing multiple independent groups according to quantitative variables as parametric tests, One-Way Anova was used, and Fisher's Least Significant Difference (LSD) test was used for Post Hoc analysis. As non-parametric tests, the Kruskal-Wallis H test was used with the Monte Carlo Simulation technique, and Dunn's Test was used for Post Hoc analysis. When comparing repeated measurements of dependent quantitative variables, the Wilcoxon Signed Ranks test was used. When examining the interaction of repeated measurements of these variables according to the groups, the General Linear Model-Repeated Anova test and Friedman's Two-Way test were used, with Dunn's Test and the Bonferroni test applied for Post Hoc analysis. When comparing groups according to categorical variables, the Pearson Chi Square and Fisher-Freeman-Holton tests were applied with the Monte Carlo Simulation technique, the

Table 3. Hemodynamic paramaters

	E (n=33)	EN (n=29)	N (n=28)	*P*
Heart Rate				
Basal	93.48±15.96	96.93±18.80	92.61±18.81	.627
Mid-surgery	90.12±14.57	87.83±15.88	88.61±15.74	.837
End of surgery	87.55±14.14	91.66±16.32	90.71±14.33	.526
P (intragroups)	**,131**	**.063**	**.176**	
Mid-basal	-3.36±18.00	-9.10±19.51	-4.00±12.06	.356
End -basal	-5.94±17.81	-5.28±17.20	-1.89±17.03	.633
End-mid	-2.58±10.55	3.83±13.72	2.11±12.21	.108
SAP				
Basal	117.18±18.55	123.48±21.75 [3]	125.11±20.65 [2 3]	.275
Mid-surgery	112.62±13.39	112.91±15.38	109.66±15.64	.658
End of surgery	113.18±13.26	111.62±17.96	104.07±15.32	.065
P (intragroups)	,383	**.025**	**<.001**	
Mid-basal	-4.56±18.35	-10.57±23.23	-15.45±19.92	.125
End -basal	-4.00±18.12[C]	-11.86±21.50	-21.04±18.63	**.004**
End-mid	0.56±9.80	-1.29±13.87	-5.59±14.20	.174
DAP				
Basal	64.85±12.99 [2 3]	72.24±15.18 [2 3]	68.07±12.27 [2 3]	.106
mid	56.41±8.35	59.34±9.82	57.21±10.59 [3]	.478
End	57.09±11.38	56.76±12.49	51.04±10.08	.079
P (intragroups)	**.004**	**<.001**	**<.001**	
Mid-basal	-8.44±13.39	-12.90±17.99	-10.86±14.67	.529
End -basal	-7.76±14.66 [C]	-15.48±16.28	-17.04±15.62	**.046**
End-mid	0.68±11.04	-2.59±12.63	-6.18±12.40	.092
Mean				
Basal	84.85±14.87 [2]	92.69±20.45 [3]	88.93±15.41 [2 3]	.204
Mid	76.67±9.10	82.19±10.51	78.73±10.46 [3]	.102
End	78.64±11.53	78.97±13.85	71.93±11.06	.053
P (intragroups)	**,017**	**.006**	**<.001**	
Mid-basal	-8.18±15.17	-10.50±22.62	-10.20±16.51	.864
End -basal	-6.21±16.16	-13.72±21.06	-17.00±16.75	.063
End-mid	1.97±11.16 [C]	-3.22±12.07	-6.80±11.27	**.014**
SPO_2				
Basal	98 (96 / 99) [3]	98 (94 / 100) [3]	98 (92 / 100) [2 3]	.462
Mid	98.5 (96 / 100)	98.5 (96 / 100)	99 (96 / 100)	.417
End	99 (96 / 100)	99 (97 / 100)	99 (97 / 100)	.779
P (intragroups)	**,011**	**.014**	**.001**	

Mid-basal	0.5 (-2 / 4)	1 (-4 / 4)	1 (-3 / 7)	0.369
End -basal	1 (-3 / 4)	1 (-1 / 4)	1 (-1 / 7)	0.787
End-mid	0 (-2 / 2)	0 (-1 / 3)	0 (-2 / 2)	0.597

General Linear Model Two-Way ANOVA(Univariate) (Method:Bootstrap); Post Hoc Test: Bonferroni, Friedman Test(Monte Carlo), Kruskal Wallis Test(Monte Carlo), Post Hoc Test : Dunn's Test,

[A]Significant for ephedrine group, [B]Significant for norephedrine + ephedrine group, [C]Significant for norephedrine group, [1] Significant for Basal, [2] Significant for mid-surgery, [3] Significant for end of surgery

column rates were compared with each other and were expressed according to Benjamini-Hochberg corrected p value results. Quantitative variables were stated asmean±standard deviation (SD) and median (minimum/maximum) values, and categorical variables were stated as number(n) and percentage (%) in the tables. Variables were evaluated with a 95% confidence level, and a value of $P < .05$ was accepted as statistically significant.

RESULTS

Mean age was similar in all the groups. There was no difference between the groups in respect of height, weight, BMI and gravida. The duration of surgery was the shortest in Group N ($P = .047$), and was longer in Group EN than in Group N ($P = .044$), and longer in Group E than in Group N ($P = .024$) (Table 1). The number of boluses of vasoactive drug was similar in all the groups. The rate of patients with ASA I score was higher in Group N than in Group E and EN ($P < .001$). The frequency of nausea-vomiting, irritability and headache was similar in all the groups.

Umblical cord venous blood pH was lower in Group EN than in Group E ($P = .047$), and Group N ($P < .001$). Venous blood HCO_3 was lower in Group EN than in Group E ($P = .011$), and Group N ($P < .001$). Umblical cord arterial blood pH was lower in Group EN than in Group N ($P = .013$) (Table 2). The 1-min APGAR score was lower in Group E than in Group NE ($P = .002$), and Group N ($P < .001$). The 5-min APGAR score was lower in Group E than in Group NE ($P = .012$), and Group N ($P < .001$). The difference between the APGAR scores at the 1st and 5th minutes was significant in each group.

The basal heart rate, heart rate in the middle and at the end of the surgery, and the change in heart rate were similar in all the groups, with no significant change determined in any group. In Groups EN and N, the heart rate decreased until the middle of surgery, then increased slightly until the end of surgery. A persistent decrease in heart rate from the beginning to the end of the surgery was determined in Group E. SBP decreased significantly at the end of the surgery compared to basal levels in Groups EN ($P = .025$) and N ($P < .001$), and did not decrease significantly in Group E. The decrease in SBP at the end of the surgery compared to the basal level was significantly higher in Group N than in Group E ($P = .001$). DBP was similar in all groups at baseline, in the middle and at the end of the surgery. DBP decreased significantly during surgery in all groups. The decrease in DBP at the end of the surgery compared to the basal level was significantly higher in Group N than in Group E ($P = .022$). MBP was similar in all groups at baseline, in the middle and at the end of the surgery. MBP decreased significantly during surgery in Groups EN and N. In Group E, mean MBP decreased in the middle of the surgery compared to the basal level, then increased slightly to wards the end of the surgery. The change in MBP at the end of the surgery compared to the middle of the surgery in Group E was significantly different from that of Group N ($P = .004$) (Table 3). There was no difference between the groups in respect of any of the measured SpO_2 levels.

DISCUSSION

As a summary of the findings of this study, umbilical cord venous blood pH and HCO3, and arterial pH were lower in Group EN than in Groups E and N. The APGAR score at the 1st and 5th minutes was lower in Group E than Groups EN and N. The APGAR score increased at the 5th minute compared to the 1st minute in all groups. Heart rate at baseline, in the middle and at the end of the surgery was similar in all groups and did not change during the surgery in any group. Maternal SBP decreased at the end of the surgery compared to baseline in Groups EN and N. Maternal DBP decreased significantly during the surgery in all groups, and to a greater extent in Group N than in Group E. Maternal MBP was similar in all groups at baseline, in the middle and at the end of the surgery. Maternal MBP decreased significantly during the surgery in Groups EN and E. However, in Group E, maternal MBP decreased in the middle of the surgery compared to baseline, then increased slightly towards the end of the surgery.

Elnabtity et al. investigated 122 patients undergoing elective CS under spinal anesthesia, and randomized them into ephedrine and norepinephrine groups according to vasoactive agent used during surgery.[9] The number of hypotensive episodes were observed to be higher in the

ephedrine group (n=61) than in the norepinephrine group (n=61) (P = .02). In that study, only systolic blood pressure was analyzed, and no study group was formed using a combination of ephedrine and norepinephrine to treat hypotension during CS. In the current study, maternal SBP did not decrease in Group E, whereas it decreased in Group EN and more so in Group N at the end of the surgery, but the difference was not statistically significant. Ephedrine is known to be the first-choice drug to prevent maternal hypotension.[10] It has a stimulant effect on both α and β adrenoceptors and therefore positive inotropic and chronotropic effects.[11] Repeated application of ephedrine may cause a decrease in the vasoconstrictive effect.[12] Norepinephrine causes α1 and β1 stimulation and maintains maternal blood pressure with a less negative effect on heart rate.[11,13] However, to the best of our knowledge, the combined effect of ephedrine and norepinephrine on maternal hemodynamics has not yet been studied in the literature. It was expected that the decrease in SBP could be less in Group EN than E. In contrast to this expectation, SBP was maintained only in the ephedrine (E) group. Ephedrine is known to have an effect of releasing endogenous norepinephrine. As the dosage of norepinephrine was lower in Group EN than in Group N, it can be assumed that this finding resulted from the emergence of physiological antagonism of ephedrine and norepinephrine on adrenoceptors. Maternal DBP and MBP were also evaluated and analyzed in addition to SBP. Maternal MBP in Group E first decreased during the surgery, then increased towards the end of surgery. This may be explained by the fact that ephedrine has a slower onset and longer duration of action than norepinephrine, and that the duration of the surgery was longest in Group E.[12,14] However, the patients could not be separated into different groups according to the duration of surgery. It might be postulated that the longer duration of surgery was associated with the higher mean blood pressure in Group E.

Elnabtity also showed that the number of boluses of vasoactive agents were higher in ephedrine group (P = .005).[9] Similarly in the current study, the percentage of higher number of boluses of vasopressor was the highest in Group E, albeit statistically non-significant. The number of boluses of vasopressor was associated with the number of hypotensive episodes. At the beginning of the surgery, the slower onset of action of ephedrine might have caused repeated hypotensive episodes and a need for additional vasopressor in Group E. The greater number of bolus in Group E might have led to a cumulative effect of ephedrine and the subsequent release of endogenous norepinephrine, and hence the smaller decrease in MBP at the end of surgery. Consequently, longer duration of surgery and a higher number of bolus of ephedrine might be associated with a lesser decrease in maternal SBP, DBP and MBP after the middle of the surgery.

In the last decade, phenlyephrine was the first choice to treat hypotension that developed during spinal anesthesia.[15] However, baroreceptor-mediated bradycardia caused by phenlyephrine might decrease cardiac output.[16] This is an especially important concern in obstetrics medicine, because of the risk of compromised uteroplacental blood flow. Kee et al. Showed that the normalized cardiac output value was greater in a norepinephrine group than in those given phenlyephrine, in a series of 104 pregnant patients applied with CS under spinal anesthesia and computer-controlled infusion of vasopressor.[11] In another study, the estimated dose equivalent to phenlyephrine 100 microgram was found to be norepinephrine 8 microgram to maintain blood pressure during CS under spinal anesthesia.[17] Sharkey et al. showed that the number of bradycardia episodes was lower in a norepinephrine group compared to a phenlyephrine group, when equipotent doses of drugs were used in CS under spinal anesthesia.[18] Elnabtity et al. showed that the frequency of bradycardia and tachycardia was less in a norepinephrine group than in an ephedrine group (P = .0002 and P = .008, respectively).[9] In the current study, the heart rate in Groups EN and N decreased until the middle of surgery, then elevated slightly until the end of surgery, whereas in Group E, there was a persistent decrease from the beginning to the end of the surgery. These findings may be explained by the beta 1 and weak beta 2 stimulatory effect of norepinephrine.[19] The activation of these receptors results in norepinephrine having a lesser negative effect on heart rate.

Uteroplacental blood flow is directly associated with maternal blood pressure, so maternal hypotension should be avoided and treated promptly to prevent fetal acidosis.[13,20] In the current study, umbilical cord venous blood pH and HCO_3, and arterial blood pH were significantly lower in Group EN. However, APGAR scores were the lowest in Group E. The use of ephedrine is known to maintain uterine blood flow[11], although the use of norepinephrine, as an alpha agonist, might compromise uteroplacental blood flow. However, Minzter et al. demonstrated that uteroplacental blood flow was not compromised after norepinephrine and it had no significant effect on fetal perfusion.[21] In the current study, the uterine artery pulsatility index was not evaluated. A previous study, has shown it to be lower in a norepinephrine group compared to an ephedrine group.[9] In the same study, APGAR scores at the 1st and 5th minutes were similar in both the ephedrine

and norepinephrine groups. The APGAR score is a subjective scoring system applied by the caregiver in the 1st and 5th minutes after delivery. Umbilical cord blood gas analysis may provide more objective knowledge about the neonatal health than the APGAR score. Therefore, based on the knowledge that norepinephrine might compromise the uteroplacental blood flow by alpha agonistic activity, it can be expected that Group N would have the lowest umbilical blood pH. Although the dosage of norepinephrine was lower in Group EN than Group N, the highest ratio of acidosis was observed in Group EN. There are multiple possible factors affecting the parameters of umbilical cord blood gas. Fetal blood gas also provides earlier information than the 1 and 5-min APGAR scores. In addition, the APGAR score may also be affected by interventions performed in the delivery room. Phenlyephrine may cause bradycardia associated with baroreceptor activation in addition to strong vasopressor activity. Norepinephrine has been known to cause fewer episodes of bradycardia.[11] Kee et al. showed that the incidence of bradycardia episodes was higher in a phenylephrine group than in a norepinephrine group in CS under spinal anesthesia.[22] If a patient group administered with phenylephrine had been included in the current study, there could have been a comparison of umbilical cord blood gas analyses of that group with Group EN. One study investigated and compared the effects of ephedrine and phenylephrine to treat post-spinal hypotension in 104 pregnant patients undergoing elective CS.[23] Umbilical arterial and venous pH and base excess were lower, and lactate concentration was higher in the ephedrine group than in the phenlyephrine group in that study. Moreover, maternal arterial pH levels were similar in both groups. The authors concluded that there was a clinical association between the effect of ephedrine causing more fetal acidosis and the higher placental transfer of ephedrine compared to phenlyephrine. Ephedrine may cause fetal stimulation of beta adrenoceptors and metabolism, and thus acidosis may ensue in fetal tissues.[15,24] Therefore, although ephedrine is known to protect uterine blood flow, by stimulating fetal beta adrenoceptors it may cause a higher frequency of fetal acidosis.[11,23] These findings are compatible with the current study results as the highest ratio of fetal acidosis was observed in Group EN. When ephedrine, which causes fetal acidosis was combined with norepinephrine, which compromises uteroplacental blood flow, the maximum effect of fetal acidosis occurred in Group EN. Maternal blood pH was not correlated with fetal blood pH in that study.[23] There are many factors regulating maternal blood pH, and the same dosage of vasopressor is expected to cause a lesser degree of acidosis in the mother than in the fetus. Maternal blood gas analysis was not included in the current study.

Strength and Limitations

To the best of our knowledge, this is the first study in literature to have investigated the combined effect of ephedrine and norepinephrine on maternal hemodynamics in CS delivery under spinal anesthesia. Several studies have investigated the effect of spinal anesthesia on SBP in CS delivery. In the current study, DBO and MBP were evaluated and analyzed in addition to SBP. No analysis of the patients could be made according to the duration of surgery, and there was no evaluation of the uterine artery pulsatility index. If a patient group administered with phenylephrine had been included, it might have been possible to demonstrate a significant difference between the groups in respect of umbilical cord blood gas analyses. Maternal blood gas analysis was not included in the study.

CONCLUSION

The findings of this study suggest that the addition of norepinephrine to ephedrine might increase the risk of fetal acidosis and the APGAR score. The longer duration of action and the higher number of ephedrine boluses might be associated with a lesser decrease in maternal SBP, DBP and MBP after the middle of the surgery. However, heart rate consistently decreased from the beginning to the end of the surgery in the ephedrine group. In conclusion, there are several advantages and disadvantages of ephedrine and norepinephrine. The selection of vasopressor to prevent and treat post-spinal hypotension should be based on the cardiac and hemodynamic characteristics of each patient. There is a need for further studies to clarify the effect of the combination of ephedrine and norepinephrine on maternal hemodynamics and fetal health.

Etik Komite Onayı: Çalışmanın etik onayı 6 Haziran 2018 tarihinde Van Yüzüncü Yıl Üniversitesi Etik Kurulu'ndan alındı (Karar No. 08).
Hasta Onamı: Çalışma hakkında bilgi verildikten sonra tüm katılımcılardan yazılı bilgilendirilmiş onam alındı.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir- CS; Tasarım-NG; Denetleme-NK; Kaynaklar-NY; Veri Toplanması ve/veya İşlemesi-NY; Analiz ve/ veya Yorum- NG; Literatür- NY; Yazıyı Yazan- CS: Eleştirel İnceleme- NK.
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

Ethics Committee Approval: Ethical approval for the study was obtained from the Van Yüzüncü Yıl University Ethics Committee on June 6, 2018 (Decision No. 08).
Informed Consent: Written informed consent was obtained from all participants after providing information about the study.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept – CS; Design – NG; Supervision – NK; Resources – NY; Data Collection and/or Processing – CS; Analysis and/or Interpretation – NG; Literature Search – NY; Writing

Manuscript – CS; Critical Review – NK

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Erdem MK, Özgen S, Coşkun F. Obstetrik Anestezi ve Analjezi. In Kişnişci H, Gökşin E, eds. Temel Kadın Hastalıkları ve Doğum Bilgisi. Ankara: Melisa Matbaacılık, 1996; 173-186.
2. Morgan GE, Mikhail SM. Clinical Anesthesiology. 2nd ed. Stamford: Appleton&Lange; 1996.
3. McDonnell NJ, Paech MJ, Clavisi OM, Scott KL; ANZCA Trials Group. Difficult and failed intubation in obstetric anaesthesia: an observational study of airway management and complications associated with general anaesthesia for caesarean section. Int *J Obstet Anesth*. 2008;17(4):292-297. doi:10.1016/j.ijoa.2008.01.017
4. Jadon A. Complications of regional and general anaesthesia in obstetric practice. *Indian J Anaesth*. 2010;54(5):415-420. doi:10.4103/0019-5049.71039
5. Morris S, Harmer M, Reynolds F. The impact of regional anesthesia on maternal mortality. In Reynolds F, eds. Regional Analgesia in Obstetrics. A Millenium Update. London: Springer; 2000: 347-356.
6. Paech MJ. Anesthesia for Cesarean Section: Handbook of in Obstetric Anesthesia. 1st ed.UK: BİOS; 2002: 82-113.
7. Lee A, Ngan Kee WD, Gin T. Prophylactic ephedrine prevents hypotension during spinal anesthesia for Cesarean delivery but does not improve neonatal outcome: a quantitative systematic review. *Can J Anaesth*. 2002;49(6):588-599. doi:10.1007/BF03017387
8. Schnittger T. Regional anaesthesia in developing countries. *Anaesthesia*. 2007;62 Suppl 1:44-47. doi:10.1111/j.1365-2044.2007.05297.x.
9. Ali Elnabtity AM, Selim MF. Norepinephrine versus Ephedrine to Maintain Arterial Blood Pressure during Spinal Anesthesia for Cesarean Delivery: A Prospective Double-blinded Trial. *Anesth Essays Res*. 2018;12(1):92-97. doi:10.4103/aer.AER_204_17
10. Turkoz A, Togal T, Gokdeniz R, Toprak HI, Ersoy O. Effectiveness of intravenous ephedrine infusion during spinal anaesthesia for caesarean section based on maternal hypotension, neonatal acid-base status and lactate levels. *Anaesth Intensive Care*. 2002;30(3):316-320. doi:10.1177/0310057X0203000308
11. Ngan Kee WD, Lee SW, Ng FF, Tan PE, Khaw KS. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anesthesia for cesarean delivery. *Anesthesiology*. 2015;122(4):736-745. doi:10.1097/ALN.0000000000000601
12. Ngan Kee WD, Khaw KS. Vasopressors in obstetrics: what should we be using?. *Curr Opin Anaesthesiol*. 2006;19(3):238-243. doi:10.1097/01.aco.0000192816.22989.ba
13. Hoyme M, Scheungraber C, Reinhart K, Schummer W. Comparison of Norepinephrine and Cafedrine/Theodrenaline Regimens for Maintaining Maternal Blood Pressure during Spinal Anaesthesia for Caesarean Section. *Obstetrics & Gynecology an International Journal*. Published online August 26, 2015:1-12. doi:10.5171/2015.714966
14. Ngan Kee WD, Khaw KS, Lee BB, Ng FF, Wong MM. Randomized controlled study of colloid preload before spinal anaesthesia for caesarean section. Br *J Anaesth*. 2001;87(5):772-774. doi:10.1093/bja/87.5.772
15. Lee A, Ngan Kee WD, Gin T. A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg*. 2002;94(4):. doi:10.1097/00000539-200204000-00028
16. Doherty A, Ohashi Y, Downey K, Carvalho JC. Phenylephrine infusion versus bolus regimens during cesarean delivery under spinal anesthesia: a double-blind randomized clinical trial to assess hemodynamic changes. *Anesth Analg*. 2012;115(6):1343-1350. doi:10.1213/ANE.0b013e31826ac3db
17. Ngan Kee WD. A Random-allocation Graded Dose-Response Study of Norepinephrine and Phenylephrine for Treating Hypotension during Spinal Anesthesia for Cesarean Delivery. *Anesthesiology*. 2017;127(6):934-941. doi:10.1097/ALN.0000000000001880
18. Sharkey AM, Siddiqui N, Downey K, Ye XY, Guevara J, Carvalho JCA. Comparison of Intermittent Intravenous Boluses of Phenylephrine and Norepinephrine to Prevent and Treat Spinal-Induced Hypotension in Cesarean Deliveries: Randomized Controlled Trial. *Anesth Analg*. 2019;129(5):1312-1318. doi:10.1213/ANE.0000000000003704

19. Practice parameters for hemodynamic support of sepsis in adult patients in sepsis. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine. *Crit Care Med*. 1999;27(3):639-660. doi:10.1097/00003246-199903000-00049
20. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. *Cochrane Database Syst Rev*. 2006;(4):CD002251. Published 2006 Oct 18. doi:10.1002/14651858.CD002251.pub2
21. Minzter BH, Johnson RF, Paschall RL, Ramasubramanian R, Ayers GD, Downing JW. The diverse effects of vasopressors on the fetoplacental circulation of the dual perfused human placenta. *Anesth Analg*. 2010;110(3):857-862. doi:10.1213/ANE.0b013e3181c91ebc
22. Ngan Kee WD, Khaw KS, Tam YH, Ng FF, Lee SW. Performance of a closed-loop feedback computer-controlled infusion system for maintaining blood pressure during spinal anaesthesia for caesarean section: a randomized controlled comparison of norepinephrine versus phenylephrine. *J Clin Monit Comput*. 2017;31(3):617-623. doi:10.1007/s10877-016-9883-z
23. Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. *Anesthesiology*. 2009;111(3):506-512. doi:10.1097/ALN.0b013e3181b160a3
24. Ngan Kee WD, Lee A. Multivariate analysis of factors associated with umbilical arterial pH and standard base excess after Caesarean section under spinal anaesthesia. *Anaesthesia*. 2003;58(2):125-130. doi:10.1046/j.1365-2044.2003.02888.x

ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Araştırma Makalesi *Research Article* DOI: 10.61745/tss.1671441

Kan Kültürlerinden İzole Edilen Gram Negatif Bakteriler ve Antibiyotik Duyarlılıkları

Gram Negative Bacteria Isolated from Blood Cultures and Their Antibiotic Susceptibility

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ÖZ

Amaç: Kan dolaşımı enfeksiyonları, hastanelerin özellikle yoğun bakım servislerinde yatan hastalarda ciddi mortalite ve morbiditeye sebep olur. Etken mikroorganizmanın en kısa sürede tespit edilmesi ve uygun antibiyotik tedavisinin planlanması mortalite oranlarını düşürmektedir. Bu çalışmanın amacı, hastanemiz cerrahi yoğun bakım servisleri başta olmak üzere çeşitli servislerden laboratuvara gelen kan kültür örneklerinde üreyen gram negatif bakterilerle bunlara etkili antibiyotikleri tespit ederek klinisyenlerin ampirik tedavi protokollerine katkı saklamaktır.

Yöntemler: Hastanemiz cerrahi yoğun bakım servisleri başta olmak üzere çeşitli servislerden laboratuvara gelen kan kültür örneklerinde üreyen gram negatif bakterilerle bunlara etkili antibiyotikler retrospektif olarak araştırıldı.

Bulgular: Kan kültüründe üreme olan 1.270 örneğin 332'sinde (%23) gram negatif bakteri üremişti. Yoğun bakım servislerinden gönderilen kan kültür örneklerinde üreme oranı 165 (%49) ile birinci sırada idi. Üreyen gram negatif bakterilerin 113'ü (%34) *Acinetobacter baumannii*, 58'i (%17*) Escherichia coli*, 51'i (%15) *Klebsiella pneumoniae,* 42'si (%12) *Pseudomonas aeruginosa*, 16'sı (%4) *Brusella spp*, 14'ü (%4) *Enterobacter spp*., 12'si (%3) *Serratia marcescens*, 12'si (%3) *Burkholderia ce*pacia, 10'u (%3) *Stenotrophomonas maltophilia*, 4'ü (%1) *Citrobacter spp*. idi. *K.pneumonaie* suşunun 37'sinde (%80), *E.coli* suşunun 28'inde (%48) genişlemiş spektrumlu beta-laktamaz (GSBL) saptandı.

Sonuç: Yoğun bakım servislerinde yatan hastaların mortalite ve morbitide oranlarını düşürmek amacıyla kan kültürü çalışan laboratuvarlar izole ettikleri etkenleri ve bunlara uygun antibiyotikleri tespit ederek klinisyenlerin tedaviye başlamalarında yardımcı olacak daha kapsamlı çalışmalar yapmalıdır.

Anahtar Kelimeler: Gram negatif bakteriler, kan kültürü, antibiyotik duyarlılık

ABSTRACT

Objective: Blood stream infections cause serious mortality and morbidity in patients, especially in intensive care units of hospitals. Detection of the causative microorganism as soon as possible and planning appropriate antibiotic treatment reduce mortality rates. The aim of this study is to determinethe gram negative bacteria grown in blood culture samples brought to the laboratory from various services, primarily surgical intensive care units of our hospital, and the antibiotics effective on them, and to contribute to clinicians initiating empirical treatment.

Methods: Gram negative bacteria grown in blood culture samples brought to the laboratory from various services, primarily surgical intensive care units of our hospital, and the antibiotics effective on them were investigated retrospectively.

Results: Gram negative bacteria were grown in 332 (23%) of 1,270 samples with blood culture growth. The growth rate in blood culture samples sent from intensive care units was in the first place with 165 (49%). Of the isolated gram negative bacteria, 113 (34%) were *Acinetobacter Baumannii*, 58 (17%) were *Escherichia coli,* 51 (15%) were *Klebsiella*

Received/ Geliş Tarihi 14.01.2025
Revision request/Revizyon Talebi 21.01.2024
Son Revizyon/Last Revision 17.03.2025
Accepted/Kabul Tarihi 21.03.2025
Publication Date/Yayın Tarihi 08.04.2025

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Cite this article: Aslan MH, Vural M. Gram Negative Bacteria Isolated from Blood Cultures and Their Antibiotic Susceptibility. *Trends Surg Sci*. 2025;4(1):11-17.

pneumoniae, 42 (12%) were *Pseudomonas aeruginosa,* 16 (4%) were *Brucella spp.,* 14 (4%) were *Enterobacterspp.,* 12 (3%) were *Serratia marcescens,* 12 (3%) were *Burkholderia cepacia,* 10 (3%) were *Stenotrophomonas maltophilia,* and 4 (1%) were *Citrobacter spp*. Extended spectrum beta-lactamase (ESBL) was detected in 37 (80%) of *K. Pneumonai* strains and 28 (48%) of *E. Coli* strains.

Conclusion: In order to reduce the mortality and morbidi ty rates of patients hospitalized in intensive care units, laboratories performing blood culture should conduc tmore comprehensive studies to identify the agents they isolate and the appropriate antibiotics to guide clinicians in initiating treatment.

Keywords: Gram negative bacteria, blood culture, antibiotic susceptibility

GİRİŞ

Birçok enfeksiyon hastalığı sırasında ve cerrahi girişimlerden sonra komplikasyon olarak mikroorganizmalar kana geçerek kan dolaşımı enfeksiyonlarına sebep olabilmektedir. Bu enfeksiyonlar kendini sınırlayan enfeksiyon şeklinde görülebildiği gibi mortalite oranı yüksek sepsis, multiorgan yetmezliği, yaygın damar içi pıhtılaşma gibi farklı kliniklerle de karşımıza çıkmaktadır. Bu nedenle erken tanı konulup uygun tedaviye hemen başlanması gerekmektedir.[1]

Kan kültürü, enfeksiyon etkeni mikroorganizmaların üretilip, etkenin tanımlanması ve uygun antibiyotik tedavisinin başlanması mikrobiyolojik tanı yöntemlerinden biridir.[2] Kan kültüründen etken mikroorganizmanın konvansiyonel metodlar ile izolasyonu en az 48 saat sürmektedir.[3] Bu nedenle başlangıç tedavide ampirik antibiyotiklerin kullanımı ön plana çıkmaktadır.[4] Tedavi başlangıcında kullanılabilecek ilaçların seçiminde klinik bulgular yanında hastaların yaş, cinsiyet, komorbidite, hastanenin düzeyi gibi epidemiyolojik veriler temel alınır.[5]

Hastanelerde tespit edilen etken mikroorganizmalar ile bunlara uygun antibiyotik duyarlılıkları zamanla değişiklikler göstermektedir.[6] Bunun için her laboratuvar ampirik tedaviyi yönlendirmesi açısından kan kültüründe üreyen etkenler ve bu etkenlerin antibiyotik duyarlılıklarını yakından izlenmelidir.[1] Bu çalışmayla hastanemiz cerrahi yoğun bakım servisleri başta olmak üzere çeşitli servislerden laboratuvarımıza gönderilen kan kültür örneklerinden izole edilen gram negatif bakterileri ve bunların antibiyotik duyarlılıklarını saptayarak klinisyenlere ampirik tedaviye başlarken yardımcı olmayı amaçladık.

YÖNTEM

Cerrahi yoğun bakım servisleri başta olmak üzere çeşitli servislerden laboratuvarımıza gönderilen kan kültür örneklerinin sonuçları retrospektif olarak değerlendirildi. Kan kültürü seti (bir anaerop, bir aerop kan kültür şişesi) olarak laboratuvara gelen örnekler Bactec FX (Becton Dickinson, ABD) otomatize kan kültür sisteminde beş gün süre ile inkübe edildi. Brusella gibi üreme süresi uzun olan ve zor üreyen mikroorganizmalar 21 güne kadar etüvde bekletildi. Cihazda üreme sinyali veren örneklerin gram boyamaları yapılarak, %5 Koyun Kanlı Agar, Eozin Metilen Blue Agar (EMB), Çikolata Agar besiyerlerine pasajları yapıldı. Besiyerleri 24-48 saat 37°C etüvde inkübasyona bırakıldı. Bu süre sonunda üreyen mikroorganizmaların identifikasyon ve antibiyotik duyarlılıkları, koloni morfolojisi ve gram boyanma özelliklerine de bakılarak, Phoenix bakteri tanımlama ve antibiyotik duyarlılık otomatize sistemi (Becton Dickinson, Sparks, Maryland, ABD) ile değerlendirmeler The European Committee on Antimicrobial Susceptibility Testing (EUCAST)[7]'a göre yapıldı. Cihazda en az beş gün inkübasyona bırakılan ve pozitif sinyal vermeyen şişeler negatif olarak değerlendirildi. Çalışmaya aynı hastaya ait sadece bir pozitif üreme dahil edildi. Hastanın her iki kolundan alınan iki kan kültürü setinde aynı bakterinin tanımlanması ve antibiyotik duyarlılık sonucunun aynı olması durumunda izole edilen bakteri etken kabul edildi. Her iki örnekte farklı bakterilerin tespit edilmesi veya tek örnekte üreme kontaminasyon olarak kabul edildi, sonuçlar çalışmaya dahil edilmedi. Çalışmaya Erzurum Bölge Eğitim ve Araştırma Hastanesi Bilimsel Araştırmalar Etik Kurulu'ndan 18 Mart 2020 tarihinde 2020/06-63 karar no'suyla alınan onayla başlanmıştır.

BULGULAR

Laboratuvarımıza 1 Ocak 2019- 30 Aralık 2020 tarihleri arasında gönderilen 1.270 kan kültürü örneğinin 332'inde (%21) gram negatif bakteri üredi. Üreyen gram negatif bakterlerin 113'ü (%34) *A. baumannii*, 58'i (%17) *E. coli,* 51'i (%15) *K.pneumoniae*, 42'si (%12,6) *P.aeruginosa,* 16'sı (%4) *Brusella spp,* 14'ü (%4) *Enterobacter spp,* 12'si (%3) *S.marcescens,* 12'si (%3) *B. cepacia,* 10'u(%3) *S.maltophilia,* 4'ü(%1) *Citrobacter spp* olarak belirlendi. *K.pneumoniae,* suşunun 37'sinde (%80), *E.coli* suşunun 28'inde (%48) genişlemiş spektrumlu beta-laktamaz (GSBL) tespit edildi. Değerlendirmeye alınan hastaların 148'i (%44) kadın, 184'ü (%55) erkekti. Ortalama yaş 65 olarak saptandı. Kan kültürlerinden izole edilen mikroorganizmaların dağılım oranları Tablo 1'de verilmiştir. Örneklerin geldiği servislere göre üremeler değerlendirildiğinde en fazla gram negatif üreme yetişkin yoğun bakım servislerinden gönderilen kan kültür 165 (%49) örneklerinde görüldü.

Tablo 1. Kan kültüründen izole edilen mikroorganizmaların dağılımı ve servislere göre dağılımı

Mikroorganizmalar	YBÜ	DS	ÇYB	ÇS	PBM	YS	YÜ	Toplam
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
A.baumannii	81 (49)	4 (2)	20 (55)	6 (18)	2 (7)	-	-	113 (34)
E.coli	18 (10)	14 (31)	4 (11)	15 (45)	2 (7)	-	5 (38)	58 (17)
K.pneumoniae	20 (12)	9 (45)	6 (16)	4 (12)	5 (19)	6 (42)	1 (7)	51 (15)
P.aeruginosa	18 (10)	8 (17)	3 (8)	2 (6)	4 (15)	5 (35)	2 (15)	42 (12)
Brucellaspp	-	10 (22)		6 (18)	-	-	-	16 (4)
Enterobacter spp	7 (4)	-			1 (3)	2 (14)	4 (30)	14 (4)
S.marcescens	6 (3)	-	3 (8)		3 (11)	1 (7)	-	12 (3)
B.cepacia	6 (3)	-	-		5 (19)	-	-	12 (3)
S.maltophilia	5 (3)	-	-		4 (15)		1 (7)	10 (3)
Citrobacter spp.	4 (2)	-	-					4 (2)
Toplam	165	45	36	33	26	14	13	332

YBÜ: Yetişkin yoğun bakımlar, DS: Dahiliye servisleri, ÇYB: Çocuk yoğun bakımlar, ÇS: Çocuk servisleri, PBM: Palyatif bakım merkezi, YS: Yanık servisi, YÜ: Yenidoğan ünitesi

Tablo 2. Gram negatif bakterilerde belirlenen antibiyotik direnç oranları

	A.baumanni, %	*E. coli,* %	*K.pneumoniae,* %	*P.aeruginosa,* %	*Entero bacter* spp %	*Serratia marcescens* %	*Citrobacter koseri* %
Amikasin	81	3	29	23	0	41	75
Gentamisin	84	31	50	33	14	58	50
Amoksisilin-klavulonat		39	78		100	83	100
Ampisilin		82	90		100	83	100
Ampisilin-Sulbactam		37	62		58	100	100
Cefepim		50	74	38	28	41	75
Ceftazidim		53	78	38	35	41	100
Ceftriakson			78		42	41	100
Cefuroksim		55	78		7		100
Ciprofloksasin	86	53	58	47	35	58	75
Levofloksasin	73	36	49	71	21	50	75
Ertapenem		10	49		28	58	100
İmipenem	84	1	49	38	7	58	100
Meropenem	86	1	54	42	0	58	100
Kolistin	98	1	19	4	0	100	0
Piperasilin-tazobaktam		22	68	16	14	41	25
Tigesiklin	13	13	35	38	0	16	75
Trimetoprim-sulfametoksazole	61	44	5		28	16	75

Bunu sırasıyla dahili servisler 45 (%13), çocuk yoğun bakım servisi 36 (%10), çocuk servisleri 33 (%9), palyatif bakım merkezi 26 (%7), yanık tedavi merkezi 14 (%4) ve yenidoğan ünitesi 13 (%3) takip ediyordu. Örneklerin kliniklere göre dağılımı incelendiğinde; en fazla tanımlanan *A.baumannii*' yetişkin yoğun bakım 81 (%49) ve çocuk yoğun bakım 20 (%17) servislerinden gelen örneklerde saptandı. Tanımlanan gram negatif bakterilerin servislere göre dağılımı Tablo 1'de verilmiştir.

Kan kültürlerinde cihaz pozitif sinyal verdikten sonra yapılan gram boyama sonuçları ile tanımlanan bakteri oranı uyumu %92 idi. Kan kültürlerinden en sık *A. baumannii* 113

(%34) izole edildi. Bunların antibiyotik duyarlılıkları incelendiğinde, 92'si (%81) amikasine, 95'i (%84) gentamisine, 96'sı (%84) imipeneme ve 98'i (%86) meropeneme dirençli tespit edildi. *A.baumannii* üreyen suşların 111'i (%98) kolistine duyarlı saptandı. İkinci sıklıkta izole edilen *E.coli* 58 (%17) örneğinin, 2'si (%3) amikasine, 8'i (%13) tigesikline dirençli bulundu. Karbapenemlere ve kolistine duyarlılık oranları yüksek tespit edildi. *E.coli* suşlarının 28'inde (%48) genişlemiş spektrumlu beta-laktamaz(GSBL) tespit edildi. *K.pneumoniae* izole edilen 51 (%15) örneğin, 15'i (%29) amikasine, 26'sı (%50) gentamisine, 10'u (%19) kolistine dirençli saptandı. Ertapeneme 25 (%49), imipeneme 25 (%49), meropeneme 28 (%54) oranında dirençlilik tespit edildi. *K.pneumoniae* suşlarının 37'sinde (%80) genişlemiş spektrumlu beta-laktamaz (GSBL) saptandı. *P.aeruginosa* izolatlarının 16'sı (%38) seftazidime, 2'si (%4) kolistine dirençli tespit edildi. *B. cepacia* ve *S.Maltophilia* suşlarının hepsi trimetoprim-sulfometaksazole duyarlı bulundu. Kan kültüründe üreyen gram negatif bakterilerin direnç oranları Tablo 2'de verilmiştir.

TARTIŞMA

Son yıllarda yapılan çalışmalarda gram negatif bakterilerin kan dolaşımı enfeksiyonlarına en sık sebep olan bakteri grubu olduğu bildirilmektedir. Tanımlanan bakterilerden *A.baumannii, P.aeruginosa, K.pneumoniae* ve *E.coli* antibiyotiklere karşı ciddi direnç oluşturmaktadırlar.[8] Bununla birlikte gram negatif bakterilerin etken olarak izole edilme oranı her yıl artış göstermektedir.[9] Artan antimikrobiyal direnç yüksek morbidite ve mortaliteye neden olmaktadır.[8,10] Bizim çalışmamızda gram negatif bakterileri değerlendirme nedenimiz; hastanemiz cerrahi yoğun bakım servisleri başta olmak üzere çeşitli servislerden izole edilen gram negatif bakterileri ve bunların antibiyotik duyarlılıklarını tespit ederek hastanemiz epidemiyolojik verilerini oluşturmak ve klinisyenlere ampirik tedaviye başlarken yardımcı olmaktır. Kan kültüründe gram negatif bakteri üreme sıklığı farklı çalışmalarda %17-59,3 arasında bildirilmektedir.[11,12] Yapılan bir başka çalışmada kan kültürlerinde üreyen bakterilerin *E.coli*, *K.pneumoniae*, *P.aureuginosa*, *Acinetobacter spp*. gibi gram negatif bakteriler olduğu bildirilmiştir.[13]

Öner ve ark.[14] yaptıkları çalışmada kan kültüründen izole ettikleri gram negatif bakterileri sıklık sırasına göre *E. coli* (%35,6), *K. pneumoniae* (%24,8), *P. aeruginosa* (%13,5) ve *A. baumannii* (%5,9) olarak saptamışlardır. *E.coli*,[15] bir çok çalışmada kan kültüründen en sık üreyen bakteri olarak tespit edilirken, Şirin ve ark.[16], Wu ve ark.[17] çalışmalarında en sık *Acinetobacter spp*. izole ettiklerini bildirmişlerdi. Tabah ve ark.[18] çok merkezli yaptıkları, 24 ülkede 162 yoğun bakım ünitesini dahil ettikleri bir çalışmada *Acinetobacter spp*. (%12,2), *Klebsiella spp.* (%11,9) ve *Pseudomonas spp*.'yi (%11,4) en sık sepsis etkenleri olarak saptamışlardı. Bu çalışmada da diğer çalışmalara benzer şekilde gram negatif bakteriler arasında en sık üreyen bakteriler sırasıyla, 113'ü (%34) *A.baumannii,* 58'i (%17) *E.coli,* 51'i (%15) *K.pneumoniae*, 42'si (%12) *P. aeruginosa*, 16'sı (%4) *Brusella spp,* 14'ü (%4) *Enterobacter spp*, 12'si (%3) *S. marcescens,* 12'si (%3) *B. cepacia*, 10'u (%3) *S. maltophilia*, 4'ü (%1) *Citrobacter spp* olarak tespit edildi.

Geniş spektrumlu antibiyotiklerin sık kullanıldığı yoğun bakım üniteleri antibiyotiklere direnç oranının en yüksek olduğu hastane alanlarıdır. Buralarda uygulanan invaziv girişimsel işlemler, hastaların genel durumlarının kötü olması, hastanede yatış sürelerinin uzun olması, geniş spektrumlu antibiyotiklerle tedaviye başlanması gibi durumlar nedeniyle dirençli suşlarla bakteriyemilere daha sık rastlanmaktadır.[12,19-21] Bizim çalışmamızda da yapılan diğer çalışmalara benzer şekilde en fazla yetişkin yoğun bakım (81, %49) ve çocuk yoğun bakım ünitesinden (20, %17) gönderilen örneklerde üreme saptandı. İran'da kardiyak yoğun bakımda yapılan bir çalışmada kan kültüründe üreyen bakterilerde gram negatif bakteri oranı %40 olup en sık üreyen bakteriler sırasıyla *K.pneumoniae* (%27,5), *E.coli* (%20,1), *S.marcescens* (%15,8), *P.aeruginosa* (%11,6) ve *Enterobacter spp* (%10,5) olarak bildirilmiştir.[22]

Acinetobacter türleri nazokomiyal enfeksiyonlardan sıklıkla izole edilen bakteriler olup son zamanlarda yapılan çalışmalarda karbapenem grubu antibiyotiklere karşı bu bakterilerde direnç gelişiminin arttığı bildirilmektedir.[23,24] Bayraktar[25] çalışmasında *A.baumannii*'de meropenem direncini %96 Çelik ve ark.[26] imipeneme direncini %96, meropeneme direncini %98 olarak bildirmiştir. Bu çalışmada da diğer çalışmalara benzer şekilde *A.baumannii* suşları için direnç oranları amikasine %81, gentamisine %84, ciproflaksasine %86, levoflaksasine %73, imipeneme %84, meropeneme %86, kolistine %98 oranında tespit edildi.

Kalaycı ve ark.[27] yaptıkları çalışmada kan kültüründe *K. Pneumoniae'yı* %19, Aygar ve ark.[28] *E. coli*'yi %14 oranında saptadıklarını bildirmişler. Bu çalışmada da literatüre benzer şekilde *E. coli* %17,4, *K. Pneumoniae* %15,3 oranında saptanmıştır. Çeşitli çalışmalarda geniş spektrumlu β-laktamaz (GSBL) üretimi *E. coli'de* %32-67, *Klebsiella spp*.'de ise %38-74 arasında değişen oranlarda bildirilmektedir.[15] Bu çalışmada da GSBL üretimi literatürle uyumlu olarak *E.coli* suşunun 28'inde (%48), *K.pneumoniae* suşunun 37'sinde (%80) saptandı.

Karbapenemler (imipenem/meropenem) GSBL üreten Enterobacteriaceaeların etken olduğu enfeksiyonların tedavisinde ilk tercih edilen antibiyotik grubudur. Bununla birlikte karbapenem direnci giderek artmaktadır.[12] Bu çalışmada da *E. coli* izolatlarına en etkili antibiyotiklerden karbapenemlere direnç oranları; ertapenem %10, imipenem %1, meropenem %1 olarak, *K.pneumania*

izolatlarının direnç oranları ise ertapenem %49, imipenem %49, meropenem %54 olarak oldukça yüksek oranda bulundu. Bu izolatlarda kolistin direnç oranları *E. coli'de* %1, *K. pneumaniae* %13 olarak saptandı. Dünyada ve ülkemizde çoklu ilaç dirençli izolatların artması ile birlikte kolistin kullanımının yaygınlaşması sonucu gram negatif bakterilerde kolistin direnci ortaya çıkmış ve bu direnç oranı sürekli olarak artmaya başlamıştır.[29,30] Bu çalışmada da kolistin direnci sırasıyla *Acinetobacter'de* %98, *E. coli'de* %1, *K. pneumania'da* % 13 olarak tespit edildi.

Pseudomonas enfeksiyonlarının tedavisinde ilk tercih edilecek antibiyotiklerden biri seftazidimdir. Çalışmamızda seftazidim direnci %38 olarak tespit edildi. *P.aeruginosa*'ya etkili antibiyotiklerden amikasin, gentamisin ve imipenemin direnç oranları sırasıyla %23, %33, %38 olarak izlendi. Dünyada ve ülkemizde *P.aeruginosa'nın* β-laktamlara karşı direncinin artmasıyla birlikte karbapenemler ilk seçenek tedavi olarak kullanılmaya başlanmıştır. Fakat son zamanlarda *P.aeruginosa* izolatlarında karbapenemaz üretimindeki artışla birlikte bu antibiyotiklere dirençte artmıştır.[31]

Çalışmamızda son yıllarda artan sıklığı nedeniyle tıbbi alanda önem kazanan gram negatif aerob bir basil olan *S.maltophilia* 4'ü (%1) oranda tespit edildi. Fırsatçı bir patojen ve nazokomiyal enfeksiyon etkeni olarak bilinen S. maltophilia enfeksiyonları ile bakteriyemi durumlarında mortalite oranı %14-69 olarak bildirilmektedir.[32] Çalışmamızda Trimetoprim-sulfametoksazole karşı *S. maltophilia* izolatlarında direnç tespit edilmedi.

"Ulusal Antimikrobiyal Direnç Sürveyans Sistemi"nin (UAMDSS) dahil olduğu Dünya Sağlık Örgütü Orta Asya ve Doğu Avrupa Antimikrobiyal Direnç Sürveyans Ağı'nın (CAESAR) 2021 raporunda Türkiye den gönderilen verilerde yoğun bakımlarda en fazla *Acinetobacter spp* (%83), ikinci sırada *K. pneumania* (%58) üremesi olduğunu bildirmiştir. Raporda *Acinetobacter spp.* Karbapenem direnci %93,3, E. coli Aminopenicillin direnci %74,8, *K. pneumoniae* 3.kuşak sefolosporin direnci %75,4, *P.aeruginosa* karbapenem direnci %39,0 olarak bildirilmiştir.[33]

SONUÇ

Hastanelerde özellikle cerrahi yoğun bakımlarda artan antibiyotik direnç oranlarının önüne geçmek için, kan kültürü çalışan her laboratuvar, en kısa sürede etken bakterilerin tanımlanması, antibiyotik direnç oranlarının belirlenmesi için gerekli çalışmaları yapmalı, hastane epidemiyolojik verileri oluşturulmalıdır. Coğrafik bölgelere, hastanede kullanılan antibiyotiklere, hastaneye yatan hasta profillerine göre değişen, uygun tedavi yaklaşımlarının belirlemesi ve nazokomiyal enfeksiyon etkenlerinin kontrolü için klinisyenin ampirik tedavi protokollerinde yol gösterici olmalıdır.

Etik Komite Onayı: Erzurum Bölge Eğitim ve Araştırma Hastanesi bilimsel araştırmalar etik kurulundan 2020/06-63 karar nosu, 18 Mart 2020 tarihli onayı alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Konsept - MHA; Tasarım - MHA; Denetim - MKV; Kaynaklar - MKV; Malzemeler - MKV; Veri Toplama ve/veya İşleme - MKV; Analiz ve/veya Yorum – MKV ; Literatür Taraması -MHA; Yazma – MHA ; Eleştirel İnceleme MHA.
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

Ethics Committee Approval: Erzurum Regional Education and Research Hospital scientific research ethics committee approved the decision number 2020/06-63, dated March 18, 2020.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept - MHA; Design - MHA; Supervision - MKV; Resources - MKV; Materials - MKV; Data Collection and/or Processing - MKV; Analysis and/or Interpretation - MKV; Literature Review -MHA; Writing - MHA; Critical Review MHA.
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.

KAYNAKLAR

1. Er H, Aşık G, Yoldaş Ö, Demir C, Keşli R. Kan Kültürlerinde İzole Edilerek Tanımlanan Mikroorganizmaların ve Antibiyotik Direnç Oranlarının Belirlenmesi. *Turk Mikrobiyoloji Cemiyeti Dergisi*. 2015;45(1):48-54.
2. Yurtsever SG, Baran N, Afşar İ, Yalçın MA, Kurultay N, Türker M. İzmir Atatürk Eğitim ve Araştırma Hastanesi'nde kan kültürlerinden izole edilen mikroorganizmalar ve antibiyotiklere karşı duyarlılıkları. *Klimik Dergisi*. 2006;19:56-59.
3. Müderris T, Yurtsever SG, Baran N, Özdemır R, ER H, Güngör S, Aksoy-Gökmen A, Kaya S. Kan kültürlerinde izole edilen mikroorganizmalar ve antimikrobiyal duyarlılık paternlerinin son beş yıldaki değişimi. *Turk Hij Den Biyol Derg.* 2019;76(3):231-242.
4. Mushtaq A, Chen DJ, Strand GJ, et al. Clinical significance of coryneform Gram-positive rods from blood identified by MALDI-TOF mass spectrometry and their susceptibility profiles-aretrospective chart review. *Diagn Microbiol Infect Dis*. 2016;85(3):372-6.
5. Johnstone J, Chen C, Rosella L, et al. Patient- and hospital-level predictors of vancomycin-resistant Enterococcus (VRE) bacteremia in Ontario, Canada. *Am J Infect Control*. 2018;46(11):1266-1271. doi:10.1016/j.ajic.2018.05.003
6. Ulusan-Gündoğdu DZ, Çopur-Çiçek A, Mutlu MA, Koçyiğit S. Kan Kültürlerinden İzole Edilen Gram

Negatif Çomaklar ve Antibiyotik Duyarlılıkları. *Eur J Health*. 2015;1(2):58-62.
7. The European Committee on Antimicrobial Susceptibility Testing. Routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST. Version 14.0, 2024. http://www.eucast.org
8. Feng Y, Wang Z, Hao Z, Du J, Jiang H. Rising Drug Resistance Among Gram-Negative Pathogens in Bloodstream Infections: A Multicenter Study in Ulanhot, Inner Mongolia (2017-2021). *Med Sci Monit*.2023;29:e940686. doi:10.12659/MSM.940686
9. Shi N, Kang J, Wang S, et al. Bacteriological Profile and Antimicrobial Susceptibility Patterns of Gram-Negative Bloodstream Infection and Risk Factors Associated with Mortality and Drug Resistance: A Retrospective Study from Shanxi, China. *Infect Drug Resist*.2022;15:3561-3578. doi:10.2147/IDR.S370326
10. Yamba K, Lukwesa-Musyani C, Samutela MT, et al. Phenotypic and genotypic antibiotic susceptibility profiles of Gram-negative bacteria isolated from bloodstream infections at a referral hospital, Lusaka, Zambia. *PLOS Glob Public Health*. 2023;3(1):e0001414. doi:10.1371/journal.pgph.0001414
11. Müderris T, Yurtsever SG, Baran N, ve ark. Kan kültürlerinde izole edilen mikroorganizmalar ve antimikrobiyal duyarlılık paternlerinin son beş yıldaki değişimi. *Turk Hij Den Biyol Derg*. 2019;76(3):231-242.
12. Çeken N, Duran H, Kula Atik T. Kan kültüründen izole edilen gram negatif bakterilerin dağılımı ve antibiyotik direnç oranları. *Turk Hij Den Biyol Derg*. 2022;79(3):451-460.
13. Kılınç Ç, Güçkan R, Kahveci M, Kayhan Y, Pirhan Y, Özalp T. Kan Kültürlerinde Üreyen Gram Negatif İzolatların Dağılımı ve Antibiyotik Direnç Profilleri. *Int J Basic Clin Med.* 2015;3(3):125-130.
14. Öner SZ, Kaleli İ, Demir M, Çalışkan A, Mete E, Şenol H. Kan kültüründen izole edilen gram negatif çomaklar ve antimikrobiyal direnç. *Turk Mikrobiyol Cemiy Derg.* 2024;54(4):274-281.
15. Köksal-Çakırlar F, Uyar Y, Özdemir S, et al. 2011-2014 yılları arasında kan kültürlerinden izole edilen mikroorganizmalar ve antimikrobiyal direnç durumları. *Turk Hij Den Biyol Derg.*2017;74(1):55-70
16. Şirin MC, Aguş N, Yılmaz N, et al. Yoğun bakım ünitelerinde yatan hastaların kan kültürlerinden izole edilen mikroorganizmalar ve antibiyotik duyarlılıkları. *Türk Hij Den Biyol Derg.* 2017; 74(3):269-278.
17. Wu JN, Gan TE, Zhu YX, et al. Epidemiology and microbiology of nosocomialbloodstream infections: analysis of 482 cases from a retrospective surveillance study. *J Zhejiang Univ Sci B*. 2015;16(1):70-77. doi:10.1631/jzus.B1400108
18. Tabah A, Koulenti D, Laupland K, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. *Intensive Care Med*. 2012;38(12):1930-1945. doi:10.1007/s00134-012-2695-9
19. Yılmaz N, Köse Ş, Ağuş N, Ece G, Akkoçlu G, Kıraklı C. Yoğun Bakım ünitesinde yatan hastaların kan kültürlerinde üreyen mikroorganizmalar, antibiyotik duyarlılıkları ve nozokomiyal bakteriyemi etkenleri. *Ankem Dergisi.* 2010;24(1):12-19.
20. Sader HS, Farrell DJ, Flamm RK, Jones RN. Antimicrobial susceptibility of Gram-negative organisms isolated from patients hospitalized in intensive care units in United States and European hospitals (2009-2011). *Diagn Microbiol Infect Dis*. 2014;78(4):443-448. doi:10.1016/j.diagmicrobio.2013.11.025
21. Aydın M, Kaşıkçıoğlu C, Koşucu SN, Timurkaynak F, Arslan H. Kan dolaşımı infeksiyonu etkenleri ve antibiyotik direnç oranları. *Klimik Derg.* 2016;29(2):82-85.
22. Sajedi Moghaddam S, Mamishi S, Pourakbari B, Mahmoudi S. Bacterial etiology and antimicrobial resistance pattern of pediatric bloodstream infections: a 5-year experience in an Iranian referral hospital. *BMC Infect Dis*. 2024;24(1):373. doi:10.1186/s12879-024-09260-w
23. Taşçı L, Güreser S, Boyacıoğlu Zİ, Karasartova D, Taylan Özkan A. Hitit Üniversitesi Çorum Eğitim ve Araştırma Hastanesinde Kan Kültürlerinden Üreyen Mikroorganizmalar ve Antimikrobiyal Duyarlılıkları. *FLORA.* 2016;21(1):27-32.
24. Bıçak İ, Varışlı AN, Peker SY. Kan Kültüründen İzole Edilen Etkenlerin Dağılımı ve Antibiyotik Duyarlılıkları: Dört Yıllık Verilerimiz. *Cerrahi Ameliyathane Sterilizasyon Enfeksiyon Kontrol Hemşireliği Dergisi*. 2020;1(1):8-19.
25. Bayraktar HS. Yoğun Bakım Ünitesi Kan Kültürlerinden İzole Edilen Enfeksiyon Etkenlerinin Dağılımı ve Antibiyotik Direnç Profilleri. *Acta Medica Nicomedia*. 2024;7(2):161-168.

26. Çelik N, Çelik O, Aslan H, Savaş G, Yılmaz G. Erzurum Bölge Eğitim ve Araş. Hastanesi'nde Tespit Edilen *Acinetobacter Baumannii* Suşlarının Antibiyotik Direnç oranları. *Sakarya Tıp Derg.* 2017;7(4):229-234.
27. Kalaycı Z. Kan Kültürü Örneklerinden İzole Edilen Gram Negatif Bakterilerin Antibiyotik Direnç Profillerinin İncelenmesi. *SABD.* 2023;13(1):80-86.
28. Aygar İS, Yapalak ZL, Korkmaz Akyüz A, Atılan K, Tekin K. Yoğun bakım ünitelerinden beş yıllık bir analiz: Kan kültürlerinden soyutlanan *Escherichia coli* antibiyotik direnci ne durumda? *Turk Mikrobiyol Cemiy Derg.* 2023;53(4):265-271.
29. Demir-Çuha M, Hazırolan G. Comparison of MIC COL, Sensititre™ and colistin agar screening plate methods with broth microdilution reference method for detection of colistin susceptibility in carbapenem-resistant Gram-negative bacteria. *Klimik Derg.* 2021;34(3):186-191.
30. Satlin MJ. The Search for a Practical Method for Colistin Susceptibility Testing: Have We Found It by Going Back to the Future? *J Clin Microbiol*. 2019;57(2):e01608-18. doi:10.1128/JCM.01608-18
31. Çetin Ş, Özekinci T, Özmen M, Sarmış A, Koçoğlu ME. 2018-2021 yılları arasında Prof. Dr. Süleyman Yalçın Şehir Hastanesi'nde kan kültürlerinden izole edilen bakterilerin tür dağılımı ve gram negatif bakterilerin antibiyotik duyarlılıkları. *Turk Mikrobiyol Cemiyeti Dergisi.* 2023;53(4):237-244.
32. Arslan GK, Esenkaya Taşbent F, Doğan M. Sınırlı antibiyotik seçeneği olan Stenotrophomonas maltophilia enfeksiyonlarında antibiyotik direnç profili. *Turk Mikrobiyoloji Cemiyeti Dergisi.* 2021;51(4):334-340.
33. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2023 - 2021 data. Stockholm: European Centre for Disease Prevention and Control and World Health Organization; 2023. [https://www.ecdc.europa.eu/en/publications data/ antimicrobial-resistance surveillance-europe-2023-2021-data] (Erişim tarihi: 15.Mayıs.2024).

ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Araştırma Makalesi *Research Article* DOI: 10.61745/tss.1671454

Okul Çağındaki Çocuklarda Ulusal Görme Tarama Programının Etkinliğinin Değerlendirilmesi

Evaluation of the Effectiveness of the National Vision Screening Program in School-Age Children

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ÖZ

Amaç: Okul çağı çocuklarında görme kusurları sık rastlanan ve okul başarısını olumsuz etkileyen etmenlerin başında gelmektedir. Okullarda rehber öğretmenleri tarafından uygulanan görme tarama programı sonucunda sorun olduğu belirtilerek Göz Hastalıkları uzmanına yönlendirilen okul çağı çocuklarının göz bulgularının ve görme tarama progmanın etkinliğinin değerlendirilmesidir.

Yöntemler: Ocak 2023-Aralık 2024 tarihleri arasında Göz Hastalıkları polikliniğine okuldaki rehber öğretmeninin yönlendirmesi nedeniyle başvuran hastaların demografik özellikleri, Snellen eşeli ile en iyi düzeltilmiş görme keskinliği, damlalı ve damlasız otorefraktometre, göz hareketleri, biyomikroskopi ve fundus muayenesi, renk körlüğü ve ek bulgular incelendi. Aileye daha önce çocuğun göz doktoruna götürülüp götürülmediği ve yapılan görme tarama programı hakkındaki bilgisi soruldu.

Bulgular: Çalışmamıza 74 olgu dahil edildi. Olguların 38 (%51,4)'i kız, 36 (%48,6)'sı erkekti. Yaş ortalaması 6,8±1,6 (4-11) idi. Olguların 36 (%48,6)'sı emetrop, 20 (%27,0)'si miyop, 4 (%5,4)'ü hipermetrop, 10 (%13,5)'u mixt astigmat, 4 (%5,4)'ü astigmattı. Olguların 12 (%16,2)'sinde ambliyopi, 2 (%2,7)'sinde ekzotropya, 1 (%1,3)'inde renk körlüğü tespit mevcuttu. Ailelerin hiçbirisi çocuklarını daha önce göz doktoruna götürmediğini belirtti. Yapılan görme tarama programı hakkında 20 (%27,0) aile okullarda yapıldığını bildiğini belirtti. Okul öncesi dönemde aile hekimliğinde yapılan görme tarama programı hakkında hiçbir ailenin bilgisi yoktu.

Sonuç: Görme tarama programlarının erken yaşta uygulanması önlenebilir görme kaybının tespitinde önemlidir. İlkokul çağından önce yapılacak görme taraması ise ambliyopi riskini azaltmada etkili olabilir. Ailelere görme tarama programı hakkında bilgi verilmesi ambliyopi riskini azaltabilir.

Anahtar kelimeler: Görme tarama programı, ambliyopi, kırma kusuru, toplum sağlığı

ABSTRACT

Objective: Visual defects are common in school-age children and are one of the factors that negatively affect school success. The aim is to evaluate the ophthalmic findings, the effectiveness of the vision screening program in school-age children who are referred to an Ophthalmologist because they have problems as a result of the vision screening program implemented by school counselors.

Methods: Our study included demographic characteristics of the patients who applied to the Ophthalmology clinic between January 2023 and December 2024 due to the guidance of the guidance counselor at school, best corrected visual acuity with Snellen chart, dilated and nondilated autorefractometer, eye movements, biomicroscopy and fundus examination, color blindness and additional findings. The family was asked whether the child had been taken to an ophthalmologist before and their knowledge of the vision screening program.

Results: 74 cases were included in our study. 38 (51.4%) of the cases were girls and 36 (48.6%) were boys. The average age was 6.8±1.6 (4-11) years. 36 (48.6%) of the cases were emmetropic, 20 (27.0%) were myopic, 4 (5.4%) were hyperopic, 10 (13.5%) were

Received/ Geliş Tarihi 30.12.2024
Revision request/Revizyon Talebi 16.01.2025
Son Revizyon/Last Revision 09.02.2025
Accepted/Kabul Tarihi 13.02.2025
Publication Date/Yayın Tarihi 08.04.2025

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Cite this article: Dertsiz Kozan B, Savar Çağlayan M. Evaluation of the Effectiveness of the National Vision Screening Program in School-Age Children. *Trends Surg Sci*. 2025;4(1):18-22

mixed astigmatic and 4 (5.4%) were astigmatic. Amblyopia was detected in 12 (16.2%) of the cases, exotropia was detected in 2 (2.7%), and color blindness was detected in 1 (1.3%). None of the families stated that they had ever taken their children to an ophthalmologist before. About the vision screening program, 20 (27.0%) families stated that they knew that it was carried out in schools. None of the families had any information about the vision screening program performed at the family doctor during the preschool period.

Conclusion: Implementation of screening vision programs at an early age is important in detecting preventable vision loss. Vision screening before primary school age may be effective in reducing the risk of amblyopia. Providing families with information about the vision screening program may reduce the risk of amblyopia.

Keywords: Vision screening program, amblyopia, refractive error, public health

GİRİŞ

Okul çağındaki çocuklarda görme bozukluğu sık rastlanır ve okul başarısını olumsuz etkileyen etmenlerin başında gelir. Hem okul çağındaki hem de okul öncesi çocuklarda benzer olarak kırma kusuru, ambliyopi, şaşılık en sık görülen oftalmik patolojilerdir. Özellikle okul öncesi çocuklar görme ile ilgili problemleri çoğunlukla anlamlandıramaz ve ifade edemezler. Bu nedenle birçok gelişmiş ülke görme tarama programları uygulamaktadır. Ülkemizde de Sağlık Bakanlığı tarafından çocuk izlem protokolleri kapsamında ulusal görme tarama programı yürütülmektedir. Program kapsamında, 2015'te yeni doğanlara, 2016'da okul öncesi çocuklara, 2018'de ise okul çağı çocuklara yönelik görme taramaları başlatıldı.[1] Aile hekimliklerinde 0-3 aylık bebeklere göz muayenesi ve kırmızı refle testi, 36-48 aylık çocuklara ve 1.sınıf okul çağı çocuklara göz muayenesi, kırmızı refle testi ve LEA Sembol Testi ile görme muayenesi yapılmaktadır. Bunun yanı sıra Milli Eğitim Bakanlığı tarafından okul rehberlik öğretmenlerinin önderliğinde Görme Tarama programına destek kapsamında Snellen testi kullanılarak görme kusurları taraması yapılmaktadır. Test sonucunda görme ile ilgili bir problem olduğu düşünülüyorsa veya sınıf öğretmeninin gözlemlediği bir problem varsa (gözde kayma, başı eğik tutma, okumada güçlük gibi) aile yazılı olarak bilgilendirilmekte ve çocuğun doktora götürülmesi önerilmektedir.[1]

Çalışmamızın amacı okullarda rehber öğretmenleri tarafından uygulanan görme tarama programı sonucunda sorun olduğu belirtilerek göz hastalıkları uzmanına yönlendirilen çocukların klinik ve demografik özelliklerini ortaya koymak ve okullarda uygulanan görme tarama programının etkinliğini değerlendirmektir.

YÖNTEM

Ocak 2023-Aralık 2024 tarihleri arasında göz hastalıkları polikliniğine okuldaki rehber öğretmeni yönlendirmesi nedeniyle başvuran hastalara ait veriler retrospektif olarak incelendi. Çalışmamız öncesinde Gazi Yaşargil Eğitim ve Araştırma Hastanesi etik kurulundan 13.09 2024 tarih ve 166 no'lu etik onay alındı. Çalışma süresince 2013 Helsinki Bildirgesi hasta hakları yönetmeliğine bağlı kalındı. Olguların demografik özellikleri (yaş ve cinsiyet), Snellen eşeli ile ölçülen düzeltilmemiş görme keskinliği (DGK) ve en iyi düzeltilmiş görme keskinliği (EİDGK), damlalı ve damlasız otorefraktometre (Topcon KR-800) değerleri, göz hareketleri, biyomikroskopi ve fundus muayenesi, renk körlüğü ve ek bulgular incelendi. Rehber öğretmen tarafından doldurulan formdaki göze ait bildirilen sorunlar kaydedildi. Aileye daha önce çocuğun göz doktoruna götürülüp götürülmediği ve yapılan görme tarama programı hakkındaki bilgisi soruldu.

İstatistiksel analiz

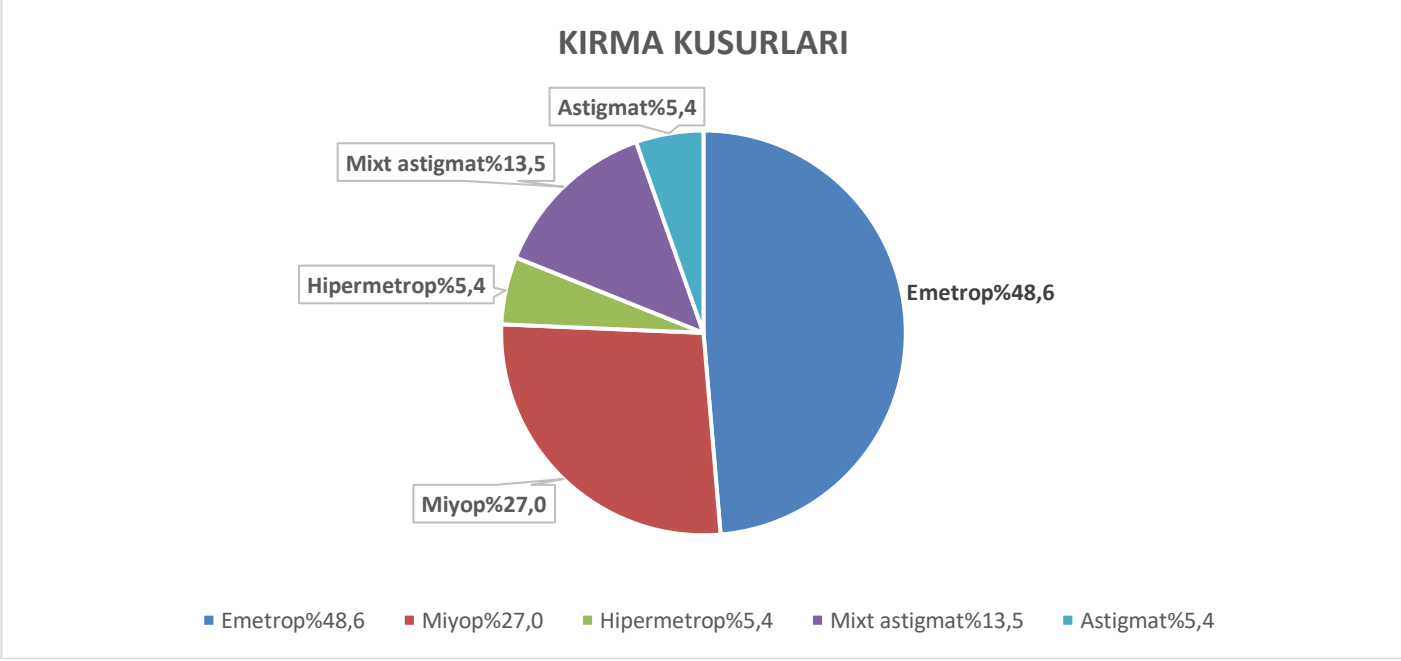
İstatiksel analiz için IBM Statistical Package for the Social Science (IBM SPSS Corp., Armonk, NY, ABD) versiyon 24 paket programı kullanıldı. Kategorik değişkenler olgu sayısı ve % olarak tanımlanırken, numerik değişkenler ortalama±standart sapma olarak tanımlandı.

BULGULAR

Çalışmamıza 74 olgu dâhil edildi. Olguların 38 (%51,4)'i kadın, 36 (%48,6)'sı erkekti. Olguların yaş ortalaması 6,8±1,6 (4-11) idi (Tablo 1). Kırma kusurları incelendiğinde olguların 36 (%48,6)'sı emetrop, 20 (%27,0)'si miyop, 4 (%5,4)'ü hipermetrop, 10 (%13,5)'u mixt astigmat, 4 (%5,4)'ü astigmattı (Grafik 1). Ek hastalıklar incelendiğinde olguların 12 (%16,2)'sinde ambliyopi, 2 (%2,7)'sinde ekzotropya, 1 (%1,3)'inde diskromatopsi tespit edildi. Olguların 59 (%79,7)'ında oftalmik patoloji yoktu (Tablo 2). Ambliyopi tespit edilen tüm olguların cinsiyeti kız idi. Ambliyopisi olan 1 olgunun pitoza bağlı geliştiği kaydedildi. Ailelerin hiçbirisi çocuklarını daha önce göz doktoruna götürmediğini belirtti. Yapılan görme tarama programı hakkında 20 (%27,0) aile, okullarda yapıldığını bildiğini belirtti. Okul öncesi dönemde aile hekimliğinde yapılan görme tarama programı hakkında hiçbir ailenin bilgisi yoktu.

Tablo 1. Olguların demografik özellikleri

Kadın	38 (%51,4)
Erkek	36 (%48,6)
Yaş	6,8±1,6 (4-11)
Toplam	74



Grafik 1. Olguların kırma kusurları oranı

Tablo 2: Ek hastalıkların cinsiyete göre dağılımı

	Ambliyop	Strabismus	Diskromatopsi	Yok	Toplam
Kadın	12 (%16,2)	1 (%1,3)	1 (%1,3)	24 (%32,4)	38 (%51,4)
Erkek	0	1 (%1,3)	0	35 (%47,2)	36 (%48,6)
Toplam	12 (%16,2)	2 (%2,7)	1 (%1,3)	59 (%79,7)	74 (%100)

TARTIŞMA

Okullarda uygulanan görme tarama programının kırma kusuru ve birçok göz hastalığının tespitinde etkili görünmektedir. Toplumda görme tarama programı hakkında bilginin az olduğu ve farkındalığın arttırılması gerekmektedir. Modern eğitimde kullanılan akıllı tahta ve bilgisayar gibi göze ve kulağa hitap eden eğitim araçlarının yaygınlaşması okul çocuğunun görme yeteneğini daha çok kullanmasını gerektirmektedir. Öğrencinin mevcut görme problemi ne yazık ki öğrenim görevini yerine getirebilmesine engel olmaktadır. Görme kusurları çocuk, ebeveyni ve öğretmen tarafından bazen anlaşılabilirken çoğu zaman küçük yaş çocukların kendini ifade etme yeteneği yeterince gelişmediğinden fark edilmeyebilir. Bu durum ise öğrencinin okul başarısını ciddi anlamda etkiler. Görme tarama programları sayesinde görme kaybına neden olan birçok hastalık erkenden yakalanabilir ve kalıcı görme kayıpları önlenebilir. Bu bağlamda Sağlık Bakanlığı aile hekimleri tarafından uygulanan okul çağı çocuklarda görme tarama programının yanı sıra Milli Eğitim Bakanlığı ile birlikte "Okulda Sağlığın Korunması ve Geliştirilmesi Programı" ile de çocukların görme ve genel sağlığına yönelik çalışmalar da yürütmektedir. Okul çağı çocuklarında en sık görülen göz problemleri kırma kusurları, ambliyopi, strabismus ve renk körlüğü olup kırma kusurları en sık görülen patolojidir.[2] Bu problemlerin çoğu erken ve doğru tedavi ile

düzelebilmektedir. Yapılan görme tarama çalışmalarında Paterson ve ark. %3, Preslan ve ark. ise %8,2 kırma kusuru (%23 oranla en sık hipermetropi) bildirmiştir.[3,4] Ülkemizde yapılan görme tarama programı çalışmalarında ise Kırağ ve ark. kırma kusuru oranını %8, Kalyoncu ve ark. %10,5, Ceylan ve ark. %12,4 ise olarak bildirmiştir.[5-7] Çalışmamıza benzer okulda yapılan görme tarama programı sonrası göz hekimine yönlendirilen hastalarda oftalmik muayene sonuçlarının incelendiği çalışmada Costa ve ark. kırma kusuru oranını %63,3 (miyopi %15,2, hipermetropi %17,6, astigmat %30,5) olarak bildirmiştir.[8] Çalışmamızda ise olguların %51,4'ünde kırma kusuru tespit edildi. Bu yüksek oran okullarda uygulanan görme tarama programlarının kırma kusuru tespitinde oldukça etkin olduğunu göstermektedir. Erken dönem tarama ambliyopi oluşumunu azaltabilir ve çocukların okul başarısı üzerine olumlu etki sağlayabilir.[9] Ek bulgular incelendiğinde strabismus oranı literatürde Cumurcu ve ark. tarafından %3,0, Khandekar ve ark. %0,5, Kvarnström ve ark. ise %3,1 olarak bildirmiştir.[10-12] Çalışmamıza benzer okulda yapılan görme tarama programı sonrası göz hekimine yönlendirilen hastalarda oftalmik muayene sonuçlarının incelendiği çalışmada Matsuo ve ark. strabismus oranını %1,28 bildirmiştir.[13] Çalışmamızda olguların 2 (%2,7)'sinde strabismus tespit edilmiş olup literatürdekine yakın değerde olmasını hem görme tarama programlarının etkinliğine hemde toplum içerisinde de strabismusun farkedilir olmasından dolayı erken tanı ve tedavi edilmesine bağlı olduğu düşünülebilir. Ambliyopi oranları incelendiğinde literatürde toplumda ambliyopi görülme sıklığı %1-3,2 olarak bildirilmiştir.[14] Ülkemizde yapılan çalışmalarda ambliyopi sıklığını Şahin ve ark. %1-3, Akyol ve ark. ise %1,5-2,9 olarak bildirmiştir.[15,16] Çocuklarda ilk 2-3 yaş, ambliyopiye en duyarlı oldukları dönem olup duyarlılık görsel gelişimin tamamlandığı 6-7 yaşına kadar, retinokortikal yolların ve görsel merkezlerin anormal görsel girdilere dirençli olduğu döneme kadar azalarak devam eder.[17] Ambliyopi tedavisinde en önemli kritik noktalar tedaviye başlama yaşı ve tanı anındaki görme keskinliğidir. Tedavide yanıt ilk 5 yaşta en üst seviyedeyken 10 yaşına doğru giderek azalır.[18] Ambliyopi tedavisi ne kadar erken yaşta başlanırsa binoküler tek görme ve steropsis o kadar iyi gelişmektedir.[19] Mathers ve ark. tarafından yapılan çalışmada çocuklarda görme tarama programlarının etkinliği, çocukların görme taramasına hangi yaşta katılmaları gerektiği ve görme tarama programlarının en etkili olması için hangi biçimi alması gerektiği incelenmiş ve ambliyopinin erken tesbiti için görme tarama programının 18 ay ile 5 yaş arasında yapılması önerilmiştir.[20] Schmdith ve ark. ilkokul çağından daha erken dönemde görme tarama muayenesinin yapılmasının önemini vurgulamaktadır.[21] Çalışmamızda olguların 12 (%16,2)'sinde ambliyopi tespit edilmiş olup oldukça yüksek bir değerdir ve toplum çocuk sağlığını etkileyen ambliyopiye dikkat çekmektedir. Bu oran yüksekliğinin sebebi toplumlarda sosyoekonomik düzey düştükçe göz kontrollerinin geç yaşlarda yapılması, anizometropinin tedavi edilmemesi olabilir. Erken dönemde uygulanan görme tarama programı ambliyopi tespitinde önemlidir. Şaşılık ambliyopisi sosyoekonomik düzeyi yüksek toplumlarda, anizometrik ambliyopi ise sosyoekonomik düzeyi düşük toplumlarda daha sık görülmektedir.[22] Çalışmamızdaki ailelerin hiçbirisi çocuklarını daha önce göz doktoruna götürmediğini, 20 (%27,0) aile ise yapılan görme tarama programını okullarda yapıldığını bildiğini belirtti. Okul öncesi dönemde aile hekimliğinde yapılan görme tarama programı hakkında hiçbir ailenin bilgisi yoktu. Literatürde Castanes ve ark. okul öncesi çağdaki çocukların %80'inin, Yıldız ve ark. ise %51,4'ünün hiç göz muayenesinin yapılmadığını bildirmişler. Ne yazık ki tıpkı ülkemizdeki gibi erken tarama programındaki uygulama ve bilgi eksikliği başka ülkelerde de yaşanmaktadır.[23,24] Daha fazla olgunun incelendiği çok merkezli çalışmalara ihtiyaç duyulmaktadır.

Çalışmanın Kısıtlılıkları

Katılımcı sayısının azlığı, tek merkezde yürütülmesi çalışmanın kısıtlılıklarını oluşturmaktadır.

SONUÇ

Okulda Sağlığın Korunması ve Geliştirilmesi Programı sayesinde aile hekimliklerince yapılması gereken görme tarama programlarında ulaşılamayan ya da gözden kaçan çocuklar öğretmenler tarafından tespit edilebilir. Ancak görme tarama programlarının daha erken yaşta uygulanması önlenebilir görme kaybının tespitinde önemlidir. Bu nedenle aile hekimliklerinin görme tarama programlarını titizlikle uygulaması ve ailelere görme tarama programı hakkında bilgi vermesi ambliyopi riskini ciddi anlamda azaltabilir.

Etik Komite Onayı: Etik kurul onayı Gazi Yaşargil Eğitim ve Araştırma Hastanesi Etik Kurulu'ndan (Tarih: 13.09.2024, Sayı: 166) alınmıştır.
Hasta Onamı: Hastane yönetimi tarafından bu retrospektif araştırmada hasta verilerine erişim ve kullanım izni verilmiştir.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir- BDK, MSÇ; Tasarım- BDK, MSÇ; Denetleme- BDK, MSÇ Kaynaklar- BDK, MSÇ; Veri toplaması/işlemesi- BDK, MSÇ; Analiz/Yorum- BDK, MSÇ; Literatür- BDK, MSÇ; Yazıyı yazan: BDK, MSÇ; Eleştirisel inceleme- BDK, MSÇ.
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

Ethics Committee Approval: Ethics committee approval was obtained from Gazi Yaşargil Training and Research Hospital Ethics Committee (Date: September 13, 2024, Number: 166).
Informed Consent: Approval was granted by the hospital management to access and utilize patient data for this retrospective investigation.
Peer-review: Externally peer-reviewed.

Author Contributions: Concept – BDK, MSÇ; Design – BDK, MSÇ; Supervision – BDK, MSÇ; Resources – BDK, MSÇ; Data Collection and/or Processing – BDK, MSÇ; Analysis and/or Interpretation – BDK, MSÇ; Literature Search – BDK, MSÇ; Writing Manuscript – BDK, MSÇ; Critical Review – BDK, MSÇ.
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.

KAYNAKLAR

1. Halk Sağlığı Genel Müdürlüğü Çocuk ve Ergen Sağlığı Daire Başkanlığı. Ulusal görme taraması programı. 2018. https://hsgm.saglik.gov.tr/tr/tarama-programlari/okul-cagi-cocuklarda-gorme-taramasi-programi.html
2. Işıklı B, Kalyoncu C. Eskişehir kırsal ilköğretim öğrencilerinde görme kusurları. *STED*. 2007;16(17):95-99.
3. Paterson B, Ruben A, Nossar V. School screening in remote aboriginal communities--results of an evaluation. *Aust N Z J Public Health*. 1998;22(6):685-689. doi:10.1111/j.1467-842x.1998.tb01470.x
4. Preslan MW, Novak A. Baltimore Vision Screening Project. Phase 2. *Ophthalmology*. 1998;105(1):150-153. doi:10.1016/s0161-6420(98)91813-9
5. Kırağ N, Temel AB. İlkokul çağı çocuklarda görme taraması ile göz sağlığı sorunlarının belirlenmesi. *F.N. Hem. Derg*. 2016;24(1):10-15.
6. Kalyoncu C, Metintaş S, Balız S, Arıkan İ. Eğitim araştırma bölgesinde ilköğretim öğrencilerinde sağlık düzeyleri ve okul tarama muayeneleri sonuçlarının değerlendirilmesi. *TAF Preventive Medicine Bulletin*. 2011;10(5):511-518.
7. Ceylan SS, Turan T. Bir İlköğretim okulunda okul sağlığı hemşireliği uygulama sonuçlarının değerlendirilmesi. *Fırat Sağlık Hizmetleri Dergisi.* 2009;4(12):35-49.
8. Costa DRD, Debert I, Susanna FN, Falabreti JG, Polati M, Susanna Júnior R. Vision for the Future Project: Screening impact on the prevention and treatment of visual impairments in public school children in São Paulo City, Brazil. *Clinics (Sao Paulo)*. 2021;76:e3062. Published 2021 Oct 1. doi:10.6061/clinics/2021/e3062
9. Rahi J, Gilbert C. Taylor and Hoyt's pediatric ophthalmology and strabismus. Saunders: Elsevier; 2017:47-57.
10. Cumurcu T, Düz C, Gündüz A, Doğanay S. Malatya ve çevresinde ilköğretim öğrencilerinde kırma kusuru sıklığı ve dağılımı. *İnönü Üniversitesi Tıp Fakültesi Dergisi*. 2011;18(3):145-148.
11. Khandekar RB, Abdu-Helmi S. Magnitude and determinants of refractive error in Omani school children. *Saudi Med J*. 2004;25(10):1388-1393.
12. Kvarnström G, Jakobsson P, Lennerstrand G. Visual screening of Swedish children: an ophthalmological evaluation. *Acta Ophthalmol Scand*. 2001;79(3):240-244. doi:10.1034/j.1600-0420.2001.790306.x
13. Matsuo T, Matsuo C. The prevalence of strabismus and amblyopia in Japanese elementary school children. *Ophthalmic Epidemiol*. 2005;12(1):31-36. doi:10.1080/09286580490907805
14. Eibschitz-Tsimhoni M, Friedman T, Naor J, Eibschitz N, Friedman Z. Early screening for amblyogenic risk factors lowers the prevalence and severity of amblyopia. *J AAPOS*. 2000;4(4):194-199. doi:10.1067/mpa.2000.105274
15. Şahin T, Buyru Y. Çocuklarda ambliyopi ve ülkemizdeki görme tarama programı. *Ortadoğu Tıp Dergisi.* 2017;9(2):79-87.
16. Akyol N, Sezer E, Aslan L, Oğuzöncül F, Dinç E. Elazığ il merke zinde ambliyopi ve ambliyojenik faktörlerin prevalansı üzerine bir çalışma. *Türkiye Klinikleri Oftalmoloji Dergisi.* 2000;9:77-82.
17. Tamçelik N. Optik Refraksiyon Rehabilitasyon Temel Bilgiler. İstanbul: Galenos Yayınevi; 2010:167-75.
18. Sanaç AŞ, Şener EC. Şaşılık ve Tedavisi. Ankara: Pelin Ofset; 2001: 83-94.
19. Denny M, Daniel J, eds. Pediatric Ophthalmology and Strabismus. San Francisco: CA; 2003:9-12.
20. Mathers M, Keyes M, Wright M. A review of the evidence on the effectiveness of children's vision screening. *Child Care Health Dev*. 2010;36(6):756-780. doi:10.1111/j.1365-2214.2010.01109.x
21. Schmidt P, Maguire M, Dobson V, et al. Comparison of preschool vision screening tests as administered by licensed eye care professionals in the Vision In Preschoolers Study. *Ophthalmology*. 2004;111(4):637-650. doi:10.1016/j.ophtha.2004.01.022
22. Vital-Durand F, Ayzac L. Tackling amblyopia in human infants. Eye (Lond). 1996;10 (2):239-244.
23. Castanes MS. Major review: The underutilization of vision screening (for amblyopia, optical anomalies and strabismus) among preschool age children. *Binocul Vis Strabismus Q*. 2003;18(4):217-232.
24. Yıldız I. Çocuklarda görme muayenesi açısından ailelerin farkındalığının değerlendirilmesi. *Journal of Child.* 2022;22(2):105-109.

ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article *Araştırma Makalesi* DOI: 10.61745/tss.1671458

Prognostic Value of Cyclin D1 Overexpression in Invasive Breast Carcinoma

İnvaziv Meme Karsinomunda Cyclin D1 Aşırı Ekspresyonunun Prognostik Değeri

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ABSTRACT

Objective: Breast cancer is the most diagnosed cancer worldwide, accounting for 11.7% of all cancers. Cyclin D1, a regulator of CDK4/6 and cell cycle progression, functions as an oncogene through overexpression, contributing to the pathogenesis of cancers including breast carcinoma. This study aimed to evaluate Cyclin D1 expression and its clinicopathological significance in invasive breast carcinoma within the Turkish population.

Methods: H&E-stained and immunohistochemical preparations from partial and total mastectomy specimens of 143 patients, diagnosed between 2007 and 2013, were examined. Cyclin D1 overexpression was evaluated in 1000 cells using an IHC score based on nuclear staining intensity (0-3) and the percentage of positive tumor cells (1-3), classified as weak ('+' or '++') or strong positive ('+++'). Pearson's Chi-Square and Spearman's rho were used to analyze the relationship between Cyclin D1 expression and clinicopathological parameters statistically.

Results: The median age of the patients was 58.5 years (Min:28, Max:92). Cyclin D1 status showed no correlation with age, T stage, or lymph node metastasis. However, a moderate positive correlation was observed with ER (r = 0.32, *P* <.001) and PR (r = 0.31, *P* <.001) scores. Among molecular subgroups, Cyclin D1 overexpression was most significant in Luminal B group (92.9%, *P* = .008), while Triple-negative group showed significantly lower overexpression (40%, *P* = .008).

Conclusion: Cyclin D1 overexpression in Luminal B and Luminal A groups, along with its positive correlation with ER, suggests its role in estrogen-sensitive breast cancer pathogenesis. Strong Cyclin D1 overexpression was associated with reduced survival time in HER2-positive cases.

Keywords: Breast, invasive breast carcinoma, Cyclin D1, histopathology, immunohistochemistry

ÖZ

Amaç: Meme kanseri, dünya genelinde en sık tanı konulan kanser olup tüm kanserlerin %11,7'sini oluşturmaktadır. Cyclin D1, CDK4/6 ve hücre döngüsü ilerlemesini düzenleyen bir onkogen olarak aşırı ekspresyon yoluyla meme karsinomu da dahil olmak üzere çeşitli kanserlerin patogenezine katkıda bulunmaktadır. Bu çalışmada, Türk popülasyonunda invaziv meme karsinomunda Cyclin D1 ekspresyonu ve klinikopatolojik önemi değerlendirildi.

Yöntemler: 2007-2013 yılları arasında tanı konulan 143 hastaya ait parsiyel ve total mastektomi örneklerinden hazırlanan H&E ve immünohistokimyasal preparatlar incelendi. Cyclin D1 aşırı ekspresyonu, nükleer boyanma şiddetine (0-3) ve pozitif tümör hücrelerinin yüzdesine (1-3) dayalı IHC skoru kullanılarak 1000 hücrede değerlendirildi. Bulgular zayıf pozitif ('+' veya '++') veya güçlü pozitif ('+++') olarak sınıflandırıldı. Cyclin D1 ekspresyonu ile klinikopatolojik parametreler arasındaki ilişki, Pearson Ki-Kare ve Spearman rho testi kullanılarak analiz edildi.

Bulgular: Hastaların medyan yaşı 58,5 yıl (Min: 28, Maks: 92) idi. Cyclin D1 durumu ile yaş, T evresi veya lenf nodu metastazı arasında anlamlı bir ilişki bulunmadı. Ancak, ER (r = 0,32, *P* < ,001) ve PR (r = 0,31, *P* <, 001) skorlarıyla orta derecede pozitif bir korelasyon gözlendi. Moleküler alt gruplar içinde, Cyclin D1 aşırı ekspresyonu en çok Luminal B

Received/ Geliş Tarihi 29.01.2025
Revision request/Revizyon Talebi 12.02.2025
Son Revizyon/Last Revision 12.02.2025
Accepted/Kabul Tarihi 12.03.2025
Publication Date/Yayın Tarihi 08.04.2025

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Cite this article: Çomut E, Kocatepe Çavdar D, Yağcı A, Vardar E, Taşlı F. Prognostic Value of Cyclin D1 Overexpression in Invasive Breast Carcinoma. *Trends Surg Sci*. 2025;4(1):23-33.

grubunda (%92,9, *P* = ,008) saptandı ve Triple negatif grupta anlamlı derecede düşük ekspresyon (%40, *P* = ,008) gözlendi.
Sonuç: Cyclin D1'in Luminal A ve Luminal B gruplarında aşırı ekspresyonu ve ER ile pozitif korelasyonu, bu proteinin östrojen duyarlı meme kanseri patogenezindeki rolünü düşündürmektedir. HER2-pozitif olgularda güçlü Cyclin D1 aşırı ekspresyonu, azalmış sağkalım süresi ile ilişkili bulunmuştur.
Anahtar Kelimeler: Meme, invaziv meme karsinomu, Cyclin D1, histopatoloji, immünohistokimya

INTRODUCTION

Breast cancer stands as the most frequently diagnosed cancer globally, with 2.3 million new cases reported in 2020, representing 11.7% of all cancer diagnoses. It ranks as the fifth most prevalent cause of cancer-related mortality, accounting for 6.9%, and exhibits higher mortality rates in developing countries when contrasted with developed nations.[1] Like global trends, breast cancer is the most prevalent cancer among women also in Turkey, with around 12,000 new cases diagnosed in 2018.[2] The breast cancer is associated with well-established risk factors such as age, family history, early menarche, late menopause, nulliparity, late age at first pregnancy, and hormone replacement therapy.

Histopathologically, invasive breast carcinoma (IBC) displays notable heterogeneity and is categorized into various subtypes, including invasive carcinoma of no special type, invasive lobular carcinoma (ILC), and others. The assessment of hormone receptor status, involving estrogen receptor (ER) and progesterone receptor (PR), through immunohistochemical methods is pivotal for identifying patients eligible for endocrine therapy. HER2 immunohistochemistry (IHC) and in-situ hybridization evaluation are also essential for identifying patients eligible to receive anti-HER2 therapy.[3] Per current protocols, essential elements for the pathological reporting of resected materials include tumor size, histological type, histological grade, lymphovascular invasion (LVI), tumor-infiltrating lymphocytes (TILs), multifocality, lymph node status, presence of in-situ components, and surgical margins. IBC is molecularly classified into four groups: luminal A, luminal B, HER2-enriched, and Basal-like triple-negative (triple-negative breast cancer, TNBC). The integration of morphologic features and molecular profiling is intended to enhance the clinical outcomes of patients.[4]

The cell cycle is meticulously controlled by cyclins and cyclin-dependent kinases (CDKs). Cyclin D1, which functions as a mitogenic sensor and activator of CDK4/6, plays a pivotal role in the progression of the cell cycle. The overexpression, accumulation, or improper cellular localization of the Cyclin D1 protein results in its acting as an oncogene.[5] Cyclin D1 has been implicated in the pathogenesis of various neoplasms, including breast carcinoma. It is involved in both the normal lobuloalveolar development of the breast and the process of breast carcinogenesis.[6] Recently, first-line therapy for postmenopausal patients with HR-positive, HER2-negative recurrent/stage IV breast cancer includes the use of CDK 4/6 inhibitors in combination with aromatase inhibitors. Similarly, for premenopausal patients undergoing ovarian ablation/suppression, this therapeutic combination is recommended.[7]

In our study, our objective was to retrospectively assess the clinical and histopathologic data of patients with IBC and elucidate the potential impact of Cyclin D1 overexpression on patient prognosis.

METHODS

Ethical approval for the study was obtained from the İzmir Bozyaka Education and Research Hospital Ethics Committee on March 25, 2021 (Meeting No. 2, Decision No. 121). From 2007 to 2013, a total of 158 cases diagnosed with breast cancer in partial or total mastectomy specimens were initially identified. Six cases, where paraffin blocks were inaccessible, and nine cases lacking sufficient tumor tissue due to technical issues during tissue microarray (TMA) block preparation, were excluded. Consequently, a total of 143 cases were included in the study. All cases were specifically diagnosed with IBC, with the exclusion of rare and salivary gland-type tumors, neuroendocrine neoplasms, mesenchymal tumors of the breast, fibroepithelial tumors, nipple tumors, malignant lymphomas, or metastatic tumors. The clinical data were sourced from the electronic patient database of the hospital.

TMA Construction

Target regions on the tumor slides were labelled, and 4 mm diameter tumor samples were extracted from the paraffin blocks using a punch biopsy tool. These samples were then embedded in TMA blocks and prepared for sectioning. Immunohistochemical staining for Cyclin D1 (Clone GM, 1:50 dilution, Leica) was performed on 5-µm-

Table 1. Overview of immunohistochemical stains

Antibody	Clone	Type of antibody	Source	Dilution
Cyclin D1	GM	Mouse monoclonal	Leica	1/50
ER	6F11	Mouse monoclonal	Leica	1/50
PR	312	Mouse monoclonal	Leica	1/100
HER2	356	Mouse monoclonal	Leica	1/40-1/80
Ki-67	SP6	Rabbit monoclonal	TFS	1/100-1/200
p53	DO7	Mouse monoclonal	Leica	1/800

Abbreviations: ER: Estrogen receptor, HER2: Human epidermal growth factor receptor 2, PR: Progesterone receptor, TFS: Thermo fischer scientific.

thick sections taken on positively charged slides, using an automated immunohistochemical stainer according to the manufacturer's guidelines (streptavidin-peroxidase protocol, BenchMark; Ventana, PA).

Immunohistochemical Analysis

IHC slides, encompassing ER, PR, HER2, Ki-67, and p53, along with hematoxylin and eosin (H&E) stained slides, were retrieved from the pathology archive. Subsequently, they underwent light microscopic reevaluation by two pathologists, with expertise spanning more than 15 years and 1-5 years, respectively (FA and EC). Cyclin D1 overexpression observed as brown granules within the cell nucleus. A total of 1000 cells were assessed, and both staining intensity and the percentage of invasive tumor cells were analyzed. IHC score, derived from multiplying the staining intensity (0-none, 1-mild, 2-moderate, 3-intense) by the percentage (1- <10%, 2- 10-50%, 3- >50%), was used for classification: 0 points as '-'; 1-2 points as '+'; 3-4 points as '++'; and >4 points as '+++'. Overall, '+' and '++' are classified as weak positive, and '+++' as strong positive group.[8] ER and PR positivity was defined as ≥1% of tumor cell nuclei showing specific staining for the receptor. Cases with 1–10% of nuclear staining for ER were classified as "low positive," while those with >10% were considered "positive." Negative cases were defined as <1% of tumor cell nuclei staining for the receptor. Both intensity (weak, moderate, or strong) and the percentage of positive cells were recorded.[9] HER2 positivity was defined as strong, complete membrane staining in >10% of tumor cells (IHC score 3+). An equivocal result (IHC score 2+) was characterized by weak to moderate, complete membrane staining in >10% of tumor cells or strong, complete staining in ≤10% of tumor cells. Cases with incomplete, faint/barely perceptible membrane staining in >10% of tumor cells (IHC score 1+) or no staining at all (IHC score 0) were considered HER2-negative.[10] HER2 status was assessed solely using immunohistochemical (IHC) analysis. FISH (Fluorescence In Situ Hybridization) was not performed in this study. Ki-67 and p53 staining in tumor cells were noted as percentages. The immunohistochemical markers were detailed in Table 1. Luminal A breast cancers were defined by the expression of estrogen receptors (ER) and/or progesterone receptors (PR), along with a low Ki-67 index (typically less than 14%) and the absence of HER2 overexpression. Luminal B breast cancers were characterized by positive estrogen receptor (ER) status, but with either a higher Ki-67 index (greater than 14%) or overexpression of HER2.

Statistical Analysis

IBM SPSS Statistics version 15 (IBM SPSS Corp., Armonk, NY, USA) was used for statistical analysis. Pearson's Chi-square test was conducted to compare Cyclin D1 expression with various clinical indicators and histopathologic parameters. Spearman's correlation method was employed to analyze the correlation between Cyclin D1 expression and various clinical parameters, including age at diagnosis, tumor size, clinical stage, and the status of ER, PR, and HER2. In this study, FISH analysis for confirmation could not be performed on cases with a HER2 score of 2+, and these cases were included in the HER2-positive group for statistical analysis. Overall survival (OS) and disease-free survival (DFS) were assessed using Kaplan-Meier analysis.

This study was conducted in accordance with the regulations outlined by the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Izmir Bozyaka Educational and Research Hospital (Decision No: 4, Year: 2016).

RESULTS

Overall Patient Characteristics

The patients' ages ranged from 28 to 92 years, with a median age of 58.5. Most of the patients (n=142) were female, while only one (0.7%) was male. Axillary lymph node metastasis was observed in 86 cases (60.1%). The clinical features of the cases are detailed in Table 2. No statistically significant correlation was evident between Cyclin D1

Table 2. Clinical features of IBC cases

Feature	n	%
Sex (n=143)		
Female	142	99.3
Male	1	0.7
Age (n=143)		
<40	13	9.1
40-60	61	42.7
>60	69	48.2
Menopausal status (n=139)		
Premenopausal	38	26.6
Postmenopausal	100	69.9
Male	1	0.7
Tumor size (n=143)		
<2 cm	28	19.5
2-5 cm	93	65.1
>5 cm	22	15.4
Multiple foci (n=143)		
Present	24	16.8
Absent	119	83.2
T stage (n=143)		
1A	1	0.7
1B	4	2.8
1C	32	22.4
2	83	58.0
3	20	14.0
4A	2	1.4
4B	1	0.7
N stage (n=143)		
0	47	32.9
1A	36	25.2
1mi	9	6.3
2A	26	18.2
3A	25	17.5
Axillary lymph node metastasis (n=143)		
Present	86	60.1
Absent	57	39.9
Stage (TNM) (n=143)		
1	18	12.6
2A	31	21.7
2B	35	24.5
3A	20	14.0
3B	5	3.5
3C	22	15.4
4	8	5.6
Recurrence (n=135)		
Present	34	25.2
Absent	101	74.8
Chemotherapy (n=137)		
Present	105	76.6
Absent	32	23.4
Radiotherapy (n=141)		
Present	98	69.5
Absent	43	30.5

Abbreviations: pN1mi: Micrometastases consisting of approximately 200 cells, measuring larger than 0.2 mm but not exceeding 2.0 mm in size.

expression and key clinical parameters, namely patient age, menopausal status, tumor multifocality, lymph node metastasis, clinical stage, or treatment status, as detailed in Table 3 ($P > .05$).

Histopathological Features

Histopathologically, 88% of the cases (n=24) were classified as invasive breast carcinoma (IBC) of no special type (NST), followed by invasive lobular carcinoma (ILC) in 8 cases (6%), invasive micropapillary carcinoma in 5 cases (2%), metaplastic carcinoma in 3 cases (2%), tubular carcinoma in 2 cases (1%), and invasive papillary carcinoma in 1 case (1%). Most tumors were histologically graded as Grade 2 (n=81, 56.6%), with 16 cases (11.2%) being Grade 1 and 46 cases (32.2%) Grade 3. An in-situ component, including ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS), was observed in 97 cases (68%). Tumor-infiltrating lymphocytes (TILs) were identified in 76 cases, with 28.9% (n=22) located in the stromal region and the majority (71.1%) as intratumoral TILs. LVI was detected in 92 cases (64.3%). Extranodal extension was observed in 50 (58.1%) of the 86 patients with axillary lymph node metastasis. No significant relationship was identified between Cyclin D1 and histological parameters, and the findings are summarized in Table 4.

Immunohistochemical Features

Cyclin D1 overexpression was observed as weakly positive in 81 cases (56.6%) and strongly positive in 38 cases (26.6%), while no expression was noted in 24 cases (16.8%). Figure 1-4 displays H&E and immunohistochemistry images illustrating cases with varying Cyclin D1 expression scores. Cyclin D1 showed a moderate positive correlation with ER ($r = 0.33$, $P < .001$) and PR ($r = 0.31$, $P < .001$), while no significant correlations were found with HER2 ($r = -0.058$) or p53 ($P = .371$) (Table 5). As detailed in Table 6, Cyclin D1 overexpression was observed in 92.9% of Luminal B cases and only 60% of Triple-negative cases ($P = .008$).

Survival Analysis

The cases were systematically followed up at 6-month

Table 3. The relationship between Cyclin D1 expression and clinical parameters of IBC cases (n=143)

	Cyclin D1 (+)		Cyclin D1 (-)		*P*
	n	%	n	%	
Age					
<40	11	84.6	2	15.4	.448
40-59	48	78.7	13	21.3	
>60	60	87.0	9	13.0	
Tumor size (cm)					
<2	21	75.0	7	25.0	.233
2-5	81	87.1	12	12.9	
>5	17	77.3	5	22.7	
Axillary lymph node metastasis					
Present	72	83.7	14	16.3	.843
Absent	47	82.5	10	17.5	
Multiple foci					
Present	19	79.2	5	20.8	.561
Absent	100	84.0	19	16.0	
Menopausal status					
Present	87	87.0	13	13.0	.075
Absent	28	73.7	10	26.3	
Chemotherapy					
Present	87	82.9	18	17.1	.404
Absent	29	90.6	3	9.4	
Radiotherapy					
Present	81	82.7	17	17.3	1.000
Absent	36	83.7	7	16.3	

intervals over an average period of 72 months. Among the 132 patients subject to follow-up, 48 succumbed to breast cancer, and 31 experienced a recurrence. The median overall survival time reached 147 months. Statistically, Cyclin D1 overexpression did not exhibit a significant impact on both OS and DFS (*P* = .189 and .06, respectively) (Figure 5). However, higher Cyclin D1 overexpression in ER-negative patients is associated with decreased DFS (*P* < .001), and similarly, it has a detrimental effect on OS and DFS in HER2-positive patients (Figure 6) (*P* = .042 and .026, respectively). Cyclin D1 overexpression had no significant effect on OS or DFS in ER-positive patients (*P* = .12 and .08, respectively).

DISCUSSION

Cyclin D1 expression in IBC patients via IHC reveal varying rates in the literature. In a recent study, Bouzidi et al. reported overall Cyclin D1 expression in IBC as 74%.[11] Our study on 143 patients showed 16.8% Cyclin D1-negative, 56.6% weakly positive, and 26.6% strongly positive, with an overall 83.2% overexpression rate, higher than reported in the literature (52-76.9%).[8,12,13] In interpreting these, findings it is crucial to consider the potential impact of threshold values and the specific Cyclin D1 clone used in the study.

Regarding clinical parameters, no significant correlation was observed between age, menopausal status, and Cyclin D1 overexpression in both the literature and our study.[8,11,12] Cyclin D1 expression and tumor size show conflicting results in the literature[11,14,15], but we found no significant correlation. Similar to our study, several publications do not report a correlation between Cyclin D1 and axillary lymph node metastasis[11,12,14], although He et al. suggest a significant and positive correlation.[15] Several studies, including ours, found no statistically significant correlation between clinical stage and Cyclin D1 expression.[8,11,12,14] However, He et al. reported a significant increase in Cyclin D1 expression among stage 1-2 patients.[15]

Due to the well-known roles of Cyclin D1 in cell migration, invasion, and metastasis[16], we aimed to investigate its potential association with parameters such as

Table 4. The relationship between Cyclin D1 and histological parameters of IBC cases

	Cyclin D1 (+)		Cyclin D1 (-)		*P*
	n	%	n	%	
Histologic type					
IBC of no special type (ductal)	103	83.0	21	17.0	.941
ILC	7	87.5	1	12.5	
Other*	9	81.8	2	18.2	
LVI					
Present	87	87.0	13	13.0	.820
Absent	28	73.7	10	26.3	
Histologic grade (NHS)					
Grade 1	14	87.5	2	12.5	.151
Grade 2	71	87.6	10	12.4	
Grade 3	32	74.4	11	25.6	
Extranodal extention					
Present	42	84.0	8	16.0	.934
Absent	30	83.3	6	16.7	
In situ component					
Present	21	75.0	7	25.0	1.000
Absent	81	87.1	12	12.9	
Stromal TIL					
Present	72	83.7	14	16.3	.534
Absent	47	82.5	10	17.5	
Intratumoral TIL					
Present	19	79.2	5	20.8	.371
Absent	100	84.0	19	16.0	

* The other histologic subgroups include invasive micropapillary carcinoma, metaplastic carcinoma, tubular carcinoma, and invasive papillary carcinoma. Abb. LVI: Lymphovascular invasion, NHS: Nottingham histologic score, IBC: Invasive breast carcinoma, ILC: Invasive lobular carcinoma, TIL: Tumor infiltrating lymphocytes.

Table 5. Correlation analysis of ER, PR, HER2, and Cyclin D1 in IBC cases (n=143)

	ER	PR	HER2	Cyclin D1
ER	1	0.550(**)	-0.289(*)	0.337(**)
PR	0.550(**)	1	-0.267(*)	0.318(**)
HER2	-0.289(*)	-0.267(*)	1	-0.083
Cyclin D1	0.337(**)	0.318(**)	-0.058	1

Pearson correlation coefficients are presented; (*) indicates significance at the 0.05 level, (**) indicates significance at the 0.01 level, and values without asterisks indicate non-significant correlations.

Table 6. Cyclin D1 expression status across different molecular subtypes of breast cancer

	Cyclin D1 (+)	Cyclin D1 (-)	*P*
Molecular Subtypes			
Luminal A	36	10	.008
Luminal B	65	5	
Triple-negative	9	6	
HER2	9	3	

HER2: Human Epidermal Growth Factor Receptor 2

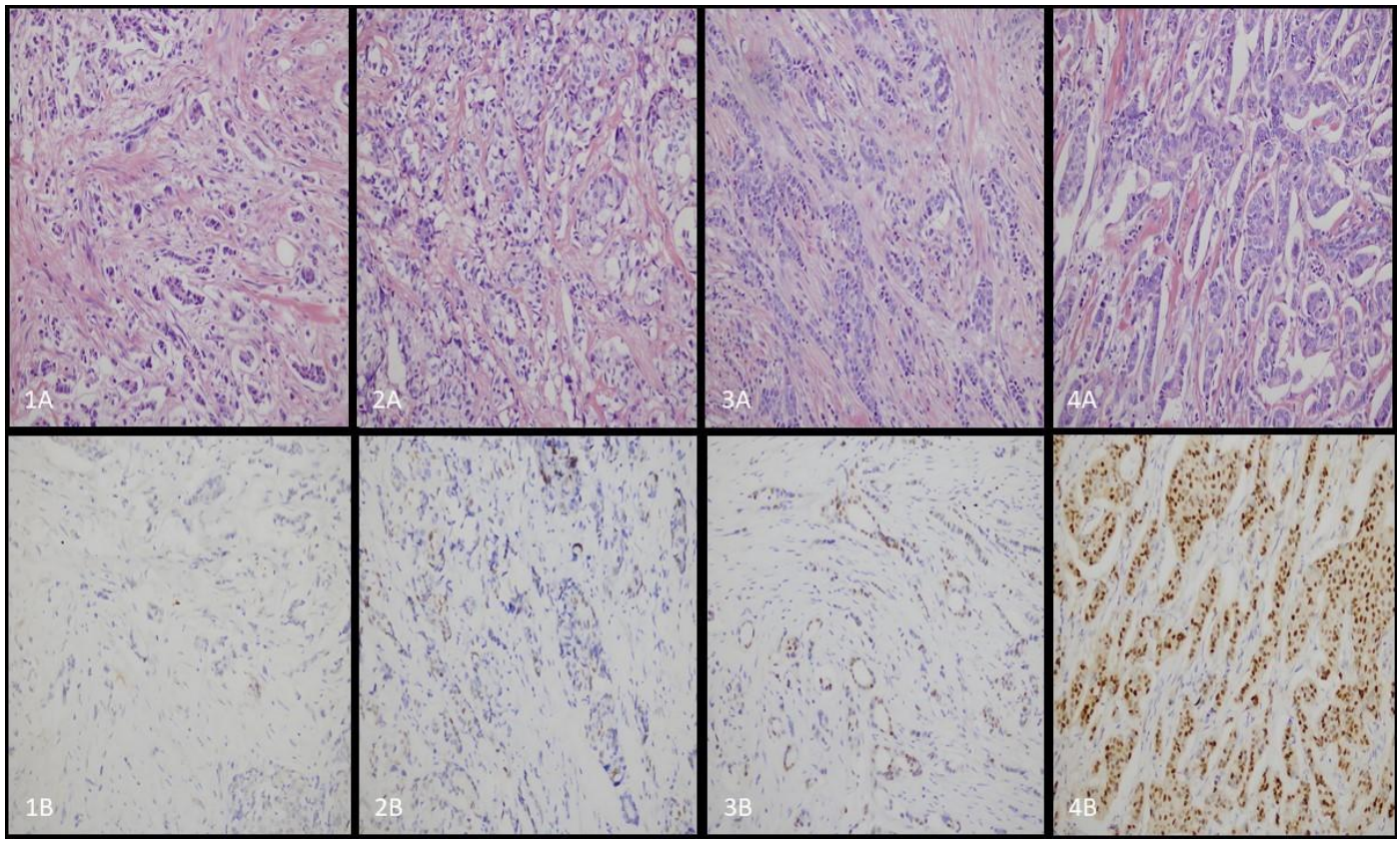

Figure 1-4. H&E and IHC images illustrating distinct Cyclin D1 expression levels in various IBC cases (H&E and IHC, x20 magnification for each image): Figure 1 shows invasive tumor (A) and Cyclin D1 negativity (B). Figure 2 shows invasive tumor (A) and score 1 Cyclin D1 positivity (B). Figure 3 shows invasive tumor (A) and 2 Cyclin D1 positivity (B). Figure 4 shows invasive tumor (A) and score 3 Cyclin D1 positivity (B).

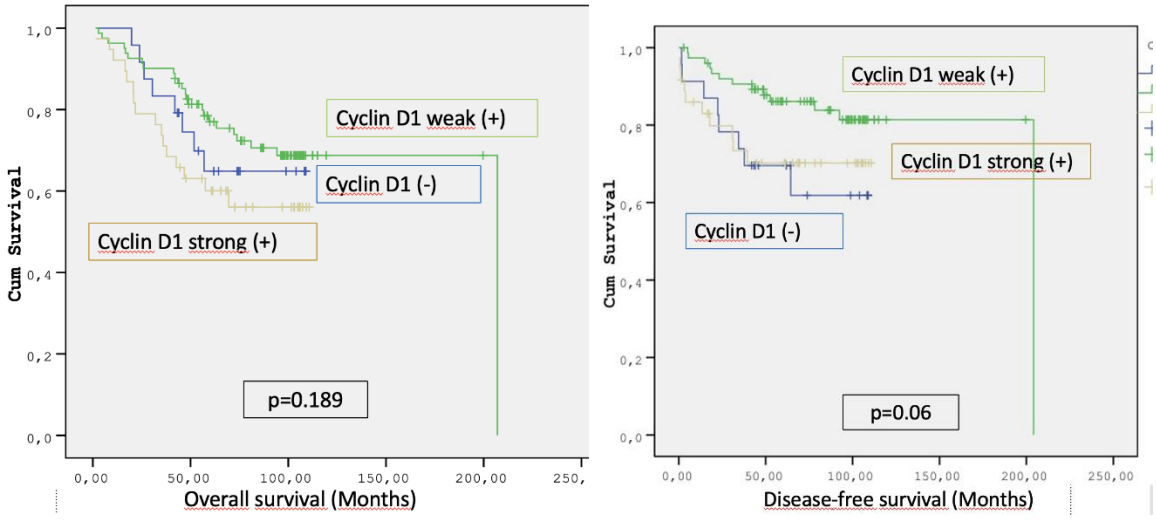

Figure 5. The correlation between Cyclin D1 expression and OS (A) and DFS (B) in unselected IBC cases.

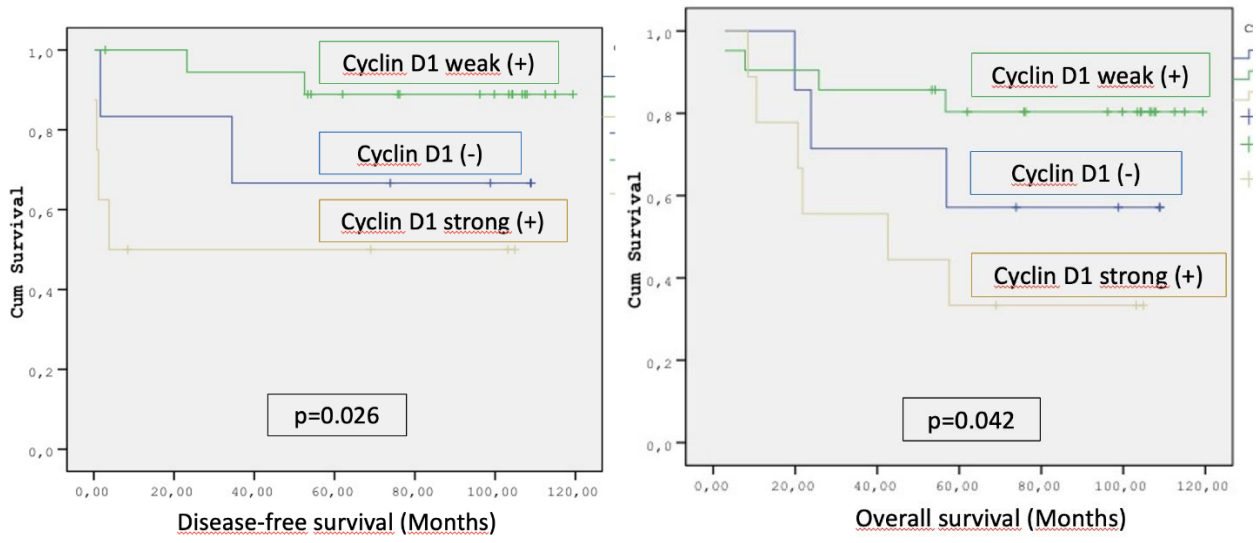

Figure 6. The correlation between Cyclin D1 expression and OS (A) and DFS (B) in HER2-positive IBC cases.

extranodal extension and LVI; however, no statistically significant correlation was found (P > .05). Similarly, the existing literature does not report any association between Cyclin D1 and LVI.[11] Studies on NHS (Nottingham Histologic Score) and Cyclin D1 relationship yielded mixed results[8,12,15]; our study found no significant correlation (P = .151). Cyclin D1's tightly regulated nature and diverse proliferation pathways in breast tumors may explain the lack of consistent correlation. No correlation was observed between the presence of carcinoma in situ and Cyclin D1, consistent with a recent study.[11] In our study, there was no observed association between Cyclin D1 and the presence of intratumoral and stromal TIL, recognized as a prognostic and predictive factor in IBC. To the best of our knowledge, there is no available data on this subject in the literature. Mylona et al. had linked Cyclin D1 overexpression to decreased p53 expression[12]; however, we observed no correlation between immunohistochemical p53 expression and Cyclin D1. This can be explained by differences in breast cancer populations from different geographic regions, tumor heterogeneity, and variations in IHC clones.

Numerous publications have consistently reported a positive correlation between overexpression of cyclin D1 and ER in breast cancer, and our study's results align with this pattern.[8,11,17] The direct interaction between Cyclin D1 and ER can activate nuclear receptors along with their coactivators, independent of CDK.[16] This CDK-independent nuclear receptor agonistic activity may also play a role in the oncogenic potential of Cyclin D1 in IBC.

HER2/*Neu* receptor amplification and Cyclin D1 overexpression are known to be associated with breast cancer. In HER2/*Neu*-induced breast tumors, the inhibitory effect of $p16^{INK4}$, a CDK 4 and 6 inhibitor, was demonstrated to block tumor formation in rats, thereby revealing an indirect link between HER2 and Cyclin D1.[18] Previous studies have indicated an increase in the expression of cell cycle pathway genes, such as CCND1 and CDK4, in HER2-enriched breast cancer.[19] In contrast to the findings of Guo et al. and Lee et al., our study did not identify a significant correlation between Cyclin D1 overexpression and HER2 (r= -0.083, P = .32). The number of HER2-positive cases in our sample was relatively limited (n=12), and divergent outcomes might be observed in more extensive datasets.

Considering molecular classes in our study, Luminal B group exhibited the highest Cyclin D1 expression, while the TNBC group showed the lowest. This finding is consistent with the known correlation between Cyclin D1 and ER and may reflect the estrogen-induced effects of this cell cycle regulator in IBC. Additionally, Guo et al. similarly found Luminal A group to have the highest Cyclin D1 expression.[8]

Conflicting findings have emerged regarding the impact of Cyclin D1 expression on OS and DFS in breast cancer. Some studies suggest an association with a favorable prognosis[8,20], while others indicate an unfavorable outcome.[8,21] In a meta-analysis of 21 breast cancer studies, Cyclin D1 gene amplification was linked to poor prognosis[22], while a 2020 meta-analysis by Binabaj et al. analyzing 34 studies found no prognostic effect of Cyclin D1 overexpression on breast cancer.[23] Furthermore, consistent with our study, certain publications propose that Cyclin D1 expression has no significant effect on prognosis.[11,24] Inconsistent results in the literature regarding prognosis and mortality may be associated with differences in Cyclin D1 measurement methods and cutoff selection, as well as

the heterogeneous nature of breast cancer. Focusing on the potential prognostic impact of Cyclin D1 in subgroups of breast cancer could provide further insights.

In ER-positive breast cancer, some studies propose an association between Cyclin D1 and a higher risk of mortality.[13,25-28] In a study parallel to ours, Cyclin D1 exhibited no impact on survival in ER-positive cancer.[29] One study examining the prognostic impact of cyclin D1 in ER-negative breast cancer identified it as a favorable factor[12], one as a negative factor[29], and other studies found no prognostic effect.[13,24,28] In our study, Cyclin D1 overexpression in ER-negative patients statistically significantly decreased DFS time ($P < .001$). ER-negative population is not homogenous and includes both HER2-positive and Triple-negative cases.

Cyclin D1 overexpression in HER2-positive patients is both related reduced DFS ($P = .026$) and OS time ($P = .042$) in our study. Research by Goel and colleagues revealed that Cyclin D1-CDK4 contributes to resistance in HER2+ breast cancer, with a crucial finding that this resistance was effectively overcome by combining CDK inhibitors and HER2-targeted therapy.[30] Despite the absence of a correlation between HER2 and Cyclin D1, the observed differences in survival times in our study could hold significant implications for the treatment of HER2-positive breast cancer. It has been suggested that the CCND1 gene may be linked to radiosensitivity in TNBC subgroup.[31] We did not find a significant relationship, but our sample size for TNBC cases was relatively small (n=15), and different results may be obtained in larger series.

Cyclin D1 has direct or indirect effects on treatment, especially in hormone-dependent breast carcinoma, and continues to be the subject of current studies. A combination of antiestrogen therapies, such as tamoxifen, along with CDK inhibitors, leads to cell cycle arrest specifically in the G1 phase.[32] The current NCCN guidelines recommend the combination of CDK 4/6 inhibitors with aromatase inhibitors as the first-line choice for a specific patient subgroup with hormone receptor-positive breast cancer.[7] Additionally, adiponectin-induced signals cause increased Cyclin D1 expression and breast tumor growth, positioning Cyclin D1 as a key target of adiponectin action in ER-positive breast cancer cells.[33] In recent years, there has been ongoing research into the role of miRNAs in the pathogenesis of IBC; however, clinical, and treatment-related implications have not yet been established. In Cyclin D1-induced breast cancer, activation of the miR-17/20 cluster is observed[34], and additionally, miR-21 and miR-93 trigger a pro-metastatic inflammatory response.[35]

Conclusively, we examined the relationship between Cyclin D1 expression and clinical-histopathological parameters in 143 cases diagnosed with IBC. A significant correlation was observed between ER and Cyclin D1. Cyclin D1 was overexpressed more in cases belonging to Luminal B group, while in Triple-negative group, it was less expressed. To the best of our knowledge, we compared the presence of stromal and intratumoral TIL, and extranodal extention with Cyclin D1 for the first time. Strong Cyclin D1 overexpression in HER2-positive cases significantly reduced OS and DFS.

Among the limitations of our study, it should be noted that our IBC cases represent a heterogeneous group. Furthermore, Cyclin D1 expression was evaluated exclusively at the protein level, without assessing mRNA, miRNA, or gene amplification. Similarly, HER2 status was determined solely by IHC, without FISH confirmation, which represents another limitation. Despite inconsistent findings in the literature regarding the potential prognostic impact of Cyclin D1, the effectiveness of CDK inhibitors in specific subgroups of breast cancer underscores the significance of conducting more extensive research in this area.

Etik Komite Onayı: Çalışmanın etik onayı 7 Haziran 2016 tarihinde İzmir Bozyaka Eğitim ve Araştırma Hastanesi Etik Kurulu'ndan alındı (Karar No. 4).
Hasta Onamı: Çalışma hakkında bilgi verildikten sonra tüm katılımcılardan yazılı bilgilendirilmiş onam alındı.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir- EÇ; Tasarım-DKÇ; Denetleme-FT; Kaynaklar-FT; Veri Toplanması ve/veya İşlemesi-EV; Analiz ve/ veya Yorum- DKÇ; Literatür-AY; Yazıyı Yazan-EÇ: Eleştirel İnceleme- FT
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

Ethics Committee Approval: Ethical approval for the study was obtained from the İzmir Bozyaka Education and Research Hospital Ethics Committee on June 7, 2016 (Decision No. 4).
Informed Consent: Written informed consent was obtained from all participants after providing information about the study.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept – EÇ; Design – DKÇ; Supervision – FT; Resources – FT; Data Collection and/or Processing – EV; Analysis and/or Interpretation – DKÇ; Literature Search – AY; Writing Manuscript – EÇ; Critical Review – FT
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185

Countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660
2. T.C. Saglik Bakanligi Halk Sagligi Genel Mudurlugu. Turkiye Kanser Istatistikleri 2018. Ankara: T.C. Saglik Bakanligi; 2022.
3. Tan PH, Ellis I, Allison K, et al. The 2019 World Health Organization classification of tumours of the breast. *Histopathology*.2020;77(2):181-185. doi:10.1111/his.14091
4. Roy M, Fowler AM, Ulaner GA, Mahajan A. Molecular Classification of Breast Cancer. *PET Clin.* 2023;18(4):441-458. doi:10.1016/j.cpet.2023.04.002
5. Tchakarska G, Sola B. The double dealing of cyclin D1. *Cell Cycle*. 2020;19(2):163-178. doi:10.1080/15384101.2019.1706903
6. Deshpande A, Sicinski P, Hinds PW. Cyclins and cdks in development and cancer: A perspective. *Oncogene*. 2005;24(17):2909-2915. doi:10.1038/sj.onc.1208618
7. Dwyer M. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Breast Cancer. NCCN.org. Published 2023. Available at: https://www.nccn.org.
8. Guo L, Liu S, Jakulin A, Yilamu D, Wang B, Yan J. Positive expression of cyclin D1 is an indicator for the evaluation of the prognosis of breast cancer. *Int J Clin Exp Med.* 2015;8(10):18656-18664.
9. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists guideline update. *Arch Pathol Lab Med.* 2020;144(5):545-563. doi:10.5858/arpa.2019-0904-SA
10. Wolff AC, McShane LM, Hammond MEH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch Pathol Lab Med*. 2018;142(11). doi:10.5858/arpa.2018-0902-SA
11. Bouzidi L, Makni S, Feki J, et al. Immunohistochemical Overexpression of Cyclin D1 in Tunisian Invasive Breast Carcinoma Women. *Arch Iran Med*. 2022;25(4):250-256. doi:10.34172/aim.2022.41
12. Mylona E, Tzelepis K, Theohari I, Giannopoulou I, Papadimitriou C, Nakopoulou L. Cyclin D1 in invasive breast carcinoma: Favourable prognostic significance in unselected patients and within subgroups with an aggressive phenotype. *Histopathology*. 2013;62(3):472-480. doi:10.1111/his.12013
13. Ahlin C, Lundgren C, Embretsén-Varro E, Jirström K, Blomqvist C, Fjällskog ML. High expression of cyclin D1 is associated to high proliferation rate and increased risk of mortality in women with ER-positive but not in ER-negative breast cancers. *Breast Cancer Res Treat*. 2017;164(3):667-678. doi:10.1007/s10549-017-4294-5
14. Guo LL, Gao P, Wu YG, et al. Alteration of Cyclin D1 in Chinese Patients with Breast Carcinoma and its Correlation with Ki-67, pRb, and p53. *Arch Med Res*. 2007;38(8):846-852. doi:10.1016/j.arcmed.2007.06.004
15. He Y, Liu Z, Qiao C, Xu M, Yu J, Li G. Expression and significance of Wnt signaling components and their target genes in breast carcinoma. *Mol Med Rep*. 2014;9(1):137-143. doi:10.3892/mmr.2013.1774
16. Montalto FI, De Amicis F. Cyclin D1 in Cancer: A Molecular Connection for Cell Cycle Control, Adhesion and Invasion in Tumor and Stroma. *Cells*. 2020;9(12):2648. doi:10.3390/cells9122648
17. Ravikumar G, Ananthamurthy A. Cyclin D1 expression in ductal carcinoma of the breast and its correlation with other prognostic parameters. *J Cancer Res Ther.* 2014;10(3):671-675. doi:10.4103/0973-1482.138135
18. Yang C, Chen L, Li C, Lynch MC, Brisken C, Schmidt E V. Cyclin D1 enhances the response to estrogen and progesterone by regulating progesterone receptor expression. *Mol Cell Biol*. 2010;30(12):3111-3125. doi:10.1128/MCB.01398-09
19. The Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. *Nature*. 2012;490(7418):61-70. doi:10.1038/nature11412.
20. Holah NS, Hemida AS. Cyclin D1 and PSA act as good prognostic and clinicopathological indicators for breast cancer. *J Immunoassay Immunochem*. 2020;41(1):28-44. doi:10.1080/15321819.2019.1677706
21. Cheng CW, Liu YF, Yu JC, et al. Prognostic significance of cyclin D1, b-catenin, and MTA1 in patients with invasive ductal carcinoma of the breast. *Ann Surg Oncol*. 2012;19(13):4129-4139. doi:10.1245/s10434-012-2541-x
22. An HX, He Q, Wu J, et al. Clinicopathological and prognostic significance of cyclin D1 amplification in patients with breast cancer: a meta-analysis. *JBUON*. 2017;22(5):1209-1216.

23. Moradi Binabaj M, Bahrami A, Khazaei M, et al. The prognostic value of cyclin D1 expression in the survival of cancer patients: A meta-analysis. *Gene*. 2020;728:144283. doi:10.1016/j.gene.2019.144283
24. Lee A, Park WC, Yim HW, Lee MA, Park G, Lee KY. Expression of c-erbB2, cyclin D1 and estrogen receptor and their clinical implications in the invasive ductal carcinoma of the breast. *Jpn J Clin Oncol*. 2007;37(9):708-714. doi:10.1093/jjco/hym082
25. Bostner J, Ahnström Waltersson M, Fornander T, Skoog L, Nordenskjöld B, Stål O. Amplification of CCND1 and PAK1 as predictors of recurrence and tamoxifen resistance in postmenopausal breast cancer. *Oncogene*. 2007;26(49):6997-7005. doi:10.1038/sj.onc.1210506
26. Beca F, Pereira M, Cameselle-Teijeiro JF, Martins D, Schmitt F. Altered PPP2R2A and Cyclin D1 expression defines a subgroup of aggressive luminal-like breast cancer. *BMC Cancer*. 2015;15:285. doi:10.1186/s12885-015-1266-1.
27. Tobin NP, Lundgren KL, Conway C, Anagnostaki L, Costello S, Landberg G. Automated image analysis of cyclin D1 protein expression in invasive lobular breast carcinoma provides independent prognostic information. *Hum Pathol*. 2012;43(11). doi:10.1016/j.humpath.2012.02.015
28. Aaltonen K, Amini RM, Landberg G, Eerola H. Cyclin D1 expression is associated with poor prognostic features in estrogen receptor positive breast cancer. *Breast Cancer Res Treat*. 2008;113(1):75-82.
29. Umekita Y, Ohi Y, Sagara Y, Yoshida H. Overexpression of cyclinD1 predicts for poor prognosis in estrogen receptor-negative breast cancer patients. *Int J Cancer*. 2002;98(3):415-418. doi:10.1002/ijc.10151
30. Goel S, Wang Q, Watt AC, et al. Overcoming Therapeutic Resistance in HER2-Positive Breast Cancers with CDK4/6 Inhibitors. *Cancer Cell*. 2016;29(3):255-269. doi:10.1016/j.ccell.2016.02.006
31. Choi C, Park S, Cho WK, Choi DH. Cyclin D1 is associated with radiosensitivity of triple-negative breast cancer cells to proton beam irradiation. *Int J Mol Sci*. 2019;20(19):4943. doi:10.3390/ijms20194943
32. Pernas S, Tolaney SM, Winer EP, Goel S. CDK4/6 inhibition in breast cancer: current practice and future directions. *Ther Adv Med Oncol*. 2018;10:1758835918786451. doi:10.1177/1758835918786451.
33. De Amicis F, Chiodo C, Morelli C, et al. AIB1 sequestration by androgen receptor inhibits estrogen-dependent cyclin D1 expression in breast cancer cells. *BMC Cancer*. 2019;19(1):1038. doi:10.1186/s12885-019-6262-4.
34. Yu Z, Wang C, Wang M, et al. A cyclin D1/microRNA 17/20 regulatory feedback loop in control of breast cancer cell proliferation. *J Cell Biol*. 2008;182(3):509-517. doi:10.1083/jcb.200801079.
35. Lu J, Zhao Q, Ding X, et al. Cyclin D1 promotes secretion of pro-oncogenic immuno-miRNAs and piRNAs. *Clin Sci*. 2020;134(7): 791-805. doi:10.1042/CS20191318

ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article *Araştırma Makalesi* DOI: 10.61745/tss.1671470

Evaluation of Preoperative and Postoperative Anxiety Levels of Patient Relatives in Patients Undergoing Anesthesia for Surgical Operation

Cerrahi Operasyon İçin Anestezi Uygulanacak Hastalarda, Hasta Yakınlarının Preoperatif ve Postoperatif Anksiyete Düzeylerinin Değerlendirilmesi

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9th International Hippocrates Congress on Medical and Health Sciences / 9-10 October 2022 İstanbul

Geliş Tarihi/Received	05.01.2025
Revision request/Revizyon Talebi	03.02.2025
Son Revizyon/Last Revision	05.02.2025
Kabul Tarihi/Accepted	18.02.2025
Yayın Tarihi/Publication Date	08.04.2025

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Cite this article: Orbak MS, Özmen Ö, Ateş İ, Aksoy M, Dostbil A, Kaşali K, et al. Evaluation of Preoperative and Postoperative Anxiety Levels of Patient Relatives in Patients Undergoing Anesthesia for Surgical Operation. *Trends Surg Sci*. 2025;4(1):34-43

ABSTRACT

Objective: Using the STAI anxiety scale, patient relatives; We aimed to evaluate preoperative, intraoperative and postoperative anxiety levels according to age, gender, familiarity levels, education, professions, anesthesia experience and type of surgery.

Methods: Preoperative, intraoperative and postoperative advice to the relatives of patients who will undergo surgery; The "STAI FORM TX-1" survey form, which is used to measure situational anxiety, was filled out according to the patient's relatives' age, gender, level of closeness with the patient, educational status, profession, anesthesia experience, type of surgery that the patient will undergo and their level of preoperative information.

Results: Each group is formed according to preoperative, intraoperative and postoperative patient age, gender, ASA, surgery type, surgery duration, anesthesia type, patient relative age, patient relative gender, past anesthesia experience, degree of closeness, frequency of meeting with the patient, education level and income level. When compared, there was a statistically significant difference in all groups except the group with patient age >74 and the group whose degree of closeness to the patient was the mother ($P < .05$). When all groups were evaluated within themselves, male gender was statistically significant for anxiety generation in terms of patient gender ($P < .05$).

Conclusion: It has been observed that there are multiple factors that can cause anxiety in patients' relatives. It has been observed that the intraoperative anxiety of patient relatives with high preoperative anxiety levels increases, and postoperatively, it decreases from preoperative levels.

Keywords: Anxiety, State-Trait Anxiety Inventory (STAI) scale, Patient relatives

ÖZ

Amaç: STAI anksiyete skalası kullanarak hasta yakınlarının; yaş, cinsiyet, yakınlık düzeyleri, eğitimi, meslekleri, anestezi deneyimleri, ameliyat türüne göre preoperative, intraoperatif ve postoperatif anksiyete düzeylerini değerlendirmeyi amaçladık.

Yöntemler: Cerrahi operasyon olacak hastaların yakınlarına preoperatif, intraoperatif ve postoperatif; hasta yakınlarının yaşı, cinsiyeti, hasta ile olan yakınlık düzeyleri, eğitim durumları, meslekleri, anestezi deneyimleri, hastalarının olacağı ameliyat türü ve preoperatif bilgi edinme düzeylerine göre durumsal kaygıyı ölçmede kullanılan "STAI FORM TX-1" anket formu doldurtuldu.

Bulgular: Hasta yaşı, cinsiyeti, ASA, cerrahi tipi, cerrahi süresi, anestezi şekli, hasta yakını yaşı, hasta yakını cinsiyeti, geçmiş anestezi deneyimi, yakınlık derecesi, hasta ile görüşme sıklığı, eğitim durumu ve gelir düzeyine göre oluşturulan herbir grup preoperative, intraoperative ve postoperative olarak karşılaştırıldığında hasta yaşı > 74 olan grup ve hasta yakınlık derecesi anne olan gruplar haricinde tüm gruplarda istatistiksel olarak

anlamlı fark mevcuttu (P < ,05). Tüm gruplar kendi içinde değerlendirildiğinde hasta cinsiyeti açısından erkek cinsiyet anksiyete oluşturma için istatistiksel olarak anlamlı idi (P < ,05).
Sonuç: Hastaların yakınlarında anksiyeteye sebep olabilecek birden fazla faktörün olduğu görülmüştür. Preoperatif kaygı durumları yüksek olan hasta yakınlarının intraoperatif kaygılarının arttığı, postoperatif ise preoperatif düzeylerden aşağıla ra indiği görülmüştür.
Anahtar Kelimeler: Anksiyete, State-Trait Anxiety Inventory (STAI) skalası, Hasta yakını

INTRODUCTION

Preoperative evaluation is a crucial process for patients of all ages before undergoing surgery. This assessment identifies comorbidities prior to the operation, allowing for the establishment of optimal conditions for anesthesia during surgery and postoperative care. Additionally, it provides an opportunity to address abnormalities detected in laboratory tests of patients unaware of any underlying conditions. Preoperative evaluation offers insights into the potential interactions of the patient's current medications with anesthetics. Preoperative evaluation also guides the development of appropriate treatment strategies both before surgery and during the postoperative hospital stay. Furthermore, it serves to address preoperative concerns of patients and their families, thereby alleviating anxiety disorders to some extent.[1]

Unresolved concerns that could lead to anxiety disorders may cause significant distress for patients' families. Such distress can result in unforeseen complications throughout the patient's hospital stay, from preoperative admission to discharge.[2] In some cases, heightened anxiety levels in patients and their families may even increase the patient's need for analgesia during hospitalization due to the underlying condition or the surgical procedure itself.[3] Despite the similarities among anxiety, depression, apprehension, and fear, various surveys have been conducted to assess these emotional disorders in patients seeking hospital treatment.[4,5] According to these surveys, anxiety-related issues are not limited to patients but also represent challenges for their families and healthcare providers, who must find ways to address or mitigate these problems.[6]

The anxiety levels of patients' families have been evaluated using the State-Trait Anxiety Inventory (STAI), developed by Spielberger. The STAI categorizes anxiety into two dimensions: state anxiety and trait anxiety.[7] It comprises two separate scales, each consisting of 20 items. This inventory is self-administered and straightforward to apply. In our study, we utilized the state anxiety scale, which measures situational anxiety. The validity and reliability of this scale for use in Turkey were established by N. Öner in 1977. Anxiety levels for state anxiety (S-anxiety) are classified as follows: low anxiety <35 points, moderate anxiety 36–46 points, and high anxiety >47 points (Table 1).

This study aimed to evaluate the preoperative, intraoperative, and postoperative anxiety levels of patients' families whose relatives were undergoing surgery with anesthesia administration.

METHODS

Study Design

This study aimed to measure and compare the anxiety levels of patients relatives in the preoperative, intraoperative, and postoperative periods. Measurements were taken during premedication in the anesthesia clinic in the preoperative period, while waiting in the surgical waiting area during the intraoperative period, and at the bedside in the postoperative period.

Study Population and Sample

Ethical approval for the study was obtained from the Atatürk University, Faculty of Medicine Ethics Committee on March 25, 2021 (Meeting No. 2, Decision No. 121). The study population included relatives (aged 18 years and older) of patients scheduled for elective or emergency surgical procedures under general or regional anesthesia in the Department of Anesthesiology and Reanimation between March 2021 and May 2021. The surgeries spanned various specialties, including Cardiovascular Surgery, Neurosurgery, ENT Surgery, General Surgery, Pediatric Surgery, Orthopedic Surgery, Urologic Surgery, Plastic and Reconstructive Surgery, Ophthalmic Surgery, and Obstetrics and Gynecology.

To ensure consistency, each questionnaire was completed by a single relative of each patient. If multiple relatives of the same patient completed questionnaires, the data were excluded. Relatives under 18 years of age or those who were illiterate were also excluded. All participants signed informed consent forms, which were documented. In the postoperative period, all patients were managed to achieve a Visual Analog Scale (VAS) pain score of ≤4.

Table 1. Spielberger Anxiety State Scale: STAI FORM TX-1

	Not at all (1)	A little (2)	Very much (3)	Completely (4)
1 I'm feeling calm.				
2 I'm feeling secure.				
3 I'm feeling tense at the moment.				
4 I'm feeling regretful.				
5 I'm feeling peaceful.				
6 I'm not feeling cheerful.				
7 I feel worried for what's waiting for me.				
8 I'm feeling rested.				
9 At the moment, I'm anxious.				
10. I'm feeling comfortable.				
11 I'm feeling confident.				
12 At the moment, I'm feeling upset.				
13 I'm very angry.				
14 I'm feeling my nerves are very tense.				
15 I'm feeling relieved.				
16 At this moment, I feel content.				
17 At this moment, I'm nervous.				
18 I'm feeling baffled with excitement.				
19 I'm joyful.				
20 At the moment, I'm in a good mood.				

The translated version of the scale in Turkish that was adapted by N. Öner in 1977

The sample size was calculated based on a previous study by Taşdemir et al.[8] using G-POWER software, with preoperative anxiety levels of 40.5 ± 12.5 and postoperative anxiety levels of 38.5 ± 12.0, a sample of 297 patient-relative pairs was determined to achieve 95% confidence and 80% power to detect a meaningful difference of 2 points.

A total of 312 patients were initially enrolled. However, 4 were excluded due to illiteracy, 2 were under 18 years of age, and 2 others were excluded because their relationship to the patient was at a friendship level. Data from 304 patients were ultimately analyzed.

Data Collection Tools

Patient relatives were asked to complete questionnaires during three visits. The first questionnaire was administered in the preoperative period outside the examination room after premedication and consultation in the anesthesia clinic. The second was administered during the

intraoperative period, 10 minutes after the patient entered the operating room, in the waiting area. The third was completed in the postoperative period, 2 hours after the patient was transferred to their hospital bed from the operating room.

The questionnaires consisted of five sections:

1. Section 1: Demographic details of the patient, date of form completion, ASA score, clinical ward, diagnosis, type of surgery, duration of surgery, consent status, and planned anesthesia method.
2. Section 2: Demographic details of the patient's relative, including gender, relationship to the patient, frequency of interaction with the patient, education level, occupation, income status, and previous anesthesia experience.
3. Section 3: Preoperative STAI form.
4. Section 4: Intraoperative STAI form.
5. Section 5: Postoperative STAI form.

In the preoperative period, relatives completed sections 1 and 2 along with the preoperative STAI form. During surgery, they filled out only the intraoperative STAI form. In the postoperative period, the relatives completed the postoperative STAI form during bedside visits.

Statistical Analysis

Data were analyzed using SPSS version 20. Numerical data (IBM Corp., Armonk, NY, USA) were presented as mean ± standard deviation, while categorical data were summarized as counts (n).

- For comparisons between two independent groups, the Independent Samples t-test was used if normality assumptions were met; otherwise, the Mann-Whitney U test was applied.
- For comparisons among more than two independent groups, ANOVA was used for normally distributed data, and the Kruskal-Wallis test for non-normally distributed data. Post-hoc analyses for ANOVA employed the Tukey test (for homogeneous variances) or Tamhane's T2 test (for non-homogeneous variances). Post-hoc tests for the Kruskal-Wallis test used the Kruskal-Wallis 1-way ANOVA (k samples) method.
- For dependent groups with repeated measures, Repeated Measures ANOVA was used for normally distributed data, and the Friedman test for non-normally distributed data. Post-hoc tests for Repeated Measures ANOVA used the Tukey or Tamhane's T2 tests based on variance homogeneity. Post-hoc analyses following the Friedman test utilized the Friedman 2-way ANOVA by ranks (k samples) method.

A p-value of $< .05$ was considered statistically significant.

RESULTS

The demographic data of 304 patients and their relatives, along with STAI form responses during the preoperative, intraoperative, and postoperative periods, were recorded and statistically compared.

Anxiety Scores Based on Patient Age:

- For patients aged 0–18 years, there was a statistically significant difference in anxiety scores between preoperative and postoperative, and intraoperative and postoperative periods in favor of the preoperative and intraoperative groups ($P < .05$). For patients aged 18–65 years, a statistically significant difference was observed across all groups ($P < .05$). For patients aged 65–74 years, a statistically significant difference was found between preoperative and intraoperative, and postoperative and intraoperative periods in favor of the intraoperative group ($P < .05$). For patients older than 74 years, no statistically significant difference was found among the groups ($P > .05$) (Table 2).

Anxiety Scores Based on Patient Gender

- For male patients, there was a statistically significant difference between preoperative and intraoperative, and postoperative and intraoperative periods in favor of the intraoperative group ($P < .05$). For female patients, a statistically significant difference was observed across all groups ($P < .05$) (Table 2).

Anxiety Scores Based on ASA Classification

- For ASA I patients, a statistically significant difference was observed across all groups ($P < .05$). For ASA II and III patients, a statistically significant difference was found between preoperative and intraoperative, and postoperative and intraoperative periods in favor of the intraoperative group ($P < .05$) (Table 2).

Anxiety Scores Based on Surgery Type

- For emergency surgeries, there was a statistically significant difference between preoperative and postoperative anxiety scores in favor of the preoperative group ($P < .05$). For elective surgeries, a statistically significant difference was observed across all groups ($P < .05$) (Table 3).

Anxiety Scores Based on Surgery Duration

- For surgeries lasting 0-30 minutes and 30-60 minutes, a statistically significant difference was observed between preoperative and postoperative anxiety scores in the preoperative group, and between intraoperative and

Table 2. Patient relative anxiety scores according to patient age, gender and ASA classification

Patients' age	n (number)	Preoperative Group	Intraoperative Group	Postoperative Group	*P*
0-18	22	44.77±8.80 [b]	48.64±11.94[a]	37±9.48	<.001
18-65	215	39.26±10.27	43.59±10.94[a]	36.86±10.02	<.001
65-74	46	38.46±8.68	47.5±10.73[a]	37.41±9.77	<.001
>74	21	39±7.60	43.04±10.13[a]	36.04±8.79	.239
Gender					
Male	132	39.47±8.85	46.48±10.10[a]	38.4±9.56	<.001
Female	172	39.55±10.59	42.99±11.49[a]	35.75±9.89	<.001
ASA					
I	143	40.35±10.04	45.08±11.04[a]	36.72±9.79	<.001
II-III	161	38.78±9.66	44.01±11.03[a]	37.06±9.88	<.001

Values are given as mean ± SD and n (number)
[a]Significant difference between intraoperative and other groups
[b]Significant difference between preoperative and postoperative groups

postoperative scores in the intraoperative group (*P* < .05). For surgeries lasting 60–90 minutes, 90–120 minutes, and over 120 minutes, a statistically significant difference was observed between preoperative and intraoperative, and postoperative and intraoperative periods in favor of the intraoperative group (*P* < .05) (Table 3).

Anxiety Scores Based on Anesthesia Type:

- For patients under general anesthesia, a statistically significant difference was observed across all groups (*P* < .05). For patients under regional anesthesia, a statistically significant difference was found between preoperative and intraoperative anxiety scores in favor of the intraoperative group (*P* < .05) (Table 3).

Anxiety Scores Based on Relative Age:

- For relatives aged 18–30 and 30–50 years, a statistically significant difference was observed across all groups (*P* < .05). For relatives older than 50 years, a statistically significant difference was observed between preoperative and intraoperative anxiety scores in favor of the intraoperative group (*P* < .05) (Table 4).

Anxiety Scores Based on Relative Gender:

- For male relatives, there was a statistically significant difference between preoperative and intraoperative, and postoperative and intraoperative periods in favor of the intraoperative group (*P* < .05). For female relatives, a statistically significant difference was found between preoperative and postoperative scores in favor of the preoperative group, and between intraoperative and postoperative scores in favor of the intraoperative group (*P* < .05) (Table 4).

Anxiety Scores Based on Anesthesia Experience:

- Regardless of whether the relative had prior anesthesia experience, a statistically significant difference was observed across all groups (*P* < .05) (Table 4).

Anxiety Scores Based on Relationship to the Patient:

- For spouses and other relatives, a statistically significant difference was observed between preoperative and intraoperative, and postoperative and intraoperative periods in favor of the intraoperative group (*P* < .05). For fathers, a statistically significant difference was found between postoperative and intraoperative periods in favor of the intraoperative group (*P* < .05). For children, a statistically significant difference was observed across all groups (*P* < .05). For mothers, no statistically significant difference was found among the groups (*P* > .05) (Table 5).

Anxiety Scores Based on Frequency of Interaction with the Patient:

- For relatives who interacted with the patient daily, a statistically significant difference was observed across all groups (*P* < .05). For relatives who interacted weekly, a statistically significant difference was found between preoperative and intraoperative, and postoperative and

Table 3. Relative anxiety scores according to surgery type, surgical duration and anesthesia type

Surgery type	n (number)	Preoperative Group	Intraoperative Group	Postoperative Group	*P*
Urgent	13	32.15±6.34	33.08±8.92 [a]	29.92±4.87	<.001
Elective	291	39.85±9.86	45.02±10.85 [a]	37.21±9.87	<.001
Surgical Duration (minute)					
0-30	20	45.75±5.69 [c]	44.60±9.41 [b]	36.85±10.97	<.001
30-60	77	41.40±10.34	43.03±8.69 [a]	37.30±9.91	<.001
60-90	36	39.42±8.77	43.97±10.77 [a]	33.81±9.21	<.001
90-120	80	37.04±9.55	42.41±11.20 [a]	36.9±9.99	<.001
> 120	91	38.77±10.10	47.80±12.45 [a]	37.8±9.54	<.001
Anesthesia type					
General	272	39.31±9.91	44.42±11.13	36.68±9.74	<.001
Regional	32	41.28±9.38	45.25±10.28	38.75±10.42	.035

Table 4. Anxiety scores according to patient relatives' age, gender end anesthesia experience

Relatives' age	n (number)	Preoperative Group	Intraoperative Group	Postoperative Group	*P*
18-30	120	38.74±10.97	43.13±11.07 [a]	36.45±9.99	<.001
30-50	161	39.61±9.84	45.19±11.04 [a]	36.47±9.25	<.001
>50	23	42.91±6.11	46.96±10.26 [b]	42.30±11.51	<.001
Gender					
Male	207	38.72±9.81	44.9±10.9 [a]	37.20±9.69	<.001
Female	97	41.22±9.78	43.68±11.32 [a]	36.26±10.12	<.001
Anesthesia experience					
No	185	39.76±10.27	44.41±11.21 [a]	37.23±10.14	<.001
Yes	119	39.13±9.19	44.66±10.78 [a]	36.39±9.33	<.001

Values are given as mean ± SD and n (number)

[a] Significant difference between intraoperative and other groups

[b] Significant difference between intraoperative and postoperative groups

Table 5. Patient relative anxiety scores according to degree of closeness and frequency of occurrence

Degree of closeness	n (number)	Preoperative Group	Intraoperative Group	Postoperative Group	*P*
Spouse	62	37.92±10.01	43.94±10.87 [a]	36.13±9.69	<.001
Mother	11	47.18±10.48	45.27±9.21	36.82±8.35	.148
Father	18	44.33±9.59	47.06±12.59 [b]	37.28±9.25	<.001
Child	150	39.33±9.20	44.51±11.34 [a]	37.25±10.28	<.001
Other	63	38.81±10.46	44.22±10.47 [a]	36.75±9.46	<.001
Frequency of occurrence					
All days	239	39.41±10.04	43.46±10.95 [a]	36.84±10.27	<.001
Once a week	43	38.30±7.16	46.30±10.96 [a]	35.63±8.12	<.001
Once a mount	22	43.09±11.86	52.41±8.51 [a]	40.05±7.09	<.001

Values are given as mean ± SD and n (number)
[a] Significant difference between intraoperative and other groups
[b] Significant difference between intraoperative and postoperative groups

Table 6. Anxiety scores according to the education level of the patient's relative and relative income

Education level	n (number)	Preoperative Group	Intraoperative Group	Postoperative Group	*P*
Elementary School	39	42.03±7.83 [a]	45.44±11.23 [a]	37.21±9.94	<.001
Middle School	43	42±9.58	49.42±9.29 [b]	40.63±8.79	<.001
High School	97	39.72±9.92	44.25±10.57 [b]	37.46±9.56	<.001
University	125	37.72±10.19	42.74±11.45 [b]	35.09±10	<.001
Relative income (Turkish Lira)					
0-5k	177	40.11±9.19	44.97±10.78 [c]	38.11±9.62	<.001
5k-10k	110	38.25±10.51	43.43±11.22 [b]	35.16±10.02	<.001
>10k	17	41.59±11.76	46.76±12.34 [b]	35.53±9.26	<.001

Values are given as mean ± SD and n (number)
[a] Significant difference between pre-intraoperative and postoperative groups
[b] Significant difference between intraoperative and other groups
[c] Significant difference between intraoperative and postoperative groups

intraoperative periods in favor of the intraoperative group ($P < .05$). For relatives who interacted monthly, a statistically significant difference was found between postoperative and intraoperative periods in favor of the intraoperative group ($P < .05$) (Table 5).

Anxiety Scores Based on Education Level:

- For relatives with primary school education, a statistically significant difference was found between postoperative and intraoperative periods in favor of the intraoperative group ($P < .05$). For relatives with middle school or university education, a statistically significant difference was observed between preoperative and intraoperative, and postoperative and intraoperative periods in favor of the intraoperative group ($P < .05$). For relatives with high school education, a statistically significant difference was observed across all groups ($P < .05$) (Table 6).

Anxiety Scores Based on Income Level:

- For relatives with low or middle income, a statistically significant difference was observed across all groups ($P < .05$). For relatives with high income, a statistically significant

difference was found between postoperative and intraoperative periods in favor of the intraoperative group ($P < .05$) (Table 6).

DISCUSSION

Preoperative evaluation is a mandatory procedure for patients undergoing surgery, aimed at mitigating potential anxiety disorders in patients and their relatives as much as possible.[1]

Any thought that could induce distress during the patient's treatment may trigger anxiety in their relatives, potentially leading to undesirable complications throughout the hospitalization, from admission to discharge.[2]

In our study, we evaluated the anxiety levels experienced by relatives of patients undergoing anesthesia and surgery. Most studies in the literature focus on assessing anxiety levels in patients. However, studies investigating the anxiety levels of patient relatives are limited.

When examining the patient's age, our study found that relatives were most concerned about patients under 18 years old in preoperative, intraoperative, and postoperative periods. Anxiety scores for patients younger than 74 years increased intraoperatively and were lowest postoperatively. For patients older than 74 years, relatives exhibited nearly similar anxiety scores in all three periods. Lim et al.[9] found anxiety scores around 60 for relatives of patients older than 70 years scheduled for surgery, while our study reported scores around 43 for the >74 age group. In contrast to our findings, Kaytancı[10] observed higher anxiety levels among relatives of elderly patients. Çağıran[11] did not find any significant difference in anxiety scores among relatives of pediatric patients, but their study focused on patients under 12 years old. In our study, anxiety scores decreased as patient age increased.

Regarding patient gender, relatives expressed higher anxiety levels for male patients. For both genders, intraoperative anxiety scores were higher than preoperative and postoperative scores. Çağıran[11] also reported similar anxiety levels among patient relatives for both genders.

Examining ASA classification, there was no significant difference in anxiety scores between ASA I and ASA II-III groups during preoperative, intraoperative, or postoperative periods. However, intraoperative anxiety scores were significantly higher in both groups. Contrary to our findings, Mıngır[12] observed that anxiety increased as ASA classification increased.

In terms of emergency versus elective surgery, our study revealed that relatives had higher anxiety scores for elective cases during all periods compared to emergency cases. This might be due to relatives of emergency cases already experiencing high anxiety levels upon hospital admission, or the longer waiting periods for elective cases. Latif et al.[13], in contrast, found higher anxiety levels in emergency cases, though their study focused on patients' anxiety rather than their relatives.

For surgery duration, our study observed that shorter surgeries were associated with higher anxiety levels among relatives. Intraoperative anxiety scores were consistently higher across all surgery durations. No similar studies on surgical duration and relative anxiety were found in the literature.[14]

Regarding the type of anesthesia, relatives of patients undergoing regional anesthesia exhibited slightly higher, though not statistically significant, anxiety scores compared to those undergoing general anesthesia. Similarly, Jansen et al.[15] reported higher anxiety scores for local anesthesia.

When analyzing relatives' age groups, intraoperative anxiety scores were higher than preoperative and postoperative scores across all age groups. Anxiety levels increased as relatives' age increased. No studies in the literature have directly assessed the correlation between relatives' age and anxiety regarding their patients' surgery. However, Türedi[16] found that anxiety levels increased with relatives' age in a study involving ICU patients, consistent with our findings.

In terms of gender, male relatives exhibited higher intraoperative and postoperative anxiety scores, while female relatives had higher preoperative scores. No literature was found regarding the impact of gender on relatives' anxiety scores. However, Taşdemir et al.[8] found that female patients exhibited higher preoperative and postoperative anxiety scores, aligning with our findings preoperatively but differing postoperatively.

Relatives with previous anesthesia experience exhibited lower preoperative anxiety scores compared to those without experience, though intraoperative scores remained high for both groups. Xavier et al.[17] found higher anxiety scores in parents without prior anesthesia or surgical experience, differing from our findings.

Regarding the relationship to the patient, mothers had the highest preoperative anxiety scores, while fathers had the highest intraoperative scores. Across all relationships,

intraoperative anxiety scores were higher than preoperative and postoperative scores. Türedi[16] similarly observed high anxiety levels among ICU patients' parents.

The frequency of patient-relative interaction also influenced anxiety levels; less frequent interaction correlated with higher anxiety scores. Across all interaction frequencies, intraoperative anxiety scores were highest. No related studies were found in the literature.

Concerning education level, anxiety scores decreased as the education level of relatives increased. Intraoperative anxiety scores were higher than preoperative and postoperative scores across all educational levels. In contrast, Çağıran[11] reported that higher education levels were associated with increased anxiety scores among mothers of pediatric patients.

Finally, income level influenced anxiety differently across periods. Preoperative and intraoperative anxiety scores increased with higher income, whereas postoperative anxiety scores decreased. Similar findings were reported by Çağıran et al.[11] and Alacacıoğlu et al.[18], who found that higher income levels correlated with increased preoperative anxiety but decreased postoperative anxiety.

CONCLUSION

Although the necessity of surgery is a well-known cause of anxiety, our study highlighted various factors influencing the severity, progression, and development of anxiety among patient relatives. These factors included the patient's age, gender, surgery type and duration, anesthesia method, ASA classification, and the relatives' demographics, socio-cultural background, and relationship to the patient.

Despite the multifactorial nature of anxiety, our findings, consistent with previous studies, indicate a decreasing trend in anxiety levels among patient relatives as the surgical process progresses. Given the complex etiology of anxiety, further research is needed to gain deeper insights and improve patient-relative support during the perioperative period.

Etik Komite Onayı: Çalışmanın etik onayı 25 Mart 2021 tarihinde Atatürk Üniversitesi Tıp Fakültesi Etik Kurulu'ndan alındı (Toplantı No. 2, Karar No. 121).
Hasta Onamı: Çalışma hakkında bilgi verildikten sonra tüm katılımcılardan yazılı bilgilendirilmiş onam alındı.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir- ÖÖ; Tasarım-MSÖ, ÖÖ; Denetleme-MA, AD; Kaynaklar-MSÖ; Veri Toplanması ve/veya İşlemesi-MSÖ, İA; Analiz ve/ veya Yorum- KK, İİ; Literatür-MSÖ, ÖÖ; Yazıyı Yazan-MSÖ,ÖÖ: Eleştirel İnceleme- AD, MA, İİ, İA
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

Ethics Committee Approval: Ethical approval for the study was obtained from the Atatürk University, Faculty of Medicine Ethics Committee on March 25, 2021 (Meeting No. 2, Decision No. 121).
Informed Consent: Written informed consent was obtained from all participants after providing information about the study.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept – ÖÖ; Design – MSO, ÖÖ; Supervision – MA, AD; Resources – MSO; Data Collection and/or Processing – MSÖ, İA; Analysis and/or Interpretation – KK, İİ; Literature Search – MSÖ, ÖÖ; Writing Manuscript – MSÖ, ÖÖ; Critical Review – AD, MA, İİ, İA
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Tobias JD. Preoperative anesthesia evaluation. *Semin Pediatr Surg*. 2018;27(2):67-74. doi:10.1053/j.sempedsurg.2018.02.002
2. Boeke S, Jelicic M, Bonke B. Pre-operative anxiety variables as possible predictors of post-operative stay in hospital. *Br J Clin Psychol*. 1992;31(3):366-368. doi:10.1111/j.2044-8260.1992.tb01008.x
3. Weis OF, Sriwatanakul K, Weintraub M, Lasagna L. Reduction of anxiety and postoperative analgesic requirements by audiovisual instruction. *Lancet*. 1983;1(8314-5):43-44. doi:10.1016/s0140-6736(83)91574-x
4. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res (Hoboken)*. 2011;63 Suppl 11(0 11):S467-S472. doi:10.1002/acr.20561
5. Facco E, Stellini E, Bacci C, et al. Validation of visual analogue scale for anxiety (VAS-A) in preanesthesia evaluation. *Minerva Anestesiol*. 2013;79(12):1389-1395.
6. Zemła AJ, Nowicka-Sauer K, Jarmoszewicz K, Wera K, Batkiewicz S, Pietrzykowska M. Measures of preoperative anxiety. *Anaesthesiol Intensive Ther*. 2019;51(1):64-69. doi:10.5603/AIT.2019.0013
7. Spielberger CD, Auerbach SM, Wadsworth AP, Dunn TM, Taulbee ES. Emotional reactions to surgery. *J Consult Clin Psychol*. 1973;40(1):33-38. doi:10.1037/h0033982
8. Tasdemir A, Erakgun A, Deniz MN, Certug A. Comparison of Preoperative and Postoperative Anxiety Levels with State-Trait Anxiety Inventory Test in Preoperatively Informed Patients. *Turk J Anaesthesiol Reanim*. 2013;41(2):44-49.doi: 10.5152/TJAR.2013.11

9. Lim S, Oh Y, Cho K, Kim MH, Moon S, Ki S. The question of preoperative anxiety and depression in older patients and family protectors. *Anesth Pain Med (Seoul)*. 2020;15(2):217-225. doi:10.17085/apm.2020.15.2.217
10. Kaytancı, M. Genç (18 ile 30), yetişkin (31 ile 64) ve yaşlılık (65 ve üstü) dönemlerinde kansere yakalanan hastaların hasta yakınlarında gözüken depresyon, kaygı ve umutsuzluk düzeylerinin değerlendirilmesi. Sosyal Bilimler Enstitüsü, Haliç Üniversitesi; 2019
11. Cagiran E, Sergin D, Deniz MN, Tanattı B, Emiroglu N, Alper I. Effects of sociodemographic factors and maternal anxiety on preoperative anxiety in children. *J Int Med Res*. 2014;42(2):572-580. doi:10.1177/0300060513503758
12. Mıngır T, Ervatan Z, Turgut N. Spinal Anaesthesia and Perioperative Anxiety. *Turk J Anaesthesiol Reanim*. 2014;42(4):190-195. doi:10.5152/TJAR.2014.99705
13. Latif A, Shamsher Khan RM, Nawaz K. Depression and anxiety in patients undergoing elective and emergency surgery: Cross-sectional study from Allama Iqbal Memorial Teaching Hospital, Sialkot. *J Pak Med Assoc*. 2017;67(6):884-888.
14. Karanci AN, Dirik G. Predictors of pre- and postoperative anxiety in emergency surgery patients. *J Psychosom Res*. 2003;55(4):363-369. doi:10.1016/s0022-3999(02)00631-1
15. Jansen P, Stoffels I, Müseler AC, et al. Salivary cortisol levels and anxiety in melanoma patients undergoing sentinel lymph node excision under local anesthesia versus general anesthesia: a prospective study. *World J Surg Oncol*. 2020;18(1):53. doi:10.1186/s12957-020-01823-w
16. Türedi D. Yoğun Bakım Hastalarının Akut Fizyolojik Durum Değişikliklerinin Hasta Yakınlarının Psikolojileri Üzerindeki Etkisi. Tıp Fakültesi, Çukurova Üniversitesi; 2011.
17. Xavier IBM, Biscarra VB, Piccoli ÂB, et al. Nursing Guidelines on Cardiac Surgery and Parents' Anxiety: Randomized Clinical Trial. *Braz J Cardiovasc Surg*. 2020;35(4):437-444. doi:10.21470/1678-9741-2019-0345
18. Alacacioglu A, Tarhan O, Alacacioglu I, Dirican A, Yilmaz U. Depression and anxiety in cancer patients and their relatives. *J BUON*. 2013;18(3):767-774.

ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Derleme *Review*

DOI: 10.61745/tss.1671472

Rotem Rehberliğinde Kanama Yönetimi

Rotem Guided Bleeding Management

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ÖZ

Rotasyonel tromboelastometri (ROTEM), çeşitli klinik ortamlarda tam kanın viskoelastik profillerinin değerlendirilmesini sağlar. ROTEM kılavuzluğunda kanama yönetimi, hasta kan yönetiminin (HKY) temel bir parçası haline gelmiştir. ROTEM kılavuzluğunda HKY; kanamayı, transfüzyon gereksinimlerini, komplikasyon oranlarını ve sağlık bakım maliyetlerini azaltmada etkili olduğu gösterilmiştir. Birkaç randomize kontrollü çalışma ve meta-analiz, kanayan hastalarda ROTEM rehberliğinin; peroperatif morbidite ve mortaliteyi iyileştirdiğine dair kanıt sağlamıştır. Sık görülen kanama senaryoları üzerinden ROTEM sonuçları ve bu sonuçlara göre yapılacak hemostatik müdahaleler tartışılmıştır.

Anahtar Kelimeler: Viskoelastik testler, rotasyonel tromboelastometri, post-partum kanama, post-travmatik kanama, **kardiyovasküler** cerrahi hastasında kanama, transfüzyon yönetimi

ABSTRACT

Rotational thromboelastometry (ROTEM) enables the assessment of viscoelastic profiles of whole blood in a variety of clinical settings. ROTEM-guided bleeding management has become an essential part of patient blood management (PBM). ROTEM-guided PBM (Patient Blood Management) has been shown to be effective in reducing bleeding, transfusion requirements, complication rates, and healthcare costs. Several randomized controlled trials and meta-analyses have provided evidence that ROTEM guidance improves perioperative morbidity and mortality in bleeding patients. ROTEM results and the corresponding hemostatic interventions for common bleeding scenarios are discussed.

Keywords: Viscoelastic Tests, Rotational thromboelastometry, Post-partum bleeding, Post-traumatic bleeding, Bleeding in cardiovascular surgery patients, Transfusion management

Received/ Geliş Tarihi 15.11.2024
Revision request/Revizyon Talebi 12.12.2024
Son Revizyon/Last Revision 14.12.2024
Accepted/Kabul Tarihi 08.02.2025
Publication Date/Yayın Tarihi 08.04.2025

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Cite this article: Yılmaz MA, Özgödek HB, Uzun N, Aydın ME, Çelik EC. Rotem Guided Bleeding Management. *Trends Surg Sci*. 2025;4(1):44-50

GİRİŞ

ROTEM rehberliğinde kanama yönetimi, Hasta kan yönetiminin (HKY) temel bir parçasıdır.[1] Kanamanın tedavisi kanamayı durdurmaktır. Fakat kanama genellikle kolayca görülebilen ve hızlıca durdurulabilecek vasküler bir yapıdan kaynaklanmaz. Anestezistlerin temel hedefi ise bu süre zarfında hemodinamiyi korumak ve gereksiz transfüzyonları önleyerek transfüzyon kaynaklı mortalite ve morbiditeleri önlemektir. Yapılan çalışmalar profilaktik veya uygunsuz yapılan kan transfüzyonun kanamayı önlemediğini tam tersine mortalite dahil olmak üzere daha kötü sonuçlarla ilişkili olduğunu göstermişlerdir.[2-5] Khan ve arkadaşları tarafından 2014 yılında yapılan çok merkezli bir çalışmada transfüzyonla ilişkili mortalitenin %66'sı, transfüzyonla ilişkili akut akciğer hasarı (TRALI), transfüzyonla ilişkili dolaşım aşırı yüklenmesi (TACO) ve hastane kaynaklı enfeksiyonlarla birlikte transfüzyonla ilişkili immünmodülasyona (TRIM) dayandırmaktadır.[6] Bu çalışmadan da anlaşılacağı üzere kanayan hastalardaki mortaliteyi kanama durdurulduktan sonra belirleyen faktörün transfüze edilen kan ve kan ürünü miktarının belirlediğidir.

Klasik oran bazlı yapılan transfüzyonlar ise koagülopatiyi düzeltmez ve şiddetli kanaması olan hastalarda mortaliteyi azaltmaz.[7,8] Oran bazlı transfüzyon düşünülüyorsa bunun kanamayı durdurmayacağı bilinmelidir. Kanamanın nedenini belirlemek ve kanamayı durdurmak için yapılacak hemostatik müdahaleye kadar zaman kazanmak için kullanılabilir. Winearls ve arkadaşları tarafından 2016 yılında yapılan reviewde bazı merkezlerin oran bazlı transfüzyon ile hedefe yönelik transfüzyonu hibrit şekilde kullandığını göstermiştir.[9] Çünkü şiddetli kanamada zaman çok kıymetlidir. Yapılan çalışmalar standart laboratuvar koagülasyon testlerinin tahmini sonuç süresini 30 ile 90 dakika arası olarak belirlemiştir buda kanayan hastada klinik kararlara rehberlik etmek için çok uzundur.[10-12] Viskoelastik yöntemler 10 ile 15 dakika içinde sonuç verir.[13] Viskoelastik yöntemler pıhtı başlangıcından sonraki 5. ve 10. dakikadaki pıhtının mm cinsinden genliğini göstererek kanayan hasta yönetiminde doğru bir rehberlik sağlar. Ayrıca Viskoelastik yöntemlerde maksimum pıhtı sertliği (*Maximum Clot Firmness*-MCF), plazma fibrinojen konsantrasyonu ve trombosit sayısı ile çok iyi korelasyon gösterir.[13] Viskoelastik yöntemler yalnızca zaman açısından değil, aynı zamanda çeşitli klinik ortamlarda kanamanın nedenini ve transfüzyon ihtiyacını belirleme açısından da standart laboratuvar testlerinden üstündür.[14-16] Viskoelastik yöntemler kılavuzluğunda HKY; kanamayı, transfüzyon gereksinimlerini, komplikasyon oranlarını ve sağlık bakım maliyetlerini azaltmada etkili olduğu gösterilmiştir. Fakat Dias ve arkadaşlarının 2024 yılında yayınlamış oldukları meta analizde ROTEM'in her ne kadar ES, TDP ve Trombosit transfüzyonunu azalttığını göstermiş olsa da; hastaların re-operasyon, hastanede kalış süresi veya mortalite oranları açısından fark gözlenmemiştir.[17]

Viskoelastik testler, tromboelastografi (TEG) ve rotasyonel tromboelastometri (ROTEM) olmak üzere ikiye ayrılır. En sık kullanılan teknik rotasyonel tromboelastometri tekniğidir. Birkaç randomize kontrollü çalışma ve meta-analiz, kanayan hastalarda ROTEM rehberliğinin; peroperatif morbidite ve mortaliteyi azalttığına dair kanıt sağlamıştır.[18-20] ROTEM kılavuzlu algoritmalar, perioperatif kanama yönetiminde kişiselleştirilmiş yaklaşımı uygular.

KOAGÜLASYON

Vasküler yaralanma bölgesinde oluşan endotel hasarı normalde kan ile teması olmayan subendotelyal yapıların ortaya çıkmasına sebep olur. Bu subendotelyal yapılar trombositleri aktive eder.[21] Aktive olan trombositler subendotelyal matrikse yapışır ve birikmeye başlarlar. Trombosit birikimi ve subendotelyal dokudan salınan doku faktörü koagülasyon kaskadını uyarır. Oluşan trombin fibrinojeni fibrine dönüştürür. Fibrin trombosit tıkacını güçlendirir. Pıhtılaşmanın sonlandırılması ve fibrinolitik sistem tarafından pıhtının uzaklaştırılması ile doku yeniden şekillenerek koagülasyon tamamlanır. Ancak, kanama yönetimini sağlamaya çalıştığımız hastalarda, temelde fibrinolitik sistemi antifibrinolitik ilaçlarla baskılamaya çalışıyoruz; çünkü oluşan pıhtı patolojik değildir. Birçok çalışma transfüzyon riski taşıyan kanamalarda ilk basamak tedavi olarak antifibrinolitik ilaç olan traneksamik asidi önermektedir (Şekil 1).[22,23] CRASH-2 randomize kontrollü çalışma: 40 ülke 274 hastaneden toplanan 20211 travma hastasından elde edilen veriler sonucunda kanamalı travma hastalarında traneksamik asidin mortaliteyi azalttığını göstermiştir.[24]

ROTEM

Kanama; kardiyopulmoner bypass, travma, post partum kanama, karaciğer nakli gibi birçok nedenden kaynaklanabilir. ROTEM kanamalı hastanın takibinde hızlı tanı ve tedavi imkânı sunmaktadır.

ROTEM çalışma tekniği olarak hastadan alınan sitratlı bir kan örneğinde salınımlı bir pimin sabit dönme kuvvetine maruz kalan tek kullanımlık kapta 37°C'ye kadar ısıtarak ölçümlere başlar. Pimin dönme hızına göre cihaz bir grafik çizer. Işık kaynağından gelen ışınlar, pim tarafından fotodedektöre yansıtılır. Pıhtı oluşmaya başlar ve giderek sertleşirse pim daha yavaş döner ve buda grafiğe yansır. Bu basit yöntem sayesinde, farklı reaktiflerle oluşturulan bölmelerde pıhtı sertlikleri ayrı ayrı ölçülebilir. ROTEM ölçümlerinden biri olarak İNTEM testinde reaktif olarak bulunan ellagik asit pıhtılaşma kaskadındaki intrensek yolağı aktive eder ve oluşan pıhtı ve pıhtının karakteristik özellikleriyle çizilen grafik intrensek yolağı temsil eder. İNTEM'deki uzamalar intrensek yolak (F12-F11-F9-F8), ortak yolak (F10-F5-F2-F1) ve trombosit eksikliklerini yansıtabilir.[25] EXTEM testinde reaktif olarak bulunan doku faktörü pıhtılaşma kaskadındaki extrensek yolağı aktive eder ve oluşan pıhtı extrensek yolağı temsil eder. EXTEM'deki uzamalar extrensek yolak (F7), ortak yolak (F10-F5-F2-F1) ve trombosit eksikliklerini yansıtabilir.[25] FİBTEM testinde reaktif olarak bulunan sitakalasin D trombositlerin mikrofilamentlerine inhibitör etkilidir buda trombosit aracılı pıhtılaşmayı önler ve sonuç olarak pıhtı fibrinojen aktivitesi ile oluşur ve fibrinojen aktivitesini yansıtır, APTEM testinde reaktif olarak eklenen aprotinin plazmini inhibe ederek pıhtı genliğinin azalmasının sebebini fibrinoliz olup olmadığını anlamamızı sağlayabilir, HEPTEM'de reaktif olarak heparinaz enzimi bulunur buda kan örneğindeki bulunan heparini parçalar ve hastanın heparinsiz kan örneğindeki pıhtı oluşumunu inceleme

imkânı sunar. Bu test ile kanamanın sebebinin heparin olup olmadığı anlaşılabilir veya yüksek heparinden dolayı kanama nedeni analiz edilemeyen hastalardan alınan kan örneğindeki heparin heparinaz ile yıkılarak heparinsiz bir numunenin sonuçları görülebilir.[13,25]

ROTEM PARAMETRELERİ

Temel çalışma prensibi tam kan dolu bir kaba dönen bir pim vasıtasıyla pıhtının karakterinin analiz edilmesini sağlar. Pıhtı kalınlaştıkça pimin dönüş hızını azaltır buda fotodedektör vasıtasıyla grafiği yansır.

Clotting Time (CT): Pıhtılaşma zamanı denilebilir. Oluşan pıhtının sertliğinin 2 mm oluncaya kadar geçen saniye cinsinden süredir (Şekil 1).[26]

Clot Formation Time (CFT): Oluşan pıhtının 2 mm'den 20 mm'ye kadar geçen saniye cinsinden süre olarak tanımlanır (Şekil 1).[26]

A5: 5. Dakikadaki pıhtının genliğinin mm olarak ifadesidir (Şekil 1). [26]

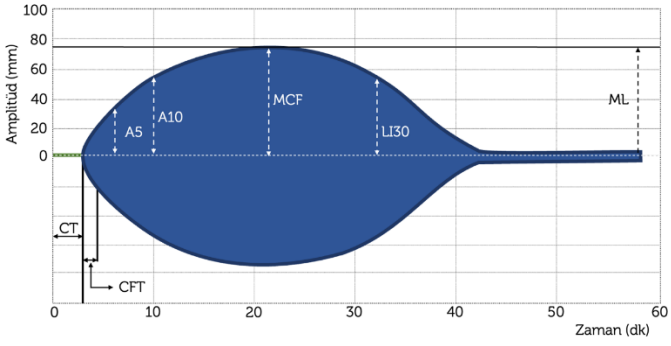
A10: 10. Dakikadaki pıhtının genliğinin mm olarak ifadesidir (Şekil 1).[26]

Maximal Clot Formation (MCF): Oluşan pıhtının maksimum genliğini mm olarak ifade etmektedir (Şekil 1).[26]

Lysis 30. Dakika (LI30): Maksimum pıhtı genliğinin 30. dakikada yüzde kaçının antifibrinolitik sistem tarafından yıkıldığının yüzdelik olarak ifadesidir (Şekil 1).[26]

Lysis 60. Dakika (LI60): Maksimum pıhtı genliğinin 60. dakikada yüzde kaçının antifibrinolitik sistem tarafından yıkıldığının yüzdelik olarak ifadesidir.[26]

Maximal Lysis (ML): Oluşan maksimum pıhtının genliğinin pıhtı yıkıldıktan sonraki genliğine oranının yüzdelik olarak ifadesidir (Şekil 1).[26]

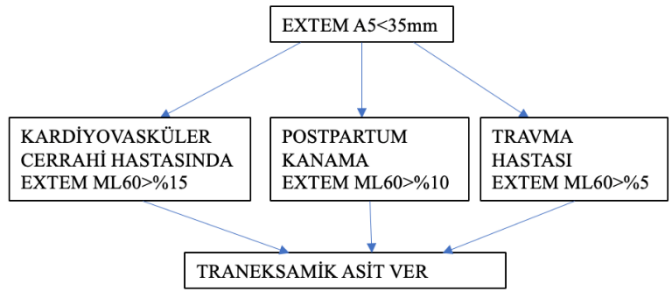


Şekil 1. Örnek bir ROTEM çizimi

CT: Clotting Time (pıhtılaşma zamanı), CFT: Clot Formation Time (pıhtı oluşum zamanı), A5: 5. dakikadaki pıhtı amplitüdü, A10: 10.dakikadaki pıhtı amplitüdü, MCF: Maximal Clot Formation (oluşan maksimum pıhtı amplitüdü), LI30: Lysis 30. Dakika, ML: Maximal Lysis

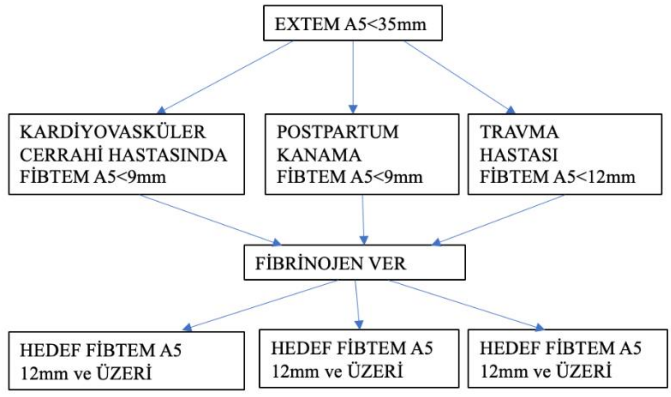
ROTEM SONUÇLARININ YORUMLANMASI

ROTEM sonuçlarının yorumlanırken belli algoritmalara uyulması gereksiz transfüzyonları önleyecektir.[13] İlk olarak



Şekil 2. EXTEM'in analizi

A5: 5.dakikadaki pıhtı amplitüdü, LI60: Lysis 60. Dakika



Şekil 3. Hipofibrinojenemide tedavi hedeflerimiz

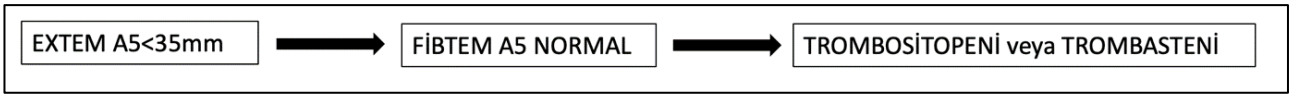
A5: 5.dakikadaki pıhtı amplitüdü

hastada kanamanın olup olmadığı, eğer kanama varsa bu kanama hastanın tolere edebileceği kanama miktarının üzerine çıkıp çıkmadığı, kanama miktarının kan ve ürünleri için transfüzyon ihtiyacı oluşturup oluşturmadığına bakılmalıdır. Potansiyel olarak transfüzyon ihtiyacı olabilecek kanamada ilk olarak fibrinoliz yönetimine odaklanılmalıdır. Kardiyovasküler cerrahiler özelinde değerlendirilirse antikoagülasyonun tersine çevrilmesinin yeterli olup olmadığına bakılmalıdır. Sonrasında oluşan pıhtının sertliğinin yönetimine odaklanılmalıdır. Yani kanaması olan bir hastada spesifik bir nedenimiz yok ise vücudun yaptığı doğal pıhtının fibrinolitikler tarafından yıkılıp yıkılmadığına bakılmalıdır. Gerek görülürse antifibrinolitikler ile müdahale edilmelidir. Oluşan doğal pıhtının özelliklerine odaklanılmalıdır. ROTEM oluşan pıhtıdaki trombosit ve fibrinojenin etkilerini ayrı ayrı gösterebilmektedir.

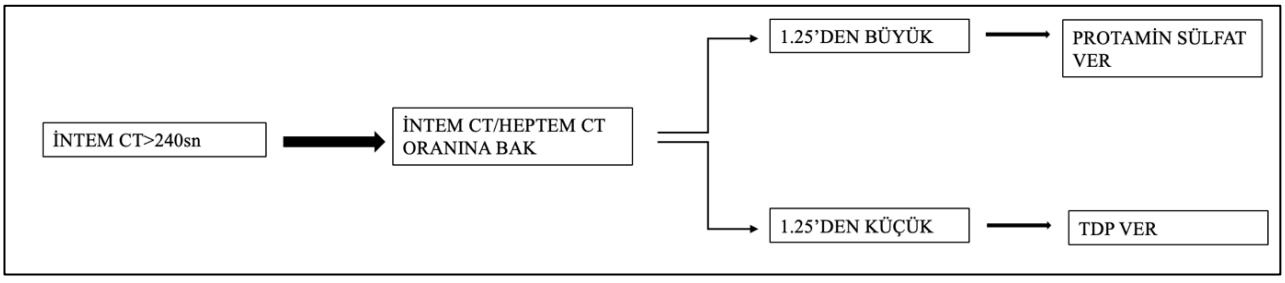
EXTEM A5 (5. dakikadaki pıhtı sertliği) 35 mm'nin altındaysa hipokoagülobiliteden bahsedilebilir ve bu hastada EXTEM ML (maximum lysis) kardiyovasküler cerrahi hastası için %15 ve üzeri ise, post-partum kanamalarda %10 ve üzeri ise, travma hastasında %5 ve üzeri ise 15-25 mg/kg da traneksamik asit endikasyonu bulunmaktadır. Bu senaryolarda temel kanama sebebi fibrinolitik sistemin aşırı aktivasyonudur.[13] Fibrinolitik

Tablo 1. FİBTEM rehberliğinde fibrinojen replasmanı

FİBTEM A5'de veya A10'da hedeflenen artış miktarı (istenilen FİBTEM A5-A10 genliği ile mevcut FİBTEM A5-A10- genliğinin farkı)	Replase edilmesi gereken fibrinojen miktarı	80 kg Erişkin hasta için replase edilmesi gereken fibrinojen miktarı
2 mm	12,5 mg/kg	1 gr
4 mm	25 mg/kg	2 gr
6 mm	37,5 mg/kg	3 gr
8 mm	50 mg/kg	4 gr
10 mm	62,5 mg/kg	5 gr



Şekil 4. Trombosit fonksiyon bozukluklarının tanınması
A5: 5.dakikadaki pıhtı amplitüdü



Şekil 5. İNTEM'in analizi
CT: Clotting Time (pıhtılaşma zamanı)

sistemin traneksamik asit ile önlenmesi hastadaki kanamanın azalmasına sebep olacaktır (Şekil 2). Ayrıca FİBTEM hiperfibrinolizis tanısında sensitif ve spesifiktir.[27] FİBTEM CT'ın 600 sn üzerinde olması da ve FİBTEM ML %10 ve üzeri ise yine hastada hiperfibrinolizis tanısı konulup traneksamik asit verilebilir.[13] EXTEM ML %15 üzerinde ve APTEM ML %0-5 arasında ise hiperfibrinolizis tanısı kesinleşir.[13]

Kanayan hasta kardiyovasküler cerrahi hastası ise heparin fazlalığından dolayı kanıyor olabilir öncelikle basit bir test olan ACT (Active Clotting Time) bakılmalıdır. ACT değeri bazal ACT den yüksek ise ve İNTEM CT'nin HEPTEM CT'ye oranının 1,25 ve üzerinde ise 0,3-0,5 mg/kg'dan protamin sülfat yapılmalıdır ve sonrasında kontrol ROTEM ve ACT bakılmalıdır.

Kanayan hastada bakılan ROTEM sonucunda EXTEM A5 sonucu 35 mm'nin altındaysa ve FİBTEM A5 pıhtı sertliği 9 mm'nin altındaysa; travma ve kardiyovasküler cerrahi hastasında kanama sebebinin fibrin polimerizasyon bozukluğundan kaynaklandığı düşünülebilir ve hastaya fibrinojen konsantresi verilmesi önerilir. Hedef FİBTEM A5 seviyesi 12 mm'dir. Eğer bu senaryo postpartum hemoraji hastasında ise FİBTEM A5 12 mm'nin altındaysa fibrinojen konsantresi endikasyonu bulunur ve hedef FİBTEM A5 değeri 16 mm'dir (Şekil 3). Hastalara ne kadar fibrinojen vermemiz gerektiğini Tablo 1 de açıklanmıştır.[13]

Eğer kanayan hastamızda sebep olarak oluşan pıhtının antifibrinolitik sistem tarafından yıkılması değil ve pıhtının özelliklerine bakıldığında fibrinojen yetersiz değil ise pıhtının diğer bileşeni olan trombosite odaklanılmalıdır. EXTEM A5 sonucu 35 mm'nin altında ve FİBTEM A5 normal ise kanamanın sebebi trombositlerin sayıca veya fonksiyonel olarak yetersiz olması olabilir (Şekil 4). Hastaya 10-15 mg/kg'dan trombosit konsantresi verilmesi önerilmektedir. Trombositopeni için standart hemogram analizi düşünülebilir. Eğer trombasteni için ileri tanı düşünülüyorsa TRAPTEM veya ADPTEM düşünülebilir.[13]

Eğer hastada EXTEM CT 80 saniyenin üzerindeyse pıhtılaşma faktör eksikliği sebebiyle oluşan bir kanama düşünülebilir ve hastaya 10-15 mg/kg'dan taze donmuş plazma (TDP) veya protrombin kompleks konsantresi (PCC) verilmelidir. İNTEM CT 240 saniyenin üzerinde ise İNTEM CT'ın HEPTEM CT'a oranı 1,25 ve üzeri ise dolaşımdaki fazla

heparin nedeniyle hasta kanıyordur protamin sülfat verilmelidir eğer oran 1.25'in altı ise hasta pıhtılaşma faktör eksikliğinden kanamaktadır TDP transfüzyon endikasyonu bulunmaktadır.

Kanaması devam eden hastaya yapılan hemostatik müdahaleden 10-15 dakika sonra tekrar ROTEM çalışılmalıdır. Çünkü kanamanın sebebi olarak izole bir neden bulunamayabilir. Ayrıca kontrol ROTEM'de EXTEM CT 45 saniyenin altındaysa hiperkoagülobilite düşünülmelidir hastada tromboz riski mevcuttur dikkat edilmelidir.[28]

ROTEM delta ve sigma için ayrı ayrı referans aralıkları; yenidoğanların, bebeklerin, çocukların, ergenlerin ve yetişkinlerin yanı sıra peripartum dönemdeki hastalar gibi çeşitli popülasyonlar için belirlenmiştir.[29-34]

ROTEM'İN KISITLILIKLARI

ROTEM'in kısıtlılıkları da bilinmelidir. ROTEM alınan kan örneğini 37°C'ye getirip çalıştığı için hastada hipotermiye sekonder gelişen bir koagülopati varsa ROTEM bunu tespit edemez. Von willebrand hastalığı gibi kalıtsal kanama bozukluğu sebebiyle oluşan kanamalarıda ROTEM belirleyemez çünkü hasar oluşan pıhtıda değildir von willebrand faktör defektinden dolayı trombositler hasarlı dokuya etki edememektedir.[35] Bu tarz kanama bozukluklarında in-vitro yapılan testlerde anormallik saptanamaz. İn-vitro ortamda pıhtı oluşumu normal olacaktır fakat bu oluşan pıhtının hasarlı dokuya tutunmasını sağlayan reseptörlerde problem vardır.

ROTEM trombosit fonksiyon bozukluğunu kısmen gösterebilir, ancak trombosit fonksiyonunu tam anlamıyla değerlendirmez. ROTEM sadece oluşan pıhtıdaki trombosit rolünü dolaylı olarak analiz eder. Trombositopeni veya trombasteni ayrımını yapamaz. Trombositopeni için klasik hemogram analizi önerilmektedir. Trombasteni ayrımı için ise ADPTEM – TRAPTEM önerilmektedir.

Viskoelastik testler her kurumda bulunan yaygın kullanılan cihazlar değildir. Çalışmak ve yorumlamak için eğitim gerektirmektedir.

SONUÇ

Son olarak ROTEM hastanın kanayıp kanamayacağını öngöremez sadece kanayan hastada nedeni bulmaya rehberlik edebilir. Kanamayan hastaya ROTEM yapılıp anormal bulgulara müdahale hiçbir çalışmada önerilmemektedir. Temel kullanım alanı kanayan hastadaki yönetime rehberlik etmek ve gereksiz transfüzyonları önlemektir.

Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir-MAY, MEA, NU; Tasarım-MAY, MEA, NU; Denetleme-HBÖ, MEA, ECÇ; Kaynaklar-MAY, MEA, NU; Veri Toplanması ve/veya İşlemesi- MAY, MEA, NU; Analiz ve/ veya Yorum-MAY, MEA, NU, ECÇ; Literatür Taraması-MAY, MEA, NU; Yazıyı Yazan-MAY, ECÇ; Eleştirel İnceleme-HBÖ, MEA, ECÇ.
Çıkar Çatışması: Bu makalenin yazarı Erkan Cem Çelik aynı zamanda bu derginin editörüdür. Bu durum çıkar çatışması yaratabilecek bir ilişki olarak değerlendirilmektedir. Tarafsız ve şeffaf bir hakemlik süreci sağlamak amacıyla, bu makalenin değerlendirmesinde Erkan Cem Çelik süreç dışında tutulmuştur. Ayrıca, çıkar çatışmalarını önlemek amacıyla bu sürecin tüm aşamaları derginin etik kuralları ve COPE, ICMJE gibi uluslararası etik yönergelerine uygun olarak yönetilmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

Peer-review: Externally peer-reviewed.
Author Contributions: Concept -MAY, MEA, NU; Design-MAY, MEA, NU; Supervision-HBÖ, MEA, ECÇ; Resources-MAY, MEA, NU; Data Collection and/or Processing-MAY, MEA, NU; Analysis and/or Interpretation-MAY, MEA, NU, ECÇ; Literature Search-MAY, MEA, NU; Writing Manuscript-MAY, ECÇ; Critical Review-HBÖ, MEA, ECÇ.
Conflict of Interest: The author of this article, Erkan Cem Çelik, is also the editor of this journal. This situation is considered as a relationship that may create a conflict of interest. In order to ensure an impartial and transparent peer review process, Erkan Cem Çelik was excluded from the evaluation of this article. In addition, in order to prevent conflicts of interest, all stages of this process were managed in accordance with the journal's ethical rules and international ethical guidelines such as COPE and ICMJE.
Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Zacharowski K, Spahn DR. Patient blood management equals patient safety. *Best Pract Res Clin Anaesthesiol*. 2016;30(2):159-169. doi:10.1016/j.bpa.2016.04.008
2. Inaba K, Branco BC, Rhee P, et al. Impact of plasma transfusion in trauma patients who do not require massive transfusion. *J Am Coll Surg*. 2010;210(6):957-965. doi:10.1016/j.jamcollsurg.2010.01.031
3. Desborough M, Sandu R, Brunskill SJ, et al. Fresh frozen plasma for cardiovascular surgery. *Cochrane Database Syst Rev*. 2015;2015(7):Cd007614. doi:10.1002/14651858.CD007614.pub2
4. Warner MA, Chandran A, Jenkins G, Kor DJ. Prophylactic Plasma Transfusion Is Not Associated With Decreased Red Blood Cell Requirements in Critically Ill Patients. *Anesth Analg*. 2017;124(5):1636-1643. doi:10.1213/ane.0000000000001730
5. Warner MA, Jia Q, Clifford L, et al. Preoperative platelet transfusions and perioperative red blood

cell requirements in patients with thrombocytopenia undergoing noncardiac surgery. *Transfusion*. 2016;56(3):682-690. doi:10.1111/trf.13414
6. Khan S, Brohi K, Chana M, et al. Hemostatic resuscitation is neither hemostatic nor resuscitative in trauma hemorrhage. *J Trauma Acute Care Surg*. 2014;76(3):561-567; discussion 567-568. doi:10.1097/ta.0000000000000146
7. Khan S, Davenport R, Raza I, et al. Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage. *Intensive Care Med*. 2015;41(2):239-247. doi:10.1007/s00134-014-3584-1
8. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471-482. doi:10.1001/jama.2015.12
9. Winearls J, Reade M, Miles H, et al. Targeted Coagulation Management in Severe Trauma: The Controversies and the Evidence. *Anesth Analg*. 2016;123(4):910-924. doi:10.1213/ane.0000000000001516
10. Toulon P, Ozier Y, Ankri A, Fléron MH, Leroux G, Samama CM. Point-of-care versus central laboratory coagulation testing during haemorrhagic surgery. A multicenter study. *Thromb Haemost*. 2009;101(2):394-401.
11. Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med*. 2011;39(12):2652-2658. doi:10.1097/CCM.0b013e3182281af5
12. Olde Engberink RH, Kuiper GJ, Wetzels RJ, et al. Rapid and correct prediction of thrombocytopenia and hypofibrinogenemia with rotational thromboelastometry in cardiac surgery. *J Cardiothorac Vasc Anesth*. 2014;28(2):210-216. doi:10.1053/j.jvca.2013.12.004
13. Görlinger K, Pérez-Ferrer A, Dirkmann D, et al. The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. *Korean J Anesthesiol*. 2019;72(4):297-322. doi:10.4097/kja.19169
14. Schöchl H, Cotton B, Inaba K, et al. FIBTEM provides early prediction of massive transfusion in trauma. *Crit Care*. 2011;15(6):R265. doi:10.1186/cc10539
15. Hagemo JS, Christiaans SC, Stanworth SJ, et al. Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. *Crit Care*. 2015;19(1):97. doi:10.1186/s13054-015-0823-y
16. Dötsch TM, Dirkmann D, Bezinover D, et al. Assessment of standard laboratory tests and rotational thromboelastometry for the prediction of postoperative bleeding in liver transplantation. *Br J Anaesth*. 2017;119(3):402-410. doi:10.1093/bja/aex122
17. Dias JD, Levy JH, Tanaka KA, Zacharowski K, Hartmann J. Viscoelastic haemostatic assays to guide therapy in elective surgery: an updated systematic review and meta-analysis. *Anaesthesia*. 2025;80(1):95-103. doi:10.1111/anae.16463
18. Weber CF, Görlinger K, Meininger D, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology*. 2012;117(3):531-547. doi:10.1097/ALN.0b013e318264c644
19. Deppe AC, Weber C, Zimmermann J, et al. Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: a meta-analysis of 8332 patients. *J Surg Res*. 2016;203(2):424-433. doi:10.1016/j.jss.2016.03.008
20. Wikkelsø A, Wetterslev J, Møller AM, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. *Cochrane Database Syst Rev*. 2016;2016(8):Cd007871. doi:10.1002/14651858.CD007871.pub3
21. Shen J, Sampietro S, Wu J, et al. Coordination of platelet agonist signaling during the hemostatic response in vivo. *Blood Adv*. 2017;1(27):2767-2775. doi:10.1182/bloodadvances.2017009498
22. Guyette FX, Brown JB, Zenati MS, et al. Tranexamic Acid During Prehospital Transport in Patients at Risk for Hemorrhage After Injury: A Double-blind, Placebo-Controlled, Randomized Clinical Trial. *JAMA Surg*. 2020;156(1):11-20. doi:10.1001/jamasurg.2020.4350
23. Gruen RL, Mitra B, Bernard SA, et al. Prehospital Tranexamic Acid for Severe Trauma. *N Engl J Med*. 2023;389(2):127-136. doi:10.1056/NEJMoa2215457
24. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*.

2010;376(9734):23-32. doi:10.1016/s0140-6736(10)60835-5
25. Drotarova M, Zolkova J, Belakova KM, et al. Basic Principles of Rotational Thromboelastometry (ROTEM(®)) and the Role of ROTEM-Guided Fibrinogen Replacement Therapy in the Management of Coagulopathies. *Diagnostics (Basel)*. 2023;13(20)doi:10.3390/diagnostics13203219
26. Brill JB, Brenner M, Duchesne J, et al. The Role of TEG and ROTEM in Damage Control Resuscitation. *Shock*. 2021;56(1s):52-61. doi:10.1097/shk.0000000000001686
27. Na HS, Shin HJ, Do SH. FIBTEM provides prediction of massive bleeding in total hip replacement arthroplasty. *Blood Coagul Fibrinolysis*. 2016;27(3):340-346. doi:10.1097/mbc.0000000000000428
28. Drotarova M, Zolkova J, Belakova KM, et al. Basic Principles of Rotational Thromboelastometry (ROTEM®) and the Role of ROTEM—Guided Fibrinogen Replacement Therapy in the Management of Coagulopathies. *Diagnostics*. 2023;13(20):3219.
29. Lang T, Bauters A, Braun SL, et al. Multi-centre investigation on reference ranges for ROTEM thromboelastometry. *Blood Coagul Fibrinolysis*. 2005;16(4):301-310. doi:10.1097/01.mbc.0000169225.31173.19
30. Schenk B, Görlinger K, Treml B, et al. A comparison of the new ROTEM(®) sigma with its predecessor, the ROTEMdelta. *Anaesthesia*. 2019;74(3):348-356. doi:10.1111/anae.14542
31. Sokou R, Foudoulaki-Paparizos L, Lytras T, et al. Reference ranges of thromboelastometry in healthy full-term and pre-term neonates. *Clin Chem Lab Med*. 2017;55(10):1592-1597. doi:10.1515/cclm-2016-0931
32. Oswald E, Stalzer B, Heitz E, et al. Thromboelastometry (ROTEM) in children: age-related reference ranges and correlations with standard coagulation tests. *Br J Anaesth*. Dec 2010;105(6):827-835. doi:10.1093/bja/aeq258
33. de Lange NM, van Rheenen-Flach LE, Lancé MD, et al. Peri-partum reference ranges for ROTEM(R) thromboelastometry. *Br J Anaesth*. 2014;112(5):852-859. doi:10.1093/bja/aet480
34. Oudghiri M, Keita H, Kouamou E, et al. Reference values for rotation thromboelastometry (ROTEM®) parameters following non-haemorrhagic deliveries. Correlations with standard haemostasis parameters. *Thromb Haemost*. 2011;106(1):176-178. doi:10.1160/th11-02-0058
35. Weyand AC, Flood VH. Von Willebrand Disease: Current Status of Diagnosis and Management. *Hematol Oncol Clin North Am*. 2021;35(6):1085-1101. doi:10.1016/j.hoc.2021.07.004

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ATATURK UNIVERSITY PUBLICATIONS

Review *Derleme*

DOI: 10.61745/tss.1671486

The Importance of Nutrition Before and Following Metabolic/Bariatric Surgery

Metabolik/Bariatrik Cerrahi Öncesinde ve Sonrasında Beslenmenin Önemi

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ABSTRACT

Obesity is a chronic disease, a global epidemic and among the non-communicable disease targets which are identified by World Health Organization (WHO). Bariatric surgery (BS) is one of the treatment approaches used in the fight against obesity. In this article, it is aimed to present general information about BS, nutritional evaluation before and after BS, various nutrition-related conditions, and information on how food supplements and diet phases should be maintained. In addition, factors that should be taken into consideration in individuals undergoing BS and new approaches in BS are included. BS has different methods, such as restrictive and malabsorptive methods. The process before and after BS differs. It is important to evaluate and follow up on an individual basis in a multidisciplinary way. BS methods may have an effect on the absorption of nutrients and the food intake may not meet the requirement due to anatomical changes after surgery. Therefore, food supplements should be given based on the need. In addition, an individual's diet should progress in stages. Considering the risk factors of individuals with BS, postoperative body weight loss should be maintained in the healthiest way. In order to use BS as an effective tool in obesity management, it is considered necessary to develop solutions for the risk factors carried by the individuals who constitute the target group for BS, to manage and maintain the process and follow-up in the most ideal way.

Keywords: Bariatric surgery, obesity, food supplements, weight loss

ÖZ

Obezite, Dünya Sağlık Örgütü (DSÖ) tarafından tanımlanan bulaşıcı olmayan hastalık hedefleri arasında yer alan, kronik bir hastalık ve küresel bir salgındır. Bariatrik cerrahi (BC), obeziteyle mücadelede kullanılan tedavi yöntemlerinden biridir. Bu makalede, BC ile ilgili genel bilgiler sunulmasının yanı sıra, BC öncesi ve sonrası beslenme değerlendirmesi, beslenmeyle ilişkili çeşitli durumlar, gıda takviyeleri ve diyet evrelerinin nasıl sürdürülmesi gerektiği konularında bilgi verilmesi amaçlanmıştır. Ayrıca, BC geçiren bireylerde dikkate alınması gereken etkenler ve BC'deki yeni yaklaşımlar bu makalede ele alınmıştır. BC'nin kısıtlayıcı ve malabsorptif yöntemler gibi farklı yaklaşımları vardır. BC öncesi ve sonrası süreçler birbirinden farklılık gösterir. Bu süreçte, multidisipliner bir yaklaşımla bireysel bazda değerlendirme ve takip yapılması önemli görülmektedir. BC yöntemleri, besin ögelerinin emilimini etkileyebilir ve ameliyat sonrası meydana gelen anatomik değişiklikler nedeniyle besin alımı, vücudun ihtiyaçlarını karşılamayabilir. Bu yüzden, bireyin gereksinimlerine göre gıda takviyeleri verilmelidir. Ayrıca bireyin diyetinin aşamalar halinde ilerlemesi gerekmektedir. BC geçiren bireylerin risk etkenleri göz önünde bulundurulduğunda, ameliyat sonrası vücut ağırlığı kaybı en sağlıklı şekilde sürdürülebilmelidir. BC'nin, obezite yönetiminde etkili bir araç olarak kullanılabilmesi için BC'nin hedef grubunu oluşturan bireylerin taşıdığı risk etkenlerine yönelik çözümler geliştirilmesi, ameliyat öncesi, ameliyat sırası ve ameliyat sonrasındaki sürecin en ideal şekilde yönetilip sürdürülmesi gerektiği düşünülmektedir.

Anahtar Kelimeler: Bariatrik cerrahi, obezite, gıda takviyeleri, vücut ağırlığı kaybı

Received/ Geliş Tarihi 19.09.2024
Revision request/Revizyon Talebi 25.09.2024
Son Revizyon/Last Revision 05.03.2025
Accepted/Kabul Tarihi 17.03.2025
Publication Date/Yayın Tarihi 08.04.2025

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Cite this article: Bayar E, Besler HT. The Importance of Nutrition Before and Following Metabolic/Bariatric Surgery. *Trends Surg Sci*. 2025;4(1):51-64

INTRODUCTION

Obesity is a risk factor for diseases which are chronic and a threat at a global level. Also, obesity is amongst the global non-communicable targets of disease identified by World Health Organization (WHO). It is stated that in 2015, 107.7 million children and 603.7 million grown-ups across the world had obesity.[1] Also, according to the World Obesity Atlas (2024), the projected increase in the prevalence and number of overweight adults (BMI ≥25-30 kg/m^2) is 1.39 billion, 1.52 billion, 1.65 billion and 1.77 billion in 2020, 2025, 2030 and 2035, respectively. In addition, the number of adults with obesity (BMI ≥30 kg/m^2) is 0.81 billion, 1.01 billion, 1.25 billion, and 1.53 billion in 2020, 2025, 2030, and 2035, respectively. The proportion of adults worldwide who are overweight or obese is expected to increase from 42% in 2020 to 54% in 2035.[2] There are various treatment methods (diet intervention, exercise, surgery, etc.) for obesity, which is a chronic, multifactorial and complex disease. Bariatric surgery (BS), one of these methods, is a method used in cases of severe obesity, and various conditions must be met for its application.[3] BS was first reported by Edward Mason in the mid-1960s, and it was stated that body weight loss could be achieved through restrictive and malabsorptive methods. Gastric bypass (GB) was first applied, and in 2001, U.S. Food and Drug Administration (FDA) confirmed the usage of Laparoscopic Adjustable Gastric Band (LAGB) method in America. The mortality rate observed with BS in the late 1990s was known to be 0.5-1.0%. The safety of BS has improved in recent years.[4] Severe obesity causes comorbidities and mortality and it is stated that BS has a reducing effect on these factors by providing long-term body weight loss.[5] BS methods can be restrictive, malabsorptive, or it can be both restrictive and malabsorptive. In restrictive methods, there is no intervention towards the digestive system but the quantity of food which can be kept in the stomach is being reduced that it leads to restriction. Vertical banded gastroplasty (VBG), (Laparoscopic) sleeve gastrectomy (L)SG and (laparoscopic) adjustable gastric banding (L) AGB methods are one of the restrictive methods. For malabsorptive methods, there is intervention towards the digestive system and it leads to malabsorption. One of the malabsorptive methods which can be mentioned is biliopancreatic diversion (BPD). And some of the methods which are both restrictive and malabsorptive are Roux-en-Y gastric bypass (RYGB), mini gastric bypass (MGB), single anastomosis duodeno-ileal bypass (SADI), single anastomosis gastric-ileal bypass (SAGI) and biliopancreatic diversion with duodenal switch (BPD-DS).[6]

Metabolic and Bariatric Surgery

Metabolic and bariatric surgery (MBS) is considered for people with a BMI of ≥35 kg/m^2, with or without comorbidity, and in the presence of metabolic disease for people with a BMI of 30-34.9 kg/m^2. For Asians, it is considered appropriate to use different BMI values (BMI ≥27.5 kg/m^2 to apply MBS) as a basis and MBS for children and adolescents should be decided upon careful evaluation. Generally for children and adolescents with BMI >120% of the 95th percentile and a major status of comorbidity, or a BMI >140% of the 95th percentile is being used as a basis to consider applying MBS. There is no upper age limit for MBS application. For the evaluation of elderly individuals, it is seen appropriate that comorbidity status and factors related to frailty to be taken into consideration.[7]

BS methods are diverse and it causes differences in the functioning of the digestive system and affects hormone levels.[3] Some of the BS methods (e.g. gastric banding) are completely anatomical and do not affect metabolic pathways. Some other methods (e.g. Roux-en-Y gastric bypass) have an effect on the anatomy of the digestive system and change physiological parameters. Methods that affect physiological parameters reduce orexigenicity and cause an increase in the number of anorexigenic hormones. Thus, physical hunger is suppressed.[6,8] Peptide hormones such as ghrelin, leptin, adiponectin, neuropeptide Y are associated with appetite and energy consumption. Appetite is regulated by central and peripheral hormones and nerve signals, which affects the individual's response to food intake. Disruption in the balance of orexigenic and anorexigenic hormones is known to be one of the main pathophysiological causes of obesity.[9] In a meta-analysis study aiming to evaluate the alterations in gastrointestinal hormones and adipokines post-BS, it was concluded that there was a significative decrease in leptin, ghrelin, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and interleukin-1β (IL-1β) levels and a significative increase in adiponectin, peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) levels.[10]

The process after BS varies depending on whether these methods affect the absorption of nutrients.[3] The estimated numbers of BS interventions from 2018 to 2022, as stated by American Society for Metabolic and Bariatric Surgery (ASMBS), are presented in Table 1[11] and some of the surgical procedures are given as Figure 1. Non-surgical procedures also include methods such as balloon, Primary Obesity Surgery Endoluminal (POSE), aspire assist and transpyloric shuttle.[1]

Table 1. Estimate of Bariatric Surgery Numbers. 2018-2022[11]

	2022	2021	2020	2019	2018
Sleeve	160.609	152.866	122.056	152.413	154.976
RYGB	62.097	56.527	41.280	45.744	42.945
Band	2.500	1.121	2.393	2.375	2.660
BPD-DS	6.096	5.525	3.555	2.272	2.123
Revision	30.894	31.021	22.022	42.881	38.971
SADI	1.567	1.025	488	-	-
OAGB	1.057	1.149	1.338	-	-
Other	6.189	7.339	1.221	6.060	5.847
ESG	4.600	2.220	1.500	-	-
Balloons	4.358	4.100	2.800	4.655	5.042
Total	**279.967**	**262.893**	**198.651**	**256.000**	**252.564**

RYGB: Roux-en-Y gastric bypass; BPD-DS: Biliopancreatic diversion with duodenal switch; SADI: Single anastomosis duodeno-ileal bypass; OAGB: One anastomosis gastric bypass; ESG: Endoscopic sleeve gastroplasty

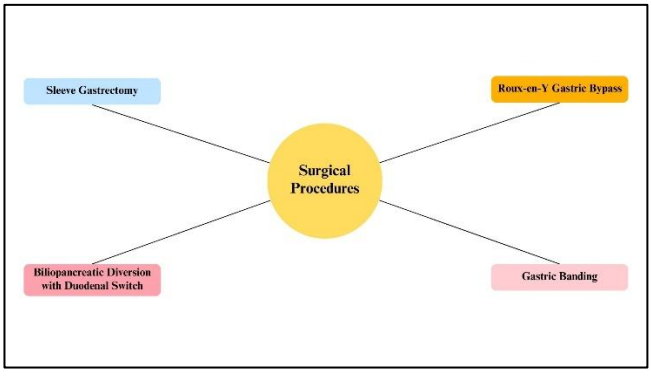

Figure 1. Surgical procedures of bariatric surgery[1]

Deficiency of some nutrients (e.g. vitamin B12, folic acid, iron) is observed after BS. It is also known that nutritional deficiencies (e.g. vitamin B12, vitamin D, folic acid, calcium, iron) are prevalent before BS. These deficiencies may be caused by absorption disorders, insufficient food intake or eating behaviors. Follow-up of patients is important in the process after BS.[3] Nutritional deficiencies after BS are due to various reasons. For example, decreased 25-hydroxyvitamin D concentrations following body weight loss are considered to be associated with increased retention and storage of vitamin D in adipose tissue. For vitamin B12, it is thought that one of the reasons may be the decrease in intrinsic factor production. For fat-soluble vitamins, it is thought that one of the reasons may be biliary pancreatic lesion that causes malabsorption of fat-soluble vitamins.[6] The impact of BS on nutritional status is mainly associated with a decrease in gastric volume and nutrient absorption.[5]

The nutrition therapy after BS should be progressed in stages, ensuring the individual's tolerance. At the same time, it should be ensured that nutritional requirements are met and digestive complications are minimized. It is important that nutritional treatment is specific to the individual and followed by a multidisciplinary team (medical specialist, BS expert dietitian, nurse, etc.). Regular follow-up should be done every 3 months for the first year post-BS, and one time in a year after the first year.[3] The most well-known BS methods include SG, RYGB, OAGB, AGB, and biliopancreatic diversion with or without duodenal switch (BPD/DS).[12]

Before Bariatric Surgery

Moderate body weight loss (about 5-10%) is recommended before BS to ease the surgery and decrease complications. For this purpose, individuals can be applied to a very low-calorie diet (600 kcal/day) or a low-calorie diet (800-1200 kcal/day). However, the situation which is catabolic and increase in oxidative stress that occur with very low-calorie diets should be taken into consideration, as they may have a negative impact on the surgery.[5] Checklist before the BS should include nutrition screening for iron, vitamin B12, folic acid and 25-vitamin D (vitamin A and vitamin E as optional). It shall be noted that in the case of malabsorptive procedures, more extensive screening is needed on the basis of indications and potential risks. Endocrine assessment (e.g. HbA1c, TSH), lifestyle evaluation (e.g. sleep quality, healthy eating, fitness), optimizing glycemic control are also included in the preprocedure checklist.[1] A calorie-restricted diet is recommended before BS to reduce perioperative complications associated with the surgery. There are contradictions regarding the effectiveness of these low-energy diets and body weight loss before the surgery on the BS process.[13] A systematic review and meta-analysis study aiming to evaluate the

Table 2. The suggested components of routine nutritional assessment and nutritional preparation process before the surgery[12]

Pre-surgery nutritional assessment	Pre-surgery nutritional preparation process
Weight-management history	Adjustment of the ideal eating and living behaviours
Eating patterns	Correcting of micronutrients deficiencies
Eating pathologies	Weight loss before the surgery
Anthropometric measurements	Progress in glycemic control for patients who have diabetes
Nutritional status	Initialisation of physical activity
Supplementation use	Building up the information on nutrition, obesity, and BS process
Skeletal status	Consultancy of nutrition
Dental hygiene	
Physical activity practices	
Bariatric surgery information	
Anticipations from the surgery	

effectiveness of body weight loss before BS concluded that body weight loss in the period before the surgery has moderate effects on the process for the perioperative period, but has no effect on long-term body weight loss.[14] However, due to the potential benefits of body weight loss in the preoperative period, it is recommended that people with a BMI over 50 kg/m^2, a large waist circumference, and a thick abdominal wall or intra-abdominal fat tissue follow a low-calorie diet. In the period which is before the operation, the target is generally to decrease the body weight by 10% or decrease 5% of excess body weight within 2 to 12 weeks before surgery. It should be taken into consideration that side reactions (e.g. gallstones, hair loss, lean mass loss, constipation) may occur if very low-calorie diets are applied in the preoperative period.[13]

Nutritional deficiencies of individuals before BS can be caused by a low-quality, high-calorie, high-fat diet that lacks nutritional diversity. At the same time, factors such as adipose tissue inflammation, increased adipose mass, and an increase in the signification of the systemic iron regulatory protein hepcidin due to obesity may cause nutritional deficiencies.[5] It is stated that the nutritional deficiencies seen in obese individuals before the BS intervention may be due not only to malabsorption and

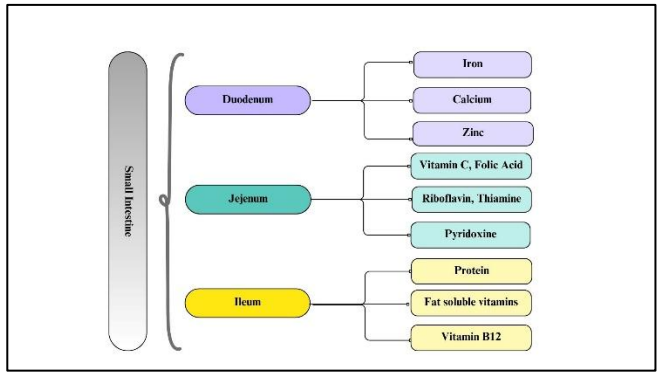

Figure 2. Absorption sites of some of the nutrients in the small bowel[18]

rapid body weight loss resulting from the surgery, but also to a malnutrition state that existed in the previous period. There may also be a decrease in the bioavailability of micronutrients in obese individuals. It is important to emphasize a healthy diet that includes all the elements.[15] Micronutrient deficiencies are frequently seen in patients before bariatric surgery. It is stated that two-thirds of patients have malnutrition before surgery. Since it is also a factor affecting the outcome of surgery, screening for malnutrition before surgery is recommended. Serum albumin and prealbumin levels are used to assess protein status in preoperative nutritional status, and low levels suggest malnutrition. It is thought that preoperative malnutrition detection accelerates recovery, reduces complications, and provides long-term health outcomes.[16] The suggested components of nutritional assessment and preparation process before BS are given as Table 2.[12]

After Bariatric Surgery

The physiological and anatomical change that the gastrointestinal system undergoes after BS may cause nutritional deficiencies. Nutritional deficiencies are related to many factors such as the surgical method applied, nutritional status before surgery, adherence to diet and food supplements given after surgery. Nutritional deficiencies are more common after malabsorptive methods compared to restrictive methods.[3] In a retrospective cohort study aimed at evaluating the occurrence status and conditions of nutritional deficiencies after BS in detail, the effect of SG, AGB and RYGB methods in the post-operative process was evaluated. As known, AGB is a restrictive method and there is no bypass of the gastrointestinal tract. Meanwhile, malabsorption is involved in the RYGB method, partial gastrectomy is performed in the SG method and hormonal changes are observed. In the study, it was concluded that RYGB and SG methods were associated with a 2.4 to 3.0 times probability of developing

Table 3. Mechanisms of nutritional deficiencies[3,19-23]

Nutrient	Reasons of deficiency	Prevalence of deficiency		Supplement Recommendations
		Pre-op	Post-op	
Iron	Low food intake Poor tolerance Malabsorption Decrease of hydrochloric acid secretion Intake of other supplements (such as calcium)	45% in patients with obesity	AGB 14% SG 18% RYGB 20–55% BPD 13–62% DS 8–50%	Required Minimum 18 mg/day (by multivitamin) (Grade C) 45-60 mg/day for menstruating patients (Grade C)
Vitamin B12	Decrease of the cobalamin stores The bypass of the surface which the vitamin is absorbed Low intake of food Low excretion of intrinsic factor Overgrowth of bacterial populations	2–18% in patients who have obesity 6–30% in patients taking proton pump inhibitors	RYGB 20% SG 4–20%	Required Orally: 350-500 µg/day As nasal spray: guided by the manufacturer Parenteral: 1000 µg/month
Folate/Folic acid	Low food intake Inadequate adherence to supplementation	54% in patients with obesity	Up to 65%	Required Orally: 400-800 µg/day (from multivitamin) (Grade B) 800-1000 µg/day for women of childbearing age (Grade B)
Calcium	Low food intake Inadequate adherence to supplementation Deficiency of Vitamin D Therapy for long-term proton-pump inhibitor The bypass of the surface which the vitamin is absorbed	66.7% in patients who are under 50 years of age and have raised values of carboxy-terminal telopeptide	RYGB 1.9% SG 9.3% BPD-DS 10%	Required BPD/DS: 1800–2400 mg/day LAGB, SG, RYGB: 1200–1500 mg/day
Vitamin D	Bile salt deficiency (which might occur with malabsorption) Overgrowth of bacterial populations Delayed blend of vitamin D	90% in patients with obesity	Up to 100%	Vitamin D3 dose: 3000 IU/day (Until blood levels of 25(OH)D are greater than the adequate level)
Vitamin B1 (Thiamine)	Low food intake The limited body stores of thiamine Persistent vomiting	29%	<1% to 49% (varies by surgery method and duration)	Required Minimum 12 mg/day (Grade C) 50 mg, once or twice in a day (Grade D)
Vitamins which are soluble in fat (Vitamin A, D, E and K)	Malabsorption	Vitamin A 14%, Vitamin E 2.2%	Vitamin A, up to 70% with RYGB and BPD/DS in 4 years. Deficiency of vitamin E and K are not common	Required Minimum 12 mg/day (Grade C) 50 mg, once or twice in a day (Grade D)

Table 3. (Continued) Mechanisms of nutritional deficiencies[3,19-23]

Zinc	Inadequate dietary intake Damage of intestinal mucosa Bypass of absorption sites	24-28% in general 74% of patients seeking BPD/DS	Up to 70% (RYGB %40 19% SG 34% AGB)	Required BPD/DS: 16–22 mg/day RYGB: 8–22 mg/day SG/LAGB: 8–11 mg/day
Copper	Inadequate dietary intake Reduced absorption due to BS procedures	70% in pre-BPD women	90% of patients RYGB 10–20%	Required BPD/DS or RYGB: 2 mg/day SG or LAGB: 1 mg/day (Copper to Zinc: 1/8-15 mg)

Grade A: Strong, Grade B: Intermediate, Grade C: Weak, Grade D: No evidence

Table 4. Prevention and treatment of prevalent gastrointestinal symptoms after bariatric surgery[27]

Symptom	Prevention and Treatment of the Symptom (Nutritional Therapies)
Dumping syndrome	Stay away from simple sugars Stay away from foods which have high glycemic index Bring together complex carbohydrates with protein and fiber in meals Keep liquids separated from solid foods
Diarrhea	Decrease fat consumption Ensure sufficient fluid intake
Constipation	Raise liquid consumption Raise consumption of foods which are rich in fiber Stay away from carbonated and sugar-sweetened beverages
Dysphagia	Eat slowly Stay away from hard and dry foods Do not continue eating in the case of dysphagia
Vomiting	Take small bites, eat slowly Keep liquids separated from solid foods Reintroduce the foods which have been associated with vomiting
Dehydration	Raise fluid intake

3 year post-operative nutritional deficiency when compared to AGB. The result of this study supports that nutritional deficiencies are observed less in restrictive methods.[17] It is known that different parts of the small bowel are responsible from the absorption of different nutrients. Therefore, nutritional deficiencies vary depending on the BS method applied. The absorption sites of nutrients in the small bowel are given as Figure 2. Decreased calorie intake is inevitable after BS, and one of the main nutritional deficiencies is protein malabsorption. Protein malabsorption is also caused by other factors related to food intake (e.g. poor intake, vomiting). Such factors might cause protein malabsorption which is characterized by low albumin levels, oedema and hearing loss.[18] Reasons and prevalence (pre-op and post-op) of some of the nutritional deficiencies and supplementation recommendations are given as Table 3.[3,19-23]

It is known that some groups are at greater risk in terms of nutritional status after BS. Patients with extreme BMI (BMI ≥50 kg/m^2), sarcopenic obesity, multiple deficiencies nutritionally, poor glycemic control, poor dental hygiene, impaired eating behaviors can be given as examples of this situation.[24] Other factors associated with postoperative risk can be mentioned as insulin resistance and diabetes, tobacco addiction, cardiovascular diseases, obstructive sleep apnea syndrome, functional disability, and hypoalbuminemia. Routine evaluation of individuals before surgery, determination of risk/benefit status and management of comorbidities are considered necessary to decrease the risk in the period post-surgery.[25] Protein-energy malnutrition and micronutrient deficiencies may occur after BS. It is known that individuals who do not comply with recommended dietary requirements are at risk of developing malnutrition. Protein malnutrition may occur especially after malabsorptive surgery methods. Individuals should be followed up for life to prevent malnutrition after BS.[26] Postoperative protein intolerance also affects bile and pancreatic enzyme secretion. Consumption of protein-rich foods may cause vomiting and gastrointestinal disorders.[16] Reactive hypoglycemia and dumping syndrome may occur after BS as well. For this situation, it is recommended to avoid quickly absorbed carbohydrates and alcoholic beverages and consume foods rich in fiber and protein.[5] Some gastrointestinal symptoms are frequently observed after BS. These symptoms and methods to prevent and treat the symptoms are given as Table 4.[27]

It is known that the change in the anatomy of the gastrointestinal system after BS affects hypothalamic

signaling and gut hormones. In addition, it is stated that BS increases satiety, affects food preferences, and causes differences in approaches regarding to tastes (such as a decrease in hedonic evaluation of sweet and fatty foods).[5] It is known that following some BS methods, an increase in satiety hormones (e.g. oxyntomodulin (OXM), glucagon-like peptide-1 (GLP-1), peptide YY (PYY)) is observed. This situation may constitute one of the main mechanisms for decreased hunger and increased satiety after surgery. In addition, it is suggested that the influence of the GLP-1 hormone on the increase in insulin excretion may be a factor. It is also thought that gut hormones can be used as a marker to reveal insufficient body weight loss post-surgery.[28] It is reported that there are alterations in taste perception and food preferences after BS. In a systematic review and meta-analysis study aiming to assess this situation, it was stated that the results were inconsistent. However, the change in the expression of sweet taste and amino acid receptors is seen mostly in the intestinal segments, while the change for fatty acid receptors is seen mostly in the colon.[29] In a cross-sectional study aiming to describe the change in individuals' food preferences after BS, it was concluded that individuals' preferences depend on factors such as sensory perceptions, follow-up time and the success level of the surgery. It was stated that there was a change in preference among individuals towards healthier food options.[30] It is known that patients constitute a risk group for eating disorders in the post-BS period. In a systematic review and meta-analysis study aiming to evaluate the relation between recurrence of eating disorders and BS, it was concluded that the prevalence of eating disorders after surgery was 7.83%.[31] It is known that eating disorders are seen at higher rates in BS candidates compared to the general population. At the same time, BS candidates' perception of shape and body weight is more dominant. This is one of the reasons that makes BS candidates a risk group in the period after the operation. It is also thought that problematic eating behaviors may be associated with body weight regain after BS.[32]

Diet Stages and Dietary Supplements After Bariatric Surgery

Rapid body weight loss after BS may cause unintentional loss of fat-free mass and muscle mass. In this process, adequate intake of protein (minimum 60 g/day or up to 1.5-2.1 g/ideal body weight (kg)/day based on individual) is considered as protective against lean body mass loss. In order to meet this protein requirement, liquid protein supplements (30 g/day) are recommended in the first months.[5] The protein source is also considered as important. For the maintenance of lean tissue, it is suggested to consume foods with high leucine content (soy products, eggs, meat, legumes). Products with high whey protein content also increase leucine intake and can be considered as a good option.[27] Due to its branched-chain amino acid content, whey protein is among the protein supplements frequently used after BS.[13] Since there are individual differences in the absorption of nutrients, food supplements should be specific to the individual and the individual's periodic laboratory routine shall be observed.[5] The continuation of multivitamin and mineral supplements should be decided based on the calorie intake level and degree of malabsorption. In cases of increased parathyroid hormone levels, decreased calcinuria and/or insufficient oral intake, calcium supplementation should be associated with vitamin D intake.[33] The dosage of calcium supplements should be divided. It is recommended to take calcium carbonate with a meal, meanwhile, there is no such condition for calcium citrate. For pregnant women, supplementation of vitamin A and K after BS are especially seen as important.[19] Similarly, in case of zinc deficiency, zinc supplementation should be associated with copper intake. Zinc supplementation should not exceed 30 mg per day and its interaction with other nutrients (folate, calcium iron, etc.) should be taken into consideration. It is known that deficiencies (although rare) in fat-soluble vitamins may occur in case of malabsorption or after long afferent loop surgery. In case of deficiency, supplementation should be considered.[33] After BS, it becomes very difficult for patients to consume solid foods due to small stomach volume and gastric oedema. Therefore, dietary intervention is based on gradual progression of the diet, starting with a liquid or very soft diet to consume solid and chewable foods within 2-4 weeks.[5] In the first weeks, intake of calorie is quite limited due to anatomical changes. It is important to complete protein intake during this period.[13] Ideal eating behaviors after BS include having 4-6 meals during the day (dividing the intake of food), consuming foods which have high protein content, chewing foods in a slow manner, finishing eating when feeling saturated, staying away from the consumption of beverages which are carbonated and calorie rich, increasing consumption of water, consuming solid and liquid foods at separate times, avoiding snacking and such.[12] Stages of diet after RYGB, LSG, LAGB and BPD/DS are given as Table 5.[13] The recommendations related to nutritional assessment before the surgery, biochemical monitoring and food supplementation after the surgery and some other recommendations related to vulnerable groups and clinical problems are given as Table 6.[34]

Table 5. Stages of diet after RYGB, LSG, LAGB, BPD/DS[13]

	Time for Beginning	Food	Key Points	Avoided/Limited/Moderated Foods	Calorie and Macronutrient Requirements
Stage 1	Right after surgery	Clear liquids (liquids with no calories) Ice chips	Fluid intake shall begin after swallow test (in case there is an issue, sipping the water is appropriate). 15 ml of liquid every 30 minute (in the first 2 hours), raise it by 15 ml every 15 minute for the rest of the day	Beverages which are carbonated, have caffeine or sugar (avoided). Using straw is limited.	**Calorie:** Post-bariatric caloric needs are up to three factors; age, sex and activity level. Negative balance in energy is needed. 400-500 calorie in first days, gradually increase it up to 900 calories in 6 months. Calorie intake shall not be over 1000 calorie in the first year of surgery. **Carbohydrates:** %35-50 of daily calorie intake. Complex or high-fiber carbohydrates are recommended. 100-130 g/day is required.
Stage 2	2nd-3rd days	Water Watered fruit juice (sugar-free) Broth Jelly (sugar-free)	30 ml liquids every 15 minutes (no beverage which are carbonated and no sugar). Liquids shall be sipped slowly. Fruit juice (dilute with water; half and half). Total fluid intake: 1500-1800 ml/day.	Caffeine is limited. Using straw is limited.	
	4th and 10-14th days	Low/skim milk Plain yoghurt Protein powder Protein shakes Watered fruit or vegetable juice Broth Jelly (sugar-free) Smooth vegetable soup	120-170 ml liquids every hour. 25-30 g protein/serving (100–200 calories; <10 g sugar; <15 g carbohydrates). Total fluid intake: 1500-1800 ml/day. Minimum 4 cups of water each day.	Plain yoghurt which contains added sugar over 25 g is limited. Salty liquids in moderation. Beverages which are carbonated, with caffeine or sugar (avoided). Using straw is limited.	
Stage 3	10-14th days and end of 3rd week	Low-fat meat (ground, pureed). Eggs. Low-fat cheese. Soups (strained). Well-cooked vegetables Fruits (non-fibrous, pureed).	3-5 small meals (when patient can tolerate 1/2 cup of food at a time, 3 small meals and 2 snacks should constitute the daily intake). Focus on protein-rich foods. Drink water 15 minute before or 30 minute after a meal). Continue protein powders.	Not drinking the water with or right after a meal	**Protein:** 60–160 g/day after RYGB and 60–80 g/day or 1.1 g/ideal body weight (kg)/day after SG. Daily consumption can be up to 2.1 g/kg/day (based on ideal body weight of individiual).
Stage 4	≥4th week	Advanced diet	Minimum 1500-1800 ml liquids (well hydration is important).	Not drinking the water with or right after a meal.	

		(according to individual's tolerance)	Introduce new foods one by one. Drink water 15 minute before or 30 minute after a meal. Include raw fruits and vegetables based on toleration of the individual. Intake of food shall increase step by step (based on suggested daily intake of calorie). Every meal shall last 20 minutes. Foods shall be chewed slowly and adequately	Consumption of bread, rice and pasta is restricted (until making sure that foods which are rich from protein are tolerated well).	**Fat:** Generally %35-42 of daily calorie intake is reported.

RYGB: Roux-en-Y gastric bypass, LSG: Laparoscopic sleeve gastrectomy, LAGB: Laparoscopic adjustable gastric banding, BPD/DS: Biliopancreatic diversion with duodenal switch

Table 6. Recommendations related to the process before and after the surgery[34]

	Preoperative nutritional assessment	Postoperative care and biochemical monitoring	Postoperative vitamin and mineral supplementation	Abnormal test results, clinical problems, pregnancy and adolescents
Grade A	N/A	N/A	N/A	N/A
Grade B	Full blood count control (e.g. haemoglobin, vitamin B12 levels). Control of serum 25-hydroxyvitamin D levels. Control of serum/plasma parathyroid hormone levels.	Control of full blood count and serum ferritin levels. Control of serum folate, 25-hydroxyvitamin D, vitamin A, vitamin E, vitamin K1, PIVKA-II, serum/plasma zinc and vitamin B12 levels.	Using iron and selenium supplement after SG, RYGB and malabsorptive procedures. Supplement of ferrous sulphate (200 mg/day), ferrous fumarate (210 mg/day), ferrous gluconate (300 mg/day) (consider it as twice in a day in menstruating women, adjust it according to the blood results). Routine supplementation of vitamin B12 with intramuscular vitamin B12 injections after malabsorptive procedures or SG, RYGB. Daily supplementation of vitamin A after malabsorptive procedures. Multivitamin and mineral supplementation (containing dietary reference intake of zinc and thiamine).	N/A
Grade C	N/A	Control of serum selenium and copper levels	Vitamin A supplementation, especially in the case of people having deficiency symptoms. Daily supplementation of vitamin E and vitamin K after malabsorptive procedures. Supplementation of 30 mg/day zinc after malabsorptive procedures.	N/A

Table 6. (Continued) Recommendations related to the process before and after the surgery[34]

	Preoperative nutritional assessment	Postoperative care and biochemical monitoring	Postoperative vitamin and mineral supplementation	Abnormal test results, clinical problems, pregnancy and adolescents
Grade D	Comprehensive assessment nutritionally before BS. Control of serum calcium levels. Control of serum thiamine levels.	Dietetic support. Follow-up (minimum two years). Monitoring the nutritional status (at least once in a year). Control of vitamin A levels in the case of steatorrhoea or signs of vitamin A deficiency. Control of serum vitamin E levels in the case of uncomprehended anaemia or neuropathy. Control of serum selenium levels in the case of diarrhoea, metabolic bone disease, uncomprehended anaemia or uncomprehended cardiomyopathy and at regular intervals.	Folic acid supplement (400-800 µg/day). Supplementation of vitamin D3 (2000-4000 IU/day after SG, RYGB, malabsorptive procedures). Using fat soluble vitamins which are miscible in water post-malabsorptive procedures as a way to improve absorption. Supplement (containing 2 mg copper) after RYGB, SG, BPD/DS. Recommendation of multivitamin and mineral supplement (which contains selenium). Oral thiamine supplementation (200-300 mg/day) in the case of poor dietary intake, dysphagia, vomiting or fast weight loss.	Considering the causes of blood loss in the case of iron deficiency anemia. Treating iron, vitamin B12 and folic acid deficiency according to NICE, CKS (National Institute for Health and Care Excellence, Clinical Knowledge Summaries) Anaemia. Applying hydroxocobalamin (1 mg/alternate days, intramuscularly) in the case of neurological involvement through vitamin B12 deficiency, consider it as in every 2 months after having no further improvement). Administering hydroxocobalamin (1 mg/three times a week for 2 weeks intramuscularly) in the case of no neurological involvement. During the treatment of vitamin B12 deficiency, maintain it as 1 mg/2-3 months lifelong (intramuscular). Folic acid supplement (5 mg/day) at least for 4 months. Treatment of vitamin A deficiency (10.000-25.000 IU/day/1-2 weeks, also checking vitamin A levels at 3 months). Oral vitamin E supplementation (100-400 IU/day) (checking at 3 months). Doing the adjustments according to serum lipids while considering the vitamin E nutritional status). Checking both zinc and copper levels while assessing replacement of one of it. Zinc/copper ratio shall be 8-15/1 mg (monitoring is important as the absorption of each mineral is linked to each other). In the case of prolonged vomiting or dysphagia, consider the risk of thiamine deficiency and plan the treatment according to that. Avoiding pregnancy following the first 12-18 months of surgery. Women (BMI <29.9 kgm^2 and planning pregnancy) taking 400 µg/day folic acid till the 12th week of pregnancy. Women (who have type 2 diabetes, BMI >30kgm^2) taking 5 mg folic acid until the 12th week of pregnancy. Nutritional screening of each trimester during pregnancy for women who had BS.

Table 6. (Continued) Recommendations related to the process before and after the surgery[34]

	Preoperative nutritional assessment	Postoperative care and biochemical monitoring	Postoperative vitamin and mineral supplementation	Abnormal test results, clinical problems, pregnancy and adolescents
GPP	Seek advise in the case of possibility of hyperparathyroidism. Control of serum vitamin A, zinc, copper and selenium levels in the case of going through malabsorptive methods of surgery. Control of serum magnesium levels. Routine control of HbA1c, lipid profile, liver and kidney functions. Treatment and correction of nutritional deficiencies.	Monitoring renal and liver functions. Monitoring full blood count and serum folate, calcium, vitamin D, vitamin E, serum/plasma zinc, copper, selenium and ferritin levels. Considering ≥75nmol/L of serum 25-hydroxyvitamin D levels as sufficient. Measuring total 25-hydroxyvitamin D in the case of vitamin D2 supplements. Control of parathyroid hormone in case it is not done before BS. Control of serum/plasma zinc levels in the case of uncomprehended anaemia, hair loss or alterations in taste acuity. Monitoring serum copper levels in the case of zinc supplementation and uncomprehended anaemia or poor wound healing. Considering the treatment of thiamine deficiency in the case of rapid weight loss, vomiting, alcohol abuse, poor dietary intake, oedema or signs of neuropathy. Monitoring HbA1c in the case of diabetes and monitoring lipids in the case of dyslipidaemia.	Reviewing and adjusting vitamin and mineral supplements. Using a complete multivitamin and mineral supplement after all surgical procedures. Recommending a supplement which contains iron (particularly to adolescents). Taking iron supplements with citrus fruits/drinks or vitamin C. Recommending people to take calcium and iron as having 2 hour apart between. Recommend vitamin B12 injections (see grade b) to be done in every 3 months. Ensuring good dietary calcium intake in the case of requirement to be higher. In the case of PTH to raise, while serum calcium and 25-hydroxyvitamin D levels are normal, think about recommending a combined supplementation which contains both vitamin D and calcium. Recommend calcium supplement to be taken in divided doses (calcium carbonate with food and calcium citrate with or without food, calcium citrate is preferred in the case of having kidney stones risk). Oral vitamin A supplementation (as 3000 µg/day and adjust it). Oral vitamin E supplementation (as 100 IU/day and adjust it). Oral vitamin K supplementation (as 300 µg/day) after malabsorptive procedures. Intake of 15 mg/day zinc through the supplement. Recommending oral thiamine 3-4 months post surgery. Clinicians to realize thiamine deficiency and	Considering the potential causes of protein malnutrition, protein energy malnutrition oedema symptoms. Considering protein, zinc, copper and selenium deficiency in the case of uncomprehended causes of anaemia or fatigue. Considering high dose vitamin D injections in the case of severe vitamin D deficiency (medical history of the patient is important). Considering vitamin A injections in the case of oral supplementations not responding to the treatment. 1-2 mg/day oral vitamin K supplement in the case of deficiency and checking the levels at 3 months. Zinc supplementation (high dose) for 3 months in the case of severe zinc deficiency and normal or borderline copper levels (rechecking the status also should be done). Referring to the reference levels specialized for pregnancy.

			people to look for advice in the case of poor dietary intake or prolonged vomiting.	

Grade A: Directly practicable to the target population, consistent overall (based on high quality and well conducted studies)
Grade B: Directly practicable to the target population, consistent overall or educed evidence (based on well conducted studies, not included the high quality meta-analyses)
Grade C: Directly practicable to the target population, consistent overall (based on well conducted case-control or cohort studies)
N/A: Not applicable
Grade D: Educed evidence (based on high quality systematic reviews and well conducted case-control or cohort studies) or based on non-analytical studies, expert opinion
GPP: Good Practice Point (based on clinical experience)

Regain of Body Weight After Bariatric Surgery

Successful loss of body weight after BS is identified as the loss of over 50% of excess body weight. After BS, 20-25% of patients experience body weight regain (progressive regain following successful loss of body weight) and insufficient loss of body weight (excessive body weight loss to be <50% within 18 months after BS) which might lead to revision of BS.[35] There are various definitions of postoperative body weight regain. These definitions may be based on the loss of excess body weight, the calculation of the nadir body weight, as well as the preoperative body weight. For example, regain of ≥10% or >15% of the nadir body weight can refer to weight regain.[36] After BS, body weight loss occurs very rapidly, especially in the first months. Loss of lean mass after BS leads to a decrease in energy expenditure and a tendency for the individual to regain body weight. The change in hormone levels after BS also causes regain of body weight.[3] Mechanisms related to hormones (increase in ghrelin, decrease in peptide YY and GLP-1 etc.), non-compliance with the diet (increase in caloric intake with time, grazing, not being followed up nutritionally), not being physically active enough, factors related to mental health (depression, control loss over eating) or surgery (enlargement of gastric pouch, stoma dilatation, or gastrogastric fistula) may cause body weight regain after BS. Body weight regain after various surgeries is as stated: 38% after LAGB, 27.8% after LSG, 3.9% after RYGB. In addition, insufficient body weight loss is 32-40% after LSG and 20% after RYGB, OAGB and LSG.[35] It is suggested that taste perception, appetite, food preferences and eating behaviors after BS are also related to postoperative body weight regain. Following some BS methods, individuals are reported to have decreased appetite and less desire for sweet foods. However, it is stated that this situation may not be long-lasting and cause body weight regain in that case.[37]

New Perspectives in Bariatric Surgery

There are approaches within the scope of future trends in the study field of BS. One of these approaches is robotic surgery. It is suggested that bariatric robotic surgery can be benefited from in individuals with high BMI, who have had previous gastrointestinal surgeries, or who will undergo revisional BS. It is thought that bariatric robot surgery, which has emerged as an innovative technique among body weight loss methods, may be a helpful factor in carrying out the process in a safer and least invasive manner.[38] The artificial intelligence can also be used in the field of BS. It is thought that it may be useful to develop algorithms that will identify the risk of postoperative complications or insufficient body weight loss specific to the individual. The use of validated algorithms may be among the future trends.[39] Another topic among future trends is the relationship between microbiota and BS. As the role of microbiota in the obesity pathogenesis is known, it is thought that gut microbiota changes based on the BS procedure.[40] After BS, changes in the bacterial population (such as an increase in the level of Escherichia coli) are observed. In addition, active compounds produced by the microbiota, (e.g. bile acids, short chain fatty acids) are known to have an influence on appetite and energy metabolism. It is thought that determining the state of microbiota before and after surgery may be an efficient factor on the security and success of BS procedures in long-term.[41]

CONCLUSIONS

Obesity is a chronic and multifactorial disease. It is also one of the factors that threaten health worldwide. BS, which constitutes the surgical intervention methods in the obesity treatment, is applied according to the degree of obesity and the accompanying comorbidity. There are different approaches for individuals who are considered vulnerable in terms of BS (adolescents, pregnant women, etc.). Individuals who constitute the target group of BS are also a group that needs to be taken into consideration due to their potential to exhibit risky behavior in terms of eating and food perception. It is considered necessary to evaluate the situation before BS in terms of nutrition-related factors to facilitate the process after BS. The effect of BS on the body (absorption of nutrients, hormones, etc.) varies depending

on the BS method applied. Considering this situation, after BS, the individual's diet should be progressed in stages as tolerated and nutritional requirements should be supplemented as needed. Body weight regain may be possible after BS. This situation suggests the necessity of taking some precautions and developing solutions regarding risk factors for the extent and sustainability of success in BS. Using innovative approaches is also among the future trends. It is considered important to develop guidelines regarding BS in the context of nutrition and dietetics, to conduct more comprehensive and long-term studies, and to define risk factors in more detail.

Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir-EB, HTB; Tasarım- EB, HTB; Denetleme- EB, HTB; Kaynaklar- EB, HTB; Veri Toplanması ve/veya İşlemesi- EB, HTB; Analiz ve/ veya Yorum- EB, HTB; Literatür Taraması- EB, HTB; Yazıyı Yazan- EB, HTB; Eleştirel İnceleme- EB, HTB.
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

Peer-review: Externally peer-reviewed.
Author Contributions: Concept - EB, HTB; Design- EB, HTB; Supervision- EB, HTB; Resources- EB, HTB; Data Collection and/or Processing- EB, HTB; Analysis and/or Interpretation- EB, HTB; Literature Search- EB, HTB; Writing Manuscript- EB, HTB; Critical Review- EB, HTB.
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Mechanick JI, Apovian C, Brethauer S et al. Clinical Practice Guidelines For The Perioperative Nutrition, Metabolic, and Nonsurgical Support of Patients Undergoing Bariatric Procedures – 2019 Update: Cosponsored By American Association of Clinical Endocrinologists/American College of Endocrinology, The Obesity Society, American Society For Metabolic & Bariatric Surgery, Obesity Medicine Association, and American Society of Anesthesiologists. *Endocr Pract*. 2019; 25, 1–75. https://doi.org/10.4158/GL-2019-0406
2. World Obesity Federation. World Obesity Atlas 2024. London: World Obesity Federation, 2024. https://data.worldobesity.org/publications/?cat=22
3. Aguas-Ayesa M, Yárnoz-Esquíroz P, Olazarán L, Gómez-Ambrosi J, Frühbeck, G Precision nutrition in the context of bariatric surgery. *Rev Endocr Metab Disord*. 2023; 24(5):979–991. Springer. https://doi.org/10.1007/s11154-023-09794-5
4. Nguyen NT, Varela JE. Bariatric surgery for obesity and metabolic disorders: State of the art. *Nat Rev Gastroenterol Hepatol*. 2017; 14(3):160–169. https://doi.org/10.1038/nrgastro.2016.170
5. Bettini S, Belligoli A, Fabris R, Busetto L. Diet approach before and after bariatric surgery. *Rev Endocr Metab Disord*. 2020; 21(3):297-306. https://doi.org/10.1007/s11154-020-09571-8
6. Miedziaszczyk M, Ciabach P, Szałek E. The effects of bariatric surgery and gastrectomy on the absorption of drugs, vitamins, and mineral elements. *Pharmaceutics*. 2021; 13(12). https://doi.org/10.3390/pharmaceutics13122111
7. Eisenberg D, Shikora SA, Aarts E, et al. 2022 American Society for Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO): Indications for Metabolic and Bariatric Surgery. *Surg Obes Relat Dis*. 2022;18(12):1345–1356. https://doi.org/10.1016/j.soard.2022.08.013
8. Ochner CN, Gibson C, Carnell S, Dambkowski C, Geliebter A. The neurohormonal regulation of energy intake in relation to bariatric surgery for obesity. *Physiol Behav*. 2010;100(5):549-559. doi: 10.1016/j.physbeh.2010.04.032
9. Or Koca A, İriz A, Hazır B et al. Relationships of orexigenic and anorexigenic hormones with body fat distribution in patients with obstructive sleep apnea syndrome. *Eur Arch Otorhinolaryngol*. 2023;280(5):2445–2452. https://doi.org/10.1007/s00405-022-07799-5
10. Huang J, Chen Y, Wang X, Wang C, Yang J, Guan B. Change in Adipokines and Gastrointestinal Hormones After Bariatric Surgery: a Meta-analysis. *Obes Surg*. 2023;33(3):789–806. https://doi.org/10.1007/s11695-022-06444-8
11. American Society for Metabolic and Bariatric Surgery. Estimate of Bariatric Surgery Numbers, 2011-2022. Accessed June 9, 2024. https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers/
12. Sherf-Dagan S, Sinai T, Goldenshluger A, et al. Nutritional assessment and preparation for adult bariatric surgery candidates: Clinical practice. *Adv Nutr*. 2021;12(3):1020–1031. https://doi.org/10.1093/advances/nmaa121
13. Tabesh MR, Eghtesadi M, Abolhasani M, Maleklou F, Ejtehadi F, Alizadeh Z. Nutrition, Physical Activity, and Prescription of Supplements in Pre- and Post-bariatric Surgery Patients: An Updated Comprehensive Practical Guideline. *Obes Surg*. 2023;33(8):2557–2572. https://doi.org/10.1007/s11695-023-06703-2
14. Kushner BS, Eagon JC. Systematic Review and Meta-Analysis of the Effectiveness of Insurance Requirements for Supervised Weight Loss Prior to Bariatric Surgery. *Obes Surg*. 2021; 31(12):5396–5408. Springer. https://doi.org/10.1007/s11695-021-05731-0
15. Kaidar-Person O, Person B, Szomstein S, Rosenthal RJ. Nutritional deficiencies in morbidly obese patients: A new form of malnutrition? Part A: Vitamins. *Obes Surg*. 2008; 18(7):870–876. https://doi.org/10.1007/s11695-007-9349-y
16. Simancas-Racines D, Frias-Toral E, Campuzano-Donoso M, et al. Preoperative Nutrition in Bariatric Surgery: A Narrative Review on Enhancing Surgical Success and Patient Outcomes. *Nutrients*. 2025; 17(3):566. https://doi.org/10.3390/nu17030566
17. Ba DM, Hu A, Shen C, et al. Trends and predictors of nutritional deficiencies after bariatric surgeries: analysis of real-world data. *Surg Obes Relat Dis*. 2023;19(9):935–943. https://doi.org/10.1016/j.soard.2023.02.013
18. Kamal FA, Fernet LY, Rodriguez M, et al. Nutritional Deficiencies Before and After Bariatric Surgery in Low- and High-Income Countries: Prevention and Treatment. *Cureus*. 2024. https://doi.org/10.7759/cureus.55062
19. Parrott J, Frank L, Rabena R, Craggs-Dino L, Isom KA, Greiman L. American Society for Metabolic and Bariatric Surgery Integrated Health Nutritional Guidelines for the Surgical Weight Loss Patient 2016 Update: Micronutrients. *Surg Obes Relat Dis*. 2017;13(5):727–741. https://doi.org/10.1016/j.soard.2016.12.018
20. Shah M, Sharma A, Wermers RA, Kennel KA, Kellogg TA, Mundi MS. Hypocalcemia After Bariatric Surgery: Prevalence and Associated Risk Factors. *Obes Surg*. 2017;27(11):2905–2911.

https://doi.org/10.1007/s11695-017-2705-7
Patients with Morbid Obesity before and after Metabolic Bariatric Surgery. *Nutrients*. 2022;14(16). https://doi.org/10.3390/nu14163319
22. Jiao Y, Liu Y, Chen S, Tang L. Zinc Deficiency After Bariatric Surgery: A Systematic Review and Meta-analysis. *Indian J Surg*. 2024. https://doi.org/10.1007/s12262-024-04082-1
23. Zarshenas N, Tapsell LC, Batterham M, Neale EP, Talbot ML. Investigating the Prevalence of Copper and Zinc Abnormalities in Patients Pre and Post bariatric Surgery—an Australian Experience. *Obes Surg*. 2023;33(11):3437–3446. https://doi.org/10.1007/s11695-023-06822-w
24. Ben-Porat T, Sherf-Dagan S. Nutritional Interventions for Patients with Severe Obesity Seeking Bariatric Surgery. Nutrients. 2023;15(3). https://doi.org/10.3390/nu15030515
25. Quilliot D, Sirveaux MA, Nomine-Criqui C, Fouquet T, Reibel N, Brunaud L. Evaluation of risk factors for complications after bariatric surgery. *J Visc Surg*. 2018;155(3):201–210. https://doi.org/10.1016/j.jviscsurg.2018.01.004
26. Lange J, Königsrainer A. Malnutrition as a Complication of Bariatric Surgery- A Clear and Present Danger? *Visc Med*. 2019;35(5):305-311. doi:10.1159/000503040
27. Dagan SS, Goldenshluger A, Globus I, et al. Nutritional recommendations for adult bariatric surgery patients: Clinical practice. *Adv Nutr*. 2017;8(2):382–394. https://doi.org/10.3945/an.116.014258
28. Papamargaritis D, Le Roux CW. Do gut hormones contribute to weight loss and glycaemic outcomes after bariatric surgery? *Nutrients*. 2020;13(3):1–28. https://doi.org/10.3390/nu13030762
29. Walmsley R, Chong L, Hii MW, Brown RM, Sumithran P. The effect of bariatric surgery on the expression of gastrointestinal taste receptors: A systematic review. *Rev Endocr Metab Disord*. 2024;25(2):421–446. https://doi.org/10.1007/s11154-023-09865-7
30. Guyot E, Dougkas A, Robert M, Nazare JA, Iceta S, Disse E. Food Preferences anTheir Perceived Changes Before and After Bariatric Surgery: a Cross-sectional Study. *Obes Surg*. 2021;31(7):3075–3082. https://doi.org/10.1007/s11695-021-05342-9
31. Taba JV, Suzuki MO, Do Nascimento FS et al. The development of feeding and eating disorders after bariatric surgery: A systematic review and meta-analysis. *Nutrients*. 2021;13(7). https://doi.org/10.3390/nu13072396
32. Brode CS, Mitchell, JE. Problematic Eating Behaviors and Eating
21. Musella M, Berardi G, Vitiello A, et al. Vitamin D Deficiency in Disorders Associated with Bariatric Surgery. *Psychiatr Clin North Am*. 2019;42(2):287–297. https://doi.org/10.1016/j.psc.2019.01.014
33. Quilliot D, Coupaye M, Ciangura C, et al. Recommandations sur la prise en charge nutritionnelle après chirurgie bariatrique : recommandations de bonne pratique et consensus d'experts SOFFCO-MM/AFERO/SFNCM/. *J Chir Visc*. 2021;158(1):53–63. https://doi.org/10.1016/j.jchirv.2020.10.002
34. O'Kane M, Parretti HM, Pinkney J, et al. British Obesity and Metabolic Surgery Society Guidelines on perioperative and postoperative biochemical monitoring and micronutrient replacement for patients undergoing bariatric surgery-2020 update. *Obes Rev*. 2020; 21(11). https://doi.org/10.1111/obr.13087
35. El Ansari W, Elhag W. Weight Regain and Insufficient Weight Loss After Bariatric Surgery: Definitions, Prevalence, Mechanisms, Predictors, Prevention and Management Strategies, and Knowledge Gaps-a Scoping Review. *Obes Surg*. 2021;31(4):1755-1766. doi:10.1007/s11695-020-05160-5
36. King WC, Hinerman AS, Belle SH, Wahed AS, Courcoulas AP. Comparison of the Performance of Common Measures of Weight Regain After Bariatric Surgery for Association With Clinical Outcomes. *JAMA*. 2018;320(15):1560-1569. doi:10.1001/jama.2018.14433
37. Zhang Y, Nagarajan N, Portwood C, et al. Does taste preference predict weight regain after bariatric surgery? *Surg Endosc*. 2020;34(6):2623–2629. https://doi.org/10.1007/s00464-019-07033-0
38. Evans L, Cornejo J, Elli EF. Evolution of Bariatric Robotic Surgery: Revolutionizing Weight Loss Procedures. *Curr Surg Rep*. 2024;12(6):129–137. https://doi.org/10.1007/s40137-024-00398-9
39. Bektaş M, Reiber BMM, Pereira JC, Burchell GL, Van Der Peet DL. Artificial Intelligence in Bariatric Surgery: Current Status and Future Perspectives. *Obes Surg*. 2022;32(8):2772–2783. https://doi.org/10.1007/s11695-022-06146-1
40. Puca P, Petito V, Laterza L, et al. Bariatric procedures and microbiota: patient selection and outcome prediction. *Ther Adv Gastrointest Endosc*. 2021;14. https://doi.org/10.1177/26317745211014746
41. Zambrano AK, Paz-Cruz E, Ruiz-Pozo VA, et al. Microbiota dynamics preceding bariatric surgery as obesity treatment: a comprehensive review. *Front Nutr*. 2024;11. https://doi.org/10.3389/fnut.2024.1393182