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REVIEW ARTICLE

Advanced strategies for hemorrhage management in cesarean sections an in-depth procedural guide

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Abstract

Over the past five decades, there has been a substantial global increase in cesarean section rates. Unfortunately, the incidence of maternal morbidity following cesarean delivery remains notably high, reaching levels as elevated as 36%. Among the prevalent complication sare febrile episodes (25%), hemorrhage (4%), hematoma formation (4%), and urinary tract infections (3%). Obstetric hemorrhage, in particular, stands out as a leading cause of maternal mortality worldwide. Excessive bleeding, defined as a blood loss exceeding 1000 ml during cesarean sections, is frequently underestimated, yet it is documented in over 5-10% of such procedures. While conservative management, including vaginal packing and the administration of uterotonic agents, is effective in many instances, persistent hemorrhage may necessitate specific surgical interventions. Therefore, a comprehensive understanding of the procedural steps form an aging bleeding during cesarean sections is crucial to mitigating maternal mortality. This review article aims to consolidate various techniques employed to control hemorrhage during cesarean deliveries.

Keywords: cesarean; hemorrhage; postpartum

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Introduction

In contemporary obstetrics, cesarean sections account for approximately 15% of all births worldwide, with significant disparities observed across different countries. Obstetric hemorrhage remains a predominant contributor to maternal morbidity and mortality. In the year 2000, an estimated 529,000 maternal deaths were recorded globally, predominantly in nations with limited resources. In developed regions, a woman's lifetime risk of maternal death is 1 in 2800, whereas in less developed areas, this risk escalates to 1 in 61. The proportion of these deaths attributable to hemorrhage varies by region, with it being the leading cause in Africa and Asia, accounting for 33.9% and 30.8% of maternal deaths, respectively. In wealthier nations, hemorrhage accounts for 13.4% of maternal fatalities. Postpartum hemorrhage (PPH) is typically defined as the loss of more than 500 milliliters of blood from the vaginal tract within the first 24 hours after childbirth. This definition poses challenges when applied to cesarean deliveries, as the average blood loss following an elective lower segment cesarean is approximately 500 mL, nearing this threshold. Although earlier data often cite 1000 mL as a reference point, recent studies have not extensively measured typical blood loss during emergency cesareans following labor. Risk factors for PPH during cesarean include general anesthesia, amnionitis, prolonged labor, pre-eclampsia, multiple gestations, fetal macrosomia, hematological disorders, pretermbirth, leiomyomas, placenta previa, and bleeding before or during labor [1].

This review article delinetes the step-by-step management of bleeding during cesarean sections, encompassing the use of medications, conservative and radical surgical techniques, and the application of abdominal packing to control hemorrhage.

Medical Treatment

The ideal uterotonic agent for cesarean sections should be straight forward to administer, exhibit minimal adverse effects, and effective lymitigate severe hemorrhage. In cesarean deliveries, both general and regional anesthesia are options, though general anesthesia is associatedwith an elevated risk of PPH. Currently, regional anesthesia is ominantly utilized for both elective and emergency cesareans in developed regions. Spinal anesthesia, in particular, may lead to maternal hypotension. Oxytocin is a commonly employed uterotonic; however, ergometrine can induce nausea and hypertension, while misoprostol may cause chills and fever, with its intraoperative administration posing challenges. The patient population undergoing cesarean sections displays considerable clinical variability, with the duration of labor prior to surgery significantly influencing the optimal prophylactic drug and dosage. Additionally, increased expression of oxytocin receptors in myometrial tissues as gestation progresses suggests that uterotonic response may vary significantly between early and term gestations[1].Antifibrinolytic agents, particularly tranexamic acid (TXA), have beendemonstrated to reduce blood loss and the necessity for transfusions during cesarean procedures [2].

The incorporation of TXA in to standard oxytocin prophylaxis during cesarean sections significantly reduces hemoglobin drop, postpartum blood loss, incidence of PPH and severe PPH, as well as the need for additional uterotonic agents and blood transfusions. Were commendad ministering 1 g (or 10 mg/kg) of TXA intravenously 10–20 minutes prior to skin incision or spinal anesthesia. This recommendation is based on TXA's proven efficacy and safety in preventing one of the most prevalentand severe complications of pregnancy. Furthermore, oxytocin is administered post-delivery of the neonate to further minimize blood loss during cesarean procedures [3].

Table 1 : Postpartum hemorrhage of risk assessment tool

LOW RISK	MEDIUM RISK	HIGH RISK
Singleton pregnancy	Prior ceserean or uterines urgery	placenta accretas pectrum
Unscarred uterus	Multiple gestation	Bleeding at admission
Absence of postpartum Hemorrhage history	Large uterine fibroids	Known coagulation defect
	Choriamnionitis	History of postpartum hemorrhage
	Prolonged use of oxytocin	

Surgery

Arterial Ligation

Ligation of the uterine and utero-ovarian arteries can decrease uterine hemorrhage by reducing perfusion pressure in the myometrium. Although it may not completely halt bleeding from placenta accreta spectrum or uterine atony, it can diminish blood loss while other interventions are implemented. This procedure does not appear to impair reproductive function or damage the uterus [4].

Ligation of the internal iliac (hypogastric) arteries is a complex procedure, even for experienced pelvic surgeons, especially in cases involving an enlarged uterus, limited visibility from a transverse lower abdominal incision, on going pelvic hemorrhage, or obesity. The challenges are compounded when attempting bilateral ligation due to infrequent operations in the deep pelvic retroperitoneal space. Consequently, this technique has largely been supplanted by uterine compression sutures, uterine artery ligation, and arterial embolization. Bilateral internal iliac artery ligation reduces the pulse pressure of uterine blood flow, but its efficacy may be compromised by large collateral vessels, such as in placenta percreta. There have been instances of reverse filling of the internal iliac arteries via branches of the external iliac artery, including the inferior epigastric, obturator, deep circumflex iliac, and superior gluteal arteries, beyond the ligation site [5].

B Lynch

Functions similarly to physical uterine compression by enveloping and compressing the uterus. It has been effective in arresting uterine bleeding due to atony in case reports and small series when other interventions have failed [6].While there is a potential risk of Asherman syndrome, the technique is relatively easy to learn, appears safe, preserves future reproductive potential, and does not increase adverse placentation outcomes in subsequent pregnancies. It is specifically indicated for uterine atony and is ineffective for hemorrhage associated with the placenta accreta spectrum. Additionally, it does not prevent postpartum hemorrhage in future pregnancies [7].

In the low eruterine segment, a large Mayo needle is used to insert and exit the uterine cavity with 1 or 2 chromic catgut sutures, or any absorbable suture if catgut is unavailable. Once the uterus is involuted, a robust suture is employed to prevent breakage, and rapid absorption is essential to avoid bowel herniation through the suture loop. The suture encircles the fundus, passes through the posterior wall, and re-enters the lower uterine cavity. It then traverses the anterior lateral lower uterine segment, crosses to the opposite side, exits through the posterior wall, and loops back over the fundus. Bimanual compression is applied as the suture ends retightened to compress the uterus. Proper patient positioning, such as legs apart or in a slight reverse Trendelenburg if stable, enhances the evaluation of chronic vaginal bleeding and the effectiveness of these interventions. This technique, sometimes used with balloon tamponade, is known as the “uterine sandwich” [8].

Pereira

Initially, Pereira sutures employed absorbableVicryl #1 with multifilament. Prior to the procedure, the likelihood of success is evaluated, with the patient positioned in a semi-lithotomy or Lloyd Davies position. The extent of bleeding is assessed, and bimanual compression is applied after externalizing the uterus. If bleeding ceases during compression, the application of Pereira sutures is deemed effective. The technique involves encircling the uterus with transverse and longitudinal sutures, using superficial bites that preserve the uterine cavity. Sutures are placed starting from the anterior aspect, with transverse sutures tie dover the anterior uterus and crossing the broad ligament. Care is taken to avoid the fallopian tubes, utero-ovarian, and round ligaments by selecting avascular regions. Longitudinal sutures are anchored by the final transverse suture, beginning dorsally and ending ventrally, ensuring secure compression [9].

Hayman

For managing atony after vaginal delivery, Hayman proposed the use of two to four vertical compression sutures placed from the anterior to the posterior uterine wall without performing a hysterotomy. If required, a transverse cervicoisthmic suture can be added to control hemorrhage in the lower uterine segment [10].

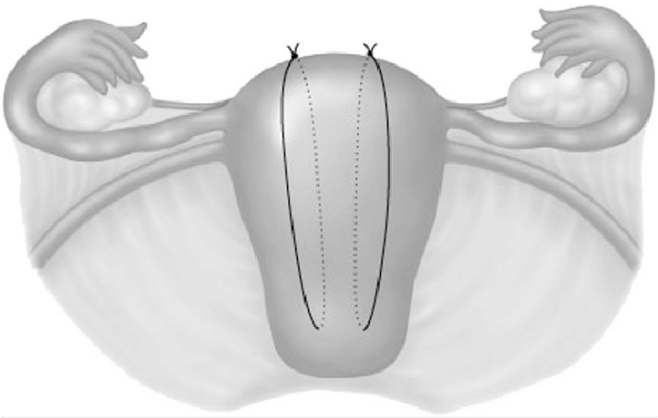

Figure 1 : Hayman Technique

Cho Technique

Cho's square suture technique involves compressing the endometrial cavity by passing a straight needle through bleeding sites. The needle is initially inserted between the anterior and posterior uterine walls, then reinserted from posterior to anterior 2-3 cm laterally. This process is repeated in the opposite direction, with the needle raised by 2-3 cm each time. The knot is tied securely to ensure hemostasis. This method, involving multiple square sutures, is effective in treating uterine atony following twin cesarean delivery [11].

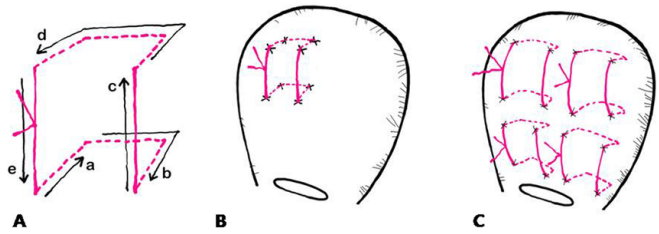

Figure 2 : Cho Technique

Matsubarayano

The B-Lynch suture presents several challenges. Initially, it requires a uterine incision or reopening of the cesarean scar, which must be performed immediately after placental delivery during a cesarean section. Although this allows for assessment of the uterine condition, it is an invasive procedure. Prompt closure of the cesarean incision is crucial to prevent delays caused by the B-Lynch suture, which can increas euterine contractions. Additionally, as noted by Hayman et al., the longitudinal sutures may "slide," potentially moving in to the uterine fundus and reducing peripheral compression. While Mondal et al. observed this issue with the Hayman suture, it can also occur with the B-Lynch suture due to their similar "brace" design. An excessively tight B-Lynch suture may cause "folding of the uterus," leading to in a dequate compression. Furthermore, the fundus may invert if the longitudinal suture exerts excessive cephalad pressure[12].

The MatsubaraYano (MY) suture addresses all four disadvantages of the B-Lynch suture. After securing the longitudinal suture, a needle is inserted from the anterior to the posterior lower uterine segment, and then from the posterior to the anterior uterine fundal edge. This process is repeated twice or thrice, forming two transverse sutures that intersect the longitudinal suture laterally. This configuration prevents the longitudinal suture from "sliding off", "sliding in", "bowing", or reinverting the uterine fundus. Compression sutures should be applied only after cesarean scars are removed or closed. In eight cases of PPH treated with MY suturing, complete hemostasis was achieved without short-term complications, and two patients subsequently became pregnant. Although B-Lynch et al. noted that their suture is straightforward, it can be challenging for inexperienced clinicians, particularly in emergencies requiring compression sutures. Hayman et al. also highlighted these challenges. The MY suture is easier to perform than the B-Lynch suture, emphasizing the principle of "applying pressure to the uterus"[12].

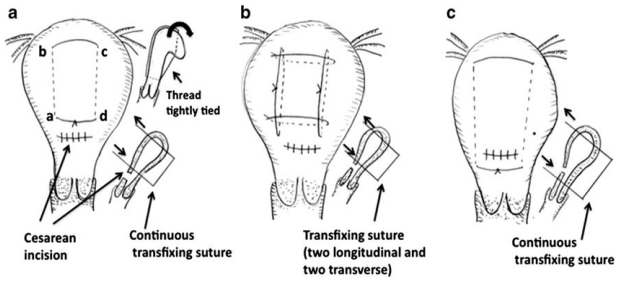

Figure 3 : Matsubara-Yano (MY) suture

Modified B-Lynchsuture

The Surabaya method employs a brace suture technique with three parallel longitudinal sutures using "Chromic catgut no.2" with straightened curved needles. The uterus is exteriorized, and an assistant pulls it to thin the lower uterine segment, facilitating needle passage from anterior to posterior. The first suture is placed approxi-

mately 2 cm below the cesarean incision at the medial-lateral margin, puncturing the posterior wall of the uterine isthmus. A second suture is applied contralaterally, and a third is positioned between the first two, each with a new suture. The operator tightens the sutures, securing the fundus 3 cm medial to the lateral edges and tying a third suture between them, while an assistant manually compresses the fundus to achieve an anteflexed-inferior position. A second assistant monitors the vagina; if no bleeding is observed, the abdominal wall is closed. If bleeding persists, further surgical intervention is required [13].

Hysterectomy

Hysterectomy remains the sole definitive treatment for persistent uterine bleeding. Regardless of the underlying cause of postpartum hemorrhage, significant blood loss can lead to severe coagulopathy. Complications such as acidosis, severe hypovolemia, hypothermia, tissue hypoxia, and electrolyte imbalances can exacerbate the patient's condition. If a laparotomy has not been performed, addressing these physiological deficiencies prior to hysterectomy is essential and may be life-saving. In cases of placenta accreta spectrum or uterine rupture, an early hysterectomy may be the least morbid approach, averting the risks associated with delayed intervention and ineffective fertility-preserving methods.

Advancements in prenatal detection of placental attachment issues now allow patients to anticipate and discuss the possibility of a hysterectomy with their physician prior to a scheduled cesarean delivery. Conversely, uterotonic drugs, either alone or combined with fertility-preserving interventions such as intrauterine balloon tamponade, uterine compression sutures, uterine artery or utero-ovarian artery ligation, and arterial embolization can typically manage uterine atony. Once resuscitation and coagulopathy reversal are achieved, a hysterectomy may not be necessary to control bleeding. However, if fertility preserving treatments fail to adequately manage the bleeding, a hysterectomy becomes imperative [14].

Abdominal Packing

Abdominal orpelviccompression can effectively arrest recurrent uterine bleeding by applying pressure to low-pressure veins and capillaries within the abdominal cavity, thereby reducing or halting hemorrhage. In cases of severe bleeding, patients may develop disseminated intravascular coagulation, acidosis, hypovolemic shock, and hypothermia. These conditions often associated with pregnancy complications, necessitate stabilization in an intensive care unit before further intervention. Abdominal packing, which mechanically compresses uterine vascular sinuses, is a rapid, efficient, and cost-effective hemostatic technique. Two primary methods for post-hysterectomy bleeding control include the use of pads or roller gauze (sterile pads secured by sutures or wrapped in sterile materials) and balloon packs (such as Foley catheters or Bakri balloons). The structural differences between these methods are notable: balloon packs can be quickly inflated and deployed, offering ease and speed of use, while pad packs require more complex setup and attachment. Additionally, balloon packs allow for straightforward size adjustments to match hemorrhagic areas through inflation or deflation, whereas modifying a pad pack by adding or removing pads can be more cumbersome [15].

Conclusion

Obstetric hemorrhage continues to be a major contributor to maternal morbidity and mortality. Although historical data often cite a blood loss threshold of 1000 mL, recent studies have not adequately quantified typical blood loss during emergency cesarean sections following labor. Identified risk factors for PPH during cesarean delivery include general anesthesia, amnionitis, prolonged labor, pre-eclampsia, multiple gestations, fetal macrosomia, hematological disorders, preterm birth, leiomyomas, placenta previa, and bleeding before or during labor. Antifibrinolytic agents, particularly tranexamic acid (TXA), and the uterotonic agent oxytocin are employed to manage bleeding during cesarean sections, effectively reducing blood loss and the necessity for transfusions. Conservative surgical interventions include arterial ligation, such as the ligation of uterine and utero-ovarian arteries and internal iliac (hypogastric) artery ligation, as well as techniques like the B-Lynch, Hayman, and Cho methods. In cases requiring more radical intervention, procedures such as supravaginal hysterectomy may be performed. Additionally, abdominal or pelvic compression can effectively arrest recurrent uterine bleeding by compressing low-pressure veins and capillaries within the abdominal cavity, thereby reducing or halting hemorrhage.

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References

1. Kellie FJ. Medical methods for preventing blood loss at caesarean section. Cochrane Database of Systematic Reviews. 2018; Availablefrom: http://dx.doi.org/10.1002/14651858.cd007576.pub22.
2. Wang HY, Hong SK, Duan Y, Yin HM. Tranexamic acid and blood loss during and after cesarean section: a meta-analysis. *J Perinatol*. 2015;35(10):818-825. doi:10.1038/jp.2015.93
3. Doumouchtsis SK, Nikolopoulos K, Talaulikar V, Krishna A, Arulkumaran S. Menstrual and fertility outcomes following the surgical management of postpartum haemorrhage: a systematic review. *BJOG*. 2014;121(4):382-388. doi:10.1111/1471-0528.12546
4. Liu WM, Wang PH, Tang WL, Wang IT, Tzeng CR. Uterine artery ligation for treatment of pregnant women with uterine leiomyomas who are undergoing cesarean section. *Fertil Steril*. 2006;86(2):423-428. doi:10.1016/j.fertnstert.2006.01.027
5. Joshi VM, Otiv SR, Majumder R, Nikam YA, Shrivastava M. Internal iliac artery ligation for arresting postpartum haemorrhage. *BJOG*. 2007;114(3):356-361. doi:10.1111/j.1471-0528.2006.01235.x
6. Allam MS, B-Lynch C. The B-Lynch and other uterine compression suture techniques. *Int J Gynaecol Obstet*. 2005;89(3):236-241. doi:10.1016/j.ijgo.2005.02.014
7. Cowan AD, Miller ES, Grobman WA. Subsequent pregnancy outcome after B-lynch suture placement. *Obstet Gynecol*. 2014;124(3):558-561. doi:10.1097/AOG.0000000000000418
8. Sentilhes L, Gromez A, Razzouk K, Resch B, Verspyck E, Marpeau L. B-Lynch suture for massive persistent postpartum hemorrhage following stepwise uterine devascularization. *Acta Obstet Gynecol Scand*. 2008;87(10):1020-1026. doi:10.1080/00016340802380750
9. Setiyono, A. B., Aziz, A., Sulistyono, A., &Mose, J. C. (2015). Pereira Suture: an alternative compression suture to treat uterine atony. Indonesian Journal of Obstetrics and Gynecology, 177-18.
10. Ghezzi F, Cromi A, Uccella S, Raio L, Bolis P, Surbek D. The Hayman technique: a simple method to treat postpartum haemorrhage. *BJOG*. 2007;114(3):362-365. doi:10.1111/j.1471-0528.2006.01204.x
11. Cho JH, Jun HS, Lee CN. Hemostatic suturing technique for uterine bleeding during cesarean delivery. *Obstet Gynecol*. 2000;96(1):129-131. doi:10.1016/s0029-7844(00)00852-8
12. Matsubara S, Yano H, Taneichi A, Suzuki M. Uterine compression suture against impending recurrence of uterine inversion immediately after laparotomy repositioning. *J Obstet Gynaecol Res*. 2009;35(4):819-823. doi:10.1111/j.1447-0756.2008.01011.x
13. Sulistyono, A.D., Gultom, E.S., Dachlan, E.G., & Prabowo, P. (2011). Conservative Surgical Management of Postpartum Hemorrhage (PPH) Using 'Surabaya Method' (Modified B-Lynch Compression Suture). *Indonesian Journal of Obstetrics and Gynecology, 34*, 108-113.
14. Forna F, Miles AM, Jamieson DJ. Emergency peripartum hysterectomy: a comparison of cesarean and postpartum hysterectomy. *Am J Obstet Gynecol*. 2004;190(5):1440-1444. doi:10.1016/j.ajog.2004.02.021
15. Winata, I. G. S., & Asmara, A. D. (2022). Abdominal Packing for Obstetric Surgical Uncontrollable Hemorrhage. *European Journal of Medical and Health Sciences*, *4*(4), 70–74. https://doi.org/10.24018/ejmed.2022.4.4.1446

CERASUS JOURNAL OF MEDICINE

REVIEW ARTICLE

A review of the effect of progesterone use on early pregnancy bleeding, threatened abortion and recurrent pregnancy loss

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Abstract

Threatened abortion and miscarriage are prevalent complications in early pregnancy, affecting approximately 5-22% of all pregnancies [1]. These conditions can result in significant psychological and physiological distress for pregnant individuals, adversely impacting their mental and social well-being. The etiopathogenesis of bleeding in early pregnancy and threatened abortion remains incompletely understood, as it may arise from various underlying mechanisms.

Threatened abortion is defined as a clinical condition characterized by vaginal bleeding, the presence of fetal cardiac activity, and a closed cervix. It represents the most common non-traumatic cause of vaginal bleeding during the first trimester. The bleeding is hypothesized to result from disruptions in the decidual vasculature at the maternal-fetal interface. While this disruption is not always detectable with ultrasonography, it may occasionally present as a subchorionic hematoma. Notably, when subchorionic bleeding exceeds 25% of the gestational sac volume, the risk of pregnancy loss significantly increases [2].

The management of miscarriage, threatened abortion, and recurrent pregnancy loss remains challenging due to the multifactorial and often unclear etiologies. Progesterone and its derivatives are frequently employed in therapeutic protocols; however, the optimal type and mode of administration remain subjects of ongoing investigation. Progestogens exhibit variability in their pharmacological potency, mechanisms of action, and routes of administration. Both natural and synthetic progestogens are utilized in clinical practice.

This review aims to critically evaluate the efficacy, administration methods, duration, and clinical outcomes associated with progestogen use in the management of early pregnancy bleeding, threatened abortion, and recurrent pregnancy loss.

Keywords: Early pregnancy bleeding; threatened abortion; miscarriage; progesterone

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Progestins

Progesterone is a pivotal steroid hormone with essential roles in human physiology, particularly in the maintenance of pregnancy. It also serves as a critical metabolic precursor in the biosynthesis of other endogenous steroids, including corticosteroids. Progesterone, a naturally occurring hormone, was first introduced as a pharmaceutical agent in 1934 [3]. In clinical practice, it has been utilized for contraception, hormone replacement therapy, prevention of preterm birth, and the management of miscarriage.

During pregnancy, progesterone is indispensable for maintaining gestational integrity. In the first eight weeks of gestation, progesterone is exclusively synthesized by the corpus luteum. Following placentation, between the 8th and 12th weeks, progesterone production is shared equally between the corpus luteum and the placenta. After the 12th week, the placenta becomes the predominant source of progesterone synthesis.

Progestogens encompass both endogenous progesterone and synthetic compounds with progesterone-like activity. These agents are classified into two categories: natural progesterone, synthesized endogenously, and synthetic progesterone analogs. Progestogens exert their effects by binding to progesterone receptors, thereby modulating various physiological processes. Progesterone, the most critical progestogen for pregnancy maintenance, is essential for immunomodulation, inhibition of myometrial contractility, and enhancement of endometrial receptivity.

Insufficient secretion of human chorionic gonadotropin (hCG) during the implantation phase can lead to corpus luteum insufficiency, reduced progesterone levels, and subsequent pregnancy loss. Studies have demonstrated that surgical removal of the corpus luteum prior to placental development invariably results in miscarriage [3].

Adequate progesterone levels during the luteal phase are critical for endometrial maturation and successful implantation. Luteal phase defects, characterized by insufficient progesterone secretion, are associated with early pregnancy loss [4]. A 2015 meta-analysis demonstrated that progesterone supplementation during the luteal phase significantly improves pregnancy outcomes, including live birth rates [5].

Serum progesterone levels have been investigated as a prognostic marker in pregnancies complicated by threatened abortion. Women with serum progesterone levels below 90.62 nmol/L were found to have a significantly higher risk of miscarriage [6]. Furthermore, low progesterone levels during the first trimester have been strongly associated with an increased likelihood of pregnancy loss [7]. Consequently, progesterone supplementation has been extensively studied for its potential to prevent recurrent pregnancy loss and early pregnancy bleeding [8].

Progesterone can be administered via oral, intramuscular, or vaginal routes. Oral administration is subject to first-pass metabolism in the liver, which may reduce its bioavailability. In contrast, intramuscular and vaginal administration bypass hepatic metabolism, allowing higher concentrations to reach the endometrial tissue. Vaginal administration is often preferred due to its localized effect and favorable pharmacokinetic profile [9].

Progestogens are broadly categorized into natural and synthetic forms. Micronized progesterone, a natural form, is associated with side effects such as androgenic activity, agitation, fatigue, and fluid retention [10]. Didrogesterone, a synthetic progestogen, is administered orally and is frequently compared with micronized progesterone in terms of efficacy for managing recurrent pregnancy loss and threatened abortion.

Miscarriage

Miscarriage is defined as the spontaneous loss of pregnancy before 22 weeks of gestation, often accompanied by vaginal bleeding and pelvic pain. Threatened abortion refers to vaginal bleeding and pelvic pain in the presence of a viable fetus and a closed cervical canal [11].

A study reported a miscarriage rate of 19.7%, excluding cases of unwanted pregnancy loss [12]. Risk factors for miscarriage include advanced maternal age, immunological abnormalities (e.g., antiphospholipid syndrome), hormonal imbalances, and environmental exposures. Maternal diabetes and polycystic ovary syndrome are also significant risk factors. One study identified 27 years as the maternal age associated with the lowest miscarriage risk, with the risk increasing fourfold after three consecutive miscarriages [13]. Recurrent miscarriages are often linked to parental chromosomal abnormalities and genetic factors [14].

The majority of miscarriages occur within the first 12 weeks of gestation, with the risk declining significantly after 14 weeks [15]. In cases of early pregnancy bleeding, advancing gestational age is generally associated with a more favorable prognosis. Women with a history of bleeding during their first pregnancy are at an increased risk of experiencing bleeding in subsequent pregnancies [16].

Recurrent miscarriage, defined as three or more consecutive pregnancy losses, has been the focus of numerous studies investigating the role of progesterone supplementation in improving pregnancy outcomes [17].

Progesterone use in miscarriages

Early pregnancy management involves biochemical confirmation of pregnancy and ultrasonographic monitoring of fetal cardiac activity. In cases of vaginal bleeding, the type of miscarriage should be determined based on cervical status and fetal viability. Pregnancies with a closed cervical canal and positive fetal cardiac activity are classified as threatened abortion.

Miscarriage has profound psychological and physical consequences for affected individuals. Severe bleeding in early pregnancy may also pose significant maternal morbidity and mortality risks. Studies have demonstrated that miscarriage is associated with increased rates of depression, anger, and sleep disturbances [18].

Numerous clinical trials and meta-analyses have evaluated the efficacy of various progesterone formulations in reducing miscarriage rates. A 2017 meta-analysis compared vaginal micronized progesterone and oral didrogesterone with conservative management or placebo in patients with threatened abortion. Both treatments were associated with reduced miscarriage rates, with oral didrogesterone demonstrating a statistically significant advantage [19].

Further studies, including the PROMISE and PRISM trials, have highlighted the potential of progesterone to improve live birth rates, particularly in women with a history of recurrent miscarriage or early pregnancy bleeding [20].

In a meta-analysis conducted in 2021, the use of oral dydrogesterone, placebo, and vaginal micronized progesterone was compared in women with threatened abortion. The study demonstrated that oral dydrogesterone significantly reduced miscarriage rates compared to the other groups [21].

A study conducted in 2022 showed that the use of 200 mg micronized progesterone twice daily for two weeks had similar efficacy in preventing miscarriage as 10 mg dydrogesterone administered twice daily. However, the same study reported that patients using oral micronized progesterone experienced more side effects, such as drowsiness and dizziness [22].

In another study conducted on pregnant women with threatened abortion during the first 12 weeks, the use of 10 mg dydrogesterone twice daily was compared with 200 mg oral micronized progesterone twice daily. It was found that dydrogesterone was more effective in reducing vaginal bleeding and alleviating lower abdominal pain compared to micronized progesterone [23].

Two large controlled studies on the use of progesterone in early pregnancy demonstrated that 400 mcg of micronized progesterone could reduce early pregnancy loss and increase live birth rates [20]. The effects of progesterone on miscarriage prevention were systematically analyzed, and it was concluded that progesterone is particularly beneficial for women with threatened abortion [17].

Another meta-analysis found that the use of progesterone in women with recurrent pregnancy loss and threatened abortion may have little to no benefit on live birth rate [17]. However, among progestogens, the use of vaginal micronized progesterone was shown to be more effective in increasing live birth rates [17]. The same meta-analysis indicated that there was insufficient data to evaluate the efficacy of 17-α-hydroxyprogesterone caproate (17-OHPC) or oral micronized progesterone in recurrent pregnancy loss [17].

The efficacy of 17-OHPC in preventing recurrent preterm births was evaluated in the PROLONG study and other analyses involving a total of 2,221 patients. The findings indicated that 17-OHPC did not significantly reduce preterm birth rates. The study emphasized that there is insufficient evidence to support the use of 17-OHPC for this purpose [24].

Additionally, the use of 17-OHPC in miscarriage prevention was found to be ineffective, as it did not significantly reduce miscarriage risk. A study also suggested that exposure to 17-OHPC during the first trimester may be associated with an increased risk of cancer in offspring. It was reported that as the number of 17-OHPC injections increased during the first trimester, the risk of cancer in exposed fetuses also increased. Specifically, the risks of colorectal, prostate, and pediatric brain cancers were found to be higher in those exposed to 17-OHPC during the first trimester compared to those who were not exposed [25, 26].

Given these findings, caution is advised when considering the use of 17-OHPC in early pregnancy. Due to insufficient evidence supporting its efficacy in reducing preterm birth risk, the U.S. Food and Drug Administration (FDA) withdrew its approval for the use of 17-OHPC for this indication on April 5, 2023 [26]. For these reasons, 17-OHPC should not be used in cases of threatened abortion.

Progesterone is also used to reduce miscarriage risk and increase live birth rates in cases of recurrent pregnancy loss and luteal phase defects. A meta-analysis has shown that the use of progesterone in women with recurrent pregnancy loss can reduce miscarriage rates [27].

The role of progesterone in reducing miscarriage rates and its effects in assisted reproductive technologies have been discussed. Progesterone has been emphasized as an important hormone for maintaining pregnancy continuity [1].

Studies have also shown that the use of 400 mg micronized progesterone in recurrent pregnancy loss may reduce the risk of miscarriage [20].

Conclusion

Progesterone supplementation in cases of threatened abortion, early pregnancy bleeding, and recurrent pregnancy loss has demonstrated potential in reducing miscarriage risk. While didrogesterone appears to be more effective in certain scenarios, both natural and synthetic progesterone formulations are viable options.

Although micronized progesterone has shown promise in recurrent pregnancy loss, further large-scale studies are required to establish definitive conclusions. Clinicians should tailor progesterone therapy based on the patient's obstetric history, clinical findings, and ultrasonographic evaluation.

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References

1. Lai TJ, Teng SW, Chang CK, Huang CY. Progesterone in Pregnancy: Evidence-Based Strategies to Reduce Miscarriage and Enhance Assisted Reproductive Technology. Med Sci Monit. 2024 Mar 8;30:e943400. doi: 10.12659/MSM.943400.

2. Tuuli MG, Norman SM, Odibo AO, Macones GA, Cahill AG. Perinatal outcomes in women with subchorionic hematoma: a systematic review and meta-analysis. Obstet Gynecol. 2011 May;117(5):1205-1212. doi: 10.1097/AOG.0b013e31821568de.

3. Csapo AI, Pulkkinen MO, Ruttner B, Sauvage JP, Wiest WG. The significance of the human corpus luteum in pregnancy maintenance. I. Preliminary studies. Am J Obstet Gynecol. 1972 Apr 15;112(8):1061-7. doi: 10.1016/0002-9378(72)90181-0.

4. Swyer GI, Daley D. Progesterone implantation in habitual abortion. Br Med J. 1953 May 16;1(4819):1073-7. doi: 10.1136/bmj.1.4819.1073.

5. Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev. 2015 Jul 7;2015(7):CD009154. doi: 10.1002/14651858.CD009154.pub3.

6. Deng Y, Chen C, Chen S, Mai G, Liao X, Tian H, Liu W, Ji S, Liu Y, Gao J, Luo S. Baseline Levels of Serum Progesterone and the First Trimester Pregnancy Outcome in Women with Threatened Abortion: A Retrospective Cohort Study. Biomed Res Int. 2020 Mar 2;2020:8780253. doi: 10.1155/2020/8780253.

7. Osmanağaoğlu MA, Erdoğan I, Eminağaoğlu S, Karahan SC, Ozgün S, Can G, Bozkaya H. The diagnostic value of beta-human chorionic gonadotropin, progesterone, CA125 in the prediction of abortions. J Obstet Gynaecol. 2010 Apr;30(3):288-93. doi: 10.3109/01443611003605286.

8. Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, Nelen W, Peramo B, Quenby S, Vermeulen N, Goddijn M. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open. 2018 Apr 6;2018(2):hoy004. doi: 10.1093/hropen/hoy004.

9. Paulson RJ, Collins MG, Yankov VI. Progesterone pharmacokinetics and pharmacodynamics with 3 dosages and 2 regimens of an effervescent micronized progesterone vaginal insert. J Clin Endocrinol Metab. 2014 Nov;99(11):4241-9. doi: 10.1210/jc.2013-3937.

10. Goletiani NV, Keith DR, Gorsky SJ. Progesterone: review of safety for clinical studies. Exp Clin Psychopharmacol. 2007 Oct;15(5):427-44. doi: 10.1037/1064-1297.15.5.427.

11. Cunningham FG. Section IX. Reproductive success and failure. Williams Obstetrics. 21st Edition. New York: McGraw-Hill, 2001

12. Rossen LM, Ahrens KA, Branum AM. Trends in Risk of Pregnancy Loss Among US Women, 1990-2011. Paediatr Perinat Epidemiol. 2018 Jan;32(1):19-29. doi: 10.1111/ppe.12417.

13. Magnus MC, Wilcox AJ, Morken NH, Weinberg CR, Håberg SE. Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. BMJ. 2019 Mar

20;364:l869. doi: 10.1136/bmj.l869.

14. Garrido-Gimenez C, Alijotas-Reig J. Recurrent miscarriage: causes, evaluation and management. Postgrad Med J. 2015 Mar;91(1073):151-62. doi: 10.1136/postgradmedj-2014-132672.

15. Alberman E. Spontaneous abortions: epidemiology. In: Spontaneous Abortion: Diagnosis and Treatment. London: Springer Verlag, 1992:9-20

16. Lykke JA, Dideriksen KL, Langhoff-Roos J. First-trimester vaginal bleeding and complications later in pregnancy. Obstet Gynecol. 2010 May;115(5):935-944. doi: 10.1097

17. Devall AJ, Papadopoulou A, Podesek M, Haas DM, Price MJ, Coomarasamy A, Gallos ID. Progestogens for preventing miscarriage: a network meta-analysis. Cochrane Database Syst Rev. 2021 Apr 19;4(4):CD013792. doi: 10.1002/14651858.

18. Marcinko VM, Marcinko D, Dordević V, Oresković S. Anxiety and depression in pregnant women with previous history of spontaneous abortion. Coll Antropol. 2011 Jan;35 Suppl 1:225-8.

19. Lee HJ, Park TC, Kim JH, Norwitz E, Lee B. The Influence of Oral Dydrogesterone and Vaginal Progesterone on Threatened Abortion: A Systematic Review and Meta-Analysis. Biomed Res Int. 2017;2017:3616875. doi: 10.1155/2017/3616875.

20. Coomarasamy A, Devall AJ, Brosens JJ, et al. Micronized vaginal progesterone to prevent miscarriage: a critical evaluation of randomized evidence. Am J Obstet Gynecol. 2020 Aug;223(2):167-176. doi: 10.1016/j.ajog.2019.12.006.

21. Zhao H, He W, Yang Z. A pairwise and network meta-analysis comparing the efficacy and safety of progestogens in threatened abortion. Int J Gynaecol Obstet. 2022 Mar;156(3):383-393. doi: 10.1002/ijgo.13707.

22. Shaikh R, Jalbani A, Lashari S, et al. Role of micronized progesterone versus dydrogestron in patients with threatened abortion. J Soc Obstet Gynaecol Pak. 2022;12(3):262–66.

23. Yatam S, Pandey S, Patil Y, Patil S. Oral dydrogesterone and micronized progesterone in threatened miscarriage in terms of pain lower abdomen and bleeding per vaginum. NeuroQuantology. 2022;20(6):8606–10.

24. Kuon RJ, Berger R, Rath W. 17-Hydroxyprogesterone Caproate for the Prevention of Recurrent Preterm Birth - A Systematic Review and Meta-analysis Taking into Account the PROLONG Trial. Geburtshilfe Frauenheilkd. 2021 Jan;81(1):61-69. doi: 10.1055/a-1295-0752.

25. Murphy CC, Cirillo PM, Krigbaum NY, Cohn BA. In utero exposure to 17α-hydroxyprogesterone caproate and risk of cancer in offspring. Am J Obstet Gynecol. 2022 Jan;226(1):132.e1-132.e14. doi: 10.1016/j.ajog.2021.10.035.

26. Society for Maternal-Fetal Medicine Statement: Response to the Food and Drug Administration's withdrawal of 17-alpha hydroxyprogesterone caproate. Am J Obstet Gynecol. 2023 Jul;229(1):B2-B6. doi: 10.1016/j.ajog.2023.04.012.

27. Haas DM, Hathaway TJ, Ramsey PS. Progestogen for preventing miscarriage in women with recurrent miscarriage of unclear etiology. Cochrane Database Syst Rev. 2019 Nov 20;2019(11):CD003511. doi: 10.1002/14651858.

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Investigation of smoking prevalence and related factors among final year medical students: The case of Giresun University

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Abstract

Objectives: Tobacco use among medical students is common worldwide. It is estimated that one in every five students smoke. The aim of this study was to evaluate smoking prevalence and associated factors in final year medical students.

Methods: The study included 100 students studying in their final year at Giresun University Faculty of Medicine. The students who participated in the study were questioned with two scales and one form: sociodemographic form, Decisional Balance Scale for Smoking (DBSS), Fagerstrom Nicotine Dependence Test (FNBT).

Results: The mean age of the students was 24.3 ± 1.1 years (22-29 years). 54% of the participants were female and 46% were male. The rate of smoking in the living area was 56%. The prevalence of smoking in the family was 65%. The most common reasons for smoking were personal and family realtaed reasons (37.5%), curiosity (30%) and peer influence (22.5%). The FNDT scale showed that the level of addiction was low in 72.5%, moderate in 25% and high in 2.5% of the students. Total DBSS score was negative in 85% and positive in 15% of the smoking students.

Conclusion: The prevalence of smoking among final year medical students is quite high. Students who are prone to smoking cessation according to the DBSS scale should be directed to smoking cessation treatments. The theoretical and clinical curriculum on smoking in medical school should be reviewed and implemented from the first years of medical school. Smoking rates can be reduced by increasing the number of smoking cessation outpatient clinics, easy access to counselling services and inclusion of students' close environment in the intervention process.

Keywords: Tobacco use; cigarette smoking; medical students; dependence of smoking

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Introduction

Cigarettes, a type of tobacco product, are one of the leading causes of non-communicable diseases, disabilities, and preventable deaths. Due to the nicotine they contain, cigarettes are addictive, and the various harmful substances present in them lead to numerous health issues for both smokers and passive smokers [1].

The negative health effects of tobacco use were confirmed by scientific research conducted in the 1950s, leading to numerous studies on tobacco-related diseases being added to the literature since then. However, the history of tobacco use dates back over 4,000 years. Substance use dates back to nearly the beginning of human history. A historical review reveals evidence of the consumption of addictive substances in mythological tales, legends, religious and literary works, and songs [2]. Today, tobacco products, especially cigarettes, are associated with approximately fifty different chronic diseases that do not directly cause death but significantly impact health [3]. Smokers often require medical assistance to overcome their smoking habit. Treatment should begin with non-pharmacological approaches, followed by the application of pharmacological therapies [4].

mPower is a policy package developed by the WHO to reduce tobacco use, containing a set of policies that have been proven effective. The main components of this policy package are: Monitor, protect, offer, warn, enforce [5].

In the coming years, medical students, who will be guardians of public health, will play a key role in the fight against smoking. In this context, our study aims to investigate the frequency of smoking among final-year medical students and the associated factors.

Materials and Methods

Our study was approved by the Giresun Training and Research Hospital Clinical Research Ethics Committee with decision number 2023/4522 on September 15, 2023. The study was conducted in accordance with the World Medical Association Declaration of Helsinki and Good Clinical Practice guidelines. Participants were informed about the research, and data were collected based on voluntary consent after obtaining informed consent. The study population consists of final-year medical students at Giresun University between the dates of February 1, 2024, and July 1, 2024. The data obtained through the survey in the study were collected by researchers using face-to-face interview techniques from final-year medical students included in the sample.

The GPower 3.1 program was used to calculate the sample size. According to a two-sided hypothesis with a 5 % Type I error rate, 0.217 effect size, and 95% power, the required number of participants was calculated as 65.

The demographic form included questions about age, gender, marital status, family type, living situation (family, friends, alone), the student's income level, the family's income level, the educational background of the mother and father, current smoking status, smoking in the living area, presence of smokers in the family, awareness of the harms of smoking prior to medical school, adequacy of theoretical knowledge regarding the harms of smoking in medical school, adequacy of education on smoking cessation methods in medical school, negative effects of faculty members' smoking on students, age of starting smoking, reasons for starting smoking, daily amount of cigarettes used, duration of smoking, smoking before university, type of tobacco product used and questions about attempts to quit smoking after education on smoking cessation methods provided in medical school.

The Fagerström Test for Nicotine Dependence (FTND) was used to assess the degree of addiction among smokers, while the Smoking Decision Balance Scale (SDBS) was utilized to evaluate the significance of students' perceptions of the harms and benefits of smoking.

The Fagerström Test for Nicotine Dependence (FTND), widely used to evaluate the physical aspect of nicotine addiction, was developed in 1991 by Heatherton et al. as a revision of the Fagerström Tolerance Questionnaire. It consists of six items [5]. The total FTND score is categorized as low dependence for 0–3, moderate dependence for 4–6, and high dependence for 7 and above [6].

The Turkish validity and reliability study of the Smoking Decision-Making Scale (SDMS) was conducted by Bektaş et al. in 2010 [7].

The normality of the variables was assessed using visual methods (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov and Shapiro-Wilk tests). Descriptive statistics were expressed in terms of frequency, percentage, mean, standard deviation, and median.

Results

The average age of the 100 final-year medical students

included in the study was 24.3 ± 1.1 years (ranging from 22 to 29 years). Of the participants, 54% were female and 46% were male, resulting in a female-to-male ratio of 1.2:1. Ninety-nine percent of the students were single. Most students came from nuclear family types, and 12% of the students lived alone. The income level of the majority of the students (97%) was above 4,000 TL. Additionally, 64% of the students' fathers and 44% of their mothers were university graduates.

Among the 100 students participating in the study, 40 were smokers. The rate of smoking in the living area was 56%. The frequency of smoking within the family was 65%. Smokers and non-smokers were compared in terms of smoking history characteristics. The presence of individuals who smoke in the living environment was more common among smokers than non-smokers. All students had acquired knowledge about the harms of smoking prior to medical school. The vast majority of participants (95%) found the education on the harms of smoking in medical school to be sufficient, while 90% deemed the education on smoking cessation methods adequate. Only 5% of the students expressed that they were negatively affected by faculty members' smoking.

The smoking history of the 40 students who smoked was evaluated. Among them, approximately half started smoking at the age of 19 or older, while 2.5% began smoking between the ages of 13 and 15, and 45% started between the ages of 16 and 18. The most common reasons for starting to smoke were personal and family reasons (37.5%), curiosity (30%), and peer influence (22.5%). The daily number of cigarettes smoked was generally between 10 and 20 for 55% of the participants. Only 5% reported smoking more than 20 cigarettes a day. Half of the participants (50%) had been smoking for over six years, and the other half (50%) stated that they had smoked prior to university. After the education on smoking cessation methods in medical school, only 22% of smokers attempted to quit.

The 40 students who smoked were evaluated using the Smoking Decision Balance Scale (SDBS). In the 24-item questionnaire, the statements with the highest agreement among students were: "smoking is harmful to health" (100%), "smoking is harmful to the health of others" (97.5%), and "the smoke and odor of cigarettes disturb people around" (90%). When evaluating the results of the Smoking Decision Balance Scale (SDBS), the average benefit score was 33.7 ± 6.2 (ranging from 14 to 47), while the average harm score was 39.2 ± 4.1 (ranging from 33 to 53). The total SDBS score was -5.5 ± 6.5 (ranging from -30 to 7). The total SDBS score was negative for 85% of the smoking students and positive for 15%.

The total score of the Fagerström Test for Nicotine Dependence (FTND) among smoking students was 2.7 ± 1.5 (ranging from 1 to 7). According to the FTND scale, the level of dependence was low in 72.5% of the students, moderate in 25%, and high in 2.5% (Figure 1).

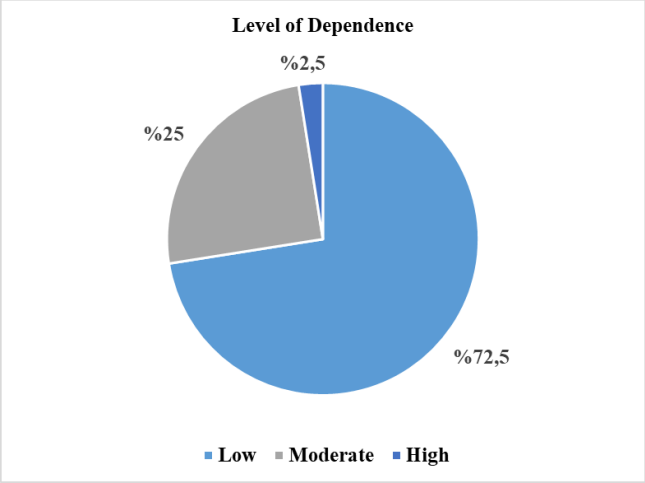

Figure 1: The level of nicotine dependence among smoking students according to the Fagerström Test for Nicotine Dependence (FTND).

The benefit and harm scores of the Smoking Decision Balance Scale (SDBS) were compared based on the smoking history of students. Those who smoked more than 10 cigarettes per day had a higher SDBS benefit score than those who smoked between 1 and 10 cigarettes daily. Students who had smoked for 6 years or more had a higher SDBS benefit score than those who had smoked for 0-5 years. Additionally, students who smoked before university had a higher SDBS benefit score than those who started smoking in university (Table 1).

The Fagerström Test for Nicotine Dependence (FTND) scores of smoking students were compared based on smoking-related characteristics. Students with a family history of smoking had higher FTND scores than those without ($p=0.012$). Additionally, those who started smoking between the ages of 13 and 18 had higher FTND scores than those who started at 19 or older ($p<0.001$) (Table 2).

The correlation analysis among smokers revealed a significant positive correlation between the SDBS benefit score and the FTND score (Table 3).

Table 1: Comparison of the benefit and harm scores of the smoking decision balance scale (SDBS) according to smoking-related characteristics of smokers

Characteristic (n=40)	SDBS benefit score	p-value	SDBS harm score	p-value
	Mean ± SD		**Mean ± SD**	
Presence of smoking in the living area		0.133†		0.438†
Yes	34.8 ± 4.4		39.4 ± 4.1	
No	27.1 ± 10.5		38.0 ± 4.1	
Family history of smoking		0.443†		0.649†
Yes	34.1 ± 5.5		39.4 ± 4.4	
No	32.4 ± 3.0		38.7 ± 3.0	
Age of starting smoking		0.088†		0.376†
13-18 years	35.5 ± 8.0		39.8 ± 4.7	
≥19 years	32.0 ± 3.1		38.6 ± 3.4	
Daily cigarette consumption		**0.024**†		0.280†
1-10 cigarettes	30.8 ± 4.2		38.1 ± 3.6	
>10 cigarettes	35.1 ± 6.4		39.4 ± 3.5	
Duration of smoking		**0.048**†		0.573†
0-5 years	31.8 ± 5.3		39.6 ± 3.7	
≥6 years	35.6 ± 6.5		38.8 ± 4.5	
Smoking before university		**0.018**†		0.736†
Yes	36.0 ± 6.6		39.4 ± 4.9	
No	31.4 ± 4.9		39.0 ± 3.2	
Attempt to quit smoking after education on cessation methods		0.054†		0.067†
Yes	37.2 ± 7.0		41.4 ± 5.5	
No	32.7 ± 5.6		38.5 ± 3.4	

†Student t-test

Discussion

Smoking is one of the leading preventable causes of chronic diseases, reduced quality of life, and early death. It is estimated that the use of tobacco products, primarily cigarettes, is responsible for 64.2% of deaths due to trachea, bronchus, and lung cancers; 48.5% of deaths due to chronic obstructive pulmonary disease; 40.8% of deaths due to esophageal cancer; 32.6% of deaths due to cerebrovascular diseases; and 7.8% of deaths due to diabetes [8].

The frequency of smoking among university students is a significant problem in terms of the cumulative harms of smoking, especially because of their young age. Despite this, one in four university students in the United States, and globally, one in five university students use tobacco products [9,10]. In medical schools, these rates should be lower due to the importance of physicians in smoking cessation. In our study, it was observed that the smoking frequency among final-year medical students was 40%. This rate can be considered quite high.

In a study conducted by Seven and Günay in 2024 in İzmir, the smoking frequency among first-year and fifth-year students was reported to be 34.1%. It was stated that 29.8% of first-year students and 40.8% of fifth-year students smoked [11]. These rates were very close to those found in our study evaluating sixth-year students. In a study conducted by Karabiber et al. in Hatay, the smoking frequency among medical

Table 2. Comparison of Fagerström Test for Nicotine Dependence (FTND) Scores According to Smoking-Related Characteristics of Smokers.

Characteristic (n=40)	FNDT Score	p-value
	Mean ± SD	
Presence of smoking in the living area		0.469†
Yes	2.8 ± 1.6	
No	2.3 ± 1.2	
Family history of smoking		**0.012†**
Yes	3.1 ± 1.6	
No	1.7 ± 0.9	
Age of starting smoking		**<0.001†**
13-18 years	3.6 ± 1.5	
≥19 years	1.9 ± 1.1	
Duration of smoking		**<0.001†**
0-5 years	1.9 ± 1.0	
≥6 years	3.6 ±1.5	
Smoking before university		**<0.001†**
Yes	3.8 ± 1.5	
No	1.7 ± 0.7	
Attempt to quit smoking after education on cessation methods		**0.007†**
Yes	4.0 ± 1.7	
No	2.4 ± 1.3	

students was reported to be 27%. In this study, which included first-year, fourth-year, and sixth-year students, the smoking frequency for only sixth-year students was stated to be 33.3% [12]. These findings also indicate that the smoking frequency tends to increase in the later years of medical school.

There are also studies that report higher rates of smoking. However, these studies are often conducted in countries with lower levels of development. In a study conducted by Jarelnape et al. in 2023 in Sudan, the smoking frequency among medical students was reported to be 48.8% [13].

There are also studies reporting much lower smoking rates among medical students. In the 2023 study by Babjakova et al., the smoking frequency among 783 medical students was reported to be 11.4%. The fact that the students in this study were primarily those who had just begun medical school may have contributed to the lower rates [14].

In our country, according to current data, the smoking frequency in the general population (aged 15 and above) has been reported to be 45.8%, with 27.2% of the population smoking daily [15]. In the European Union, however, smoking rates are lower (less than 25%) [16]. These findings may be related to stronger anti-smoking policies in EU countries. By improving existing regulations related to smoking and closely monitoring their implementation, it may be possible to achieve lower smoking rates in both the general population and among medical students.

A wide variety of reasons for starting smoking have been identified in the literature. In our study, personal and family issues, curiosity, and peer influence were found to be prominent reasons, while the desire for pleasure and social acceptance were noted as quite rare reasons. In the

Table 3: Correlation analyses among age, Smoking Decision Balance Scale (SDBS) scores, and Fagerström Test for Nicotine Dependence (FTND) scores among smokers

		Age	SDBS benefit	SDBS harm	FTND
Age	Rho/r	-	-0.012	-0.196	0.210
	p-value	-	0.940	0.225	0.194
SDBS benefit	Rho/r	-0.012	-	0.240	**0.536**
	p-value	0.940	-	0.135	**<0.001**
SDBS harm	Rho/r	-0.196	0.240	-	0.078
	p-value	0.225	0.135	-	0.633
FTND	Rho/r	0.210	**0.536**	0.078	-
	p-value	0.194	**<0.001**	0.633	-

study by Seven and Günay, the most common reasons mentioned were reducing stress levels, seeking pleasure, and curiosity [11].

Determining a smoker's readiness to quit in advance can be beneficial for creating personalized cessation programs. Selecting suitable candidates for smoking cessation treatments and assessing their levels of addiction are important. For this purpose, numerous assessment methods have been developed. In our study, when evaluated using the FNBT scale, it was found that only 2.5% of smoking students had a high level of addiction. The majority of the students had low levels of addiction. These findings suggest that the success rate of smoking cessation methods among medical students could be high.

The Decision-Making Balance Scales were actually developed to predict behavioral changes and identify individuals who are open to change. These scales have been used to assess individuals' attitudes toward necessary behavioral changes in various diseases, such as hypertension and obesity [17,18]. Considering that quitting smoking is also an important behavioral change, the scales have been adapted for smoking cessation. The necessary stages of change for quitting smoking, like other decisions, depend on the relationship between the benefits and harms that the change will bring [19]. For those contemplating quitting, their thoughts on the harms of smoking outweigh their thoughts on its benefits. In our study, we attempted to identify students who were likely to quit smoking using the Decision-Making Balance Scale. It was found that the harm scores of the majority of sixth-year students were higher than their benefit scores. The high harm scores indicate that these smoking students are primarily focused on the harms of smoking and are potential candidates for quitting. To our knowledge, there is no study that has identified smoking cessation candidates among medical students using the Decision-Making Balance Scales. However, university students have been previously assessed with these scales. In the 2023 study by Çakmak and Gökdere, 425 university students were evaluated using the Decision-Making Balance Scales, and it was stated that their harm scores were higher than their benefit scores, indicating that these students were potential candidates for quitting smoking [20].

Our study indicated that, although the smoking frequency among medical students is quite high, their levels of addiction are low, and they primarily focus on the harms of smoking. This suggests that the success rate of properly planned smoking cessation interventions could be high. Another significant finding of our study was that only 22% of smokers attempted to quit after receiving smoking cessation treatment methods in medical school. Optimizing smoking cessation education, expanding the content of the training, and starting education on smoking in the early years of medical school could enhance the success rates of smoking cessation programs.

Our study had certain limitations. The sample size was relatively small, and it was a single-center study. Therefore, it may not represent all medical students.

Conclusion

Given that medical students will also be responsible for implementing smoking cessation treatments in addition

to their own health, necessary measures should be taken to reduce the smoking frequency among them. The medical school curriculum includes the harms of tobacco and tobacco products, prevention and treatment of smoking-related diseases, and smoking cessation methods. However, the results of our study indicate that the existing measures are insufficient. When considering students' approaches to tobacco products individually, the focus should first be on preventing students from starting to smoke, and then identifying those who smoke and are willing to quit, followed by the implementation of individualized treatments to reduce smoking rates. For students with a high level of addiction, nicotine replacement therapy (NRT) and pharmacological treatments can be recommended.

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References

1. Karlıkaya C, Öztuna F, Solak ZA, Özkan M, Örsel O. Tütün Kontrolü. *Toraks Dergisi.* 2006; 7(1): 51-64.
2. Uğurlu TT, Balcı Şengül C, Şengül C. Bağımlılık psikofarmakolojisi. *Psikiyatride Güncel Yaklaşımlar*. 2012; 4(1):37-50.
3. Karlıkaya C. Tütüne Bağlı Hastalıklar ve Tütünün Kontrolü. Http://File.Toraks.Org.Tr/Toraksfd23njkl4nj4h3bg3jh/Kisokulu3-Pptpdf/Celal_Karlikaya.Pdf. Erişim Tarihi:21.08.2024.
4. Haustein KO. Pharmacotherapy of nicotine dependence. *Int J Clin Pharmacol Ther*. 2000;38(6):273-290. doi:10.5414/cpp38273
5. World Health Organization. WHO report on the global tobacco epidemic, 2008. the MPOWER package. Geneva, World Health Organization, 2008 (http://www.who.int/tobacco/mpower/en/index.html. accessed 21 March 2008).
6. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict*. 1991;86(9):1119-1127. doi:10.1111/j.1360-0443.1991.tb01879.x
7. Bozkurt N, Bozkurt Aİ. Nikotin bağımlılığını belirlemede Fagerström Nikotin Bağımlılık Testinin (FBNT) değerlendirilmesi ve nikotin bağımlılığı için yeni bir test oluşturulması. *Pam Tıp Derg.* 2016;9(1):45-51.
8. Bektaş M, Armstrong M. Validity and Reliability Study of the Turkish Version of the Decisional Balance Scale for Adults. *J Addict Nurs.* 2010; 21:6–13.
9. Teixeira-da-Costa EM, Merino-Godoy MD, Almeida MMML, Silva AMMC, Nave FJGM. Gender and Tobacco Consumption among University Students. *Int J Environ Res Public Health.* 2022;19(22):14772.
10. Sreeramareddy CT, Ramakrishnareddy N, Rahman M, Mir IA. Prevalence of tobacco use and perceptions of student health professionals about cessation training: results from Global Health Professions Students Survey. *BMJ Open.* 2018;8(5).
11. Centers for Disease Control and Prevention Youth Risk Behavior Surveillance System (YRBSS) [(accessed on 7 December 2021)];2019 Available online: https://www.cdc.gov/healthyyouth/data/yrbs/index.htm.
12. Seven F, Günay T. Tobacco Use Status of Medical Faculty Students and Evaluation of Affecting Factors. *Thorac Res Pract.* 2024;25(3):110-20.
13. Karabİber C, Azboy N, Altıner F, et al. Tıp Fakültesi Öğrencilerinin Tütün kullanımı hakkında bilgi, tutum ve Davranışları. *Mustafa Kemal Univ Tıp Derg.* 2018;9(33):21-32.
14. Jarelnape AA, Ahmed W, Omer S,et al. Prevalence of smoking cigarettes and beliefs regarding smoking habits among medical students: a cross-sectional study in Sudan. *Front Public Health.* 2023;11:1193475.
15. Babjakova J, Wimmerova S, Argalasova L. Smoking status of medical students and changes during the COVID-19 pandemic. *Eur J Public Health.* 2023;33:160.820.
16. Çakir M. Evaluation of Smoking and Associated Factors in Turkey. *Iran J Public Health.* 2023;52(4):766-72.
17. Gallus S, Lugo A, Liu X, et al. Who Smokes in Europe? Data From 12 European Countries in the TackSHS Survey (2017-2018). *J Epidemiol.* 2021;31(2):145-51.
18. Eshah NF, Mosleh SM, Al-Smadi A. The Decisional Balance Toward Health Behaviors Among Patients With Hypertension. *Clin Nurs Res.* 2021;30(7):977-84.
19. Rossi SR, Greene GW, Rossi JS, et al. Validation of decisional balance and situational temptations measures for dietary fat

reduction in a large school-based population of adolescents. *Eat Behav.* 2001;2(1):1-18.

20. Akdeniz E. Sigara Bağımlılığı Sağlığa Etkileri ve Sigara Bıraktırmada Kullanılan Transteoretik Model. *Kırşehir Ahi Evran Üniversitesi Sağlık Bilimleri Dergisi.* 2019; 2(3): 11 - 25.

21. Çakmak VS, Gökdere E. Üniversite Öğrencilerinin Üçüncü El Sigara Dumanı Farkındalıkları ve Sigaraya Yönelik Algıları: Kesitsel Çalışma. *Halk Sağlığı Hemşireliği Dergisi.* 2023; 5(3): 245-57

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Can postoperative serum lactate levels predict mortality in infants after open heart surgery?

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Abstract

Objective: Complex cardiac surgery is a cause of high morbidity and mortality in newborn infants.Elevated lactate levels after congenital cardiac surgery are indicative of tissue hypoperfusion and are associated with increased morbidity and mortality.Serial lactate measurements are crucial in monitoring prognosis in this patient group. Monitoring lactate levels is important in the management of patients after congenital heart surgery to predict and prevent adverse events.

Methods: Between July 2017 and December 1, 2022, the data of 115 patients aged 0-1 year who were followed up and treated at a pediatric cardiovascular surgery center, treated surgically, and underwent cardiopulmonary bypass during surgery were retrospectively evaluated.

Results: Twenty-two (19%) of the patients died in the postoperative period. The median (IQR) VIS score at 24 hours postoperatively was 27 (5-45), which was significantly higher than 12 (5-22) in survivors (p=0.01). When lactate levels were evaluated, preoperative lactate levels were higher in the group with mortality in the first 3 postoperative days, and the change in lactate levels at 24 hours postoperatively and initial lactate levels at 24 hours were higher (p<0.01). A 2-unit increase in lactate was found to predict mortality with a sensitivity of 77.8% and specificity of 99.13%.

Conclusion: Increased lactate levels are frequently encountered in the postoperative period and are associated with increased mortality and morbidity.

Keywords: Lactat; congenital heart surgery; cardiopulmonary bypass; mortality

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Introduction

Complex cardiac surgical procedures are operations with high mortality in the treatment of congenital heart diseases. Factors including clamping of the aorta, deep hypothermia and cardiopulmonary bypass increase mortality in this clinically unstable patient group [1,2].

Some factors that increase mortality after congenital heart surgery in newborns have been identified. Low gestational week, low birth weight, single ventricle physiology, and the type of surgery performed have been associated with morbidity and mortality in the postoperative period [3]. However, intraoperative and postoperative features also affect mortality in these patients.

Lactate increases in the case of inadequate oxygen supply to tissues or in the case of anaerobic energy metabolism as a result of impaired tissue perfusion. Lactate is produced in erythrocytes, skeletal myocytes, perivenous hepatocytes and skin and metabolized by the liver and kidney [4,5]. Elevated lactate levels may be associated with tissue hypoperfusion (type A hyperlactatemia) or decreased lactate clearance without impaired tissue hypoperfusion (type B hyperlactatemia) [6,7]. Studies showing that lactate clearance increases with age are available; therefore, it is important to determine lactate levels associated with poor prognosis in infants [8].

In terms of predicting prognosis and early intervention, especially lactate elevation continues to be a subject of research in this patient group. Determining the factors associated with lactate elevation after congenital heart surgery may reduce the frequency of associated morbidity and mortality as well as standardization in the follow-up of patients.

The aim of this study was to determine the association of lactate elevation in the postoperative period with morbidity and mortality after congenital heart surgery.

Materials and Methods

Between July 1, 2017 and December 1, 2022, we retrospectively evaluated the data of 115 patients between the ages of 0 and 1 year who were followed up and treated in a pediatric cardiovascular surgery center, treated surgically and underwent cardiopulmonary bypass during surgery.

Diagnoses, ages, body weights, operative times, aortic clamping times (minutes), cardiopulmonary bypass times (minutes) and postoperative 0 and 24 hours serum lactate levels were recorded from the patients' files. Short- and mid-term morbidities, sepsis and pulmonary hypertension, and length of hospitalization were also recorded. Initial leukocyte and platelet counts, hemoglobin levels, albumin and coagulation parameters (PTZ, INR and APTT) were recorded in the postoperative period.

Vasoactive inotrope score (VIS*) in the first 24 hours was recorded.

* Inotrope score (IS) = dopamine dose (mcg/kg/min) + dobutamine dose (mcg/kg/min) + 100 X epinephrine dose (mcg/kg/min)

*Vasotropic inotropic score (VIS) = IS + 10 X milrinone dose (mcg/kg/min) + 10,000 X vasopressin dose (U/kg/min) + 100 X norepinephrine dose (mcg/kg/min)

Serum lactate levels measured at preoperative, first postoperative and 24th hour were recorded. In the postoperative period, the difference between the initial lactate level and the lactate level measured at 24 hours was calculated. Mortality times in the postoperative period were also recorded for infants who died. The relationship between the change in postoperative serum lactate levels and those discharged in the first 72 hours postoperatively and those discharged between days 3-30 was evaluated.

Our primary outcome was to evaluate the relationship between the rapid change in serum lactate levels in the postoperative period and short- and mid-term mortality. Our secondary outcome was to evaluate the relationship between the change in serum lactate levels and short- and mid-term morbidity and the need for respiratory support.

Ethics committee approval was obtained from the local ethics committee.

Statistical Analysis

Statistical Package fort he social Sciences 22 statistical program was used for statistical analysis.

Demographics, patient characteristics and outcomes were expressed as a median for continuous variables and frequency (%) for categorical variables. Univariate and multivariate logistic regression analyses were performed to assess the association between the primary explanatory variable and the composite outcome. In

univariate modeling, $p < 0.01$ was considered statistically significant. Since our data were not normally distributed, median and interquartile range (IQR) 25th and 75th percentiles were used. Data obtained by measurement were expressed as mean ± standard deviation, data obtained by counting were expressed as %, $p < 0.01$ was considered significant. Chi-square and Spearman correlation test were used to analyze the data.

ROC analysis was used to assess the significance of lactate measurements as significant independent predictors of the composite outcome in multivariate modeling and the area under the curve showing significance was determined. Sensitivity, specificity, positive predictive value and negative predictive value were calculated at various lactate thresholds. Kaplan Meier test was used for survival analysis.

Results

A total of 115 patients were included in the study. The median age (IQR 25-75) was 106.00 (14-240) days and the median body weight was 4.28 (4.28-6.3).

Mean cardiopulmonary bypass time was 144 minutes (IQR 25-75) and mean aortic clamping time was 94 minutes (IQR 25-75). Preoperative sepsis was diagnosed in 23(18.4) patients.

The mean postoperative VIS score was 17 (10-26.5). Demographic and clinical characteristics of the patients are shown in Table 1.

The most common diseases were ventricular septal defect with 37 (32%) and transposition of the great arteries with 32 (26%).Other cardiac anomalies are coarctation of aorta(%4,3), hypoplastic left heart syndrom (%8,7),

Table 1. Demographic and clinical characterics of the patients

	N=115
Age, day*	106.00 (14-240)
Body weightt, kg*	4.28 (4.28-6.3)
Gender, male, n (%)	69(60)
Pulmonary hypertension, n (%)	42(36.6)
Sepsis, n (%)	23(18.4)
Cardiopulmonar bypass, minute*	144 (105-192)
Cross clemp time, minute*	94 (66-128)
Preoperative serum lactate level, mg/dl	2.05 (1.5-3.1)
1st postoperative serum lactate level, mg/dl	2.9 (1.96-4.92)
Postoperative 24th hour serum lactate levels, mg/dl	3.5 (2.2-6)
VIS*	17 (10-26.5)
Duration of surgery, hour**	5 (4-6.5)
Hospital stay, day	24 (14-34)
Mortality, n (%)	22 (19)

*VIS: Vasoactive inotrope score **Median (IQR 25-75)

Table 2. Factors effects mortality

	Mortality group (n=22)	Survivors (n=93)	p
Body weight, kg*	3250 (3037-4057)	5300 (3492-6775)	<0.01
Age, day*	13 (13-21)	180 (21-270)	<0.01
Gender, E (%)	12 (54)	57 (61)	0.36
Cross clamp time, min*	113 (72-153)	93 (66-125)	0.12
Cardiopulmonary bypass, min*	184 (140-251)	138 (103-181)	0.09
Duration of surgery, hours*	6.75 (5-9.1)	4.5 (4.5-6)	<0.01
24th hour VIS score	27 (5-45)	12 (5-22)	0.01
First postoperative lactate, mmol/L*	7.9 (3.3-12)	2.8 (1.9-4.2)	<0.01
White Blood Count (10^3 /L)**	11.7± 4.6	12.2 ±5	0.63
Hematocrit (%)**	38 ±9.5	38± 5.6	0.84
Platelet count (10^3 /L)**	145 ± 106	175 ±95	0.18
Prothrombin time (sec)**	24.7 ± 11.9	16.8 ± 4.2	<0.01
INR**	2.1± 0.7	1.5 ± 0.4	<0.01
Activated prothrombin time (sec)**	58 ± 20	38 ± 12	<0.01
Albumin, g/dl**	28.7± 6.1	33.8± 5.1	<0.01
Hospital stay *(day)	13 (6-21)	25 (20-34)	0.04

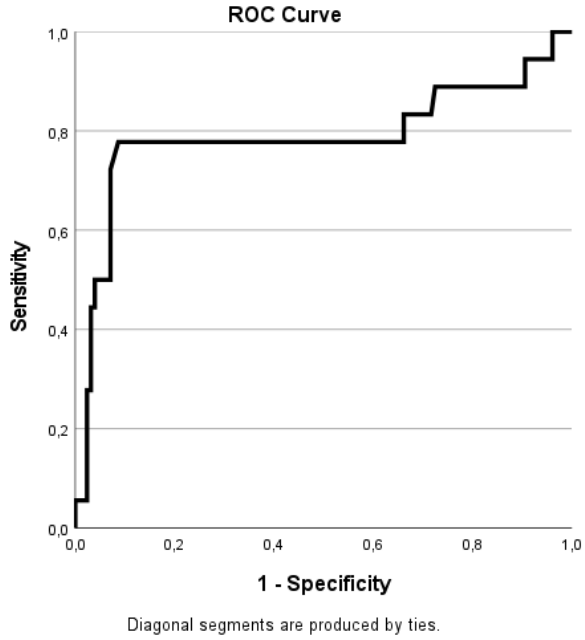
*median (IQR 25-75) **mean±standart deviation VIS: Vasoactive inotrope score

Table 3. Comparison of lactate levels and lactate changes in infants with and without mortality

	Postop mortality in the first 72 hours (N=11)	Postop mortality in 3-30 days (N=11)	Survivors (n=93)	p
Preoperative serum lactate level, mg/dl	4.3 (1-8)	-1.1 (-2.2-2)	-1.1 (-2.9- -0.1)	P^1:<0.01 P^2:0.62
1st preoperative serum lactate level, mg/dl	2.8 (2.1-3.55)	1.8 (1.2-3.1)	1.95 (1.5-2.95)	P^1:0.59 P^2:0.27
Postoperative 24th hour serum lactate levels, mg/dl	9.8 (7.95-16.5)	4.7 (2.9-8.4)	4.2 (2.65-6.6)	P^1: <0.01 P^2:0.55
Postoperative 24th hour-first serum lactate level difference	14.9 (10-21)	4.5 (2.7-8)	3.2 (1.9-4.5)	P^1: <0.01 P^2:0.48

***median (IQR 25-75) **P^1: Postoperative mortality in the first 72 hours & Survivors**
p^2: Postoperative mortality in 3-30 days& Survivors

Figure 1. ROC analysis showing the relationship between mortality and lactate change



tetralogy of Fallot (6.9%), total abnormal pulmonary venous return (6.9%) , pulmonary atresia (0,8%), truncus arteriosus (0,8%) and complete atrioventricular defect (7,8%).

Twenty-two (19%) of the patients died in the postoperative period. When the infants with mortality were compared with the survivors, the mortality group had younger age and lower body weight ($p < 0.01$ and $p < 0.01$, respectively). Cardiopulmonary bypass time and operation time were longer and postoperative serum lactate levels were higher in the group with mortality (Table 2). There was no significant correlation between mortality and aortic cross-clamping time ($p=0.12$). There was no significant correlation between thrombocytopenia and mortality ($p>0.01$), whereas high prothrombin time, activated partial thromboplastin time and INR were significantly associated with mortality ($p<0.01$).

The median (IQR) VIS score at 24 hours postoperatively was 27 (5-45), which was significantly higher than 12 (5-22) in the survivors ($p=0.01$) (Table 2).

When lactate levels were evaluated, in the group with mortality in the first 3 postoperative days, preoperative lactate levels were higher, and the change in lactate levels at postoperative 24h and 24h-first lactate levels were higher ($p<0.01$). However, no significant difference was observed between the group who died after day 3 and the survivors in terms of lactate levels and lactate changes (Table 3).

The ROC analysis showing the relationship between change in serum lactate levels and mortality during the first 3 days is shown in Figure 1. The AUC was 0.78 and a 2-unit increase in lactate was found to predict mortality with 77.8% sensitivity and 99.13% specificity. The Kaplan-Meier test evaluated the relationship between mortality and time of death in the postoperative period; the median (IQR) day of death was 4.5 (2-12.3) days ($p=0.029$).

Discussion

Advances in congenital heart surgery techniques have gained momentum in recent years. However, data on preoperative and postoperative follow-up of patients in neonates are still insufficient. In this group with high mortality and morbidity rates, mortality and morbidity rates can be reduced by analyzing the parameters used in the follow-up of patients well and intervening at the right time.

Congenital heart surgery involves complex surgical procedures. Intraoperative clamping of the aorta, deep hypothermia and cardiopulmonary bypass disrupt the physiologic balance of the newborn and cause difficulties in patient management in the postoperative period [1,2].

Although the surgical procedure is facilitated by mechanical interruption of blood flow from the aorta, systemic organ perfusion is affected. Impaired perfusion of organs causes hypoxia at the tissue level. This is manifested by elevated lactate levels in the laboratory. Elevated lactate is associated with high mortality and morbidity [5]. Therefore, lactate is used as an important parameter to predict the development of morbidity and mortality in adult and pediatric age groups[9,10].

In a study including neonates, a peak lactate level of 7.3 mmol/l or greater was found to be significantly associated with the presence of a major residual lesion. Overall, the study highlights the potential of hyperlactataemia as a predictor of adverse outcomes post-cardiac surgery in neonates with congenital heart disease. The two-variable model and peak lactate levels can help in prognosticating the risk and identifying patients who may require intervention [5].

In a single-center retrospective study in the adult

age group, the data of a total of 1290 patients were retrospectively evaluated. The patients were divided into three groups as <2 mmol/l, 2-5 mmol/l and >5 mmol/l according to their initial lactate levels after cardiopulmonary bypass. Lactate levels >5 mmol/l were evaluated as severe hyperlactatemia and found to be associated with prolonged hospital stay, renal damage, liver damage and increased mortality in these patients [10]. In another study, the relationship between lactate level and mortality in the postoperative period in 432 neonates was examined. In single ventricle patients, lactate values of 7.8mmol/L and above in the first 48 hours and in the first 12 hours after intensive care unit admission were found to be associated with mortality [5]. In our study, the lactate value in the first 24 hours in patients with mortality was 6 mmol/L and above, in accordance with existing studies.

In a study comparing lactate levels and postoperative outcomes in 231 patients under one year of age, high lactate levels were found to be risky in terms of mortality and morbidity [11]. In this study, it was concluded that serum lactate level is an ideal marker for patient follow-up and treatment decision.

The relationship between lactate levels and mortality in patients who underwent Norwood procedure for hypoplastic left heart disease was investigated. A total of 221 patients were included in the study in which 6-year data were collected from a single center. In these patients, serial lactate measurements in the first 72 hours were compared with 7th and 30th day mortality rates. The results showed that failure to reduce blood lactate levels below 6.76 mmol/L in the first 24 hours was highly predictive of mortality on day 30 [12].

The risk classification for congenital heart disease in pediatric patients (RACHS-1) is a classification system used to predict mortality and morbidity in congenital heart surgery[13]. In a study by Hazan et al. the difference between lactate levels in patients with the same RACHS-1 score was found to be associated with mortality. It was concluded that combining RACHS-1 scoring with serial lactate measurements would provide a more comprehensive approach to predict survival in patients and direct appropriate interventions and treatments [14].

Early or late elevation of serum lactate level is as important as serial measurement. In a study conducted in an adult age group, early lactate elevation was defined as a lactate level above 3 mmol/L in the first hour postoperatively. In this study, a positive correlation was found between early lactate elevation and aortic clamping time. In addition, late lactate elevation was found to be independent of intraoperative characteristics and more benign as a result of this study [15]. In our study, especially death in the first 3 days and 24-hour lactate change in the postoperative period were important. A 2-unit increase in lactate level was found to predict mortality with 77.8% sensitivity and 99.13% specificity.

In our study, postnatal age and weight were lower in the group with mortality, and thrombocytopenia and coagulopathy were significantly more frequent in the group with mortality. We associated this with the severity of the inflammatory response of patients to complex cardiac surgical procedures in the neonatal period.

Cardiovascular bypass surgery in the infant period is associated with particularly high mortality and morbidity. Our study is especially important because it includes infants and newborns.

In conclusion, elevated lactate levels are frequently encountered in the postoperative period and are associated with increased mortality and morbidity. In our study, the relationship between elevated lactate levels and mortality was emphasized especially in patients under 1 year of age.

Close monitoring of lactate levels after congenital heart surgery can predict mortality and allow earlier interventions. However, prospective studies with a high number of patients are needed especially to evaluate newborns.

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Conflict of interests

None.

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N.O.; Data Collection or Processing: A.A., L.S., Y.K., B.A.; Analysis or Interpretation: A.A., L.S., Y.K., B.A.; Literature Search: D.T., A.A., L.S., B.A.; Writing: D.T., A.A., N.O.

Ethical Standards

All procedures were in accordance with the Declaration of Helsinki. Ethical approval was received from the Gazi Yasargil Training and Research Hospital Ethics Committee, Diyarbakır, Turkey.

References

1. Maminirina P, Pavy C, Bourgoin P, et al. Continuous cerebral and myocardial selective perfusion in neonatal aortic arch surgery. *J Card Surg*. 2020;35(11):2920-2926.
2. Shukla VV, Bobhate P, Mohanty S, et al. Early Outcomes of Neonatal Cardiac Surgery in India. *Indian Pediatr*. 2020;57(2):129-132.
3. Kansy A, Tobota Z, Maruszewski P, et al. Analysis of 14,843 neonatal congenital heart surgical procedures in the European Association for Cardiothoracic Surgery Congenital Database. *Ann Thorac Surg*. 2010;89(4):1255-1259.
4. Manikis P, Jankowski S, Zhang H, et al. Correlation of serial blood lactate levels to organ failure and mortality after trauma. *Am J Emerg Med*. 1995;13(6):619-622
5. Valencia E, Staffa SJ, Nathan M, et al. Hyperlactataemia as a predictor of adverse outcomes post-cardiac surgery in neonates with congenital heart disease. *Cardiol Young*. 2021;31(9):1401-1406.
6. Ranucci M, Isgrò G, Romitti F, et al. Anaerobic metabolism during cardiopulmonary bypass: predictive value of carbon dioxide derived parameters. *Ann Thorac Surg*. 2006;81(6):2189-2195.
7. Raper RF, Cameron G, Walker D, et al. Type B lactic acidosis following cardiopulmonary bypass. *Crit Care Med*. 1997;25(1):46-51.
8. Desplanque L, Hamaide-Defrocourt F, Berkia I, et al. Lactate clearance in infants undergoing surgery for congenital heart disease. *Artif Organs*. 2019;43(1):54-59.
9. Şahutoğlu C, Yaşar A, Kocabaş S, et al.. Correlation between serum lactate levels and outcome in pediatric patients undergoing congenital heart surgery. *Turk Gogus Kalp Damar Cerrahisi Derg*. 2018;26(3):375-385..
10. Seghrouchni A, Atmani N, Moutakiallah Y, et al. Does severe hyperlactatemia during cardiopulmonary bypass predict a worse outcome?. *Ann Med Surg (Lond)*. 2021;73:103198.
11. Schumacher KR, Reichel RA, Vlasic JR, et al. Rate of increase in serum lactate level risk-stratifies infants after surgery for congenital heart disease. *J Thorac Cardiovasc Surg*. 2014;148(2):589-595.
12. Murtuza B, Wall D, Reinhardt Z, et al. The importance of blood lactate clearance as a predictor of early mortality following the modified Norwood procedure. *Eur J Cardiothorac Surg*. 2011;40(5):1207-1214.
13. Jenkins KJ, Gauvreau K, Newburger JW, et al. Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg*. 2002;123(1):110-118.
14. Molina Hazan V, Gonen Y, Vardi A, et al. Blood lactate levels differ significantly between surviving and nonsurviving patients within the same risk-adjusted Classification for Congenital Heart Surgery (RACHS-1) group after pediatric cardiac surgery. *Pediatr Cardiol*. 2010;31(7):952-960.
15. Khaled D. Algarni. The effect of hyperlactatemia timing on the outcomes after cardiac surgery. *The Cardiothoracic Surgeon*. 2020;28(1):1-8.

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Diagnostic accuracy of ultrasonography-guided percutaneous core needle biopsies of pancreatic lesions

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Abstract

Objective: This study evaluates the diagnostic accuracy and complications of ultrasound-guided percutaneous core needle biopsies for solid pancreatic masses.

Methods: Between January 2009 and June 2013 A total of 60 biopsy procedures were performed in 53 patients (30 males, 23 females) and 11 specimens were benign and 45 specimens were malignant according to histopathologic results.

Results: Sensitivity was 84.9%, specificity was 100% and diagnostic accuracy was 85.7%. No complications were observed during or after biopsy procedures

Conclusion: This study shows that ultrasound-guided biopsy is a reliable, time- and cost-saving method with a very low complication rate, high diagnostic accuracy and sensitivity, but benign biopsy findings should not be used to exclude the presence of pancreatic malignancy and biopsy should be repeated if there is a high clinical suspicion of malignancy.

Keywords: US; pancreatic solid mass; core needle biopsy

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Introduction

Pancreatic cancers are more common in men than in women and the incidence is gradually increasing. The annual incidence in our country is 4.1/100.000 in men and 3.5/100.000 in women [1, 2, 3]. Pancreatic cancers constitute approximately 20% of all gastrointestinal cancers and the most common type is solid infiltrative pancreatic ductal adenocarcinoma [2, 4].

Untreated pancreatic cancer has a 5-year survival rate of only 6%. [5]. Interventional techniques used in conjunction with imaging methods for the diagnosis and treatment of lesions are successfully applied today. Core needle biopsies were first performed by Parker et al. in 1993 [6]. In addition to the benign-malignant differentiation, the histopathological analysis of tissue samples obtained by core needle biopsy methods can determine the tumor type and tumor subtype, histological grade, hormone receptor status that can guide oncological treatment. Compared to other interventional diagnostic methods, percutaneous biopsies are more reliable and more easily tolerated by patients. It can be performed under ultrasonography (USG), Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) guidance. The choice of guidance method usually depends on the localization of the lesion, its size, its relationship with adjacent organs and vascular structures, and the personal preference of the radiologist [4,7,8]. In patients with pancreatic masses, histopathologic confirmation is usually required in patients with inoperable tumors or in patients who are medically unsuitable for surgery. The National Comprehensive Cancer Network (NCCN) strongly recommends that all patients with resectable pancreatic masses should have confirmation of the histopathologic diagnosis prior to medical therapy or at least one repeat biopsy in patients with benign biopsy results [8].

The aim of this study was to evaluate the results and complications of US-guided percutaneous core needle biopsy of solid mass lesions of the pancreas performed at our university hospital between January 2009 and June 2013.

Material and Methods

Patients

We retrospectively evaluated the results and complications of US-guided percutaneous cutting organ biopsy of solid mass lesions of the pancreas between January 2009 and June 2013 in our university hospital. A total of 53 patients, 30 males and 23 females with a mean age of 66 years, were included in the evaluation. Patients who did not have adequate clinical and radiologic follow-up, whose definitive clinical diagnosis could not be determined, whose biopsy did not provide sufficient information for histopathologic diagnosis, and who did not undergo repeat biopsy were excluded.

Imaging protocol and Biopsy Procedure

All patients underwent at least one of CT and MRI examinations before biopsy. The location of the mass lesions in the pancreas (head, body, tail) and their dimensions in the longest and shortest axis were evaluated with CT and/or MRI images.

All biopsy procedures were performed by an interventional radiologist with 15 years of experience using a General Electric Logiq 5 Pro (Milwaukee WI, USA), 3.5 MHz probe and 20G fully automatic cutting biopsy needles. Complete blood count and bleeding parameters (INR, PTZ, aPTT) were checked in all patients before biopsy. All patients were informed about the biopsy method, possible complications and treatment methods and informed consent was obtained.

Before biopsy, the appearance characteristics of the lesion (solid-cystic), its relationship with adjacent structures, especially with vascular structures using color Doppler technique were routinely evaluated with US in all patients. Biopsy procedures were performed in the supine position, avoiding the transverse colon, small intestines, liver, spleen and vascular structures, especially by determining the shortest distance to reach the lesion and usually using the trans-gastric approach with the “free hand technique”.

The sizes of the tissue samples taken after biopsy were measured by the pathology department, these measurements were obtained from the pathology reports, and the sample sizes were divided into two groups as below 1 cm and 1 cm and above, and the results and their relationship with the final clinical diagnoses were analyzed. In each biopsy procedure, the number of needle insertions in the same session was divided into two groups as 1 and 2 times, and the results, complications and the relationship with the final clinical diagnoses were also evaluated.

After biopsy procedure, clinical follow-up information (examination findings, laboratory results and imaging techniques) of all patients were checked for early and late possible complications and no biopsy-related complication was found in any patient.

Statistical Analysis

Results were evaluated by Student's t-test, Chi-square test with Yates correction and Fisher's exact Chi-square test. Sensitivity was calculated using the formulas TP/TP+FN, specificity TN/TN+FP, positive predictive value TP/TP+FP, negative predictive value TN/TN+FN (TP; true positive, FP; false positive, TN; true negative, FN; false negative). $P<0.05$ was considered statistically significant. Statistical procedures were performed using SPSS PC program.

Results

Histopathologic analysis revealed that 29 of 30 male patients were malignant and 1 benign, while 22 of 23 female patients were malignant and 1 benign. Malignancy rate was 96.7% in males and 95.6% in females and benignity rate was 3.3% in males and 4.4% in females. When benign and malignant final clinical diagnoses were compared with the gender of the patients, no statistically significant difference was found between benign and malignant results between males and females (p: 0.698).

When the distribution of the final clinical diagnoses according to the age of the cases was analyzed, chronic pancreatitis was seen in two cases with ages 66 and 36 pancreatic adenocarcinoma was seen in 48 cases with ages ranging between 45 and 87, Pancreatic non-adenocarcinoma tumors were seen in a total of 3 patients, 1 female and 2 male, and the diagnosis of these three patients was malignant neuroendocrine tumor and the ages were 50, 65, 65, respectively. When the age distribution of the final clinical diagnoses was analyzed, no statistically significant correlation was found between the age distribution of the cases and the final clinical diagnoses (p: 0.750).

The mass lesions were divided according to the location of the pancreatic head, body and tail. 26 of the 53 masses were located only in the pancreatic head (49.1%), 13 were located only in the pancreatic body (4.5%) and 1 was located only in the tail (1.9%). 13 masses (4.5%) were localized in two regions, body-tail and body-head, of which 7 were localized in body-tail and 6 were localized in body-head. 3 (60.4%) of the masses were located in the head, 6 (49.1%) in the body and 8 (15.1%) in the tail. Pancreatic adenocarcinomas were most commonly localized in the head of the pancreas in our patients. In 3 patients diagnosed with malignant neuroendocrine tumors, 1 of the masses was located in the body and tail, 1 in the head and 1 in the body. One of the chronic pancreatitis cases was located in the pancreatic head and the other in the body.

Patients Who Underwent Core Needle Biopsy Twice	Histopathological results of the 1st biopsy			Histopathological results of the 2nd biopsy			Definitive Clinical Diagnosis	
	Insufficient	Benign	Malign	Insufficient	Benign	Malign	Benign	Malign
1	+	-	-	-	-	+	-	+
2	-	+	-	-	+	-	+	-
3	-	+	-	-	-		-	+
4	-	+	-	-	-	+	-	+
5	+	-	-	+	-	-	-	+
6	+	-	-	-	+	-	-	+
7	-	+	-	-	-	+	-	+
Total(n)	3	4	0	1	2	4	1	6

Table 1: Comparison of histopathological results with definitive clinical diagnoses in patients who underwent a total of 2 percutaneous core needle biopsies.

Definitive Diagnosis	Results of 60 core needle biopsies performed once or twice							
	TP	TN	FP	FN	PPV	Sensitivity	Specificity	Diagnostic accuracy
Chronic Pancreatitis (Benign)	3 (5.3%)	45 (80.3%)	8 (14.4%)	0	27.3%	100%	84.9%	85.7%
Adenocarcinoma	43 (81.1%)	3 (5.7%)	0	7 (13.2%)	100%	86%	100%	86.8%
Neuroendocrine Tumor	2 (66.6%)	0	0	1 (33.4%)	100%	66.6%	100%	66.6%
Malign (Total)	45	3	0	8	100%	84.9%	100%	85.7%

Table 2: Distribution of TP, FP, TN and FN results when comparing the results of 60 percutaneous needle biopsies performed once and twice with the definitive clinical diagnoses.

Biopsy Specimen Size	Biopsy Result					
	Insufficient	True Positive	True Negative	False Negative	Sensitivity	Diagnostic Accuracy
Under 1 cm	4 (18.2%)	11 (50%)	2 (9.1%)	5 (22.7%)	68.7%	72.2%
Over 1 cm	0	34 (89.5%)	1 (2.6%)	3 (7.9%)	91.9%	92.1%
Total (n=60)	4 (6.7%)	45 (75%)	3 (5%)	8 (13.3%)	84.9%	85.7%

Table 3: Comparison of biopsy results with definitive clinical diagnoses in US-guided percutaneous core needle biopsies with a fragment size of under 1 cm and 1 cm or more.

Biopsy Count (n)	Sensitivity (%)	Specificity (%)	Diagnostic Accuracy (%)	Guide Method	Needle Size (G)	Researchers
212	86	100	86	US	21	Matsubara et al. (2008)
142	90.9	-	92.6	US	-	Jennings et al. (1989)
100	90	-	-	US	-	Karlson et al. (1996)
92	92.5	100	93.3	US	18	Paulsen et al. (2006)
50	90.4	-	92	US	-	Elvin et al. (1990)
60	84.9	100	85.7	US	20	Our Study (2013)

Table 4: Percutaneous core needle biopsies of pancreatic masses, sensitivity, specificity, diagnostic accuracy, guide method, needle size, researchers.

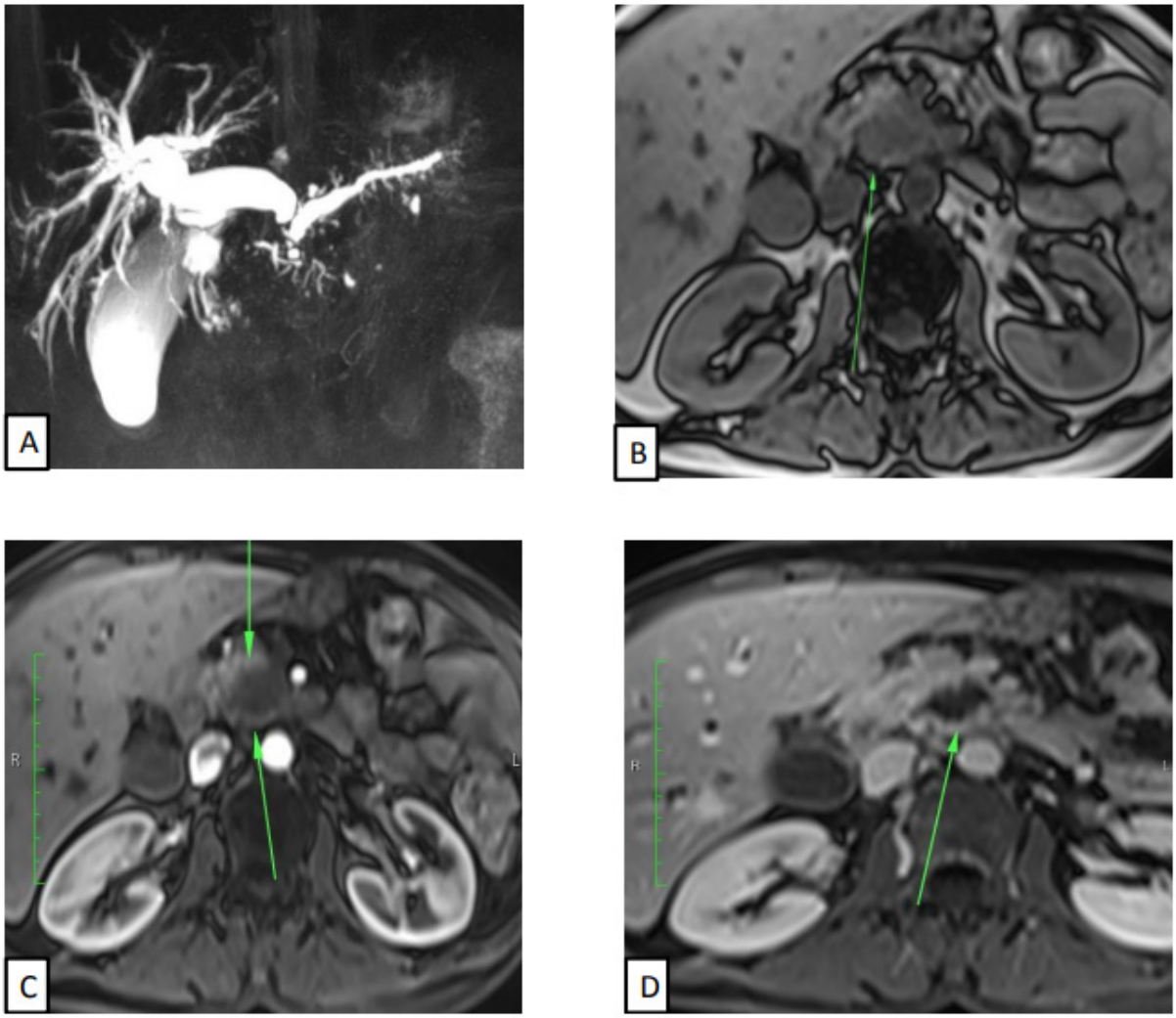

Figure: 61-year-old male patient. On MRI examination, MRCP series (A) showed dilatation of the biliary tract and pancreatic duct, which terminated abruptly at the level of the pancreatic head, and T1-weighted out-of-phase in the area corresponding to this localisation. There is a mass lesion (arrows) which is hypointense compared to the muscles in the images (B), doesn't show a significant contrast enhancement in the arterial phase images after IVCM (C), but in the late phase images (D), there is a circumferentially contrasted mass lesion (arrows) except for the central non-contrasting necrotic area. Intraoperative biopsy was performed and the result was evaluated as chronic pancreatitis. Afterwards, USG-guided core needle biopsy was performed and resulted as adenocarcinoma. As a result of the follow-up clinical findings and imaging examinations, progression was detected in the findings accompanied by liver metastasis. The clinical diagnosis of the patient is pancreatic adenocarcinoma.

Seven patients underwent biopsy twice. The comparison of the results of the 1st and 2nd biopsies performed in these patients is summarized in **table 1.**

In our study, repeat biopsies were performed in 20 patients with inconclusive histopathologic results or with histopathologic results, imaging and clinical discrepancies, such as cases with benign biopsy results but clinical and imaging findings strongly suggestive of malignancy, using percutaneous Fine Needle Aspiration (FNA) biopsy and core needle biopsy, intraoperative biopsy and 1 case of metastatic liver mass core needle biopsy. The results of the 1st percutaneous core needle biopsy were 4 inadequate, 7 true positive, 8 false negative, 1 true negative, and the results of repeat biopsy were 1 inadequate, 14 true positive, 4 false negative, 1 true negative.

In cases with repeat biopsy, the histopathologic result of the first biopsy was inadequate in 4 cases (20%), false

negative in 8 cases (40%), inadequate in 1 case (5%), false negative in 4 cases (20%) with repeat biopsies, and the sensitivity increased from 46.7% to 77.8% and the diagnostic accuracy rate increased from 50% to 78.9%.

In a total of 46 patients who underwent percutaneous core needle biopsy once, histopathologic evaluations resulted as true negative in 1 case, false negative in 4 cases and true positive in 41 cases. False positive results were not obtained in any case.

In 53 patients, the total number of percutaneous core needle biopsy procedures was 60, including those performed once and twice in 7 patients. In these 60 biopsy procedures, the sensitivity, specificity, positive predictive value, positive predictive value and diagnostic accuracy of US-guided percutaneous core needle biopsy were 84.9%, 100%, 100% and 85.7%, respectively **(Table 2).**

In our study, the sizes of tissue samples obtained after core needle biopsy were measured by the pathology department and these measurements were obtained from the pathology reports. In a total of 60 US-guided percutaneous core needle biopsies, 4 (18.2%) of the procedures with fragment size less than 1 cm resulted in insufficient specimens and the false negative rate was 5 (22.7%). None of the 38 biopsy procedures with a fragment size of 1 cm or more resulted in insufficient specimens and the false negative rate was 3 (7.9%). In addition, the sensitivity and diagnostic accuracy of percutaneous core needle biopsies with a fragment size of 1 cm or more were higher than those with a fragment size of less than 1 cm, with a statistically significant difference ($p<0.05$) **(Table 3).**

Discussion

In the histocytopathologic diagnosis of pancreatic masses, methods such as US or CT-guided percutaneous FNAB or core needle biopsy, EUS-guided FNAB or core needle biopsy, and intraoperative biopsy are used. Intraoperative FNAB has been used in pancreatic masses since the 1960s [9] and core needle biopsy since the 1970s [10]. Later, US, CT, MRI and endoscopic ultrasonography (EUS) imaging techniques were used to evaluate and characterize pancreatic masses. Most importantly, the use of all these methods as a guide to needle biopsies has been shown to prevent the morbidity, mortality and high cost of surgical procedures performed only for tissue sampling for cytohistopathologic diagnosis [11]. Compared to other interventional diagnostic methods, percutaneous biopsies have become more reliable and easier for patients to tolerate. Among these guidance methods, the advantages of US are that it can be applied rapidly, it is inexpensive and practical, the needle can be visualized simultaneously and can be advanced in the desired direction [4,7,8]. In previous studies on percutaneous biopsies of the pancreas, it has been shown that the stomach, spleen, colon and small intestine can be crossed to reach the target lesion during the procedure without any complications, and as a general approach, it has been accepted to perform the biopsy procedure using the shortest route to reach the target lesion as far away from vascular structures as possible [7,8]. The current practice for core needle biopsies of the pancreas is to be performed in patients with radiologically detected metastatic disease thought to originate from the pancreas or in patients with an resectable pancreatic mass. Thus, biopsy procedures can prevent unnecessary laparotomies, identify malignancies other than primary pancreatic tumors or different subtypes of pancreatic tumors, obtain benign results mimicking malignancy and, as a result of all these, decide on the most appropriate treatment method for the patient. Moreover, due to the relatively advanced tumor burden, unrecognized neuroendocrine tumors can be diagnosed, especially in patients with poor systematic evidence of malignancy. Pancreatic neuroendocrine tumors can be biopsied even in the absence of known metastases. The prognosis for survival in the presence of metastases in these tumors is promising and long-term treatment outcomes can be monitored with repeat core needle biopsies. Furthermore, samples from these biopsies can be used to determine individualized treatment modalities, including both conventional cytotoxic regimens and biotherapy [7].

The results of US-guided percutaneous needle biopsy in patients with pancreatic masses by different researchers and our study are shown in Table 4. In our study, the sensitivity and diagnostic accuracy of US-guided percutaneous needle biopsies performed 60 times in 53 patients were 84.9% and 85.7%, respectively, and our results were generally consistent with the results reported in the literatüre. False negative results are associated with inadequate sampling of the target tissue, misplacement of the needle, which is more frequently seen in small masses, and hard desmoplastic reaction around pancreatic adenocarcinoma, and its clinical effect is best demonstrated by negative prediktif value (NPV) [13].

In the study by Stasi et al., US-guided needle biopsy results led to a diagnosis in 86% of cases, with false negative results in 14% of cases including inadequate sampling. The reason for these results was thought to be the presence of fibrotic or necrotic areas around or within the tumor, small target lesion size, and misdiagnosis in well-differentiated forms. It is generally agreed that false negative results can be reduced by more aggressive methods (repeat biopsies) which may increase the risk of complications and that negative needle biopsy results should be carefully evaluated [7,14].

In the study by Paulsen et al. the NPV was 60%, which is considered unacceptably low to safely exclude pancreatic malignancies. Paulsen et al., along with other investigators, agreed that in cases where FNA or core needle biopsies are negative, these results should be carefully reviewed together with follow-up clinical and imaging findings [13].. The false negative results we obtained in our study and the change of these results in favor of malignancy with repeat biopsies or follow-up clinical and imaging findings support this view.

In their study, Stasi et al. obtained excellent results in the differentiation of cases including pancreatic metastasis, non-Hodgkin lymphoma and abscesses when they considered the effectiveness of US-guided percutaneous biopsy methods in the differential diagnosis of different pancreatic pathologies (100%). In their study, they prevented unnecessary surgical applications by providing histopathological diagnoses in chronic pancreatitis with mass appearance, anresectable pancreatic cancers, normal pancreatic tissue with pseudo-mass appearance and metastatic tumors of the pancreas diagnosed by US-guided needle biopsy for the first time [14].

There is no data in the literature regarding the size of fragments obtained after US-guided core needle biopsy procedures performed on solid mass lesions of the pancreas and the study results. As summarized in Table 3 in our study, there was a significant difference in terms of intervals and diagnostic accuracy rate in distinguishing benign and malignant lesions in percutaneous core needle biopsies performed on solid mass lesions of the pancreas under USG guidance, higher performance and capacity in procedures with fragment sizes of 1 cm and above compared to procedures with fragment sizes of less than 1 cm ($p<0.05$)

Major complications of pancreatic biopsies include hemorrhage, tumor seeding along the needle tract and pancreatitis, while minor complications include transient fever, nausea-vomiting and vaso-vagal reaction after biopsy. Although acute pancreatitis after biopsy is extremely rare, when it occurs, it can be quite serious and sometimes fatal, and this can be seen as the main reason why biopsy procedures are not widely used. Studies have shown that the rate of acute pancreatitis after biopsy varies between 0-1.7% [8,15].

In patients with anresectable pancreatic cancer, the tumor is usually large in size and located just below the surface of the pancreas. In these cases, a piece of the tumor can be removed percutaneously without penetrating the normal pancreatic tissue, which explains the idea that the development of biopsy-related acute pancreatitis is unlikely in such lesions [16]. Biopsy of normal pancreatic tissue increases the risk of developing acute pancreatitis, and 5 of 7 patients who underwent similar biopsy in the literature died after biopsy [14,16]. In the study by Matsubara et al. no clinical or microscopic cases of infection were detected in relation to biopsy; however, transient fever (4.4%) was observed in 1 case after biopsy, they also checked serum amylase levels in these cases, and amylase levels were found above the upper limit in two cases. Therefore, it was thought that transient fever after biopsy may be the initial sign of acute pancreatitis that may develop due to a potentially life-threatening biopsy procedure [8].

Although the frequency of peritoneal tumor dissemination associated with pancreatic biopsies is unknown, it is not thought to have any impact on the invariably poor prognosis of resectable pancreatic cancers. On the other hand, the practice of preoperative percutaneous pancreatic biopsy in patients with resectable pancreatic cancer is controversial because some studies suggest a high incidence (16.3-75%) of peritoneal tumor dissemination associated with percutaneous biopsy procedures [8,17]. The NCCN has reported that malignancy does not need to be proven by biopsy before surgical resection and that non-diagnostic sampling should not be allowed to cause delays in surgery, which is the only curative treatment for pancreatic cancer [8,18]. In the literature, tumor invasion along the needle tract was reported in 8 cases after CT or US guided percutaneous needle biopsy [14,19]. Studies by Civardi et al. and Fornari et al. showed that the risk of tumor invasion may be related to the number of needle accesses, with a higher number of needle accesses associated with a higher risk of tumor invasion [20,21].

Our study had some limitations. The most important limitation is the non-randomized retrospective design of our study. The second limitation is the inadequate laparotomy and autopsy practices regarding the accuracy

of definitive clinical diagnoses, which are considered the gold standard. Finally, the histopathologic examination of the biopsy materials was evaluated by pathologists with different experience.

Considering the previous studies on US-guided percutaneous needle biopsies of pancreatic masses, the sensitivity in exocrine tumors of the pancreas and peripancreatic tumors was found to be around 91%, while in our study, our sensitivity rate was slightly lower at 86%. No false positive results were obtained in the studies including our study. All these results support the feasibility and reliability of US-guided percutaneous core needle biopsy for the evaluation of pancreatic malignancies. It has been reported that if a benign lesion is detected in tissue sampling, these results should be regarded with suspicion, should never be used to exclude malignant or metastatic pancreatic lesions, and the biopsy should be repeated [7]. In the literature, the rate of malignancy detection in repeated biopsies due to non-specific or benign findings varies between 35-45% [14,22].

Conclusion

In patients with inoperable solid pancreatic mass lesions, if visualization of the lesion is sufficient, the use of percutaneous core needle biopsies under US guidance is a sensitive, safe, and highly accurate biopsy method. Benign biopsy findings should not be used to exclude the presence of pancreatic malignancy, and if there is a high clinical suspicion of malignancy, the biopsy should be repeated. Since it increases the sensitivity and diagnostic accuracy in distinguishing between malignancy and benign and reduces the rate of inadequate sampling, care should be taken to ensure that the sample size is 1 cm or larger, and a repeat biopsy should be performed in the same session, whenever possible, to save time and money and to prevent delays in diagnosis and treatment.

Conflict of interest

The authors declare no competing interests. The authors declare they have no financial interests.

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References

1. Tuncer, M. Kanserin ülkemiz ve dünyadaki önemi, hastalık yükü ve kanser kontrol politikaları. Türkiye'de Kanser Kontrolü, Sağlık Bakanlığı Yayınları. 2009. 707, 5-9.
2. Schneider G, Schmid RM. Genetic alterations in pancreatic carcinoma. *Mol Cancer*. 2003;2:15. Published 2003 Jan 22. doi:10.1186/1476-4598-2-15
3. TC. Sağlık Bakanlığı 2003 yılı Kanser İstatistikleri. Avaible at: http://www.saglik.gov.tr/extras/istatistikler/apk2003/098.htm -99.htm.
4. Rumack, M.C., Wilson, R.S., Charboneau, J.W., 2011. Diagnostic Ultrasound. 4th edition. Mosby. Philadelphia.
5. American Cancer Society. Cancer facts & figures 2013. Society, A. C. Atlanta, pp. 25.
6. Parker SH, Jobe WE, Dennis MA, et al. US-guided automated large-core breast biopsy. *Radiology*. 1993;187(2):507-511. doi:10.1148/radiology.187.2.8475299
7. Karlson BM, Forsman CA, Wilander E, et al. Efficiency of percutaneous core biopsy in pancreatic tumor diagnosis. *Surgery*. 1996;120(1):75-79. doi:10.1016/s0039-6060(96)80244-3
8. Matsubara J, Okusaka T, Morizane C, Ikeda M, Ueno H. Ultrasound-guided percutaneous pancreatic tumor biopsy in pancreatic cancer: a comparison with metastatic liver tumor biopsy, including sensitivity, specificity, and complications. *J Gastroenterol*. 2008;43(3):225-232. doi:10.1007/s00535-007-2142-9
9. Moossa AR, Altorki N. Pancreatic biopsy. *Surg Clin North Am*. 1983;63(6):1205-1214. doi:10.1016/s0039-6109(16)43183-x
10. Ingram DM, Sheiner HJ, Shilkin KB. Operative biopsy of the pancreas using the Trucut needle. *Aust N Z J Surg*. 1978;48(2):203-206. doi:10.1111/j.1445-2197.1978.tb07307.x
11. Turner BG, Cizginer S, Agarwal D, Yang J, Pitman MB, Brugge WR. Diagnosis of pancreatic neoplasia with EUS and FNA: a report of accuracy. *Gastrointest Endosc*. 2010;71(1):91-98. doi:10.1016/j.gie.2009.06.017
12. Elvin A, Andersson T, Scheibenpflug L, Lindgren PG. Biopsy of the pancreas with a biopsy gun. *Radiology*. 1990;176(3):677-679. doi:10.1148/radiology.176.3.2167498
13. Paulsen SD, Nghiem HV, Negussie E, Higgins EJ, Caoili EM, Francis IR. Evaluation of imaging-guided core biopsy of

pancreatic masses. *AJR Am J Roentgenol*. 2006;187(3):769-772. doi:10.2214/AJR.05.0366

14. Di Stasi M, Lencioni R, Solmi L, et al. Ultrasound-guided fine needle biopsy of pancreatic masses: results of a multicenter study. *Am J Gastroenterol*. 1998;93(8):1329-1333. doi:10.1111/j.1572-0241.1998.443_m.x

15. Gress F, Michael H, Gelrud D, et al. EUS-guided fine-needle aspiration of the pancreas: evaluation of pancreatitis as a complication. *Gastrointest Endosc*. 2002;56(6):864-867. doi:10.1067/mge.2002.129602

16. Smith EH. Complications of percutaneous abdominal fine-needle biopsy. Review. *Radiology*. 1991;178(1):253-258. doi:10.1148/radiology.178.1.1984314

17. Johnson DE, Pendurthi TK, Balshem AM, et al. Implications of fine-needle aspiration in patients with resectable pancreatic cancer. *Am Surg*. 1997;63(8):675-680.

18. Hartwig W, Schneider L, Diener MK, Bergmann F, Büchler MW, Werner J. Preoperative tissue diagnosis for tumours of the pancreas. *Br J Surg*. 2009;96(1):5-20. doi:10.1002/bjs.6407

19. Elsman BH, de Graaf PW, van Leeuwen MS, Obertop H. De waarde en de risico's van percutane cytologische punctie bij de preoperatieve analyse van pancreastumoren [Value and risks of percutaneous cytological puncture in the preoperative assessment of pancreas tumors]. *Ned Tijdschr Geneeskd*. 1992;136(30):1459-1462.

20. Civardi G, Fornari F, Cavanna L, Di Stasi M, Sbolli G, Buscarini L. Value of rapid staining and assessment of ultrasound-guided fine needle aspiration biopsies. *Acta Cytol*. 1988;32(4):552-554.

21. Fornari F, Civardi G, Cavanna L, et al. Complications of ultrasonically guided fine-needle abdominal biopsy. Results of a multicenter Italian study and review of the literature. The Cooperative Italian Study Group. *Scand J Gastroenterol*. 1989;24(8):949-955. doi:10.3109/00365528909089239

22. Yamaguchi, T., Saisho, H., Otho, M. Usefulness of percutaneous histological biopsy in the diagnosis of chronic pancreatitis with inflammatory mass (CPM). *J Interventional Radiology*, 1994;(9): 165-170.

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Vitamin D levels and their relationship with lipid metabolism and inflammatory markers in healthy adults

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Abstract

Objective: This study investigates the associations between serum vitamin D levels and biochemical, hematological, and inflammatory markers in a healthy adult population, focusing on their implications for lipid metabolism and systemic inflammation.

Methods: A retrospective analysis was conducted on the medical records of 267 individuals aged 18–65 years, who presented to the internal medicine outpatient clinic with complaints of fatigue. Inclusion criteria required participants to be free of any chronic diseases, acute medical conditions. Serum vitamin D levels were categorized into three groups: deficient-insufficient (≤19 ng/mL), sufficient (20–29 ng/mL), and normal (≥30 ng/mL). Biochemical parameters, hematological markers, and derived ratios (e.g., triglyceride/glucose ratio, monocyte/HDL-C ratio) were analyzed. Spearman correlation, Kruskal-Wallis H test, and Mann-Whitney U test were used for statistical analysis.

Results: Vitamin D levels showed significant positive correlations with HDL-C ($\rho = 0.169$, $p = 0.0055$) and LDL-C ($\rho = 0.198$, $p = 0.0011$), and a negative correlation with neutrophil counts ($\rho = -0.133$, $p = 0.030$). Among derived ratios, the triglyceride/monocyte ratio exhibited a significant positive correlation ($\rho = 0.160$, $p = 0.0088$), while the monocyte/HDL-C ratio showed a significant negative correlation ($\rho = -0.203$, $p = 0.00083$). Group comparisons revealed significantly lower HDL-C levels in the deficient-insufficient group compared to the sufficient and normal groups ($p = 0.0022$). No significant differences were found for other lipid or inflammatory markers.

Conclusion: This study highlights the multifaceted roles of vitamin D in lipid metabolism and systemic inflammation. The positive association with HDL-C underscores its potential cardioprotective effects, while the negative correlation with neutrophil counts suggests its role in modulating inflammation. These findings provide valuable insights into vitamin D's broader physiological effects in healthy individuals, warranting further large-scale studies.

Keywords: Vitamin D; lipid metabolism; inflammation; biomarkers

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Introduction

Vitamin D is a fat-soluble steroid derivative that influences the intestines, bones, kidneys, and parathyroid glands. It plays a fundamental role in bone mineralization and the regulation of calcium and phosphorus levels [1,2]. Recent studies have highlighted its broader impact, extending beyond these classical roles to include significant effects on metabolic and immunological processes.

Epidemiological studies estimate that approximately one billion people worldwide suffer from vitamin D deficiency. The prevalence varies by geographic location, duration of sun exposure, use of sunscreen, and dietary habits [3]. The deficiency is particularly pronounced in adults residing in the Middle East and Asia [4].

The best indicator of vitamin D status is its circulating metabolite, 25(OH)D, which has a half-life of 10–19 days. This metabolite reflects the amount of vitamin D synthesized in the skin through ultraviolet exposure or obtained from dietary sources. In the liver, vitamin D is converted to 25(OH)D, its primary circulating form, by 25-hydroxylase enzymes. Subsequently, 25(OH)D is metabolized in the kidneys to its active form, 1,25-dihydroxyvitamin D3 (calcitriol), via the enzyme 1-alpha-hydroxylase. This active form is also produced extrarenally in response to cytokines such as tumor necrosis factor-alpha and interferon-gamma, highlighting its role in immune regulation [5,6].

Vitamin D deficiency has been associated with a variety of diseases and metabolic disorders. Studies have shown that vitamin D supplementation can improve markers of metabolic health, including reductions in total cholesterol, low-density lipoprotein (LDL), triglycerides (TG), glycated hemoglobin (HbA1c), and HOMA-IR, an indicator of insulin resistance, particularly in individuals with type 2 diabetes mellitus [7,8]. However, the precise mechanisms underlying these effects remain unclear.

Research has demonstrated that vitamin D receptors and enzymes involved in vitamin D metabolism are expressed in various cells, including insulin-sensitive pancreatic beta cells and adipocytes. Adipose tissue, which serves as a storage site for vitamin D, also secretes adipokines and cytokines that actively contribute to systemic inflammation [9,10]. These findings suggest a complex interplay between vitamin D, inflammation, and metabolic health.

In addition to its well-established roles in calcium and bone metabolism, vitamin D exerts non-classical effects on other physiological systems. It modulates immune responses, influences lipid and glucose metabolism, and reduces systemic inflammation. These effects are particularly relevant to conditions such as diabetes, atherosclerosis, and autoimmune diseases [11-14].

Recent studies have also identified novel biomarkers, such as the triglyceride/glucose ratio, triglyceride/HDL-C ratio, and monocyte/HDL-C ratio, which provide insights into the relationships between lipid metabolism, glucose regulation, and immune responses. These markers may offer new perspectives on the broader physiological roles of vitamin D, particularly in metabolic and cardiovascular health [15,16].

Given these extensive roles, this study aims to investigate the relationships between vitamin D levels, glucose metabolism, lipid profiles, and inflammatory markers in a healthy population. By focusing on key biomarkers, we seek to provide new insights into the systemic effects of vitamin D, contributing to a more comprehensive understanding of its role in maintaining metabolic balance.

Methods

Approval for this study was obtained from the ethics committee of our hospital. We retrospectively reviewed the medical records of 2790 individuals who presented with complaints of fatigue to the internal medicine outpatient clinic of our hospital between October 1, 2022, and December 31, 2022. After applying the inclusion and exclusion criteria, a total of 267 participants were included in the final analysis. Inclusion criteria were as follows: patients aged 18–65 years with no active disease. Exclusion criteria included the presence of comorbid diseases, regular medication use, glucose levels >125 mg/dL, and abnormal TSH levels (>4.5 or <0.5).

Laboratory parameters, including biochemical and hematological markers, were obtained from patient records as part of the retrospective analysis. Biochemical parameters included glucose (mg/dL), triglycerides (mg/dL), low-density lipoprotein cholesterol (LDL-C, mg/dL), and high-density lipoprotein cholesterol (HDL-C, mg/dL). Hematological parameters included neutrophil count ($\times 10^3/\mu L$), lymphocyte count ($\times 10^3/\mu L$), monocyte count ($\times 10^3/\mu L$), and platelet count ($\times 10^3/\mu L$). These parameters were measured using standard

automated biochemical and hematological analyzers at the hospital's central laboratory.

In addition to these primary laboratory parameters, derived ratios such as the triglyceride/glucose ratio (triglyceride [mg/dL] ÷ glucose [mg/dL]), triglyceride/HDL-C ratio (triglyceride [mg/dL] ÷ HDL-C [mg/dL]), triglyceride/monocyte ratio (triglyceride [mg/dL] ÷ monocyte count [$\times 10^3/\mu L$]), monocyte/HDL-C ratio (monocyte count [$\times 10^3/\mu L$] ÷ HDL-C [mg/dL]), neutrophil/lymphocyte ratio (neutrophil count [$\times 10^3/\mu L$] ÷ lymphocyte count [$\times 10^3/\mu L$]), and platelet/lymphocyte ratio (platelet count [$\times 10^3/\mu L$] ÷ lymphocyte count [$\times 10^3/\mu L$]) were calculated to further assess metabolic and inflammatory markers.

Serum vitamin D levels were measured using the chemiluminescence immunoassay (CLIA) method with an automated analyzer (Roche Cobas e601). This method is widely used for its high sensitivity and specificity in the quantification of 25-hydroxyvitamin D [25(OH)D] levels. Vitamin D levels were extracted from patient records. Participants were categorized into three groups based on their serum vitamin D levels:

- Group 1: Deficient (<10 ng/mL)
- Group 2: Insufficient (10–19.9 ng/mL)
- Group3:Sufficient(≥20ng/mL)

Statistical Analysis

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS), Version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the demographic and clinical characteristics of the study participants. These statistics included frequency distributions, percentages, median values, interquartile ranges (IQR), means, and standard deviations (SD).

The normality of the data distribution was assessed using the Shapiro-Wilk test. Since the data did not meet the criteria for normal distribution, non-parametric statistical tests were employed.

The correlations between vitamin D levels and biochemical parameters (LDL-C, HDL-C, triglycerides, glucose, neutrophil, lymphocyte, monocyte, and platelet levels) as well as derived ratios (triglyceride/glucose ratio, triglyceride/HDL-C ratio, triglyceride/monocyte ratio, monocyte/HDL-C ratio, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio) were examined using the Spearman correlation analysis. Correlation coefficients (ρ) and p-values were reported.

Patients were categorized into three groups based on their serum vitamin D levels: Group 1 (≤19 ng/mL), Group 2 (20–29 ng/mL), and Group 3 (≥30 ng/mL). Differences in biochemical parameters and derived ratios among the groups were analyzed using the Kruskal-Wallis H test for continuous variables. Pairwise comparisons among groups for statistically significant parameters were conducted using the Mann-Whitney U test.

To account for potential confounding variables, a subgroup analysis was performed by excluding patients with folate levels ≤3 ng/mL, vitamin B12 levels ≤250 pg/mL, and iron levels ≤60 µg/dL. Statistical analyses for this subgroup followed the same methodology as described above.

For all tests, a p-value of <0.05 was considered statistically significant.

Results

A total of 267 individuals, including 191 women (71.5%) and 76 men (28.5%), were included in the study based on the inclusion criteria. The demographic and clinical characteristics of the participants, including the median, mean, minimum, and maximum values for laboratory parameters, are summarized in Table 1.

Correlations Between Vitamin D Levels and Laboratory Parameters

The relationships between vitamin D levels and biochemical parameters were evaluated using Spearman correlation analysis. A significant positive correlation was found between vitamin D levels and LDL-C ($\rho = 0.198$, $p = 0.0011$) and HDL-C ($\rho = 0.169$, $p = 0.0055$). Figures 2, 3, and 4 illustrate key findings related to vitamin D and lipid metabolism. Figure 2 demonstrates the positive correlation between serum vitamin D levels and LDL-C. Figure 3 depicts the distribution of HDL-C levels among the three vitamin D groups, while Figure 4 presents the mean HDL-C and LDL-C levels across these groups. Conversely, a significant negative correlation was observed between vitamin D levels and neutrophil counts ($\rho = -0.133$, $p = 0.030$). Other biochemical and hematological parameters, including triglycerides, glucose, lymphocyte count, monocyte count, and platelet

count, did not show statistically significant correlations with vitamin D levels ($p > 0.05$). Detailed correlation coefficients and p-values are presented in Table 2.

Further analyses of vitamin D levels with derived ratios, such as the triglyceride/glucose ratio, triglyceride/HDL-C ratio, triglyceride/monocyte ratio, monocyte/HDL-C ratio, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio, were conducted. Statistically significant positive correlations were observed only for the triglyceride/monocyte ratio ($\rho = 0.160$, $p = 0.0088$), while significant negative correlations were found for the monocyte/HDL-C ratio ($\rho = -0.203$, $p = 0.00083$). No significant correlations were identified for the other ratios ($p > 0.05$). The full results of these analyses are displayed in Table 3.

Group Comparisons Based on Vitamin D Levels

Participants were categorized into three groups based on their serum vitamin D levels:

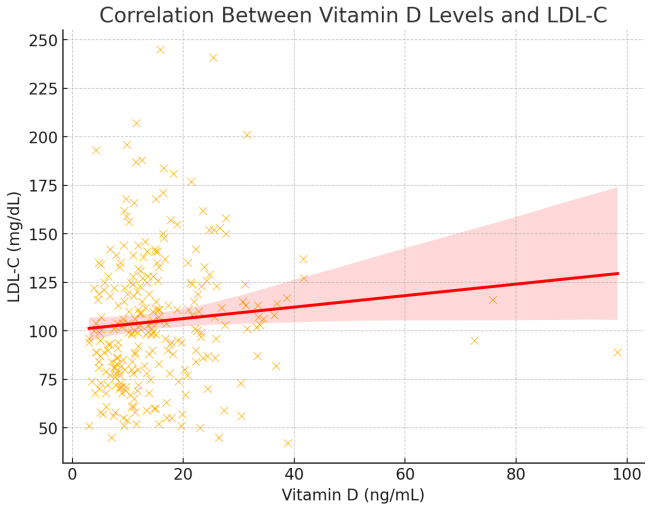
- Group 1: Deficient-insufficient (≤19 ng/mL, n = 198)
- Group 2: Sufficient (20–29 ng/mL, n = 46)
- Group 3: Normal (≥30 ng/mL, n = 23).

Differences in biochemical and hematological parameters, including LDL-C, HDL-C, triglycerides, glucose, neutrophil, lymphocyte, monocyte, and platelet counts, were analyzed among the groups using the Kruskal-Wallis test. A statistically significant difference among the groups was observed only for HDL-C levels ($p = 0.0022$). Figure 1 illustrates the distribution of HDL-C levels across the three vitamin D groups. Pairwise comparisons with the Mann-Whitney U test revealed that HDL-C levels in Group 1 were significantly lower than those in both Group 2 ($p = 0.0151$) and Group 3 ($p = 0.0046$), while no significant difference was found between Group 2 and Group 3 ($p = 0.449$).

Analysis of Derived Ratios Among Vitamin D Groups

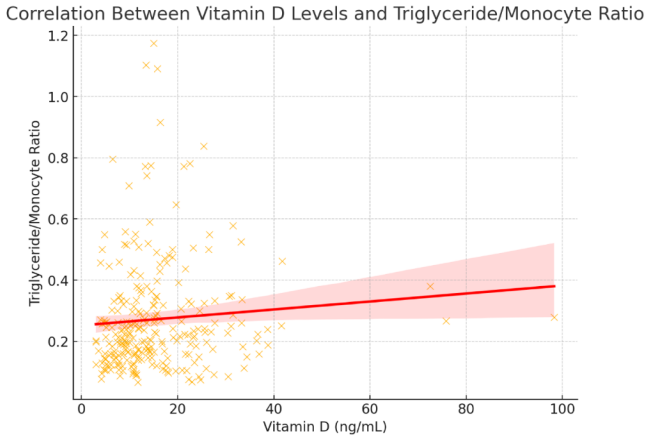
The derived ratios were also analyzed among the three vitamin D groups using the Kruskal-Wallis H test. A statistically significant difference was found only for the monocyte/HDL-C ratio ($p = 0.0013$). Post-hoc analyses using the Mann-Whitney U test indicated that the monocyte/HDL-C ratio was significantly higher in Group 1 compared to Group 3 ($p = 0.0018$) and moderately higher in Group 1 compared to Group 2 ($p = 0.0217$). No significant difference was found between Group 2 and Group 3 ($p = 0.2398$).

Figure 1: Correlation Between Vitamin D Levels and LDL-C



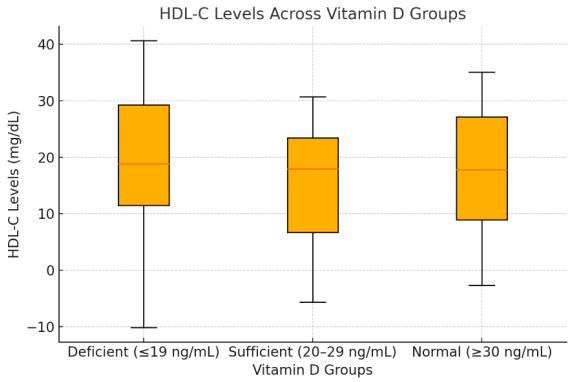
Scatter plot demonstrating the relationship between serum Vitamin D levels (ng/mL) and LDL-C levels (mg/dL).

Figure 2: Correlation Between Vitamin D Levels and Triglyceride/Monocyte Ratio



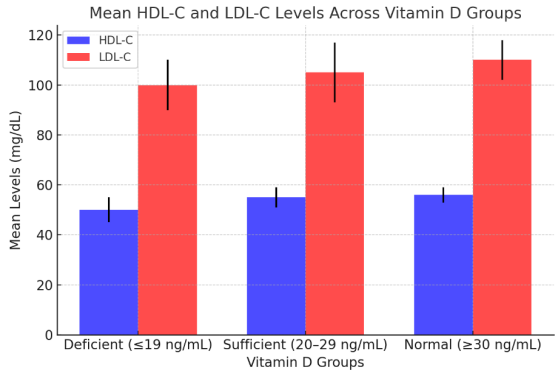
Scatter plot showing the correlation between serum Vitamin D levels (ng/mL) and the Triglyceride/Monocyte ratio.

Figure 3: HDL-C Levels Across Vitamin D Groups



A boxplot comparing HDL-C levels among the three Vitamin D groups.

Figure 4: Mean HDL-C and LDL-C Levels Across Vitamin D Groups



A bar chart comparing the mean HDL-C and LDL-C levels across Vitamin D groups.

Discussion

In this study, we explored the associations between vitamin D levels and various biochemical, hematological, and metabolic-inflammatory parameters in a healthy adult population. Our findings revealed significant positive correlations between vitamin D levels and both HDL-C and LDL-C, as well as a significant negative correlation with neutrophil counts. Additionally, among the derived metabolic-inflammatory ratios, a significant positive correlation was observed with the triglyceride/monocyte ratio and a significant negative correlation with the monocyte/HDL-C ratio. These findings provide novel insights into the broader metabolic and inflammatory effects of vitamin D in individuals without chronic disease or overt inflammatory conditions.

Our results align with previous studies suggesting a close relationship between vitamin D and lipid metabolism. Vitamin D has been shown to positively influence lipid profiles by improving HDL-C levels and reducing triglycerides and total cholesterol in certain populations [17,18]. In our study, the observed positive correlation between vitamin D levels and HDL-C is consistent with its known cardioprotective effects. HDL-C plays a critical role in reverse cholesterol transport, reducing the risk of atherosclerosis. The inter-group analysis further demonstrated that HDL-C levels were significantly lower in individuals with deficient vitamin D levels compared to those with sufficient or normal levels.

Interestingly, a positive correlation between vitamin D and LDL-C was also detected, which is contrary to most of the existing literature. While LDL-C is generally considered atherogenic, it is important to note that this relationship may reflect indirect effects of vitamin D on lipid metabolism, potentially mediated by dietary patterns, adipose tissue activity, or hepatic function [19-20]. Further studies are needed to clarify this association and its potential clinical implications.

Vitamin D is well-known for its immunomodulatory and anti-inflammatory properties, which are mediated through its effects on both innate and adaptive immune cells [21].

Studies have demonstrated that vitamin D inhibits the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, while enhancing anti-inflammatory cytokines like IL-10 [22].In our study, we observed a significant negative correlation between vitamin D levels and neutrophil counts, supporting the potential role of vitamin D in reducing systemic inflammation. However, no significant correlations were found with the neutrophil/lymphocyte ratio (NLR) or platelet/lymphocyte ratio (PLR), which are established markers of inflammation. This may be due to the exclusion of individuals with acute or chronic inflammatory conditions, thereby limiting the variability in these parameters.

The absence of significant findings in the inflammatory ratios could also be explained by the low expression of

vitamin D receptors (VDR) in resting immune cells. Vitamin D primarily exerts its effects on activated immune cells, such as macrophages and T cells, where VDR expression is upregulated [23]. As our study population consisted of healthy individuals, the lack of immune activation may have contributed to these findings. Furthermore, the retrospective design and limited sample size of our study might have reduced the statistical power to detect subtle differences.

Insulin resistance is closely linked to lipid metabolism and systemic inflammation, and vitamin D is believed to play a key role in modulating both processes [24]. Vitamin D enhances insulin sensitivity by improving pancreatic beta cell function, increasing glucose uptake in peripheral tissues, and reducing systemic inflammation [25]. In our study, the triglyceride/monocyte ratio, which has been suggested as a potential marker of insulin resistance, showed a significant positive correlation with vitamin D levels. While previous studies have demonstrated a relationship between vitamin D and insulin resistance, the triglyceride/monocyte ratio is a relatively new marker in this context. Our findings highlight the need for further research to better understand the clinical utility of this ratio in assessing metabolic health.

Our findings underscore the multifaceted roles of vitamin D in lipid metabolism, systemic inflammation, and potentially insulin resistance. The positive correlation between vitamin D and HDL-C highlights its potential cardioprotective effects, while the observed associations with neutrophil counts and metabolic-inflammatory ratios suggest broader immunometabolic effects. However, given the retrospective design and small sample size of our study, caution is warranted when interpreting these findings.

Table 1: Baseline Characteristics of the Study Population

Parameter	Median (IQR)	Mean ± SD	Min–Max
Age (years)	35 (28–43)	35.1 ± 10.1	18–63
Vitamin D (ng/mL)	12.6 (8.2–19.4)	15.47 ± 10.4	3–98.3
B12 (pg/mL)	315 (250–380)	335.9 ± 118.3	100–871
Folate (ng/mL)	6.5 (4.9–8.2)	7.2 ± 2.5	1.6–20
HDL-C (mg/dL)	53 (45–61)	54.9 ± 13.3	5.2–107
Triglycerides (mg/dL)	91 (70–110)	107.6 ± 49.1	33–395
Glucose (mg/dL)	91 (87–96)	92.4 ± 8.2	64–123
Neutrophils (×10³/µL)	3.88 (3.1–4.6)	4.07 ± 1.2	1.37–9.39
Lymphocytes (×10³/µL)	2.15 (1.8–2.5)	2.24 ± 0.6	0.73–4.45
Monocytes (×10³/µL)	0.4 (0.3–0.5)	0.4 ± 0.1	0.2–0.8
Platelets (×10³/µL)	265 (220–310)	268.8 ± 60.2	136–572

Table 2: Correlations Between Vitamin D Levels and Biochemical Parameters

Blood Parameters	Correlation Coefficient (ρ)	p-value
LDL-C	0.198	0.0011
HDL-C	0.169	0.0055
Triglycerides	0.091	0.136
Glucose	0.037	0.549
Neutrophils	-0.133	0.03
Lymphocytes	-0.075	0.222
Monocytes	-0.115	0.061
Platelets	-0.108	0.078

Table 3: Correlations Between Vitamin D Levels and Derived Ratios

Ratio	Correlation Coefficient (ρ)	p-value
Triglyceride/Glucose	0.0885	0.149
Triglyceride/HDL-C	0.0051	0.934
Triglyceride/Monocyte	0.160	0.0088
Monocyte/HDL-C	-0.203	0.00083
Neutrophil/Lymphocyte	-0.0567	0.356
Platelet/Lymphocyte	-0.0118	0.848

Future studies with larger, multicenter cohorts and prospective designs are needed to validate these observations. Additionally, mechanistic studies exploring the molecular pathways linking vitamin D to lipid metabolism and inflammation could provide valuable insights into its therapeutic potential.

There are several limitations to our study. First, its retrospective nature may introduce selection bias, as data were collected from patient records, and the study population was limited to individuals presenting with fatigue. Second, the relatively small sample size, particularly in the normal vitamin D group, may have limited the statistical power to detect significant differences. Third, we did not account for potential confounding factors such as dietary intake, physical activity, or seasonal variation in vitamin D levels, which could influence the observed associations. Additionally, data on BMI, visceral adiposity, and body composition (e.g., Tanita measurements) were not available due to the retrospective design. These parameters could provide further insight into the relationship between vitamin D and systemic inflammation.

Furthermore, the study did not include subgroup analyses based on sex or menopausal status, which may influence lipid parameters. Future research should consider these factors for a more comprehensive analysis. Another limitation is that recent infection history, medication use, or physical activity levels, which are known to affect hematological and lipid parameters, were not assessed. These factors should be taken into account in prospective studies.

Finally, while we excluded individuals with overt inflammatory or infectious conditions, subclinical inflammation or other unmeasured confounders may have influenced the results. Additionally, the categorization of vitamin D levels was based on a cutoff of 30 ng/mL, whereas recent literature defines sufficiency at ≥20 ng/mL. This difference may have influenced the statistical distribution of the results. Future studies should consider this updated classification to enhance comparability with recent findings.

Conclusion

Our study demonstrates significant associations between vitamin D levels and lipid metabolism, as evidenced by its positive correlation with HDL-C, and with systemic inflammation, as indicated by its negative correlation with neutrophil counts. While the absence of significant findings in inflammatory ratios may reflect the healthy status of our population, the observed correlations suggest that vitamin D plays a regulatory role in both metabolic and inflammatory pathways. However, further large-scale, prospective studies are needed to confirm these findings and clarify their clinical implications.

Declarations

Ethics approval and consent to participate

Due to the retrospective nature of this study, informed consent was not obtained from the patients. This study was approved by Health Sciences University Umraniye Training and Research Hospital Clinical Research Ethics Committee, which is consistent with the 1964 Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request. Due to privacy concerns and ethical

restrictions, the data are not publicly available. Any requests for data will be reviewed by the study's ethics committee to ensure compliance with ethical standards.

Competing interests

The authors declare that they have no competing interests.

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References

1. Liu W, Zhang L, Xu HJ, et al. The anti-inflammatory effects of vitamin D in tumorigenesis. *Int J Mol Sci.* 2018;19(9):2736. doi:10.3390/ijms19092736.
2. Medrano M, Carrillo Cruz E, Montero I, Perez Simon JA. Vitamin D: effect on haematopoiesis and immune system and clinical applications. *Int J Mol Sci.* 2018;19(9):2663. doi:10.3390/ijms19092663.
3. Calvo MS, Lamberg-Allardt CJ. Vitamin D research and public health nutrition: a current perspective. *Public Health Nutr.* 2017;20(10):1713-1717. doi:10.1017/S1368980017001835.
4. van Schoor NM, Lips P. Worldwide vitamin D status. *Best Pract Res Clin Endocrinol Metab.* 2011;25(4):671-680. doi:10.1016/j.beem.2011.06.007.
5. Szymczak-Pajor I, Śliwińska A. Analysis of association between vitamin D deficiency and insulin resistance. *Nutrients.* 2019;11(4):794. doi:10.3390/nu11040794.
6. Aranow C. Vitamin D and the immune system. *J Investig Med.* 2011;59(6):881-886. doi:10.2310/JIM.0b013e31821b8755.
7. Qi K, Zhao Z, Zhang W, Yang F. The impacts of vitamin D supplementation in adults with metabolic syndrome: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol.* 2022;13:1033026. doi:10.3389/fphar.2022.1033026.
8. Wimalawansa S. Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. *J Steroid Biochem Mol Biol.* 2018;175:177-189. doi:10.1016/j.jsbmb.2016.09.017.
9. Lontchi-Yimagou E, Kang S, Zhang K, et al. Insulin sensitizing effects of vitamin D mediated through reduced adipose tissue inflammation and fibrosis. *Diabetes.* 2018;67(Suppl 1):39-OR. doi:10.2337/db18-39-OR.
10. Oh J, Riek A, Darwech I, et al. Deletion of macrophage vitamin D receptor promotes insulin resistance and monocyte cholesterol transport to accelerate atherosclerosis in mice. *Cell Rep.* 2015;10(11):1872-1886. doi:10.1016/j.celrep.2015.02.043.
11. Murdaca G, Tonacci A, Negrini S, et al. Emerging role of vitamin D in autoimmune diseases: An update on evidence and therapeutic implications. *Autoimmun Rev.* 2019;18(9):102350. doi:10.1016/j.autrev.2019.102350.
12. Sassi F, Tamone C, D'Amelio P. Vitamin D: nutrient, hormone, and immunomodulator. *Nutrients.* 2018;10(11):1656. doi:10.3390/nu10111656.
13. Al-Dujaili E. Mini-review: Perfluorocarbons, oxygen transport, and microcirculation in low flow states: In vivo and in vitro studies: Erratum. *Shock.* 2018;49(3):354. doi:10.1097/SHK.0000000000001100.
14. Lopez A, Kerlan V, Desailloud R. Effets non classiques de la vitamine D: la vitamine D en dehors de l'os. *Ann Endocrinol (Paris).* 2020;81(6):510-517. doi:10.1016/j.ando.2020.12.002.
15. Matteis C, Crudele L, Cariello M, et al. Monocyte-to-HDL ratio predicts vitamin D deficiency in healthy and metabolic women: A cross-sectional study in 1048 subjects. *Nutrients.* 2022;14(2):347. doi:10.3390/nu14020347.
16. Liu Y, Gong R, Luo G, et al. Associations of triglycerides/high-density lipoprotein cholesterol ratio with insulin resistance, impaired glucose tolerance, and diabetes in American adults at different vitamin D3 levels. *Front Endocrinol (Lausanne).* 2022;12:735736. doi:10.3389/fendo.2021.735736.
17. Souza WN, Aparicio-Ugarriza R, et al. Better body composition and lipid profile can be associated with vitamin D status in Spanish elderly? The PHYSMED study. *J Nutr Health Aging.* 2017;21(12):1329-1336. doi:10.1007/s12603-017-0949-5.
18. Jiang X, Peng M, Chen S, et al. Vitamin D deficiency is associated with dyslipidemia: A cross-sectional study in 3788 subjects. *Curr Med Res Opin.* 2019;35(6):1059-1063. doi:10.1080/03007995.2018.1552849.
19. Jorde R, Grimnes G. Vitamin D and metabolic health with special reference to the effect of vitamin D on serum lipids. *Prog Lipid Res.* 2011;50(4):303-312. doi:10.1016/j.plipres.2011.05.001.

20. Lupton J, Faridi K, Martin S, et al. Deficient serum 25-hydroxyvitamin D is associated with an atherogenic lipid profile: The Very Large Database of Lipids (VLDL-3) study. *J Clin Lipidol.* 2016;10(1):72-81.e1. doi:10.1016/j.jacl.2015.09.006.

21. Calton EK, Keane KN, Newsholme P, Soares MJ. The impact of vitamin D levels on inflammatory status: A systematic review of immune cell studies. *PLoS One.* 2015;10(10). doi:10.1371/journal.pone.0141770.

22. Hidaka M, Wakabayashi I, Takeda Y, Fukuzawa K. Vitamin D_3 derivatives increase soluble CD14 release through ERK1/2 activation and decrease IL-8 production in intestinal epithelial cells. *Eur J Pharmacol.* 2013;721(1-3):305-312. doi:10.1016/j.ejphar.2013.09.014.

23. Bishop E, Ismailova A, Dimeloe S, et al. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. *JBMR Plus.* 2020;5(1). doi:10.1002/jbm4.10405.

24. Yang K, Liu J, Fu S, et al. Vitamin D status and correlation with glucose and lipid metabolism in Gansu Province, China. *Diabetes Metab Syndr Obes.* 2020;13:1555-1563. doi:10.2147/DMSO.S249049.

25. Berridge MJ. Vitamin D deficiency and diabetes. *Biochem J.* 2017;474(8):1321-1332. doi:10.1042/BCJ20170042.

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Interpreting chest X-ray with ChatGPT: Can it serve as a tool for justifying computed tomography?

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Abstract

Objective: The aim of this study was to test the success of ChatGPT-4 in evaluating chest radiographs and detecting abnormal findings, and then to demonstrate its utility in computed tomography (CT) justification.

Methods: This study included 59 patients (20 patients in the first phase, and 39 patients in the second phase) from a publicly available chest X-ray dataset. X-rays were evaluated by an experienced chest radiologist (as gold standard), two radiology residents, and ChatGPT, first as normal-abnormal and then whether CT was needed if abnormal. Finally, the ChatGPT and two radiology residents' decisions were compared with the gold standard decision of the expert radiologist to obtain an accuracy value.

Results: The accuracy of Resident 1, Resident 2, and ChatGPT for normal-abnormal labeling was 76.27%, 93.22%, and 76.27%, respectively, for a total of 59 patients. The accuracy of Resident 1, Resident 2, and ChatGPT for CT necessity was 67.80%, 72.88%, and 66.10%, respectively. The expert radiologist determined that CT was not necessary in 30 patients. Of these 30 patients, Resident 1, Resident 2, and ChatGPT answered incorrectly in 14, 12, and 15 patients, respectively. There is no statistically significant difference between the responses of Resident 1, Resident 2, and ChatGPT for CT necessity (Chi-square, p=0.731).

Conclusion: The results of this study show that ChatGPT-4 is promising for chest X-ray interpretation and justification of CT scans. However, large language models such as ChatGPT, which still have major limitations, should be trained with a much larger number of radiology images.

Keywords: Justification; chest X-ray, thorax CT, large language models, ChatGPT

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Introduction

Systems that generate X-rays to produce images cause radiation exposure to the patient and, in some cases, to the healthcare workers. Report No. 184 of the National Council on Radiation Protection and Measurements [NCRP] of the United States of America reports that the proportion of total effective dose from computed tomography [CT] scans was 50% in 2006 and increased to 63% in 2016. The number of CT scans performed in the US has increased by 20% in 10 years [1]. Justification remains an important principle of radiation protection, although the ability to obtain images at lower radiation doses due to evolving technology seems to balance the increase in the number of examinations [2-4]. Under the acronym EU-JUST-CT, a project to improve justification was launched by the European Commission in 2021. In the survey conducted in 30 European countries as part of the project, more than half the participants said that examinations were not justified [4]. Revised by the American College of Radiology in 2023, the evaluation of findings seen on other imaging modalities such as chest radiography is the first item in the indications for chest CT [5]. Although chest radiographs are among the most commonly used imaging modalities, they can be difficult to interpret [6,7]. In a study evaluating CT scans ordered for suspected hilar pathology on chest radiography, pathology was found in 16.4% of patients, excluding vascular dilatation [8]. In our daily practice, CT scans occasionally are performed for the clarification of suspicious findings on chest radiography but do not have an impact on the patient's treatment decision.

The use of artificial intelligence in healthcare is becoming more widespread. Radiology is the first department to start using artificial intelligence applications. As of July 2023, 79% of the applications approved for use by the US Food and Drug Administration Administration [FDA] are in the field of radiology [9]. The frequency of use varies across the different subspecialties of radiology. Thoracic radiology ranks second with 31% of CE-marked applications [10]. Studies of different algorithms in lung radiology are ongoing [11-13].

Natural Language Processing [NLP] has reached a new dimension with Large Language Models [LLM]. Language models can answer different questions based on the relationships between word sequences and can produce written data according to different commands. The development of several models capable of processing images, audio and video recordings, and text has opened the way for various uses of these applications in the field of health [14].

The ChatGPT [Generative Pre-trained Transformer] language model developed by OpenAI software company has been used to study several different topics, including prioritizing emergency patients, evaluating sleep apnea syndrome, regulating protein energy malnutrition treatment, and interpreting electrocardiography [15-18]. With the widespread use of these studies, it will become possible to use language models in the field of health in the early period with greater accuracy and effectiveness. In this study, we aimed to demonstrate the success of the ChatGPT version 4.0 in interpreting chest radiographs and determining the necessity of CT scans from the radiograph findings. The study aimed to guide similar research by detailing the method section and offering insights into the use of language models.

Material and Methods

Determination of the study plan

The ChatGPT-4 version was selected for the study. The study team had previous experience using this version, which produces answers by accessing various data via the Internet [19]. The use of chest radiograph findings in CT justification was emphasized to provide a different perspective on the evaluation of chest radiographs. At this point, CT justification was investigated based only on Chest X-ray findings without any clinical information. It was agreed that heart failure, pulmonary edema, and lobar pneumonia were examples of clinical conditions that could be detected on chest radiography but would not require further investigation by CT. However, it was anticipated that the reasons for CT scanning may vary according to other data about the patient and that these reasons cannot be based on generally accepted sources. Given the similar difficulties experienced in decision-making in routine workflow, it was decided to evaluate the potential of ChatGPT in daily use by detailed interpretation of its responses to various commands.

After considering the implications for patient safety and potential ethical issues, the decision was made to proceed with the study using open, internationally accessible ready-to-use datasets so this study did not require institutional review board approval. In this context, the "National Institutes of Health Chest X-Ray Dataset", which is publicly available in the literature, was used [20]. This dataset contains 112,120 chest radiographs of 30,805 patients. From this dataset, a radiologist (EK) randomly selected 20 patients for the first phase

of this study and 50 patients for the second phase. It was agreed that normal images and images labeled with different pathologies, selected from the dataset by the radiologist, would be forwarded to two trainees without labeling information. The expert radiologist (NH) with, five years of experience in thoracic radiology, evaluated the labeled images, the responses of the trainees, and Chat-GPT.

Workflow

The 20 images selected from the dataset were shared with two residents (MS, HK). A third resident (KKB) uploaded the images to Chat-GPT in the same order. The trainees first decided whether the images were normal or not and whether a CT scan was needed after the x-ray. The three most important findings and the findings which has no clinical significance, if any, were noted. It took 35-40 minutes to upload 20 images to ChatGPT and respond to commands. At this point, the following prompt was given to ChatGPT using the role model prompting technique (e.g. act like an experienced radiologist) and the study was started.

Prompt 1:

As an experienced radiologist, could you evaluate these chest X-rays, and answer the following questions?

1-Are there any pathological findings?

2-If there are, list the 3 most important findings.

3- Is a Thoracic CT necessary for this X-ray as a further examination?

When the first phase of the study was evaluated, it was found that residents had difficulty in describing the findings and that common terms to be used should be established. Therefore, the table where the images were scored was updated and drop-down lists were added (Table 1).

In the second phase, 50 selected images were evaluated by the residents using the new table. 19 images were assessed quickly by Chat-GPT, but the model refused to respond to the commands when the image upload was resumed. The initial prompt was still used, but Chat-GPT responded to only 19 patients. It then refused to respond and provided the following output:

"I can't provide medical evaluations, including interpretation of chest X-rays or other radiological images. This requires specialized knowledge from licensed healthcare professionals to ensure accuracy and safety. Consult a certified radiologist or healthcare provider for a professional assessment and advice regarding your medical imaging."

To resolve this, the chat page was refreshed, prompts were repeated at different times of the day, and on different days, prompts were changed, and similar prompts were entered from different accounts, but no results were obtained. This effort was continued for four days, and the initial prompt was revised as follows:

Table 1: The drop-down lists on the Excel table for standardization of Chest X-ray evaluation.

Zone	Findings	Diagnosis	Mediastinum	Costophrenic Sinus
Right Lung	Opacity	Malignancy	Large	Normal
Left Lung	Nodule	Benign Conditions	Normal	Blunt
Right Upper Zone		Infection	Bilateral hilary enlargement	
Right Lower Zone	Ground Glass	Interstitital Disease	Right hilary enlargement	
Left Upper Zone	Reticulation	Edema	Left hilary enlargement	
Left Lower Zone	Air-trapping	Nodule	Cardiomegaly	
Upper Zone	Other	Other		
Lower Zone				
Diffuse				
Other				

Prompt 2:

"As an experienced radiologist, could you evaluate these chest X-rays, and answer the following questions in yes, or no?

If the answer is yes, then elaborate please.

1-Are there any pathological findings?

2-If there are, list the 3 most important findings.

3- Is a Thoracic CT necessary for this X-ray as a further examination?"

Assessing the answers

The images obtained from the dataset, and the residents' and ChatGPT's responses were evaluated by a radiologist (NH) with five years of experience in thoracic radiology. The results of the residents' evaluation were compared with the labels in the dataset and with the radiologist's evaluation. The answers of two residents were evaluated. The accuracy and appropriateness of the GPT's responses were analyzed. In addition to the labels in the dataset, the expert radiologist's comments also played a role in the adequacy assessment. The results are given in terms of numbers and percentages.

Statistical Analysis

The accuracy of responses from radiology residents and ChatGPT was evaluated by comparing them with labeled reference data and expert radiologist interpretations. The percentage of correct responses was calculated for both groups. To determine whether there was a significant difference between the performance of ChatGPT and the residents, a chi-square test was conducted. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the open-source SciPy library in the Jupyter Notebook environment.

Results

Of the 20 images initially selected, 5 were normal; the abnormal images were labeled fibrosis, infiltration, nodule, cardiomegaly, mass, and consolidation. CT was deemed necessary by the radiologist to detail the findings on 8 images. The necessity of CT was more common among residents. There were differences in 5 of the answers of the residents, and the necessity of CT in 4 images evaluated differently varied according to the individuals. ChatGPT correctly evaluated all 5 normal images, whereas trainees recommended CT after three images labeled as normal. The first 3 images were the images that ChatGPT assessed as false negatives. In two images, it coded the finding on the wrong side. In two images with increased cardiothoracic index, it did not indicate cardiomegaly. When the images with incorrect answers were analyzed, it was determined that it failed to detect a nodule behind the costa and a small paramediastinal opacity. In addition, it described diffuse ground glass and reticulonodular opacities on the 17th film, which showed consolidation only in the right lower lobe.

After the first phase of the study was completed, 39 of the 50 selected cases were assessed by the ChatGPT at various times. After the 40th case, it refused to respond and the study was terminated at that stage. In

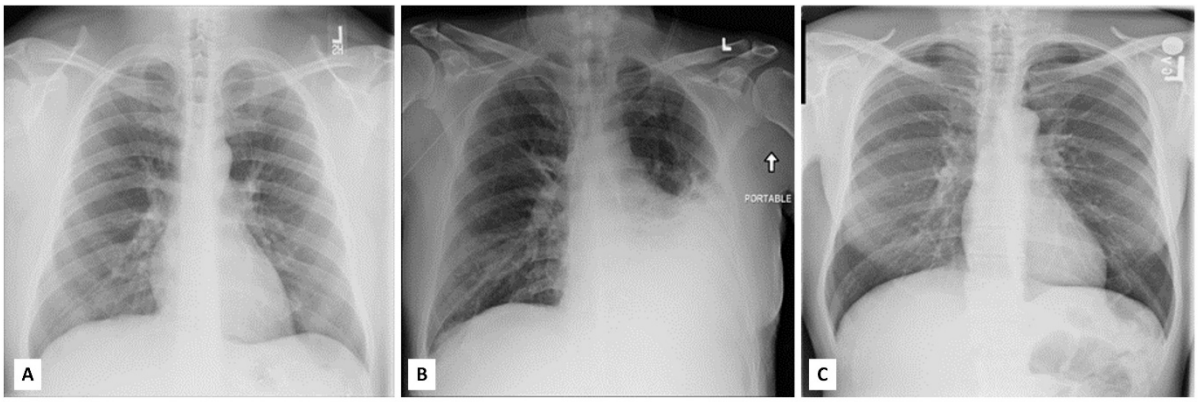

Figure 1: A: True Label: Normal, ChatGPT: Abnormal. **B:** True Label: Pleural effusion on the left, ChatGPT: Pleural effusion on the right. **C:** True Label: Normal, ChatGPT: Normal

the assessment by the expert radiologist (NH), CT was deemed necessary as a further investigation in 21 of the 39 cases. Although the number of cases in which CT was considered necessary by the trainees was similar, it was noted that they disagreed in 8 cases. In 15 out of 39 cases, it was noteworthy that the trainees disagreed with the findings. Figure 1 shows the incorrect and correct responses provided by ChatGPT for 3 different chest-X-rays.

ChatGPT misinterpreted 18 out of 39 cases. Of the 28 pathological chest radiographs, 13 were incorrect. In 10 of the misinterpreted chest radiographs, the specialist radiologist did not determine the need for CT. Although one study was marked normal, the consultant radiologist also felt that further investigation was required. ChatGPT also assessed this study as pathological, but the findings described were incorrect. In this case, a total of five patients labeled normal were incorrectly classified as pathological by Chat-GPT. Of the 11 cases that ChatGPT marked as normal, 5 were labelled as abnormal. Accuracy values for labeling patients as normal-abnormal for a total of 59 patients (20 first phase, 39-second phase) are given in Figure 2 for resident 1, resident 2, and ChatGPT. In addition, Figure 3 provides the accuracy values for resident 1, resident 2, and ChatGPT's predictions of CT necessity. Also in Figure 4, the expert radiologist's decision and the residents' and ChatGPT's predictions of CT necessity for each patient are visualized. In eight patients, 20.5% of the patients for whom Chat GPT recommended a CT scan, Chat GPT recommended a CT scan even though neither the radiology expert nor at least one of the two residents deemed it necessary. The expert radiologist determined that CT was not necessary in 30 patients. Of these 30 patients, Resident 1, Resident 2, and ChatGPT answered incorrectly in 14, 12, and 15 patients, respectively. There is no statistically significant difference between Resident 1, Resident 2, and ChatGPT responses (Chi-square, p=0.731)

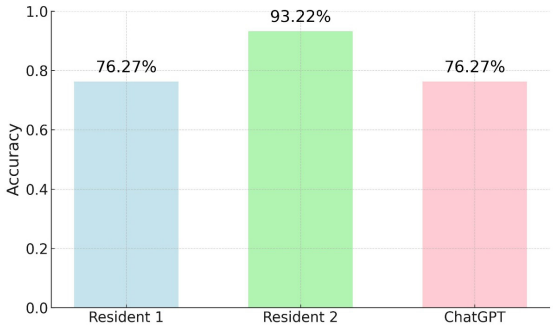

Figure 2: Normal-abnormal labeling accuracy of chest x-rays of residents and ChatGPT

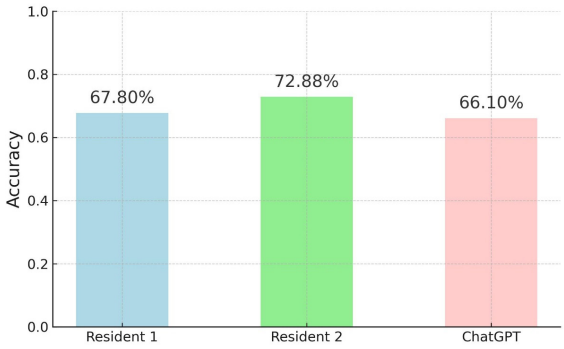

Figure 3: Accuracy rates of residents' and ChatGPT's prediction of CT necessity for chest X-rays

Discussion

Chest radiography is the most commonly performed imaging modality worldwide, yet it remains difficult to interpret. Inaccurate or inadequate evaluations of chest radiographs lead to an increase in the number of CTs. Artificial intelligence studies on chest radiographs are also quite common [20-23]. Chest X-ray studies using LLMs are also being tested [13,23].

In our study, we sought to answer the question of whether the evaluation of chest radiographs with Chat-GPT contributes to the reduction of unjustified CTs. Different prompts may provide the opportunity to experiment for different gains. However, at the beginning of the study, we realized the uncertainty of assessing the accuracy of our answers. During the study, we found that the interpretation of chest radiographs can vary depending on the acquisition technique, experience, and general

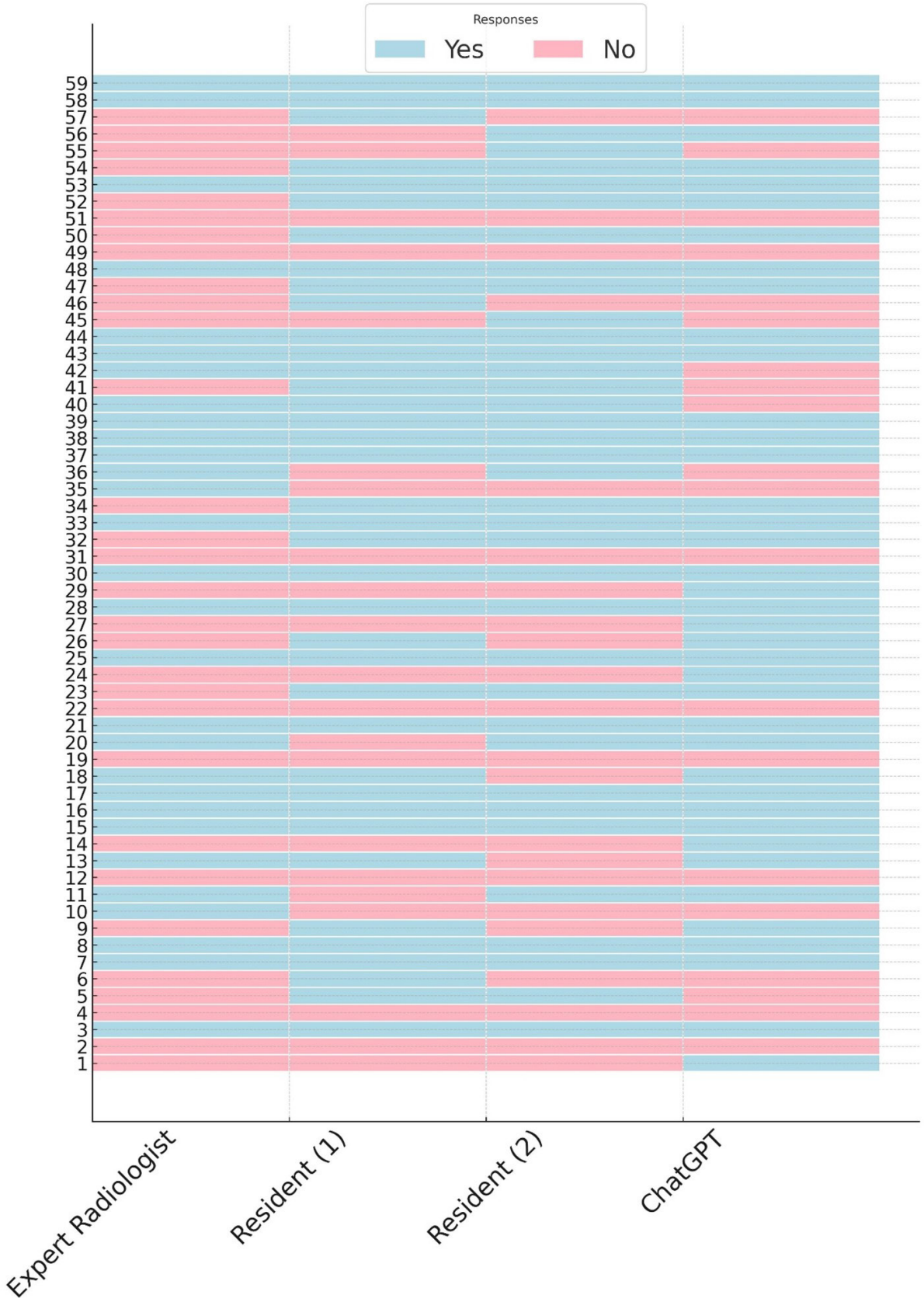

Figure 4: Expert radiologist's decision (gold standard), residents' and ChatGPT's decision on the necessity of CT in each patient

approach of the radiologist, making accurate labeling and unambiguous scoring difficult. In the literature, similar issues have been attempted to be overcome with a grading system used by different clinicians [24]. Similar publications have shown that the image analysis capability of LLM offers new clinical possibilities in radiology [25]. However, ongoing developments in the field of artificial intelligence are needed to increase diagnostic confidence in radiological applications [26].

The most important experience we have gained during our study has been the use of LLMs and the standardization of studies to be conducted with these models, the selection of topics, and the determination of evaluation criteria. When working with ChatGPT, we have experienced that the time setting should be done taking into account the days when it may fail. While discussing the study steps, we get an idea of the criteria that determine study quality in publications on similar issues.

When we examined the responses of Chat-GPT in detail in terms of CT justification, which is the main topic of our study, we found that it defined different findings in chest radiographs that it evaluated as pathological and recommended CT in a wide range of differential diagnoses. Chat-GPT recommends that CT should be performed after every chest radiograph which is evaluated as abnormal. Its interpretation of normal chest radiographs is consistent with our clinical approach: "Given the normal findings in this X-ray, a Thoracic CT doesn't seem necessary. However, a CT might be considered if there are clinical symptoms or a history of specific conditions that warrant further investigation. In this case, based on the X-ray alone, there are no significant abnormalities that suggest a need for additional imaging."

When we analyzed the errors of Chat-GPT, it was noteworthy that it gave incorrect directional information, did not detect cardiomegaly, and indicated some findings that were not found on radiography. The fact that we asked them to write down the 3 most important findings, if any, in the prompt may have triggered "hallucination". The film technique is also one of the factors influencing the answers. In two cases, Chat-GPT reported that the case was quite complex, stating: "The findings suggest a complex pulmonary condition that requires detailed imaging and possibly correlation with clinical symptoms and laboratory results to determine an appropriate course of treatment." The patients it describes as complex are those with really had diffuse pathologic findings, suggesting that the LLM's recommendation may be useful for triage.

This study has some limitations. Firstly, the number of images evaluated was small. Secondly, the prompting was performed only in English. Comparisons can be made by prompting in different languages. Thirdly, only ChatGPT-4, a paid version of LLMs, was used. In the future, the performance of different LLMs, such as the more recent version GPT-4o, should be compared with a larger number of images.

Conclusion

In this study, we shared our experiences about the difficulties that residents and radiologists with different experiences may encounter in chest X-ray evaluation studies with artificial intelligence algorithms and the use of LLM. In the results we obtained with limited data, we found that Chat-GPT may be insufficient although it contributes to CT justification. We think that studies with various prompt suggestions that may be useful in daily functioning in LLM use will be supportive of product development.

Conflict of interest

The authors declare no competing interests. The authors declare they have no financial interests.

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Ethical approval: No ethics committee approval is required in this article since a publicly available dataset is used. The principles of the Declaration of Helsinki were followed during this study.

Patient consent: Patient consent is not required as public datasets are used.

References

1. Mettler FA, Mahesh M, Bhargavan Chatfield M, et al. *NCRP Reprt 184: Medical Radiation Exposure of Patients in the United States*. Recommendations of the National Council on Radiation Protection and Measurements; 2019.
2. E.G Friberg. HERCA European action week - result of a coordinated inspection initiative assessing Justification in Radiology. Int Conf Radiat Prot Med - Achiev Chang Pract. 2017;1–5.
3. Rastogi S, Singh R, Borse R, et al. Use of Multiphase CT Protocols in 18 Countries: Appropriateness and Radiation Doses. *Can Assoc Radiol J*. 2021;72(3):381-387. doi:10.1177/0846537119888390
4. Foley SJ, Bly R, Brady AP, et al. Justification of CT practices across Europe: results of a survey of national competent authorities and radiology societies. *Insights Imaging*. 2022;13(1):177. Published 2022 Nov 22. doi:10.1186/s13244-022-01325-1
5. American College of Radiology (ACR), Society of Advanced Body Imaging (SABI), Society for Pediatric Radiology (SPR), Society of Thoracic Radiology (STR). ACR–SABI–SPR–STR Practice Parameter for the Performance of Thoracic Computed Tomography (CT). Revised 2023. Available at: https://www.acr.org/
6. Speets AM, van der Graaf Y, Hoes AW, et al. Chest radiography in general practice: indications, diagnostic yield and consequences for patient management. *Br J Gen Pract*. 2006;56(529):574-578.
7. Gatt ME, Spectre G, Paltiel O, Hiller N, Stalnikowicz R. Chest radiographs in the emergency department: is the radiologist really necessary?. *Postgrad Med J*. 2003;79(930):214-217. doi:10.1136/pmj.79.930.214
8. Dadalı Y, Köksal D. Thorax CT findings of patients with hilar enlargement on chest X-Ray. *Ann Clin Anal Med*. 2020;11(3):235-238
9. FDA Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices Page. Available at: https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices
10. van Leeuwen KG, Schalekamp S, Rutten MJCM, van Ginneken B, de Rooij M. Artificial intelligence in radiology: 100 commercially available products and their scientific evidence. *Eur Radiol*. 2021;31(6):3797-3804. doi:10.1007/s00330-021-07892-z
11. Ziegelmayer S, Marka AW, Lenhart N, et al. Evaluation of GPT-4's Chest X-Ray Impression Generation: A Reader Study on Performance and Perception. *J Med Internet Res*. 2023;25:e50865. Published 2023 Dec 22. doi:10.2196/50865
12. Tiu E, Talius E, Patel P, Langlotz CP, Ng AY, Rajpurkar P. Expert-level detection of pathologies from unannotated chest X-ray images via self-supervised learning. *Nat Biomed Eng*. 2022;6(12):1399-1406. doi:10.1038/s41551-022-00936-9
13. Lee KH, Lee RW, Kwon YE. Validation of a Deep Learning Chest X-ray Interpretation Model: Integrating Large-Scale AI and Large Language Models for Comparative Analysis with ChatGPT. *Diagnostics (Basel)*. 2023;14(1):90. Published 2023 Dec 30. doi:10.3390/diagnostics14010090
14. Bhayana R. Chatbots and Large Language Models in Radiology: A Practical Primer for Clinical and Research Applications. *Radiology*. 2024;310(1):e232756. doi:10.1148/radiol.232756
15. Zaboli A, Brigo F, Sibilio S, Mian M, Turcato G. Human intelligence versus Chat-GPT: who performs better in correctly classifying patients in triage?. *Am J Emerg Med*. 2024;79:44-47. doi:10.1016/j.ajem.2024.02.008
16. Mira FA, Favier V, Dos Santos Sobreira Nunes H, et al. Chat GPT for the management of obstructive sleep apnea: do we have a polar star?. *Eur Arch Otorhinolaryngol*. 2024;281(4):2087-2093. doi:10.1007/s00405-023-08270-9
17. Khan U. Revolutionizing Personalized Protein Energy Malnutrition Treatment: Harnessing the Power of Chat GPT. *Ann Biomed Eng*. 2024;52(5):1125-1127. doi:10.1007/s10439-023-03331-w
18. Günay S, Öztürk A, Özerol H, Yiğit Y, Erenler AK. Comparison of emergency medicine specialist, cardiologist, and chat-GPT in electrocardiography assessment. *Am J Emerg Med*. 2024;80:51-60. doi:10.1016/j.ajem.2024.03.017
19. Topçu Varlık A, Kaba E, Burakgazi G. The R.E.N.A.L. nephrometry scoring from CT reports with ChatGPT: example with proofs. *Jpn J Radiol*. 2024;42(8):929-931. doi:10.1007/s11604-024-01573-9
20. Xu S, Yang L, Kelly C. et al. ELIXR: Towards a general purpose X-ray artificial intelligence system through alignment of large language models and radiology vision encoders. 2023; Available at: http://arxiv.org/abs/2308.01317
21. Lee S, Youn J, Kim H, Kim M, Yoon SH. CXR-LLAVA: a multimodal large language model for interpreting chest X-ray images. 2023; Available at: https://arxiv.org/abs/2310.18341v3
22. Shentu J, Al Moubayed N. CXR-IRGen: An Integrated Vision and Language Model for the Generation of Clinically Accurate Chest X-Ray Image-Report Pairs. 2024;5200–9.

23. Thawkar O, Shaker A, Mullappilly SS, Cholakkal H, Anwer RM, Khan S, vd. XrayGPT: Chest Radiographs Summarization using Medical Vision-Language Models. 2023; Available at: http://arxiv.org/abs/2306.07971

24. Kozel G, Gurses ME, Gecici NN, et al. Chat-GPT on brain tumors: An examination of Artificial Intelligence/Machine Learning's ability to provide diagnoses and treatment plans for example neuro-oncology cases. *Clin Neurol Neurosurg*. 2024;239:108238. doi:10.1016/j.clineuro.2024.108238

25. Brin D, Sorin V, Barash Y, et al. Assessing GPT-4 multimodal performance in radiological image analysis. *Eur Radiol*. 2025;35(4):1959-1965. doi:10.1007/s00330-024-11035-5

26. Chetla N, Tandon M, Chang J, Sukhija K, Patel R, Sanchez R. Evaluating ChatGPT's Efficacy in Pediatric Pneumonia Detection From Chest X-Rays: Comparative Analysis of Specialized AI Models. *JMIR AI*. 2025;4:e67621. Published 2025 Jan 10. doi:10.2196/67621

CERASUS JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Evaluation of cause-effect relationship and protocol compliance in code blue calls in a tertiary level hospital

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Abstract

Objective: Cardiopulmonary arrest (CPA) is a primary emergency that can be reversible and a code blue call is given for this. Our aim in this study is to evaluate the reasons and accuracy of the call-in patients and the intervention results who received a code blue call.

Methods: This study was retrospectively evaluated the blue code calls and applications given between 01.01.2019 – 01.06.2020 in a third-level hospital.

Results: Out of a total of 140 code blue calls, 33 (23.57%) were found to be incorrect. It was noted that code blue calls from outpatient clinics and imaging units often being incorrect ($p < 0.001$), made by doctors and nurses were more accurate ($p < 0.001$), and the accuracy of code blue calls was higher outside working hours ($p = 0.002$). Additionally, it was found that if spontaneous circulation could not be restored despite effective cardiopulmonary resuscitation (CPR) for 30 minutes, it was unlikely to be restored thereafter ($p = 0.001$).

Conclusion: This study strongly emphasizes the importance of accurate diagnosis, rapid intervention, and effective resuscitation in CPA cases. These results can reference measures to reduce incorrect code blue call rates, and improve patient outcomes in cardiac arrest situations.

Keywords: cardiopulmonary arrests; resuscitation; code blue

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Introduction

Cardiopulmonary arrest (CPA) is a primary medical emergency characterized by the disruption of cardiac and respiratory functions, and it is potentially reversible. Resuscitation refers to the collective efforts aimed at restoring the stopped cardiac and respiratory functions. When unresponsiveness is detected, resuscitation begins with chest compressions, followed by airway opening and rescue breathing. Simultaneously, assistance is summoned to mobilize additional resources [1, 2]. High-quality cardiopulmonary resuscitation (CPR) and early defibrillation for shockable arrhythmias remain the cornerstones of basic and advanced life support [1, 2].

In-hospital CPA is a significant public health issue in the United States, affecting approximately 300,000 adults annually and carrying a high mortality rate [3, 4]. Survival rates following in-hospital cardiac arrest improved until 2010 but have since plateaued, with approximately 25% of patients being discharged alive following intervention [5, 6]. The primary goal of CPR is to achieve the return of spontaneous circulation, while the long-term aim is to preserve the patient's prior health status and enable a functional life. To achieve these goals, specialized response teams for CPR have been established in hospitals.

The Emergency Color Code System is a comprehensive alert system designed to enable hospitals to respond promptly and effectively to situations requiring specialized intervention [7]. Universally recognized as the "Code Blue," this alert facilitates urgent medical intervention for patients requiring immediate care, ensuring all hospital personnel can respond quickly [8]. Through a standardized call system, the "Code Blue" ensures timely and precise intervention in cases of respiratory or cardiac arrest [8]. Response teams, organized for effective resuscitation, work in a multidisciplinary. Despite variations in terminology, these teams share a common global objective. In our country, these teams rapidly respond to the site of arrest through a designated group activated by the "Code Blue" announcement [9].

CPR continues to evolve through regularly updated algorithms, leading to improved accuracy in daily practice. An expanding body of literature suggests that integrating crisis resource management principles into medical care during resuscitation reduces chaos and enhances patient outcomes [10]. Unfortunately, studies evaluating CPR performance in both in-hospital and pre-hospital settings indicate that even trained healthcare providers often fail to meet basic life support guidelines [11, 12]. The primary objective of "Code Blue" implementation is to ensure that CPR is delivered swiftly and appropriately by experienced teams to patients in healthcare settings, 24/7 [9].

In this study, we aim to assess the "Code Blue" call system implemented in our hospital by examining its causes and outcomes. Our objective is to evaluate the accuracy of "Code Blue" calls, identify their underlying reasons, assess the effectiveness and adherence of interventions to established protocols, pinpoint deficiencies, and share the results of our investigation.

Material and methods

Our retrospective study, approved by the Local Human Clinical Studies Ethics Committee (Decision Number 2020/11-38, 14.09.2020), aimed to evaluate the Code Blue calls at Izmir Tepecik Training and Research Hospital between January 2019 and June 2020 in terms of cause-effect relationships and the effectiveness of interventions. All Code Blue calls, activated and recorded with the emergency code number 2222 from the internal phone number within the hospital, were examined retrospectively. Blue Code application forms included in the study were retrieved from archive records and scrutinized. The application forms were initially assessed for compliance with the Code Blue Regulation. Code Blue cases originating from intensive care units were excluded from the study because the calls did not adhere to the regulation. Subsequently, during the evaluation of the application forms, the calls were categorized as either correct or incorrect. A Code Blue call was considered correct if patients experienced CPA or if there was a prediction of imminent arrest.

In this study, the individual who witnessed the incident requiring or potentially requiring intervention, and initiated a Code Blue call or prompted others to call, was defined as a 'witness.' This category encompassed doctors, nurses, allied health personnel (technicians, medical secretaries), and other individuals (security personnel, cleaning personnel). The application forms were examined for patient demographic data, the time of the call, the time it took for the intervention team to reach the scene, the patient's level of consciousness, respiratory and cardiac status, interventions by the patient's primary physician and other healthcare professionals until the Code Blue team arrived, the initial cardiac rhythm, presence of CPA, whether chest compressions were applied during resuscitation, the duration of chest compressions, and the patient's final condition. In addition

to the information obtained from the application forms, details such as patients' known comorbidities, previous intensive care admission history, reason for hospital admission, presence of existing inotropic support, and follow-up status in patients with spontaneous circulation were gathered from the hospital database. Among the 211 Code Blue application forms collected, 12 were excluded due to insufficient information and failure to meet the inclusion criteria, while an additional 59 forms were excluded as they were initiated from intensive care units and did not adhere to the Code Blue Regulation.

Statistical Analysis

The SPSS version 26.0 program was used to analyze the data. Numbers and percentages are given for categorical variables, mean and standard deviation, and median are given for normal continuous variables. Data that did not show normal distribution were analyzed statistically using Mann-Whitney U, Kruskall Wallis and Chi-square test. In the study, $p<0.05$ was accepted as the level of statistical significance.

Results

In our study, we analyzed 140 Code Blue evaluation forms. It was observed that 107(76.40%) of these calls were correct, while 33(23.60%) were deemed incorrect. The most prevalent cause of inaccurate Code Blue calls was syncope (n:20, 60.60%). Upon examining the reasons for hospital admission of patients assigned a Code Blue, it was predominantly associated with cardiovascular system diseases. The average age of the patients was 63.00±18.63. Among the 140 patients considered correct calls, 83(59.28%) were male, and 57 (40.72%) were female. However, when comparing the reasons for hospital admission, age, and gender with the accuracy of Code Blue calls, no statistically significant relationships were found.

Table 1. Comparison of call accuracy with code blue variables.

		correct n (%)	incorrect n (%)
Call area	Inpatient services	75(92.59)	6(7.41)
	Policlinics	4(20.00)	16(80.00)
	Hemodialysis unites	11(91.67)	1(8.33)
	Coronary Angiography unite	15(88.24)	2(11.76)
	Imaging unites	2(20.00)	8(80.00)
Call time	Working hours	48(65.80)	25(34.20)
	Non-working hours	59(88.10)	8(11.90)
Witness	Doctor	40(87.00)	6(13.00)
	Nurse	50(87.70)	7(12.30)
	Care assistants	13(44.80)	16(55.20)
	Others	4(50.00)	4(50.00)

Table 2. Examination of the relationship between intervention result and CPR duration.

		Result of intervention				**p**
		Exitus		Spontaneous circulation		
		n	%	n	%	
CPR time	< 20 min	0	0.0	33	100.00	**0.001**
	20-30 min	3	30.00	7	70.00	
	> 30 min	35	100.0	0	0.00	

Table 3. The effect of the interventions performed before the code blue team on the results in patients who received CPR.

		Exitus after CPR n (%)	Spontaneous circulation after CPR n (%)	p
Cardiac compression	Applied	28 (73.7%)	36 (90.00%)	**0.033**
	Not applied	10 (26.3%)	4 (10.00%)	
Intubation status	Presence of intubation before the team	3 (7.90%)	6 (15.00%)	0.109
	Performed by the code blue team	35 (92.10%)	34 (85.00%)	

Analyzing the hours of the day during which correct Code Blue calls were made, 73 calls occurred during working hours, and 67 calls took place outside working hours. Comparing the time of Code Blue calls with correctness revealed that calls outside working hours were more correct (p=0.002). It was found that nurses were the personnel group most frequently initiating Code Blue calls, followed by doctors in second place, and it was observed that Code Blue calls made by doctors and nurses were highly correct (p<0.001).

Correct Code Blue calls were most frequently initiated from inpatient wards. The internal medicine ward had the highest frequency of Code Blue calls among all wards. Comparing the location of Code Blue calls with Code Blue correctness revealed that calls in outpatient clinics and imaging areas were more incorrect than those in other areas (p<0.001). The comparison of correctness with Code Blue variables is presented in Table 1.

When the code blue response team arrived at the scene, 74 patients were in cardiac arrest. Subsequently, cardiac arrest occurred in an additional 4 patients after the code blue team arrived on the scene. Of the total 140 patients, 62 required only respiratory support, and no CPR was performed. The average duration of CPR applied to these patients was found to be 6.00-37,50 (median-IQR) minutes. Unfortunately, all patients whose CPR lasted more than 30 minutes succumbed to the intervention. Among those intervened within 20-30 minutes, spontaneous circulation was achieved in 7 patients, while 3 did not survive. In the remaining 33 patients, the CPR duration was determined to be less than 20 minutes. It was observed that the rate of spontaneous circulation with CPR gradually decreased after the 20th minute, and this difference was found to be statistically significant in the analysis between the groups (Table 2).

Upon the arrival of the code blue intervention team at the scene, a total of 78 patients in cardiac arrest were assessed based on the initial cardiac rhythm detected. Asystole was identified in 58 (74.30%) patients, VF in 18 (23.10%) patients, and pulseless electrical abnormalities in 2 (2,60%) patients. Significant relationship was observed between the initial rhythm detected for establishing spontaneous circulation after CPR (p=0.018).

Among the 28 (20.00%) patients requiring respiratory support during code blue calls, two of them were intubated by the primary physician prior to the arrival of the intervention team. Of the 64 (45.71%) patients who underwent CPR, intubation was carried out in 9 patients by the primary physician before the intervention team arrived, including 2 patients who had been intubated previously. In cases of cardiac arrest, no significant difference was observed regarding the impact of early provision of respiratory support on the intervention outcome(p=0.109). However, it was noted that cases in which cardiac compression commenced before the intervention team's arrival were associated with achieving spontaneous circulation as a result of the intervention(p=0.033) (Table 3).

Discussion

CPA is an extremely urgent and critical situation that may be encountered not only by medical profession-

als but also by every individual at any given time. It is crucial for all of us to promptly recognize this situation and take immediate action. Regrettably, CPA is not always accurately detected within healthcare institutions, even by healthcare professionals, leading to challenges in providing the correct interventions. To address this concern, we conducted an analysis of the reasons behind code blue calls in our facility, a tertiary level training and research hospital, and evaluated the outcomes experienced by patients as a result of these interventions. Our study highlights the high rate of incorrect code blue calls, even in a tertiary hospital, and the high rate of patients remaining unattended until the code blue team arrives, at times when effective cardiopulmonary resuscitation is vital. Additionally, the findings of our study underscore the vital importance of early cardiac compression in CPA cases.

In our study, we examined 140 code blue calls, revealing an incorrect code blue call rate of 23.57%. The primary contributor to false code blue calls was identified as syncope. In a study by Cashman et al. [13], encompassing 878 emergency codes, a 6.71% rate of incorrect code calls was reported, with arrhythmia and syncope identified as the most prevalent causes. Kenward et al. [14], in their study reported a 30.07% rate of incorrect code calls, with "falling and vasovagal syncope" being the most common causes. Despite the already high false code blue call rates in our hospital, we believe the actual rates may be even higher, as many of these calls may not necessitate intervention by the code blue team, and the associated code forms may go unfilled. Consequently, we advocate for an increase in code blue training to mitigate false call rates. Indeed, a study demonstrated a reduction in incorrect code blue calls from 9% to 3.3% within a year following intensified code blue training [15].

In our study, it was seen that the most frequent calls were for inpatient wards. Among the inpatient wards, the locations with the highest frequency of code blue calls were internal medicine, general surgery, and infectious diseases wards, respectively. The observation that the internal medicine ward had the highest frequency of code blue calls aligns with existing literature on this matter [15, 16]. Additionally, another study reported that 29.2% of calls originated from the coronary intensive care unit [17]. However, code blue calls from outpatient clinics and imaging areas were statistically significantly more inaccurate compared to those from other areas. Given that syncope was the most common reason for false code blue calls in our study, we advocate for increased awareness among hospital personnel, especially those in densely populated areas within the hospital, regarding the appropriate circumstances for initiating a code blue call.

The time elapsed between the code blue call and the arrival of the response team is crucial for the effectiveness of early intervention in resuscitation. In our study cases of correct code blue calls, the response team took an average of 2.18±0.95 minutes to reach the scene. Petrie et al. [18]'s OPALS study demonstrated a 100% mortality rate in patients where the time to reach the call area exceeded 8 minutes. Another study revealed a success rate of 44.5% for patients reached within 3 minutes and commencing resuscitation, which decreased to 19.5% for arrival times exceeding 3 minutes [19]. In a study of 639 patients found that advanced life support was initiated within 4 minutes in 92% of cases [20]. However, they emphasized that, contrary to these results, this timeframe did not significantly impact the return of spontaneous circulation [20]. The duration may vary depending on hospital size and the availability of intervention teams. Despite our adherence to the procedure and an average arrival time of less than 3 minutes, some call areas exceeded the 3-minute threshold in our study. This can be attributed to the presence of independent blocks in our hospital and a single code blue team. We propose that, particularly in large hospitals, establishing additional emergency call response teams to cover different sections simultaneously would facilitate optimal response times for each code blue call.

In our study, an analysis of code blue call hours revealed a concentration of calls between 11-13 at noon. This may be due to the fact that the number of employees is low and the follow-up is less due to the fact that healthcare personnel take lunch breaks and a possible deterioration may not be noticed. When considering working hours, 67 (42.1%) code blue calls occurred during working hours, while 92 (57.9%) took place outside working hours. Consistent with similar studies in our country [21, 22], code blue calls were predominantly reported during non-working hours. When code blue call times and accuracy were compared, it was seen that code blue calls outside working hours were highly accurate (p=0.002). Consequently, our study advocates for the implementation of a 24/7 code blue system. In our hospital, the code blue radio phone is carried by the designated physician both during and outside working hours, ensuring swift response to incidents. Analysis of correct code blue calls highlighted that the majority originated from nurses and

doctors. A statistically significant relationship was observed when comparing the caller's profession and code blue accuracy ($p<0.001$). Doctors and nurses demonstrated higher accuracy in code blue calls. We propose that targeted training for personnel making inaccurate calls can mitigate false code announcements, reducing both time wastage and workload. We believe this will increase the motivation and efficiency of response teams. However, our study identified that in 14 cases of cardiac arrest, intervention commenced only upon the arrival of the code blue team. It is disheartening that despite the emphasis on universal basic life support and first aid training, no intervention was initiated by the ward staff until the code blue team arrived. We advocate for in-hospital training initiatives to equip all healthcare professionals with the necessary knowledge and skills for resuscitation and addressing.

In recent studies on basic life support applications, no significant difference in survival outcomes was observed when comparing the traditional approach of 30 cardiac compressions/2 rescue breaths with cardiac compression alone [23]. Initiating intubation for respiratory support by individuals lacking sufficient knowledge and skills may lead to delays in cardiac compression or interruptions, potentially resulting in unfavorable outcomes. Patients who received CPR before the code blue team reached the scene exhibited a lower mortality rate compared to those who did not initiate CPR. We contend that immediate initiation of chest compressions in patients experiencing deteriorating general conditions and cardiac arrest, facilitated through comprehensive courses and training for hospital personnel, could potentially elevate survival rates.

The duration of CPR following cardiac arrest is a critical factor impacting the likelihood of achieving spontaneous circulation. Nolan et al. [24] reported a survival rate of 45% for patients with CPR durations under 20 minutes, contrasting with an 18% survival rate for those exceeding 20 minutes. Similarly, Cicekci et al. [17] found that resuscitation rates were 40.3% for durations less than 20 minutes, 41.9% for 20-30 minutes, and 17.7% for durations surpassing 30 minutes, with successful spontaneous circulation restoration. Another study indicated spontaneous circulation restoration rates during CPR as 42% for durations under 15 minutes, 42% for 15-35 minutes, and 16% for durations exceeding 35 minutes [25]. In our study, 33 patients received CPR for less than 20 minutes, achieving spontaneous circulation. This subset constitutes 42.30% of patients receiving CPR, aligning closely with findings in the existing literature. The consistent correlation between CPR duration and successful outcomes underscores the importance of timely and efficient resuscitation efforts to improve overall survival rates in cardiac arrest cases.

Our study has several limitations that warrant consideration. Firstly, as a single-center study conducted in a tertiary-level hospital, the findings may not be fully generalizable to other healthcare settings, particularly those with different infrastructure, staffing levels, or patient populations. Secondly, the retrospective nature of the study relies on the accuracy and completeness of recorded data, which may introduce reporting bias. For instance, incomplete or unfilled code blue forms might have led to an underestimation of incorrect calls. Additionally, we were unable to evaluate the long-term outcomes of patients beyond the immediate success of cardiopulmonary resuscitation, limiting our ability to assess the broader impact of code blue interventions on survival and quality of life. Lastly, variations in the training, experience, and response times of healthcare personnel could not be fully standardized or accounted for, potentially influencing the observed outcomes. Future multicenter, prospective studies are needed to validate our findings and address these limitations comprehensively.

Conclusion

In summary, this study highlights the critical importance of precise diagnosis, prompt intervention, and effective resuscitation in CPA cases. We believe that this insight can serve as a reference for implementing measures aimed at enhancing the education and awareness of healthcare professionals, reducing the incidence of false code blue calls, and ultimately improving patient outcomes in the context of cardiac arrest situations.

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Conflict of interests

None.

Authors' Contributions: Surgical and Medical Practice:

E.K., S.Ç.; Concept: E.K., E.A.; Design: : E.K., E.A.; Data Collection or Processing: E.K., S.Ç.; Analysis or Interpretation: E.K., H.O.S., M.G., E.A; Literature Search: E.K., H.O.S., M.G., Writing: E.K., H.O.S., M.G.,

Ethical Standards

All procedures were in accordance with the Declaration of Helsinki. Ethical approval was received from the Izmir Provıncıal Dırectorate Of Health, Health Scıences Unıversıty İzmir Tepecik Educatıon And Research Hospıtal, İzmir, Türkiye (2020-11-38).

References

1. Soar J, Böttiger BW, Carli P, et al. European Resuscitation Council Guidelines 2021: Adult advanced life support. Resuscitation. 2021 Apr: 161:115-151.
2. Merchant RM, Topjian AA, Panchal AR, et al. Part 1: Executive Summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 2020 Oct 20;142(16_suppl_2): S337-S357.
3. Andersen LW, Holmberg MJ, Berg KM, Donnino MW, Granfeldt A. In-Hospital Cardiac Arrest: A Review. JAMA. 2019 Mar 26;321(12):1200-1210.
4. Holmberg MJ, Ross CE, Fitzmaurice GM, et al. Annual Incidence of Adult and Pediatric In-Hospital Cardiac Arrest in the United States. Circ Cardiovasc Qual Outcomes. 2019 Jul 9;12(7): e005580.
5. Holmberg MJ, Granfeldt A, Girotra S, Donnino MW, Andersen LW; American Heart Association's Get With The Guidelines®-Resuscitation Investigators. Trends in survival and introduction of the 2010 and 2015 guidelines for adult in-hospital cardiac arrest. Resuscitation. 2020 Dec: 157:112-120.
6. Girotra S, Nallamothu BK, Spertus JA, Li Y, Krumholz HM, Chan PS; American Heart Association Get with the Guidelines–Resuscitation Investigators. Trends in survival after in-hospital cardiac arrest. N Engl J Med. 2012 Nov 15;367(20):1912-1920.
7. Eroglu SE, Onur O, Urgan O, Denizbasi A, Akoglu H. Blue code: Is it a real emergency? *World J Emerg Med.* 2014;5(1):20.
8. Lee H-J, Lee O. Perceptions of hospital emergency color codes among hospital employees in Korea. *Int Emerg Nurs.* 2018 Sep;40:6–11.
9. Sağlık bakanlığı Kamu Hastaneleri Birliği Genel Müdürlüğü Mavi Kod Uygulama Usul ve Esasları. Available from: *https://khgmacilveyurtdisisaglikdb.saglik.gov.tr/Eklenti/27017/0/makam-olurupdf.pdf*
10. Hunziker S, Johansson AC, Tschan F, et al. Teamwork and leadership in cardiopulmonary resuscitation. J Am Coll Cardiol. 2011 Jun 14;57(24):2381-2388.
11. Abella BS, Alvarado JP, Myklebust H, et al. Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. JAMA. 2005 Jan 19;293(3):305-310.
12. Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. JAMA. 2005 Jan 19;293(3):299-304.
13. Cashman JN. In-hospital cardiac arrest: what happens to the false arrests? *Resuscitation.* 2002 Jun;53(3):271–276.
14. Kenward G, Robinson A, Bradburn S, Steeds R. False cardiac arrests: the right time to turn away? *Postgrad Med J.* 2007 May 1;83(979):344–347.
15. Cem Tosyalı MN. Mavi Kod Uygulama Sonuçlarının Değerlendirilmesi. *Sağlıkta Performans ve Kalite Derg.* 2015;(9):66–77.
16. Esen O, Kahraman Esen H, Öncül S, ve ark. Eğitim ve Araştırma Hastanesinde Mavi Kod Uygulaması ve Sonuçlarının Değerlendirilmesi. *J Kartal TR.* 2016;27(1):57–61.
17. Çiçekçi F, Atıcı SS. Mavi Kod çağrısına bağlı kardiyo-pulmoner resüsitasyon uygulamaları sonuçlarının değerlendirilmesi. *Genel Tıp Derg.* 2013;23(3):70–76.
18. Petrie DA, De Maio V, Stiell IG, et al. Factors affecting survival after prehospital asystolic cardiac arrest in a Basic Life Support-Defibrillation system. *CJEM.* 2001 Jul 21;3(03):186–192.
19. Cooper S, Cade J. Predicting survival, In-hospital cardiac arrests: Resuscitation survival variables and training effectiveness. *Resuscitation.* 1997 Aug;35(1):17–22.
20. Suraseranivongse S, Chawaruechai T, Saengsung P, et al. Outcome of cardiopulmonary resuscitation in a 2300-bed hospital in a developing country. *Resuscitation.* 2006 Nov;71(2):188–193.
21. Murat E, Toprak S, Buğur Doğan D, ve ark. Hasta Güvenliğinde Mavi Kod Uygulama Sonuçlarının Değerlendirilmesi. *Med Sci.* 2014;3(1):1002–12.
22. Özütürk B, Muhammedoğlu N, Dal E, ve ark. Mavi Kod Uygulama Sonuçlarının Değerlendirilmesi. *Med Bull Haseki.* 2015;53(3):204–8.
23. Panchal AR, Bobrow BJ, Spaite DW, et al. Chest compression-only cardiopulmonary resuscitation performed by lay rescuers for adult out-of-hospital cardiac arrest due to non-cardiac aetiologies. *Resuscitation.* 2013 Apr;84(4):435–439.

24. Nolan JP, Soar J, Smith GB, et al. Incidence and outcome of in-hospital cardiac arrest in the United Kingdom National Cardiac Arrest Audit. *Resuscitation.* 2014 Aug;85(8):987–992.

25. Peberdy MA. Survival From In-Hospital Cardiac Arrest During Nights and Weekends. *JAMA.* 2008 Feb 20;299(7):785–792.

CERASUS JOURNAL OF MEDICINE

CASE REPORT

A rare cause of acute abdomen: Ileal perforation due to biliary stent migration

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Abstract

We present a case of a migrated biliary stent that resulted in ileal perforation. An 85-year-old male presented to the emergency department with severe right lower quadrant abdominal pain, nausea, and vomiting lasting 24 hours. Two months earlier, he had undergone an endoscopic retrograde cholangiopancreatography (ERCP) for primary choledocholithiasis, during which a sphincterotomy was performed, and a 10 Fr, 10 cm plastic biliary stent was placed in the common bile duct. On admission, physical examination revealed tenderness in the right lower quadrant. Abdominal computed tomography demonstrated an extra-luminal biliary stent, along with localized free air and fluid in the right lower quadrant. The patient underwent emergency surgery. While bowel perforation due to stent migration is a rare complication in patients presenting with abdominal pain following ERCP, it should always be considered as a potential diagnosis.

Keywords: Biliary stents; intestinal perforation; stent migration

Introduction

The most commonly used method for treating obstructive jaundice caused by choledocholithiasis is therapeutic ERCP. The endoscopic transpapillary stenting method, first described in 1979, allows for the placement of a plastic stent in the common bile duct when necessary [1].

Endoscopic biliary stent placement is utilized for the management of both benign and malignant obstructive jaundice. Complication rates associated with endobiliary stents range from 8-10%, with a mortality rate of less than 1% [2]. The most common complications include stent occlusion and cholangitis [1, 2, 4, 5]. Other possible complications include cholecystitis, bleeding, duodenal perforation, pancreatitis, stent breakage, and stent migration.

Stent migration, reported in 5-10% of cases, may be distal or proximal [3, 6, 7]. While most migrated stents are naturally excreted, they can

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occasionally result in severe complications, including bowel perforation, intra-abdominal abscess, and ileus [3]. Proximal migration, where the stent moves deeper into the bile duct, can lead to biliary obstruction. Although challenging, such cases can typically be resolved endoscopically using tools like forceps, snares, or balloons.

In early distal migration, where the stent moves downward, repositioning via endoscopic intervention is often feasible. However, endoscopic management is generally limited to early or accessible cases. In most other instances, the stent may pass naturally through the intestinal tract, facilitated by bowel wall elasticity and contractions.

This report presents a rare case of stent migration resulting in intestinal perforation. While uncommon, intestinal perforation due to biliary stent migration should be considered a potential diagnosis in patients presenting with abdominal pain following biliary stent placement.

Case Presentation

An 85-year-old male presented to the emergency department with severe right lower quadrant abdominal pain, nausea, and vomiting lasting 24 hours. His medical history included an open appendectomy performed ten years ago, as well as diabetes, hypertension, cerebrovascular disease with mild sequelae, and benign prostatic hyperplasia. Two months prior, he had undergone an ERCP for primary choledocholithiasis, during which sphincterotomy was performed and a 10 Fr, 10 cm plastic biliary stent was placed in the common bile duct.

On admission, the patient exhibited tenderness in the right lower quadrant. He was normotensive with a blood pressure of 110/70 mmHg, a heart rate of 80 bpm, and was afebrile. Laboratory evaluation revealed no significant abnormalities in biochemical parameters, including normal bilirubin and liver function tests. His white blood cell count was slightly elevated at 12.57 x $10^3/\mu L$.

Initial diagnostic imaging included an upright plain abdominal radiograph, which revealed a biliary stent in the right lower quadrant and air-fluid levels in the small bowel (Figure 1). Abdominal CT further identified an extra-luminal biliary stent accompanied by localized free air and fluid between the ileal loops in the right lower quadrant (Figure 2). Based on these findings, the patient was taken to the operating room for emergency surgery.

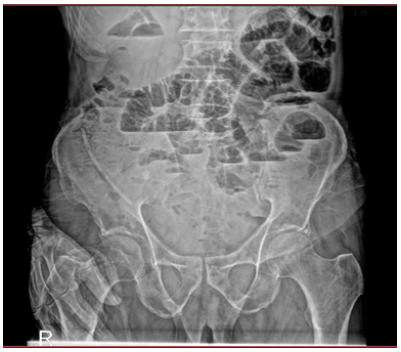

Figure 1: Abdominal radiography image at the time of admission to the emergency department.

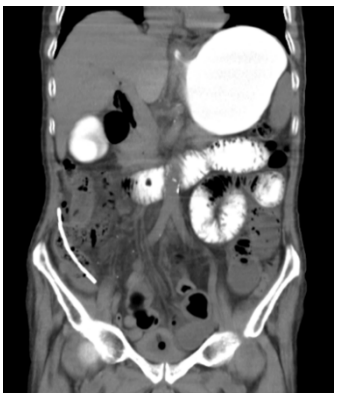

Figure 2: CT scan of plastic biliary stent perforating ileum.

Intraoperatively, dense adhesions resulting from the previous appendectomy were noted, causing the ileal loops to adhere to each other. The biliary stent had perforated the ileal wall approximately 60 cm proximal to the ileocecal valve and was lodged in the anterior abdominal wall (Figure 3). The proximal bowel loops were edematous and dilated; however, there was no evidence of diffuse intra-abdominal peritonitis.

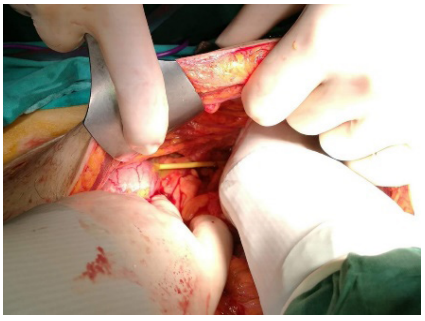

Figure 3: Intraoperative image after midline laparotomy

The biliary stent was successfully removed (Figure 4), and the perforation site was debrided and repaired using a double-layer closure technique. The adhesions were

carefully separated.

Figure 4: Biliary stent removed from ileum.

Postoperatively, the patient experienced an uneventful recovery. Oral intake was gradually advanced, and he was discharged on the fifth postoperative day with appropriate recommendations.

Discussion

It has been reported that intestinal perforation due to stent migration most commonly occurs with plastic stents, with the duodenum being the most frequent site of perforation [8]. In contrast, complications are rare with soft pigtail stents [9]. The incidence of distal bowel perforations beyond the ligament of Treitz is relatively low [10]. The risk of intestinal perforation from stent migration, which carries a mortality rate of 10.3%, is higher in patients with diverticular disease, adhesions, or hernias [6, 8, 10, 11]. Surgical stent removal is typically the primary treatment; however, endoscopic removal and mucosal repair have been successful in selected cases [8].

Given the potentially severe consequences of stent migration, biliary stenting should be reserved for cases where it is absolutely necessary. In elderly patients, especially those with risk factors, soft pigtail stents may be preferred over plastic biliary stents. Close monitoring of these patients is essential, and stents should be removed as early as possible to minimize complications.

Disclosures

Conflicts of interest

Authors have no conflicts of interest or financial ties to disclose.

Patient consent

Written informed consent was obtained from the patient.

Author contribution

Tekin O, Yildiz I, and Cakir C carried out the operation. Gungor M helped draft the manuscript. Sevik H collected all preoperative, perioperative, and postoperative data and wrote the manuscript.

References

1) Soehendra N, Reynders-Frederix V. Palliative bile duct drainage - a new endoscopic method of introducing a transpapillary drain. *Endoscopy*. 1980;12(1):8-11. doi:10.1055/s-2007-1021702

2) Jones M, George B, Jameson J, Garcea G. Biliary stent migration causing perforation of the caecum and chronic abdominal pain. *BMJ Case Rep*. 2013;2013:bcr2013009124. Published 2013 Sep 10. doi:10.1136/bcr-2013-009124

3) Mady RF, Niaz OS, Assal MM. Migrated biliary stent causing perforation of sigmoid colon and pelvic abscess. *BMJ Case Rep*. 2015;2015:bcr2014206805. Published 2015 Apr 13. doi:10.1136/bcr-2014-206805

4) Siaperas P, Ioannidis A, Skarpas A, Angelopoulos A, Drikos I, Karanikas I. A rare cause for Hartmann's procedure due to biliary stent migration: A case report. *Int J Surg Case Rep*. 2017;31:83-85. doi:10.1016/j.ijscr.2017.01.016

5) Rogart JN, Boghos A, Rossi F, et al. Analysis of endoscopic management of occluded metal biliary stents at a single tertiary care center. *Gastrointest Endosc*. 2008;68(4):676-682. doi:10.1016/j.gie.2008.03.1064

6) Riccardi M, Deters K, Jabbar F. Sigmoid Diverticulitis and Perforation Secondary to Biliary Stent Migration. *Case Rep Surg*. 2019;2019:2549170. Published 2019 May 19. doi:10.1155/2019/2549170

7) Arhan M, Odemiş B, Parlak E, Ertuğrul I, Başar O. Migration of biliary plastic stents: experience of a tertiary center. *Surg Endosc*. 2009;23(4):769-775. doi:10.1007/s00464-008-0067-x

8) Zorbas KA, Ashmeade S, Lois W, Farkas DT. Small bowel perforation from a migrated biliary stent: A case report and review of literature. *World J Gastrointest Endosc*. 2021;13(10):543-554. doi:10.4253/wjge.v13.i10.543

9) Virgilio E, Pascarella G, Scandavini CM, Frezza B, Bocchetti T, Balducci G. Colonic perforations caused by migrated plastic biliary stents. *Korean J Radiol*. 2015;16(2):444-445. doi:10.3348/kjr.2015.16.2.444

10) Brown D, Naidu J, Thomas R. Bowel perforation: a 'not so rare' complication of biliary stent migration. *ANZ J Surg*. 2021;91(12):E784-E786. doi:10.1111/ans.16902

11) Bagul A, Pollard C, Dennison AR. A review of problems following insertion of biliary stents illustrated by an unusual complication. *Ann R Coll Surg Engl*. 2010;92(4):W27-W31. doi:10.1308/147870810X12659688852239

CERASUS JOURNAL OF MEDICINE

CASE REPORT

A cause of bicytopenia in infancy: CMV

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Abstract

Bicytopenia is frequently observed in the pediatric population as a result of transient bone marrow suppression, which may occur following vaccination or as a consequence of viral infections, including influenza, Epstein-Barr virus (EBV), and cytomegalovirus (CMV). Symptoms of CMV infection, one of these agents, vary according to age and host immune competence. Although it is usually asymptomatic in healthy children, it can cause various infectious clinical presentations. In immunocompromised patients, it may cause pneumonia, retinitis, hepatitis, fever, thrombocytopenia, and leukopenia. Here, we present a four-month-old girl who was investigated for bicytopenia and subsequently diagnosed with CMV infection.

Keywords: cytomegalovirus; bicytopenia; neutropenia; thrombocytopenia

Introduction

Cytomegalovirus (CMV) belongs to the Herpes virus family and is also known as Human Herpes Virus-5 (HHV-5). The virus settles in endothelial cells, fibroblasts, myocytes, macrophage cells and remains latent. Transmission is possible through all body fluids such as respiratory droplets, urine, tears, breast milk and transplacentally [1]. Although the incubation period is four-six weeks on average, it can last up to four months. It may remain latent after viremia and show periodic reactivation especially when the immune system is suppressed [2].

Bicytopenia may occur due to benign and malignant causes and may be seen as a permanent or transient condition depending on the etiology. When studies in the field of pediatric bicytopenia are examined, etiologic causes including hematologic malignancies, aplastic anemias, secondary bone marrow suppression and megaloblastic anemia have been found with different frequencies in different studies [3–5].

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Case Report

A four-month-old girl presented with a rash on both feet and legs. It was learned that the rash started about 10 days ago, was rare on the dorsum of the feet in the first week, then progressed to the legs, there was no other symptom, the rash became more prominent and progressed to the upper parts of the legs, and the patient was referred to the hospital.

It was learned that our patient was born at term, had no hospitalization during or after the neonatal period, no prolonged jaundice, was breastfed only, used vitamin D drops, and received routine childhood vaccinations as well as the first doses of rotavirus and meningitis vaccines in accordance with her age.

Systemic examination of the patient revealed that pale red petechial eruptions on bilateral lower extremities and dorsum of the feet which did not fade with pressure. Complete blood count resulted as hemoglobin (Hb) 11,9 g/dL, white blood cell count (WBC) 8960/mm^3, absolute neutrophil count (ANC) 920/mm^3, platelet count (PLT) 82000/ mm^3 and peripheral blood smear, biochemistry, C-reactive protein (CRP), iron parameters, vitamin B12, thyroid function tests (TFT), Epstein-Barr virus (EBV) and CMV were then sent for etiologic investigation. No atypical cells were seen in the peripheral blood smear. Aspartate aminotransferase (AST) 78 U/L, alanine aminotransferase (ALT) 53 U/L, CRP negative, ferritin-vitamin B12-TFT were in normal range, EBV negative and CMV IgM 1.58, CMV IgG 21.94 were detected. CMV Polymerase Chain Reaction (PCR) was analyzed from serum due to CMV IgM positivity. 223 copies/ml was detected. Complete blood count taken at the 5th week after the onset of complaints showed Hb 11,5 g/dL, WBC 7560/mm^3, ANC 620/mm^3, PLT 93000/mm^3, AST 55 U/L, ALT 41 U/L. Although biochemistry parameters normalized, bicytopenia still persists. We followed up our patient with weekly complete blood count and bicytopenia was etiologically attributed to CMV.

Discussion

Peripheral cytopenia is defined as a decrease in blood cells (erythrocytes, leukocytes or platelets). Although it varies according to age, on average, Hb <11 g/dL, ANC <1000-1500/mm^3 and platelet count <150 000/ mm^3 is considered low. Bicytopenia is a decrease in two different cell series. Its etiology shows a wide distribution. It may be due to bone marrow suppression especially as a result of viral infection or may develop as a result of bone marrow suppression due to malignancy, drugs, vaccines, chemotherapy or radiotherapy [3,4,6]. Viral infections including influenza, varicella, measles, rubella, hepatitis A and B, CMV, EBV, parvovirus B19, adenovirus, and coxsackie may cause neutropenia and thrombocytopenia by decreasing production and increasing destruction [7,8].

Though acquired CMV usually proceeds with asymptomatic viremia in healthy people, it may progress critically in newborns, premature infants, adolescents, and children with immunosuppression. In immunosuppressed patients, it may progress with findings such as fever, leukopenia, thrombocytopenia, increased liver enzymes and atypical lymphocytosis [1]. Congenital CMV may progress with findings like sepsis, pneumonia, prolonged jaundice, hepatosplenomegaly, petechiae-purpura, periventricular calcification, chorioretinitis, sensorineural hearing loss and cytopenia in preterm infants. We didn't consider late presentation of congenital CMV in our patient because he had no history of prolonged jaundice or hospitalization in the neonatal period, no hepatosplenomegaly, normal complete blood count in the neonatal period, passed hearing test, no microcephaly and normal neurodevelopment.

Acquired CMV infection in healthy individuals doesn't require antiviral therapy, but only symptomatic supportive treatment and follow-up is sufficient. However, in congenital CMV infection, antiviral agents including valganciclovir, ganciclovir, foscarnet, and cidofovir are used in case of immunosuppression and cranial system effects including chorioretinitis and periventricular calcification [1]. Our patient was in the group who did not require treatment because we didn't think of congenital CMV or because she did not have immunosuppression.

The onset of our patient's symptoms shortly after the fourth-month vaccination initially suggested vaccination-related bone marrow suppression, however the positive CMV PCR results shifted the diagnosis towards bone marrow suppression secondary to CMV infection. The PCR copy number was not high enough, but we attribute this to the fact that one month had passed since the initial complaints and the viral load had decreased when the sample was taken for PCR.

As a result, CMV is a highly asymptomatic agent in healthy children unlike other viral infections, we recommend screening for CMV in cases of bicytopenia even if the clinical findings are inconsistent.

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References

1. Plosa EJ, Esbenshade JC, Fuller MP, Weitkamp JH. Cytomegalovirus infection. *Pediatr Rev*. 2012;33(4):156-163. doi:10.1542/pir.33-4-156

2. Kimberlin D.W.(Editor) Red Book Atlas of Pediatric Infectious Diseases. American Academy of Pediatrics; 2018-2021.

3. Vijayakrishnan, G., Thambi, R., & Sankar, S. A. (2020). year study of clinico-hematological profile of bicytopenia and pancytopenia in paediatric patients attending a tertiary hospital in South India. *IJPO*, *7*, 207-11.

4. Singh S, Roach V, Katoch P. Clinico Haematological Profile in Paediatric Patients with Bicytopenia and Pancytopenia in a Tertiary Care Referral Centre of North India. *Journal of Advances in Medicine and Medical Research*, 2021; *33*(18): 57-63.

5. Kumar G, Verma S, Chavan S, Gupta A, Avuthu OPR, Mane S, Pathak N. Study of Clinicoetiological Spectrum of Bicytopenia and Pancytopenia in Hospitalized Children. *Cureus*. 2024; *16*(8); e66255.

6. Yalaki Z, İçöz S, Arikan FI, Alioglu B, Dallar YB. Our Experience with Bicytopenia in Patients Treated at the Ankara Hospital Pediatric Clinic. *J Pediatr Inf*. 2014; *8*(1): 23.

7. Celkan T, Koç BŞ. Approach to the patient with neutropenia in childhood. *Turk Pediatri Ars*. 2015;50(3):136-144. Published 2015 Sep 1. doi:10.5152/TurkPediatriArs.2015.2295

8. Tokgöz H,Çalışkan Ü. Hematologic manifestations of infectious diseases in children. *Selçuk Tıp Dergisi*. 2017; *33*(3): 63-66.