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# LABOR ANALGESIA – YESTERDAY, TODAY, TOMORROW

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The pain during childbirth, as one of the greatest pains in life and pain relief during that intense pain, have their own rich history. That history is a fascinating intersection of medicine, culture, religion and women's rights.

In 1847 Dr. James Young Simpson administered ether to a woman with a deformed pelvis during childbirth which is a huge step forward in the progress of Western civilization (1). Few years later John Snow successfully administered chloroform to Queen Victoria during the birth of her eighth child, Prince Leopold. Although controversial due to moral and religious objections, these represent the beginning of the modern era of obstetric anesthesia. The development of neuraxial anesthesia in obstetrics dated back to the late 19th century with the intrathecal use of cocaine, the first epidural catheter appeared in the 1930s, in the 1960s - 70s epidural analgesia gained popularity, and since the 1980s, it has experienced a real boom (2). Opioids have been used in obstetrics for over 100 years; the beginnings are with a mixture of morphine and scopolamine called "twilight sleep" (3), and since the 1950s, meperidine-pethidine has been used. Opioids such as fentanyl and alfentanil have proven to be insufficiently good in the past due to insufficient analgesia and prolonged concern for the health of the newborn (4). The emergence of remifentanil in the 1990s opened a new opportunity for intravenous labor analgesia.

Today, the goal of modern obstetric anesthesia is to offer the mother safe and effective pain relief during labor, focusing on the mother's wishes and, above all, her well-being. Obstetric anesthesia goes far beyond just pain relief and anesthesia during labor. Day by day obstetric anesthesiologists increasingly provide high-quality obstetric care for both healthy and high-risk obstetric patients. Neuraxial techniques are the most effective and commonly used techniques for analgesia during labor. Epidural analgesia is the gold standard for analgesia in obstetrics. In addition to epidural analgesia, combined spinal epidural (CSE) and the recently popular dural puncture epidural (DPE) techniques, are also very commonly used and are particularly suitable for conversion to anesthesia for cesarean section (5,6). Spinal techniques (single-shot spinal technique and continuous spinal) provide a faster onset of analgesia, excellent analgesia, including sacral analgesia, but are used less frequently because of their short duration of action. In addition to neuraxial anesthesia techniques, there are many alternative methods. These methods can provide some degree of analgesia, with moderate maternal satisfaction, they are much less invasive but have their own side effects (mostly sedation and respiratory depression). These methods can be particularly useful for patients in whom neuraxial techniques are contraindicated or unavailable. Pharmacological methods include fentanyl, meperidine, mixtures of oxygen and nitrous oxide, and more and more popular remifentanil (7). There are also non-pharmacological options for pain relief during labor that are widely supported in holistic and obstetric models of care.

The future of obstetric anesthesia is likely to focus on safety, personalization, less invasiveness, widespread availability, and increased use of technology. What we can expect in the future are:

portable analgesia devices in underdeveloped regions for global availability of painless childbirth; a personalized approach to each patient in terms of their genetic characteristics and individual needs; the development of non-opioid analgesics for fewer side effects for both the mother and the newborn and the integration of nanotechnology with anesthesia for more precise, personalized, long-lasting, and safer control of labor pain (8). And finally, labor analgesia using artificial intelligence (AI): whether it is computer software when placing central neuraxial blocks or the use of artificial neural networks in predicting the correct interval and the correct dose for breakthrough pain during maintenance of labor with epidural analgesia or prediction of nausea and vomiting and other side effects or early identification of patients who may develop complications in the postoperative period, etc (9).

The future ahead is sure to be dynamic and innovative. Developing ethical frameworks for the use of AI in healthcare is equally important to ensure the safe and responsible use of AI. But what we should never forget is that AI greatly assists but does not eliminate the need for a trained obstetric anesthesiologist. At least for now...

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# IMPLEMENTATION OF P16/KI67 DUAL STAINING CYTOLOGY FOR DETECTING CERVICAL DYSPLASIA

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## Abstract:

Cervical cancer is the fourth most common cancer among women worldwide. Vaccination against oncogenic human papillomaviruses (HPV) and effective screening have made cervical cancer preventable. Current screening methods, including cytology, HPV testing, and a combination of both, have limitations, highlighting the need for additional markers to identify high-grade cervical lesions (CIN2+).

p16/Ki67 dual immunocytochemistry staining is a biomarker with high sensitivity and specificity for detecting CIN2+ lesions. Incorporating this biomarker in triage, alongside cytology and HPV testing, can help avoid unnecessary referrals for colposcopy and biopsy.

This study, conducted at the University Clinic for Gynecology and Obstetrics in Skopje over a one-year period, involved 40 female patients aged 21 to 65 years, all of whom underwent HPV DNA testing, cytological testing (LB) and p16/Ki67 dual staining. The study found a significant association between High-Grade Squamous Intraepithelial Lesion (HSIL) and p16/Ki67 dual staining (p=0.012), while no significant association was observed between Low-Grade Squamous Intraepithelial Lesion (LSIL) and p16/Ki67 staining (p=1.0).

***Key Words****: cervical dysplasia*; *HPV; immunocytochemistry; p16/Ki67.*

## Introduction

Cervical cancer is the fourth most common malignant tumor in women globally and remains a major public health challenge, particularly in low- and middle-income countries (1). In 2020, 604,000 women were diagnosed with cervical cancer, and 342,000 died from it (2). However, vaccination against high-risk human papillomaviruses (HPV) and effective screening have made the disease mostly preventable (3).

The World Health Organization (WHO) launched a global initiative in 2020 to eliminate cervical cancer, aiming to bring its incidence below 4 cases per 100,000 women annually in all countries (1,4). The WHO's 90–70–90 target to be achieved by 2030, is for 90% vaccination of girls by age 15, 70% screening of women with high-performance tests at least twice by age of 45, and 90% treatment of women diagnosed with cervical precancer or invasive cancer (1,4).

In the Republic of North Macedonia, cervical cancer continues to be a significant concern. The incidence was 7 per 100,000 women in 2020, with 68 deaths in 2019 (5). The disease is most

commonly diagnosed in women aged 35 to 44 years, with a mean age of diagnosis at 50 years. Notably, over 20% of cases occur in women older than 65 years (6).

Cervical cancer primarily develops because of chronic infection with high-risk HPV types, especially HPV 16 and HPV 18, which are responsible for 70% of cervical cancers worldwide (7,8). While the most of HPV infections resolve within one to two years without developing cancer, chronic infections can cause precancerous lesions that, if untreated, may progress to invasive cancer (9). Risk factors for cervical cancer include the oncogenic potential of the HPV type, immune status, sexually transmitted infections, parity, early pregnancy, hormonal contraceptive use and smoking (10).

Chronic HPV infection contributes to carcinogenesis via the E6 and E7 proteins, which deregulate the cell cycle (11). Abnormal cervical cells typically take 15–20 years to develop into cancer, though in immunocompromised patients, e.g., untreated HIV infection, this will be sooner (10). Screening for cervical cancer has traditionally relied on cytology, either conventional (CC) or liquid-based (LBC). As the most of cervical cancers result from persistent high-risk HPV infection, many countries have implemented HPV DNA screening as the primary test (8). The WHO recommends HPV DNA testing as a primary screening method, with partial genotyping for HPV 16 and 18, cytology or colposcopy for triaging positive patients (12).

The WHO also recommends HPV DNA testing as the primary screening test for both the general female population and HIV-infected women (12). In places where HPV DNA screening is not yet feasible, the WHO suggests regular screening every 3 years using cytology or colposcopy as the primary test for both the general population and women living with HIV (5).

While cytology is very specific, it is not sensitive, resulting in large number of false-negative results (13,14). On the other hand, HPV DNA testing, is very sensitive (around 90%) but not specific, which can lead to unnecessary referrals to colposcopy or biopsy, particularly in younger women. Therefore, more effective triage markers are needed to identify women at higher risk for CIN2+ lesions despite normal cytology (15,16).

p16/Ki67 dual cytological staining is a promising triage test that is highly sensitive and specific for detecting high-grade cervical lesions (17).

p16 inhibits cyclin-dependent kinases and regulates the cell cycle, while Ki67 is a marker of cell proliferation (13,17). The co-expression of these proteins indicates cell cycle deregulation and can predict the development of high-grade lesions (13).

This study aims to explore the correlation between p16/Ki67 immunocytochemical status and cytologically verified squamous intraepithelial lesions.

## Materials and Methods

This study was conducted over a one-year period and involved 40 patients, aged between 21 and 65 years. All the patients underwent HPV DNA testing with typing, cytological testing (Liquid-Based Cytology or LBC), and p16/Ki67 dual cytological staining. Only patients who tested positive for high-risk HPV types during screening were included in the analysis, regardless of whether they had cytologically confirmed lesions. The study took place at the University Clinic

of Gynecology and Obstetrics in Skopje, and all cytological tests (LBC) and p16/Ki67 immunocytochemical staining were performed in the University Cytology Laboratory.

Liquid-Based Cytology (LBC) was used for sample collection in this study. In this method a sample is obtained using a brush, which is placed in a liquid medium. The cervical smears are classified according to the Bethesda system (2001).

For p16/Ki67 dual cytological staining, the CINtec® PLUS cytology kit was used to detect cells with neoplastic transformation by identifying the presence of both p16 and Ki67 proteins. A positive test result is indicated when at least one cervical epithelial cell shows brown cytoplasm and a red-stained nucleus.

HPV DNA testing was performed using real-time multiplex PCR assays. The extracted DNA samples undergo real-time PCR amplification using commercial kits that allow simultaneous detection and differentiation of DNA from 19 high-risk HPV types (hrHPV: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82) and 9 low-risk HPV types (lrHPV: 6, 11, 40, 42, 43, 44, 54, 61, 70), along with an internal control.

The participants were selected based on specific inclusion and exclusion criteria. The inclusion criteria were the following: patients aged 21 to 65 years, patients with cytologically confirmed low- or high-grade squamous intraepithelial lesions (LSIL or HSIL) who tested positive for high-risk HPV types via HPV DNA testing, and patients who tested positive for high-risk HPV (HR-HPV) DNA but had normal cytology results. The exclusion criteria included patients with low-risk HPV types and patients diagnosed with invasive cervical cancer on clinical examination, regardless of cytological findings.

The patients were divided into three groups. One group consisted of patients who tested positive for HR-HPV DNA but negative for cytology. The second group consisted of patients who tested positive for HR-HPV DNA and had a cytological diagnosis of LSIL. The third group consisted of patients who tested positive for HR-HPV DNA and had a cytological diagnosis of HSIL

## Results

**Table 1.** Total Number of p16/Ki67 Immunocytochemistry Positive Patients.

| Category | Frequency of p16/Ki67 Immunocytochemistry | |
|---|---|---|
| | No. | Percentage |
| Positive | 6 | 15% |
| Negative | 34 | 85% |

A total of 40 patients with high-risk HPV were included in the study, out of which 6 patients were positive for the p16/Ki67 dual cytological staining, while the remaining 34 were negative.

**Table 2 & 3.** Average Age of Patients.

| No. | Average Age | Minimum age | Maximum age | Std. Dev. |
|---|---|---|---|---|
| 40 | 34 | 21 | 65 | 11.03607 |

| p16/Ki67 | No. | Average Age | Std. Dev. |
|---|---|---|---|
| Positive | 6 | 35.5000 | 15.65567 |
| Negative | 34 | 33.7353 | 10.31124 |

The average age of the patients included in the study is 34 years. The average age of patients who were positive for dual cytological staining is 35.5 years, while for the negative patients, it is 33.7 years. The value of the Independent Samples Test T-test is 0.58 > p 0.05.

**Table 4.** Representation of Cytological Findings

| Category | No. | Percentage |
|---|---|---|
| Low-Grade Squamous Intraepithelial Lesion (LSIL) | 26 | 65% |
| High-Grade Squamous Intraepithelial Lesion (HSIL) | 2 | 5% |
| Negative PAP Test | 12 | 30% |

Out of the 40 patients, who underwent LBC cytology, Low-Grade Squamous Intraepithelial Lesion (LSIL) was detected in 26 patients (65%) and High-Grade Squamous Intraepithelial Lesion (HSIL) was detected in 2 patients (5%).

**Table 5.** LSIL/HSIL - p16/Ki67 Co-distribution

| LBC | | Immunocytochemistry Positive for p16/Ki67 | Immunocytochemistry Negative for p16/Ki67 | Total |
|---|---|---|---|---|
| HSIL | **No.** | 2 | 0 | 2 |
| | **%** | 33.33% | / | |
| LSIL | **No.** | 4 | 22 | 26 |
| | **%** | 66.67% | 64.71% | |
| Negative PAP test | **No.** | 0 | 12 | 12 |
| | **%** | / | 35.29% | |
| **Total** | | 6 | 34 | 40 |

In the group of patients with LSIL obtained by LBC cytology, out of a total of 26 patients, 4 patients were positive and 22 were negative for the p16/Ki67 dual cytological staining. This subgroup accounts for 66.7% of the total number of positive patients for the dual staining. In the patients with LSIL, 15.4% were positive for the p16/Ki67 dual staining test.

In the group of patients with HSIL obtained by LBC cytology, out of a total of 2 patients, both were positive for the p16/Ki67 dual cytological staining, which corresponds to 33.3% of the total number of patients who were positive for dual cytological staining. Among the patients positive for HSIL, 100% were also positive for the dual cytological staining test.

## Discussion

The study included 40 patients who were positive for high-risk HPV. Among these, 6 (15%) were positive for the p16/Ki67 dual cytological staining, and 34 (85%) were negative. The aver-

age age of patients was 34 years, with the positive group averaging 35.5 years and the negative group 33.7 years. However, the T-test result ($p = 0.58$) indicated no statistically significant age difference between the groups.

Cytological findings showed that LSIL was present in 65% of the patients, HSIL in 5%, and 30% had a negative PAP test. All patients with HSIL were positive for p16/Ki67, indicating a strong correlation between this biomarker and high-grade lesions. In contrast, among LSIL cases, only 15.4% were p16/Ki67 positive, and this association was not statistically significant (Fisher's exact test, $p = 1.0$).

Due to this discrepancy between LSIL findings and p16/Ki67 immunocytochemical staining, there is a risk of missing CIN2+ lesions in these patients. This highlights the need for introducing an additional method to verify precancerous lesions and cervical cancer.

These findings support the diagnostic value of p16/Ki67 dual staining in identifying high-grade cervical lesions. Its use could help triage women more effectively, reducing overtreatment in low-risk cases while ensuring timely intervention for those at greater risk.

## Conclusion

This study demonstrates a strong association between p16/Ki67 dual immunocytochemical staining and high-grade cervical lesions- HSIL. These findings support the use of p16/Ki67 as an adjunctive tool to improve the accuracy of cervical cancer screening and aid in the early identification of high-risk cases. Further research should aim to validate these results through histological correlation to strengthen its clinical utility.

## Acknowledgements

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# CAN AN M-HEALTH APPLICATION IMPROVE THE BLOOD PRESSURE CONTROL IN NEWLY DIAGNOSED PATIENTS WITH ARTERIAL HYPERTENSION?

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## Abstract

**Introduction.** Hypertension is a leading cause of overall morbidity and mortality worldwide. The use of telemonitoring opens new opportunities for close monitoring of patients with hypertension through self-monitoring of blood pressure at home and timely transfer of these to primary care physicians.

**Objective.** To assess the effect of using an mHealth application in improving blood pressure control in patients with newly diagnosed hypertension.

**Methods and materials.** Results from the first 6 months of a prospective randomized controlled multicenter trial with 12-months follow-up of newly diagnosed patients with hypertension. The intervention group received standard care + mHealth app, while the control group received standard care alone. The study monitored ambulatory blood pressure measurements at 0, 1, 3, 6 and 12 months.

**Results.** 95 participants in the intervention group and 97 in control group were recruited. In terms of systolic blood pressure values after 6 months, a decrease in the average systolic blood pressure was observed in both groups, with a decrease in the average by 22mmHg in the intervention, i.e. 20mmHg in the control group with a difference of 2mmHg in favor of the intervention group. A reduction in the average diastolic bood pressure of 13.4mmHg occurred in the intervention, i.e. 12.75mmHg in the standard care group, with a difference of 0.65mmHg in favor of the intervention group.

**Conclusion.** An mHealth application that enables two-way patient-physician communication is an auxiliary tool to standard care that may improve blood pressure control in newly diagnosed patients with hypertension.

***Key Words:*** *Family doctor; hypertension; mHealth application; self-monitoring.*

## Introduction

Hypertension (HTN) is a global public health problem and a leading cause of overall morbidity and mortality worldwide (1,2). In 2023, 1.28 billion of the world's population were diagnosed

with HTN (1,2). and the prevalence is expected to reach 1.56 billion diagnosed patients in 2025 (3,4). According to the WHO report (5), in the Republic of North Macedonia (RNM) in 2019, the prevalence of diagnosed patients with HTN was 45%, of which 49% were male patients and 51% were female (6). Oot of these, 52% were patients prescribed with antihypertensive therapy, but only 23% of them managed to achieve good BP control (7).

Untimely diagnosed, untreated and/ or poorly managed hypertension is a direct cause of cardioe vascular diseases (cerebrovascular stroke, myocardial infarction, heart failure, blindness, sexual dysfunction and chronic renal failure) (8). High blood pressure (BP) has a negative impact on the microcirculation and macrocirculation in organs with low resistance, such as the brain, kidneys, heart, eyes and blood vessels, which undergo corresponding anatomical and functional changes. Levingston et al., in a prospective study, showed that for every 20mmHg increase in ambulatory measured systolic blood pressure (SBP) or 10mmHg increase in diastolic blood pressure (DBP), the risk of fatal coronary arterial disease or stroke doubles (9). Reducing BP can significantly reduce overall premature morbidity and mortality (10). In a randomized study of intensive versus standard BP control (SPRINT study), it was shown that intensive BP control to target values for SBP<120mmHg compared to the standard target of SBP <140mmHg reduces the risk of cardiovascular diseases (CVD) by 25%, all-cause mortality by 27% and acute decompensation of heart failure by 36% (11,12). In contrast, Sobieraj et al., in a post-hoc analysis of the research data, showed that achieving low values for DBP had no significant effects on reducing CV risk (13). In the latest recommendations of the European Society of Cardiology (ESC) from 2024, the target values for blood pressure in patients with HTN are 120-129 for SBP and 70-79mmHg for DBP or, if this is not possible, the lowest value that can be reasonably achieved and is tolerable for the patient (14). According to these recommendations, the general practitioner/ family doctor, when diagnosing and also when managing patients with hypertension, needs to make an individualized plan for managing hypertension, which would lead to faster achievement of target values for BP and reduction of CVD risk. Proactive management of HTA also includes structured control examinations aimed at, through a holistic approach, the values obtained from the measured BP and appropriate investigations to promptly intensify therapy and achieve targeted treatment goals in a timely manner. Home BP monitoring for hypertension management is recommended as an intervention to achieve better BP control (Class 1, Level of Evidence B, ESC, 2024) (14). There are over 50 trials of different interventions based on self-monitoring (15). Self-monitoring of BP is associated with lower mean SBP at 12 months [-3.2 mmHg; 95% confidence interval (CI) -4.9 to -1.6 mmHg] (16).

In the past few years, there has been an increase in the use of mobile health (mHealth) applications within mobile technology, in the diagnosis and monitoring of many chronic non-communicable diseases (17,18) including hypertension (19). However, mHealth applications cannot provide independent monitoring of patients with HTN, i.e. they should be used as an auxiliary tool to standard care, regulated by the guidelines for managing HTN (20).

Purpose of this paper is to evaluate the effectiveness of an mHealth application in improving blood pressure control in patients with newly diagnosed hypertension.

## Method and Materials

The study was designed as a prospective randomized controlled multicenter study with 12-months follow-up of newly diagnosed patients with HTN (2023/2024), followed by 19 fami-

ly physicians on the territory of the RNM. This paper presents the initial results of a analysis of the BP control in the first 6 months from the beginning of the study.

The sample of family physicians was determined by fulfilling the following criteria. Inclusion criteria: ≥500 family patients aged 35-70 years, possessing ≥1 computer (with at least Windows 7), stable internet connection, desire and signed consent to participate in the study. Exclusion criteria: doctors who are mutual substitution in patients' care according to an agreement with the Health Insurance Fund of RNM (HIFRNM), (because a patient in RNM can receive health-care from their primary care physician and their official replacement in the HIFRNM, and very often the doctors who are replacing each other work in the same clinic. For this reason, the doctors who are replacing each other cannot enter the study together, because it is impossible to follow the protocol, and it also challenges the protection of personal data), lack of readiness and desire to participate in the study. Since this was a multicenter study at the level of the entire territory, in order to achieve equal representation of patients, we invited 2 family doctors from each region (a total of 8 regions), with the exception of the city of Skopje, where we invited 6 family doctors. As a model for determining the number of doctors, we used the official division by statistical regions from the State Statistical Office of RNM (21).

Participants were required to meet the following criteria - Inclusion criteria: newly diagnosed patients with HTN (ambulatory measured SBP ≥140mmHg and/or DBP ≥90mmHg) age 35-70 years, possession of a smartphone, having a standardized semi-automatic or automatic sphygmomanometer, willingness and desire to participate in the study. Exclusion criteria: comorbidities (heart failure, chronic renal failure, hepatic failure, malignant diseases, secondary hypertension), pregnancy, cognitive diseases or problems with understanding instructions and patients who would not sign an informed consent.

For the included family physicians for each region, a 1:1 randomization was performed, through simple random selection, i.e., physicians who lead an intervention (IG) or control group (CG) from each region were included. Patients who met the criteria belonged to the IG, i.e. CG, according to the distribution by group of the family doctor who assigned the patient. Patients in the IG received standard care & mHealth application, while those in the CG received standard care only. The blood pressure was measured with clinically validated upper arm blood pressure monitor - Omron M2, for the participants in the both groups at baseline, 1, 3, 6 and 12 months after inclusion in the study. The patients were informed of the entire protocol upon entry into the study by their primary care physicians and signed an informed consent. Upon entry into the study, the participants from both groups were educated by their physicians about: technique for correct blood pressure measurement with an upper arm sphygmomanometer and planned examinations as part of standard care. Additionally, the participants from IG were educated about self-monitoring of BP at home and entering BP and pulse values into the mHealth application and using SMS messages within the application itself.

The target values for good blood pressure control in the patients with hypertension were <130mmHg for SBP and <80mmHg for DBP, according to the latest recommendations of ESC, 2024 (14).

## Intervention Description

The mHealth application was created with the support of the software company "Angor AG" Struga, RNM and consisted of 2 parts: a mobile application for patients and a program with a

database for family doctors involved in the study.

The mobile application consisted of 3 parts: a part where the patient entered the measured values for BP and pulse, a part intended for two-way exchange of messages between the doctor and the patient in 2 forms: an info message, a message with an attached document and an informational part for the patient with access to a video link for the technique of correct BP measurement with a document for a hygiene-dietary regimen and appropriate physical activity. The mobile application was installed on the mobile smartphone of the patient included in the intervention group and it was activated by the family doctor with the patient's mobile phone number.

The program with the database for doctors consisted of 3 parts: a part with patients' data, a part for monitoring the measured values for BP and pulse that the patient entered in his application, and a part intended for two-way exchange of SMS messages between the doctor and the patient in 3 forms: info message, message with attached document and message with warning (for high BP, change of therapy or calling the patient to the outpatient clinic). Entry into the program was possible only with a special code and password provided for each doctor in order to protect patients' data. Participants from the intervention group on day zero received education on downloading and activating the application on the patients' mobile phone and training on its use for entering measured BP values at home. Patients also received a short leaflet on the frequency of entering measured BP values.

## Statistical Analysis

The data obtained with the research were processed in the SPSS software package, version 26.0 for Windows. The analysis of the qualitative series was done by determining the coefficient of relationships, proportions and rates, and they were displayed as absolute and relative numbers. The numerical (quantitative) series were analyzed with the measures of central tendency (average, median, minimum values, maximum values, ranks), as well as measures of dispersion (standard deviation and standard error). Pearson Chi square test, Post Hoc Test, Wilcoxon Signed Ranks Test, Fischer exact test and Fisher Feeman Halton exact test were used to determine the association between certain attributive dichotomous traits. Difference test was used to compare proportions.

## Results

According to the inclusion and exclusion criteria, the study included a total of 192 (100%) patients with HTN who were divided into intervention (n=95) and control group (n=97) using a simple random selection method. The recruitment period lasted approximately 9 months (February/ September 2023). The patients in the IG group received standard care + mHealth application, while those in the CG group received only standard care. The study assessed the effect of using the mHealth application in achieving targeted BP values. After 6 months of follow-up, 92 participants from the IG (2 patients from the Skopje region and 1 patient from the Polog region voluntarily left the study) and 96 participants (1 patient from the Polog region voluntarily left the study) from the CG remained included in the study and continued with follow-up until the completion of the entire 12-month protocol.

Regarding the gender distribution of 95 (100%) patients from the IG, it indicated the presence of 46 (48.42%) men and 49 (51.58%) women. In the CG out of a total of 97 (100%) patients, the presence of males and females was consistently 51 (52.58%) vs. 46 (47.42%). No significant association was found between the gender of the patients included in the study and the group to which they belonged (Pearson Chi-square test=0.332; df=1; p=0.5647). The mean age of the IG patients was 49.53±8.90 [95% CI (47.71–51.34)] years with an age range of 35/ 70 years. The CG patients had a mean age of 48.43±7.30 [95% CI 46.96–49.90)] years with an age range of 35/ 66 years. There was no significant difference between patients from the two groups (IG/KG) in terms of age (Mann-Whitney U Test: Z=(-0.619; p=0.5356). The proportion of participants from urban or rural areas in the entire research sample was consistently 126 (65.63%) vs 66 (34.38%). In both the IG and the CG, the majority of patients lived in urban areas, consistently 56 (58.95%) vs 70 (72.16%). 39 (41.05%) of the patients in the IG and 27 (27.84%) of those in the CG lived in rural areas. There was no significant association between the place of residence (village/ city) and the group to which the patients belonged for the Pearson Chi-square test: X2=3.717; df=1; p=0.0539.

In both groups of patients, IG and CG, an analysis was performed regarding the values of SBP and DBP (mmHg) at 4 follow-up times: zero time, 1, 3 and 6 months after the intervention.

The analysis of the distribution of the values obtained for SBP expressed in mmHg at each of the 4 follow-up times (zero, 1, 3 and 6 months after the intervention) indicated an irregular distribution of frequencies for: a) 0 time - Shapiro-Wilk W=0.8134; p=0.00001; b) 1 month - Shapiro-Wilk W=0.8832; p=0.00001; c) 3 months - Shapiro-Wilk W=0.9603; p=0.0057 and 6 months - Shapiro-Wilk W=0.9439; p=0.00062. According to the obtained distribution for SBP, appropriate tests were applied in the analysis. The values obtained for SBP were compared at each of the 4 measurement times, both intragroup and intergroup in IG and CG. Intragroup comparisons were made for SBP values in each of the two groups individually for the 4 follow-up times. In both groups, IG and CG, a significant decrease (Friedman Test: Chi-Square) in SBP was observed between the 4 follow-up times, with the highest value at time zero before the intervention and the lowest average value at 6 months after entering the study.

**Table 1.** Intragroup comparison of systolic blood pressure at four times.

| Intragroup Analysis | SBP (mmHg) | | | | | p |
|---|---|---|---|---|---|---|
| | Number (N) | Mean± SD | (Min/ Max) | Median (IQR) | Mean Rank | |
| **Intervention group - IG** | | | | | | |
| "0" time | 95 | 151±12.27 | 130/ 200 | 148 (144-157) | 4.95 | Chi-Square (92)=212.89; df=4; p=0,0001* |
| 1 month | 95 | 133±12.99 | 112/ 190 | 130 (125-140) | 3.05 | |
| 3 months | 95 | 129±9.49 | 110/ 160 | 130 (122-135) | 2.47 | |
| 6 months | 92 | 129±9.18 | 110/ 160 | 130 (120-137) | 2.59 | |
| **Control group-CG** | | | | | | |
| "0" time | 97 | 152±11.32 | 128/ 193 | 150 (145-160) | 4.71 | Chi-Square (96)=234,90; df=4; p=0,0001* |
| 1 month | 97 | 142±11.81 | 110/ 180 | 140 (135-150) | 3.56 | |
| 3 months | 97 | 137±9.24 | 110/ 160 | 135 (130-142) | 2.84 | |
| 6 months | 96 | 132±10.38 | 85/ 180 | 130 (130-140) | 2.18 | |
| IQR = 25th – 75th percentiles; Friedman test; *significant p<0.05 | | | | | | |

To determine the reason for the significance of the differences between the SBP values, in each of the groups individually, Post Hoc Test analysis was applied. The differences in 6-time combinations were analyzed by testing with Wilcoxon signed rank test. In order to avoid Type 1 error, according to the Bonferroni correction, for the interpretation of the obtained results, a significant level of p<0.01 was accepted (Table 1-2).

In the IG, the average SBP was highest at the time 0 before the intervention and was 151±12.27mmHg with a min/max value of 130/200mmHg. In the post-intervention follow-up period, the average SBP value gradually decreased with the lowest average value after 6 months, namely 129±9.18mmHg with a min/max value of 110/160mmHg. A significant difference was found between the 4 measurement times in terms of the value for the SBP (Friedman Test: Chi-Square (92)=212.89; df=4; p=0.0001) (Table 1).

**Table 2.** Comparison of systolic blood pressure in six time combinations – IG/CG.

| Intervention group | SBP (mmHg) | | | | | |
|---|---|---|---|---|---|---|
| | 1month/ 0 time | 3 months/ 0 time | 6 months/ 0 time | 3 months / 1 month | 6 months / 1 month | 6 months / 3 months |
| Z | (-8.243)[c] | (-8.379)[c] | (-8.258)[c] | (-3.824)[c] | (-2.836) | (-0.238)[c] |
| Asymp. Sig. (2-tailed) | 0.0001* | 0.0001* | 0.0001* | 0.0001* | 0.005* | 0.812 |
| Change confirmed | SBP1<SB P0 -90<br>SBP1>SB P0 -0<br>SBP1=SB P0-5 | SBP3<SB P0 -93<br>SBP3>SB P0-0<br>SBP3=SB P0 -2 | SBP6<SB P0-90<br>SBP6>SB P0-1<br>SBP6=SB P0 -1 | SBP3<SB P1-55<br>SBP3>SB P1-27<br>SBP3=SBP1-13 | SBP6<SB P1-56<br>SBP6>SB P1-27<br>SBP6=SB P1-9 | SBP6<SB P3 -31<br>SBP6>SB P3-39<br>SBP6=SB P3 -22 |
| Control group | 1month/ 0 time | 3 months/ 0 time | 6 months/ 0 time | 3 months / 1 month | 6 months / 1 month | 6 months / 3 months |
| Z | (-7.116)[c] | (-7.994)[c] | (-8.094)[c] | (-4.668)[c] | (-6.102) | (-4.104)c |
| Asymp. Sig. (2-tailed) | 0.0001* | 0.0001* | 0.0001* | 0.0001* | 0.0001* | 0.001* |
| Change confirmed | SBP1<SB P0 -81<br>SBP1>SB P0 -9<br>SBP1=SB P0-7 | SBP3<SB P0 -86<br>SBP3>SB P0-5<br>SBP3=SB P0 -6 | SBP6<SB P0-88<br>SBP6>SB P0-2<br>SBP6=SB P0 -6 | SBP3<SB P1-65<br>SBP3>SB P1-17<br>SBP3=SB P1- 15 | SBP6<SB P1-72<br>SBP6>SB P1-11<br>SBP6=SB P1- 13 | SBP6<SB P3 -58<br>SBP6>SB P3-18<br>SBP6=SB P3 -20 |
| Wilcoxon Signed Ranks Test: according to Bonferroni correction significant at p<0.01<br>c. based on positive ranks; | | | | | | |

In the intervention group, for Bonferroni correction of p<0.01, a significant difference in the value of the SBP was determined by the Wilcoxon Signed Ranks Test in 5 out of 6 analyzed time combinations. In the IG a significantly lower SBP was registered at each subsequent measure-

ment up to 6 months compared to zero time. In this group, the highest proportion of patients with reduced SBP compared to zero time was at 3 months – 93 (97.89%) from 95 followed by reduced BP at 1 and 6 months for 90 (97.82%) from 92 patients. After 6 months compared to zero, unchanged SBP was registered in only 1 (1.08%) patient at 6 months, and an increase in SBP was also registered in only 1 patient (1.08%) (Table 2).

Regarding the average SBP in the CG, the highest value was recorded at 0 time and was 152±11.32mmHg with a min/max value of 128/193mmHg. In the 6 months follow-up period, the average SBP value gradually decreased with the lowest average value of 132±11.32mmHg with a min/max value of 85/180mmHg after 6 months. In the CG, a significant difference was determined between the 4 measurement times in terms of SBP height (Friedman Test: Chi-Square (96)=234.90; df=4; p=0.0001) (Table 1). In the CG, for Bonferroni correction of p<0.01, a significant difference in the level of SBP was determined with the Wilcoxon Signed Ranks Test in all 6 analyzed time combinations. In the CG, a significantly lower SBP was registered at each subsequent measurement compared to the previous one in all 6-time combinations. We determined that 81 (83.50%) from 97 patients had a reduced SBP after 1 month compared to zero, and after 6 months compared to zero, a total of 88 (91.67%) from 96 patients. After 6 months compared to zero, an unchanged SBP was found in 6 (6.25%) patients, and an increase in SBP was determined in 2 patients (Table 2). After the results of the intergroup analysis, a comparison was made between the two groups - IG and CG, in terms of the obtained SBP values. The comparison was made before and at each of the four times after the intervention (Table 3).

**Table 3.** Intergroup comparison of SBP at four times.

| Intergroup comparison | SBP (mmHg) | | | | p |
|---|---|---|---|---|---|
| | (N) | Mean± SD | Min/Max | Median (IQR) | |
| **„0" time** | | | | | |
| **IG** | 95 | 151±12.27 | 130/ 200 | 148 (144-157) | Z=(-1.112; p=0.266 |
| **CG** | 97 | 152±11.32 | 128/ 193 | 150 (145-160) | |
| **1 month** | | | | | |
| **IG** | 95 | 133±12.99 | 112/ 190 | 130 (125-140) | Z=(-5.691; p=0.0001* |
| **CG** | 97 | 142±11.81 | 110/ 180 | 140 (135-150) | |
| **3 months** | | | | | |
| **IG** | 95 | 129±9.49 | 110/ 160 | 130 (122-135) | Z=(-5.587; p=0.0001* |
| **CG** | 97 | 137±9.24 | 110/ 160 | 135 (130-142) | |
| **6 months** | | | | | |
| **IG** | 92 | 129±9.18 | 110/ 160 | 130 (120-137) | Z=(-2.333; p=0.020* |
| **CG** | 96 | 132±10.38 | 85/ 180 | 130 (130-140) | |
| IQR = 25th – 75th percentiles; IG = standard care & mHealth app.; CG= standard care<br>Mann-Whitney U Test; *significant p<0.05 | | | | | |

The comparison of IG and CG at each of the four follow-up times after the intervention indicated a significant difference in terms of SBP (Table 3 and Figure 1).

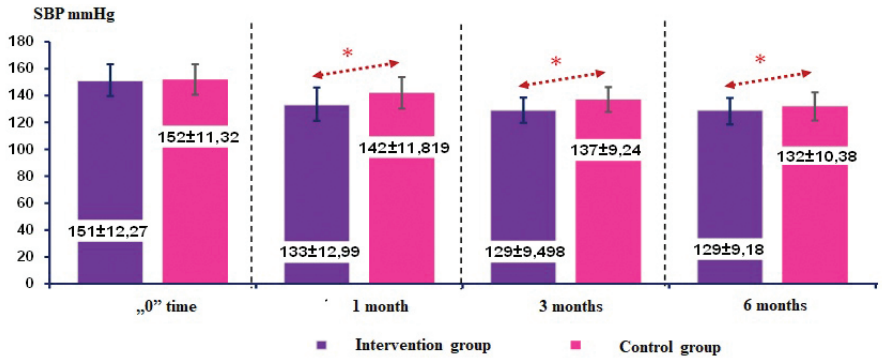


**Figure 1.** Intergroup comparison of systolic blood pressure at four times.

In both groups of participants, an analysis of DBP (mmHg) values was performed at four follow-up times: "0" time, 1, 3 and 6 months after the intervention. The analysis of the distribution of the values obtained for DBP expressed in mmHg at each of the 4 follow-up times indicated an irregular distribution of frequencies for: a) 0 time - Shapiro-Wilk W=0.9407; p=0.0003; b) 1 month - Shapiro-Wilk W=0.8832; p=0.00001; c) 3 months - Shapiro-Wilk W=0.6898; p=0.00001; d) 6 months - Shapiro-Wilk W=0.9470; p=0.0009. The values obtained for DBP were compared at each of the 4 measurement times, both intragroup and intergroup in the IG and CG (Table 4).

**Table 4.** Intragroup comparison of diastolic blood pressure at four times.

| Intragroup analysis | (mmHg) | | | | | p |
|---|---|---|---|---|---|---|
| | (N) | Mean± SD | (Min/Max) | Median (IQR) | Mean Rank | |
| **Intervention group** | | | | | | |
| **""0"" time** | 95 | 94.40±7.65 | 80/ 120 | 93 (90-100) | 4.66 | Chi-Square (92)=169.81; df=4; p=0.0001* |
| **1 month** | 95 | 83.88±7.42 | 70/ 110 | 84 (80-90) | 3.14 | |
| **3 monthss** | 95 | 80.78±7.36 | 68/ 100 | 80 (74-88) | 2.57 | |
| **6 monthss** | 92 | 81.00±6.25 | 68/ 92 | 80 (78-85) | 2.54 | |
| **Control group** | | | | | | |
| **""0" " time** | 97 | 94.43±7.04 | 80/ 110 | 90 (90-100) | 4.54 | Chi-Square (96)=165.165 df=4; p=0.0001* |
| **1 month** | 97 | 87.19±7.79 | 64/ 110 | 90 (82-90) | 3.29 | |
| **3 monthss** | 97 | 84.58±6.78 | 70/105 | 85 (80-90) | 2.64 | |
| **6 monthss** | 96 | 83.31±7.09 | 60/ 100 | 82 (80-90) | 2.45 | |
| IQR = 25th – 75th percentiles; Friedman test; *sognficant p<0.05 | | | | | | |

In both groups, a significant decrease (Friedman Test) in DBP was observed between all follow-up times, with the highest value at time zero before the intervention and the lowest average value at 6 months after the intervention (Table 4). To determine the reason for the significance in the differences between DBP values, in each of the groups individually, Post Hoc Test analysis was applied. The differences in 6-time combinations were analyzed by testing with Wilcoxon signed rank test. In order to avoid Type 1 error, according to the Bonferroni correction, for the interpretation of the obtained results, a significance level of p<0.01 was accepted.

In the IG, the average DBP was the highest at time 0 before the intervention and was 94.40±7.65mmHg with a min/max value of 80/120mmHg. During the follow-up period, the mean DBP value gradually decreased with the lowest mean value after 3 months, 80.78±7.36mmHg with a min/max value of 68/100mmHg. In this group, for Bonferroni correction of p<0.01, a significant difference in DBP values was determined with the Wilcoxon Signed Ranks Test in 5 out of 6 analyzed time combinations for consecutive (Table 5). In IG, a significantly lower mean DBP was registered at each subsequent measurement up to 6 months compared to zero time. In this group, the highest proportion of patients with reduced DBP compared to zero time was after 6 months for 83 (89.58%). After 6 months compared to zero, unchanged DBP was registered in 4 (4.16%) patients, and an increase in DBP was in 5 (5.2%) patients (Table 5).

**Table 5.** Comparison of diastolic blood pressure in six-time combinations – IG/CG.

| (mmHg) | | | | | | |
|---|---|---|---|---|---|---|
| **Intervetion group** | **1 month/ 0 time** | **3 months/ 0 time** | **6 months/ 0 time** | **3 months / 1 month** | **6 months / 1 month** | **6 months / 3 months** |
| **Z** | (-7.602)c | (-7.964)c | (-7.885)c | (-3.916)c | (-8,.47) | (-0.353)c |
| **Asymp. Sig. (2-tailed)** | 0.0001* | 0.0001* | 0.0001* | 0.0001* | 0.005* | 0.724 |
| **Change confirmed** | DBP1<DBP 0 -78<br>DBP1>DBP 0 -3<br>DBP1=DBP 0-14 | DBP3<DBP 0 -81<br>DBP3>DBP 0-6<br>DBP3=DBP 0 -8 | DBP6<DBP 0-83<br>DBP6>DBP 0-4<br>DBP6=DBP 0 -5 | DBP3<DBP 1-49<br>DBP3>DBP 1-17<br>DBP3=DBP 1- 29 | DBP6<DBP 1-0<br>DBP6>DBP 1-92<br>DBP6=DBP 1-0 | DBP6<DBP 3 -33<br>DBP6>DBP 3-31<br>DBP6=DBP 3 -28 |
| **Control group** | **1 month/ 0 time** | **3 months/ 0 time** | **6 months/ 0 time** | **3 months / 1 month** | **6 months / 1 month** | **6 months / 3 months** |
| **Z** | (-6.697)c | (-7.726)c | (-7.747)c | (-3.410)c | (-8.525) | (-2.010)c |
| **Asymp. Sig. (2-tailed)** | 0.0001* | 0.0001* | 0.0001* | 0.0001* | 0.0001* | 0.044 |
| **Change confirmed** | DBP1<DBP 0 -72<br>DBP1>DBP 0 -8<br>DBP1=DBP 0-17 | DBP3<DBP 0 -83<br>DBP3>DBP 0-7<br>DBP3=DBP 0 -7 | DBP6<DBP 0-81<br>DBP6>DBP 0-6<br>DBP6=DBP 0 -9 | DBP3<DBP 1-56<br>DBP3>DBP 1-19<br>DBP3=DBP 1- 22 | DBP6<DBP 1-0<br>DBP6>DBP 1-96<br>DBP6=DBP 1- 0 | DBP6<DBP 3 -39<br>DBP6>DBP 3-26<br>DBP6=DBP 3 -31 |
| Wilcoxon Signed Ranks Test: according to Bonferroni correction significant at p<0.01<br>c. based on positive ranks; | | | | | | |

In the CG, the average DBP in this group was the highest at time „0" before the intervention and was 94.43±7.04mmHg with a min/max value of 80/110mmHg. During the follow-up period, the average DBP value gradually decreased with the lowest average value of 83.31±7.09mmHg with a min/max value of 60/100mmHg after 6 months. In the CG, a significant difference was determined between the 4 measurement times in terms of DBP height (Friedman Test: Chi-Square (96)=165.165; df=4; p=0.0001). In this group, for Bonferroni correction of p<0.01, a significant difference in the height of the DBP was determined with the Wilcoxon Signed Ranks Test in all

6 analyzed time combinations for consecutive. In this group, significantly lower DBP was registered at each subsequent measurement compared to the previous one in 5 out of 6 time combinations. We determined that 86 (85.66%) from 97 patients had reduced DBP after 3 months compared to zero, and after 6 months compared to zero, a total of 81 (84.38%) from 96 patients. After 6 months compared to zero, unchanged DBP was in 9 (9.38%) patients, and in 6 (6.25%) an increase in DBP was determined (Table 6).

**Table 6.** Intergroup comparison of DBP at five times.

| Intergroup comparison | (mmHg) | | | | p |
|---|---|---|---|---|---|
| | (N) | Mean± SD | (Min/Max) | Median (IQR) | |
| **„0" time** | | | | | |
| **IG** | 92 | 94.40±7.65 | 80/ 120 | 93 (90-100) | Z=(-0.418; p=0.676 |
| **CG** | 96 | 94.43±7.04 | 80/ 110 | 90 (90-100) | |
| **1 month** | | | | | |
| **IG** | 92 | 83.88±7.42 | 70/ 110 | 84 (80-90) | Z=(-3.240; p=0.001* |
| **CG** | 96 | 87.19±7.79 | 64/ 110 | 90 (82-90) | |
| **3 months** | | | | | |
| **IG** | 92 | 80.78±7.36 | 68/ 100 | 80 (74-88) | Z=(-3.199; p=0.001* |
| **CG** | 96 | 84.58±6.78 | 70/105 | 85 (80-90) | |
| **6 months** | | | | | |
| **IG** | 92 | 81.00±6.25 | 68/ 92 | 80 (78-85) | Z=(-2.645; p=0.008* |
| **CG** | 96 | 83.31±7.09 | 60/ 100 | 82 (80-90) | |
| IQR = 25th – 75th percentiles; Mann-Whitney U Test; *significant p<0.05 | | | | | |

A comparison was made between the two groups in terms of the obtained DBP values. The values obtained from the individual analysis of the comparison of the two groups (Mann-Whitney U Test) in terms of the height of the DBP for each of the 4 follow-up times indicated a significant difference for all times, except for the "0" time (Table 6 and Figure 2).

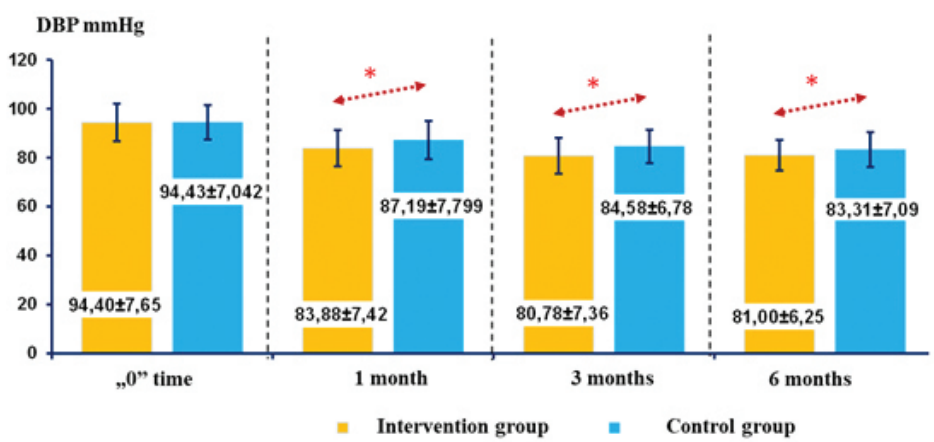


**Figure 2.** Intergroup comparison of dyastolic blood pressure at four times.

## Discussion

In this randomized controlled trial, we aimed to assess the impact of a smartphone-based mHealth application + standard care on blood pressure control in newly diagnosed hypertensive patients. To obtain baseline data on the impact of this intervention, an analysis of blood pressure measurements obtained during planned outpatient check-ups at primary care physicians at 0, 1, 3 and 6 months after study entry, was performed in the intervention and control groups. At study entry, no statistically significant difference was observed in SBP and DBP values, gender, age, place of residence (urban/ rural) between subjects in the two groups. Regarding SBP values, a decrease in mean SBP was observed at all 4 follow-up times in both groups, with a decrease in mean SBP of 22mmHg in the intervention group, i.e., 20mmHg in the control group, i.e., 14.56%, i.e., 13.15% respectively, with a difference of 2mmHg in favor of the intervention group. Better SBP control was also shown in the intragroup analysis with a significantly higher number of patients with reduced SBP compared to the control group. These reduced SBP values were also sustainable after 6 months of the study with 97.8% of the subjects in the intervention group, i.e., 91.5% of the control group with reduced SBP values. Regarding DBP values, a significantly lower DBP was registered at each subsequent measurement up to 6 months compared to zero time with reduced DBP after 6 months, 89.58% in the intervention group, i.e. 84.38% in the control group. In the study, in both groups after 6 months of follow-up, a reduction in the average DBP of 13.4mmHg occurred in the group receiving standard care + mHealth application, i.e., 12.75mmHg in the standard care group, with a difference of 0.65mmHg in favor of the intervention group. The data obtained support the idea that the m-health application can help as an additional intervention to standard healthcare to achieve a slightly higher percentage of good BP control.

The available literature has been rapidly investigating the effect of telemonitoring on hypertension control over the past 2 decades. In the TASMINH4 (22) study (2018), the effect of telemonitoring on blood pressure control was investigated, compared to self-monitoring and standard care. After 12 months of follow-up, systolic blood pressure values were lower in both intervention groups than in the standard care group (self-monitoring: 137.0 [SD 16.7]mmHg, telemonitoring: 136.0 [SD 16.1]mmHg, standard care: 140.4 [SD 16.5]mmHg). This study is significant in its contribution due to results indicating that self-monitoring of CP has an exceptional role in good control of CP, while telemonitoring is a tool that timely informs the patient and involves the doctor in monitoring the patient's condition, which is consistent with the goals set in our study.

In a randomized controlled trial by McManus et al. (2021), 622 patients with hypertension were followed by 76 primary care physicians. Patients in the intervention group transferred their home blood pressure measurements to a secure online platform, where the patient and primary care physician had access to the data. This platform offered a feedback system for BP measurements, optional lifestyle counseling and motivational support. After 12 months, data were available from 552 participants with imputation for the remaining 70 participants (11.4%). The mean SBP decreased from 151.7/86.4 to 138.4/80.2mmHg in the intervention group and from 151.6/85.3 to 141.8/79.8mmHg in the standard care group, yielding a mean difference in SBP of -3.4mmHg (95% confidence interval -6.1 to -0.8mmHg) and a mean difference in DBP of -0.5mmHg (-1.9 to 0.9mmHg). The results of this study, due to the similarity of the study design, can be easily compared to the results of our study, which point towards slightly improved BP control with the use of an mHealth application.

In a similar randomized controlled trial by McKinstry et al (23) in a six-months intervention with self-monitoring and transmission of blood pressure values to a secure website for review by a nurse or physician from the primary care clinic, showed that the intervention led to significant improvement in SBP (4.3mmHg; 95% CI, 2.0 to 6.5; p= 0.0002) and non significant improvement in DBP (0.9mmHg; 95% CI, 0.9 to 3.6; p=0.001) with standard care. The results of our study are in line with those of McKinstry's study, as in a relatively short period of hypertension management by general practitioners through self-measurement at home by patients with telemonitoring, more effective results were obtained in reducing BP values than usual care.

In a meta-analysis by Paula, Maldonado and Gadelha (24) including 76 studies, where the aim was to assess the effectiveness of telehealth-based interventions on disease control rates and clinical parameters in patients with chronic non-communicable diseases, including systolic and diastolic blood pressure, telehealth technologies were shown to significantly improve blood pressure and could be a valuable additional tool for comprehensive hypertension management. In a randomized study by Chavami et al. (25) with 6-months follow-up, patients in the intervention group were more likely to have successfully controlled their blood pressure (88.6% vs. 78.5%; P < 0.001) and had a higher chance of successfully controlling their blood pressure (odds ratio [OR]: 2.13; 95% CI: 1.51 - 3.03). Also in the study by Gong et al. (26) after 6 months of monitoring the effect of the mHealth application, participants in the intervention group at the end of the study showed a significantly greater reduction in SBP and DBP than the control group (P < 0.05) and the percentage of participants with controlled blood pressure was higher in the intervention group (P < 0.05).

The mHealth application used in our study enabled two-way doctor-patient communication via SMS messages through the application, which enabled smooth and fast communication, the possibility of timely intensification of therapy and monitoring of the patient's condition. In the randomized study by Leopold et al. (27) which monitored the impact of a complex mHealth application, with two-way doctor-patient communication, on blood pressure, the results have shown that the intervention increased the BP control rate significantly by 23.1% points (95% CI: 5.4-40.8%): intervention 59.8% (95% CI: 47.4-71.0%) compared to 36.7% (95% CI: 24.9-50.3%) in the control group. Systolic BP decreased by 21.1mmHg in the intervention and 15.5mmHg in the control group, which indicated a relevantly better control of BP with the help of the application.

Some studies have not shown a positive effect of telemonitoring on BP control. One such study is the randomized controlled trial by Mehta et al. (28) that included patients aged 18–75 years treated in family medicine outpatient clinics in Philadelphia. Patients had been seen at least twice in the previous 24 months and had at least 2 elevated blood pressure measurements (>150/90mmHg or >140/90mmHg for patients aged 18–59 years or with diabetes or chronic kidney disease) during the visits. Patients were randomized 2:2:1 to telemonitoring of blood pressure and medication adherence (RM), telemonitoring of blood pressure and medication adherence with feedback provided to a social support partner (SP) and usual care (UC). Patients were followed for 4 months. 246 patients were included in the analysis: 100 patients in the RM group, 97 in the SP group and 49 in the UC group. Compared to the control group, there was no significant difference in SBP or DBP at the 4-month visit in the RG group (mean difference adjusted for SBP, -5.25 [95% CI, -10.65 to 0.15]mmHg; mean difference adjusted for DBP, -1.94 [95% CI, -5.14 to 1.27]mmHg) or the SP group (mean difference adjusted for SBP, -0.91 [95% CI, -6.37 to 4.55]mmHg; mean difference adjusted for DBP, -0.63 [95% CI, -3.77 to 2.51]

mmHg). Out of the 206 patients at 4 months, blood pressure was controlled in 49% of patients in the RG group, 31% of patients in the SS group, and 40% of patients in the control group; these rates did not differ significantly between the intervention and control groups.

The mHealth application in our study, in addition to enabling the transfer of BP values in real time to the family doctor, also had a section in its structure intended for educating the patient on the correct BP measurement technique and a section with data on the hygiene and dietary regimen, in order to improve the patient's education about the disease and his active involvement in the treatment itself. An educated patient is an equal ally of the doctor who actively invests, especially in the part of adhering to an appropriate hygiene and dietary regimen. In the study by Liu et al., (29) after 6 months of follow-up, in addition to a statistically significant improvement in BP in the intervention group versus the control group, the same group also improved in knowledge about hypertension, lifestyle, healthy diet, adherence, salt intake and physical activity. In our research, risk factors associated with HTN were determined, but monitoring of the impact of the mHealth application on them was not planned.

In the available literature, no study could be found that investigated the effect of an mHealth application on blood pressure control in patients with newly diagnosed hypertension, which is of exceptional importance because the rapid reduction in blood pressure values and their maintenance, especially in newly diagnosed patients, significantly delays target organ damage.

To confirm the effect of this type of application and sustainability over a longer period of time, it is necessary to complete our research by fulfilling the entire protocol and following up with the participants within 12 months. In order to define the applicability of mHealth applications in different regions of the world, future research is recommended in which the effect on blood pressure control will be monitored in different settings.

## Limitations of the Study

The study had several limitations. First, all participants in the intervention group owned mobile phones and were likely to have higher socioeconomic status. In addition, not having a smartphone makes it difficult to recruit individuals for clinical trials and to collect accurate and complete data for trials, especially when relying on mobile technologies for data collection and monitoring progress in self-management. Second, patients' blood pressure was monitored based on their self-reported blood pressure readings, rather than accurate measurements by healthcare professionals. Although participants were educated to measure their blood pressure more accurately according to a given schedule and were shown a video on the app showing proper blood pressure measurement technique, it was not guaranteed that everyone followed the instructions, which could introduce bias into the measurement results. Strategies for assessing the accuracy of patient-reported data and how to involve family members to facilitate self-monitoring in patients who are unable to manage their condition themselves also need further investigation. Third, there is a lack of previous research studies investigating the impact of an mHealth application in patients with newly diagnosed HTN that would allow for comparison of results, as self-monitoring of BP in these patients is of utmost importance for the purpose of timely titration of antihypertensive therapy to achieve targeted values.

## Conclusion

An mHealth application that enables two-way patient-physician communication is an intervention that, as an auxiliary tool to standard care, can improve blood pressure control in newly diagnosed patients with hypertension. In order to confirm the complete effect of the mHealth application on blood pressure control and the benefit for family physicians when using it in managing patients with hypertension, it is necessary to complete the planned protocol.

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# CT SCANNING WITH POLYTRAUMA PROTOCOL: IS THE PATIENT OVER-SCANNED?

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## Abstract

Trauma is the leading cause of death in individuals under 45 years old. CT scan with polytrauma protocol plays a crucial role in the rapid assessment of trauma patients. However, its routine usage may result in unnecessary imaging, increased radiation exposure and higher healthcare costs.

This study aimed to evaluate the overuse of CT scans performed with polytrauma protocol based on clinician's request.

**Materials and Methods:** A retrospective review of 138 trauma patients referred to polytrauma CT scans between March and May 2025, that was conducted using PACS data from two institutions. The average patients' age was 46.3 years (range: 4–89 years), with 79% being male.

Inclusion criteria were trauma patients referred to CT with polytrauma protocol. The number of injured body parts was compared to the number of parts scanned to assess scan necessity.

**Results:** Out of 138 patients 49 (35.5%) had positive CT findings. Out of 49 patients 32 (65.3%) met polytrauma criteria. Only 4 patients (8.2%) had indication for CT scan with polytrauma protocol. 45 (91.8%) of the patients were over-scanned. 75% excess scanning had 17 patients (37.7%), 50% over-scanning had 20 patients (44.4%), and 25% over-scanning was done in 7 patients (15.5%). The most unnecessary examinations were performed to neck in 85.7% and abdomen in 46.6%, in comparison to chest (33.3%).

**Conclusion:** A significant number of patients underwent unnecessary CT scanning, particularly involving the neck and abdomen. These findings underscore the importance of clinical guidelines to reduce over-scanning, minimize radiation, lower costs and improve trauma care efficiency.

***Key Words:*** *CT polytrauma protocol; over-scanning.*

## Introduction

Trauma has become the leading cause of death in young patients under the age of 45 years (1). The management of trauma patients should be focused on identifying and resolving life–threat-

ening injuries. Polytrauma is defined as traumatic injuries that involve at least two body parts or systems, such as the head, chest, abdomen, or one or more extremity, with one of those or the combination of them potentially fatal for the patient (2).

After clinical examination of the traumatized patient, according to the body systems affected, the imaging protocol starts with X-rays (cervical, thoracic and pelvic), focused assessment with trauma sonography (FAST), and eventually Computed Tomography (CT) (3,4). CT should be done only if indicated, not by default, and should be selective for specific body regions (3).

Imaging modalities should be taken in consideration, as well as radiological workflow, in order to chronologically define the protocol, and avoid overlooking life–threatening diagnosis (5). MDCT has indisputable role and is set as the most important imaging modality according to submillimeter isotropic data acquisition. Mainly, CT is used in patients with multiple injuries that do not allow exclusive evaluation of each of them, such as combined brain, thoracic injuries, thoraco-abdominal injuries or multiple abdominal injuries, and in case of vessel injury.

The trauma management algorithm recommends CT scan with polytrauma protocol for "polytrauma" patients (6). The main standard is an immediate interpretation of CT scan on the first images available, and then reassessment and making reconstructions, at least in the three standard planes (axial, coronal and sagittal) (7). Post-processing reconstructions, such as three-dimensional (3D) multiplanar reconstructions (MPR) and volume rendering reconstructions, are also helpful in identifying and characterizing the exact location of some injuries, such as vascular, skeletal, etc. However, currently no agreement on the optimal CT-protocol is achieved (8-11). But non-enhanced CT has become a single polytrauma protocol, which consists of CT scans of the head (including facial skeleton), neck, chest and abdomen/ pelvis (12), when possible, a 'feet first' patients' position is preferred to allow better visualization of weight-bearing structures.

The aim of the study was to assess the unnecessary CT scanning with polytrauma protocol according to the diagnosed injuries.

## Materials and Methods

Retrospectively, an initial CT scans of 138 patients with clinical indication for polytrauma were analyzed in a three-months period from March to May in 2025, using PACS system from two institutions. Patients' mean age was 46.3 years old (range from 4 to 89 years), and 79% were male. Inclusion criteria were trauma patients sent by the clinicians for CT scans with polytrauma protocol, suspected of having more than one body system injured.

In all patients a single polytrauma CT scan protocol was performed, non-contrast enhanced, with thin slices, followed by thinner slice reconstructions in three planes. In some cases, when clinically visceral or vascular injury was suspected, post-contrast CT scanning was obtained. Post-processing reconstructions, such as three-dimensional (3D) multiplanar reconstructions (MPR) and volume rendering reconstructions were done to identify and characterize the exact location of some injuries, such as vascular, skeletal, etc. CT images were reported by radiologists at emergency departments in both institutions. Non-enhanced CT polytrauma protocol consists of scanning of the head with scanning the brain, skull, facial bones, then neck, chest, abdomen and pelvis. The head images were evaluated for skull and facial bones fracture and for brain

injury; neck - for spine and soft tissue trauma, chest CT was assessing the lung injury, presence of pneumothorax, hemothorax, mediastinal structures injury or thoracic spine, and chest wall injury as well; abdomen /pelvis CT scans were assessed in order to identify injuries to abdominal, retroperitoneal or pelvic organs injury, as well as skeletal injury. CTs of the extremity were performed when injury was suspected by the clinicians.

On CT scans the types of injuries were analyzed, focusing in dependance on which body parts were affected, in comparison to body parts that were scanned, to exclude the ones that do not correlate to the indication for scanning. The over-scanned body region/s were recognized, and the percentage of unnecessary performed CT examinations was calculated.

## Results

Out of 138 patients scanned with polytrauma indication, in 49 patients (35.5%) positive results on CT scans were identified, out of which 32 cases (65.3%) were positive for polytrauma, and in 17 cases (34.7%) only one body part was affected.

Out of the 32 patients that were positive on polytrauma, 13 patients (40.6%) had pulmonary and skeletal trauma (Figure 1), 11 patients (34.3%) had neural and skeletal trauma (Figure 2), and abdominal and skeletal trauma was found in only one patient (3.1%). Neural, lung and skeletal trauma were diagnosed in 3 patients (9.3%), whereas in one patient (3.1%) neural, abdominal and skeletal trauma were found, and in another one (3.1%) all four systems were affected – neural, lung, abdominal and skeletal trauma were found. On the other hand, out of 17 patients with trauma in only one body part, 15 patients (88.2%) had skeletal trauma, 5 patients (33.3%) were with fractures in 2 bones; 1 patient (6.67%) with fractures in 6 bones; 2 patients (13.3%) with serial rib fracture, and in 2 patients (13.3%) spine injury was detected. One patient (5.9%) was identified with only neural trauma, presented as subdural hematoma and in 1 patient (5.9%) was found only lung contusion.

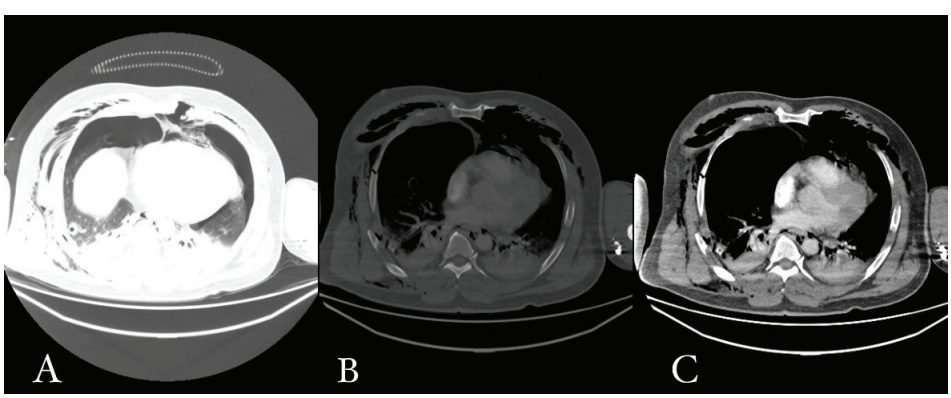


**Figure 1.** CT scan with polytrauma protocol in patient after car accident. Clinically, he was positive on chest injury and skeletal trauma. There is a sign for bilateral lung contusion with partial pneumothorax and bilateral subcutaneous emphysema, more pronounced at the right side (A, B) with rib fractures at several ribs on the right hemithorax (C).

Out of all patients sent for CT scanning, that had been reported positive on trauma (49 patients), only 4 patients (8.2%) were confirmed positive for the indication for scanning. 45 patients (91.8%) were over-scanned, according to the indication, with over-scan rate ranging from 25%

to 75% per patient. 17 patients (37.7%) had 75% excess in scanning, 20 patients (44.4%) had 50% excess in scanning, and 7 patients (15.5%) had 25% excess in scanning. The most unnecessary examinations were performed to the neck in 85.7% (42 cases), then head CT scans 40% (18 cases), whereas abdomen CT over-scanning was more often performed (in 46.6%) than in the thorax CT scans (33.3%).

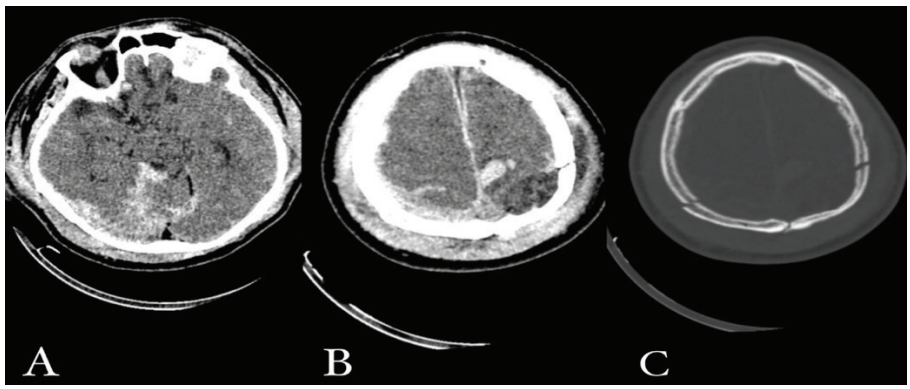


**Figure 2.** CT scan performed with polytrauma protocol, non-contrast scans. Patient injured in car accident. CT scans show two systems affected, brain and skeletal trauma. Subarachnoid hemorrhage supratentorially and temporally was seen (A) with intracerebral hemorrhage in the parietal left lobe (B) and hemorrhage in parafalx area. Axial plane at bone window shows parietal bone fracture (C).

## Discussion

The CT scanning with polytrauma protocol remains a cornerstone in the rapid evaluation of trauma patients, especially in the presence of altered mental status or multiple suspected injuries. However, the results in our study demonstrate that a large proportion of patients, 91.8% underwent scanning of more body regions than ultimately warranted by injury patterns. The findings of this study highlight a significant rate of over-scanning **in** the application of the polytrauma CT protocol.

This discrepancy between clinical suspicion and actual findings **is** not unique. Prior studies have raised similar concerns. For instance, Salim et al. and Linsenmaier et al. (13,14), have shown that polytrauma CT protocol frequently identifies incidental or clinically irrelevant findings, while less than a half of the scans detect true polytrauma. In our study, out of 138 patients, asked by the clinician for CT scan with polytrauma protocol, only 23.2% of the cases had injuries affecting more than one body system, and even among those, 78.1% had trauma confined to just two parts. This suggests that routine CT polytrauma protocol may result in over-scanning, particularly when applied indiscriminately.

In our study the highest rates of over-scanning were observed in neck CTs (85.7%), followed by the abdominal CTs (46.6%) and thoracic CTs (33.3%). This pattern reflects the common inclusion of these regions in default trauma protocols, despite the absence of focal signs or symptoms. Notably, head CT was also over-scanned in 40% of cases, often without intracranial findings. Such over-scan not only increases radiation exposure but also contributes to higher healthcare costs, scanner overload and potential delays in reporting. According to Huber-Wagner et al., the application of CT polytrauma protocol in hemodynamically stable patients with minor mechanisms of injury should be reconsidered, as clinical examination combined with selective

imaging often suffices (5). The over-scan rate in our study, ranging from 25% to 75% per patient, strongly supports this more tailored approach. Clinical decision tools, such as the REACT-2 protocol or NEXUS criteria (for cervical spine), may help in limiting unnecessary imaging without compromising diagnostic accuracy (Priti Kharel (16)).

Interestingly, only 8.2% of the patients had trauma findings that fully matched the indication for CT scanning in polytrauma protocol, indicating a low predictive value of clinical suspicion in this setting. This could stem from a combination of factors: limited initial assessment in unstable patients, defensive medicine practices, or institutional reliance on pre-set trauma imaging protocols.

Nevertheless, it is important to recognize the value of negative findings in trauma imaging. In patients who are unconscious, intoxicated or intubated, polytrauma protocol CT scanning can rule out life-threatening injuries quickly, and can guide safe early mobilization or surgical planning. Thus, over-scanning must be balanced with the risk of under diagnosis**,** especially in high-energy trauma.

This study demonstrates a significant rate of over-scanning in the use of whole-body CT protocols for trauma patients, with significantly exceeding the necessary diagnostic scope based on injury patterns. While CT scans with polytrauma protocol remain essential for the rapid assessment of severely injured or unresponsive patients, our findings underscore the importance of more selective imaging strategies. These highlight the need for greater adherence to clinical decision-making tools and tailored imaging protocols to minimize unnecessary radiation exposure, reduce healthcare costs, and streamline trauma care.

Limitation of the study is being a retrospective one, and that includes only two centers, which may limit generalizability. Data on long-term patients' outcomes or how imaging influenced management decisions were not included. Furthermore, although excess scanning was quantified, we did not assess cumulative radiation dose, which would offer additional insight into the clinical implications of over-imaging.

Implications for practice are that more selective approach to polytrauma imaging, guided by clinical judgment and validated triage tools, may significantly reduce unnecessary scans, limit radiation exposure and optimize resource use. Additionally, protocol review and interdisciplinary communication between radiologists, emergency physicians and trauma surgeons, could further refine imaging strategies.

## Conclusion

This study demonstrates a significant rate of over-scanning with CT scan with polytrauma protocol in trauma patients. Majority of the patients did not fully match the indication for scanning. Over-scanning was the most prevalent in neck and abdominal CTs, reflecting the routine application of full protocols even when not clinically justified. These findings highlight the need for greater adherence to clinical decision-making tools and tailored imaging protocols to minimize unnecessary radiation exposure, reduce healthcare costs and streamline trauma care. Future prospective studies should further evaluate the impact of protocol adjustments on clinical outcomes and resource utilization.

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# DISTINCT MRI PHENOTYPES OF NEUROGENIC VS. NON-NEUROGENIC CERVICOBRACHIAL PAIN: A COMPARATIVE STUDY

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## Abstract

The differentiation of cervicobrachial pain into neurogenic and non-neurogenic etiology, is crucial for appropriate clinical management. A clear distinction based on objective findings can guide therapeutic strategies. The goal of this paper is to compare the demographic, anamnestic and magnetic resonance imaging (MRI) characteristics between patients with neurogenic and non-neurogenic cervicobrachial pain. This analytical, cross-sectional study included 130 patients with symptoms of cervicobrachial syndrome referred to cervical spine MRI. Based on radiological findings of nerve root or spinal cord compression, patients were divided into a neurogenic pain group (n=85) and a non-neurogenic pain group (n=45). Demographic and anamnestic data were collected via a questionnaire. Statistical analysis was performed using Student's t-test and the $X^2$-test. The non-neurogenic pain group was significantly younger than the neurogenic group (mean age 39.0±13.5 vs. 46.5±12.9 years, p=0.0023). The history of a motor vehicle accident (MVA) was significantly more frequent in the neurogenic group (23.5% vs. 4.4%, p=0.0058). Advanced degenerative findings, such as spondylosis (58.8% vs. 4.4%, p<0.0001) and Modic changes (14.1% vs. 2.2%, p=0.031), were significantly more prevalent in the neurogenic group. Conversely, isolated disc dehydration was significantly more common in the non-neurogenic group (81.2% vs. 48.9%, p=0.00013). In conclusion, neurogenic and non-neurogenic cervicobrachial pain exhibit distinct demographic and radiological profiles. Neurogenic pain is associated with older age, a history of trauma and advanced degenerative changes. Non-neurogenic pain is more characteristic in younger patients, predominantly female, and is associated with early degenerative findings like disc dehydration.

***Key Words:*** *Cervicobrachial Syndrome, Degenerative Disc Disease, Magnetic Resonance Imaging (MRI), Neurogenic Pain, Spondylosis.*

## Introduction

Neck pain, often radiating to the arm as cervicobrachial syndrome, represents a major global health burden, with a point prevalence estimated to be as high as 20% in the adult population, leading to significant disability and economic cost (1). While its pathogenesis is often attributed to cervical radiculopathy from disc herniation, clinical practice reveals a more complex picture.

Many patients suffer from debilitating pain without clear radiological evidence of neural impingement, creating diagnostic and therapeutic challenge.

This challenge underscores the need to differentiate the etiology of pain into two broad categories: neurogenic and non-neurogenic. Neurogenic pain is the direct consequence of mechanical or inflammatory irritation of neural structures, typically from disc herniation or osteophytes causing spinal or foraminal stenosis (2). In contrast, non-neurogenic pain arises from other anatomical sources. This includes pain originating from the zygapophyseal (facet) joints, ligaments, muscles or the intervertebral disc itself - a condition known as discogenic pain (3, 4). Discogenic pain is thought to be caused by nociceptive stimulation within the annulus fibrosus of a structurally compromised disc, even in the absence of nerve root compression (5).

Distinguishing between these etiologies is crucial, as it directly guides management. Neurogenic pain may require interventional or surgical approaches, whereas non-neurogenic pain is primarily treated with conservative measures like physical therapy and pharmacotherapy. This distinction is not only critical for surgeons and physical therapists but also for anesthesiologists specializing in pain management, as an accurate etiological diagnosis is paramount for the success of interventional procedures such as cervical epidural steroid injections or nerve root blocks. Magnetic Resonance Imaging (MRI) is the gold standard for visualizing cervical spine anatomy, yet its findings often correlate poorly with clinical symptoms (6). Given the high prevalence of degenerative findings in asymptomatic individuals, simply identifying a pathological finding is often insufficient (7). Therefore, stratifying symptomatic patients based on the presumed pain generator (neurogenic vs. non-neurogenic) may offer a more clinically relevant approach to understand the source of pain.

Therefore, the aim of this study was to perform a comparative analysis of the demographic, anamnestic and detailed MRI findings in patients with symptomatic cervicobrachial pain, classified by a neurogenic versus non-neurogenic etiology, in order to identify distinct patients' phenotypes and contribute to a better understanding of the underlying pathophysiology.

## Materials and Methods

This analytical, cross-sectional study was conducted at the University Institute of Radiology in Skopje. The study included 130 patients, aged 18 to 80 years, with a working diagnosis of cervicobrachial syndrome or cervical radiculopathy. Exclusion criteria were age under 18 or over 80 years, pain of somatic origin due to neoplastic changes or spondylodiscitis, prior cervical spine surgery and pain lasting less than two weeks. All participants provided informed consent.

All patients underwent an MRI examination on a 1.5T Magnetom Essenca system (Siemens). Standard protocols included T1-weighted and T2-weighted pulse sequences in sagittal and axial planes, as well as a T2-weighted sequence with fat suppression in the sagittal plane. Prior to the examination, each participant completed a questionnaire to collect demographic and anamnestic data.

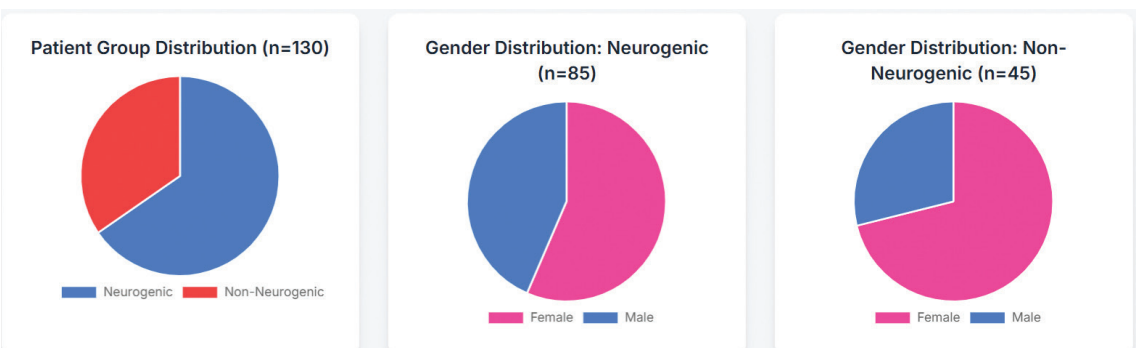
Based on the radiological findings, patients were stratified into two groups: 1. Neurogenic Pain Group (n=85): Patients with MRI evidence of spinal and/ or neuroforaminal stenosis caused by disc herniation or a posterior disc-osteophyte complex, resulting in visible compression or displacement of the spinal cord or nerve roots that correlated with the clinical presentation. 2.

Non-Neurogenic Pain Group (n=45): Patients with clinical symptoms but without radiological evidence of significant neural compression.

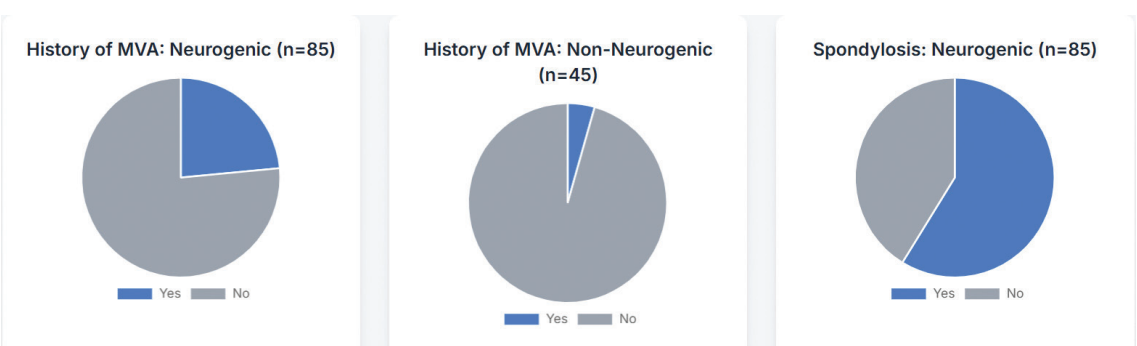
Statistical analysis was performed using SPSS 23.0. A Student's t-test was used to compare continuous variables (age), and the $X^2$-test was used for categorical variables (gender, presence/absence of findings). A p-value of <0.05 was considered statistically significant.

## Results

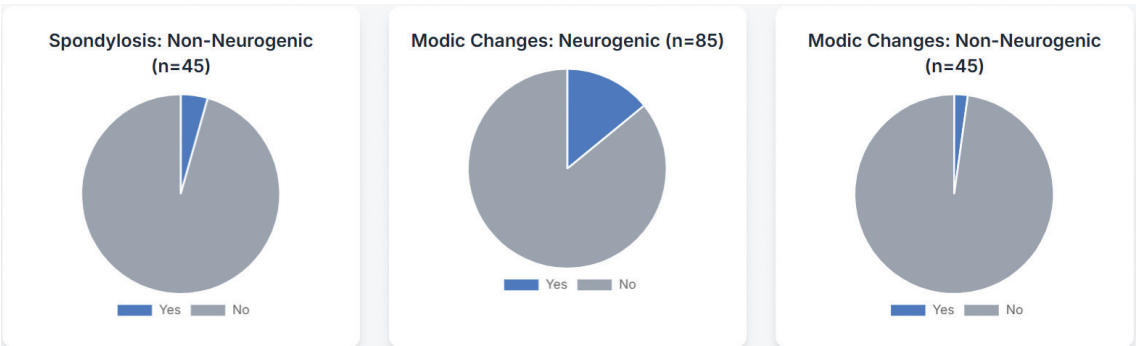
Out of the 130 participants, 85 (65.4%) were classified into the neurogenic pain group, and 45 (34.6%) into the non-neurogenic pain group. Patients with non-neurogenic pain were significantly younger, with a mean age of 39.0±13.5 years, compared to 46.5±12.9 years in the neurogenic group (t=3.11, p=0.0023). Although not statistically significant, there was a higher proportion of females in the non-neurogenic group (71.1% vs. 56.5% in the neurogenic group, p=0.1).



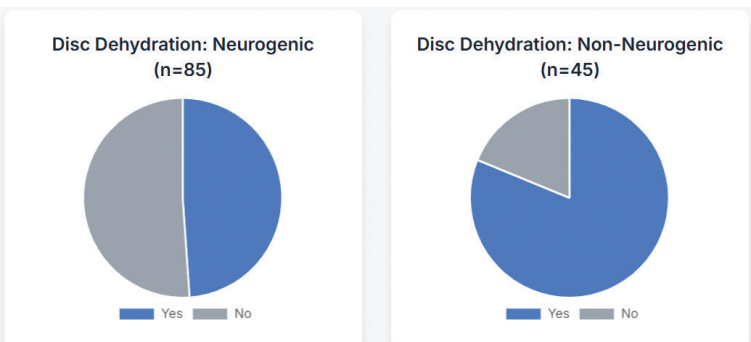

A history of a prior motor vehicle accident (MVA) was reported with a significantly higher frequency by patients in the neurogenic pain group (23.5%) compared to the non-neurogenic group (4.4%) ($X^2$=7.62, p=0.0058).




The comparison of MRI findings revealed significant differences. Cervical spondylosis was diagnosed in 50 (58.8%) patients with neurogenic pain, but in only 2 (4.4%) patients with non-neurogenic pain, a highly significant difference ($X^2$=36.25, p<0.0001). Similarly, Modic changes, representing vertebral endplate pathology, were detected in 12 (14.1%) patients with neurogenic pain, compared to only 1 (2.2%) patient with non-neurogenic pain (p=0.031) (8).




Disc dehydration, as an early degenerative finding, was significantly more common in patients with non-neurogenic pain (81.2%) than in those with neurogenic pain (48.9%) ($X^2$=14.61, p=0.00013). The prevalence of facet arthropathy did not show a statistically significant difference between the groups (24.7% in the neurogenic group vs. 17.8% in the non-neurogenic group, p=0.37).




## Discussion

Our study reveals that neurogenic and non-neurogenic cervicobrachial pain are not merely different points on a single degenerative continuum but rather represent two distinct clinicopathological entities. The non-neurogenic profile represents the initial stage of the degenerative cascade, driven by internal disc disruption, while the neurogenic profile signifies the end-stage of this process, characterized by structural compression and often accelerated by prior trauma.

The first phenotype, non-neurogenic pain, is characteristic of a younger, predominantly female demographic. The cornerstone radiological finding in this group was a high prevalence of disc dehydration. This strongly suggests that the pain source is primarily discogenic, arising from internal disc disruption rather than external neural compression. As the disc dehydrates, it loses its hydrostatic pressure and mechanical integrity, leading to the development of annular fissures. These fissures can allow inflammatory mediators from the nucleus pulposus to leak into the richly innervated outer annulus, stimulating nociceptors and generating pain.

In stark contrast, the neurogenic pain phenotype is associated with an older patient population where the degenerative cascade is far more advanced. The significantly higher prevalence of spondylosis and Modic changes in this group points to a long-standing process of biomechanical failure and instability. Spondylosis, characterized by osteophyte formation, directly nar-

rows the spinal canal and neural foramina, leading to mechanical compression. Modic changes, particularly Type 1, are now understood to represent an active inflammatory and edematous process in the vertebral endplate, often associated with segmental instability and severe pain (8). Our findings show a particular concentration of these advanced changes at the C5-C6 level, which is consistent with biomechanical studies identifying this segment as the apex of cervical lordosis and the zone of greatest flexion-extension motion, thus subjecting it to maximal mechanical stress (9).

A pivotal finding from our study is the strong association between the history of MVA (whiplash) and the development of neurogenic pain. Our findings support the hypothesis that trauma may act as an "initiator" or "accelerator" of the degenerative cascade (10). Whiplash injuries can cause occult microfractures of facet joints and vertebral endplates, leading to chronic low-grade inflammation, ligamentous laxity and segmental instability. Over time, this instability promotes the accelerated development of spondylosis and disc herniation, ultimately culminating in the neurogenic compression seen in our older cohort (11, 12).

This study has several limitations. Its cross-sectional design allows us to identify associations but not to establish causality. The sample size is relatively modest, and the unequal group sizes may limit statistical power. As a single-center study, the results may have limited generalizability. Furthermore, the reliance on a patient's questionnaire for anamnestic data introduces the possibility of recall bias. Crucially, we did not include an asymptomatic control group. It is well-documented that degenerative findings are highly prevalent in the pain-free population, which complicates the direct attribution of any single finding as the definitive cause of pain (7).

## Conclusion

In conclusion, this study demonstrates that neurogenic and non-neurogenic cervicobrachial pain are associated with distinct and recognizable patient profiles. Non-neurogenic pain is primarily a condition in younger individuals, linked to early discogenic changes. Neurogenic pain is a manifestation of advanced, multi-faceted degenerative disease in an older population, often accelerated by prior trauma. This etiological stratification, guided by careful synthesis of patient's history and targeted MRI analysis, provides a more nuanced pathophysiological framework that can empower clinicians to select more precise and effective therapeutic strategies, ultimately improving patients' outcomes.

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# THE ROLE OF ENDOMETRIAL THICKNESS AND SERUM BETA-HUMAN CHORIONIC GONADOTROPIN LEVELS AS PREDICTIVE MARKERS OF DELAYED FAILURE IN MEDICAL ABORTION

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## Abstract

**Introduction:** Medical abortion, also known as medical termination of pregnancy (MToP) or MA, employs pharmaceutical agents to trigger a process similar to miscarriage, serving as an alternative to surgical methods. Extensive evidence, global practices and guidelines from the World Health Organization (WHO) validate the effectiveness of administering 200mg of mifepristone followed by 800mcg of misoprostol taken 24-48 hours later for pregnancies up to nine weeks in gestation.

**Objective:** This study aims to assess the predictive value of ultrasonographic measurements of endometrial thickness and serum human beta chorionic gonadotropin (β-hCG) levels in identifying late failure in patients undergoing medical abortion with mifepristone and misoprostol.

**Material and Methods:** A prospective observational study was carried out at the University Clinic for Gynecology and Obstetrics in Skopje from January to June 2023. The research involved 97 women seeking medical abortions who reported experiencing residual vaginal bleeding lasting 15 days or longer following outpatient medical induction for pregnancies not exceeding nine weeks. Each participant underwent transvaginal ultrasound and serum β-hCG testing prior to cervical dilation and endometrial curettage performed under anesthesia. Based on histopathological analysis of uterine contents, participants were categorized into those with incomplete abortions (19 cases; 19.59%) showing products of conception, and those with complete abortions (78 cases; 80.41%) lacking such evidence. Correlations between transvaginal ultrasound findings and quantitative β-hCG levels with histopathological results were analyzed to determine the reliability of these markers in predicting complete abortion.

**Results:** Baseline characteristics were comparable across both groups. Endometrial thickness measurements showed significant differences: averaging 11.2±3.9mm in the complete abortion group compared to 14.6±6.1mm in the incomplete group (P=0.003). Serum β-hCG levels also varied significantly: averages were found at 73.92±23.86 IU/L for complete abortions versus 109.37±68.36 IU/L for incomplete ones (P<0.001). An endometrial thickness threshold of ≥12mm yielded a sensitivity of 88.46%, specificity of 73.68%, positive predictive value (PPV) of 93.24%, and positive likelihood ratio (LR+ve) of 85.57%. Similarly, a serum β-hCG level ≥100 IU/L indicated incomplete abortion with a sensitivity of 87.2%, specificity of 78.9%, PPV of 94.4% and LR+ve of 85.6.

**Conclusion:** Quantitative serum β-hCG levels along with measurements of endometrial thickness are valuable diagnostic tools for predicting late failure after medical abortion; however, they should be employed as complementary assessments alongside thorough clinical evaluations.

***Key Words:*** *Transvaginal ultrasonography, Endometrial thickness, Serum β-hCG, Oral misoprostol, Early pregnancy failure.*

## Introduction

Medical abortion refers to the use of medications to terminate a pregnancy in a manner akin to a miscarriage. Despite an overall decline in abortion rates, the prevalence of medical abortion has markedly increased since its approval by the FDA in 2000. While some nations continue to enforce regulations that limit access, others are investigating methods to enhance accessibility by permitting non-physician clinical providers to prescribe mifepristone, and evaluating the effectiveness of telemedicine in widening access to abortion services for those who need them. Medical abortion serves as an alternative to surgical abortion (1. It is recognized as an effective and acceptable option for abortion care (2-3). Due to minimal medical requirements for the safe administration of medical abortion drugs and the fact that women can generally manage the process themselves, there is a rising percentage of induced abortions in both the United States (US) and globally that are classified as medical abortions (4-5). Expanding access to medical abortion, including increasing the gestational ages at which it can be safely administered, is one approach aimed at reducing unsafe abortions, particularly in areas where trained surgical providers are scarce. The most efficacious regimen for medical abortion combines mifepristone with misoprostol; however, differences exist regarding dosage, timing and method of administration for these two medications. Extensive evidence, international practices, and recommendations from the World Health Organization (WHO) endorse a regimen consisting of a 200mg dose of mifepristone followed by 800μg of misoprostol for pregnancies up to 63 days gestation (6-7), with recent findings suggesting its application could extend to 70 days gestation (8). Misoprostol is taken 24-48 hours following mifepristone, and facilitates uterine emptying through cramping and bleeding similar to early miscarriage. A follow-up appointment is usually arranged one or two weeks later to verify pregnancy termination using ultrasound or blood tests. The efficacy of all regimens is influenced by gestational age, showing reduced effectiveness after nine weeks; hence, it is recommended that misoprostol doses be repeated starting late in the first trimester. Home administration of misoprostol demonstrates comparable effectiveness to clinical administration up to 63 days gestation and is recognized as a safe practice (9,10). Future studies on later gestational ranges would also need to prove similar efficacy, acceptability, and adverse event rates associated with home use of medical abortion medications (11). As avenues for providing abortions have been streamlined and enhanced, several affluent countries have seen an uptick in medication abortions compared to aspiration procedures while simultaneously experiencing improved access and fewer complications related to medical abortions (12). In regions where abortive medications (mifepristone/ misoprostol) can be obtained directly from pharmacies - bypassing physician dispensations - abortions tend to occur significantly earlier in gestation (13). In the United States, approximately 40 percent of all abortions were classified as medical abortions in 2018; notably, most occurred at or before nine weeks of gestation (14-16). When conducted according to established guidelines, medical abortion constitutes a safe method for terminating pregnancies. Although numerous studies have explored acceptance levels concerning medical abortions, considerably less research has focused on factors affecting

women's satisfaction with surgical procedures over the past fifteen years. Evidence suggests high acceptability rates among women who obtain accessible abortion services; these data indicates general contentment among women who successfully secure an abortion (17).

In Republic of North Macedonia, abortion has been legal since 1972; however, medical abortion was only legalized for use in May 2019 under the Law on Pregnancy Termination, Republic of North Macedonia (18). Following the implementation of Clinical Guidelines on Safe Abortion in December 2020, we initiated a pilot project focusing on medical abortions during both the first and second trimesters (19). Even though medical abortive drugs lack formal registration within the country's healthcare system due largely to favorable political attitudes toward reproductive rights observed over recent years, the government allocated funds through its Preventive Program for Mother and Child Health Care budget specifically aimed at acquiring these drugs for introduction into services at the University Clinic for Gynecology and Obstetrics.

The primary objective when monitoring patients undergoing medical abortion is confirming successful termination without complications. Post-abortion monitoring parameters may encompass serum-hCG levels assessment alongside sonographic evaluations regarding endometrial thickness patterns observed during bleeding episodes or serial hemoglobin/ hematocrit measurements(20). Furthermore, sonographic assessments measuring endometrial thickness serve as crucial indicators when diagnosing incomplete abortions post-first trimester spontaneous losses; they may also assist clinicians assessing potential treatment needs following medicated terminations (21). Nonetheless, a clear strategy remains elusive concerning whether women with ultrasound indications suggestive of incomplete termination truly necessitate any intervention based solely on retained products diagnosis.

## Objectives

The objectives of the study were to evaluate the serum-hCG levels and ultrasonographic measurement of endometrial thickness as predictors of failure to complete abortion in patients designated for medical abortion using mifepristone and misoprostol.

## Materials and Methods

We carried out a prospective observational study involving 97 women who sought medical abortion at the University Clinic of Gynecology and Obstetrics in Skopje, Republic of North Macedonia, from January to June 2023. Following gynecological assessment and ultrasound evaluations to confirm gestational age, participants were administered 200mg of mifepristone orally, followed by 800μg of misoprostol sublingually after a 24-hours period for at-home use. Data regarding socioeconomic status, body mass index (BMI), reproductive history, outcomes of the medical abortions during follow-up examinations, requirements for surgical intervention due to retained uterine contents, side effects experienced and other relevant information were collected through dedicated questionnaires. Prior to any procedure, written informed consent was secured from all participants involved in the study. Serum human chorionic gonadotropin (hCG) levels were measured on days 7 and 14 post-treatment. Transvaginal ultrasounds were conducted during each follow-up visit to assess the presence of the gestational sac. Women exhibiting minimal bleeding with an empty uterus on ultrasound were monitored until day 15;

those who continued to bleed beyond this point were included in the study. Participants experiencing significant bleeding received a clinical diagnosis of incomplete abortion confirmed through ultrasonography and subsequently underwent surgical evacuation of the uterus. Individuals with severe vaginal bleeding (with or without signs of shock), those presenting with a dilated cervical os or indications of cervical abortion were excluded from the analysis. After providing explanations about the procedures and objectives of the study, all subjects underwent transvaginal ultrasound scans as well as serum hCG assays before proceeding with cervical dilation and endometrial curettage or uterine evacuation under general anesthesia. Based on histopathological examination results of the uterine contents, participants were classified into two groups: those with incomplete abortions (19 cases; 19.6% showing evidence of products of conception) and those with complete abortions (78 cases; 80.4% showing no evidence of products of conception). The findings from transvaginal ultrasound examinations and quantitative serum hCG levels were compared to histopathological results to determine their effectiveness in predicting complete abortion outcomes.

**Table 1.** Baseline characteristics of the study groups.

| | Complete abortion (n=78) | Incomplete abortion (n=19) | P |
|---|---|---|---|
| Maternal age (years ± SD) | 29.15±4.4 | 28.73±4.8 | 0.715 |
| Parity (n (%)) | | | |
| Primipara | 37 (47.4%) | 8 (42.1%) | 0.676 |
| Multipara | 41 (52.6%) | 11 (57.9%) | |
| Maternal BMI (Kg/m2± SD) | 31.4 ± 4.1 | 30.6 ± 4.4 | 0.448 |
| Gestational age in days at induction* | 38.5 (33–46) | 46.5 (39–56) | 0.026† |
| History of previous miscarriage* | 1 (0–3) | 1 (0–3) | 0.751 |
| Induction–presentation interval in days* | 18.5 (14–22) | 15 (14–24) | 0.624 |

BMI: Body mass index; *Data are given in median (range);†statistically significant difference.

Endometrial thickness was measured using a 5–7.5MHz transvaginal ultrasound probe. The method of examination was consistent with published recommendations (13). When ultrasonography confirmed that the gestational sac had been expelled, the maximal anteroposterior endometrial thickness, including any blood and clots, in the longitudinal plane of the uterus was measured. If the sac had not been expelled, the endometrial thickness was not measured. Quantitative-B hCG (Betha chorionic gonadotropin) Assay - Venipuncture samples were transferred within 30 minutes to the laboratory, where centrifugation was performed to separate serum. The results were expressed as IU/L. This assay can detect whole molecule (intact) hCG as well as free-hCG subunits. The analytical sensitivity of hCG detection in serum is 2 IU/L (with a correlation coefficient of 0.95), and the cut-off level for a positive test in serum is 25 IU/L. The comparison of quantitative variables across the study groups was conducted utilizing the Mann Whitney U test for independent samples. Categorical data comparisons were carried out using the chi-square test, and Yates correction was applied when the expected frequency fell below 5. The accuracy of the results was expressed through sensitivity, specificity, positive predictive

value, negative predictive value, as well as the likelihood ratios for both positive and negative tests. To identify the optimal cut-off values for the diagnostic markers under investigation, receiver operating characteristic analysis was employed. A statistical significance threshold was established at P<0.05.

## Results

Out of the 97 women enrolled in the study, 78 were found to have had a complete abortion (80.4%) and 19 to have had an incomplete abortion (19.6%), as determined by histopathological examination of uterine curetting. The baseline characteristics of women in each group were similar (Table 1). There was a statistically significant difference in estimated gestational age between the complete abortion and incomplete abortion groups (38.5 days and 46.5 days, respectively; P=0.026). The mean endometrial thickness in the two groups was 11.2±3.9mm in the complete abortion group and 14.6±6.1mm in the incomplete abortion group, a statistically significant difference (P=0.003) (Table 2). Mean serum-hCG levels also were statistically different in the two groups (73.9±23.9 IU/L in the complete abortion group and 109.4±68.4 IU/L in the incomplete abortion group; P<0.001). The accuracy of the studied markers in predicting complete abortion is shown in Table 3. An endometrial thickness of 12mm predicted incomplete abortion with a sensitivity of 88.5%, a specificity of 73.7%, a PPV of 93.2% and an LR+ve of 85.6. On the other hand, a serum-hCG level 100IU/L predicted incomplete abortion with a sensitivity of 87.2%, a specificity of 78.9%, a PPV of 94.4% and a LR+ve of 85.6.

**Table 2.** Ultrasonographic results and quantitative-hCG assay in the study groups.

| | Complete abortion (n =78) | Incomplete abortion (n = 19) | P |
|---|---|---|---|
| Endometrial thickness (mm)* | 11.2 ± 3.9 | 14.6 ± 6.1 | 0.003† |
| Serum-hCG (IU/L)* | 73.9 ± 23.9 | 109.4 ± 68.4 | < 0.001† |

*Data are given in mean ± SD; † statistically significant difference.

**Table 3.** Accuracy of the studied markers in diagnosing complete abortion.

| | Sensitivity | Specificity | PPV | NPV | LR+ve | LR-ve |
|---|---|---|---|---|---|---|
| Endometrial thickness (12mm) | 88.5% | 73.7% | 93.2% | 60.9% | 85.6 | 3.4 |
| Serum-hCG (100 IU/L) | 87.2% | 78.9% | 94.4% | 60.0% | 85.6 | 4.1 |

## Discussion

The safety and efficacy of medical termination of early pregnancy with mifepristone and misoprostol has been previously demonstrated in multiple studies (5,6). With the availability of mifepristone and misoprostol, it is expected that many women experiencing abortion may prefer a medical method of uterine evacuation because it allows them to avoid a surgical procedure. The clinical course of medical abortion closely resembles that of a spontaneous miscarriage.14 hCG values or measured endometrial thickness but following the patients' clinical course after two weeks follow-up, we were able to analyze the prognostic value of serum-hCG assay and ul-

trasonography as predictors of late failure. Serum-hCG was measured according to the internationally accepted standard reference. The overall percentage decline in-hCG is consistent with earlier findings (22, 20). In the present study, both the quantitative values of serum-hCGand and the endometrial thickness after medical abortion were higher in women who proved to be late failures than in women whose treatment was successful. Although most of the studies have reported an average duration of bleeding after medical abortion of approximately seven days, bleeding may last for as long as 21 days (23,24,25). In the event of persistent bleeding, surgical intervention should be applied. In addition to ordinary sonographic parameters, Markovitch et al., performed Doppler flow studies in patients after medically induced abortion (26). These authors found no correlation between the patients' reports of symptoms and the sonographic findings, and they found that an intrauterine echogenic mass with or without Doppler flow signals may not infrequently be detected two weeks after medical termination of pregnancy. Because most of the women with this finding subsequently resumed normal menses, they concluded that this finding could indicate remnants of trophoblastic tissue that will pass spontaneously without the need for dilatation and curettage (26). Steier et al., studied serum-hCG levels in women following the first trimester surgical abortion and demonstrated that the median time to reach a level of less than 10IU/L after surgical abortion was 30 days (range 16–60 days), compared to a median of 19 days (range 9–35 days) after spontaneous abortion (27). Honkanen et al., reported that serum-hCG concentrations have declined by 99.4% ±10% by day 14 after medical abortion, and that the route of medication administration (oral or vaginal) has no effect on the kinetics of serum-hCG (28). Another study reported that failed or incomplete abortion occurs when pregnancy tests with sensitivities of at least 1000 IU/L are positive within two weeks after surgical abortion (29). In our study we found that threshold levels of serum-hCG and endometrial thickness with high positive predictive values had a low sensitivity, leading to identification of only a minority of the failures. Higher positive predictive values were achieved by combining changes in serum-hCG levels and endometrial thickness, but still at the expense of sensitivity. Nevertheless, both parameters were acceptable as a diagnostic test because of their high positive predictive value. Based on the results of this study, we recommend the use of ultra-sonography and serum-hCG assays to help prompt diagnosis and management if patients have an uncertain outcome or suspected retained products of conception should be considered only after careful evaluation of the patient. The suspected late failures in the present study were identified after day 15, reflecting a long and tiring course of bleeding and/or pain. Being able to diagnose these failures earlier would optimize the medical abortion procedure. The data presented in this report, describing the regression of serum-hCG levels and endometrial thickness measurements, may be useful adjuncts for clinical management, especially when vaginal bleeding is prolonged or when serum-hCG levels and endometrial thickness measurements are much above expected values. The consequences of overlooking failed uterine evacuation are limited, because the risk of serious morbidity associated with retained tissue is minimal and because failures ultimately will be revealed clinically. With this background we conclude that the analyzed variables used as diagnostic tests would lead to a reduced number of unnecessary interventions. A thickened endometrium after miscarriage is a normal finding. An understanding of the relationship between endometrial thickness and the need for future surgical intervention is important. Our findings suggest that such a relationship exists, and that endometrial thickness measurements are likely to be predictive of incomplete abortion or the need for further treatment. In this study, a wide range of endometrial thickness was observed after expulsion of the gestational sac, and we observed a statistically significant difference in the mean endometrial thickness between women who had a complete termination and those who had an incomplete termination (11.2±3.9mm and 14.6±6.1mm, respectively). It should be emphasized that choosing a low endometrial thick-

ness cut-off point for clinical intervention would lead to unnecessary surgical treatment for a significant number of patients. Increasing the cut-off would decrease the false positive rate and improve the specificity of the test measurement. In our study, when the cut-off point for endometrial thickness was 12mm, the positive likelihood ratio was 85.57 and the negative likelihood ratio was 3.36.

## Conclusion

Quantitative serum-hCG levels and endometrial thickness, both were significantly higher in women with failed medical abortion than in women whose treatment was successful. Both of these measures are clinically useful in predicting late failure after medical abortion, and can be helpful in uncertain clinical situations, but should be considered as supplementary to a general clinical evaluation.

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# CONTEMPORARY APPROACH IN BLEEDING AND TRAUMA COAGULOPATHY MANAGEMENT: FIBRINOGEN AS A MAGIC BULLET

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## Abstract

Acute hemorrhage results in blood loss followed by consummation of procoagulants, as well as in circulating clotting factors. In acute bleeding, significant amounts of fibrinogen are lost, therefore both cellular and cascade phase of coagulation could be affected leading to coagulopathy. Fluid resuscitation in bleeding patients leads to dilution coagulopathy lowering the levels of circulating coagulation factors including fibrinogen even more further starting a vicious cycle. Many studies have shown that fibrinogen levels below 1g/l in bleeding patients are associated with bleeding and worse outcome suggesting that fibrinogen levels must be measured in trauma patients serving as a threshold for initiation of fibrinogen replacement therapy. Exogenous fibrinogen as a treatment option in critically bleeding patients with low fibrinogen levels has been shown to decrease transfusion needs. Algorithm-based individualized goal-directed use of fibrinogen resulted in highly significant reduction in transfusion needs, adverse outcomes, in certain studies even mortality, and where investigated - reduced costs, with high safety levels at the same time. It has been well established that low fibrinogen levels in patients who undergo cardiac surgery, liver transplantation surgery, in obstetrics, as well as in trauma patients are associated with higher bleeding risk demanding a proactive approach in early fibrinogen supplementation and replacement in order to a better outcome achievement. Although traditionally fibrinogen replacement and supplementation were performed via administration of fresh frozen plasma or cryoprecipitate, the use of lyophilized fibrinogen (concentrate) has become more prevalent in many countries. Recent reports relating to the efficacy of fibrinogen concentrate, suggest that it is a viable alternative to traditional hemostatic approaches, also being a cost-effective when compared to other replacement options which should be considered in a daily practice as well.

***Key Words:*** *Bleeding; Fibrinogen; Trauma Coagulopathy.*

## Introduction

Fibrinogen as a coagulation factor plays a crucial role in both cellular and fluid phase of the coagulation process. In the cellular phase fibrinogen by itself has a pivotal function in platelet activation via Glycoprotein IIb/IIIa, while in the fluid phase it is cleaved by thrombin to monomers of fibrin which polymerize in between resulting in formation of the clot. Since, in bleeding patients plenty of coagulation factors are lost, fibrinogen is most prominently lost, precipitating

coagulopathy. Not only coagulation factors, but thrombocytes are lost as well in cases of acute blood loss. Thrombocytes play significant role in the cell phase where they promote thrombin generation on their own surface. So, in cases of thrombocytopenia where thrombin generation is questioned it is more than essential that at least the levels of fibrinogen are within normal ranges in order to avoid hemostasis devastation.

## Trauma Coagulopathy, Bleeding and Fibrinogen Supplementation in Clinical Practice: an Evidence-based Review

It has been estimated that around 24-34% of trauma patients develop Trauma Induced Coagulopathy (1) which is described as an inflammatory condition of hemostasis derangement involving hypofibrinogenemia, coagulation factors depletion, increased systemic endothelial activation, platelet dysfunction, increased tPA activity and dysregulation of Protein C function (2). Trauma induced coagulopathy (TIC) is characterized with inability for clot forming due to lack of coagulation factors because of their consumption, shock, acidosis and endothelial damage. According to many guidelines the mainstay in treatment of Trauma Induced Coagulopathy is application of tranexamic acid, fresh frozen plasma, cryoprecipitate and coagulation factors concentrates. Usage of prothrombin complex concentrates and human fibrinogen concentrates have many benefits over fresh frozen plasma and cryoprecipitate supplementation as they offer a bigger and standardized concentration of coagulation factors with lower rate of viral infections transmission, not needing blood type matching. Since clear definition of trauma induced coagulopathy is lacking, difficulties in recognizing this entity could arise. Therefore, on time treatment could be questioned in many cases. Until now the definition for trauma induced coagulopathy was based on clinical aspects like presence of diffuse bleeding from injured and non-injured sites with laboratory findings of prolonged prothrombin time (PT). In reality in many cases PT is not prolonged while still patients are bleeding diffusely leading to a coagulation factors consumption. Nevertheless, treatment should be started immediately in patients who are bleeding despite the absence of laboratory evident disorders in hemostasis. When it comes to laboratory values that could be used in definition of trauma induced coagulopathy, many authors have different opinions making the definition of this condition even more complex and uncertain. Actually, analyzing the results of PT, aPTT and INR were widely used but at different thresholds according to different authors. According to Peltan et al., INR values greater than 1.5 suggest presence of trauma induced coagulopathy, while Frith et al., consider that INR greater than 1.2 should be considered as a threshold for initiation of therapy (1). Another group of authors suggest that extrinsic pathway viscoelastic tests like EXTEM with CA5<40mm and fibrinogen thromboelastometry FIBTEM <9mm are indicating presence of Trauma Induced Coagulopathy. In order to be more consensual when speaking about TIC, authors have created a scoring system that stratifies TIC patients into 3 groups according to severity of the condition. This stratification of severity corresponds to a patient with bleeding, shock and one of the following: TIC 1: fibrinogen level <1.5g/L; TIC 2: fibrinogen level <1.5g/L and INR >1.5; TIC 3: fibrinogen level <1.5g/L and INR >1.5 with platelet count <100,000×109/L (1).

Hypofibrinogenemia detected in trauma patients has been identified as an early predictor for massive transfusion, therefore early fibrinogen supplementation has been strongly recommended (3). Since it is well known that hypofibrinogenemia is a parameter who indicates a need for starting a Massive Transfusion Protocol as soon as possible, viscoelastic tests for FIBTEM as a point of care test could have a great impact in early and on time initiation of massive transfusion.

Massive transfusion protocol is indicated in patients with bleeding and shock, hemodynamically unstable patients, those with hemoglobin levels lesser than 9g/dl, base deficit greater than -6mmol/l and patients with FIBTEM <10mm. According to most of the recommendations and guidelines, a massive transfusion protocol should start with application of Tranexemic acid as soon as possible. Many studies have proven that application of Tranexemic acid could lower the mortality in trauma patients. According to the CRASH 2 study, application of Tranexemic acid within 8 hours and according to CRASH 3 study application of tranexamic acid within 3 hours of trauma, could significantly lower the risk of death due to bleeding in trauma patients and patients with traumatic brain surgery respectively.

During acute hemorrhage, fibrinogen is the first coagulation factor that reaches critically low levels promoting even more significant bleeding and coagulation factors consumption. Therefore, hypofibrinogenemia has been associated with a poor outcome in trauma patients and was identified as an independent mortality predictor. Fibrinogen is lost very early after trauma happens, leading to coagulopathy, therefore according to most of the recommendations and European trauma guidelines, early supplementation after hospital admission even before laboratory testing has been recommended (1). Fibrinogen supplementation in bleeding patients resulted in significant reduction of transfusion needs, adverse outcomes, and in certain studies it was associated with reduced mortality (4). European trauma guidelines recommend RBC:FFP or RBC:FHC as an initial treatment intervention. Since Fibrinogen Concentrate offers a significantly higher concentration of fibrinogen delivered in a small amount of liquid with significantly less risk for infection transmission, according to the European Expert meeting, it is recommended to be used instead of FFP when treating patients with TIC, delivering to the patient a well-known and fixed concentration of fibrinogen as soon as possible. Supplementation of Fibrinogen either as Fibrinogen Human concentrate or Cryoprecipitate is recommended in bleeding patients with hypofibrinogenemia rather than supplementation with FFP which is not recommended according to the European trauma guidelines. According to the study of Kikura M. et al., patients who have received fibrinogen supplementation either as a cryoprecipitate or fibrinogen concentrate have lower incidence of bleeding 50% versus 75% in the control group who did not receive any type of fibrinogen supplementation. Therefore, 2–3g of fibrinogen replacement reduces the incidence of major bleeding in patients with hypofibrinogenemia during cardiopulmonary bypass in thoracic aortic surgery (5). A meta-analysis that has included 14 randomized controlled trials, where fibrinogen concentrate was given, concluded that the patients that received fibrinogen concentrate have significantly lower mortality rate and lower need of blood transfusion, as well as they have experienced significantly less bleeding. Furthermore, this study has highlighted the fact that no differences in the rate of thrombotic events and myocardial infarction were observed in patients receiving fibrinogen compared to those who did not receive fibrinogen (6). In other words, fibrinogen infusion resulted in an increase in fibrinogen concentration and increased clot stability, while when it was combined with platelet transfusion, shortening of clotting time, increased clot stability and improved platelet aggregation were observed. This result confirms that supplementation of fibrinogen together with platelets improves coagulation and platelet aggregation followed by significantly less bleeding in patients undergoing cardiac surgery (7). Another study has confirmed that administration of fibrinogen has been associated with better clot firmness and lowered need for substitution of blood products as well (8).

It has been reported that fibrinogen supplementation reduces the need for blood products transfusions by 53% (9). Regarding fibrinogen supplementation, German and British guidelines recommend fibrinogen supplementation in patients with fibrinogen levels lower than 1.5g/l in dose

of 3-4g. According to the European consensus, human fibrinogen concentrate is recommended as the first line therapy in bleeding patients with hypofibrinogenemia. They recommend that fibrinogen should be administered even in bleeding patients in which fibrinogen levels are above the threshold value. Many societies have published recommendations for application of Prothrombin Complex Concentrate (PCC) in trauma patients where criteria for TIC are met in order to support thrombin generation and stability. Since in the very early stages of hemorrhage thrombin generation is not impaired, rather potentiated, therefore application of PCC should not be the first goal during the treatment of TIC, but hypofibrinogenemia should be firstly corrected instead. Preoperative levels of fibrinogen strongly corelate with the amount of bleeding as well as with the need for blood transfusion. According to this study patients who undergo spinal surgery with preoperative levels of fibrinogen lower than 1.9g/l will bleed significantly more than those with higher preoperative levels of fibrinogen (10). Another study confirmed that lower levels of fibrinogen in the preoperative setting in patients who undergo spinal fusion surgery could identify the patients with increased bleeding risk (11). Therefore, preoperative testing of fibrinogen levels in patients undergoing major surgery could reveal if the patient is prone to bleeding and its possible benefit of early supplementation of fibrinogen. Since lower fibrinogen levels were found to be associated with bleeding in patients who undergo liver transplantation, preoperative measurement of fibrinogen should be assessed in order to recognize those patients where fibrinogen administration will be beneficial (12).

Traditionally, fibrinogen supplementation was done with application of fresh frozen plasma (FFP) and/or cryoprecipitate, where FFP contains 2.0 to 4.5g/L of fibrinogen while cryoprecipitate contains 15 to 17g/L (13). Human fibrinogen concentrate is made from pooled human plasma and can be found in single-use vials containing 900 to 1300mg lyophilized fibrinogen concentrate powder for reconstitution. Human fibrinogen concentrate should be applied with an infusion rate of 10-15min for 1g of Fibrinogen compared to the FFP and Cryoprecipitate which need at least 30 minutes for thawing.

Cost effectiveness of fibrinogen concentrate has been questioned recently, since the price of the human fibrinogen concentrate is higher than the price of cryoprecipitate as a source of fibrinogen. Beyond the price of a single dose of Fibrinogen concentrate in comparison to Cryoprecipitate, there are multiple interventions, transfusions and care that when taken all at once can make the cost of fibrinogen concentrate versus cryoprecipitate more objective and real. Apparently, the question about the cost and effectiveness of fibrinogen concentrate versus usage of cryoprecipitate as an alternative source of fibrinogen, was examined in the study of Abrahamyan L. where 495 patients were included and randomized in 2 groups receiving Fibrinogen concentrate versus Cryoprecipitate due to cardiac surgery. In both groups number of transfusions in the first 24 hours and in the 7 postoperative days, as well as total cost of health care services and hospital stay were measured. According to the results of the study, in the group where Fibrinogen concentrate was given, lower amount of transfusions were met in comparison to cryoprecipitate group in both times at 24 hours as well as at the 7th day (14). They have found that the cost for transfusions in the first 7 days was lower in the fibrinogen group with 2.280$ versus 2.770$ in the group of patients receiving cryoprecipitate. The cost of hospital treatment at day 28th was lower in the fibrinogen group than in the cryoprecipitate group with total amount of 38.180$ versus 38.790$. Therefore, application of fibrinogen concentrate in hypofibrinogenemic patients is more suitable and cost effective when compared to cryoprecipitate delivering fixed and predictable dose of fibrinogen in more safe form with lowered risk for infection transmission which is not the case with cryoprecipitate where the amount of fibrinogen delivered to the patient is not

predictable neither standardized while transmission of infections is still possible (14). Human fibrinogen concentrate has many advantages over cryoprecipitate when treating hypofibrinogenemia. Actually, HFC is lyophilized and stored at a room temperature or refrigerated versus cryoprecipitate which is frozen needing more time for preparation due to proper thawing. Cryoprecipitate has a shelf life of 1 year while HFC has 3 years of shelf life (15). When we talk about near patient storage, rapid preparation and injection, human fibrinogen concentrate is superior to cryoprecipitate. Most importantly HFC is a pathogen reduced composition versus cryoprecipitate, where pathogen reduction and inactivation could be questioned. Fibrinogen content is another important task worth discussing because HFC is a preparation that offers uniform fibrinogen content to be delivered to the patient, which is not the case when cryoprecipitate is given considering that fibrinogen content could be highly variable and unpredictable. Pureness is another advantage of HFC regarding the process of preparation where fibrinogen is highly purified, while numerous impurities could be met in cryoprecipitate preparation which contains many other factors that could interfere with hemostasis. Actually, cryoprecipitate contains significant amount of factor XIII which could be very beneficial in bleeding control, but other factors, such as Factor VIII, platelet microparticles and vWF could elevate the risk for thrombosis. Regarding the risk for thrombosis in cardiac patients the FIBRES study has shown that usage of HFC in bleeding patients is associated with lower rate of arterial and venous thrombotic events when compared to cryoprecipitate. In another study in patients undergoing abdominal surgery, it was found that the patients who received HFC had 0% of thrombotic events versus 30% when patients were receiving Cryoprecipitate. Another difference between HFC and cryoprecipitate is that HFC acts on the process of fibrin polymerization while cryoprecipitate interferes in all phases of hemostasis which may be considered as an advantage or disadvantage too, depending of the case. Cryoprecipitate after thawing has a significantly shorter life span of 4-6 hours when compared to HFC after reconstitution which life span is 24 hours (15). Order to needle time has been discussed as well, which is considered to be 30min when HFC is given to the patients versus 2.7 hours after trauma in the group of patients who had received cryoprecipitate, which is significantly longer time and according to many authors is considered very late because those patients have already received in average 8 units of blood or blood products (15). Real disadvantage of HFC over cryoprecipitate is the higher price that could be an issue in a low-income country. In the study of Ayaganov et al., 88 patients undergoing cardiac surgery were randomized to receive Cryoprecipitate or HFC in order to manage bleeding, so 48 hours after administering either of the preparations, no significant differences between plasma concentration of fibrinogen were observed while treatment of patients with Cryoprecipitate was significantly more expensive with 1505$ versus 631$ in comparison to the group where HFC was administered showing again that HFC is non inferior to Cryoprecipitate when treating bleeding patients but is significantly cheaper (16). Another study have examined the effectiveness of HFC versus Cryoprecipitate in neonates undergoing cardiac surgery where no significant differences in clot degradation were observed while significantly less blood transfusions, bleeding and thrombosis after CPB were observed in HFC group (17). Regarding the acutely bleeding trauma patients, administering HFC in comparison to Cryoprecipitate was found to be associated with lower need for blood and blood products transfusions and shorter ICU and In-hospital length of stay while no differences in complications and mortality was observed between both groups (18). Moreover, the effect of HFC application in patients with trauma induced coagulopathy was recently examined in RETIC study ("Reversal of Trauma-induced Coagulopathy using First-line Coagulation Factor Concentrates or Fresh-Frozen Plasma") where patients were randomized to receive HFC as a first line therapy either other sources of coagulation factors as FFP or PCC. The results have shown that HFC given in patients with Fibrinogen levels greater than 1.0g/l in

dose of 63mg/kg only once sufficiently has corrected the plasma levels of fibrinogen as well as ROTEM results, while those patients with fibrinogen levels lower than 1.0g/l needed doubled dose of HFC or approximately 126mg/kg to achieve normalization of plasmatic fibrinogen levels as well as ROTEM testing results (19). According to the RETIC study, early achievement of plasmatic fibrinogen concentration greater than 2.0g/l is associated with better clot firmness, significantly lower rates of massive transfusion and has prevented lowering of platelet count followed by lowered rate of platelet transfusion. This study has concluded that despite the body weight, initial fibrinogen levels have significant impact when proper dosing of HFC is questioned in order to prevent massive blood loss (19).

## Conclusion

Many of the above-cited studies have highlighted the advantages of HFC when used in special occasions where objective indication exists. According to all previously mentioned, we can conclude that Human Fibrinogen Concentrate is a safe source of fixed concentration of purified fibrinogen offering predictable correction of plasmatic fibrinogen concentration when dosed properly without any significant prothrombotic events even in patients undergoing cardiovascular interventions. Advantages of HFC over other alternative sources of fibrinogen, such as Cryoprecipitate and Fresh Frozen Plasma, have been clearly discussed making HFC the most reliable source of Fibrinogen in clinical practice. The significance of on-time fibrinogen supplementation in bleeding patients and those experiencing TIC has been entitled in all guidelines and European Trauma Consensuses recommending the usage of HFC as a first line therapy in order to prevent massive transfusion and many other bleeding associated complications.

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# TRAIN-OF-FOUR MONITORING AND THE PERSISTENT PROBLEM OF RESIDUAL NEUROMUSCULAR BLOCKADE

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Residual neuromuscular blockade (RNMB) continues to be a pervasive and underestimated perioperative risk. Recent observational studies report RNMB incidence ranging from approximately 33% in patients without objective monitoring to 5–16% when quantitative monitoring and appropriate reversal were used, highlighting both the prevalence and preventability of this complication (1).

## Physiology and Value of Train-of-Four (TOF) Monitoring

Train-of-Four stimulation (four supramaximal stimuli at 2Hz) produces a measurable twitch-fade response. A TOF ratio of ≥ 0.9, ideally measured via acceleromyograph, electromyography, is necessary for the safe return of upper airway tone, pharyngeal coordination and ventilatory drive (2). Subjective assessment is grossly insensitive, and clinicians typically cannot detect fading at TOF ratios above 0.4, meaning patients may appear to breathe adequately yet still be at significant risk of postoperative airway compromise.

## Clinical Consequences of RNMB

Objective evidence demonstrates that TOF ratios < 0.9 correlate with increased symptoms of muscle weakness in the PACU. Patients with residual blockade report more weakness signs and have more severe symptoms compared to those with TOF ≥ 0.9 (3). In a randomized trial, extubating guided by ensuring a TOF ratio ≥ 0.9 significantly reduced critical respiratory events - such as hypoxia, upper airway obstruction and airway manipulation - compared to clinical judgment alone (4).

## Incidence of RNMB: The Impact of Monitoring

A 2025 prospective observational study found RNMB (TOF ≤ 0.9) in about 5% of the patients, some of whom required supplemental oxygen postoperatively - that is, RNMB remains relevant even when the best practices are used (5). A meta-analysis of 12,664 patients across over 50 studies revealed that without neuromuscular monitoring, the average RNMB incidence is approximately 33% (6). Even with sugammadex, arguably the most effective reversal agent, residual blockade can still be detected in around 5% of the cases when monitoring is not used (7).

"Post-anesthesia pulmonary complications after the use of muscle relaxants" (POPULAR) is a large prospective observational cohort study across 211 hospitals in 28 European countries. 22,803 patients undergoing general anesthesia (excluding cardiac surgery) were analyzed to as-

sess the impact of neuromuscular blocking agents (NMBAs) on postoperative pulmonary complications. The use of NMBAs was associated with a significantly increased risk of PPCs (adjusted OR 1.86), with no protective effect observed from neuromuscular monitoring, reversal agents or the use of sugammadex compared to neostigmine. These findings suggest that while NMBAs may be useful for surgical conditions, their usage carries a measurable increase in pulmonary risk that anesthesiologists must carefully weigh against potential intraoperative benefits (8).

In 2023, the European Society of Anesthesiology and Intensive Care published its first comprehensive, evidence-based guidelines on the peri-operative management of neuromuscular block. These guidelines provide key recommendations on the use of muscle relaxants for intubation, optimization of surgical conditions, monitoring to prevent residual paralysis, and safe strategies for pharmacological reversal. Together, they aim to standardize practice, enhance patients' safety, and reduce postoperative complications related to neuromuscular blockade. Inappropriate management of neuromuscular block remains common, with residual paralysis and related postoperative complications despite the availability of reliable monitoring and reversal agents. Using structured literature review (88 relevant studies from 24,000 screened), GRADE methodology, and a Delphi consensus, recommendations were formulated on key clinical questions regarding intubation, depth of blockade during abdominal surgery, and strategies for diagnosing and treating residual paralysis. Strong recommendations include the use of muscle relaxants for tracheal intubation, pharyngeal/ laryngeal protection, and rapid sequence induction; deepening blockade when required to optimize surgical conditions; quantitative neuromuscular monitoring; and sugammadex for reversal of amino-steroidal agents (9).

## Pharmacologic Reversal: Neostigmine vs. Sugammadex

Sugammadex offers rapid, predictable reversal of amino-steroidal NMBAs. A Cochrane review confirms its superiority over neostigmine in terms of reducing residual paralysis, bradycardia, nausea and vomiting - and targeted use with quantitative monitoring, can effectively eliminate RNMB. Nevertheless, even sugammadex fails in a small percentage of cases when used empirically without monitoring (7-9). While neostigmine can facilitate TOF recovery to ≥ 0.9, its efficacy is dose- and timing-dependent; suboptimal use may paradoxically worsen neuromuscular function (10).

## Barriers to Implementation of Quantitative Monitoring

Despite compelling data, implementation remains uneven. Surveys and studies reflect ongoing reliance on subjective assessment or time-based dosing (11). Guidelines from major bodies - such as the Association of Anesthetists of Great Britain and Ireland and the Australian and New Zealand College of Anesthetists - call for mandatory use of quantitative monitoring (with TOF ratio ≥ 0.9) to confirm neuromuscular recovery before extubating. Yet, adoption in routine practice is patchy, due to cost, logistic, educational and cultural barriers. Residual neuromuscular blockade (RNMB) remains a persistent and clinically significant problem, even in the era of modern anesthesia. Despite advances in pharmacology and monitoring technology, patients continue to face the risks associated with incomplete recovery from neuromuscular blocking agents. Quantitative train-of-four (TOF) monitoring and evidence-based reversal should no longer be regarded as optional or discretionary; they represent the standard of care that every anesthesiologist must embrace (12). Professional societies worldwide have already issued strong recommendations in

favor of quantitative monitoring, yet practice often lags policy. The next step is clear: integration. Monitoring must be woven into institutional protocols, embedded in training curricula, and made a mandatory element of perioperative safety checklists. Only through systematic adoption we can ensure consistent protection for every patient. Each time quantitative monitoring is neglected, patients are exposed to avoidable risks - hypoxemia, airway obstruction, reintubation and other serious postoperative complications (13). Such outcomes are not inevitable; they are the result of a preventable gap between evidence and practice. The time for half-measures has passed. Patients' safety demands nothing less than full commitment to monitoring, reversal and vigilance in every anesthetic practice.

## Conclusion

Residual neuromuscular blockade persists as a significant hazard in modern anesthesia, despite decades of evidence and the availability of effective solutions. Subjective assessment is inadequate; pharmacologic reversal is not foolproof; and patients' safety is compromised when TOF monitoring is neglected. Routine quantitative TOF monitoring, integrated into clinical pathways and supported by appropriate reversal strategies, should be regarded as a minimum standard of perioperative care. Adoption will require education, institutional support and a cultural shift in anesthetic practice. The cost of inaction - avoidable pulmonary complications, delayed recovery and patient's harm - is too high.

Ensuring full neuromuscular recovery before extubating is not a technical nicety; it is a fundamental responsibility. The time has come for anesthesia practice worldwide to make residual neuromuscular blockade a problem of the past.

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*CASE REPORT* *UDK: 616.153.857-056.7*

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# RHABDOMYOLYSIS AND MULTIORGAN FAILURE CAUSED BY CARNITINE PALMITOYL TRANSFERASE TYPE 2 DEFICIENCY

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## Abstract

**Background**: Carnitine palmitoyl transferase 2 (CPT-2) deficiency is the most common inherited disorder of long chain fatty acid mitochondrial transport, and the cause of recurrent rhabdomyolysis in children and adults.

**Case presentation**: Here we present a case of a six-years-old child with severe rhabdomyolysis, where multiorgan failure (renal, hepatic, respiratory, cardiovascular, neurological) occurred and full multiple organ intensive care unit support was needed. A CPT 2 deficiency was established with genetic testing.

**Conclusions**: A suspicion of CPT deficit should always be present, in case of elevated levels of creatinine kinase and rhabdomyolysis, with early rehydration therapy promptly started, hemodiafiltration, respiratory and cardiovascular support if needed.

***Key words:*** *Carnitine palmitoyl transferase; multi organ failure; rhabdomyolysis; renal failure.*

## Introduction

Carnitine palmitoyl transferase 2 (CPT-2) deficiency is the most common inherited disorder of long-chain fatty acid mitochondrial transport, and the cause of recurrent rhabdomyolysis in children and adults. It is an autosomal recessive disorder.

Carnitine palmitoyl transferases are enzymes located within the walls of mitochondria. Their primary role is to transport long-chain fatty acids (LCFA) through the wall of mitochondria inside, in order for them to go through a process of ß-oxidation. This is as follows: After conjugation to coenzyme-A (CoA) with a long-chain fatty acyl-CoA synthetase, they are transported across the mitochondrial membrane with the carnitine enzymes. CPT 1 is at the outer membrane and CPT 2 on the inner membrane. CPT 2 acts to transfer the conjugated fatty acids from carnitine within the mitochondrial matrix (1,2). After this transport LCFAs go through a process of ß oxidation, in order to get energy.

As a result of depletion of energy, due to not being able to transport LCFAs inside the cell, an increased intracellular calcium happens. This is caused by depletion of adenosine triphosphate or/ and direct injury of the plasma membrane. This leads to myocyte breakdown and release of creatinine kinase, myoglobin and electrolytes such as potassium (3).

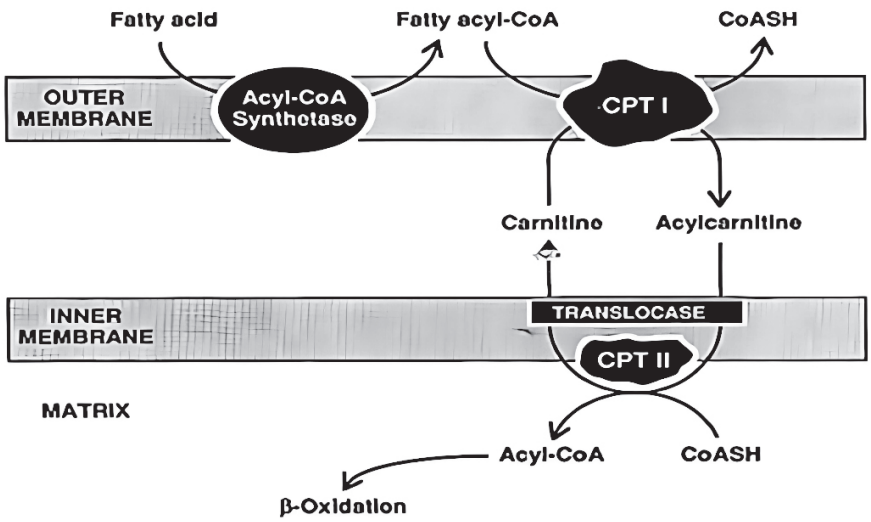


**Figure 1.** The mitochondrial carnitine palmitoyl transferase system, located on the mitochondrial wall, from McGarry and Brown analysis. Eur J Biochem 1997; 244 (1).

There are three variant forms of CPT II deficiency: lethal neonatal, severe infantile hepatocardiomuscular and myopathic (4). The first two present with hypoketotic hypoglycemia, liver failure, cardiomyopathy, cardiac arrythmia and peripheral myopathy. The third is the classical myopathic form which is characterized by recurrent episodes of muscle pain, muscle weakness and rhabdomyolysis triggered by exercise, stress or viruses.

## Case Presentation

A six-years-old male child was admitted in the ICU, with a one-day history of fever, vomiting and diarrhea, with impaired consciousness, oligoanuria and dark urine. After admission, he was placed on oxygen support with high-flow nasal cannulas, basic and extended microbiological and biochemical analyses were taken, and rehydration therapy was initiated. However, the very next day, due to respiratory and cardiovascular failure, he was intubated and placed on mechanical ventilation and inotropic support, due to severe hypotension. Because of severe hyperkalemia, anuria and impaired peripheral perfusion, a femoral dialysis catheter (Medcomp 8F/12cm) was placed and venovenous hemodiafiltration was initiated (Prismaflex).

After microbiological analyses for a positive PCR test for Influenza type A and Varicella virus, Tamiflu and Acyclovir and broad-spectrum antibiotics were included, with systemic corticosteroid and immunoglobulins. Due to convulsive approaches, antiepileptic therapy was introduced, and a lumbar puncture was performed with a finding of viral meningoencephalitis. Because of signs of pronounced SIRS were found, an interleukin 1(IL1) blocker, anakinra, was included.

In the following period, his hemodynamics improved, and gradual weaning from catecholamine support was performed. Three weeks after starting treatment, the child began urinating again

and quickly entered the polyureic phase of acute kidney injury, after which hemofiltration was stopped. A total of thirteen hemofiltration filters were used. Due to impaired consciousness and muscle weakness, a tracheotomy was performed. After that, weaning from the respirator was slowly carried out, and the child was left to breathe spontaneously in room air, with the need for aspiration of tracheobronchial secretions.

Blood was taken from the child and parents, and sent for genetic analysis, which proved the existence of a homozygous form of carnitine palmitoyl transferase type 2 deficiency. Appropriate dietary adaptation was made, and genetic counseling was performed. For the last ten days of the stay, the child was reunited with his mother, and she was trained to care for him. The child was discharged for home treatment, with a tracheostomy, due to still present muscle weakness.

**Table 1.** Laboratory findings

| **Days of hospitalization** | **1** | **2** | **3** | **4** | **5** | **7** | **14** | **31** | **54** |
|---|---|---|---|---|---|---|---|---|---|
| Leu 109/L 4.5-13.5 | 10.84 | 15.88 | 14.23 | 10.87 | 8.41 | 11.45 | 25.41 | 4.76 | 9.28 |
| Hct % | 37.4 | 36 | 31.5 | 33 | 26.6 | 27.6 | 32.8 | 33 | 39.0 |
| Trb 109/L 200-436 | 233 | 127 | 71 | 44 | 44 | 51 | 92 | 174 | 388 |
| CRP mg/dL 0.0-1.2/ PCT ng/ml 0-0,5 | 3.7/ 0.75 | 16.47/ >100 | 12.16/ >100 | 6.06/ >100 | 3.37/ >100 | 1.52/ | 1.27/ 0.89 | 2.13/ 0.44 | 0.17/ 0.08 |
| Urea mmol/L 1.7-8.0/ Creatinine µmol/L 28-52 | 2.9/ 35 | 9.0/ 94 | 4.9/ 54 | 3.8/ 37 | 3.3/ 32 | 2.3/ 28 | 11.6/ 97 | 10.9/ 141 | |
| Protein g/L 60-80/ Albumin g/L 38-54 | 72/ 45 | 52/ 26 | 49/ 31 | | 57/ 35 | 63/ 35 | 53/ 34 | 57/ 35 | 71/ 41 |
| AST U/L 0-40/ ALT U/L 0-41 | 1934/ 324 | 5852/ 1162 | >7000/ 2853 | >35000/ 2972 | 7541/ 2302 | 4281/ 2040 | 177/ 556 | 40/ 44 | 48/ 51 |
| CK U/L 31-152/ CK-Mb U/L | 99601/ 1645 | >289546 | >408480 | >466339/ 12861 | >331333/ 7369 | >11234/ 2504 | 4447/ 94 | 160/ 55 | 134/ 41 |
| Na+ mmol/L 132-145/ K+ mmol/L 3.1-5.1 | 131/ 4.19 | 135/ 6.09 | 135/ 3.17 | 135/ 3.6 | | 133/ 4.05 | | | 141/ 4.14 |
| INR 0.8-1.25 | 1.12 | 4.26 | 1.56 | 0.92 | 0.93 | 1.01 | | | 1.04 |
| D-dimers µg/ml < 0.5 | 0.8 | 1.85 | 1.41 | | 3.71 | | | | 0.68 |

| Days of hospitalization | 1 | 2 | 3 | 4 | 5 | 7 | 14 | 31 | 54 |
|---|---|---|---|---|---|---|---|---|---|
| IL6 pg/ml 0-7 | | 294 | 79.06 | 43.35 | 26.6 | 16.98 | | | 12 |
| BNP pg/ml <125 | | | 51374 | | | 19703 | | | |

Leu (leukocytes); Hct (hematocrit); Trb (thrombocytes); CRP (C-reactive protein); PCT (procalcitonin); AST (aspartate aminotransferase); ALT (alanine aminotransferase); CK (creatinine kinase); INR (international normalized ratio); IL6 (interleukin 6); BNP (B-natriuretic peptide).

## Discussion

We presented a patient with fever, respiratory and heart failure and acute kidney injury, that required hemofiltration. Our patient presented severe symptoms from the beginning of the admission. Most of the other cases that we reviewed (5-15), suggest a risk of developing a renal failure, and also generate a hypothesis that the CK levels on admission were connected with early organ support (16). However, this requires further directed study in order to prove this.

As we can see from the laboratory findings, on the first day of admission, they indicated elevated creatinine kinase (CK) and CK-Mb, but the whole picture was shown on the second and the next consecutive days. The levels of CK were the highest on the fourth day >466 339, which suggested massive rhabdomyolysis and no wonder an acute kidney injury occurred. These high levels of CK were not presented in the other case reports we reviewed (5-15).

The clinical condition worsened on the second day, despite rehydration therapy, with acute hyperkalemia and anuria, when hemofiltration was started. The urea and creatinine levels were normal most of the time, but that is due to hemofiltration. The patient was anuric for three weeks. After that the renal function was normalized and needed no support.

The patient's condition was very bad not only due to the rhabdomyolysis, but also due to the intense systemic inflammatory response syndrome, manifested as profound hypotension which required high doses of inotropes, systemic glucocorticoids and IL1 blocker.

Children tend to develop symptoms from more organ systems, such as fever, convulsions, anuria, respiratory insufficiency and multiple organ dysfunction, as our patient did, compared to adults where they mostly develop myalgia and sometimes renal symptoms (17). Also, one case report described CPT 2 deficiency in 13-years-old girl, which resulted in death due to hyperkalemia, renal failure, hypertension and life-threatening arrhythmias (18).

Scharman et al. (19) believed that early fluid resuscitation within the first 6 hours of muscle injury can reduce the occurrence of acute renal failure. In this paper, all 4 cases of rhabdomyolysis induced by exercise showed myalgia and tea-colored urine after exercise (squats, frog jumps, long-distance running). None of them developed acute renal failure, which may be related to timely medical treatment and early treatment, small lesion range (limb muscle injury), no chronic disease and good organ function.

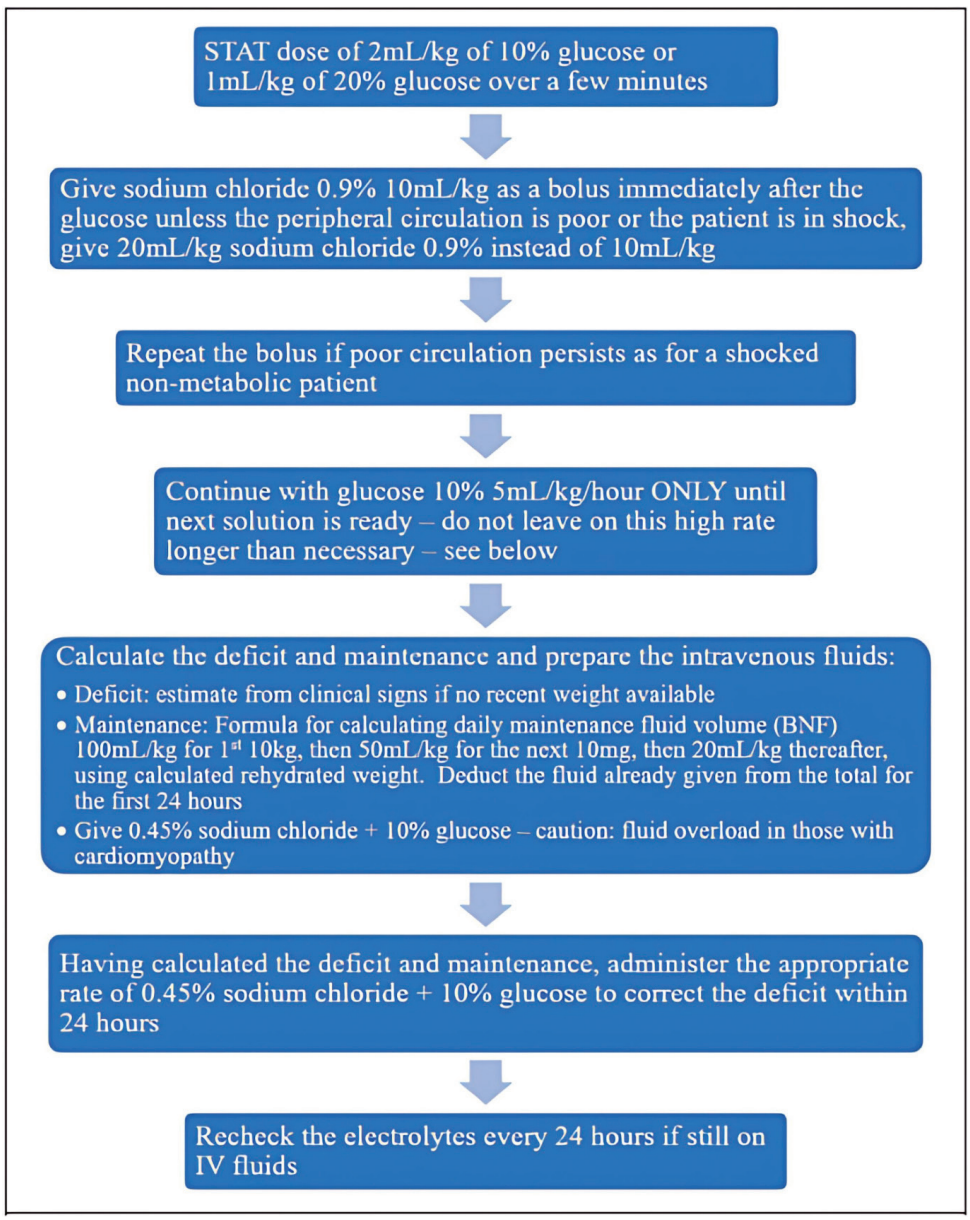


**Figure 2.** Intravenous glucose management in acute rhabdomyolysis in acutely decompensated LCFA disorders, from the British Inherited Metabolic Disease Group (20).

Establishing the diagnosis of CPT 2 deficiency, can be done with acylcarnitine analysis with tandem mass spectrometry. Also, laboratory findings, such as increased serum plasma creatinine kinase, transaminases, low carnitine levels, are found in these patients. But a definitive diagnosis is made with sequencing of the CPT2 gene for mutation analysis.

Long-term treatment is mainly based on an adapted diet: Avoidance of fasting, high-carbohydrate and low-fat diet, frequent meals, supplementation with medium-chain fatty acids and carnitine. Also, prevention should be emphasized, such as protection from infections, stress, prolonged exercise, exposure to cold, fever, fasting and prohibition of some medications (ibuprofen, valproic acid). The medium-chain fatty acid triheptanoin has been described to be effective in the late-onset CPT II deficiency (21).

## Conclusion

A suspicion of carnitine palmitoyl transferase deficit should always be present, in case of elevated levels of creatinine kinase and rhabdomyolysis. Early rehydration therapy should promptly be started. If the symptoms are worsening, these patients need to be placed in an intensive care unit setting, in order to start early with adequate support, such as hemodiafiltration, respiratory and cardiovascular support.

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# ANESTHESIA AND ANESTHESIOLOGICAL STRATEGIES IN A PATIENT WITH SEVERE LEFT VENTRICULAR DYSFUNCTION UNDERGOING PROSTATECTOMY

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## Abstract

This case describes the perioperative management of a 62-years-old male with a complex medical history, including ischemic heart disease (IHD), type 2 diabetes, hypertension, hyperlipidemia, chronic heart failure and a prior myocardial infarction (MI), requiring stenting. He was scheduled for prostatectomy due to prostate cancer and had a left ventricular ejection fraction (LVEF) of 37%, reflecting chronic dilated cardiomyopathy.

The patient was transitioned from oral anticoagulants to low-molecular-weight heparin preoperatively, and his glycemia was well-controlled. A carefully tailored anesthetic plan was implemented. The patient's vital signs remained stable throughout the three-hours surgery, with no immediate postoperative complications, and pain control was effectively managed.

Despite the patient's complex medical background, he emerged from surgery in stable condition and is currently recovering well, with ongoing radiation therapy for his prostate cancer. This case highlights the vital importance of thorough preoperative assessment, careful anesthetic management and continuous postoperative monitoring, in high-risk patients with cardiovascular comorbidities, underscoring the need for tailored treatment to prevent complications like MACE and MINS and to improve overall outcomes.

***Key Words:*** *Anesthesia for high-risk patients; chronic dilated cardiomyopathy; mortality risk.*

## Introduction

Ischemic heart disease (IHD) is becoming more common. There is also an increase in the number of ischemic heart disease patients getting non-cardiac surgical procedures, whether or not they have interventions. Patients are more susceptible to cardiac ischemia, myocardial infarction (MI), conduction abnormalities, and increased morbidity and mortality during the perioperative period. Patients who have recently suffered a myocardial infarction are at much higher risk

for these occurrences (1). Current Hospital Episode Statistics indicate that over 35,000 people in the UK die within 30 days of surgery each year. Major adverse cardiac events (MACE) are the primary cause of perioperative mortality, representing at least 30% of deaths (2).

We present a case of a 62-years-old male with significant cardiovascular comorbidities who underwent prostatectomy for cancer, highlighting the challenges and considerations in perioperative management of high-risk patients.

## Case Presentation

A 62-years-old male patient, obese, non-smoker, with a significant medical history, was scheduled for prostatectomy due to prostate cancer diagnosed in 2024. The patient had multiple comorbidities, including type 2 diabetes mellitus regulated with insulin injections, hypercholesterolemia with high LDL levels, hypertension, a history of acute myocardial infarction in 2017 which required LDA stenting, chronic ischemic dilated cardiomyopathy with recurrent episodes of pulmonary edema, and chronic renal disease characterized by mild elevations in creatinine and urea levels despite the absence of a history of dialysis. He had been on long-term oral anticoagulant therapy since his myocardial infarction. A 2023 cardiac MRI revealed a left ventricular ejection fraction (LV EF) of 18.59%. A preoperative echocardiography in 2024 showed an improved EF of 37%, though he remained in chronic dilated cardiomyopathy with severe left ventricular systolic dysfunction. Additional findings included mild ascending aortic dilatation and moderate aortic valve insufficiency.

Due to initially reduced ejection fraction, the patient was initiated on guideline-directed medical therapy comprising agents from several therapeutic classes, including anticoagulants, beta blockers, ACE inhibitors, calcium channel blockers, statins, diuretics, SGLT2 inhibitors, antiplatelets, and antidiabetics; follow-up after treatment optimization revealed marked improvement in cardiac function.

Oral anticoagulant therapy was discontinued two weeks before surgery and transitioned to low-molecular-weight heparin via subcutaneous injections. Preoperative glycemia was controlled at 5mmol/L. Chest X-ray revealed cardiomegaly accompanied by chronic signs of pulmonary congestion, and hemostasis parameters were within normal limits. Given his compromised cardiac function, a detailed anesthetic plan was formulated to minimize perioperative cardiovascular risks.

The induction protocol was weight-based and consisted of fentanyl at 1μg/kg, lidocaine at 1mg/kg, propofol at 2mg/kg and atracurium at 0.5mg/kg. Maintenance of anesthesia was achieved with remifentanil at infusion via perfusion pump at 0.25-0.5mcg/kg/min IV and sevoflurane administered at a MAC of 0.5-0.7%. Perioperative medications included antibiotics, antiemetics and analgesics.

The patient's vital signs remained stable throughout the three-hours procedure, with continuous invasive arterial blood pressure monitoring and standard electrocardiographic, capnography and pulse oximetry surveillance. Hemodynamic parameters remained within normal limits, with no episodes of hypotension or tachycardia. Fluid therapy was carefully tailored to support physiological stability, using balanced crystalloids at a rate of approximately 8mL/kg/h to maintain adequate intravascular volume and tissue perfusion. The patient responded well to volume

administration, and there was no need for vasopressor support.

The emergence from anesthesia was smooth and uneventful. The patient regained consciousness with stable respiratory and hemodynamic status, and no signs of agitation or discomfort. Pain was effectively managed from the immediate postoperative period, and the patient did not report any pain upon waking. Postoperative analgesia continued to be successful over the following days, with minimal pain scores and no requirement for rescue analgesics. There were no signs of postoperative nausea, vomiting or other complications.

Now, nearly five months after surgery, the patient remains in stable condition and has entered the next phase of oncological treatment. He is recovering well, with good functional status, and has commenced adjuvant radiation therapy under close outpatient follow-up. The patient admits to episodes of incontinence.

## Discussion

Dr. Jessica Spence from the Population Health Research Institute in Hamilton, Canada, pointed out that patients often assume the danger has passed once surgery is complete. However, this isn't always the case, as recent findings show that many postoperative deaths after non-cardiac procedures are primarily due to cardiovascular complications (3).

Reducing the patient's perioperative anesthetic and surgical morbidity and mortality, as well as facilitating a prompt return to optimal functioning, are the primary objectives of preoperative medical evaluation. It is important to note that "perioperative" risk is complex and varies depending on the kind of anesthetic used, the degree of invasiveness of the surgical procedure, and the patient's health prior to the procedure (1).Three primary mechanisms can lead to perioperative myocardial ischemia: coronary artery stenosis, which can cause an imbalance between oxygen supply and demand and become flow-limiting during perioperative hemodynamic fluctuations; acute coronary syndrome (ACS), which is brought on by stress-induced rupture or erosion of vulnerable atherosclerotic plaques, along with the pro-inflammatory and hypercoagulable states brought on by surgery, as well as hemodynamic stress from fluid shifts and anesthesia; and increased bleeding risks during surgery, which may require stopping anti-platelet therapy and possibly result in stent thrombosis in patients who have recently had coronary stent placements prior to non-cardiac surgery (4). A comprehensive history and physical examination, with an emphasis on risk factors for heart and lung issues, as well as an evaluation of the patient's functional ability, must be part of any preoperative evaluation (1).

Hofmann degradation, a spontaneous process of breakdown at body temperature and pH (45%), and metabolism by non-specific esterases in the plasma (45%) are both processes that atracurium endures. In healthy patients, only approximately 10% of a bolus dose is excreted in the urine over a 24-hours period. The chronic kidney disease does not affect the pharmacokinetics and pharmacodynamics of atracurium (5). Sevoflurane does not exacerbate epinephrine-induced cardiac arrhythmias and reduces myocardial contractility similarly to equianesthetic doses of isoflurane and desflurane. Like other volatile anesthetics, sevoflurane decreases baroreflex function. The incidence of myocardial ischemia, infarction and cardiac outcomes, did not differ between treatment groups in a number of multicenter studies that randomly assigned patients with CAD or patients at high risk for CAD to receive either sevoflurane or isoflurane during cardiac or noncardiac surgery. Therefore, as compared to other volatile anesthetics, sevoflurane

has not been linked to undesirable cardiovascular alterations in volunteers or in patients undergoing elective surgery. Additionally, it seems to provide more stable heart rate profile than either isoflurane or desflurane (6). Compared to other volatile anesthetics, postoperative AKI in patients undergoing noncardiac surgery was not linked to intraoperative exposure to sevoflurane anesthesia for longer than three hours. Selecting a particular volatile anesthetic drug for patients undergoing noncardiac surgery is not as crucial in preventing postoperative renal injury as predicting high-risk patients and improving intraoperative renal perfusion (7). Remifentanil possesses a distinctive pharmacokinetic profile characterized by a fast onset and cessation of activity, along with plasma metabolism. Its application is advisable even in patients with renal impairment, hepatic dysfunction, or compromised cardiovascular function. A possible cardioprotective preconditioning effect has been proposed. Adverse effects associated with the drug appear to be similar to those of other opioids. Numerous randomized controlled trials in cardiac surgery have shown that the advantages of remifentanil encompass significant protection against intraoperative stressors, as well as expedited postoperative recovery, prompt weaning from mechanical ventilation and early extubating (3).

The incorporation of procedure-specific hazards into preoperative patient's evaluation and optimization is essential to perioperative treatment (8). Perioperative myocardial infarction (PMI) is a possible outcome for people having major non-cardiac surgery. The frequency of postoperative myocardial infarction was significantly underestimated since it was only recognized by clinical symptoms and electrocardiographic changes before the development of ischemic damage biomarkers like troponin. Often, analgesia masks discomfort. Additionally, because postoperative ECG monitoring is rarely used, transient ischemic changes may go undetected, which could result in a missed diagnosis. MINS (Myocardial Injury after Non-cardiac Surgery) is the term used to describe myocardial injury that occurs after non-cardiac surgery. According to the IV global definition of myocardial infarction, a troponin reading that is higher than the 99th percentile of the upper reference limits, indicates myocardial injury (9).

40,004 patients, 45 years of age or older, who had noncardiac surgery and spent at least one night in the hospital were included in the VISION study. Patients from 27 sites across 14 countries (covering regions of North and South America, Europe, Asia, Africa and Australia) were followed up for 30 days after surgery to check for complications. The researchers discovered that 715 (1.8%) of the patients passed away within 30 days following noncardiac surgery. Out of these, 505 (71%) died in the hospital, including four [0.6%] in the operating room, while 210 (29%) died after being released. "Almost all patients passed away after leaving the operating room, one in 56 patients passed away within 30 days following noncardiac surgery, and over a quarter passed away after being released from the hospital," Dr. Spence stated. Eight perioperative problems, including five cardiovascular occurrences, were linked to death within 30 days following surgery (10).

Nearly 75% of all deaths were caused by the three primary outcomes: infection (20%), severe hemorrhage (25%), and myocardial damage following noncardiac surgery (MINS; 29%). Myocardial ischemia is believed to stem from an imbalance between oxygen supply and demand in the heart, occurring during an acute sickness episode. The precise process by which this occurs remains mostly unidentified. Recent investigations indicate that acute postoperative endothelial dysfunction contributes significantly, particularly through decreased endothelial nitric oxide generation. Vagal dysfunction, resulting in failure to acclimatize to the physiological demands of surgery, has been proposed as a potential etiology of MINS. MINS is generally recognized as linked to elevated 30-days mortality; however, research on effects extending beyond this period is limited (11).

## Implications for Anesthesia Practice:

Patients identified with elevated cardiovascular risk might utilize perioperative methods to reduce the likelihood of postoperative Major adverse cardiac events (MACE) and Myocardial damage following noncardiac surgery (MINS). [12]

1. Preoperative Risk Assessment:

- The VISION trial showed that a simple blood test measuring high-sensitivity troponin T can detect MINS early, enabling timely intervention to prevent complications (10).

Optimization of Comorbid Conditions:

- While clinicians aim to provide effective and equitable care, delays in surgery can lead to deconditioning and increased risk of complications postoperatively. Chronic diseases may stem from behavioral risk factors (e.g., poor nutrition, frailty, smoking, alcohol use) or medical comorbidities. Both affect perioperative outcomes, and patients often present with conditions from both groups. Identifying and managing these factors can help improve patients' ASA scores preoperatively (13).
- Recent recommendations suggest that even patients not previously on statins - regardless the cholesterol levels - may benefit from perioperative statin therapy to reduce cardiovascular risk. Elevated cholesterol also affects anesthetic metabolism, such as slowing propofol clearance (14).
- Our understanding of hypertension's role in cardiovascular disease has led to improved blood pressure management, contributing to a 60% drop in cardiovascular mortality from the mid-1950s to the mid-1990s. This decline is linked to better awareness and control of hypertension, dyslipidemia and smoking (15).

2.Tailored Anesthetic Strategies:

- A thorough preoperative assessment is key in selecting a safe anesthetic technique (16).
- Continuous invasive arterial pressure monitoring helps detect rapid fluctuations in high-risk patients, with careful removal of artifacts like over- or under-damping (13).
- Unless contraindicated, patients should receive a combination of acetaminophen, NSAIDs or COX-2 inhibitors, dexamethasone and a regional analgesic or local anaesthetic (17).

3. Postoperative Monitoring and Management:

- Postoperative vigilance is crucial due to the high risk of myocardial infarction within 72 hours of the surgery, requiring careful management of prescriptions, oxygen, analgesia, DVT prophylaxis, clinical observations, early warning scores and blood reviews (12).
- Managing MINS postoperatively involves minimizing triggers like hemodynamic instability and anemia, with long-term pharmacologic strategies including beta-blockers, statins, antiplatelets and anticoagulants. Research suggests MINS is preventable and that its sequelae can be reduced (11).
- Recent ESC guidelines recommend routine troponin screening for at-risk patients undergoing non-cardiac surgery, reflecting the growing importance of MINS detection.

Post-surgery, patients are monitored every 4 to 8 hours in the hospital, with follow-up care after 3 to 4 weeks (18).

Research indicating continuous pulse oximetry and blood pressure monitoring in surgical patients reveals that numerous individuals experience extended periods of hypoxia and hypotension, which often go unrecognized by healthcare professionals. Research indicates that hypoxia and hypotension can precede postoperative complications. Implementing remote automated monitoring technology, coupled with the availability of a healthcare provider to address early signs of potential complications, may enhance postoperative outcomes, akin to the improvements in intraoperative results achieved through the involvement of anesthesiologists and advanced monitoring techniques. Evaluation of these interventions in prospective studies is necessary. Considering that 99.3% of deaths among adults undergoing noncardiac surgery occur postoperatively, enhancing postsurgical care in both hospital and home environments may significantly decrease mortality rates (18).

Since they were first published in 1996, the ACC/AHA recommendations on the perioperative cardiovascular examination and management of patients having noncardiac surgery, have taken into account the growing body of research. Compared to previous iterations, the 2007 revision of these guidelines placed more emphasis on preoperative clinical risk assessment and less emphasis on standard preoperative cardiac testing in patients with suspected or confirmed coronary heart disease. Laboratory tests should be used cautiously before surgery, but only if the findings have the potential to significantly impact patient's care (19). Due to the susceptibility of these patients to myocardial ischemia, infarction, and arrhythmias during the perioperative period, a comprehensive evaluation of their history and tests is essential. Every risk factor that can be changed needs to be taken care of. It is necessary to order additional tests if needed. The involvement of cardiologists, surgeons, treating physicians and patients is essential due to the collaborative nature of this undertaking. During the perioperative period, anti-failure medications such as beta-blockers and statins must be given regularly. Guidelines for anticoagulant medication must be adhered to when using regional anesthesia. Factors that change the myocardial oxygen supply-demand ratio must be addressed. For the early identification of ischemia and irregular heartbeats, monitoring is crucial (20).

Clinicians should advise patients who have radical prostatectomy, that while incontinence is normal in the short term and usually returns to baseline by 12 months following surgery, it may still occur and need to be treated (21).

In addition, randomized research conducted in 2025 on patients having severe cancer surgeries found that compared to usual care, remote perioperative telemonitoring greatly improved functional recovery and decreased major postoperative sequelae.[22] In order to lower perioperative mortality, research on prevention, early detection and therapy should concentrate on these problems. The median time to these events can be used to determine the optimal period to monitor each complication in order to maximize effectiveness. Prioritizing the prevention, early detection, and treatment of sepsis, MINS and substantial bleeding, may reduce perioperative mortality (19).

## Conclusion

The substantial risks involved in treating individuals with ischemic heart disease (IHD) having non-cardiac surgery are highlighted by this example. The significant death rate among these

patients emphasizes the necessity of thorough preoperative assessment and careful perioperative care. In order to lower risks and enhance results in high-risk surgical patients, this instance highlights the significance of personalized care.

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# THORACIC OUTLET SYNDROME

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## Abstract

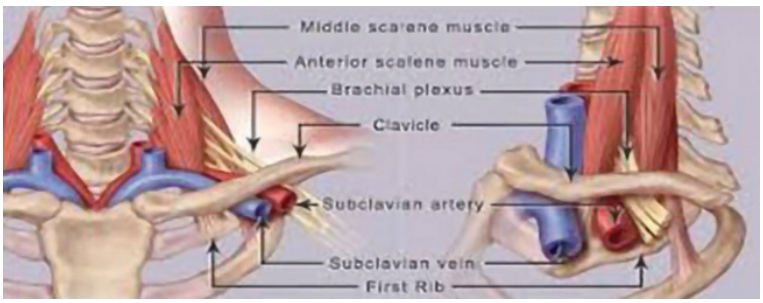
Thoracic outlet is a space that borders the clavicle, the first rib and the scalene muscles. In this space an extra rib can also be inherently present. The subclavian artery and vein, as well as the nerve roots of the brachial plexus, pass through this space. Compression on any of these structures can result in symptoms and cause an arterial, venous or neurogenic type of thoracic outlet syndrome. In the arterial type dominate symptoms of painful and cold arm. In the venous type of pain and edema and in the neurogenic type of pain - tingling and burning sensation in the upper extremity can be present.

A case report is of a patient who had unspecified neurologic symptoms of tingling, burning sensation and pain in the right arm that exacerbated especially when the patient was sleeping on the left side of the bed. The patient had consulted several specialists regarding the symptoms; internists, orthopedic doctors, neurologists and rheumatologists, whose therapies proved unsuccessful. When in the right supraclavicular fossa appeared a formation with solid consistency and the needle biopsy proved presence of osteocytes, a CT examination of this region was proposed. The result of the CT scan proved presence of an accessory cervical rib that compresses the brachial plexus and was the cause for the neurological symptoms. Thoracic outlet is still a diagnostic challenge, and regarding the treatment plan several experienced specialists from different specialties should be consulted due to its multicausality.

***Key Words:*** *Extra rib; plexus brachialis; subclavian – artery and vein; thoracic outlet syndrome.*

## Introduction

Thoracic outlet is an anatomical region which borders: the first rib, the clavicle, the anterior and middle scalene muscles, and there are also neurovascular structures present (1). In this relatively narrow space are located: the subclavian artery and vein and the nerve roots of the brachial plexus (Picture 1). Due to the close proximity of the aforementioned structures a compression is possible on one of them.




**Picture 1.** Anatomy of the thoracic outlet space.

In this space some patients can have an accessory rib that is called a cervical rib (2). This cervical rib can fuse with the first rib through bone or fibrous tissue. Sometimes inherent fibrous tracks, ligaments and muscles that normally are not in this anatomical region can be present in this space and increase the pressure in it. Thoracic outlet syndrome may also result from trauma, repetitive arm movements, tumor and pregnancy.

Synonyms for this term are the following: upper aperture syndrome, accessory rib syndrome, brachial plexus compressive syndrome, retroclavicular compressive syndrome etc.

Patients with thoracic outlet syndrome are classified in two groups:

1. Group with compression of blood vessels (subclavian artery and vein), and
2. Group with compression of nerves (brachial plexus).

The compression of blood vessels can be arterial or venous.

During arterial compression of thoracic outlet syndrome (TOSa), the main clinical manifestation is painful, cold and bruised arm (3).

The venous compression of thoracic outlet syndrome (TOSv) manifests with edema, pain and redness of the arm (4).

Symptoms that appear in brachial plexus compression – neurogenic type of thoracic outlet syndrome (TOSn) are tingling, paresthesias and pain in the arm and hand, and are more frequent compared to those of vascular compression (5).

The clinical manifestations can be a combination of the neurogenic as well as the vascular type of this syndrome. However, patients with compression of the brachial plexus are more complex because neurogenic symptoms can be caused by more causes, primarily cervical spondylosis. The goal of this publication is to present a case report of a patient who has made many medical examinations, spent much time consulting several medical specialists, and none of them has pointed out that this diagnosis is possible as a differential diagnosis.

## Case Report

The patient is a 55-years-old intellectual woman who takes care of her health. She has made regular occupational health checkups and was without any significant health issues. Occasionally she complained of cold arms, especially of the right arm and tingling of the right arm that

worsened during sleeping on the right side of the bed. The GP explained these symptoms as part of cervical spondylosis and menopause.

On a routine breast checkup, an enlarged lymph node was detected with the size of a walnut in the right supraclavicular region which was not painful on touch.

The patient was disturbed because her older sister was diagnosed with Non-Hodgkin lymphoma and an enlarged lymph node in the femoral region before 4 years, on the same age as her younger sister.

The following tests were recommended: blood work for inflammatory markers, lymph node biopsy, X ray of the cervical spine and lungs, ultrasound of the abdomen, consultation with a hematologist.

The blood work, primarily for inflammatory markers, sedimentation, leukocytes, blood differential test, CRP, RF and AST were all within the reference ranges.

The X ray of the cervical spine and the lungs were normal for that age.

The ultrasound examination of the abdomen was in physiological range except for the involuted changes of the uterus.

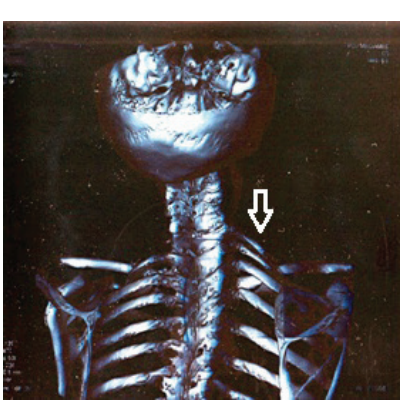
Ultrasound of the breast and surrounding structures findings were the following:

- Unclearly limited formation with solid consistency with dimensions of 3x2 cm and is located deep in the soft tissues of the right supraclavicular fossa;
- Bilaterally above the clavicles, lymph nodes and blood vessels with dimensions of 6.5mm;
- In the axillary fossa normal lymph nodes.

Findings of the biopsy of a lymph node.

With puncture and aspiration, it was unable to break through the bone consistency of the formation. The punctured formation fits mostly with benign osteoma or osteocartilaginous exostosis. Atypical and malignant cells were not found.

The GP who ordered these tests analyzed the data, and said that the diagnosis is unspecific, so he proposed a CT scan of the neck and upper part of the thorax.



**Picture 2.** CT of the neck and upper thoracic region. The arrow points to the extra rib.

The CT scan of the cervical spine has shown a right accessory (cervical) rib which originates from the C7 vertebral body, and the end of the rib touches the first rib and makes a small pseudoarthrosis (Picture 2). Degenerative changes of the C5-C6 vertebral bodies on the touching surfaces of the vertebral bodies were present, and no spinal canal stenosis and no enlarged lymph nodes.

The CT scan has helped in making the diagnosis: Thoracic Outlet Syndrome – accessory cervical rib right with neurological manifestations.

## Discussion

Thoracic outlet syndrome is a condition in which there is a compression of the nerves, veins or arteries in the superior thoracic aperture, the passageway from the neck to the armpit known as the thoracic outlet.

This condition was first described in 1818 and the term "thoracic outlet syndrome" for the first time was used in 1956 (6).

This condition is relatively rare, represented with frequency of 1% of the population, more common in women than in men and the most commonly manifested at the age of 20-50 years (7).

Making the diagnosis of this syndrome can be controversial. This group of patients visits doctors of many different specialties: internists, rheumatologists, orthopedic doctors, neurologists, psychiatrists, without an accurate diagnosis, and of course without a significant effect in therapy.

The patient presented in our case report had neurological issues such as tingling, burning and pain in the right arm especially while sleeping on the right side for years and visited several specialists. The explanations were that she had cervical spondylosis, rheumatic issues and menopause. In several instances X ray of the cervical spine was performed, and an accessory cervical rib was not detected. The compression of the cervical rib confused the pathologist who thought that he was performing a biopsy of an enlarged lymph node, and he was later surprised by the result findings of osteocytes in the tissue sample.

The neurologic type of thoracic outlet syndrome is the most common type of this condition with frequency of 85-90% from the whole count of cases of this syndrome, and the vascular type, arterial and venous type of TOS are 10-15% (8).

Almost all patients with neurogenic type of TOS report exacerbation of symptoms when they elevate their arms above their heads. Some activities may provoke symptoms such as prolonged work on a computer, long driving on motorcycle, long time holding the phone while speaking, putting the clothes to dry etc. In clinical examinations, the infraclavicular space should be palpated so that the symptoms linked to compression of the brachial plexus can be revealed in 40-50% of the patients with TOS (9).

One of the most important components of the physical examination for TOS is the Elevated Arm Stress Test (EAST). Patient is positioned with the arms elevated in a 90/90 degree "surrender" position and asked to repetitively open and close the hands for up to 3 minutes. Most of the patients with TOSn report the rapid onset of pain in upper limbs within 20-30 seconds (10).

When this test is positive electrophysiological testing is additionally performed.

In patients suspicious of the vascular type of TOS, the arterial and venous circulation is estimated to be with duplex ultrasound.

The treatment of the neurogenic type of TOS is controversial with advice to avoid positions that exacerbate symptoms and physical therapy. Medicaments that are most often used are NSAIDs, muscle relaxants and Botox treatment that alleviates the spasm if the compression is from the scalene or pectoral muscle (11).

The most radical treatment is surgical resection of the accessory rib (extra rib) or the muscles that make the compression. The surgical procedure is linked to possible complications and should be performed in centers that have experience with this medical issue.

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# LEFT VENTRICULAR TRUE ANEURYSM: CARDIAC CT ANGIOGRAPHY DIAGNOSIS AND DIFFERENTIATION FROM PSEUDOANEURYSM

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## Abstract

Left ventricular true aneurysms (LVTA) are uncommon, but clinically significant sequelae of myocardial infarction (MI), most frequently arising weeks to months after transmural infarction due to progressive ventricular remodeling and scar formation. Accurate differentiation from left ventricular pseudoaneurysm (LVPA) is critical, as LVPA represents a contained myocardial rupture with a substantially higher risk of fatal rupture, often necessitating urgent surgical repair. LVTA, in contrast, is generally more stable and can be managed conservatively in selected cases.

We report a case of a 68-years-old male with a history of anterior ST-elevation MI who presented with progressive exertional dyspnea. Cardiac CT angiography (CTA) was performed for further evaluation, and it demonstrated a large anterolateral LV outpouching with a broad neck (orifice-to-cavity diameter ratio of ~0.9), preserved myocardial continuity, traceable coronary arteries along the aneurysmal wall, and traceable mural calcifications - features consistent with chronic LVTA. No pericardial effusion, mural thrombus, or signs of rupture were present.

This case underscores the diagnostic value of CTA in characterizing LV outpouchings, particularly when echocardiography or MRI is unavailable or inconclusive. CTA offers high spatial resolution, multiplanar assessment, and precise measurement of the aneurysm's neck and cavity, enabling confident differentiation between LVTA and LVPA, guiding clinical decision-making and preventing unnecessary urgent surgery.

***Key Words:*** *Cardiac CT angiography; left ventricular aneurysm; myocardial infarction; pseudoaneurysm; true aneurysm.*

## Introduction

True LV aneurysms are defined as dyskinetic outpouchings of the ventricular wall containing endocardium, epicardium and fibrous myocardial tissue (1,2). They develop in fewer than 5% of the patients following ST-elevation myocardial infarction (STEMI), typically within 5 days to 3 months (1,3). Pathophysiology involves infarct expansion and remodeling, resulting in thinning and bulging of scarred myocardium during systole (4).

In contrast, LVPA is a contained myocardial rupture, with the sac wall composed predominantly of pericardium and fibrous adhesions (1,5). LVPA carries a high risk of rupture and sudden

death, often requiring urgent surgery (5,6).

Morphologically, LVTA usually presents with a broad neck (orifice: cavity ratio ~0.9–1.0) and preserved myocardial continuity, whereas LVPA exhibits a narrow neck (ratio 0.25–0.5) and lacks myocardium in the sac wall (1,5,7). Cardiac CT angiography offers high spatial resolution and multiplanar assessment, enabling accurate measurement of the neck and cavity dimensions, wall calcification, thrombus, and coronary artery course (1,5,8). Cardiac magnetic resonance imaging (MRI) further enhances diagnostic accuracy by providing superior myocardial tissue characterization, enabling differentiation between fibrotic scar and viable myocardium, and confirming the integrity of myocardial layers in suspected aneurysms (3,9).

## Case Presentation

A 68-years-old male with a history of anterior STEMI 10 weeks earlier, treated with primary PCI to the proximal left anterior descending artery, presented with progressive exertional dyspnea. Examination revealed a laterally displaced apical impulse and no audible murmurs. ECG showed persistent ST-segment elevation and deep Q waves in leads V2–V5.

CTA Protocol: A retrospectively ECG-gated CTA was performed on a 128-slice scanner following intravenous iodinated contrast injection. Multiplanar reconstructions were obtained.

CTA Findings, Figure 1a–c:

- A large, broad-necked aneurysmal dilatation of the anterolateral LV wall measuring 49 × 41mm in maximal dimensions.
- The neck measured 43mm, giving an orifice-to-cavity diameter ratio of ~0.9, consistent with a true aneurysm morphology (1,5).
- The aneurysm wall was thinned but continuous with adjacent myocardium, with traceable coronary arteries along its course.
- Traceable specks of mural calcifications along the sac wall indicated chronicity.
- No pericardial effusion, hemopericardium, or active contrast extravasation was present.
- No mural thrombus was detected.

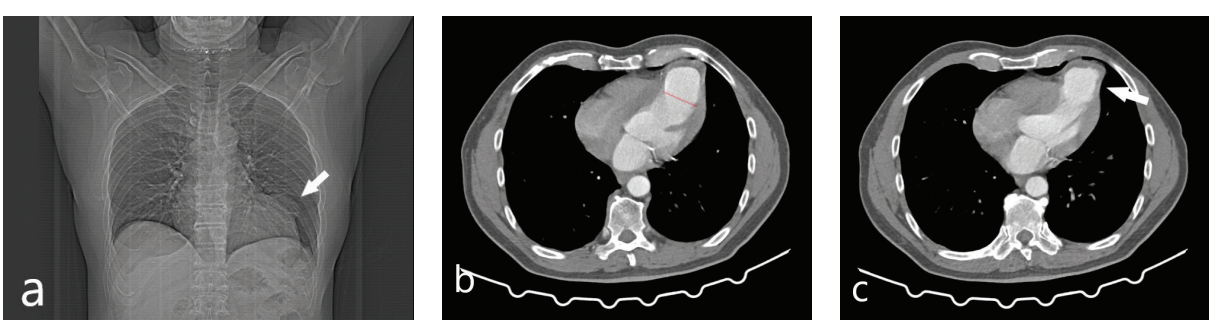


**Figure 1.** (a) Chest radiograph demonstrating a focal anterolateral outpouching along the left ventricular contour, consistent with aneurysmal dilatation. (b) and (c) Axial cardiac CT angiography images showing a broad-necked aneurysm of the anterolateral left ventricular wall, with preserved myocardial continuity and tiny specks of mural calcifications.

Given the absence of complications or rupture risk indicators, conservative management with optimized heart failure therapy was continued.

## Discussion

CTA is increasingly recognized as a key tool in the evaluation of LV outpouchings, particularly when echocardiography is inconclusive or when detailed anatomical assessment is required (1,5,8).

Differentiating LVTA from LVPA on CTA, *Table 1*:

- Neck size: Broad neck (ratio ~0.9–1.0) in LVTA; narrow neck (0.25–0.5) in LVPA (1,5,7).
- Wall composition: LVTA shows myocardial continuity and may have mural calcification; LVPA walls lack myocardium and are pericardial in nature (1,5).
- Coronary arteries: In LVTA, coronary vessels can be traced along the aneurysm wall; LVPA walls are avascular (1,5).
- Additional features: Presence of chronic mural thrombus or calcification suggests LVTA, whereas pericardial effusion/hemopericardium favors LVPA (2,5).

**Table 1.** Imaging Features of Left Ventricular True Aneurysm (LVTA) vs. Left Ventricular Pseudoaneurysm (LVPA).

| Feature | LV True Aneurysm (LVTA) | LV Pseudoaneurysm (LVPA) |
|---|---|---|
| **Neck size (orifice: cavity ratio)** | Broad (~0.9–1.0) | Narrow (0.25–0.5) |
| **Wall composition** | Myocardium + endocardium + epicardium (continuous wall) | Pericardium and fibrous tissue only; no myocardium |
| **Wall thickness** | Thinned but intact | Thin, often discontinuous |
| **Coronary artery course** | Coronary vessels traceable along aneurysm wall | No coronary vessels in sac wall |
| **Calcification** | Common in chronic cases | Rare |
| **Thrombus** | May be present chronically | May be present |
| **Pericardial effusion / hemopericardium** | Rare | Often present |
| **Rupture risk** | Low | High |

Comparison to Other Imaging Modalities:

While CTA provides high spatial resolution, multiplanar capabilities, and precise anatomical measurements, other imaging modalities play important roles:

- Transthoracic echocardiography (TTE): Widely available, rapid and non-invasive; useful for initial screening but limited by acoustic windows and operator dependency.
- Transesophageal echocardiography (TEE): Superior resolution for posterior structures; invasive and less suitable for unstable patients.

- Cardiac MRI (CMR): Gold standard for myocardial tissue characterization; allows detection of fibrosis, infarct size and integrity of myocardial layers; limited availability, longer acquisition time, and contraindicated in certain patients (e.g., with incompatible devices).
- CTA: Especially valuable when MRI is unavailable or contraindicated, or when precise measurement of the aneurysmal neck and detection of calcification are needed.

Clinical Decision-Making and Follow-Up:

In stable LVTA without high-risk features, conservative management is often appropriate. This includes optimized heart failure therapy, anticoagulation when indicated, and periodic imaging surveillance (e.g., echocardiography or CTA every 6–12 months, or sooner if symptoms change). Surgery is reserved for refractory heart failure, systemic embolization or malignant arrhythmias (3,8). In contrast, suspected LVPA generally warrants urgent surgical repair given its high rupture risk.

In this case, CTA demonstrated all hallmarks of a chronic LVTA: broad neck, preserved myocardial continuity, specks of mural calcification and absence of pericardial effusion. These findings aligned with previously reported CT differentiation criteria (1,5,8). The patient's stable clinical status and absence of rupture indicators supported a conservative management strategy with regular follow-up.

## Conclusion

This case highlights the pivotal diagnostic value of cardiac CT angiography (CTA) in differentiating left ventricular true aneurysm (LVTA) from pseudoaneurysm (LVPA), particularly when other imaging modalities are unavailable or inconclusive. CTA provides high-resolution, multiplanar visualization, enabling precise measurement of the aneurysmal neck, evaluation of myocardial continuity, assessment of wall composition and identification of ancillary findings such as mural calcification or thrombus. Recognizing these morphological hallmarks allows for confident diagnosis, facilitates appropriate risk stratification, and supports tailored patient's management. In selected stable cases, accurate differentiation can prevent unnecessary urgent surgical intervention, while ensuring timely follow-up and intervention if clinical status changes.

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# ANESTHETIC CONSIDERATIONS IN DUODENAL GASTROINTESTINAL STROMAL TUMOR RESECTION IN A PATIENT WITH NEUROFIBROMATOSIS TYPE 1

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## Abstract

**Introduction:** Neurofibromatosis type 1 (NF1), also known as Von Recklinghausen disease, is a rare autosomal dominant neurocutaneous disorder. It is clinically characterized by multiple café au lait macules, intertriginous freckling, multiple cutaneous neurofibromas and learning disability or behavior problems. About half of the people with Neurofibromatosis type 1 (NF1) develop internal plexiform neurofibromas and may remain undiagnosed. Other organ systems can also be affected. Choosing the appropriate anesthesia for patients with neurofibromatosis is a unique challenge.

**Case Presentation:** This case report presents the perioperative management of a 54-years-old male diagnosed with the challenging condition of neurofibromatosis type 1 (NF1) who underwent surgery for resection of a duodenal gastrointestinal stromal tumor (GIST). To mitigate the risks associated with a possible difficult airway and neuraxial anesthesia, an awake video-laryngoscopy before induction was done, and a bilateral Transversus Abdominis Plane (TAP) block was performed for pain management. The operation proceeded uneventfully, recovery was without complications and with satisfactory postoperative pain control. The patient reported minimal discomfort and did not require additional analgesics during the recovery period. He was discharged home in good general condition on the fifth postoperative day.

**Conclusion:** Optimal anesthetic care in NF1 is inherently patient-specific, driven by systematic assessment of organ involvement and anticipation of perioperative complications.

***Key Words**: Anesthesia challenging, Neurofibromatosis type 1; Transversus Abdominis Plane (TAP) block; video-laryngoscopy.*

## Introduction

Neurofibromatosis type 1 (NF1), also known as Von Recklinghausen disease, is a rare autosomal dominant neurocutaneous disorder. It is characterized by multiple café au lait macules, intertriginous freckling, multiple cutaneous neurofibromas and learning disability or behavior problems. About half of the people with NF1 have plexiform neurofibromas, most of which are internal and may not be clinically suspected. Plexiform neurofibromas can cause pain, neurologic deficits and abnormalities of involved or adjacent structures. Less common but potentially more serious manifestations include optic nerve and other central nervous system gliomas, malignant peripheral nerve sheath tumors, osteoporosis, scoliosis, tibial dysplasia, vasculopathy, and gastrointestinal, endocrine, or pulmonary disease (1).

The incidence of NF1 is approximately 1 in 2,600 to 3,000 live births. There is no predilection for the male or female gender (2).

The mutation or deletion of the NF-1 gene results in the phenotypic and genotypic manifestations of the disorder. The NF-1 gene encodes a protein called neurofibromin, which is expressed in various tissues (3). Neurofibromin functions as a GTPase-activating protein that inhibits the rat sarcoma (RAS) signaling pathway (4). Mutations in the NF-1 gene result in a lack of neurofibromin expression, thereby promoting tumorigenesis. Neurofibromas develop when both alleles of the NF-1 gene are mutated. Neurofibromas embody Schwann cells, perineural cells, mast cells and fibroblasts. Cutaneous neurofibromas (cNF) involve dermal nerve terminals, whereas plexiform neurofibromas (pNF) characteristically affect the nerve plexuses and fascicles.

The diagnosis of NF1 is established in a proband with two or more of the characteristic clinical features or one characteristic clinical feature and a heterozygous NF-1 pathogenic variant.

There is no definite therapy for this genetic disorder, so the treatment for NF1 is primarily symptomatic, whereas, for plexiform neurofibromas, surgical removal is the only treatment option but may be associated with damage to involved nerves or adjacent tissues. Complete surgical excision, when possible, of malignant peripheral nerve sheath tumors is the treatment of choice; chemotherapy may be beneficial in some individuals.

## Case Presentation

A 54-years-old male patient, 185cm tall and weighing 107kg (BMI: 31.2kg/m$^2$), with neurofibromatosis type 1 (NF1), was admitted to the University Clinic for Abdominal Surgery in Skopje for an elective resection of a duodenal gastrointestinal stromal tumor (GIST). This tumor was diagnosed with a computed tomography scan and by a gastroscopic biopsy. The patient had a significant surgical history related to Neurofibromatosis type 1 (NF1), including a right crural amputation twenty years ago due to neurofibroma infiltration and resection of a jejunal gastrointestinal stromal tumor (GIST) sixteen years ago. He also had surgery for a pancreatic cyst and chronic pancreatitis, requiring lifelong pancreatic enzyme replacement therapy. Comorbidities included well-controlled epilepsy managed with antiepileptic medication and osteoporosis treated regularly. Preoperative assessments showed normal cardiovascular and respiratory findings. Airway examination revealed adequate mouth opening, Mallampati class II, normal neck mobility and a few small oral mucosal neurofibromas. Laboratory investigations, coagulation profile and chest radiograph were within normal limits.

The planned anesthetic technique involved general endotracheal anesthesia (GETA) in combination with a bilateral transversus abdominis plane (TAP) block for perioperative pain management. The associated risks and procedures were thoroughly discussed, and written informed consent was obtained.

On the day of surgery, the patient continued taking his regular medications and received antibiotic prophylaxis. At the operating room, standard ASA monitoring was established, which included ECG, non-invasive blood pressure (NIBP), and oxygen saturation ($SpO_2$). The baseline parameters recorded were the following: blood pressure of 160/80mmHg, heart rate of 80 beats per minute, and $SpO_2$ at 98%.

After preoxygenation with 100% oxygen via a tight-fitting non-rebreathing facial mask with a fresh gas flow of 20L/min for 3 minutes and administering premedication with 2mg of midazolam and 50μg of fentanyl, video-laryngoscopy was performed, revealing several small neurofibromas around the epiglottis, none of which obstructed the airway. Anesthesia induction was then achieved with the following medications: propofol (2mg/kg/BW), fentanyl (1mcg/kg/BW), lidocaine (0.6mg/kg/BW), and rocuronium (0.6mg/k/BW). Tracheal intubation was successfully performed using a video-laryngoscope.

An ultrasound-guided bilateral transversus abdominis plane (TAP) block was performed in the midaxillary line between the costal margin and the iliac crest. After confirming negative aspiration, a total of 20mL of 1% lidocaine and 20mL of 0.25% bupivacaine was injected.

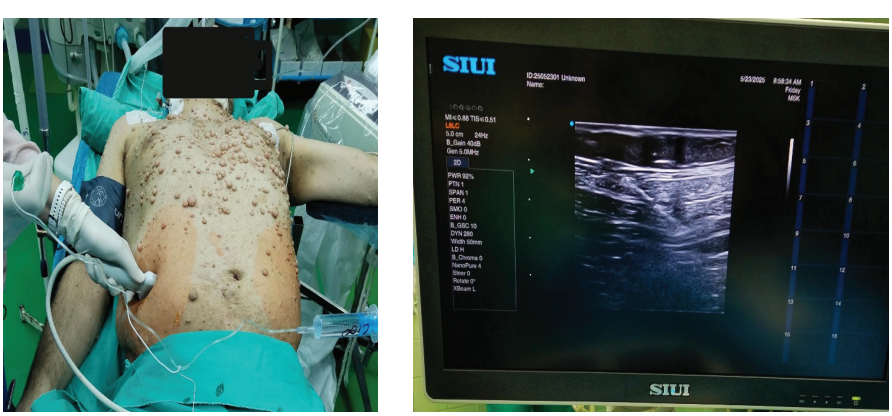


**Figure 1.** Ultrasound-guided TAP block performed in the patient with neurofibromatosis type 1:
(a) The anesthesiologist performing the block with the ultrasound probe.
(b) Ultrasound view showing the needle advancing through the fascial plane between the internal oblique and transversus abdominis muscle.

Additional analgesia included 100μg of fentanyl, 1g of paracetamol and 1.5g of magnesium sulfate. Anesthesia was maintained with sevoflurane at 1.0 MAC. During the surgery, the patient remained hemodynamically stable. The estimated blood loss was minimal. The total duration of the surgery was 180 minutes. At the end of the procedure, after reversing the residual neuromuscular blockade, the patient was extubated uneventfully in the operating room.

Postoperatively, the patient received antibiotics, anticoagulation and multimodal analgesia with paracetamol and metamizole. His regular antiepileptic therapy was resumed immediately. The postoperative course was without any complications, and the patient was discharged home on the fifth postoperative day in good general condition.

## Discussion

Patients with neurofibromatosis type 1 (NF1) pose unique challenges for anesthesiologists due to the multisystem involvement of the disease. Airway, neurological, cardiovascular and skeletal manifestations must all be carefully considered when planning anesthetic management.

Intraoral manifestations occur in approximately 5% of the patients with Neurofibromatosis Type 1 (NF1) (5). Sharma and Fisher have described cases where discrete neurofibromas were found on the tongue or larynx, with the aryepiglottic folds and arytenoids being the most commonly affected areas. This is likely due to the dense presence of terminal nerve plexuses in these regions (6,7). Involvement of these structures may lead to airway obstruction, with symptoms such as shortness of breath, stridor, difficulty swallowing or changes in voice serving as critical clinical indicators of a potentially difficult airway. In our patient, video-laryngoscopy revealed small neurofibromas around the epiglottis that did not obstruct the airway. Nevertheless, the possibility of sudden airway compromise underscores the importance of preparedness for a difficult airway scenario.

The patient's prior abdominal surgeries - jejunal GIST resection and pancreatic cystectomy for chronic pancreatitis - further complicated anesthetic planning by increasing the likelihood of adhesions and unpredictable intra-abdominal dynamics. Chronic pancreatitis might also impair absorption and alter the pharmacokinetics of fat-soluble drugs, while nutritional deficiencies could influence anesthetic drug dosing. Consequently, meticulous hemodynamic monitoring and individualized fluid management were essential.

Neurofibromatosis type 1 (NF1) is also associated with central nervous system tumors, vasculopathies and seizures (8). Epilepsy, often treated with antiepileptic drugs (AEDs), may alter anesthetic metabolism through hepatic enzyme induction. Ensuring perioperative continuation of AEDs is critical to avoid breakthrough seizures. Although our patient did not exhibit any active neurological symptoms, continuous vigilance remained paramount. From a cardiovascular perspective, patients with Neurofibromatosis type 1 (NF1) have a higher risk of developing secondary hypertension, most commonly due to pheochromocytoma or renal artery stenosis (9). Although our patient was normotensive and did not exhibit catecholamine-related symptoms preoperatively, the literature emphasizes maintaining a high index of suspicion, as an unrecognized pathology may precipitate catastrophic intraoperative hemodynamic instability.

Regarding analgesia, the use of neuraxial techniques in patients with Neurofibromatosis Type 1 (NF1) is not contraindicated if spinal imaging (CT or MRI) excludes the presence of neurofibromas along the neuraxis. In our case, because spinal imaging had not been performed, neuraxial anesthesia was avoided (10). Instead, we employed a multimodal analgesic strategy that included a bilateral ultrasound-guided transversus abdominis plane (TAP) block. This approach is well-documented in the literature and has been integrated into Enhanced Recovery After Surgery (ERAS) protocols for both open and laparoscopic abdominal surgery (11, 12). Ultrasound guidance ensured precise administration, minimizing the risk of infiltration into neurofibroma-infiltrated tissues, and effectively reduced opioid consumption while providing stable analgesia.

## Conclusion

NF1 is presented with a wide range of clinical manifestations, requiring personalized anesthetic planning driven by a systematic evaluation of organ involvement and the anticipation of poten-

tial perioperative complications. A comprehensive preoperative assessment is crucial for managing difficult airways, ensuring safe intubation with video-laryngoscopy. A balanced general anesthesia approach, combined with an ultrasound-guided transversus abdominis plane (TAP) block, provided adequate intraoperative and postoperative analgesia, minimized opioid requirements, and maintained hemodynamic stability.

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# THE GIANT STAGHORN CALCULUS: ANESTHETIC IMPLICATIONS IN DEVELOPING HEALTHCARE SETTING

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## Abstract

The giant staghorn calculus represents a serious form of kidney stone disease characterized by the presence of large, bifurcating calculi that occupy the renal pelvis and extend into multiple calyces, resembling the antlers of a stag. Giant staghorn calculi may remain asymptomatic for prolonged periods, and if left untreated can lead to progressive kidney damage, loss of kidney function and life-threatening complications such as urosepsis. Thus, managing a patient with such an extraordinary and advanced renal pathology in a resource-constrained healthcare setting unfolds clinical and anesthetic challenges that demand vigilance and flexibility. We present the case of a 62-years-old male from a rural village near a small city, with an impressive medical history of persistent nephrolithiasis that progressed for years, due to inconsistent follow-up caused by limited financial means. He underwent right nephrectomy for a massive staghorn calculus with negligible functional renal parenchyma. Given the patient's compromised health status and the presence of a large, fully-configurated complete staghorn calculus, which posed a significant surgical challenge due to its sheer magnitude, it was evident that potential anesthetic risks included hemodynamic instability, sepsis, and altered drug metabolism. Nonetheless, a comprehensive preoperative evaluation, continuous intraoperative monitoring and readiness for rapid intervention ensured a stable perioperative course without complications. Alongside the rarity of this pathology, this case highlights the critical role of anesthesiologists in anticipating and managing the complex challenges posed by such unique pathologies, demonstrating that meticulous planning and resilience enable the delivery of solid and life-sustaining care, even when presented with a narrow spectrum of choices.

***Key Words**: nephrectomy; staghorn calculus; urosepsis.*

## Introduction

Staghorn nephrolithiasis represents one of the most formidable manifestations of nephrolithiasis, where the process of formation and enlargement of these renal calculi occupying the renal pelvis and calyces is associated with infection and destruction of renal parenchyma. These renal stones, typically composed of struvite and carbonate apatite, can lead to chronic diseases, calyceal distortion and loss of renal function (1). Besides mechanical obstruction and infection, staghorn calculi can promote chronic inflammation leading to perinephric fibrosis and scarring, which further complicates surgical dissection and impacts long-term renal recovery. In resource-limited environments, delayed presentation of this pathology with complete loss of

any functional renal parenchyma, often necessitates open nephrectomy, which intensifies the logistical and monitoring challenges (2). From an anesthetic point of view, staghorn nephrolithiasis presents substantial perioperative risks, including significant hemorrhage due to the extensive vascularity and inflammation associated with large calculi. The chronic infectious nature of these stones predisposes patients to perioperative sepsis, requiring ample antimicrobial management. Additionally, fluid and electrolyte imbalances are common due to impaired renal function, complicating intraoperative fluid therapy. Furthermore, accompanying renal and hepatic impairment alter the pharmacokinetics and pharmacodynamics of anesthetic agents, requiring careful selection and dosing to minimize toxicity and ensure hemodynamic stability (3). This paper aims to showcase the specificity of our patient's fully configured giant staghorn calculus, which, despite the theoretical risk, had an unremarkable intraoperative course and remained hemodynamically stable.

## Case Presentation

A 62-year-old male from a rural village near Radovish, Republic of North Macedonia, was presented with a history of longstanding nephrolithiasis, with only tamsulosin as his chronic therapy in use. At his young age 37 years ago, he underwent an open right pyelolithotomy for large renal calculi, which was allegedly exhibited in a science display due to its striking size. Nevertheless, the patient continued experiencing symptoms potentially aligned with persisting nephrolithiasis over the years but had limited access to medical check-ups, reflective of the challenges in a developing healthcare setting. In 2022, he underwent emergency surgery for a bleeding gastric ulcer. The following year (2023), he was diagnosed with acute hepatitis B, necessitating a 24-days hospitalization at the University Clinic for Infectious Diseases. Later that year, he developed acute kidney failure, requiring a 10-days admission to the University Clinic for Nephrology. In 2025, the patient was admitted to the University Clinic for Urology with complaints of flank pain, recurrent urinary tract infections and obvious signs of renal insufficiency. Imaging studies revealed a massive calculus occupying the right renal pelvis and calyces with extensive destruction of renal parenchyma, confirmed by markedly reduced function on nuclear renal scans. Given the negligible residual function of the right kidney and the risk of ongoing infection, right nephrectomy was indicated as the definitive treatment. Preoperative assessment highlighted risks related to compromised renal and hepatic function, potential massive intraoperative blood loss and perioperative sepsis. Per institutional protocol, after three minutes of preoxygenation with 8L/min of 100% oxygen, the patient underwent induction of general anesthesia with intravenous midazolam 2mg, fentanyl 0.1mg, and propofol 160mg. Neuromuscular blockade was achieved with rocuronium 50mg to facilitate tracheal intubation using an 8.5mm endotracheal tube. Anesthesia maintenance was secured through sevoflurane and continuous propofol infusion. The surgery proceeded for three hours and 45 minutes, without intraoperative complications. During the nephrectomy, the entire right kidney was excised intact. Upon extraction, the calculus was presented as a full-scale anatomic cast of the renal collecting system, occupying the renal pelvis and extending into all three major calyces. Its architecture had a striking resemblance to the internal renal structure, with branches replicating the superior, medial and inferior calyceal paths. Its size and shape confirmed its classification as a complete staghorn stone, with gross dimensions definitely surpassing 14cm, rivaling the size of the kidney itself (Figure 1: A, B). The patient remained hemodynamically stable throughout the procedure, with no significant bleeding. Medications were carefully chosen to his compromised renal and hepatic function, while fluid balance was meticulously maintained. Vital signs were continuously

monitored and documented at regular intervals, ensuring vigilant intraoperative care. Postoperatively, recovery was uneventful, and the patient was discharged in good health after 11-days hospitalization.

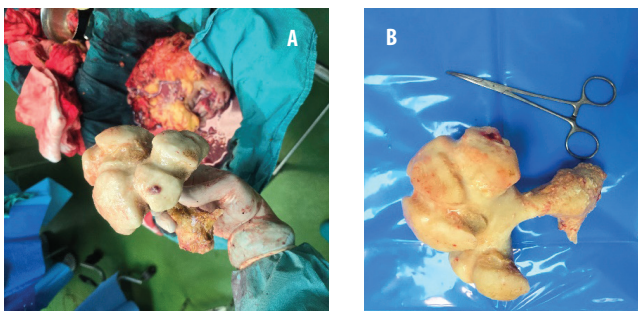


**Figure 1**. When compared to the surgeon's gloved hand, it nearly fills the palm and extends beyond the grip of the fingers, indicating a size far exceeding common renal stones (A), whereas comparing it to the standard 15cm length of the hemostatic forceps, it measures approximately ~15–17cm along its longest axis, ~9–10cm in width and ~5-7cm in depth, confirming it as a giant intact staghorn calculus, an entity rarely reported in literature (B).

## Discussion

When viewed against published literature, the sheer size of this staghorn calculus places it among the largest reported, emphasizing both its rarity and clinical challenge. Thus, this paper provides an opportunity to reflect not only on the anesthetic approaches required for such extreme pathology, but also on the realities of delivering complex surgical care in a developing healthcare setting. It is important to emphasize that staghorn calculi are associated with substantial renal parenchymal loss, often leading to non-functioning kidneys if left untreated (4). Figure 1 depicts an unusual morphology with a cast-like configuration, exhibiting a full 3D negative mold of the renal collecting system. The multiple lobulated protrusions mimic calyceal structures, indicates that the stone grew by mineral deposition within each calyx. Its surface is characterized by a pale yellow-white color and orange-red discoloration, which consists of struvite (magnesium ammonium phosphate) and/ or carbonate apatite composition (common in infection stones). Smooth but lobulated surface indicates long-term formation within a fluid-filled system (rather than rough, spiculated stones seen in rapid crystallization). Absence of sharp points suggests slow, uniform mineral growth in a dilated collecting system. Staghorn calculi, especially ones composed of struvite and carbonate apatite, are infection stones resulting from urease-producing organisms (5). These stones are associated with chronic infection and can harbor embedded bacteria, posing a risk of systemic inflammatory response during surgical manipulation, which makes the surgical choice of treatment, as well as the anesthetic approach, more crucial (2, 3). While making important decisions, it is also essential to note the remarkable size of our patient's staghorn calculus. This specimen (Figure 1), with approximately ~16×10×6cm, stands alongside - or even surpasses - many of those previously reported in the literature. A case report by Thapa et al. (2023), describes an asymptomatic staghorn calculus measuring approximately 11.8×8.8×6.9cm, removed by open pyelolithotomy, which suited resource-limited settings (6). A similar case report by Kesharwani et al. (2022), discusses another asymptomatic 8cm diameter staghorn stone, managed via open pyelolithotomy, again far exceeding the sizes typically managed by PCNL (7). Literature shows cases of very large stones managed by PCNL as the gold standard, but intact removal without fragmentation in constrained settings remains exceptional. According to Winoker et al., staghorn calculus management requires more than assessing size;

it needs standardized morphometric frameworks and awareness of anatomical challenges to guide effective treatment in nephron-sparing procedures such as PCNL - the first line of treatment (8), already defined by guidelines of the European Association of Urology (EAU) and the American Urological Association (AUA). However, the already mentioned cases highlight the choice for open surgery, due to stone size, thin renal cortex and limited local resources (6,7). Now, reflecting on our case, comparing it to the common PCNL-manageable staghorn calculi (typically 3–5cm in size) (8), the extracted specimen in this case far surpasses these norms. Such extreme morphology and volume are associated with near-total renal parenchymal replacement, often rendering the affected kidney non-functioning and justifying definitive surgical removal (4). Nephrectomy may not only be justified but also appropriate and sometimes even the safest solution for the patient. While surgical technique often depends on stone size and location, the type of staghorn calculus, whether struvite, calcium oxalate or cystine, can significantly inform anesthetic planning, infection control and postoperative risk management (9, 10). Struvite staghorn calculi, composed of magnesium ammonium phosphate, are commonly represented as "infection stones", often formed in infected and obstructed systems, immediately predisposing a high urosepsis risk (11). Whereas calcium oxalate calculi and cystine calculi have lower to non-infection risk. Stone type isn't just a chemical detail; it's a predictor of sepsis risk, surgical complexity and anesthetic strategy. In particular, struvite stones warrant heightened pre-op vigilance, infection control and anesthetic preparedness for hemodynamic instability. Bringing these points together, the successful management of this rare and massive staghorn calculus is especially significant in a developing healthcare setting, where limited resources and delayed presentations dictate the choice for open surgery. Similar reports from other developing countries confirm that, despite such constraints, safe outcomes are achievable through solid planning and good care (12, 13). Looking alike published cases allow us to see where our experience fits within the broader clinical landscape. It highlights not only the rarity and scale of this pathology but also the practical challenges of managing such a case in a developing healthcare setting. Such citations therefore enrich the discussion, reinforcing the relevance of our findings while contributing to the collective understanding of managing extreme cases safely and effectively.

## Conclusion

This case highlights the successful management of a rare, giant staghorn calculus in a resource-limited setting, where delayed care and limited access shaped both the pathology and treatment approach. Despite the risks posed by infection, hemodynamic instability and impaired organ function, careful anesthetic planning and intraoperative attention ensured a stable and complication-free outcome. While open nephrectomy is less common in high-resource centers, in this case, it was the most appropriate option given the extent of renal damage and local limitations. Ultimately, this case emphasizes the value of teamwork and solid clinical judgment in safely managing complex conditions, even in less-than-ideal environments.

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# AT THE EDGE OF PATHOLOGY AND THE PROMISE OF SCIENCE: WHERE CANCER GENOMICS MEETS INSPIRATION - A PATHOLOGY RESIDENT'S PERSPECTIVE ON ESHG 2025

The annual European Human Genetics Conference 2025, held in Milan (May 24–27) was a profound professional experience for me as a pathology resident and a PhD student in molecular medicine with a strong interest in cancer biology and gene therapy.

As expected, since its beginning, the program delivered an ample and thoughtfully compiled scientific agenda. As a pathology resident, I was particularly engaged in sessions and workshops devoted to cancer complexity and the ever-evolving landscape of cancer genomics, as well as advancing cancer prevention, detection and individualized cancer treatments utilizing the latest technologies. The lectures within the "Cancer Complexity: Variants, Therapies and AI-Driven Insights" session provided fascinating insights into oncogenesis, immune escape and the integration of machine learning into oncologic diagnostics - areas increasingly relevant to both molecular pathology and clinical decision-making. Furthermore, the masterful lectures in the "Rewriting Cancer Treatment and Resistance" symposium provided a much-needed inspiration and a new way of thinking about cancer treatment options and pathways for overcoming cancer resistance.

The sheer depth of interdisciplinary integration as a concept of the congress, enabled every participant to immerse oneself into different subjects and compile knowledge that can be implemented in everyday practice. Not often can one be a part of a conference that simultaneously showcases the molecular frontier and challenges ethical, clinical and societal frameworks. The sessions and workshops addressing the tools for genetic editing, cancer evolution and ultra personalized medicine reinforced the daily dilemmas we face in diagnostic pathology - when histology alone is no longer enough.

The crowning event of the conference was the final plenary. The lecture by Dr. Katalin Karikó, recipient of the 2023 Nobel Prize in Physiology or Medicine, was nothing short of historic. It was a testament to the persistence and resilience behind world changing science. Her reflections on mRNA technology, from conceptual resistance to global impact, resonated deeply not only with researchers, but with every clinician in the audience. In pathology, where we often witness disease at its most devastating level, her story reinforced that innovation at the molecular level can indeed translate into hope.

ESHG 2025 reminded me and confirmed the reasons why I entered this field. It was an event where science met humanity, where difficult questions were asked, and ambitious answers were encouraged. I returned to the Institute of Pathology with a sharpened sense of purpose, widened horizons in the possibilities of molecular medicine, and inspired by the global community of students and professionals striving to reimagine medicine at the genetic level.

Sincerely,
Tamara Angelovska,
Pathology resident and PhD student,
Institute of Pathology, Faculty of Medicine, Skopje

# REFLECTION ON VOLUNTEERING IN ANESTHESIOLOGY AND INTENSIVE CARE: A YOUNG DOCTOR'S PERSPECTIVE

As a recent medical graduate, I had the opportunity to volunteer in the Department of Anesthesiology and Intensive Care at the University Clinic for Surgical Diseases "St. Naum Ohridski" in Skopje. Though brief, this experience has had a lasting impact on both my professional orientation and personal growth. It helped me discover the true essence of anesthesiology - an often underestimated, yet absolutely vital pillar of modern medicine.

At the time, I was uncertain about which specialty to pursue. The chance to join the anesthesia team as a volunteer gave me firsthand insight into a field that is intellectually rigorous, technically demanding and deeply rewarding. Despite its quiet presence, anesthesiology is essential across all stages of surgical care. From preoperative assessment and intraoperative physiological management to postoperative analgesia and critical care, anesthesiologist safeguards the patient's life throughout the entire perioperative course.

What particularly inspired me was the dual nature of the specialty. It requires both acute cognitive skills and precise hands-on interventions. The ability to manage airways, titrate complex drug regimens, respond to emergencies within seconds, and lead resuscitation and intensive care scenarios makes anesthesiology a discipline that combines mastery of knowledge with rapid life-saving action.

Medical school often presents anesthesia in a narrow context - focused mainly on induction and maintenance of anesthesia. However, during my volunteering period, I witnessed its much broader scope: the coordination between surgical and critical care teams, the responsibility for patient's stability during high-risk procedures, and the role in organ support and end-of-life decisions in the ICU. I came to see why anesthesiologists are often called the "silent protectors" in the operating theatre. Without their presence, no surgical intervention could proceed safely.

What I valued most was the mentorship I received. The medical team treated me as a colleague, shared their knowledge generously, and involved me in discussions and decision-making processes. Their support gave me confidence and a sense of belonging in the field I now feel deeply passionate about.

Today, I can honestly say: I didn't choose anesthesiology - anesthesiology chose me. It captured my attention not only as career, but as a calling. For other young doctors standing at a professional crossroads - I encourage them to look beyond the surface of this specialty. Its complexity, relevance and elegance, make it one of the most rewarding fields in modern medicine.

Sincerely,
Filipche Ana
MD, Faculty of Medicine
University "Ss Cyril and Methodius"
Republic of North Macedonia

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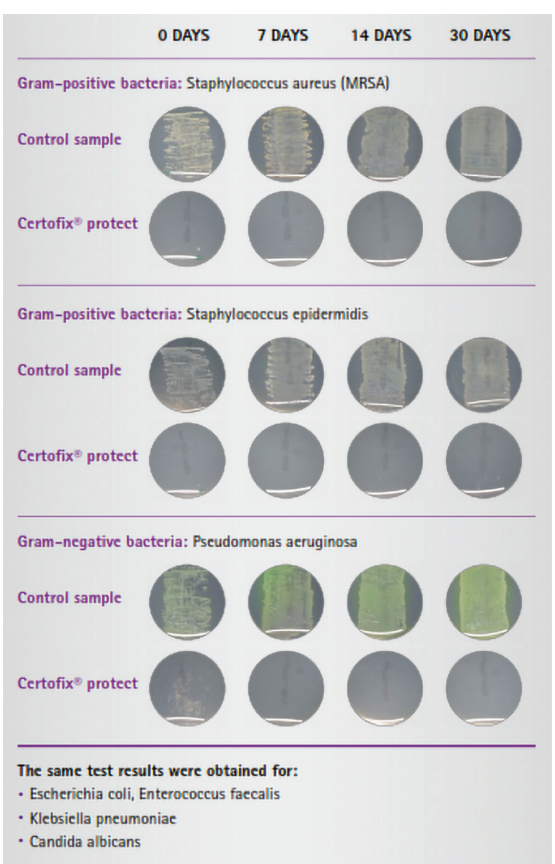


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