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ALL UNDERGRADUATE ACADEMIC DISSERTATIONS SHOULD BE PUBLISHED AS SCHOLARLY ARTICLES

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Keywords: academic dissertations, thesis, publishing, scholarly publishing, journal article

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Undergraduate students are often required to produce an academic dissertation (thesis). Such a dissertation should showcase that a student has acquired various important skills, including the ability to define a topic area, use academic writing, structure work, and study literature in-depth in a given field. Undergraduate academic dissertations may include original research or be based on a literature review (1).

In Croatia, most higher education institutions providing nursing studies allow students to choose between a research-based and review-based dissertation. In 2020/2021, Marendic et al. examined attitudes and factors influencing the choice of thesis type (original research versus review) among Croatian nursing students (2). This survey of 912 students indicated that mentor encouragement, knowledge, and sense of ability to conduct research were positively associated with the score on the Students' Attitudes Toward Research (SAR) questionnaire. The expectation that a research-based thesis will extend the study duration was negatively associated with the SAR score. A higher SAR score was associated with a higher likelihood of selecting a research-based thesis. The study indicated that modifiable factors were associated with the choice of conducting a research-based thesis among nursing students (2).

While that study explored students' intentions, an analysis of defended undergraduate dissertations can provide insight into real-life decisions of health sciences students regarding the type of academic dissertations they chose to conduct. Furthermore, although dissertations include creation of new knowledge, they remain grey literature, i.e., literature that is not published in scholarly journals (3). Thus, it would be important if the content of academic dissertations was disseminated into scientific literature.

In 2022 and 2023, the Master of Nursing thesis by Kristina Kraljić analyzed the type of academic dissertations conducted by health sciences students in Croatia and the number of them published in a scholarly journal. The analysis involved all eligible dissertations that were included in the online National Repository of Bachelor and Master Dissertations (Croatian: *Nacionalni repozitorij završnih i diplomskih radova* ZIR) by May 2022 (4).

Of 10,668 eligible dissertations, we analyzed 9,861 that could be accessed. Namely, many dissertations included in the ZIR are not publicly accessible, and some of the institutions involved did not give their consent to access them. The selected sample included 81 % Bachelor dissertations and 19 % Master dissertations. All but 21 dissertations were written in the Croatian language. Among the Bachelor dissertations, 21 % were based on original research, compared to 66 % among the Master dissertations. Most dissertations based on research included cross-sectional studies. By combining a survey of mentors and literature search, we found that the contents of only 2.8 % of the dissertations were published as scholarly articles. The majority of those articles (83 %) were published in Croatian journals (4). When asked about the reasons why the content of a dissertation was not published as a scholarly

article, most mentors indicated a lack of interest among students and insufficient quality of the dissertations (4).

Based on these findings, it can be concluded that very few academic dissertations of health sciences students were published as scholarly articles. This is detrimental for society, but also for students, mentors, and institutions. Namely, original contributions contained in a number of dissertations often remain hidden within the national repository and the Croatian language. It is not very likely that those searching for novel information will search national repositories of dissertations. Thus, academic dissertations remain grey literature, accessible to a very limited audience.

Writing a scholarly article is another academic skill that can be a useful part of university training. By publishing articles from academic dissertations, mentors could be advancing biomedical sciences, as well as their pragmatic criteria for academic advancement. Scientometric indicators of institutions rely on publications, and thus dissertations that are not published as scholarly articles remain a missing opportunity for institutions.

Therefore, academic institutions should invest more effort into enabling and motivating students and mentors to not only conduct original research within academic dissertations, but also to raise awareness about the importance of publishing the content of those dissertations as articles in scholarly journals.

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PRESERVING TRUST IN THE PHYSICIAN-PATIENT RELATIONSHIP AND ADDRESSING MORAL INJURY OF PHYSICIANS

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Abstract

In recent decades, which have brought about dramatic changes in medicine, the relationship of trust between patients and doctors has come under severe pressure. In parallel with the increasing needs and complexity of patients who demand more individual time from their physicians (including the explanatory duty required by law), the administrative burden of the latter is increasing. The performance metrics of individual physicians has either already been introduced or is planned to be introduced, forcing physicians into the "production line" of healthcare services. Although physicians represent a small percentage of all employees in the healthcare enterprise, generally less than 10 %, they are the main target of performance metrics in healthcare. The administrative burden and metrics approach are enhanced by the corporatization of healthcare systems, both in private as well as public healthcare organizations.

Patients and physicians are no longer the main figures in medical decision making, as many other individuals and entities have since joined, described as "strangers at the bedside" in a book by Professor David Rothman. They include bioethicists, lawyers, court rulings, economists, psychologists, civil society, and activists. The introduction of artificial intelligence into healthcare and its role in medical decision making will be assessed in the near and distant future.

Patients do not want to be part of a healthcare production line. They want a human touch from their physician, whom they trust to fight for and protect their best interests, their health, and their lives. Patients need this trustful relationship at least as much as medications and healthcare services. Physicians want and need the same. A trustful relationship between patient and physician has been the core value of medicine for thousands of years, and should be protected and consolidated for the future. Our duty as physicians is the fight to sustain it in the challenging times ahead.

Key words: **trust, physician – patient relationship, moral injury**

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INTRODUCTION

Trust between patient and physician has been a critical component of their relationship for thousands of years. It is precious and beneficial to both patient and physician, and an important component of the success of medical treatment.

During the past decades that have brought dramatic changes in medicine, this relationship has been under huge pressure. Patients and physicians are no longer the main figures in medical decision making, as many others have since joined. The evolution of this process has been described in the book "Strangers at the bedside: A history of how bioethics and health law has transformed medical decision making", published in 1991 and authored by David J. Rothman, Professor of Social Medicine and Professor of History at Columbia University (1). Not only bioethicists and lawyers, but many other outsiders have since joined patients and physicians in making medical decisions, e.g., insurers, economists, psychologists, sociologists, civil society, activists, emerging artificial intelligence... (2,3)

In parallel with the increasing needs and complexity of patients who demand more individual time from their physicians (including the explanatory duty required by law), the administrative burden of physicians is increasing. The performance metrics of individual physicians has either already been introduced or is planned to be introduced, forcing physicians into the "production line" of healthcare services.

Although physicians represent a small percentage of all employees in the healthcare enterprise (for example, at the Mayo Clinic less than < 10 % of 76,000 employees are physicians), they are usually the main target of performance metrics. The administrative burden and metrics approach have been enhanced by the corporatization of healthcare systems (4, 6).

The introduction of artificial intelligence into healthcare and its role in medical decision making will be assessed in the near and distant future. Although the expectations of benefits from artificial intelligence in healthcare are extremely high, one should not overlook the unfulfilled benefit expectations from information technology in healthcare (2). As Dean and Talbot wrote in their paper, "massive information technology investments, which promised efficiency for healthcare providers, have instead delivered a triple blow: they have diverted capital resources that might have been used to hire additional caregivers, diverted the time and attention of those already engaged in patient care, and done little to improve patient outcomes (7)."

Last but not least, legalizing euthanasia and assisted suicide in an increasing number of high-income countries, together with the ensuing pressure on physicians to be involved in the termination of their patients' lives, are only adding to the already existing pressure, hyper-responsibility and moral injury of physicians (8, 9). All these issues are the reason why trust in the patient-physician relationship is now being challenged more than ever.

Moral stress and moral injury in physicians

On June 15, 2023 a paper by Eyal Press was published in the NY Times under the title "Moral Crisis of the American Doctors: The corporatization of healthcare has changed the practice of medicine, causing many physicians to be alienated from their work" (10). Press was inspired by psychiatrist Wendy Dean, who reported a high suicide rate among physicians, even higher than among active military servicemen, and focused on moral injury in physicians, which had originally been described by psychiatrist Jonathan Shay from his experience in treating Vietnam war veterans (11, 12).

After talking with a number of physicians, Press reported that the major causes of stress were a lack of time to talk with and care for patients, the high administrative burden of electronic medical records, battling with insurers about whether individuals with a serious illness would be preapproved for medications, and performance metrics forcing physicians to reduce their already insufficient time for direct contact with patients. RVU (relative value units) metrics were introduced to calculate individual physician reimbursements. Physicians were said to resemble "laborers in Amazon warehouses, productivity tracked on an hourly basis and being pressured by management to work faster". The author was especially surprised by the fact that physicians were not prepared to talk in public, being aware that some of their colleagues had been fired after speaking about safety concerns in their healthcare practice (9).

The most critical situations were in emergency departments, where understaffed workplaces have become reality through corporatization and profit-oriented healthcare practices. Emergency physicians were outsourced and could be fired without due process, especially after having publicly addressed their incapability to provide safe healthcare services. Physicians were pushed to discharge Medicare and Medicaid patients, rewarded to prescribe desirable (from the reimbursement point of view) diagnostic and therapeutic services over talking and listening to patients. Through such pressures, physicians could be turned into instruments of patient betrayal (9). All these pressures may be among the reasons why physicians are increasingly thinking of leaving their institutions or profession (13).

Moral injury describes the challenge of simultaneously knowing what kind of care patients need, but being unable to provide it due to constraints that are beyond an individual's control (6). Moral injury is critically different from burnout. It is not the physician that is "broken" and needs help to increase resiliency, it is the system that is broken; yoga, wellness, and other strategies aiming to ameliorate burnout in individual physicians cannot help in ameliorating moral injury (6).

It should not be overlooked that the healthcare system in the U.S. is much more complex and different in many components from the healthcare systems in Europe and Slovenia. Some problems of the U.S. healthcare system are not (yet) present in European countries. However, it is wise to follow what is occurring in the U.S., because their practices may influence and be adopted (with more or less delay) in the healthcare practices of other countries. Lessons learned from problems and failures in the U.S. healthcare system may be useful in trying to avoid generating even more problems in our healthcare systems than are already present today.

Decreasing authority of physicians in the healthcare system in parallel with hyper-responsibility

A recent criminal case in the United Kingdom illustrates that a similar corporatization management atmosphere as described in private healthcare corporations is also present in public hospitals (NHS – National Healthcare Service). In August 2023, a 33-year-old nurse, Lucy Ledby, was sentenced to life in prison after killing seven newborns and causing severe injury to others in a northern England NHS hospital (14). She carried out the killings and caused the injuries by injecting air, applying insulin shots, or overfeeding babies. The striking details in this process were that on several occasions senior physicians had warned the hospital management about the nurse in question after having observed unexpected newborn deaths on her shift only, and had asked the management to investigate and call the police. Despite the warnings, the hospital management did not act. On the contrary, they used procedures to punish those who had raised safety concerns, as witnessed by a lead consultant of the Neonatal Unit, Dr. Stephen Brearey, who had raised concerns about the nurse in October 2015 (15). Being threatened with disciplinary measures, the physicians were forced to undergo mediation and apologize to the nurse, while she was transferred to the Quality Department of the hospital.

Physicians' involvement in controversial practices

Physicians themselves, especially when involved in ethically controversial practices (like euthanasia or mutilating surgery in minors with gender dysphoria), may contribute to jeopardizing the trusting patient-physician relationship.

The explosion of euthanasia cases in Canada, which legalized euthanasia and assisted suicide in June 2016, may serve as an example of a slippery slope with physicians involved. By the end of 2022, as many as 44,958 euthanasia procedures had been performed in Canada, with more than a 30 % annual increase over previous years. It was reported that 1,745 Canadian physicians (out of 96,020, i.e., 1.8 %) were engaged as euthanasia providers in 2022 (16). One of them celebrated his first 100 euthanized patients in a medical journal (17). It is not surprising that fear of physicians may have subsequently developed in patients, as illustrated by the tattoo "Do not euthanize me" on the shoulder of a woman in her 80s from Calgary, Canada – the first tattoo in her life (18). Who is this tattoo meant for? Physicians? Without physicians involved, the explosion of euthanasia cases in Canada would not have been possible. Although only a minority of physicians were involved in providing euthanasia, the shadow may fall on the whole profession.

Another controversial aspect of modern medicine are the mutilating and sterilizing interventions in minors with transgender dysphoria. A number of patients who had been admitted for these interventions at a young age and later regretted them ("transgender regret") claimed that doctors had failed them, that they were the victims of invalid informed consent based on lack of evidence, and of activist-driven rather than evidence-based medicine. Such patients have lectured physicians, saying "you need a really, really good evidence base in place if you're going straight to an invasive treatment that is going to cause permanent damage to your body" (19).

On April 14, 2023 Elon Musk made the following statement on X (previously Twitter): "Any parent or doctor who sterilizes a child before they are a consenting adult should go to prison for life" (20). Support for this statement was impressive. What should not be overlooked is the fact that only the parents and doctors were considered responsible. No one mentioned bioethicists, psychologists, lawyers, insurers, sociologists, activists, politicians, or society as having a role in or share of the responsibility for these practices, although they were all involved, directly or indirectly.

Recently, a paper on gender-affirming chest reconstruction (mainly bilateral mastectomy) among adolescents in the U.S. showed a steep rise in the number of these procedures, including girls as young as 12 years (21). The policy of reimbursement from insurers may also be associated with such an increase of these procedures.

On the other hand, physicians had to struggle to provide routine treatment for a child with a serious, progressive, and debilitating disease, navigating through unnecessary hospitalizations (and inducing further suffering to the child) just to help in getting treatment as soon as possible, along with battling insurers and an increasingly complex administration on the way to helping and healing a suffering child (22).

Without physicians' involvement, some controversial practices would not have been possible – not only euthanasia or mutilating gender-affirming surgery as adopted in some high-income countries, but also illegal organ transplantations performed by highly trained physicians (23).

Social values can change

However, social values can change. What is considered acceptable, ethical, and desirable by society today may become a crime against humanity tomorrow. This already happened in the 20th century, when the philosophy of eugenics and "life unworthy of living" was widely accepted by society. In such times, all armchair "strangers at the bedside" may disappear, leaving physicians as the only ones responsible for performing services once required by society.

Physicians should always keep this in mind and never betray their core values and mission of healing (and not killing), never harm their patients, or fail to protect the weak and vulnerable.

Autonomy, paternalism, and conscientious objection

In medicine, like generally in life, the right balance is critical for finding the optimal solution and making the optimal decision. However, the weight given to the principle of "autonomy" is increasingly becoming too disproportionate in medical decision making. Wise interference or suggestions from physicians in the best interest of the patient may be stigmatized and condemned as "paternalism" (24).

In an increasing number of countries, a patient's request that the physician terminate their life or perform mutilating and irreversible surgery, even by a minor desiring to change gender, is considered ethical. All is done in the context of respecting the patient's autonomy, yet neglecting the fact that, for example, brain maturation in minors is not completed, or that the patient may change his/her mind in the future, or that "sickness is the biggest thief of autonomy" (25).

However, the four main principles of bioethics: respecting autonomy, non-maleficence, beneficence, and justice, should have equal weight, as pointed out by the fathers of bioethics, Bechaump and Childress, in their paper published in 2019, 40 years after the first edition of their landmark book "Principles of biomedical ethics", published in 1979 (26). "...respect for autonomy is always relevant as a prima facie principle, along with other prima facie principles, but it has no more or less weight than the others in the abstract..... and we never use an a priori ranking of principles and rights...."(26)

Utilitarian bioethicists claim that physicians should not have the right to conscientious objection. They argue that society (and not physicians) defines the framework of a physician's profession, thus physicians who do not provide the healthcare services requested by society in a specific period should be punished by revocation of their professional license and other mechanisms of law: ".... Doctors are first and foremost providers of healthcare services. Society has every right to determine what kind of services they ought to deliver...." (27-29)

It should be kept in mind that philosophers and bioethicists do not bear responsibility for their positions and arguments, or for the consequences of their doings. Frequently, the more eccentric or even morbid their positions are, the more glory and citations they may receive. For instance, Wilkinson and Savulescu have suggested that organ donation in a euthanasia candidate should be started while the person is still alive, thus procuring their organs while the heart is still beating. The heart should be the last organ to be removed, and with this act euthanasia would be performed (30). Of course, he himself would not be personally involved in such procedures. He would let physicians do the job he proposed, while physicians would be responsible for and live with the consequences of such actions.

Young physicians are particularly vulnerable when exercising conscientious objections and need support form senior colleagues. Being in a subordinate position in the medical hierarchy, they may be exposed to significant harms: either compromising their moral integrity or compromising their careers by objecting to being involved in euthanasia (31).

Physicians are selected, trained, and capable of being resilient under huge pressure

Physicians are selected and trained to become resilient in the course of their medical school studies, which have been among the most demanding areas of study for centuries. Physicians are trained to be responsible for their actions. They are trained for and used to making the most difficult life or death decisions under huge pressure and within limited time, any time of the day or night.

Doctors are trained for and used to taking responsibility for their actions and decisions. They put their signatures on and authorize various documents many times each day. And every one of these many thousands of documents may become crucial evidence in a court of law. The physician's responsibility will be the same regardless of the time available to create such documents, whether it is three minutes or three hours.

Physicians are used to being under continuous supervision, and may face threatening litigations, media exposure, or physical assault.

As Talbot and Dean claim in their contribution on moral injury: "Physicians are smart, tough, durable, resourceful people. If there were a way to MacGyver themselves out of this situation by working harder, smarter, or differently, they would have done it already." (10).

I strongly believe that, regardless of all the dramatic and many unfavorable changes in modern healthcare, the majority of physicians in most medical fields are capable of preserving a deeply intimate and trustful relationship with their patients, fighting together with them for their health and life, and respecting the autonomy of each individual patient as a unique person.

Professional organizations, medical institutions, and healthcare systems can aid physicians

Intensive education on medical ethics should be provided during the medical studies. Professional organizations should intensify education aimed to assist physicians in navigating ethical dilemmas through case studies, discussions, and workshops for practical ethical decision-making advice. Policies and guidelines delineating ethical practices and procedures should be established to aid physicians in understanding their duties and the standards expected of them, thus mitigating moral uncertainty. Education in medical and criminal law focused on a physicians's legal obligations and responsibility is also important. Professional organizations should systematically advocate for changes in healthcare policies, to support ethical practices and address the root causes of moral distress and injury of physicians and healthcare professionals.

Medical institutions should offer access to ethics consultants or committees for guidance on challenging ethical decisions, providing personalized advice and support. They should encourage open communication within healthcare teams and between physicians and patients, to address ethical concerns promptly and foster collaborative decision-making. They should acknowledge the emotional toll of ethical dilemmas on physicians and help them manage stress and moral injury. They should promote an organizational culture that values ethical decision-making and the moral integrity of healthcare professionals, and create a safe environment for discussing ethical concerns.

By formulating and implementing these strategies, healthcare organizations can ensure that physicians are adequately supported to face moral and ethical challenges, leading to improved patient care and a healthier working environment for physicians.

Final thoughts

During the past decades which have seen dramatic changes in medicine, the trusting patient-physician relationship has been under huge pressure. In parallel with the increasing needs and complexity of patients, the administrative burden of physicians is expanding, and the performance metrics force physicians into the "production line" of healthcare services.

The introduction of artificial intelligence into healthcare and its role in medical decision making will be assessed in the near and distant future. Although expectations of the benefits of artificial intelligence in healthcare are extremely high, one should not overlook the unfulfilled benefit expectations from information technology in healthcare, which resulted in high costs, unconvincing improvement in patients' outcomes, an increased administrative burden, and a reduction of the already insufficient time physicians can devote to talking and listening to patients.

Patients do not want to be part of a healthcare production line. They want a human touch from their physician, whom they trust to protect their best interests, their health, and their lives. Patients need this trustful relationship at least as much as medications and healthcare services. Physicians want and need the same. A trustful relationship between patient and physician has been the core value of medicine for thousands of years, and should be protected and consolidated for the future. It is the physicians' duty to fight to sustain it in the challenging times ahead.

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SAŽETAK

OČUVANJE POVJERENJA U ODNOSU IZMEĐU LIJEČNIKA I PACIJENTA I MORALNA OZLJEDA U LIJEČNIKA

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Povjerenje između pacijenta i liječnika posljednjih je desetljeća pod velikim pritiskom, zbog dramatičnih promjena u medicini. Usporedo sa sve većim potrebama i složenošću pacijenata koji zahtijevaju od liječnika da svakome od njih posvete više vremena (uključujući dužnost objašnjavanja propisanu zakonom), povećava se administrativni teret liječnika, a mjerenje produktivnosti pojedinih liječnika je ili već uvedeno ili se planira uvesti, tjerajući liječnike u „proizvodnu liniju" zdravstvenih usluga. Iako liječnici predstavljaju mali postotak svih zaposlenika u zdravstvenom poduzeću, tj. obično manje od 10 %, oni su glavna meta mjerenja produktivnosti u zdravstvu. Administrativno opterećenje i metrički pristup povećavaju se procesom korporativnosti zdravstvenih sustava, kako u privatnim, tako i u javnim zdravstvenim organizacijama.

Pacijenti i liječnici više nisu jedine osobe koje sudjeluju u donošenju medicinskih odluka, jer su se pridružili mnogi drugi. U knjizi profesora Davida Rothmana opisani su kao «stranci pored (bolesničkog) kreveta«. Među njima su bioetičari, pravnici, ekonomisti, psiholozi, civilno društvo, aktivisti. Uvođenje umjetne inteligencije u zdravstvo i njezina uloga u donošenju medicinskih odluka ocjenjivat će se u bližoj i daljoj budućnosti.

Pacijenti ne žele biti dio proizvodne linije zdravstvenih usluga. Oni žele humani kontakt sa svojim liječnikom, za kojeg vjeruju da će se boriti za njih i štititi njihov najbolji interes, zdravlje i živote. Očuvanje odnosa međusobnog povjerenja sa svojim liječnikom pacijentima je potrebno jednako kao i lijekovi i zdravstvene usluge.

Liječnici to također žele i trebaju. Odnos povjerenja između pacijenta i liječnika temeljna je vrijednost medicine tisućama godina i potrebno ga je zaštititi i učvrstiti i ubuduće. Naša dužnost kao liječnika jest boriti se da ga sačuvamo u izazovnim vremenima koja su pred nama.

Ključne riječi: povjerenje, odnos liječnik – pacijent, moralna ozljeda

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PROGNOSTIC VALUE OF HEMOGLOBIN TO RED CELL DISTRIBUTION WIDTH RATIO FOR PATIENTS WITH HODGKIN LYMPHOMA

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Abstract

Aim: To examine whether the value of hemoglobin to red blood cell distribution width ratio (HRR) at the time of diagnosis of Hodgkin lymphoma (HL) was an independent prognostic factor of overall survival (OS), event-free survival (EFS), and response to therapy, as well as to test the interrelations of HRR with demographic, clinical, and laboratory characteristics.

Materials and methods: This research was designed as a retrospective cohort study of patients with histologically verified HL, diagnosed at the Clinical Hospital Center Osijek in the period from April 2005 to August 2022.

Results: A total of 83 subjects, with a median age of 36 years, ranging from 19 to 82, participated in the research. A significant difference in HRR was found depending on the outcome of treatment, OS, and EFS. A lower HRR was associated with a worse therapeutic response, a higher risk of relapse, and other worse prognostic factors. A positive correlation of HRR with middle corpuscular volume, number of erythrocytes, and albumin level was found, and a negative correlation with erythrocyte sedimentation rate, number of platelets, and C-reactive protein concentration.

Conclusion: Lower HRR was associated with unfavorable clinical and pathological characteristics of HL. There is a good potential for HRR as a prognostic marker and it should be applied with other known biochemical and hematological markers.

Keywords: hemoglobin, Hodgkin lymphoma, red blood cell distribution width, hemoglobin to red blood cell distribution width ratio, survival

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INTRODUCTION

Hodgkin lymphoma (HL) is a rare monoclonal lymphoid neoplasm primarily characterized by malignant transformation of B-lymphocytes, called Reed-Sternberg cells, within an inflammatory microenvironment (1). Cure rates are around 80 % (2). However, despite the high cure rate with initial therapy, approximately 5 to 10 % of HL patients are resistant to initial treatment, and 10 to 30 % of patients will relapse after achieving initial complete remission (3, 4). The International Prognostic Score (IPS) is a widely accepted tool for advanced-stage HL risk stratification. Patients with five or more factors have a 5-year progression-free survival of 42 %, while those without negative prognostic factors have an 84 % chance of being progression-free after 5 years (5, 6). Identifying additional factors for early detection of adverse treatment outcomes is crucial for improved risk stratification and personalized treatment.

Hemoglobin and red cell distribution width (RDW) are laboratory findings widely available and routinely measured in blood tests. Hemoglobin to RDW ratio (HRR) emerges as a potential marker for predicting

outcomes in various cancers, as well as in cardiovascular and cerebrovascular diseases. Within the context of cancer prognosis, it demonstrates the intricate interplay between hematologic parameters and disease trajectory. Low HRR reflects nutritional insufficiency and a higher inflammatory burden resulting in worse disease outcomes (7). Studies of malignancies such as lymphoma and lung carcinoma show that a low HRR correlates with shorter survival, advanced disease, and poorer outcomes (7–12). In cardiovascular contexts, low HRR predicts heart failure mortality and cardiovascular hospitalizations (13–15). Further research is needed to standardize HRR thresholds and assess their inclusion in risk models for diverse conditions.

To our knowledge, there are no studies concerning the association between HRR and HL. Therefore, our aim was to examine whether the value of HRR at the time of HL diagnosis was an independent prognostic factor of overall survival (OS), event-free survival (EFS), and response to therapy, as well as to test the interrelations of HRR with demographic, clinical, and laboratory characteristics.

PARTICIPANTS AND METHODS

The research was conducted on all adult patients with histologically verified HL diagnosed at the Clinical Hospital Center Osijek in the period from April 2005 to August 2022. A total of 83 patients were enrolled. The inclusion criteria required necessary clinical data availability, while exclusion criteria encompassed incomplete clinical data and patients diagnosed with nodular lymphocyte-predominant HL.

Data collection involved reviewing the medical documentation and hospital information system for each participant. The collected information included general participant features, laboratory characteristics, IPS, Ann Arbor disease stage, therapy response (complete or partial remission/progression/relapse/death), Eastern Cooperative Oncology Group Performance status (ECOG), initial HRR (hemoglobin value divided by RDW), EFS (calculated from the day of diagnosis until one of the following: disease progression, initiation of another anti-lymphoma treatment, relapse, death, or last follow-up), and OS (calculated from the day of diagnosis until death or the last follow-up).

Table 1. *Distribution of patients by characteristics (N = 83)*

	Number (%) of patients
Gender	
Male	42 (51)
Female	41 (49)
Clinical Stage Ann Arbor	
Stage I	5 (6)
Stage II	36 (43.4)
Stage III	14 (16.9)
Stage IV	28 (33.7)
PHD*	
Nodular sclerosis	50 (60.2)
Mixed cellularity	18 (21.7)
Lymphocyte predominance	13 (15.7)
Not subtyped	2 (2.4)
B symptoms present	34 (41)
Protocol	
ABVD†	66 (79.5)
eBEACOPP‡	11 (13.3)
Other	6 (7.2)

*pathohistological diagnosis; †doxorubicin, bleomycin, vinblastine, dacarbazine; ‡etoposide, bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

Statistical analysis

Categorical data were presented using absolute and relative frequencies. The normality of numerical variable distributions was assessed using the Shapiro-Wilk test. Continuous data were described using the median and interquartile range or range from minimal to maximal value. Differences between the two groups were analyzed using the Mann-Whitney U test (with Hodges-Lehmann and a 95% confidence interval of the difference), while the Kruskal-Wallis test was used for three or more independent groups. The association was measured using the Spearman correlation coefficient. The predictive value of the HRR ratio on survival was visualized *via* Kaplan-Meier curves. Receiving operating characteristics (ROC) analysis evaluated the diagnostic utility of the HRR ratio in OS and EFS outcomes. All *P* values were two-tailed, with significance set at alpha = 0.05. Statistical analysis utilized the MedCalc® Statistical Software version 20.218 and IBM SPSS 23.

RESULTS

The study involved 83 patients, with a median age of 36 years (interquartile range 25 – 57), ranging from 19 to 82, at diagnosis. The distribution of patients by characteristics is presented in Table 1.

The HRR was significantly lower in patients with clinical Ann Arbor stages III and IV and in patients who had B symptoms (Table 2).

Spearman's correlation coefficient was used to examine the association of HRR with biochemical indicators. It was observed that as HRR decreased, the values of red blood cells, mean corpuscular volume (MCV), and albumin levels also decreased, while the values of erythrocyte sedimentation rate (ESR), platelet count, and C-reactive protein levels (CRP) values increased and *vice versa* (Table 3).

The largest proportion of patients had an IPS from 0 to 2 (62.7 %), while the smallest number of participants had an IPS from 5 to 7 (10.8 %). In the observed group of subjects, 84.3 % achieved complete remission, 8.4 % relapsed, and 9.6 % died.

The HRR ratio was significantly lower in patients experiencing partial remission compared to those in complete remission, while there was no significant difference in patients with disease progression. Patients experiencing relapse also exhibited significantly lower

Table 2. *Differences in hemoglobin to red cell distribution width ratio based on gender and clinical characteristics (N = 83)*

	Median (IQR‡) HRR‖	§Difference (95% confidence interval)	*P**
Gender			
Male (n = 42)	9.03 (7.91 – 10.35)	-0.47	0.36
Female (n = 41)	8.58 (7.11 – 10.36)	(-1.42 - 0.49)	
Ann Arbor stage			
Stage I and II (n = 41)	9.65 (8.39 – 11.01)	-1.93	**< 0.001**
Stage III and IV (n = 42)	8.14 (6.03 – 9.09)	(-2.76 - -1.09)	
PHD¶			
Nodular sclerosis (n = 50)	8.95 (7.91 – 10.43)		
Mixed cellularity (n = 18)	6.95 (5.59 – 9.65)		0.09†
Lymphocyte predominance (n = 13)	9.42 (8.2 – 10.38)		
Not subtyped (n = 2)	8.25 (7.4 – 9.09)		
B symptoms			
No (n = 49)	9.42 (8.29 – 10.59)	-1.88	**< 0.001**
Yes (n = 34)	7.71 (5.74 – 9.09)	(-2.82 - -0.93)	
Protocol			
ABVD** (n = 66)	9.02 (7.6 – 10.43)		0.15†
eBEACOPP†† (n = 11)	8.85 (7.68 – 9.81)		
Other (n = 6)	7.83 (6.55 – 9.12)		

*Mann-Whitney U test; †Kruskal-Wallis test (*post hoc* Conover); ‡ interquartile range; §Hodges-Lehmann median difference; ‖hemoglobin to red cell distribution width ratio; ¶pathohistological diagnosis; **doxorubicin, bleomycin, vinblastine, dacarbazine; ††etoposide, bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

HRR ratios. In patients with IPS scores of 3 and 4, as well as greater than 4, the HRR ratio was significantly lower compared to patients with an IPS score of 0 to 2 (Table 4).

To assess the diagnostic value of HRR, the ROC curve calculation method was used (based on specificity and sensitivity), gradually changing the values that distinguished patients concerning positive/negative outcomes

Table 3. *Association of hemoglobin to red cell distribution width ratio with biochemical indicators (Spearman's correlation coefficient), N = 83*

	Spearman's correlation coefficient of HRR*	
	Correlation coefficient ρ (Rho)	*P*†
ESR‡ (mm/3.6ks)	-0.698	< 0.001
Erythrocytes (x10^9/L)	0.637	< 0.001
MCV§ (fL)	0.447	< 0.001
Leukocytes (x10^{12}/L)	-0.124	0.27
Lymphocytes (%)	0.076	0.5
Platelets (x10^9/L)	-0.371	0.001
CRP‖ (mg/L)	-0.54	< 0.001
Albumins (g/L)	0.567	< 0.001
LDH¶ (U/L)	-0.173	0.12

*hemoglobin to red cell distribution width ratio; †Spearman's correlation coefficient; ‡erythrocyte sedimentation rate; §mean corpuscular volume; ‖C-reactive protein; ¶lactate dehydrogenase

Table 4. *Differences in hemoglobin to red cell distribution width ratio according to the treatment outcome, relapse, and International Prognostic Score (N = 83)*

	Median (IQR§) HRR‖	‡Difference (95% confidence interval)	*P**
Treatment outcome			
Complete remission (n = 70)	9.09 (7.91 – 10.45)		**0.008†**
Partial remission (n = 7)	7.23 (5.83 – 8.06)		
Disease progression (n = 6)	7.45 (6.4 – 9.09)		
Relapse			
No (n = 76)	9.02 (7.59 – 10.43)	-2.21 (-3.72 - -0.69)	**0.01**
Yes (n = 7)	6.62 (5.27 – 8.3)		
IPS¶			
0, 1, 2 (n = 52)	9.59 (8.5 – 10.82)		**< 0.001†**
3, 4 (n = 22)	7.36 (5.76 – 8.38)		
5, 6, 7 (n = 9)	6.67 (5.46 – 9.08)		

*Mann-Whitney U test; †Kruskal-Wallis test (*post hoc* Conover); ‡Hodges-Lehmann median difference; §interquartile range; ‖hemoglobin to red cell distribution width ratio; ¶International Prognostic Score

(alive/deceased). The cut-off point for each group was adjusted to create a ROC curve objectively determining the value that best distinguished the compared groups. In the data, considering a negative outcome (death) and the occurrence of events (relapse, progression, death) (EFS outcome), HRR was a significant diagnostic indicator. The cut-off point for HRR value for a negative outcome (death) was ≤ 6.67, and for the occurrence of disease, the cut-off point for HRR was ≤ 8.64 (Table 5, Figure 1).

For analysis of the association of HRR with the observed parameters, the participants were divided into two groups based on the HRR cut-off value for OS (≤ 6.67) obtained from the ROC analysis. Significant differences between the groups of participants with lower HRR and higher HRR values were found in all observed numerical and categorical parameters, except for the number of leukocytes, lymphocytes, lactate dehydrogenase levels, gender, and age. Participants with HRR ≤ 6.67 had signi-

Table 5. *Difference in demographic, clinical, and laboratory parameters according to the category of hemoglobin to red cell distribution width ratio value (N = 83)*

Biochemical indicator		Median (IQR†)		P^*
		HRR‡ ≤ 6.67 (n = 17)	HRR > 6.67 (n = 66)	
Albumin (g/L)		37.7 (31.1 - 40.5)	42.4 (39.7 – 46)	**< 0.0001**
CRP§ (mg/L)		116.3 (91.4 - 160.9)	12.45 (3.2 - 50.5)	**< 0.0001**
Erythrocyte (x10^9/L)		3.9 (3.6 - 4.3)	4.6 (4.3 - 4.9)	**< 0.0001**
Leukocyte (x10^{12}/L)		10.7 (7.2 - 19.8)	8.5 (6.6 - 12.2)	0.13
LDH‖ (U/L)		240 (168 - 327.5)	191 (161.5 – 235.5)	0.07
Lymphocyte (%)		1.45 (0.89 - 2.71)	1.42 (0.97 - 2)	0.45
MCV¶ (fL)		76.3 (72.9 - 83.1)	84.8 (80.6 - 88.03)	**0.001**
ESR** (mm/3.6ks)		98 (71 - 110)	32 (15 - 55)	**< 0.0001**
Platelets (x10^9/L)		424 (256 - 585.5)	292.5 (243.3 – 356)	**0.03**
Age [n (%)]	≤ 60 years	10 (59)	54 (82)	0.06
	> 60 years	7 (41)	12 (18)	
Gender [n (%)]	Female	7 (41)	31 (47)	0.38
	Male	10 (59)	35 (53)	
ECOG†† [n (%)]	0 and 1	12 (71)	62 (94)	**0.02**
	> 2	5 (29)	4 (6)	
B symptoms [n (%)]	Yes	13 (77)	21 (32)	**0.001**
	No	4 (23)	45 (68)	
Ann Arbor stage [n (%)]	I and II	27 (32.5)	40 (61)	**< 0.001**
	III and IV	15 (18.1)	26 (39)	
Relapse [n (%)]	Yes	4 (23)	3 (5)	**0.03**
	No	13 (77)	61 (95)	

*Mann-Whitney test; †interquartile range; ‡hemoglobin to red cell distribution width ratio; §C-reactive protein; ‖lactate dehydrogenase; ¶mean corpuscular volume; **erythrocyte sedimentation rate; ††Eastern Cooperative Oncology Group Performance status

ficantly higher values of ESR, CRP, and platelet values, as well as lower albumin, MCV, and erythrocyte levels. Individuals with HRR less than 6.67 more commonly had B symptoms, advanced stage, higher ECOG value, and relapsed more frequently (Table 5).

The median follow-up of our cohort was 43 months, ranging from a minimum of 4 to a maximum of 199. The 5-year OS and EFS were 90.4 % and 84.3 % for all patients, respectively. Kaplan–Meier analysis showed a significant difference in OS and EFS between the two groups (HRR ≤ 6.67 *vs* HRR > 6.67). The 5-year OS and

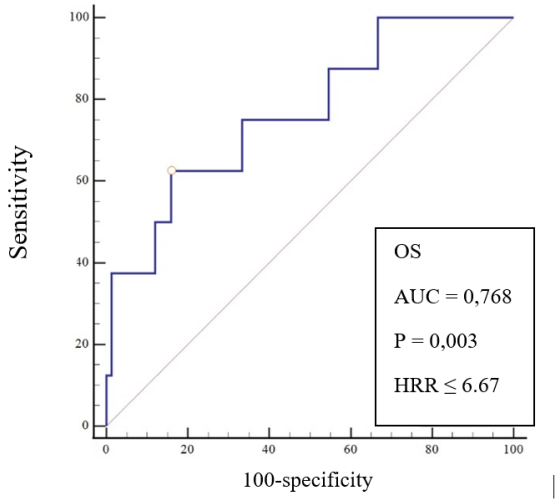

Figure 1a. *Hemoglobin to red cell distribution width ratio (HRR) as a diagnostic indicator of overall survival (OS) (Receiving Operating Characteristics analysis), N = 83. AUC – area under the curve*

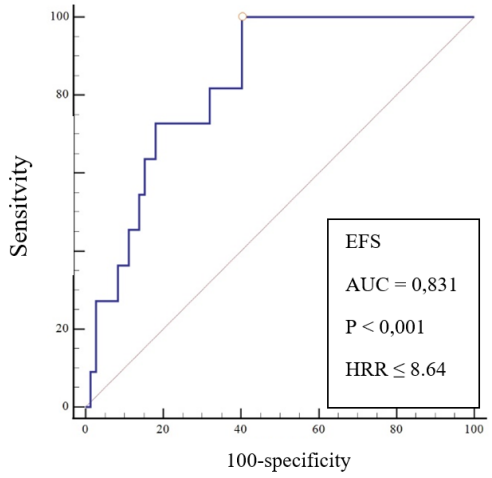

Figure 1b. *Hemoglobin to red cell distribution width ratio (HRR) as a diagnostic indicator of event-free survival (EFS) (Receiving Operating Characteristics analysis), N = 83. AUC – area under the curve*

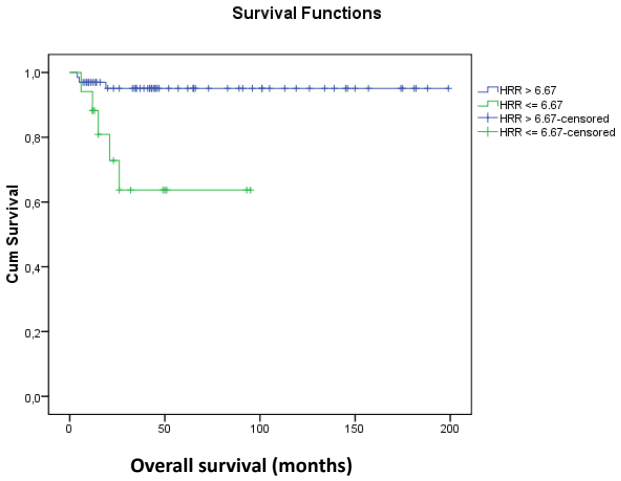

Figure 2a. *Kaplan–Meier curves for overall survival according to baseline hemoglobin to red cell distribution width ratio, HRR (normal > 6.67 (n = 66), low ≤ 6.67 (n = 17)) in patients with Hodgkin lymphoma (N = 83). (64 % vs 95 %, P = 0.001)*

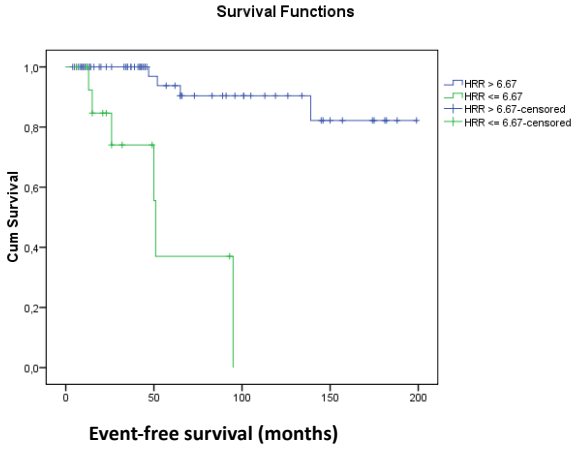

Figure 2b. *Kaplan–Meier curves for event-free survival according to baseline hemoglobin to red cell distribution width ratio, HRR (normal > 6.67 (n = 17), low ≤ 6.67 (n = 66)) in patients with Hodgkin lymphoma (N = 83). (37 % vs 94 %, P < 0.001)*

5-year EFS were significantly lower in those with HRR ≤ 6.67 (64 % *vs* 95% for OS, $P = 0.001$) [Figure 2a] (37 % *vs* 94 % for EFS, $P < 0.001$) [Figure 2b] in comparison with patients with HRR > 6.67. The 5-year OS and EFS for all patients were observed based on the cut-off value for OS.

DISCUSSION

This study showed that a low HRR at diagnosis of HL was associated with a poor prognosis. To our knowledge, this is the first report on the prognostic value of HRR in patients with HL. In our study, HRR strongly correlated with the main prognostic factors in HL, and HRR ≤ 6.67 was shown to be an adverse prognostic factor for EFS and OS.

A lower HRR ratio was associated with adverse outcomes, higher IPS value, advanced clinical stage, elevated CRP, ESR, and platelet levels, as well as reduced albumin, MCV, and erythrocyte levels.

The HRR ratio stands as a significant biomarker initially proposed to predict outcomes in esophageal squamous cell carcinoma and subsequently utilized in various cancer types (7, 8, 2). It is regarded as a novel prognostic marker because it reflects overall health, encompassing nutritional status, inflammation, and immune function (7). Accordingly, our study revealed that lower HRR is associated with more frequent microcytic anemia, elevated inflammatory markers, low albumin levels, and thrombocytosis. Microcytic anemia affects approximately a third of HL patients due to factors such as bone marrow involvement by cancer cells or chronic inflammation (16, 17). Anemia in lymphoma patients independently predicts worse treatment outcomes and higher mortality rates (6, 18, 19). However, the precise association between anemia and poor survival remains incompletely understood. Potential reasons include severe anemia indicating more aggressive tumors, hypoxia from anemia encouraging tumor invasiveness and reducing treatment sensitivity, and the release of cytokines like tumor necrosis factor alpha and interleukin 6 triggered by anemia (20–24). Further research is necessary to elucidate the relationship between anemia and cancer progression, with nutritional status and weakened physical resilience potentially contributing to a poorer prognosis.

The association of lower HRR values with high ESR and CRP levels, as well as low albumin levels, reflects the inflammatory processes and nutritional status. This connection suggests that lower HRR may indicate a higher inflammatory burden and a more pronounced acute phase response, signaling a poorer prognosis. This systemic inflammatory response may elucidate most of the B symptoms present in patients with HL, and our study demonstrated a correlation between lower HRR and the presence of B symptoms and the advanced disease stage. Recent studies investigating the prognostic role of RDW in HL have highlighted a significant association between RDW and hypoalbuminemia, which serves as an indicator of malnutrition and mortality (25-27). Elevated proinflammatory cytokines disrupt erythropoietin production and erythrocyte maturation, resulting in poor nutritional status (hypoalbuminemia) and higher RDW values (28). Inflammation and malnutrition may impair erythropoiesis, thus contributing to increased RDW, which consequently leads to lower HRR values.

In our study, lower HRR values were associated with poorer treatment response, a higher risk of relapse, and higher IPS scores, indicating a worse disease outcome. Alongside all the aforementioned parameters of poor nutritional status and inflammatory burden, platelets also showed a negative correlation with low HRR in our study. In HL, thrombocytopenia is common, while thrombocytosis, though rare, can occur in response to inflammation or infection associated with lymphoma, especially in HL (29). Platelets play a role in tumor cell protection and promote invasion, metastasis, and thrombosis by activating certain pathways (30, 31). Studies indicate that thrombocytosis correlates with a poor cancer prognosis (32, 33). One of the newer prognostic factors that could find its role in future clinical practice is the platelet/lymphocyte ratio (34), and by combining it with HRR it is possible to achieve better specificity and sensitivity (35). Larger studies across different institutions are needed to establish a reliable platelet cut-off for poor prognosis.

However, it is important to consider the limitations of the study. The retrospective study design and data collection from a single center may introduce bias. The sample size was relatively small, which could impact the generalizability of the findings. Further studies with larger sample sizes and prospective designs are warranted to validate the results and evaluate the clinical utility of HRR in treatment decision making and outcome prediction in HL.

CONCLUSION

To our knowledge, this is the first study conducted on the prognostic significance of HRR in HL. In conclusion, the results of this study demonstrate that lower HRR is associated with unfavorable clinical and laboratory characteristics, as well as poorer disease outcomes, therapeutic response, and prognostic factors. While underscoring the potential of HRR as a prognostic marker, further investigations are warranted, emphasizing its integration with established biochemical and hematological markers. Incorporating HRR into risk stratification and treatment decision making processes holds promise for enhancing a personalized and efficacious management of HL patients.

ABBREVIATIONS

ABVD – doxorubicin, bleomycin, vinblastine, dacarbazine

CRP – C-reactive protein

eBEACOPP – etoposide, bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

ECOG – Eastern Cooperative Oncology Group Performance status

EFS – event-free survival

ESR – erythrocyte sedimentation rate

HL – Hodgkin lymphoma

HRR – hemoglobin to red cell distribution width ratio

IPS – International Prognostic Score

IQR – interquartile range

MCV – mean corpuscular volume

OS – overall survival

RDW – red cell distribution width

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SAŽETAK

PROGNOSTIČKA VRIJEDNOST OMJERA VRIJEDNOSTI HEMOGLOBINA I ŠIRINE DISTRIBUCIJE ERITROCITA U BOLESNIKA S HODGKINOVIM LIMFOMOM

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Ciljevi istraživanja: Istražiti je li vrijednost omjera hemoglobina i širine distribucije eritrocita (HRR, prema eng. hemoglobin to red blood cell distribution width ratio) u vrijeme utvrđivanja dijagnoze Hodgkinovog limfoma (HL) neovisan prognostički čimbenik ukupnog preživljenja, preživljenja bez događaja, odgovora na terapiju te ispitati međusobni odnos HRR-a i demografskih, kliničkih i laboratorijskih obilježja. ***Ispitanici i postupci:*** Istraživanje je ustrojeno kao povijesno kohortno. U istraživanje su uključeni svi bolesnici s histološki verificiranim HL-om u kojih je bolest dijagnosticirana od travnja 2005. do kolovoza 2022. godine u Kliničkom bolničkom centru Osijek. ***Rezultati:*** U istraživanju je sudjelovalo ukupno 83 ispitanika, medijana dobi 36 godina, u rasponu od 19 do 82. Pronađena je značajna razlika prosječne vrijednost HRR-a ovisno o ishodu liječenja, ukupnom preživljenju te preživljenju bez događaja. Manji omjer HRR-a bio je povezan s lošijim terapijskim odgovorom, većim rizikom od relapsa i lošijim drugim prognostičkim čimbenicima. Pronađena je pozitivna korelacija HRR-a s srednjim volumenom eritrocita, brojem eritrocita i razinom albumina, te negativna korelacija sa sedimentacijom eritrocita, brojem trombocita i koncentracijom C-reaktivnog proteina. ***Zaključak:*** Manji HRR bio je povezan s nepovoljnim kliničko-patološkim obilježjima HL-a te postoji dobar potencijal HRR-a kao prognostičkog biljega i potrebno ga je rabiti i s drugim do sada poznatim biokemijskim i hematološkim biljezima.

Ključne riječi: hemoglobin, Hodgkinov limfom, širina distribucije eritrocita, omjer hemoglobina i širine distribucije eritrocita, preživljenje

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IS IT SAFE TO REMOVE THE PERITONEAL CATHETER DURING KIDNEY TRANSPLANTATION SURGERY?

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Abstract: Transplantologists have not reached agreement on whether the optimal time for peritoneal catheter for peritoneal dialysis removal is during or at a later point after kidney transplant surgery. One of the main reasons for not removing the peritoneal catheter during kidney transplant surgery is delayed allograft function and the need for dialysis. On the other hand, an increased risk for peritoneal catheter-related infections is the main argument for earlier (simultaneously with kidney transplantation surgery) peritoneal catheter extraction. The aim of our study was to investigate outcomes of peritoneal catheter removal during kidney transplant surgery in our transplant center. During a 10-year period (2013 – 2022) 509 kidney transplantations were performed in our center. The retrospective study included all 78 (15 %) adult kidney transplant recipients who were on peritoneal dialysis at the time of the transplantation. In 75 of them, the peritoneal catheter was removed during the kidney transplant surgery and they were included in further analysis. Delayed graft function developed in 18 patients, requiring hemodialysis. Peritonitis or surgical complications related to peritoneal catheter removal did not occur during the post-transplantation period in any of the 75 patients. One-year patient survival was 99 %, and graft survival was 99 % as well. Kidney graft function at 1 year was good (median serum creatinine 114 μmol/L, ranging from 49 to 427). Our ten-year experience with 75 patients in whom peritoneal catheter removal was performed during the kidney transplant surgery provided clear evidence that such a timing approach should be considered safe and without complications, thus rendering avoidance of one more anesthesia, while possibly reducing the risk of peritonitis as well as the costs involved.

Keywords: peritoneal catheter extraction, time, peritonitis, kidney transplantation

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INTRODUCTION

Kidney transplantation (TX) is considered the optimal renal replacement therapy and many patients with end-stage kidney disease undergoing peritoneal dialysis (PD) will eventually receive a kidney allograft (1). There is as yet no definite agreement among transplantologists whether the optimal time for peritoneal catheter (PC) for PD removal is during or some time after kidney TX surgery (2-7). One of the main reasons against PC removal during kidney TX surgery is providing a dialysis access ready in case of delayed allograft function (DGF) or allograft failure (8). On the other hand, an increased risk for PC-related infections due to immunosuppression is the main argument for earlier (simultaneously with kidney TX surgery) PC extraction (3). In one study, the need for dialysis support (PD or hemodialysis, HD) after TX was associated with an increased risk for peritonitis (9). According to one study among the pediatric population, PC should not be removed until one month after kidney TX (6). In another study, PC removal was undertaken between eight and 12 weeks after kidney TX (7). In certain circumstances, such as infectious or mechanical complications, PC should be removed before or during kidney TX (4, 6, 7). In simultaneous pancreas and kidney transplantation (SPKT) there is no option to leave PC for PD *in situ*, and this is an

additional circumstance where immediate removal of PC for PD should be considered. Additionally, in living donor kidney TX, which is associated with a lower risk of DGF, prompt PC removal should be considered (8). According to the 2005 European Best Practice Guidelines for peritoneal dialysis, PC can be left *in situ* for three to four months even with a functioning graft, but earlier PC removal after a successful kidney TX is also appropriate (10). More recently, Zawistowski et al. conducted a systematic review and meta-analysis of observational studies comparing patients with PC for PD left in place or removed during kidney TX (2). The meta-analysis included five studies with a total of 338 patients. The results showed that patients with PC left *in situ* were at a higher risk of needing dialysis, and experienced more catheter-related infections compared to patients in whom PC was removed during kidney TX (2). Nevertheless, the authors concluded that owing to scarce evidence and the absence of randomized trials, the question of the ideal time for PC removal cannot be answered as yet (2). The aim of our study was to investigate outcomes of PC removal during kidney TX surgery in our transplant center.

MATERIALS AND METHODS

During a 10-year period (2013 – 2022) 509 kidney TXs were performed in our center. The retrospective study included all 78 (15 %) adult kidney TX recipients who were on PD at the time of TX. In 75 of them, PC for PD was removed during kidney TX surgery. In three patients, PC for PD was left *in situ* at the time of kidney TX surgery at the surgeon's discretion, and was removed some time after TX. For those three patients in whom PC for PD was left *in situ*, data were available only for one patient. That patient had DGF and PD was used for dialysis but the efficiency was suboptimal, and therefore a central venous catheter (CVC) for dialysis was placed. There were no infectious complications related to the PC for PD *in situ* and it was removed 10 months after TX. One year after TX, allograft function was good (estimated glomerular filtration rate 39 mL/min/1.73m^2 body surface area). The 75 patients whose PC was removed simultaneously with kidney TX were included in the further analysis. Hospital and outpatient data records including gender, age, duration of chronic dialysis, peritonitis after kidney TX, surgical complications related to PC removal, patient survival at one year after TX, allograft survival at one year after TX, and allograft function at one year after TX were analyzed. DGF was defined by the need for dialysis in the first week post-transplant, and slow graft function (SGF) was defined by serum creatinine > 265 μml/L on post-transplantation day five but without need for dialysis[11]. The study was conducted according to the Declaration of Helsinki.

STATISTICS

Continuous variables are expressed as medians (min. – max.) and categorical variables as absolute numbers (percentages). Differences between the groups were analyzed using the Mann-Whitney test for continuous variables and the Chi-square test, or Fisher exact test, when appropriate, for categorical variables. Statistical analysis was performed using the Social Science Statistics software at https://www.socscistatistics.com/tests/, and $P < 0.05$ was considered significant.

RESULTS

There were 75 analyzed patients, of whom 39 (52 %) were men. Median age was 49 years at the time of TX, ranging from 20 to 77 years. Sixty-one patients had kidney TX, and 14 patients underwent SPKT. Living kidney TX was performed in four patients. Median duration of chronic dialysis was 2 years, ranging from 0 to 8 years. DGF requiring HD was recorded in 18 patients. SGF was observed in six patients who did not require dialysis. The remaining patients had immediate graft function (68 %). Among the patients who developed DGF requiring dialysis, there were no infectious complications regarding CVC. In 12 of them CVC was placed in the jugular vein (in 11 on the right side). In one patient CVC was placed in the left jugular vein, but due to malposition it was extracted and another catheter was placed in the right jugular vein. The subclavian vein was used for CVC placement in 5 patients (4 on the right side), and in one patient CVC was placed into the femoral vein. Kidney biopsy was performed in six patients. Acute cellular rejection IA was diagnosed in three patients, and was treated with boluses of steroids. Of those patients with DGF, only one patient did not recover kidney function. Peritonitis did not occur during the post-transplantation period in any of the 75 patients that underwent PC removal during kidney TX surgery, and no surgical complications were recorded either. One-year patient survival was 99 % (one patient died in a traffic accident) and overall graft survival was 97 % (one patient expe-

rienced primary graft failure). Kidney graft function at 1 year expressed as median serum creatinine was 114 μmol/L, ranging from 49 to 427 (Table 1).

DISCUSSION

The optimal time for PC removal in kidney TX recipients is a matter of debate (2, 8). A potential need for dialysis support due to DGF or allograft failure on the one hand, and the risk of PC-associated peritonitis on the other, are of concern (3, 8). We retrospectively investigated the safety of early PC for PD removal performed simultaneously with kidney TX surgery. Our research showed that none of the patients had infectious or surgical complications related to PC removal during kidney TX surgery. Furthermore, allograft function at one year after kidney TX was good, and allograft and patient survival were excellent. Among the patients who developed DGF and required dialysis, CVC was placed without any infectious complications. Only in one patient CVC malposition occurred, requiring replacement. Our cohort consisted of almost all PD patients that received kidney transplants during the period 2013 – 2022. Rizzi et al. showed that patients in whom PC for PD was used within six weeks after TX had a more than three times higher risk for developing peritonitis compared to those who did not use PC after kidney TX. In the same study, 9 % of patients developed peritonitis after TX (9). In the cohort of 112 patients with PC left *in situ* until optimal allograft function was established,

Table 1. *Patient, donor, and transplant characteristics*

Patient characteristics (N = 75)	
Age (years)	median 49 (min. 20 – max. 77)
Males : females (n)	39 (52 %) : 36 (48 %)
Duration of chronic dialysis (years)	median 2 (min. 0 – max. 8)
DGF : SGF : IGF (n)	18 (24 %) : 6 (8 %) : 51 (68 %)
DGF TX from a living donation TX from a brain-dead person (marginal donors)	n = 18 n = 0 n = 18 (n = 3, 16.7 %)
Peritonitis after TX (n)	0
Surgical complication related to PC removal (n)	0
Patient survival at 1 year	99 %
Overall graft survival at 1 year	97 %
Creatinine at 1 year (μmol/L)	median 114 (min. 49 – max. 427)
Donor characteristics (N = 75)	
Age (years)	median 48 (min. 30 – max. 56)
Males : females (n)	47 (62.7 %) : 28 (37.3 %)
Transplant characteristics (N = 75)	
Kidney TX : SPKT (n)	61 (81.3 %) : 14 (18.7 %)
Living kidney TX (n)	4 (5.3 %)
Number of HLA MM (A-, B-, DR locus) (n = 71)*, (n) 0 1 - 2 3 - 4 5 - 6	 2 (2.8 %) 8 (11.3 %) 47 (66.2 %) 14 (19.7 %)

*only for deceased donors; TX = transplantation, SPKT = simultaneous pancreas and kidney transplantation, DGF = delayed graft function, SGF = slow graft function, IGF = immediate graft function; PC = peritoneal catheter, HLA – human leukocyte antigen, MM - mismatch

8 % developed PC-related infection during an eight-month follow-up (4). Another study advocates leaving PC *in situ* up to 45 days after TX. In that study, which included 65 PD patients who had kidney TX, one patient developed peritonitis while waiting for PC removal (5). Another study tried to elucidate in which patients safe PC removal during kidney TX can be performed (8). It was found that, taking into account a small risk of DGF, living donor kidney recipients are great candidates for early PC removal (8). It was also shown that catheter-related complication rates were similar in PD and HD patients (4.5 % PD *vs* 2.6 % HD; $P = 0.3$) (8). Warren et al. showed that 7 % of patients with PC left *in situ* and not used after kidney TX developed infectious complications, while complications in those in whom PC for PD had been used occurred in more than 50 % of cases (33 % developed peritonitis, and 20 % dialysate-derived fluid leaks) (3). Considering the high rate of complications associated with PC remaining *in situ* after TX, the authors concluded that PC removal should be considered during kidney TX surgery (3). Other reasons for early PC removal include avoiding patient exposure to additional invasive procedures, anesthesia, and hospitalization. There have been no prospective studies on that subject so far. A recently conducted systematic review and meta-analysis analyzed the best time for PC for PD removal in transplant patients. The study included eight observational studies, and five of them comprising 338 patients were taken into meta-analysis. The results showed that the incidence of PC-related infections (peritonitis and exit-site infections) was 10.2 % in patients with PC left *in situ*, while it was rare in patients with PC removed (2). According to the literature data, there are various protocols regarding management of PC for PD in patients undergoing kidney TX (2-8). Our ten-year experience with 75 patients in whom PC for PD removal was performed during the kidney TX surgery provided clear evidence that such a timing approach should be considered safe and without complications, thus rendering avoidance of one more anesthesia and possibly reducing the risk of peritonitis. A randomized study would provide the best insight into PD outcomes in kidney transplant patients depending on whether the PC for PD has been removed during kidney TX or at a later point. The limitations of our study include single-center analysis, the retrospective nature of the study, a small cohort, and absence of a control group.

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SAŽETAK

JE LI SIGURNO ODSTRANITI PERITONEJSKI KATETER TIJEKOM BUBREŽNE PRESADBE?

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Optimalno vrijeme za odstranjenje peritonejskog katetera za peritonejsku dijalizu predmet je debate među transplantacijskim nefrolozima. Odgođena funkcija presatka i potreba za dijalizom glavni su argumenti za kasnije odstranjenje peritonejskog katetera (tj. nakon bubrežne presadbe), dok je povećan rizik od infekcije glavni argument za ranije odstranjenje peritonejskog katetera (tj. tijekom bubrežne presadbe). Cilj našega istraživanja bio je analizirati ishode prilikom odstranjenja peritonejskog katetera tijekom bubrežne presadbe u našem transplantacijskom središtu. Tijekom 10-godišnjeg razdoblja bilo je 509 presadbi bubrega u našem središtu. U retrospektivno istraživanje uključeno je svih 78 (15 %) primatelja bubrega koji su bili na peritonejskoj dijalizi. U 75 bolesnika peritonejski kateter odstranjen je tijekom operativnog zahvata bubrežne presadbe i oni su uključeni u daljnju analizu. Odgođenu funkciju presatka razvilo je 18 bolesnika i oni su zahtijevali hemodijalizu. Peritonitis, kao ni kirurške komplikacije vezane uz odstranjenje peritonejskog katetera, nisu zabilježeni ni u jednog bolesnika u poslijetransplantacijskom praćenju. Jednogodišnje preživljenje bolesnika iznosilo je 99 %, a jednogodišnje preživljenje presatka također 99 %. Funkcija presatka godinu dana nakon presadbe bila je dobra (medijan serumskog kreatinina 114 μmol/l, od 49 do 427). Naše 10-godišnje iskustvo sa 75 bolesnika kojima je peritonejski kateter odstranjen tijekom bubrežne presadbe dalo je jasan dokaz da je ovakav pristup siguran, bez komplikacija, a omogućuje izbjegavanje dodatne anestezije, moguće i smanjenje rizika za peritonitis, kao i smanjenje troškova liječenja.

Ključne riječi : odstranjenje peritonejskog katetera, vrijeme, peritonitis, bubrežna presadba

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EFFICACY AND SAFETY OF NPH (NEUTRAL PROTAMINE HAGEDORN) INSULIN COMPARED WITH INSULIN GLARGINE IN PATIENTS WITH TYPE 2 DIABETES

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Abstract

Background: Insulin therapy is often required for achieving adequate glycemic control in patients with type 2 diabetes mellitus (DM2). For that purpose, the insulin analogue glargine is most commonly used in clinical practice, while only a minority of patients are given the cheaper NPH (Neutral Protamine Hagedorn) human insulin. ***Methods:*** In this observational multicenter study we compared the efficacy and safety of insulin glargine and human NPH insulin. During a six-month follow-up period two groups of patients with DM2 were observed. One group was administered NPH insulin while insulin glargine was administered in the other group (53 and 48 participants, respectively). ***Results:*** After six months, both patient groups achieved the same hemoglobin A1c (HbA1c) level (7.5 ± 1 %). In both groups a small statistically nonsignificant increase in body weight was observed. The daily dose of insulin (measured in international units, IU) was significantly higher in the glargine group than in the NPH insulin group (22.4 ± 8.5 IU *vs* 18.6 ± 7.8 IU). The incidence of hypoglycemia was similar in both groups. ***Conclusion:*** Our study revealed no significant difference in the risk of hypoglycemia or in efficacy between insulin glargine and NPH insulin in patients with DM2. Accordingly, our results suggest that human NPH insulin may be an effective and safe treatment for the majority of patients with DM2.

Keywords: type 2 diabetes mellitus, insulin glargine, NPH insulin, hypoglycemia, long-acting insulin

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INTRODUCTION

In the last three decades, the prevalence of diabetes mellitus (DM) has increased fourfold, mainly due to the worldwide increase in obesity. The current prevalence of DM is around 9 %, and DM type 2 (DM2) contributes to 90 % of all DM cases, which makes DM2 an important public health issue (1).

The treatment of DM2 usually begins with a combination of lifestyle changes and peroral antidiabetic medications. Unfortunately, in a large proportion of DM2 patients this combination does not lead to adequate glycemic control (2). In the case of poor glycemic control, insulin treatment is sometimes needed in patients with DM2 (3). Neutral Protamine Hagedorn (NPH) insulin, a synthetic basal human insulin created using a recombinant DNA (deoxyribonucleic acid) technology, has been used in DM2 patients for decades. However, in the last twenty years, a new class of insulin, so-called insulin analogues, has been developed with the main goal to modify and improve insulin pharmacokinetic properties. The chemical structure of insulin analogues differs from the structure of NPH insulin in several amino acids, which partially changes their pharmacokinetic profile. As a result, insulin analogues do not show peak activity (typically occurring 4 – 6 hours after NPH administration), which ensures uniform insulin activity during its action (4). Accordingly, phase III clinical trials demonstrated that administration of the insulin analogue glargine was associated with a lower incidence of hypoglycemia episodes compared to NPH insulin (5).

However, further studies that reflected everyday clinical practice reported contradictory results regarding the frequency of hypoglycemia in patients treated with insulin analogues or NPH insulin (6, 7). For example, a recent meta-analysis showed no difference between insulin glargine and NPH insulin in the occurrence of severe hypoglycemia (6). Lipska et al. also reported that the choice of basal insulin in DM2 patients did not affect the frequency of hospital admissions due to hypoglycemia (7).

The controversial results of previous studies, the fact that patients with DM2 are generally less prone to hypoglycemia due to insulin resistance, as well as the cost of treatment, which is considerably higher for insulin analogues compared to NPH insulin, question the validity of insulin analogue usage in a situation where a potentially equally efficacious and safe, and yet cheaper, alternative is available (8-10). Since data on this topic are still rather scarce, the main aim of the study was to compare the risk of hypoglycemia and efficacy when using NPH insulin and insulin glargine in patients with DM2 in everyday clinical practice.

METHODS

Patients

This observational multicenter study was conducted between June 2019 and June 2021 across five hospitals in Croatia (University Hospital Zagreb, University Hospital Osijek, University Hospital Split, Clinical Hospital Merkur, and County Hospital Slavonski Brod). Patients aged 18 - 85 years with a confirmed diagnosis of DM2 and inadequate blood glucose control during the use of oral antidiabetic drugs (OAD) for at least three months (HbA1c > 7 %) were enrolled. The study did not include patients with a confirmed diagnosis of DM type 1, body mass index < 20 kg/m^2 or > 35 kg/m^2, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m^2 body surface area, treatment with corticosteroids or glucagon-like peptide-1 agonists, pregnancy, liver cirrhosis, heart failure, and active alcohol or drug abuse. Informed consent was obtained from all patients before initiating procedures related to the study, in accordance with the principles of the Helsinki Declaration. The study was approved by the University Hospital Zagreb and the University of Zagreb School of Medicine ethics committees.

Study protocol

The study protocol consisted of a baseline visit and three follow-up visits. At the baseline visit, data about medical history, duration of DM2, previous diabetes treatment, and family medical history were obtained. In addition, all patients underwent weight and height measurements, as well as routine laboratory investigations. Insulin treatment with either NPH insulin or insulin glargine was initiated, depending on the physician's preference. Insulin was administered once daily, between 9 pm and 11 pm, and the starting dose was either 10 international units, IU, or 0.2 IU/kg of body weight, also depending on the physician's preference. The patients were educated about insulin self-administration and self-monitoring of blood glucose levels by a certified nurse educator. They were advised to increase the insulin dose by 2 IU every three days until fasting glucose reached the level of < 7 mmol/L. On the other hand, in the case of a hypo-

glycemic event (glycemia < 3.9 mmol/L) the patients were advised to decrease the insulin dose by 2 IU. Along with the insulin treatment, they continued to take their oral hypoglycemic medications with the exception of sulfonylureas, where dose reduction or discontinuation was considered. The patients were instructed to measure fasting glucose levels every morning, using a standardized glucometer, and to record any hypoglycemic events. At the first follow-up visit, performed 2 – 4 weeks after the baseline visit, insulin doses were revised based on the fasting glucose levels and episodes of hypoglycemia recorded by the patients. The second and the third (final) follow-up visits were performed three and six months after the initiation of insulin treatment, respectively, during which body weight, insulin doses, frequency and severity of hypoglycemic episodes, and HbA1c levels were assessed.

The primary endpoints of the study were a change in HbA1c levels and the incidence of hypoglycemic episodes, whereas the secondary endpoints included changes in body weight and proportions of patients with adequate glycemic control at the end of the study.

Hypoglycemic episodes were categorized as mild, moderate and severe. Mild hypoglycemia was defined as a plasma glucose level between 3 and 3.9 mmol/L, whereas moderate hypoglycemia was defined as a plasma glucose level < 3 mmol/L, both of which could be associated with the presence or absence of mild to moderate hypoglycemic symptoms. In contrast, severe hypoglycemia was defined as an episode of hypoglycemia associated with symptoms during which the patient required the assistance of another person.

Statistical analysis

Statistical analysis was done using SPSS 17.0 (SPSS, Chicago, USA), with significance set at $P < 0.05$. Variables were described as mean and standard deviation. A difference between two independent numerical variables was tested using Student's t-test, and the Chi-square test was applied to test a difference between two categorical variables. The analysis of repeated samples was done using the Wilcoxon test.

RESULTS

A total of 101 patients, 53 treated with NPH insulin (NPH group) and 48 treated with glargine (glargine group), were included in the study. At enrollment, the study subjects were taking 1–4 OADs (metformin and/or dipeptidyl peptidase, DPP4, agonist and/or sulfonylurea and/or pioglitazone). Twelve subjects were taking one OAD, 45 patients two, 40 patients three, and four study subjects were taking four OADs. Eighty subjects were taking metformin. In the glargine group, 37 patients received glargine-U100, and 11 received glargine-U300.

At baseline, the groups were matched for age, sex, body weight, body mass index (BMI), duration of DM2, use of metformin, number of OADs before insulin administration, and initial insulin dose. The baseline HbA1c level was significantly higher in the NPH group compared to the glargine group (9.8 ± 1.6 % *vs* 9 ± 1.3 %, $P = 0.02$). Patient demographics and clinical characteristics are shown in Table 1.

Table 1. *Demographic and clinical characteristics of the patients (N = 101)*

	NPH insulin (n = 53)	**Insulin glargine (n = 48)**	***P***
Sex (male/female) (n)	31/22	29/19	0.84
Age (years)	63.7 ± 9	62.6 ± 9.1	0.63
DM2 duration (years)	11.9 ± 8	12.1 ± 7.6	0.7
Body weight (kg)	83.4 ± 16	84.8 ± 14.4	0.86
Body mass index (kg/m^2)	28.7 ± 4.6	28 ± 3.7	0.82
Number of oral antidiabetic drugs	2.34 ± 0.75	2.38 ± 0.73	0.05
Metformin (yes/no) (n)	42/11	38/10	0.33
Hemoglobin A1c (%)	9.8 ± 1.6	9 ± 1.3	0.02
Initial insulin dose (international units)	15.1 ± 5.9	15.6 ± 5.3	0.53

NPH - Neutral Protamine Hagedorn; DM2 - diabetes mellitus type 2

During the six months of follow-up, no significant difference in the occurrence of hypoglycemic episodes was observed between the treatment groups. Thirteen patients (24.5 %) in the NPH group experienced hypoglycemia, of which 12 patients had blood glucose levels in the range 3 – 3.9 mmol/L, one had blood glucose level < 3 mmol/L, and no patient had severe hypoglycemia. On the other hand, in the glargine group, six patients had a hypoglycemic episode (12.5 %): four of them reported blood glucose levels of 3 – 3.9 mmol/L, one had glucose level < 3 mmol/L, and another one experienced severe hypoglycemia (Table 2). Patients who experienced hypoglycemic episodes had lower end-of-study HbA1c compared to those without hypoglycemia (7 ± 1 % *vs* 7.6 ± 1 %: $P = 0.03$). In both study groups, most hypoglycemic episodes occurred more than 3 months after the start of insulin treatment (NPH group 9/13; glargine group 5/6).

With regard to the efficacy of insulin treatment, no difference was observed between the groups in terms of the target HbA1c values at the end of the study. The level of HbA1c < 7 % was achieved in 17 patients (32.1 %) and 16 (33.3 %) patients in the NPH and glargine groups, respectively. On the other hand, 25 patients (47.1 %) in the NPH group and 21 patients (43.8 %) in the glargine group had HbA1c levels > 7.5 % at the last study visit (Table 3). However, a significantly higher decrease in HbA1c was observed in the NPH group compared to the glargine group (-2.3 ± 1.9 % *vs* -1.5 ± 1.5 %; $P = 0.03$) (Table 2).

At the start of the study, the insulin dose between the groups was not different. In contrast, at the last study visit insulin doses in the glargine group were significantly higher in comparison to the NPH group (22.4 ± 8.5 IU *vs* 18.6 ± 7.8 IU; $P < 0.02$). In both study groups, a modest weight gain was observed during insulin treatment (Table 2).

Table 2. *Clinical characteristics of patients after six months of follow-up (N = 101)*

	NPH group (n = 53)	**Glargine group (n = 48)**	***P***
Hemoglobin A1c (%)	7.5 ± 1	7.5 ± 1	0.95
Δ Hemoglobin A1c (%)	-2.3 ± 1.9	-1.5 ± 1.5	0.03
Body weight (kg)	84.4 ± 14.6	85.4 ± 13.2	0.53
Δ Body weight (kg)	0.63 ± 4.5	0.19 ± 3.7	0.6
Body mass index (kg/m^2)	28.7 ± 4.6	28 ± 3.7	0.82
Insulin dose (IU)	18.6 ± 7.8	22.4 ± 8.5	0.02
Hypoglycemia (n)	13	6	0.06
Mild	12	4	0.13
Moderate	1	1	> 0.999
Severe	0	1	0.47

NPH - Neutral Protamine Hagedorn; IU – international unit

Table 3. *HbA1c after six months of insulin treatment (N = 101)*

HbA1c %	**NPH insulin (n = 53) n (%)**	**Insulin glargine (n = 48) n (%)**	***P***
< 7	17 (32.1)	16 (33.3)	0.84
7 – 7.5	11 (20.8)	11 (22.9)	0.94
> 7.5	25 (47.1)	21 (43.8)	0.92

DISCUSSION

Insulin is one of the most frequently used medications in the treatment of DM2 diabetes, administered to 23 – 26 % of these patients (11, 12). Human insulins were the gold standard in the treatment until the early 2000s when the use of recombinant DNA technology enabled the synthesis of insulin analogues which were expected to have a favorable pharmacokinetic profile. As a result, despite their higher price, insulin analogues have become more popular in everyday clinical practice and their use exceeds that of human insulins (11, 13).

Although randomized clinical trials and meta-analyses reported some benefits of basal insulin analogues compared to human insulins with respect to reduced risk of nocturnal hypoglycemia, insulin analogues have not been shown to reduce the risk of severe hypoglycemia (6, 14–16). In addition, no difference in hospital admissions or emergency department visits related to hypoglycemia was observed between patients on NPH insulin and those on insulin glargine (7). Finally, when compared to NPH insulins, the use of basal insulin analogues was not associated either with better glycemic control or with better clinical outcomes in patients with DM2 (5, 7).

Similar to those reports, our study demonstrated no significant difference in the risk of hypoglycemic events between basal insulin analogues and human insulin, and no difference between the patient groups was observed either in terms of the HbA1c level at the end of the study, which is also in accordance with previous reports (5, 6, 17, 18). However, patients using NPH insulin had a significantly higher decrease in HbA1c levels during six months of treatment compared to those who were taking the basal insulin analogue glargine. This difference can probably be attributed to a higher baseline HbA1c level in the NPH group, as numerous studies have shown that the pretreatment HbA1c level is a key parameter that determines the magnitude of HbA1c decrease during treatment (19–21).

Apart from hypoglycemia, weight gain is another well-known side effect of insulin therapy. Previous studies reported a gain of 3 – 7.5 kg after one year of insulin treatment (22, 23). In our study, body weight remained stable during the six-month treatment period in both study groups, probably owing to the concomitant administration of metformin in a significant proportion of patients. This is in accordance with previous reports showing a positive effect of the insulin-metformin combination on weight gain (23).

Furthermore, the cost of insulin is an important parameter that should be taken into consideration when discussing the treatment of patients with diabetes. A recent paper by Gotham et al. reported that prices of insulin analogues are much higher than NPH insulin prices worldwide (10). Similarly, in the Croatian market insulin glargine is more expensive than NPH insulin by 44 – 105 %, depending on the brand name. Moreover, the results of our study showed that a significantly higher dose of insulin glargine compared to NPH insulin is needed to achieve comparable glycemic control, which further increases the cost of treatment with insulin glargine. These higher costs would be justified in the case of improved glycemic regulation or a decreased risk of adverse effects such as clinically important hypoglycemia and weight gain. However, the present study demonstrated no significant difference in the efficacy and safety profile between insulin glargine and NPH insulin, which is in accordance with previous reports (6, 7). Therefore, the use of insulin analogues might not be justified in the vast majority of DM2 patients.

The strength of our study is reduced by the relatively small number of patients involved, which limits the merits of its results. Accordingly, it is possible that studies with a larger number of participants would obtain somewhat different results. Furthermore, the fact that almost half of the patients in our cohort did not have adequate glycemic control at the end of the study (HbA1c > 7.5 %) could have affected the frequency of hypoglycemia. Likewise, we observed lower end-of-study HbA1c in patients who had hypoglycemia compared to those who did not. Finally, the non-randomized design of the study represents another important limitation as the decision on the type of insulin given to patients, NPH or insulin glargine, was at the discretion of their physicians. Nevertheless, strict and controlled conditions in which randomized clinical trials are conducted differ greatly from everyday practice and, therefore, real-life studies may provide a better insight into the effectiveness of the intervention.

CONCLUSION

Our study revealed no significant difference in the risk of hypoglycemia and efficacy between NPH insulin and insulin glargine in patients with DM2. Accordingly, our

results suggest that human insulin is an effective and safe treatment in patients with DM2.

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SAŽETAK

TERAPIJA BAZALNIM INZULINOM U BOLESNIKA SA ŠEĆERNOM BOLEŠĆU TIPA 2; USPOREDBA UČINKA I NUSPOJAVA INZULINSKOG ANALOGA GLARGINA I HUMANOG (NPH, NEUTRAL PROTAMINE HAGEDORN) INZULINA

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Uvod: Terapija inzulinom često je potrebna za postizanje odgovarajućeg nadzora glikemije u bolesnika sa šećernom bolešću tipa 2 (ŠBT2). U tu se svrhu trenutačno u kliničkoj praksi najčešće koristi inzulinski analog glargin, a znatno rjeđe jeftiniji humani inzulin NPH (Neutral Protamine Hagedorn). ***Metode:*** U ovom opservacijskom multicentričnom istraživanju usporedili smo učinkovitost i sigurnost inzulina glargina i humanog NPH inzulina. Tijekom šestomjesečnog razdoblja praćenja promatrane su dvije skupine bolesnika sa ŠBT2. U jednoj skupini primijenjen je inzulin NPH (n = 53), dok je drugoj skupini primijenjen inzulin glargin (n = 48). ***Rezultati:*** Nakon šest mjeseci obje skupine bolesnika postigle su istu razinu hemoglobina A1c (HbA1c) (7,5 ± 1 %). U obje skupine uočeno je blago statistički neznačajno povećanje tjelesne mase. Dnevna doza inzulina (iskazana u međunarodnim jedinicama, IU, od engl. *international units*) bila je značajno veća u skupini koja je primala glargin nego u skupini koja je primala inzulin NPH (22,4 ± 8,5 IU prema 18,6 ± 7,8 IU). Učestalost epizoda hipoglikemije bila je podjednaka u objema skupinama. ***Zaključak:*** Naše istraživanje nije pokazalo značajnu razliku ni u riziku od hipoglikemije niti u učinkovitosti između inzulina glargina i inzulina NPH u bolesnika s ŠBT2. Sukladno tome, naši rezultati upućuju na to da humani inzulin NPH može biti učinkovit i siguran izbor liječenja za većinu bolesnika sa ŠBT2.

Ključne riječi : šećerna bolest tip 2, inzulin glargin, inzulin NPH, hipoglikemija, dugodjelujući inzulin

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DIAGNOSTIC ACCURACY OF BRONCHIAL BRUSHING CYTOLOGY AND IMPRINT CYTOLOGY FOR DIAGNOSIS OF LUNG CANCER USING FLEXIBLE BRONCHOSCOPY

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ABSTRACT

Objective: The goal of our study was to assess the sensitivity and specificity as well as the positive and negative predictive value of bronchial brushing cytology (BBC) and imprint cytology, and their usefulness in the diagnosis of lung cancer using flexible bronchoscopy. *Materials and methods:* This study was conducted at the Department of Pathology, Cytology, and Forensic Medicine of the University Hospital Mostar. Data were collected from the archives for the period from January 2016 to December 2020. Data for 1936 patients were retrieved. A selection of 508 patients who had a histopathological and/or cytological confirmation of lung cancer were included in this study. Samples were obtained by flexible fiberoptic bronchoscopy. Brushing specimens were obtained with a sterile, single-use brush that was enclosed within a catheter sheath, and after that bronchial washing was performed. Tissue sampling techniques were performed using forceps endobronchial and transbronchial biopsies. The cytology and histopathology slides were viewed independently by three clinical cytologists and pathologists. *Results*: Using histopathological findings for lung cancer diagnosis we have found a significant degree of concordance between cytology and pathology ($\kappa = 0.135$; $P < 0.001$). However, 107 patients were cytologically positive for lung cancer while being pathologically negative. Upon further investigation into their medical histories we found the following results: in 69 patients, lung cancer had already been suspected by some other method (radiological/CT imaging or atypical findings during bronchoscopy) and the cytological confirmation of malignant cells was sufficient to start surgical or oncological treatment of the patient, while 38 patients had false positive cytology reports. BBC had shown a specificity of 98.77 %, sensitivity of 83.3 %, positive predictive value of 93.5 %, and negative predictive value of 96.5 %. Imprint cytology had a specificity of 98.3 %, sensitivity of 96.5 %, positive predictive value of 94.8 %, and negative predictive value of 98.9 %. *Conclusion:* In our research BBC and imprint cytology were shown to be useful methods for the diagnosis of lung cancer, and should be considered in clinical centers where biopsy samples can only be obtained using non-guided flexible bronchoscopy or where endobronchial ultrasound bronchoscopy is not available.

Keywords: bronchial brushing cytology; imprint cytology; bronchoscopy; sensitivity; specificity; lung cancer

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INTRODUCTION

Lung cancer remains the leading cancer-related cause of death in men and the second most common cancer-related cause of death in women worldwide with a median survival rate of 20 % (1). One of the reasons for such high mortality rates is the fact that lung cancer is frequently diagnosed in an advanced inoperable stage. The earliest possible diagnosis for lung cancer is crucial in order to improve the survival rate of the patient (2). Only histopathological biopsy or cytological findings of atypical cells can confirm a lung cancer diagnosis (3, 4). Histopathological biopsy samples are considered to be the gold standard (5). Because all lesions are not adequate for histopathological biopsy due to their localization or degree of tumor necrosis (3), diagnostic procedures other than classic lung biopsy should be considered for the diagnosis of lung cancer (6). As early as in 1984, cytological diagnoses of sputum samples had shown to be very accurate at detecting some forms of early lung cancer (7). With new technological developments, such as the use of radial probe bronchoscopy (Radial Endobronchial Ultrasound – R-EBUS), the availability of samples for cytological diagnosis has improved exponentially (8). There are two main groups of methods which are used to obtain samples for cytology: exfoliate cytology (bronchial brushing cytology – BBC, sputum, bronchoaspirate, imprint, bronchoalveolar lavage) and fine needle cytology aspiration (9). These methods can have significant clinical differences within the same group (10). For example, BBC showed higher sensitivity than bronchoaspirate when it came to the diagnosis of endobronchial lesions (11). Since 2015, the World Health Organization (WHO) has been putting emphasis on early cancer diagnosis and the principle of the 'least amount of tissue sampling for the most accurate diagnoses', focusing on immunohistochemical staining and morphological diagnosis (12). These principles were reaffirmed in the last issue of the WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart; however, the added determination of molecular markers (such as programmed death-ligand 1 – PDL-1, reactive oxygen species – ROS, anaplastic lymphoma kinase – ALK, and epidermal growth factor receptor – EGFR) increased the importance of cytological methods even further (13). Cytological methods require less tissue sampling than pathological methods. Previous studies showed that cytological findings correlate with the histopathological diagnosis; moreover, cytological samples can also be used for immunohistochemical staining and molecular markers (9, 14, 15).

The aim of this study was to assess the correlation between the most commonly used cytological methods and their histopathological findings in order to evaluate their usefulness in lung cancer diagnosis. A special focus was placed on BBC, as it is the most tissue-sparing method and can yield high diagnostic value in settings where R-EBUS is not available.

MATERIALS AND METHODS

This study was conducted at the Department of Pathology, Cytology, and Forensic Medicine of the University Hospital Mostar. Data were collected from the Department archives and the medical documentation of selected patients in the period from January 2016 to December 2020. First, a selection of 1936 patients who underwent a bronchoscopic biopsy was analyzed. Next, 508 patients were selected who had been diagnosed with lung cancer using pathological and cytological methods. This study was approved by the institutional ethics committee.

Samples were obtained by flexible fiberoptic bronchoscopy (FB). Before the FB procedure, chest computed tomography (CT) findings were reviewed, including the location and size of the target tumor and the presence of a bronchus sign (a finding in the bronchus leading to or contained within the target tumor). Brushing specimens were obtained with a sterile, single-use brush that was enclosed within a catheter sheath, and followed by bronchial washing. Tissue sampling techniques were performed using forceps endobronchial biopsy and transbronchial biopsies. Imprint cytology samples were prepared by placing forceps biopsy specimens on a glass slide and gently touching and rolling them over the surface. Special care was taken to avoid damage to the specimen.

Slides with BBC, cytospin from bronchial washing, and imprint slides were fixed in dry air and stained by the May-Grunwald Giemsa (MGG) method. The cytology and histopathology slides were viewed independently by three clinical cytologists and pathologists.

Statistical analysis

The obtained data were statistically analyzed to determine sensitivity, specificity, positive predictive value, and negative predictive value with 95% confidence inter-

vals. In the statistical data processing the Chi-square test was used. $P < 0.05$ was regarded as statistically significant. The analysis was performed using the SPSS 13.0 for Windows statistical software (SPSS Inc., Chicago, Illinois, USA).

RESULTS

In this study we collected 1936 small biopsy findings obtained by bronchoscopy, 508 of which were confirmed, either cytologically or pathologically, as lung cancer. There was a significantly higher number of men (79.29 %) diagnosed with lung cancer than women. In most cases the right lung (56.1 %) was affected, followed by the left lung (39.37 %), while a very small percentage of cancers were located bilaterally (1.77 %). In 2.76 % of cases the localization was unknown. The upper bronchi were more often affected (35.46 %) than the lower bronchi (17.53 %), while the other parts were less affected (principal bronchus 12.96 %, intermediate bronchus 9.18 %, medial basal bronchus 9.58 %, lingual segmental bronchus 8.39 %, pulmonary bronchus 6.9 %). The most common cancer was squamous cell carcinoma (33.6 %), followed by adenocarcinoma (29.45 %), and small cell lung carcinoma (20.16 %), while metastatic cancer was found in 16.79 % of cases. The youngest patient diagnosed with lung cancer was 21 years old while the oldest was 88 years old; median age was 65.

Using histopathological findings as the gold standard for lung cancer diagnosis we have found a significant degree of concordance between cytology and pathology (Table 1). Fifty patients had a positive histopathological lung cancer diagnosis with a false negative cytology report (Table 1).

Upon further investigation into the medical documentation of the 107 patients that were cytologically positive for lung cancer while they were pathologically negative, the following results were yielded: in 69 patients lung cancer had already been suspected by some other method (radiological/computed tomography – CT imaging or an atypical finding during bronchoscopy) and the cytological confirmation of malignant cells was sufficient to start the surgical or oncological treatment of the patient. Thirty-eight out of 107 patients had false positive cytology reports.

All three cytological methods have shown a statistically significant difference in their results. BBC and imprint were the most accurate methods in discovering malignant cells, while bronchoaspirate was the least accurate method (Table 2).

BBC had shown a specificity of 98.77 % (95% CI 99.36 - 99.95 %), sensitivity of 83.3 % (95% CI 78.14 - 85.23 %), positive predictive value of 93.5 % (95% CI 96.34 - 99.61 %), and negative predicitive value of 96.5 % (95% CI 95.05 - 98.12 %). Imprint cytology had a sensitivity of 96.5 % (95% CI 94.55 - 98.12 %), specificity of 98.3 % (95% CI 99.36 - 99.95 %), positive predictive value of 94.8 % (95% CI 97.9 - 99.78 %), and negative predictive value of 98.91 % (95% CI 98.23 - 99.34 %) (Table 3).

In 309 cases all three cytological methods were performed and a comparison between each method and the other two was conducted. In 130 (42.1 %) cases all three methods confirmed the presence of malignant cells in the tested samples. In 102 cases (33 %) the BBC and imprint methods were positive for malignant cells while bronchoaspirate was not. In 63 cases (20.4 %) the bron-

Table 1. *Comparison of cytological and pathological findings. Values are presented as numbers (%)*

	PATHOLOGY MALIGNANT	PATHOLOGY BENIGN	TOTAL
CYTOLOGY MALIGNANT	351 (76.6)	107 (23.4)	458 (100)
CYTOLOGY BENIGN	50 (3.4)	1428 (96.6)	1478 (100)
Total	401 (20.7)	1535 (79.3)	1936 (100)

Table 2. *Bronchial brushing cytology (BBC), bronchoaspirate, and imprint accuracy (N = 1936)*

	Number (%) of cases		
Malignant cells	BBC	Bronchoaspirate	Imprint
found	245 (83.3)	194 (42.6)	420 (96.7)
not found	49 (16.7)*	260 (57.4)*	15 (3.3)*
Total	294	454	435

Chi-square test, $^{*}P < 0.001$

Table 3. *Bronchial brushing cytology (BBC) and imprint cytology sensitivity and specificity (N = 1936)*

Method	**BBC**	**IMPRINT CYTOLOGY**
Pathology-confirmed and cytology-confirmed cancer diagnoses	245 (TP*)	420 (TP*)
Pathology-confirmed and cytology-confirmed non-cancer diagnoses	1367 (TN*)	1367 (TN*)
Pathology-confirmed non-cancer diagnoses and cytology positive for cancer diagnoses	17 (FP*)	23 (FP*)
Pathology-confirmed cancer diagnoses and cytology negative for cancer diagnoses	49 (FN*)	15 (FN*)

*TP = true positive; TN = true negative; FP = false positive; FN = false negative

choaspirate and BBC methods were negative for malignant cells, while the biopsy imprint was positive. In two cases the bronchial imprint and bronchoaspirate were positive while BBC was negative for malignant cells. Comparatively, the BBC and cytological imprint methods were concordant in 234 (75.7 %) cases, of which 232 were positive for malignant cells while two were negative.

DISCUSSION

We found a significant degree of concordance between cytology and pathology for lung cancer diagnosis. Bronchial brushing cytology and imprint cytology showed high positive and negative predictive value, as well as high sensitivity and specificity for the diagnosis.

In this study, lung cancer was more frequently diagnosed in men, which is consistent with the trends shown by other studies (15). The median age of the cancer patients was 65, similar to other research results (9, 16). In addition, there was a higher incidence of squamous cell cancer than adenocarcinoma. In contrast, Dela Cruz et al. found that in the last thirty years the incidence of adenocarcinoma has increased, and become the most prevalent type of lung carcinoma (17). This discrepancy might be explained by the significant risk of both active and passive smoking in our country, due to a lack of policies that prohibit smoking in restaurants and cafes. In support of this, all patients in our cohort were smokers (89 %).

Due to the increase of lung cancer cases in our country, there is a need for accurate diagnosis in order to provide adequate lung cancer therapy. Although there have been technological advances in fiber bronchoscopy worldwide, numerous countries and centers have still not established R-EBUS as the gold standard (18-20). Namely, peripherally located neoplasms unavailable to classic fiber-bronchoscopy present a unique challenge in the case of early lung cancer diagnosis, and can often be very difficult to access for a pulmonologist (19). Therefore, pulmonologists in these countries need to invest considerable effort to overcome this difficulty, by new approaches to obtaining sufficient and required biopsy material from precise tumor locations (by bronchus sign). The bronchus sign is a sign on a CT scan that represents the presence of a bronchus leading toward a peripheral pulmonary lesion. Accordingly, most biopsies included in this study were taken by a classic bronchoscopic method, while peripherally located lesions were biopsied using transbronchial biopsy combined with CT imaging that previously found the suspected peripherally located lesion.

The importance of cytological analysis also lies in the fact that there are a number of lung cancers that are not available for histopathological biopsy, and in such cases cytological methods are needed to diagnose lung cancer as early as possible (10). The importance of molecular markers for lung cancer diagnosis in the 2021 WHO Classification of Lung Tumors has also stressed the principle of the 'least amount of tissue sampling for the most accurate diagnosis' which, in turn, placed new importance on cytological sampling (13). It is of great importance to get a sufficient number of samples, from any above-mentioned method, not only for immunohistochemical staining, but also for the usage of molecular markers (such as ROS, ALK, and EGFR) (21). This is why it is important to evaluate each cytological method currently used and determine which one would be most effective to meet the principle of 'least amount of tissue sampling for the most accurate diagnosis'.

In our study both cytological methods showed high positive and negative predictive values as well as high sensitivity and specificity for lung cancer diagnosis, which also correlated with the histopathological diagnosis. This is in accordance with previous research, indicating that cytological methods are highly useful tools in lung cancer detection (22, 23).

Although pathological diagnoses are still viewed as the gold standard, we should note that there were 69 cases in which patients were treated for lung cancer, oncologically or surgically, based on the combination of cytological and radiological findings. This can be attributed to a variety of factors, such as the methods by which the biopsies were taken, the presence of necrotic tissue, methods of preservation of the tissue samples, and potential morphological mimicry (24).

Findings in which pathology was positive and the cytological method was negative can be attributed to the localization of the tumor, the performance of the cytological method, the correct preservation of the sample, and the ability of the cytologist to accurately identify malignant cells (23).

According to the literature, the sensitivity and specificity of BBC in the diagnosis of lung cancer vary depending on the study and the technique used. A meta-analysis of bronchial brushing cytology showed a summary sensitivity of 67 % and a summary specificity of 91 % (19). In our study, BBC and cytological imprint were the most accurate methods in discovering malignant cells, while bronchoaspirate was the least accurate method. Furthermore, BBC and imprint cytology were concordant in most cases, which indicates the usefulness of combined use of these methods in lung cancer diagnosis (25). BBC had shown a specificity of 98.77 %, which was similar in other studies (19, 25). However, we found that BBC had larger sensitivity (83.3 %) in the diagnosis of lung cancer than in other studies (16). This finding might indicate a higher certainty of flexible bronchoscopy that uses the bronchus sign in the hands of experienced pulmonologists and cytologists. Namely, in our study the pulmonologists who performed flexible bronchoscopy and the cytologists who evaluated the specimens had more than 20 years of professional experience. Therefore, BBC has been shown to have high specificity and sensitivity, especially together with imprint cytology, which supports the clinician's certainty of the presence of lung cancer in the specimen and makes further invasive diagnostic procedures unnecessary. Imprint cytology had a sensitivity of 96.5 % and specificity of 98.3 %, which is consistent with the trends observed in previous research (25, 16). However, the specificity and sensitivity of BBC can be further improved with the use of advanced techniques such as ThinPrep bronchial brushing cytology (26).

CONCLUSION

In conclusion, BBC in the hands of experienced pulmonologists and cytologists can be used to increase sensitivity and specificity in the definitive diagnosis of lung cancer as well as for better cancer management. However, the WHO Reporting System for Lung Cytopathology emphasizes that an essential tool for standardizing diagnostic cytopathology practice would be of utmost importance, and could serve as a vehicle for the translation of cytopathology research into practice (27). Combining small biopsy, BBC, and imprint cytology specimens with other diagnostic techniques such as molecular testing, can improve the overall accuracy in determining the precise lung cancer type and thereby the validity of the diagnosis.

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SAŽETAK

DIJAGNOSTIČKA TOČNOST CITOLOGIJE OBRISKA ČETKICOM I CITOLOGIJE OTISKA U DIJAGNOSTICI TUMORA PLUĆA UZORAKA DOBIVENIH KORIŠTENJEM FLEKSIBILNOG BRONHOSKOPA

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Cilj: Cilj našeg istraživanja bio je procijeniti osjetljivost, specifičnost, pozitivnu i negativnu prediktivnu vrijednost citološkog uzorka četkanja bronha i citologije otiska uzorka biopsije te njihovu korisnost u dijagnostici raka pluća korištenjem nenavođene fleksibilne bronhoskopije. ***Materijali i metode:*** Istraživanje je provedeno na Odjelu za patologiju, citologiju i sudsku medicinu Sveučilišne kliničke bolnice Mostar. Podaci su prikupljani iz arhive u razdoblju od siječnja 2016. do prosinca 2020. te su skupljeni podaci za 1936 bolesnika. U istraživanje je uključeno 508 bolesnika koji su imali patohistološki i/ili citološki potvrđen karcinom pluća. Uzorci su dobiveni fleksibilnom fiberoptičkom bronhoskopijom. Uzorci za četkanje bronha dobiveni su sterilnom četkicom za jednokratnu uporabu koja je bila zatvorena unutar omotača katetera i nakon toga je provedeno ispiranje bronha. Otisak dobivenog uzorka napravio se nakon endobronhalne biopsije i transbronhalne biopsije. Citološke i histopatološke rezove neovisno su pregledala tri klinička citologa i patologa. ***Rezultati:*** Korištenjem histopatoloških nalaza kao „zlatnog standarda" za dijagnozu raka pluća, pronašli smo značajan stupanj podudarnosti između citologije i patologije (κ = 0,135; P < 0,001). Međutim, 107 bolesnika bilo je citološki pozitivno na karcinom pluća, dok su patološki bili negativni. Daljnjim istraživanjem njihove povijesti bolesti pronašli smo sljedeće rezultate: u 69 bolesnika se na rak pluća već sumnjalo na temelju neke druge dijagnostičke metode (radiološkim/kompjutorsko tomografskim snimanjem ili atipičnim nalazom tijekom bronhoskopije) i citološka potvrda zloćudnih stanica bila je dovoljna da se započne kirurško ili onkološko liječenje bolesnika, dok je 38 bolesnika imalo lažno pozitivne citološke nalaze. Bronhalna četkica pokazala je specifičnost od 98,77 %, osjetljivost od 83,3 %, pozitivnu prediktivnu vrijednost od 93,5 %, a negativnu prediktivnu vrijednost od 96,5 %. Citologija otiska biopsije imala je specifičnost od 98,3 %, osjetljivost od 96,5 %, pozitivnu prediktivnu vrijednost od 94,8 %, a negativnu prediktivnu vrijednost od 98,9 %. ***Zaključak:*** U našem istraživanju pokazalo se da su citologija četkanja bronha i otiska biopsije korisni postupci za dijagnosticiranje raka pluća i treba ih razmotriti u kliničkim središtima gdje se citološki uzorci i biopsija mogu dobiti samo nenavođenom fleksibilnom bronhoskopijom ili gdje endobronhalna ultrazvučna bronhoskopija nije dostupna.

Ključne riječi: citologija bronhalnog obriska četkicom, bronhoskopija, osjetljivost, specifičnost, rak pluća

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UTJECAJ PANDEMIJE KORONAVIRUSA U HRVATSKOJ NA KONTINUITET SKRBI ZA PACIJENTE OBOLJELE OD ŠEĆERNE BOLESTI U ORDINACIJAMA OBITELJSKE MEDICINE

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SAŽETAK

Uvod: **Za vrijeme pandemije koronavirusne infekcije (eng. *coronavirus disease 2019, COVID-19*), koja je trajala od ožujka 2020. do svibnja 2023. godine, javnozdravstvene mjere zaštite i ponavljajuće zabrane kretanja, kao i ograničeno korištenje zdravstvene zaštite, tzv. *lockdown* (od engl. zatvaranje), uvelike su utjecale na aktivno otkrivanje bolesti, kao i rutinsko praćenje kroničnih bolesnika sa šećernom bolesti.**

Metode: **Provedeno je retrospektivno multicentrično populacijsko istraživanje u 110 ordinacija obiteljske medicine u Republici Hrvatskoj pri čemu se pratilo razdoblje od 2018. do 2021. godine kako bi se prikazao posredan utjecaj pandemije COVID-19 na kontinuiranost skrbi i kontrolu šećerne bolesti na primarnoj razini zdravstvene zaštite.**

Rezultati: **Dobiveni rezultati u razdoblju *lockdowna* pokazuju zamjetan pad u broju novootkrivenih bolesnika sa šećernom bolesti (2072 bolesnika 2019. te 1880 bolesnika 2020. godine), smanjeno propisivanje uputnica za laboratorije primarne zdravstvene zaštite (pad od 7,95 % u 2020. u odnosu na 2019.) te smanjen broj pregleda bolesnika u ordinacijama obiteljskog liječnika. Istovremeno, može se uočiti trend smanjenja vrijednosti hemoglobina A1c (HbA1c) u promatranim ordinacijama, veći udio telemedicinskih konzultacija, veći broj propisanih A5 uputnica dijabetologu (od svega 11 u 2019. do 208 A5 uputnica u 2021. godini) te veći udio bolesnika sa šećernom bolesti s HbA1c manjim od 7 %.**

Zaključak: **S pojavom pandemije COVID-19 skrb za oboljele od šećerne bolesti bila je prema promatranim pokazateljima manje učestala i s većim udjelom telemedicinskih konzultacija sa strane obiteljskih liječnika. Proglašavanjem kraja pandemije, preventivni prigodni i ciljani probiri trebaju ponovo dobiti na važnosti te je za očekivati da će se trend porasta broja oboljelih od šećerne bolesti, kao i intenzivnije praćenje i liječenje već oboljelih, uz povećanje broja konzultacija s bolničkim specijalistima, nastaviti tijekom niza godina.**

Ključne riječi: **šećerna bolest, pandemija, koronavirus, obiteljska medicina, skrb**

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UVOD

Pandemija koronavirusne infekcije (eng. *coronavirus disease 2019*, COVID-19) u Hrvatskoj trajala je od ožujka 2020. do svibnja 2023. godine. U ožujku 2020. godine proglašen je prvi tzv. *lockdown* (od engl. zatvaranje), kada su zatvorene škole, popularizirao se rad od kuće, komuniciralo se isključivo elektroničkim putem, a sve u svrhu smanjenja kretanja stanovnika i širenja zaraze. Osim nezaobilaznog straha od zaraze teškim akutnim respiratornim sindromom koronavirusom 2 (engl. *severe acute respiratory syndrome coronavirus 2*, *SARS-CoV-2*), pandemija je ostavila dugotrajne posljedice na zdravlje bolesnika o kojima skrbe obiteljski liječnici (1). Za vrijeme pandemije COVID-19 javnozdravstvene mjere zaštite i ponavljajuće zabrane kretanja, kao i ograničeno korištenje zdravstvene zaštite, uvelike su utjecale na aktivno otkrivanje bolesti, kao i rutinsko praćenje kroničnih bolesnika. Striktne mjere, novčano kažnjavanje ako se iste ne poštuju, veliki natpisi na zdravstvenim ustanovama za zabranjen ulaz bez zaštitnih maski i sl. odbili su bolesnike koji su zahtijevali skrb. Komunikacija primarne i sekundarne razine zdravstvene zaštite svela se na stručno izmjenjivanje informacija o pacijentu bez pregleda istoga u svrhu održavanja, eventualne titracije terapije, a ne kontinuiranog praćenja.

CILJ RADA

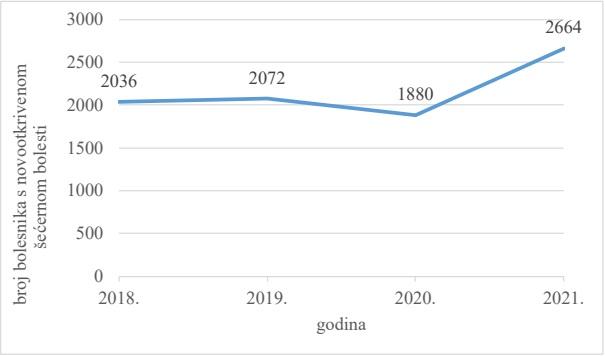
Cilj ovog istraživanja provedenoga u 110 ordinacija obiteljske medicine u Hrvatskoj jest prikazati posredan utjecaj pandemije SARS-COV-2 na kontinuiranost skrbi i kontrolu bolesti u bolesnika oboljelih od šećerne bolesti tip 1 i tip 2 u razdoblju od 2018. do 2021. godine.

METODE RADA

Provedeno je retrospektivno multicentrično populacijsko istraživanje u 110 ordinacija obiteljske medicine u Republici Hrvatskoj u razdoblju od 2018. do 2021. godine. Prikupljeni su podaci o broju oboljelih od šećerne bolesti, broju uputnica i specijalističkih/laboratorijskih nalaza te nalazima hemoglobina A1c (HbA1c). Podaci su preuzeti iz Centralnog zdravstvenog informacijskog sustava Republike Hrvatske (CEZIH) te iz baze podataka programske podrške onih ordinacija koje su dale suglasnost za sudjelovanje u istraživanju. Analiza dobivenih podataka deskriptivne je prirode, uz obradu podataka koristeći Microsoft Excel za Office 365 (Microsoft® Excel® za Microsoft 365 MSO (Verzija 2310 Build 16.0.16924.20054) 64-bit). Imena, dob i spol bolesnika, kao ni nazivi i lokacija promatranih ordinacija nisu bili dostupni istraživačima (tim bez nositelja, specijalistička ordinacija, dom zdravlja, privatna ordinacija, ruralna/urbana sredina i sl., op.a.).

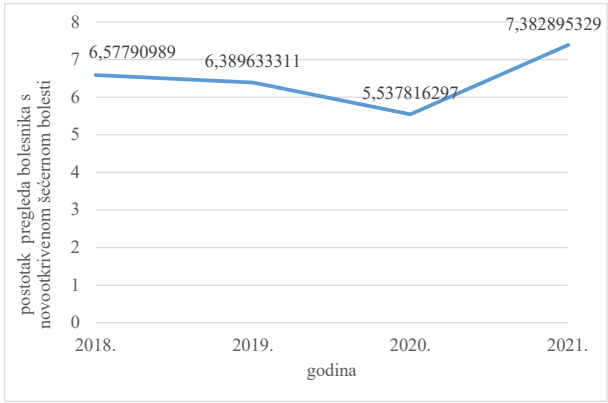
REZULTATI

U 110 promatranih ordinacija u razdoblju od 2018. do 2021. godine ukupan broj pacijenata oboljelih od šećerne bolesti iznosio je redom prema godinama: 13131, 14026, 14616 te 15999. Broj novootkrivenih osoba oboljelih od šećerne bolesti po ordinaciji obiteljske medicine u 2018. godini prosječno je iznosio devetnaest, 2019. godine također devetnaest, 2020. sedamnaest, a 2021. čak dvadeset i četiri. (Slika 1.)



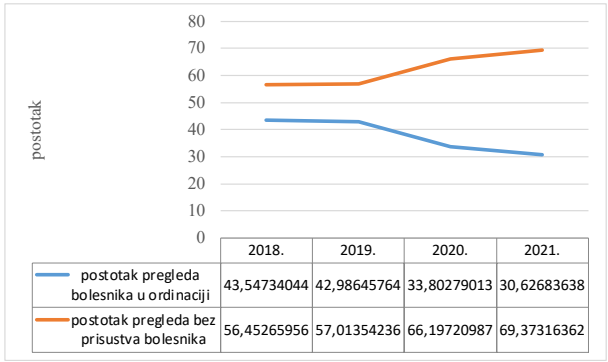
Slika 1. *Ukupan broj bolesnika s novootkrivenom šećernom bolesti u promatranim ordinacijama u razdoblju 2018. – 2021. godine.*

Iz prikupljenih se podataka vidi kako je postotak novodijagnosticiranih bolesnika sa šećernom bolesti u promatranim ordinacijama u 2020. godini bio u padu u odnosu na prethodne godine, dok se 2021. bilježi trend porasta postotka novootkrivenih bolesnika i da je 2020. godine 12,86 % novootkrivenih, a 2021. godine 16,65 % novootkrivenih dijagnoza šećerne bolesti. Postotak pregleda bolesnika s novootkrivenom šećernom bolesti sukladan je gore navedenom te podaci pokazuju kako je u 2018. godini 6,58 % pregleda pacijenata sa šećernom bolesti obuhvaćalo preglede novodijagnosticiranih bolesnika sa šećernom bolesti, a od 2019. do 2021. godine ti su postotci slijedom godina bili 6,39 % - 5,54 % -7,38 %. (Slika 2.)



Slika 2. *Postotak pregleda bolesnika s novootkrivenom šećernom bolesti po godini u promatranim ordinacijama*

Promatrajući apsolutan broj pregleda oboljelih od šećerne bolesti, prati se trend porasta nakon završetka *lockdown* faze pandemije COVID-19, uz trend smanjenja broja fizičkih pregleda u ordinaciji obiteljskog liječnika u odnosu na prethodne prijepandemijske godine. Za 2021. prosječno u promatranim ordinacijama nalazimo podatke pregleda uz prisustvo bolesnika od 30,63 % u ukupnom broju pregleda, dok je 2018. godine taj postotak bio 43,55 %. Broj konzultacija bez prisustva bolesnika raste iz godine u godinu te je tako 2021. godine postotak takvih pregleda iznosio 69,37 %, što je za trinaest posto više u odnosu na 2018. godinu, odnosno 12 posto više u odnosu na 2019. godinu. (Slika 3.)

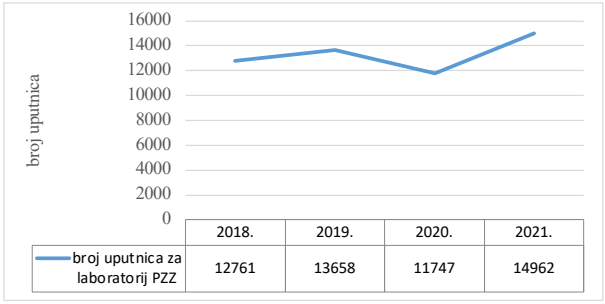


	2018.	2019.	2020.	2021.
postotak pregleda bolesnika u ordinaciji	43,54734044	42,98645764	33,80279013	30,62683638
postotak pregleda bez prisustva bolesnika	56,45265956	57,01354236	66,19720987	69,37316362

Slika 3. *Udjeli vrste pregleda bolesnika sa šećernom bolesti po godinama u promatranim ordinacijama*

Liječnici obiteljske medicine (LOM) učinili su prosječno po 11 pregleda ili konzultacija sa svakim oboljelim od šećerne bolesti u svakoj od četiri promatrane godine. Iz prikupljenih podataka vidljivo je kako se svake godine povećava broj kontakata LOM-a s oboljelima od šećerne bolesti, pa je tako 2018. godine taj broj iznosio 143313, a 2021. 171193, što je 27880 više kontakata prema LOM-u.

Iz prikupljenih podataka o propisivanju uputnica za primarne laboratorije s uputnim dijagnozama Međunarodne klasifikacije bolesti (MKB) E10 - E11.9 može se zaključiti kako je u 2020. godini bilo propisano manje uputnica nego u ostalim promatranim godinama. U apsolutnim brojevima to je iznosilo 11747 za 2020. godinu dok je za 2021. godinu propisano 14962 uputnice. (Slika 4.)

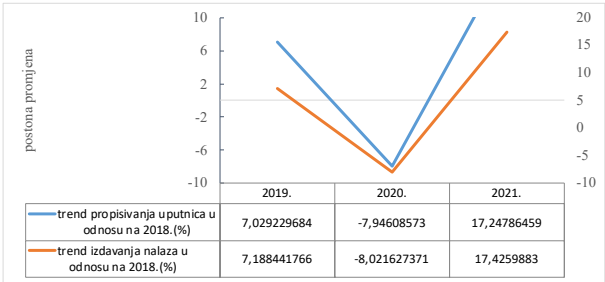


	2018.	2019.	2020.	2021.
broj uputnica za laboratorij PZZ	12761	13658	11747	14962

Slika 4. *Trend propisivanja uputnica za laboratorij primarne zdravstvene zaštite (PZZ) s uputnim dijagnozama E10-E11.9 prema Međunarodnoj klasifikaciji bolesti (MKB) za promatrane ordinacije u razdoblju 2018. – 2021. godine*

Prosječno je u 2020. za navedene dijagnoze po timu promatranih ordinacija propisano 107 uputnica za laboratorije primarne zdravstvene zaštite, dok taj broj za 2021. godinu iznosi 136. Postotak učinjenih postupaka uzimanja uzoraka krvi za određivanje u laboratorijima primarne zdravstvene zaštite (PZZ) – realizirane uputnice, tijekom sve četiri promatrane godine u odnosu na broj izdanih uputnica laboratorijima PZZ-a, 2018. i 2020. godine bio je 88 %, a 2019. te 2021. godine 89 %.

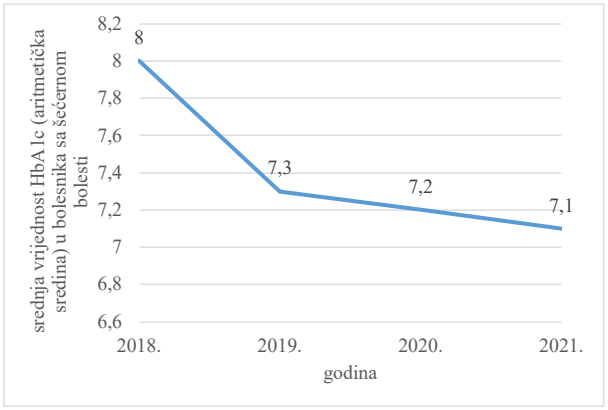
Promatrajući trend propisivanja uputnica za laboratorij PZZ-a u odnosu na 2018. godinu, podaci pokazuju kako je u 2019. godini propisano 7,03 % više uputnica, a u 2020. postoji smanjenje od 7,95 %, što je odnosu na 2019. čak 13,98 % manje. U 2021. godini bilježi se veliki porast izdavanja uputnica od 17,25 % u odnosu na 2018. (+9,55 % u odnosu na 2019.). (Slika 5.)



	2019.	2020.	2021.
trend propisivanja uputnica u odnosu na 2018.(%)	7,029229684	-7,94608573	17,24786459
trend izdavanja nalaza u odnosu na 2018.(%)	7,188441766	-8,021627371	17,4259883

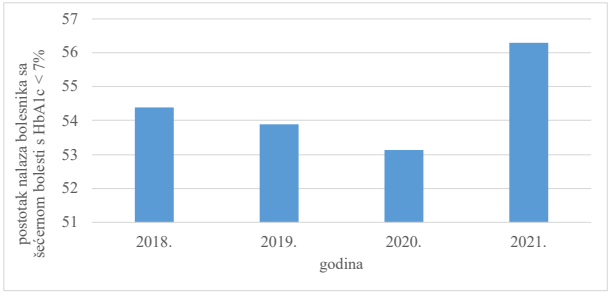
Slika 5. *Trendovi propisivanja uputnica i izdavanja laboratorijskih nalaza PZZ-a u odnosu na 2018. godinu*

Uspoređivanjem podataka izvršenog određivanja HbA1c za promatrane četiri godine u odnosu na broj propisanih uputnica za laboratorije primarne zdravstvene zaštite dobije se da je 2019. godine 91 % izdanih uputnica sadržavao upravo tu pretragu, a 2018., 2020. te 2021. njih 93 %. Nadalje, za 2018. godinu u promatranim ordinacijama prosječna vrijednost HbA1c iznosila je 8 % (± 3,2), 2019. godine, 7,3 % (± 1,62), 2020. 7,2 % (± 0,8) te 2021. godine 7,1 % (±0,9) (Slika 6.).



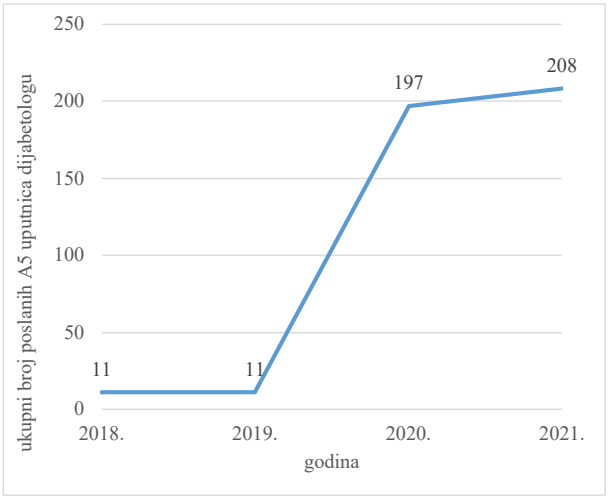
Slika 6. *Srednja vrijednost hemoglobina A1c (HbA1c), aritmetička sredina, u bolesnika sa šećernom bolesti po godinama u promatranim ordinacijama, standardna devijacija vrijednosti HbA1c za 2018. 3,2 %, 2019. 1,62 %, 2020. 0,8 % i 2021. godinu 0,9 % (broj izvršenih pretraga HbA1c 2018. = 11813; 2019. = 12473, 2020. = 10886, 2021. = 13542)*

Udio oboljelih od šećerne bolesti s HbA1c manjim od 7 % za odabrana razdoblja prema dostupnim podacima kreće se silaznom putanjom od 54,38 % u 2018. i 53,89 % u 2019. godini do 53,13 % u 2020., nakon čega raste na 56,29 % u 2021. godini (Slika 7.).

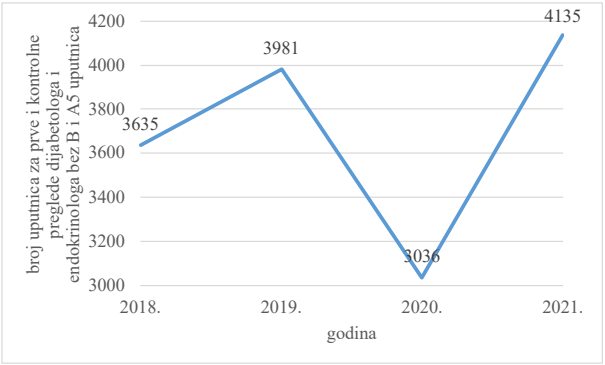


Slika 7. *Postotak nalaza bolesnika sa šećernom bolesti s HbA1c manjim od 7 % u promatranim ordinacijama po godinama (broj bolesnika 2018. = 6730, 2019. = 7034, 2020. = 6021, 2021. = 7880)*

Podaci o broju poslanih A5 uputnica (konzultacija bez prisutnosti pacijenta) dijabetologu pokazuju kako su se 2018. i 2019. ukupno izdale 22 uputnice u 110 ispitanih ordinacija obiteljske medicine. U 2020. poslano je 197, a u 2021. godini 208 A5 uputnica s uputnom dijagnozom E10-E11.9 (Slika 8.). Za ista promatrana razdoblja broj uputnica za prve i kontrolne preglede endokrinologa/dijabetologa (ukupan broj bez B i A5 uputnica, op.a.) iznosi 3635 u 2018. te 3981 u 2019. odnosno 3036 te 4135 u 2020./2021. godini. (Slika 9.)



Slika 8. *Ukupan broj poslanih A5 uputnica (konzultacija bez prisutnosti pacijenta) dijabetologu u promatranim ordinacijama po godinama*



Slika 9. *Broj uputnica za prve i kontrolne preglede dijabetologa i endokrinologa bez B i A5 uputnica*

Iz dobivenih podataka o propisivanju uputnica za specijalističke preglede oftalmologa iščitava se da je u 2020. godini propisano 25,69 % manje uputnica u odnosu na 2019. godinu. Uspoređujući podatke za 2020. i 2021., zamjetan je porast broja propisanih uputnica za oftalmološki pregled za 27,63 %.

RASPRAVA

Podaci iz programskih baza podataka koji su bili dostupni za potrebe ovog istraživanja pokazuju kako postoji trend smanjenja HbA1c na razini praćenja kroničnih bolesnika sa šećernom bolesti (s HbA1c od 8 % 2018., na 7,1 % 2021.godine) te povećanje udjela oboljelih s HbA1c < 7 % s 54,38 % 2018. na 56,29 % 2021. godine. Prema Izvješću CroDiab registra za 2021. godinu, dobru (HbA1c < 6,5 %) te granično zadovoljavajuću glikemiju (HbA1c 6,5 – 7,5 %) imalo je ukupno 69,85 % prikazanih oboljelih od šećerne bolesti (3). U izvješću Jug i sur. nema značajne razlike u vrijednostima HbA1c u pandemijskim godinama u usporedbi s prijepandemijskim godinama (4). Istovremeno se može uvidjeti kako postoji približno desetpostotni udio u neizvršenim laboratorijskim uzorkovanjima u sve četiri godine praćenja. Za pretpostaviti je da se radi ili o tome da bolesnici nisu učinili tražene laboratorijske pretrage ili da su iste učinjene u privatnim laboratorijima čije vrijednosti zbog načina prikupljanja podataka nismo mogli uvrstiti u ove izračune.

Promatrajući način praćenja bolesnika sa šećernom bolesti iz dostupnih podataka razvidno je da je pandemija promijenila način praćenja ovih bolesnika, s posebnim naglaskom na telemedicinu (6). Iz prikupljenih podataka o propisanim uputnicama za prve i kontrolne preglede endokrinologa/dijabetologa (bez B i A5 uputnica za MKB dijagnoze E10 E11.9, op.a.) primjećuje se trend porasta s 3635 propisanih uputnica u 2018. na 4135 u 2021. godini. Jednako tako, povećao se broj propisanih uputnica za oftalmološke preglede u 2021. godini. Sve je veći udio konzultacija s liječnikom obiteljske medicine, dok je udio pregleda smanjen na godišnjoj razini u svim promatranim godinama. Cerovečki i sur. su zabilježili drastičan pad ispunjenih panela za dijabetes u ambulantama obiteljske medicine za vrijeme trajanja pandemije (7, 8). Unatoč tome, iz dostupnih podataka statistički proizlazi kako je od 2018. do 2021. godine svaki oboljeli pacijent s MKB dijagnozom E10 – E11.9 jedanaest puta godišnje bio u kontaktu s LOM-om, no podatak o tome koliko je tih kontakata bilo vezano uz konzultaciju, pregled ili telefonsko naručivanje kronične terapije nije bio dostupan iz prikupljenih podataka.

Pandemija „novog normalnog“ dovela je do pomaka u suradnji obiteljskih i bolničkih liječnika, što je najbolje vidljivo kroz korištenje A5 uputnice – konzultacije bez prisutnosti pacijenta – uputnice koja je godinama prisutna u zdravstvenom sustavu, ali koja je tek u pandemiji omogućila lakši pristup liječnicima obiteljske medicine u bolnički sustav s ciljem prepoznavanja i trijažiranja bolesnika s neodgodivom potrebom za konzultacijom bolničkog specijalista. Dobrobiti A5 konzultacija najbolje se mogu očitovati i mjeriti u praćenju oboljelih od šećerne bolesti čija je bolest stabilna. Isti sada imaju sve manje potrebe za fizičkim kontrolnim konzilijarnim pregledima dijabetologa i endokrinologa, odnosno konzultacije vezane uz eventualnu promjenu ili titraciju medikamentozne terapije prepuštaju formalnoj komunikaciji između svojih liječnika koja se odvija putem sustava CEZIH-a. Istovremeno porast broja novodijagnosticiranih bolesnika sa šećernom bolesti iz priloženih rezultata govori kako krivulja rasta broja oboljelih od 2021.godine ima strmiji uspon nego u prijepandemijskim godinama, a jedan od razloga tome je zasigurno otklanjanje dijela administracije kojom su timovi obiteljske medicine bili zatrpani u vrijeme pandemije.

Prema odluci osiguravatelja iz 2023. godine, LOM-ovi sada mogu uputiti bolesnike s hiperglikemijom bez jasno potvrđene dijagnoze E10 – E11.9 na određivanje vrijednosti HbA1c, uz vodeću radnu MKB dijagnozu R73 – *Povećana razina glukoze u krvi (Hyperglycaemia)*, u laboratorije primarne zdravstvene zaštite. Time se rasterećuje bolnički laboratorijski sustav, olakšava se postavljanje dijagnoze šećerne bolesti u bolesnika, jednostavnije se može pratiti tijek predijabetesa i dijabetesa u pacijenata u riziku te se – bez dupliranja pretraga u laboratorijima primarne i sekundarne/tercijarne zdravstvene zaštite i dodatnog trošenja novčanih resursa (osiguravatelja i/ili *out-of-pocket* plaćanja, dani bolovanja u slučaju određivanja oralnog testa tolerancije na glukozu...) – obuhvat rizične populacije u skrbi LOM-a uvelike povećava. Imajući na umu kako su najnovije preporuke Američkog dijabetološkog udruženja *(eng. American Diabetes Association, ADA)* usmjerene na HbA1c kao dijagnostičkog testa kojim se smanjuje mogućnost pogrešnog (ne)dijagnosticiranja ŠB-a, postoje naznake kako će se u narednim godinama broj bolesnika s novodijagnosticiranom šećernom bolesti (ponajprije tipa 2) značajno povećati (5).

Za vrijeme pandemije koronavirusa okosnica rada obiteljskog liječnika bila su akutna febrilna stanja uzrokovana COVID-19, dok je briga za bolesnike sa šećernom bolesti bila održavajuća. Oboljeli od šećerne bolesti su, kao i mnogi drugi kronični bolesnici, u vrijeme početka i vrhunca pandemije odga-

đali kontrolne preglede kako obiteljskih liječnika, tako i bolničkih specijalista. Dodatno, većina oboljelih od šećerne bolesti ima pridružene komorbiditete koji predstavljaju potencijalnu opasnost za nastanak komplikacija uslijed COVID-19 (2). U vezi s pitanjem kako je pandemija koronavirusa utjecala na kontinuiranost skrbi za pacijente oboljele od šećerne bolesti u ambulantama obiteljske medicine u Republici Hrvatskoj, ovo istraživanje dalo nam je uvid u praćenje i usporedbu podataka prijepandemijskih, pandemijske 2020. godine te 2021. godine kada su mjere tzv. *lockdowna* bile ublažene, godine koja u radovima Jug i sur. te Cerovečki i sur. zbog prikupljanja podataka zaključno s 2020. godinom nije prikazana (4,8).

ZAKLJUČAK

U razdoblju *lockdowna* zamjetan je pad u broju novootkrivenih bolesnika sa šećernom bolesti, smanjeno propisivanje uputnica za laboratorije primarne zdravstvene zaštite te je smanjen broj pregleda bolesnika u ordinacijama obiteljskog liječnika. Istovremeno, uočen je trend smanjenja vrijednosti HbA1c u promatranim ordinacijama, veći udio telemedicinskih konzultacija, veći broj propisanih A5 uputnica dijabetologu te veći udio bolesnika sa šećernom bolesti s HbA1c manjim od 7 %. Unatoč tome, već neposredno prije nego što je proglašen kraj pandemije koronavirusom, liječnici obiteljske medicine primijetili su porast zahtjeva pacijenata za pregledima i praćenjem na svim razinama zdravstvene zaštite, no jednako tako uočava se sve veći aktivan angažman obiteljskih liječnika za ciljanim pozivanjem oboljelih od šećerne bolesti na proširene kontrolne preglede.

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SUMMARY

IMPACT OF CORONAVIRUS PANDEMIA IN CROATIA ON THE CONTINUITY OF CARE FOR PATIENTS WITH DIABETES IN FAMILY MEDICINE PRACTICE

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Introduction: During the coronavirus disease 2019 (COVID-19) pandemic that lasted from March 2020 to May 2023, public health protection measures and recurring movement restrictions, popularly called lockdown, as well as limited use of health care greatly affected the active detection of the disease, as well as routine monitoring of chronic patients with diabetes.
Methods: A retrospective multicenter population study was conducted in 110 family medicine practices in the Republic of Croatia, monitoring the period from 2018 to 2021 to show the indirect impact of the COVID-19 pandemic on the continuity of care and control of diabetes at the primary level of health care.
Results: The results obtained in the period of "lockdown" showed a noticeable decrease in the number of newly discovered patients with diabetes mellitus (2072 patients in 2019 vs 1880 patients in 2020), reduced prescribing of referrals for primary health care laboratories (decrease by 7.95 % in 2020 vs 2019), and a decrease in the number of examinations of patients in family practices. At the same time, there has been a visible trend of decreasing hemoglobin A1c (HbA1c) values in the observed clinics, a higher proportion of telemedicine consultations, a higher number of prescribed A5 referrals (from 11 in total in 2019 to 208 A5 referrals in 2021), and a higher proportion of patients with diabetes mellitus with HbA1c less than 7 %.
Conclusion: With the emergence of the COVID-19 pandemic, care for people with diabetes was, according to the observed indicators, less frequent and with more telemedicine consultations by family doctors. By declaring the end of the pandemic, preventive appropriate and targeted screenings are again gaining importance and it is expected that the trend of increasing numbers of patients with diabetes, as well as more intensive monitoring and treatment of the already diagnosed, along with an increase in the number of consultations with hospital specialists, will continue for many years.

Keywords: diabetes, pandemia, coronavirus, family medicine, care

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OSVIJEŠTENOST OBITELJSKIH LIJEČNIKA U REPUBLICI HRVATSKOJ O DEBLJINI KAO BOLESTI

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SAŽETAK

Uvod: Prekomjerna tjelesna masa i debljina predstavljaju sve veći javnozdravstveni izazov na svjetskoj razini, s dalekosežnim zdravstvenim i ekonomskim posljedicama. Ovo istraživanje ima za cilj ispitati prevalenciju prekomjerne tjelesne mase i debljine u bolesnika u ordinacijama liječnika obiteljske medicine te učestalost bilježenja dijagnoze debljine E66 od strane liječnika obiteljske medicine u Republici Hrvatskoj (RH). Svrha istraživanja je isticanje problema zanemarivanja debljine kao bolesti unutar zdravstvenog sustava RH.

Metode: Istraživanje je obuhvatilo 54 ordinacije obiteljske medicine u RH, pružajući podatke o ukupnom broju ugovorenih pacijenata starijih od 18 godina, raspodjeli po spolu, mjerenih vrijednosti opsega struka (OS) i indeksa tjelesne mase (ITM) kategoriziranih po spolu te konačno, broju zabilježenih dijagnoza debljine u liječničkim kartonima.

Rezultati: Istraživanje je uključilo 81562 pacijenta. U 51,93 % i 46,79 % njih zabilježeni su podaci o ITM-u, odnosno OS-u. U pacijenata s dostupnim podacima, 78,04 % muškaraca i 62,41 % žena imalo je prekomjernu tjelesnu masu ili je bilo pretilo, dok je 66,27 % muškaraca i 72,72 % žena bilo visceralno debelo. Samo 12 % debelih muškaraca i 18 % debelih žena imalo je zabilježenu dijagnozu debljine u svojim liječničkim kartonima.

Zaključak: Zabilježena je velika prevalencija debljine među obuhvaćenim pacijentima obiteljskih liječnika, dok je isto rijetko bilo zabilježeno pod dijagnozom bolesti E66. To ukazuje na nisku razinu svijesti među liječnicima primarne zdravstvene zaštite o prepoznavanju debljine kao bolesti. Ovo istraživanje naglašava važnost preuzimanja vodeće uloge liječnika u prepoznavanju, sprječavanju i liječenju debljine. Poziva na pojačanu svijest o navedenom problemu ne samo među zdravstvenim radnicima, već i unutar šire zajednice.

Ključne riječi: indeks tjelesne mase, opseg struka, prekomjerna tjelesna masa, debljina, prevencija, obiteljski liječnik

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UVOD

Masno tkivo je složen, metabolički visoko aktivan endokrini organ čija je glavna uloga skladištenje energije u obliku masti. Sastoji se većim dijelom od adipocita uz preadipocite, fibroblaste, endotelne stanice, makrofage masnog tkiva, zajednički nazvanima stromalnom žilnom frakcijom. Osim što toplinski izolira i mehanički štiti naše tijelo te pohranjuje i oslobađa energiju u obliku masnih kiselina, također ima i važnu endokrinu funkciju proizvodnjom hormona kojima sudjeluje u regulaciji unosa hrane i potrošnje energije, kao i imunosnu ulogu otpuštanjem proupalnih biljega adipocitokina (1).

Prekomjerno nakupljanje masnog tkiva u tijelu, kao i njegova nedostatna količina, rezultiraju razvojem patoloških stanja. Ubrzani način života 21. stoljeća praćen konzumacijom visokoenergetičke hrane bogate mastima i brzim ugljikohidratima uz trend smanjenja tjelesne aktivnosti rezultirao je razvojem pandemije debljine.

Prema podacima Svjetske zdravstvene organizacije, u svijetu više od 1,9 milijardi odraslih ima prekomjernu tjelesnu masu, od čega ih je 650 milijuna debelo, a u čemu prednjači ženska populacija s 15 % u odnosu na 11 % pripadnika muške populacije (2).

Debljina nije samo estetički problem. Riječ je o jednom od najvećih javnozdravstvenih problema današnjice u čije se rješavanje na globalnoj razini ulažu enormni napori. Usko je povezana s porastom rizika i razvojem danas vodećih kroničnih nezaraznih bolesti: šećerne bolesti tipa 2, srčanožilnih bolesti, različitih zloćudnih bolesti te niza duševnih poremećaja, rezultirajući smanjenjem životne kakvoće. Usto predstavlja i velik gospodarski problem zemalja širom svijeta, kako smanjenjem poslovne sposobnosti i produktivnosti populacije, tako i financijskim opterećenjem zdravstvenih sustava (3).

Svjetska federacija za debljinu u uskoj je suradnji sa Svjetskom zdravstvenom organizacijom 2023. godine objavila novi Svjetski atlas debljine koji predstavlja globalne, regionalne i nacionalne projekcije prevalencije debljine za djecu, adolescente i odrasle uz prikaz ekonomskog utjecaja pretilosti na gospodarstvo zemalja, za razdoblje od 2020. do 2035. godine. Prema dostupnim podacima očekivani porast svjetske populacije s prekomjernom tjelesnom masom (indeks tjelesne mase, ITM, 25 - 29,9 kg/m^2) iznosi 12 %, s 38 % u 2020. godini na 50 % u 2035. godini, dok one s razvijenom pretilošću (ITM > 30 kg/m^2) iznosi 10 %, sa 14 % u 2020. godini na 24 % u 2035. godini (4).

Ekonomske posljedice prekomjerne tjelesne mase i debljine za područje Republike Hrvatske (RH) prema procjenama će u 2035. godini premašiti 3,15 milijardi američkih dolara, što iznosi 3 % hrvatskog BDP-a. Prema trenutačnim trendovima za razliku od 23 % debele odrasle populacije u RH u 2019. godini, njih 37 % biti će debelo u 2035. godini (5).

CILJ

Cilj je bio utvrditi prevalenciju prekomjerne tjelesne mase i debljine među pacijentima u ordinacijama liječnika obiteljske medicine i učestalost evidentiranja takvih pacijenata s pomoću dijagnoze za debljinu E66 sa strane obiteljskih liječnika. Svrha ovog rada ukazati je na problematiku zanemarivanja debljine kao dijagnoze od strane liječnika primarne zdravstvene zaštite u RH te osvješćivanje važnosti ranog uočavanja, prevencije i liječenja debljine, imajući na umu socioekonomsku podlogu razvoja te potrebu za multidisciplinarnim djelovanjem u svrhu njenog rješavanja.

METODE

Provedeno je presječno multicentrično populacijsko istraživanje na uzorku od 53 ordinacije obiteljske medicine u RH koje su ustupile podatke o ukupnom broju ugovorenih pacijenata starijih od 18 godina, udjelima muškaraca i žena u ukupnom broju ugovorenih pacijenata starijih od 18 godina, izmjerenim vrijednostima opsega struka (OS) i ITM-a razvrstanih prema spolu te o broju u liječnički karton upisanih dijagnoza pretilosti E66. Kao kriterij osviještenosti liječnika obiteljske medicine u RH o debljini kao bolesti, izabrano je bilježenje dijagnoze bolesti u zdravstveni karton prema MKB-10 klasifikaciji. Osobni podaci pacijenata te nazivi i lokacije promatranih ordinacija koje su dale suglasnost za sudjelovanje u istraživanju nisu bili dostupni istraživačima. Analiza dobivenih podataka deskriptivne je prirode, a kao alat obrade podataka korišten je Microsoft Excell za Office 365.

ITM je najčešći alat definiranja prekomjerne tjelesne mase i debljine u epidemiološkim istraživanjima. On predstavlja omjer tjelesne mase izražen u kilogramima i kvadrata tjelesne visine izražene u metrima, a izražava se mjernom jedinicom kg/m^2. S obzirom na vrijednosti moguća je klasifikacija nutritivnog statusa u nekoliko skupina. Vrijednosti ITM <18,5 kg/m^2 označuju

pothranjenost, ITM 18,5 - 24,9 kg/m^2 normalnu tjelesnu masu, ITM 25 - 29,9 kg/m^2 prekomjernu tjelesnu masu te ITM ≥ 30 kg/m^2 pretilost ili preuhranjenost, odnosno debljinu. Debljina se dodatno klasificira u tri kategorije: debljina 1. stupnja (ITM 30 - 34,9 kg/m^2), debljina 2. stupnja (ITM 35 - 39,9 kg/m^2) i debljina 3. stupnja (ITM ≥ 40 kg/m^2). Iako je kao alat široko rasprostranjen, ITM ima važna ograničenja koja moramo imati na umu. Riječ je o matematičkom modelu dizajniranom na način da odgovara širokoj populaciji, ne uzimajući u obzir specifičnosti pojedinca u vidu dobi, spola, mišićne i koštane mase, masnog tkiva te drugih čimbenika, rezultirajući mogućim potcjenjivanjem ili precjenjivanjem debljine. Primjerice, u sportaša udio mišićne mase u odnosu na tjelesnu visinu je velik, no to ne znači da imaju prekomjernu tjelesnu masu, dok stariji ljudi s nižim udjelom mišićne mase mogu biti medicinski debeli, iako je njihov ITM klasificiran kao idealna tjelesna masa (6).

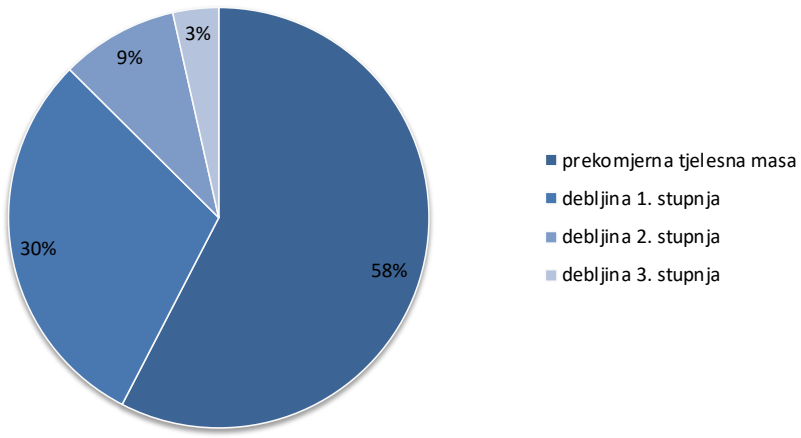
Prema klasifikaciji Svjetske zdravstvene organizacije, vrijednosti ITM-a za područje Europe iste su za oba spola. Kako bismo što točnije mogli procijeniti tip debljine te rizike obolijevanja od bolesti vezanih uz debljinu, uputno je uz ITM pridodati i mjeru OS-a. Razlikujemo nekoliko tipova debljine, od kojih je onaj visceralni, poznat i kao abdominalni ili androidni tip debljine u najvećoj korelaciji s razvojem metaboličkih i srčanožilnih bolesti. Međunarodna federacija za dijabetes definirala je visceralnu debljinu kao onu kod koje je OS u žena ≥ 80 cm, a u muškaraca ≥ 94 cm. Naime, utvrđeno je da su masne nakupine lokalizirane između visceralnih organa u trbušnoj šupljini metabolički aktivnije od onih potkožnih, lučeći adipocitokine koji imaju važnu ulogu u patogenezi inzulinske rezistencije i metaboličkog sindroma te posljedično povećanog srčanožilnog rizika (7).

REZULTATI

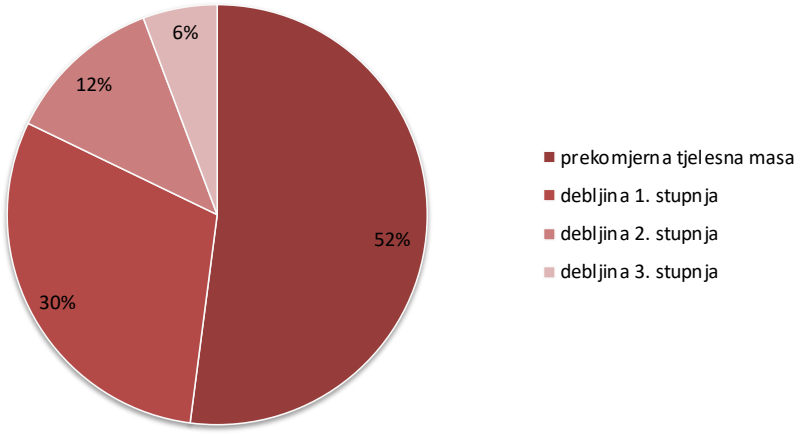
U uzorku od 81562 pacijenta starijih od 18 godina (39019 muškaraca i 42543 žena), upisanih u 54 ordinacije obiteljske medicine u RH, njih 42355 (51,93 %) u liječničkom kartonu ima izračunatu i zabilježenu vrijednost ITM-a. S obzirom na spol, 50,9 % odraslih muškaraca te 52,88 % odraslih žena imalo je zabilježenu vrijednost ITM-a u liječničkom kartonu.

Udio pacijenata s prekomjernom tjelesnom masom i debljinom u ukupnom broju zabilježenih ITM-a iznosio je 78,04 % (u 15499) za muškarce te 63,61 % za žene (u 14039), od čega je udio onih s prekomjernom tjelesnom masom (ITM 25 - 29,9 kg/m^2) iznosio 38,33 % (u 16235), a onih s debljinom (ITM > 30 kg/m^2) 31,41 % (u 13303).

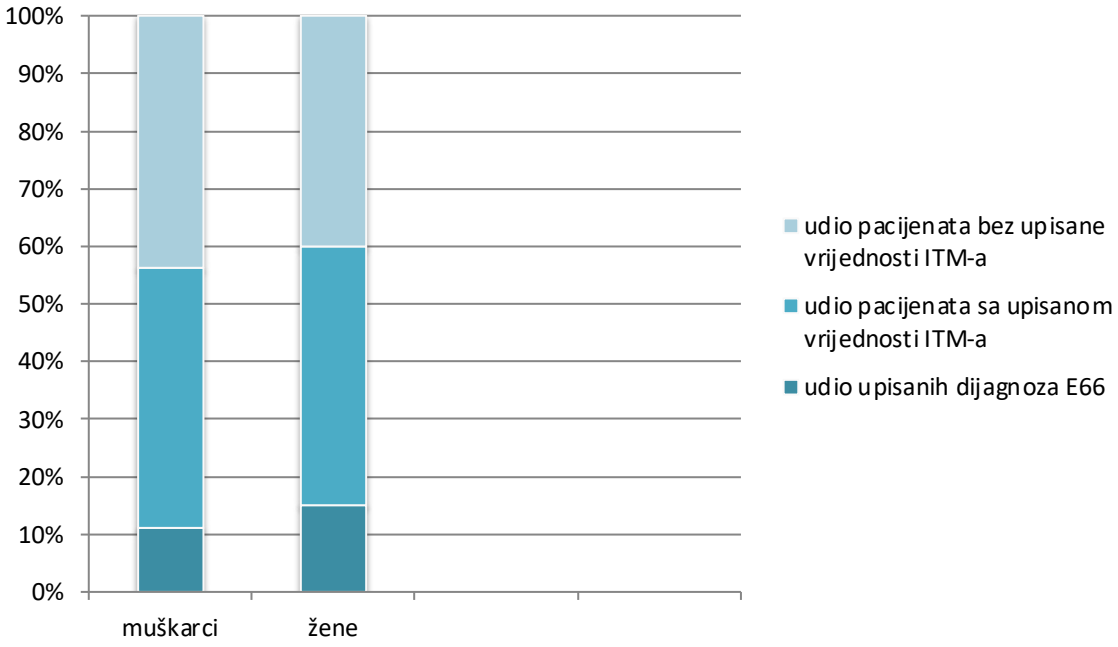
Prekomjernu tjelesnu masu imalo je 44,94 % muškaraca (njih 8926), dok ih je 33,1 % bilo debelo (n = 6573), a u slučaju žena njih 32,49 % (n = 7309) imalo je zabilježenu prekomjernu tjelesnu masu te je 29,92 % imalo zabilježenu debljinu (njih 6730).



Slika 1. *Udjeli kategorija prekomjerne tjelesne mase i debljine u muškaraca s ITM-om ≥ 25 kg/m^2 u ispitivanim ordinacijama među onim s raspoloživim podacima (n = 15499, 39,72 % od ukupno 39019 muškaraca uključenih u istraživanje)*



Slika 2. *Udjeli kategorija prekomjerne tjelesne mase i debljine u žena s ITM-om ≥ 25 kg/m² u ispitivanim ordinacijama među onim s raspoloživim podacima (n = 14039, 32,99 % od ukupno 42543 žena uključenih u istraživanje)*



Slika 3. *Prikaz udjela pacijenata s upisanom vrijednosti indeksa tjelesne mase (ITM) u ukupnom broju pacijenata sudjelujućih ordinacija te prikaz udjela upisanih dijagnoza debljine E66 prema klasifikaciji MKB-10*

Izmjerenu i zabilježenu vrijednost OS-a imalo je 46,96 % pacijenata (n = 38166). U slučaju muškaraca, njih 45,55 % imalo je izmjeren OS (n = 17774), od čega je 66,27 % bilo visceralno debelo (n = 11779), dok je u žena izmjeren OS imalo njih 47,93 % (n = 20392), sa 72,72 % onih s visceralnom debljinom (n = 14830).

Udio postavljenih šifri dijagnoza E66 (debljina) na temelju u liječničkim kartonima zabilježenih vrijednosti ITM-a u istraživanjem obuhvaćenim ordinacijama obiteljske medicine iznosio je 14,96 % (n = 4418). 12,45 % muškaraca (n = 1930) i 17,72 % žena (n = 2488) sa zabilježenom vrijednošću ITM-a imalo je prepoznatu i zabilježenu dijagnozu prekomjerne tjelesne mase i debljine.

RASPRAVA

Udio prekomjerne tjelesne mase i debljine među raspoloživim podacima bio je sveukupno 69,74 %, 78,04 % muškaraca i 62,41 % žena imalo je prekomjernu tjelesnu masu i debljinu. Svega 12 % muškaraca i 18 % žena sa zamijećenom prekomjernom tjelesnom masom ili debljinom vođeno je u liječničkim kartonima pod dijagnozom debljine. Prema tim rezultatima za zaključiti je da u RH osviještenost liječnika u sustavu primarne zdravstvene zaštite o debljini kao bolesti te važnosti njenog pravodobnog prepoznavanja, prevencije i liječenja nije zadovoljavajuća. Za usporedbu, vodeći se podacima iznesenima u istraživanjima provedenima u Sjedinjenim Američkim Državama (SAD), Španjolskoj i Ujedinjenom Kraljevstvu (UK) godine 2013., 2014. i 2017., osviještenost naših liječnika obiteljske medicine ne zaostaje za onom u svijetu. U području SAD-a jedna trećina odrasle ispitivane populacije primarne zdravstvene zaštite nije imala izračunatu i upisanu vrijednost ITM-a. Od onih upisanih, njih 68,3 % kategorizirano je kao prekomjerna tjelesna masa, dok ih je 34,4 % u nekoj od kategorija debljine. Postavljenu dijagnozu debljine imalo je tek 17,1 %, odnosno 30,1 % ispitanika (8). Španjolsko istraživanje dalo je još nereprezentativnije rezultate - tek 27 % ispitanika primarne zdravstvene zaštite imalo je upisanu vrijednost ITM-a u liječnički karton, a podatak o udjelu postavljene dijagnoze debljine ne navode (9). UK je proveo sustavni pregled istraživanja od 2006. do 2016. godine, kroz osam elektroničkih baza, koje su mjerile udio odraslih pacijenata (≥ 16 godina) s dokumentiranom vrijednosti ITM-a ili ponuđenim intervencijskim planom za gubitak tjelesne mase u primarnoj zdravstvenoj zaštiti u UK-u. Rezultati su pokazali da je 58 – 79 % pacijenata imalo zabilježenu vrijednost ITM-a, od čega tek 43 – 52 % onih u nekoj od kategorija pretilosti, a siromašnih 15 – 42 % pretilih uključeno je u pokušaj intervencije i prevencije daljnjeg razvoja pretilosti (10). I ovo istraživanje, kao i ono SAD-a, Španjolske pa i ovo naše ukazuju na činjenicu da su pretilost kao bolest te ITM (uz OS) kao alat njenog prepoznavanja, evidentiranja, praćenja i intervencije nešto što liječnicima primarne zdravstvene zaštite, ali i društvu kao cjelini prolazi „ispod radara" unatoč svojoj velikoj važnosti, ne samo zdravstvenoj za pojedinca i populaciju, nego i socioekonomskoj, kako na nacionalnoj razini, tako i na onoj globalnoj. Zamjetan je i još jedan pokazatelj zanemarenosti ove teme u medicinskim krugovima - nedostatak provedenih recentnijih istraživanja i praćenja epidemiologije debljine diljem svijeta. Kako bismo točnije mogli odrediti zaostajemo li mi u RH osviješćenošću o navedenoj problematici za liječnicima primarne zdravstvene zaštite u svijetu, potrebna su nam novija istraživanja i podaci.

Prema posljednjim dostupnim statističkim podacima za područje europskog kontinenta, RH je na nezavidnom drugom mjestu po broju osoba s prekomjernom tjelesnom masom za oba spola, njih 65 %, dok debljina u muškaraca drži visoko 4. mjesto, a u žena 6. mjesto. Među zemljama članicama Europske unije, Hrvati su druga najdeblja nacija, odmah nakon Malte (11).

Imajući na umu brojne globalne i nacionalne rizike koje debljina kao bolest nosi sa sobom, od onih zdravstvenih do socioekonomskih, Svjetska zdravstvena organizacija je u svibnju 2022. godine prihvatila nadopunjeni niz preporuka pod nazivom „WHO Acceleration plan to STOP obesity" (engl., Plan Svjetske zdravstvene organizacije za zaustavljanje debljine). On predstavlja univerzalno dostupne i održive alate za prevenciju, liječenje i upravljanje debljinom kao bolešću, a koji integriraju zdravstvene i socijalne sastavnice primjenjive s obzirom na zemljopisno područje, okolnosti i potrebe te uključuje intervencije u već postojeće modele zdravstvene skrbi. Time se izbjegava vremenski i financijski opterećujuća potreba stvaranja u potpunosti novih modela (12).

Na razini RH, Ministarstvo zdravstva je povodom Svjetskog dana debljine, koji se obilježava 4. ožujka, godine 2022. osnovalo Radnu skupinu za izradu Nacrta prijedloga Akcijskog plana za prevenciju debljine, a koji je od listopada 2022. javno dostupan te pruža razrađene metode prevencije, dijagnostike i liječenja debljine za razdoblje od 2023. do 2026. godine (13).

Liječnicima obiteljske medicine u RH dostupne su i Hrvatske smjernice za liječenje odraslih osoba s debljinom, koje je izdalo Hrvatsko društvo za debljinu u travnju 2022. godine. One za cilj imaju pravovremeno prepoznavanje i primjereno liječenje osoba s prekomjernom tjelesnom masom i debljinom od strane svakog liječnika, uz naglašen individualizirani bihevioralno-kognitivni pristup svakom pacijentu. Također ističu važnost edukacije ne samo oboljelih osoba, nego i cijelih zajednica u svrhu destigmatizacije debljine kao bolesti i posljedično boljih ishoda na područjima prevencije i liječenja.

U pristupu osobama s nekom vrstom poremećaja tjelesne mase možemo se voditi pravilom 5-P: prepoznati,

procijeniti, **p**reporučiti, **p**ostaviti cilj, **p**ratiti. Imajući na umu da nisu sve osobe s prekomjernom tjelesnom masom ili pretilošću jednako motivirane za liječenje, važno je kao liječnik otkriti najbolji način pristupa svakom pacijentu pojedinačno, educirajući ga i motivirajući za suradnju te stvarajući odnos povjerenja i podrške s ciljem postizanja optimalnih ishoda liječenja. Pacijente trebamo motivirati prvenstveno na promjenu životnih navika u vidu nutritivno prilagođene prehrane te povećanja tjelesne aktivnosti, a ako je potrebno moguće je predložiti i farmakoterapijski pristup te u najtežim slučajevima debljine i onaj kirurški u vidu barijatrijske kirurgije (7).

ZAKLJUČAK

Nađena je velika prevalencija prekomjerne tjelesne mase i debljine, u više od 60 – 70 % pacijenata. Tek je u oko polovice pacijenata u ordinacijama obiteljskih liječnika evidentirana mjera moguće debljine (ITM ili OS), što ukazuje na nedovoljnu osviještenost obiteljskih liječnika o problemu debljine. Na nama je liječnicima, a osobito obiteljskim, da u borbi protiv debljine preuzmemo vodeću ulogu i neprestano ističemo potrebu za razvojem veće svijesti, ne samo nas samih, nego i čitave zajednice, o debljini kao bolesti, te potrebu za neprestanom edukacijom naših pacijenata i njihove okoline, kao i važnost destigmatizacije debljine kao dijagnoze, jer samo zajedničkim snagama možemo pobijediti ovog neprijatelja.

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SUMMARY

ADDRESSING THE NEGLECT OF OBESITY IN PRIMARY HEALTHCARE IN THE REPUBLIC OF CROATIA

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Introduction: Overweight and obesity pose a growing public health challenge globally, with far-reaching health and economic consequences. This study aims to examine the prevalence of overweight and obese patients in patients of family physicians' (FP) offices and the frequency of FPs recording the diagnosis of obesity by its E66 code. The purpose is to highlight the issue of neglecting obesity as a disease within the healthcare system of the Republic of Croatia.

Methods: The research involved 54 family medicine practices in Croatia, providing data on the total number of contracted patients aged 18 and above, the gender distribution among these patients, measured waist circumference and body mass index (BMI) categorized by gender, and, finally, the number of recorded diagnoses of obesity in the medical records.
Results: The study included 81562 patients. In 51.93 % and 46.79 % of them, respectively, data on BMI and weight circumference were recorded. Out of the patients with available data, 78.04 % of men and 62.41 % of women were overweight or obese, while 66.27 % of men and 72.72 % of women had visceral obesity. Only 12 % of obese men and 18 % of obese women had an obesity diagnosis in their medical records.
Conclusion: Although a high prevalence of obesity was recorded among FP patients, the frequency of the recorded disease diagnosis E66 was low. This reflects the low level of awareness among primary healthcare physicians regarding the recognition of obesity as a disease. In conclusion, the study underscores the urgency for healthcare professionals to take a leading role in recognizing, preventing, and treating obesity. It calls for increased awareness of the problem not only among healthcare practitioners but also within the broader community.

Keywords: body mass index, waist circumference, overweight, obesity, prevention, family physician

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KLINIČKA OBILJEŽJA BOLESNIKA LIJEČENIH CISTEKTOMIJOM ZBOG KARCINOMA MOKRAĆNOGA MJEHURA: TROGODIŠNJE ISKUSTVO KLINIČKOG BOLNIČKOG CENTRA RIJEKA

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SAŽETAK

Cilj rada bio je prikazati klinička obilježja bolesnika u kojih je zbog karcinoma mokraćnoga mjehura učinjena radikalna cistektomija u našem središtu. *Postupci:* U ovom su povijesnom kohortnom istraživanju obrađeni bolesnici koji su nakon odluke multidisciplinarnog tima podvrgnuti radikalnoj cistektomiji zbog karcinoma mokraćnoga mjehura. Svi bolesnici operirani su na Klinici za urologiju Kliničkog bolničkog centra Rijeka u razdoblju između 2017. i 2019. godine. Analizirana su njihova demografska i klinička obilježja. *Rezultati:* U promatranom trogodišnjem razdoblju radikalna cistektomija učinjena je u 96 bolesnika kao postupak izbora u liječenju bolesnika s mišićno-invazivnim karcinomom mokraćnoga mjehura, odnosno mišićno-neinvazivnim karcinomom mokraćnoga mjehura visokoga rizika. Od toga je muškaraca bilo 74 (77,1 %), a žena 22 (22,9 %). Sedamdeset pet bolesnika (78,1 %) bilo je u dobi od 65 i više godina. Ureterokutanostomija je učinjena u 46 (47,9 %) bolesnika, neovezika u 27 (28,1 %) bolesnika, a *ileum conduit* po Brickeru u 20 (20,8 %) bolesnika. Konačan patohistološki nalaz bio je *carcinoma in situ* u 4 bolesnika (4,2 %), pT1 u 11 (11,5 %), pT2 u 31 (32,3 %), pT3 u 27 (28,1 %) te pT4 u 23 (23,9 %) bolesnika. Lokalno uznapredovalu bolest imalo je 43 (44,8 %) bolesnika, a metastatsku bolest 17 (17,7 %) bolesnika. Neoadjuvantna kemoterapija primijenjena je u 4 (4,2 %) bolesnika, adjuvantna kemoterapija u 13 (13,5 %), a radioterapija u 18 (18,8 %) bolesnika. *Zaključak:* Karcinom mokraćnoga mjehura bio je češći u starijih bolesnika i u muškaraca. Ureterokutanostomija je bila najčešći oblik urinarne derivacije. Onkološko liječenje bilo je potrebno u oko trećine bolesnika.

Ključne riječi: cistektomija; tumor mokraćnog mjehura; kemoterapija; urinarna derivacija

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UVOD

Karcinom mokraćnog mjehura četvrti je po učestalosti zloćudni tumor u muškoj te jedan od češćih u ženskoj populaciji (1). Od njega je 2020. godine oboljelo više od 570 000 bolesnika diljem svijeta, a umrlo više od 200 000 bolesnika (2, 3). Češće se javlja u muškaraca (u omjeru 4:1). Medijan dobi dijagnosticiranja bolesti je 69 godina u muškaraca i 71 godina u žena te se po tome može zaključiti da je starija životna dob rizični čimbenik za nastanak ovog karcinoma (4). Karcinom mokraćnog mjehura u obiteljskoj anamnezi, izloženost duhanskom dimu i nekim kemikalijama, prethodno zračenje zdjelice, kronična infekcija mokraćnog mjehura i korištenje nekih lijekova (npr. ciklofosfamid) među češćim su rizičnim čimbenicima, a utvrđena je i pozitivna korelacija između nastanka karcinoma mokraćnog mjehura i humanog papilomavirusa, šećerne bolesti i pretilosti (1). Patohistološki, karcinom mokraćnog mjehura najčešće je karcinom prijelaznog epitela (5).

Mišićno neinvazivni karcinom mokraćnog mjehura (engl. non-muscle-invasive bladder cancer - NMIBC) jest onaj kod kojeg nije dokazana invazija u detruzor i on obuhvaća *carcinoma in situ* (CIS) i tumore izolirane u urotelu (stadij Ta) i u lamini propriji (stadij T1). Bolesnici s tumorom T1 stadija (visokoga stupnja), kao i oni s CIS-om, spadaju u skupinu visokorizičnih bolesnika zbog veće mogućnosti progresije karcinoma u detruzor. Tumori kod kojih je patohistološkom analizom utvrđeno da invadiraju detruzor nazivaju se mišićno-invazivni karcinomi mokraćnog mjehura (engl. muscle-invasive

bladder cancer - MIBC) i to su agresivni karcinomi s visokim rizikom metastaziranja (1, 5, 6). MIBC čini otprilike 20 – 30 % novootkrivenih karcinoma mokraćnog mjehura, a u oko 50 % bolesnika razvijaju se udaljene metastaze. Osnova kirurškog liječenja MIBC-a je radikalna cistektomija s urinarnom derivacijom, a ostale su mogućnosti parcijalna cistektomija i trimodalna terapija (transuretralna resekcija tumora mjehura + radioterapija + kemoterapija) (7). U prvom dijelu operacije radi se o odstranjenju mokraćnoga mjehura s dijelom muških odnosno ženskih spolnih organa, a nakon toga se radi zdjelična limfadenektomija. Dok je prvi dio operacije ekstirpativan, drugi je dio operacije rekonstruktivan. Urinarne derivacije su u rasponu od jednostavnih (ureterokutanostomija) do onih složenijih, koje zahtijevaju crijevni segment (*ileum conduit* odnosno neovezika). Sveukupno to dovodi do povećanog broja komplikacija u osoba koje su podvrgnute ovom zahvatu. Petogodišnje preživljenje u bolesnika s MIBC-om kreće se između 60 i 70 %, ovisno o stadiju u kojem je bolest otkrivena i o primijenjenoj terapiji (4, 8).

CILJ RADA

Cilj rada bio je prikazati klinička obilježja bolesnika s karcinomom mokraćnoga mjehura koji su liječeni cistektomijom u našoj ustanovi u razdoblju od tri godine.

ISPITANICI I POSTUPCI

U izradi ovog rada korištena je medicinska dokumentacija bolesnika koji su na Klinici za urologiju Kliničkog bolničkog centra Rijeka operirani zbog karcinoma mokraćnog mjehura radikalnom cistektomijom u razdoblju od 1. siječnja 2017. godine do 31. prosinca 2019. godine. Indikacija za cistektomiju postavljena je na sastanku multidisciplinarnog tima za urogenitalne tumore. Analizirani su demografski i klinički podatci bolesnika (dob i spol bolesnika, simptomi i znakovi zbog kojih su upućeni na urološku obradu, histološki podtip, stadij tumora prema TNM klasifikaciji prije i nakon radikalne cistektomije, nalaz slikovnih metoda, primjena radioterapije te primjena neoadjuvantne ili adjuvantne kemoterapije). Također, bolesnici su dodatno podijeljeni u tri skupine prema metodi učinjene urinarne derivacije: neovezika po Hautmannu ili Studeru, *ileum conduit* po Brickeru te ureterokutanostomija. Stadij tumora određen je na osnovi klasifikacije koja uključuje proširenost tumora na samom organu, zahvaćenost limfnih čvorova i prisutnost udaljenih limfogenih ili hematogenih metastaza (TNM klasifikacija). Lokalno uznapredovala bolest predstavljala je stadij T3b-T4 odnosno N1-N3. Kirurške komplikacije prikazane su po klasifikaciji Clavien-Dindo. Bolesnike smo pratili tri mjeseca nakon operacije.

Podatci za ovo retrospektivno istraživanje dobiveni su iz informatičkog bolničkog sustava IBIS. Prikupljeni su podatci uneseni i obrađeni u računalnim programima *Microsoft Office Excel* i *Statistica 10,* a u programu *Microsoft Office Word* za obradu teksta. Korišteni su deskriptivni statistički postupci.

Istraživanje je odobrilo Etičko povjerenstvo Kliničkog bolničkog centra u Rijeci, klasa 003-05/22-1/47; ur.broj:2170-29-02/1-22-2.

REZULTATI

U razdoblju od 1. siječnja 2017. godine do 31. prosinca 2019. godine na Klinici za urologiju radikalna cistektomija zbog karcinoma mokraćnoga mjehura učinjena je u ukupno 96 bolesnika. Sedamdeset pet bolesnika (78,1 %) bilo je u dobi od 65 i više godina. Muških je bolesnika bilo 74 (77,1 %), a ženskih 22 (22,9 %) (tablica 1). Asimptomatska hematurija bila je prisutna u 73,9 % bolesnika. Tumor je utvrđen ultrazvučnim pregledom u 56,8 % bolesnika, a u svih je bio vidljiv na cistoskopskom pregledu. Prosječna prijeoperacijska vrijednost procijenjene brzine glomerulske filtracije (eGFR, od engl. *estimated glomerular filtration rate*) iznosila je 62,8 ml/min /1,73 m^2 tjelesne površine, prosječna vrijednost kreatinina 135,6 μmol/l, a ureje 10,3 mmol/l. U svih je bolesnika prethodno učinjena transuretralna resekcija tumora mjehura kojom je najčešće dokazan karcinom prijelaznoga epitela. U većine je bolesnika već nakon inicijalne transuretralne resekcije tumora mjehura postavljena indikacija za cistektomiju. Odmah nakon učinjene cistektomije učinjena je urinarna derivacija i to u 46 bolesnika (47,9 %) ureterokutanostomija, u 20 (20,8 %) bolesnika *ileum conduit* po Brickeru, a u 27 (28,1 %) bolesnika neovezika. Jednom je bolesniku postavljena nefrostomija kao konačno rješenje, a u dvoje bolesnika nije uopće učinjena urinarna derivacija (jedan je bio anefričan, a drugi je bio na kroničnom programu hemodijalize). Perioperacijske komplikacije (ileus, dehiscencija rane, infekcija rane, pneumonija, transfuzija krvi, vrućica) zabilježene su u 50 % bolesnika (slika 1). Infekcija rane je bila prisutna u 15 (15,6 %)

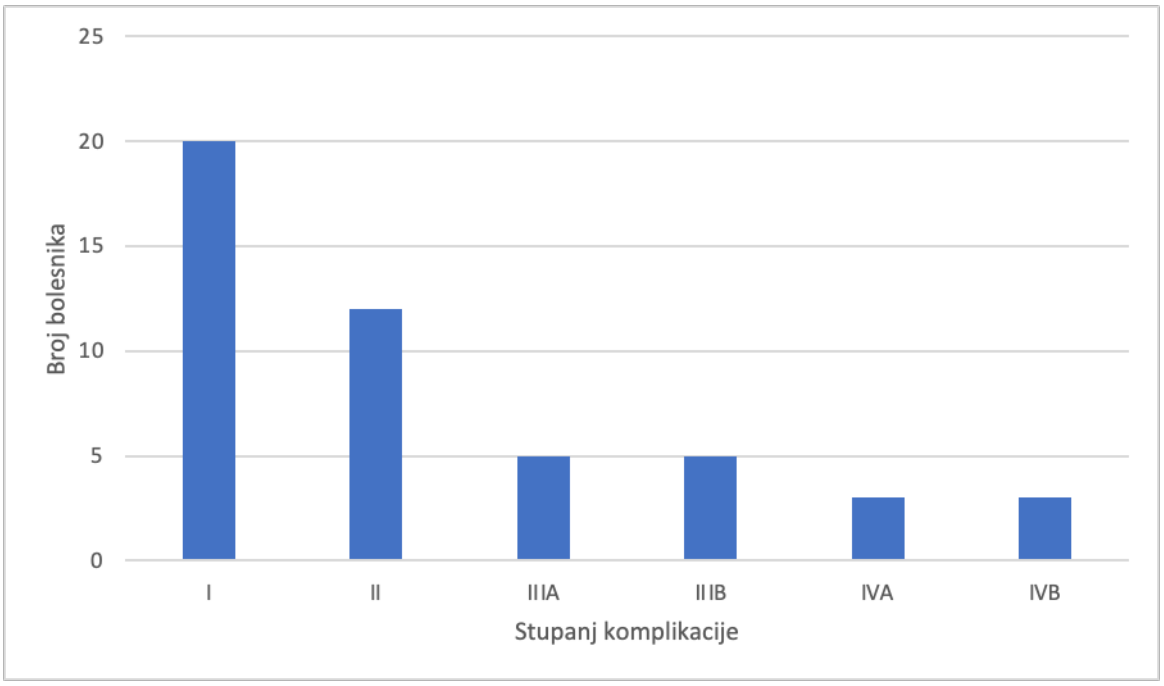
Tablica 1. *Demografska i klinička obilježja bolesnika. (N = 96)*

Obilježje	n	%
Spol		
-ženski	22	77,1
-muški	74	22,9
Dob		
-do 65 godina	21	21,9
-≥ 65 godina	75	78,1
Vrsta urinarne derivacije		
-ureterokutanostomija	46	47,9
-neovezika	27	28,1
-Bricker	20	20,8
-ostalo	3	3,2
Histološki tip tumora		
-karcinom prijelaznoga epitela	92	95,9
-planocelularni karcinom	3	3,1
-adenokarcinom	1	1
TNM klasifikacija (prije cistektomije)		
-carcinoma in situ	1	1
-T1	29	30,3
-T2	62	64,6
-T3	3	3,1
-T4	1	1
TNM klasifikacija (nakon cistektomije)		
-carcinoma in situ	4	4,2
-pT1	11	11,5
-pT2	31	32,3
-pT3	27	28,1
-pT4	23	23,9
Lokalno uznapredovala bolest		
-da	43	44,8
-ne	53	55,2
Metastatska bolest		
-da	17	17,7
-ne	79	82,3
Komplikacije nakon cistektomije		
-da	48	50
-ne	48	50
Radioterapija		
-da	18	18,8
-ne	78	81,2
Neoadjuvantna kemoterapija		
-da	4	4,2
-ne	92	95,8
Adjuvantna kemoterapija		
-da	13	13,5
-ne	83	86,5

Tablica 2. *Demografska i klinička obilježja bolesnika s obzirom na tip urinarne derivacije (N = 93)*

Obilježje	Ureterokutanostomija n = 46	Neovezika n = 27	Bricker n = 20
Spol n (%)			
-ženski	12 (26,1)	5 (18,5)	4 (20)
-muški	34 (73,9)	22 (81,5)	16(80)
Dob n (%)			
- do 65 godina	2 (4,3)	13 (48,1)	6 (30)
-≥ 65 godina	44 (95,7)	14 (51,9)	14 (70)
eGFR (ml/min/1,73 m^2 tjelesne površine)	44,9	83,1	76,8
Komplikacije n (%)	21 (45,6)	14 (51,6)	13 (65)
Lokalizirani karcinom n (%)	18 (39,1)	20 (74)	15 (75)
Neoadjuvantna kemoterapija n (%)	0	3 (11,1)	1 (5)
Adjuvantna kemoterapija n (%)	2 (4,3)	7 (25,9)	4 (20)
Radioterapija n (%)	8 (17,4)	6 (22,2)	4 (20)

eGFR – od engl. *estimated glomerular filtration rate*, procijenjena brzina glomerulske filtracije



Slika 1. *Prikaz kirurških komplikacija (n = 48) stupnjevanih po klasifikaciji Clavien-Dindo.*

bolesnika, a u 5 (5,2 %) bolesnika je zbog dehiscencije rane učinjena reoperacija u ranom poslijeoperacijskom razdoblju. Ileus je bio prisutan u 9 (9,3 %) bolesnika, a u svih bolesnika je liječen konzervativno. U 4 (4,2 %) bolesnika je primijenjena neoadjuvantna kemoterapija i to kombinacija cisplatine i gemcitabina. Dijagnoza lokalno uznapredovale bolesti nakon konačnog patohistološkog nalaza postavljena je u 43 (44,8 %) bolesnika, a 17 (17,7 %) bolesnika imalo je metastatsku bolest. Adjuvantnu kemoterapiju dobilo je 13 (13,5 %) bolesnika i to kombinaciju cisplatine i gemcitabina, kombinaciju karboplatine i gemcitabina odnosno atezolizumab. Radioterapija je primijenjena u 18 (18,8 %) bolesnika. U tablici 2. navedeni su osnovni demografski i klinički podaci bolesnika ovisno o vrsti urinarne derivacije. Vidljivo je kako je ureterokutanostomija kao najjednostavniji oblik urinarne derivacije korištena češće u starijih bolesnika, kao i u onih s uznapredovalom bolešću. Također su veći broj komplikacija imali bolesnici u kojih je za urinarnu derivaciju korišten segment crijeva u odnosu na one u kojih je učinjena ureterokutanostomija.

RASPRAVA

U ispitanika našeg istraživanja više je operiranih bilo muškog spola nego ženskoga. To je u skladu s činjenicom da je incidencija karcinoma mokraćnog mjehura u Hrvatskoj 2020. godine bila 56,3 bolesnika na 100 000 stanovnika za muškarce i 13,9 oboljelih na 100 000 za žensku populaciju (9). Na razini Europske unije incidencija u muškoj populaciji nešto je veća, s 58,9 oboljelih na 100 000 stanovnika i 13,4 na 100 000 u ženskoj populaciji (9,10). Iz toga proizlaze omjeri 4,1:1 u Hrvatskoj i 4,4:1 u Europskoj uniji u „korist" muškaraca (9, 10). U našem istraživanju omjer je bio 3,4:1 u „korist" muškog spola.

Asimptomatska makrohematurija simptom je koji se najčešće nalazi u bolesnika s karcinomom mokraćnoga mjehura i može biti prisutna u 85 – 90 % bolesnika (11). U naših bolesnika bila je prisutna u više od 70 % bolesnika.

Tijekom zahvata, a nakon učinjene radikalne cistektomije, nužno je učiniti i jedan od oblika urinarne derivacije. Tip urinarne derivacije ovisi o lokalizaciji tumora u mjehuru odnosno uretri, postojanju metastaza, dobi bolesnika, bubrežnoj funkciji, mentalnom kapacitetu bolesnika te komorbiditetima (12, 13). Najčešća urinarna derivacija u naših bolesnika bila je ureterokutanostomija (oko 50 % bolesnika), zatim neovezika od segmenta tankog crijeva te *ileum conduit* (operacija po Brickeru). S obzirom na to da je ureterokutanostomija najjednostavniji oblik urinarne derivacije, ovaj tip derivacije korišten je u starijih bolesnika, kao i u onih s uznapredovalom bolešću. *Ileum conduit* i neovezika rađeni su u pravilu u mlađih bolesnika bez metastatske bolesti, iako je u nekih od njih konačan patohistološki nalaz govorio u prilog lokalno uznapredovalog karcinoma ili se poslije razvila metastatska bolest. Slične je rezultate pokazalo i istraživanje koje je učinjeno u Zagrebu (14).

Prema preporukama Europskog urološkog udruženja, u bolesnika s agresivnim karcinomom mjehura preporučuje se primijeniti neoadjuvantnu kemoterapiju temeljenu na platini (15). Takva neoadjuvantna kemoterapija dovodi do povećanog petogodišnjeg preživljenja za 5 – 8 %. U naših je bolesnika samo 4,2 % bolesnika primilo neoadjuvantnu kemoterapiju. Iako većina bolesnika nije bila u primjerenom medicinskom stanju da bi mogla primiti ovu terapiju, zbog dokazanog povećanog preživljenja u budućnosti bi trebalo težiti da više „budućih" sličnih bolesnika primi neoadjuvantnu kemoterapiju.

Lokalno uznapredovalu bolest imalo je 43 bolesnika (44,8 %), a metastatsku bolest 17 (17,7 %) bolesnika. U bolesnika s metastatskom bolešću, a nakon rasprave na multidisciplinarnom timu, odlučili smo se za cistektomiju radi kontrole lokalnih simptoma (najčešće izražene makrohematurije). Palijativnu radioterapiju nakon cistektomije primilo je 18 (18,8 %) bolesnika, a adjuvantnu kemoterapiju 13 (13,5 % bolesnika). Ovi nam podatci govore da značajan broj bolesnika bude dijagnosticiran u uznapredovaloj fazi bolesti te liječenje mora biti agresivnije, dok su sami rezultati liječenja slabiji. Nažalost, zasad ne postoji tumorski biljeg, poput prostata-specifičnog antigena kod karcinoma prostate, koji bi mogao pomoći u ranom otkrivanju karcinoma mjehura.

Očekivano, u 92 (95,8 %) bolesnika patohistološkom je analizom pronađen karcinom prijelaznoga epitela, a planocelularni karcinom i adenokarcinom bili su veoma rijetki, što je usporedivo s ostalim istraživanjima (14, 16).

Broj komplikacija u našem istraživanju bio je relativno velik (u 50 %). Veći broj komplikacija imali su bolesnici u kojih je za urinarnu derivaciju korišten segment crijeva. U različitim se istraživanjima postotak komplikacija kretao od 30 do 92 % (17-19). Relativno visok postotak komplikacija posljedica je složenog kirurškog zahvata u, najčešće, starijoj populaciji. U retrospektivnom istraživanju na 604 bolesnika u kojih je učinjena radikalna cistektomija i urinarna derivacija učestalost poslijeope-

racijskih komplikacija unutar 30 dana od operacije bila je 49,4 % (komplikacije I i II stupnja) odnosno 13,9 % (komplikacije III-V stupnja) u 445 bolesnika u kojih je učinjen *ileum conduit,* dok je u 159 bolesnika učinjena neovezika i u tih bolesnika je učestalost komplikacija I i II stupnja bila 50,3 %, a III-V stupnja 9,4 %. Učestalost kratkoročnih i intermedijarnih komplikacija bila je slična između ovih dviju skupina bolesnika, ali su dugoročne komplikacije (nakon 90 dana od cistektomije) bile češće u bolesnika s neovezikom (39,7 % prema 49 %) (20). Kod ureterokutanostomija je učestalost komplikacija I i II stupnja bila 47 %, a III stupnja 1,1 % (21). U našem je istraživanju također najveći broj komplikacija bio I i II stupnja po Clavien-Dindo klasifikaciji.

Nedostatak je našeg istraživanja to što se radi o povijesnom istraživanju iz jednog središta. Također nismo određivali ukupno preživljenje niti preživljenje ovisno o karcinomu. Nedostatak je našeg istraživanja i kratkotrajno praćenje.

ZAKLJUČCI

Značajno više radikalnih cistektomija učinili smo u starijih i u muških bolesnika oboljelih od karcinoma mokraćnoga mjehura. Najčešći je tip učinjene urinarne derivacije bila ureterokutanostomija, što je ovisilo o proširenosti tumora, kao i o dobi samih bolesnika. Poslijeoperacijske komplikacije, pogotovo kada je za urinarnu derivaciju korišten segment tankog crijeva, bile su relativno česte. Onkološko liječenje bilo je potrebno u oko trećine bolesnika.

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SUMMARY

CLINICAL CHARACTERISTICS OF BLADDER CANCER PATIENTS TREATED WITH CYSTECTOMY: THREE-YEAR EXPERIENCE FROM THE CLINICAL HOSPITAL CENTER RIJEKA

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The *objective* of the study was to present clinical characteristics of patients operated for bladder cancer in our center. *Methods:* In this retrospective study we present patients who underwent radical cystectomy due to bladder cancer. All patients were operated at the Department of Urology, Clinical Hospital Center Rijeka, between 2017 and 2019. Their demographic and clinical characteristics were analyzed. *Results:* In the observed three-year period radical cystectomy was performed in 96 patients due to muscle-invasive bladder cancer or high-risk non-muscle-invasive bladder cancer. Of these, 74 (77.1 %) were men, and 22 (22.9 %) were women. Seventy-five patients (78.1 %) were 65 years old or older. Ureterocutaneostomy was performed in 46 (47.9 %) patients, neobladder in 27 (28.1 %) patients, and *ileum conduit* according to Bricker in 20 (20.8 %) patients. The definitive pathohistological finding was *carcinoma in situ* in 4 (4.2 %) patients, pT1 in 11 (11.5 %), pT2 in 31 (32.3 %), pT3 in 27 (28.1 %), and pT4 in 23 (23.9 %) patients. At the time of the surgery locally advanced disease was present in 43 (44.8 %) and metastatic disease in 17 (17.7 %) patients. Neoadjuvant chemotherapy was administered in 4 (4.2 %) patients, adjuvant chemotherapy in 13 (13.5 %), and radiotherapy in 18 (18.8 %) patients. *Conclusion:* Bladder cancer was more frequently found in male and elderly patients. Ureterocutanostomy was the most frequent type of urinary diversion. Oncological treatment was necessary in approximately one third of the patients.

Keywords: radical cystectomy, urinary bladder tumors, chemotherapy, urinary diversion

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UNCONVENTIONAL HEMODIALYSIS ACCESS: PERCUTANEOUS TRANSHEPATIC VENOUS ACCESS AS A LIFESAVING OPTION - A SINGLE-CENTER EXPERIENCE AND LITERATURE REVIEW

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Abstract

Introduction Hemodialysis catheters and arteriovenous fistulas are currently considered the gold standard of dialysis vascular access. Primary venous accesses are the internal jugular, subclavian, and femoral veins. Due to the nature of chronic kidney disease itself and its impact on the vascular system, frequent thrombotic occlusions of the vascular access occur, rendering it dysfunctional and sometimes leading to the lack of any possible conventional venous access for renal replacement therapy. Published data showed the noninferiority of nonconventional (transhepatic, translumbar) routes compared with the conventional ones regarding infectious complications. However, the long-term viability of these accesses remains questionable, while there is a high incidence of postprocedural access dysfunction.

Case reports We present two cases from June 2023, of patients in need of nonconventional vascular access for hemodialysis as a vital indication, in which a catheter was placed via the transhepatic route into the inferior caval vein with the tip positioned in the right atrium. Conventional venous access routes were ruled out in both patients after a detailed radiologic workup showed inadequate flow and severe occlusions. The skin was punctured in the anterior axillary line and a Hickman-type (double luminal) catheter was inserted in the right hepatic vein with ultrasound guidance using the Seldinger technique. It was passed through the inferior caval vein with the tip positioned in the right atrium. After that, a tunnel was created on the anterior abdominal wall. The placed catheters provided sufficient flow for hemodialysis procedures in both patients.

The first presented case provided the patient with adequate renal replacement therapy sessions until his death that ensued after postprocedural complications of cardiac surgery. In the second case, the access was a successful salvage bridging method after previous catheter dysfunction until the patient was conditioned for long-term automated peritoneal dialysis.

Conclusion The two presented cases show successful transhepatic dialysis catheter insertion as a method of vascular access in vital indications.

Keywords: hemodialysis, renal replacement therapy, transhepatic venous access, tunneled dialysis catheter, vascular access

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INTRODUCTION

Hemodialysis catheters (HDC) along with arteriovenous (AV) fistulas represent the cornerstone of modern hemodialysis vascular access. However, these access points are sometimes just a temporary solution due to frequent development of an AV fistula or HDC dysfunction upon the vascular burden of end-stage renal disease (ESRD) itself, or vascular complications of long-term use (1, 2).

Lifesaving HDC insertion routes, after jugular, femoral, and subclavian vein failure include the inferior caval vein (ICV) via translumbar or transhepatic approach (2–5).

First studies about the outcomes of transhepatic catheter placement published in the 1990s reported a total of 51 patients across 3 different studies, proclaiming the access not as suitable as imagined due to high complication rates (2–4, 6).

A more recent study by Şanal et al. reporting outcomes of 38 patients with transhepatic hemodialysis catheterization proved that the transhepatic route provided a relatively reliable lifesaving approach to those patients (7).

Here we report on two cases from June 2023 which represent the start of transhepatic catheterization as a salvage approach at the Clinical Hospital Merkur in Zagreb, Croatia. To our knowledge, these were the first transhepatic HDC cases in our country as well.

Patient selection

The two patients we present in this study were selected exclusively after no other viable vascular approach was available due to thrombosis of the main vascular access points.

Procedure

The patients' hematologic and coagulation parameters were confirmed to be within normal ranges before each intervention, per previously established inclusion criteria for all patients undergoing tunneled HDC placement. The patients were informed about the procedure and informed consent was obtained. The procedures were performed while the patients were conscious and a local anesthetic (solution of 20 mg/mL lidocaine) was administered. Both procedures were performed by the same two operators with great experience in intravenous HDC placement.

Surgical skin cleansing was performed on the right thoracoabdominal area by standard antiseptic procedure. Imaging guidance was provided by ultrasound (US) with a sterile coated probe.

The transhepatic intervention was done through the right hepatic lobe in the front axillary line in both patients. The access to the hepatic vein was created through the peripheral branches draining to the right hepatic vein. Both cases required the use of 32-cm double luminal tunneled catheters (Medcomp SST OTW) of the Hickman type. The entrance site incision was widened after placing the guidewire. The catheter was inserted after widening the entrance site with a dilator system using the standard Seldinger technique. Following an incision made approximately 4 cm anteroinferior to the skin access site for the tunnel, the catheter was tunneled subcutaneously with the help of a tunneling device. The incision was closed with subcuticular suturing. The catheters were flushed with heparinized solution and the position of the catheter was confirmed using conventional X-ray imaging. The tip of the catheter was positioned in the right atrium in both patients.

Case 1

A 72-year-old male patient was transferred to our Department in June 2023 after HDC failure during a hemodialysis session. His disease burden included two cerebrovascular incidents, one transient ischemic attack, paroxysmal atrial fibrillation, and coronavirus disease 2019 (COVID-19). The patient started undergoing renal replacement therapy in 2016 and had experienced previous HDC-related complications. In December 2021 he had also been admitted to our Department due to *Providencia stuartii* extended spectrum beta-lactamase (ESBL) and OXA-48 catheter-related sepsis, and was treated with ceftazidime avibactam. During the same hospital stay the catheter had been replaced in the same location with surgical help, as the first catheter was placed in the right exterior iliac vein by open surgery (per laparotomy). As the postoperative course was complicated with development of collections surrounding the placed HDC, the surgical decision was to

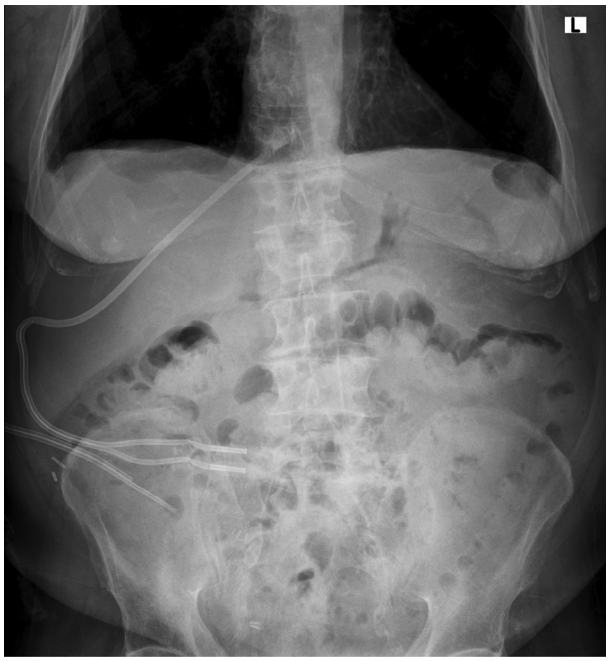

Figure 1 – *Anteroposterior x-ray view of the placed hemodialysis catheter via transhepatic access through the right hepatic vein, inferior vena cava, with the tip positioned in the right atrium*

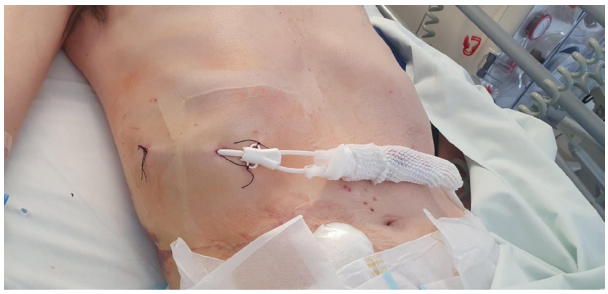

Figure 2 – *View of the tunneled dialysis catheter placed via the transhepatic access*

insert a percutaneous drain rather than a new surgical solution. The drainage was dysfunctional and thus removed. The team considered other dialysis options such as peritoneal dialysis, which was not suitable for the patient due to his poor eyesight, but after a detailed consultation with the patient's wife, automated peritoneal dialysis (APD) was an option after resolving the inflammatory condition surrounding the previously placed catheter. The pretransplant workup discovered multiple occlusions due to thrombosis in the right subclavian vein, both brachiocephalic veins, proximal superior caval vein, and both exterior iliac veins, as well as partial thrombosis of the ICV. The transplant team decided against a renal transplantation option due to the lack of a favorable vascular attachment point. The patient had a total of five hospitalizations after the operative catheter placement due to multiple episodes of sepsis, one with methicilin-resistant Staphylococcus aureus (MRSA) isolate.

In April 2023 he was admitted to a local hospital due to sepsis with accompanying acute heart failure caused by infective endocarditis affecting primarily the aortic valve with severe aortic valve insufficiency, along with moderate stenosis, but with no microbiological isolate. Also, multiple infectious vegetations related to the HDC tip were noticed and thought to contribute to the aortic insufficiency. A computed tomography (CT) scan was done after extensive antibiotic treatment, visualizing a lamellar collection encapsulating the whole length of the placed catheter without any significant abscess formations, and requiring removal with placement of a new HDC.

After the transfer to our Department, the patient was continuously monitored and treated with broad antibiotic therapy without development of fever. Blood cultures were drawn twice, with no bacteremia detected. Due to the insufficient blood flow rate with the current HDC, the team decided on a transhepatic approach after CT angiography showed a partial thrombosis of the ICV between the iliac inlets and the hepatic vein inlet, as well as a complete right subclavian thrombosis and unclear finding of opacity of the left subclavian vein. A 32-cm Medcomp SST OTW catheter was placed under US guidance through a peripheral branch of the right hepatic vein in the VI liver segment, via IVC with the tip positioned in the right atrium (Figures 1 and 2). There were no immediate postprocedural complications, and the flow rate during hemodialysis was > 350 mL/min, enabling adequate hemodialysis sessions, as well as improving the patient's overall clinical condition. Vancomycin was added to the treatment regimen, and the previously surgically placed catheter was removed from the right external iliac vein several days thereafter. The patient was transferred back to his local hospital for further follow-up and chronic dialysis procedures.

The HDC remained functional for a month until the patient's death during a revision procedure which was warranted after development of hemopericardium as a complication of a cardiac surgery performed in July 2023.

***Case* 2**

A 49-year-old male patient was referred to our Department in June 2023 due to insufficient hemodialysis flow rate. The patient was on a chronic renal replacement therapy regimen from July 2020. His chronic kidney disease started after he suffered a stroke a the early age of 34, with consequential aphasia and severe spastic tetraparesis. Shortly thereafter, the patient suffered multiple episodes of chronic pyelonephritis followed by a bilateral pyelotomy in 2017. The course of his chronic kidney disease progressed to the need for renal replacement therapy. His first vascular approach was an AV fistula that soon became dysfunctional with no additional possibilities for AV fistula formation, after which the first non-tunneled HDC was inserted in the left internal jugular vein, to be replaced by a tunneled one soon thereafter. The tunneled catheter remained in function for two years until March 2022, when it was spontaneously dislodged from the tunnel, and a new tunneled HDC was inserted into the right femoral vein. A CT venography scan was done in March 2020 and showed a complete thrombosis of the left subclavian, left brachiocephalic, and right subclavian veins, with thrombosis at the point of the inlet to the caval vein, leaving the aforementioned venous drainage relying completely on the collateral circulation. There were no suitable venous access points in the upper caval vein and its branches.

The existing vascular approach showed an insufficient flow rate and demanded thrombolysis treatment to allow for a satisfactory hemodialysis procedure, after which the patient was urgently referred to our Department. The vascular access was first treated with alteplase, but without a satisfactory response, after which the team decided to place a new vascular access point into the right femoral vein, which also proved dysfunctional in view of the required hemodialysis flow rate. Due to the dysfunction and recirculation of the newly placed catheter, a new CT angiography was performed, which showed ICV thrombosis up to the level of the hepatic vein inlet, with a stationary finding of the superior caval vein branches. Due to the vital indication for a new vascular access, the team opted for a hepatic vein vascular access point. Under US guidance, a 32-cm Medcomp SST OTW double luminal catheter was inserted in the peripheral branch of the right hepatic vein in the VI liver segment, via intercostal access in the front axillary line due to a high colon placement which made the subcostal approach unsuitable. There were no immediate postprocedural complications, and the catheter tip was positioned in the right atrium via the ICV. The catheter blood flow rate was > 350 mL/min, enabling adequate hemodialysis sessions during the first week post insertion.

Unfortunately, due to the patient's highly respiratory mobile liver, the catheter tip started to migrate peripherally, which resulted in compromised blood flow and eventual loss of function after the first week of hemodialysis. Meanwhile, the patient was conditioned for automated peritoneal dialysis (APD). A peritoneal catheter was surgically placed, and the dysfunctional hepatic vein catheter was removed soon thereafter.

The patient was transferred back to his local hospital for further follow-up and chronic dialysis procedures, and to our knowledge the peritoneal access has been functional to date.

DISCUSSION

These two case reports represent the start of alternative HDC placement options in our Department. The two selected patients carried a heavy disease burden specific to each case, and as such had a vital indication after current HDC failure.

The primary catheter placement choice in concordance with the current guidelines are the internal jugular veins, as they do not compromise possible future catheter placement sites, as well as the upper and lower extremity circulation in view of grafting AV fistulas (8, 9). Secondary approaches, such as the subclavian and femoral veins, carry a higher risk of stenosis or occlusion (9, 10).

Both the translumbar and transhepatic approach were considered in our patients, but based on the current available research and the specific requirements and options in each case, we decided on the transhepatic approach due to the verified ICV thrombosis. The transhepatic route carries a higher risk of immediate complications, as they occur in up to one third of the patients in some studies (3). We found no evidence of hepatic artery injury or perihepatic hematoma using real-time US guidance.

As previously stated by Stavropoulos et al., transhepatic HDC can be placed safely, as the infectious complications are acceptable compared to the other sites. However, the researchers in that study experienced lower primary patency rates in comparison with previously published reports (2, 10–13).

In our cases, no issues related to catheter thrombosis or infection were found, primarily due to the very short endpoints in both patients, as one catheter remained functional until the patient's death one month later, and the other became dysfunctional after the first week due to tip migration. This complication was reported in 37 % of the cases in some studies, which is theorized to have been caused by the relatively short intravascular distance between the hepatic veins, the ICV, and the right atrium, accompanied by high organ mobility, as well as the fact that the hepatic veins are relatively short and narrow (4).

The urgency to investigate the possible cause of lower flow rates due to this complication is greater in comparison with the common internal jugular vein approach, as the migration could lead to serious complications. In our case, the catheter had migrated primarily due to the patient's anatomy and neurological condition, therefore making the alternative of APD a more durable option in this case.

This presentation and review of the other published cases shows that the transhepatic access can be reliable in life-saving situations, even as only a bridging method, like in our second case. There is still considerable experience to be gained from implementing this method, thus limiting the current failure rates.

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SAŽETAK

NEKONVENCIONALNI KRVOŽILNI PRISTUP ZA HEMODIJALIZU: PERKUTANI TRANSHEPATIČNI VENSKI PRISTUP KAO OPCIJA SPAŠAVANJA ŽIVOTA, ISKUSTVO JEDNOG SREDIŠTA I PREGLED LITERATURE

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Uvod: Hemodijalizni kateteri (HDK) su uz atrerijskovenske fistule zlatni standard u dijaliznim žilnim pristupima današnjice. Primarni žilni putevi postavljanja HDK-a su unutarnje jugularne, potključne i femoralne vene. Zbog same prirode kronične bubrežne bolesti i njenog utjecaja na žilni sustav, često se događaju trombotičke okluzije žilnih puteva koje dovode do disfunkcije dijaliznog puta te ponekad do iscrpljenja svih mogućnosti konvencionalnih žilnih pristupa u svrhu nadomještanja bubrežne funkcije. Objavljena izvješća pokazuju da nekonvencionalni pristupi (transhepatični, translumbarni) nisu inferiorni konvencionalnima u pogledu infektivnih komplikacija. Ipak, ostaje upitna njihova dugoročna korist budući da su praćeni velikom incidencijom disfunkcije pristupa.

Prikazi slučaja: Ovo je prikaz dvaju slučajeva bolesnika iz lipnja 2023. godine koja su kao vitalnu indikaciju zahtijevala postavljanje nekonvencionalnog HDK-a transhepatičnim putem hepatičnim venama u donju šuplju venu do desnog atrija. U oba bolesnika svi konvencionalni pristupi prethodno su bili iskorišteni i bili su bez radiološki prikazanog prikladnog protoka kroz te vene. Pod ultrazvučnim nadzorom u lokalnoj je anesteziji punktirana hepatična vena u razini prednje aksilarne crte i Seldingerovom tehnikom postavljen dvoluminalni Hickmanov kateter duljine 32 cm s vrhom u desnom atriju. Potom je kreiran tunel na prednjoj trbušnoj stijenci. Kateteri su u oba bolesnika omogućili zadovoljavajući protok i korišteni su za hemodijalizu. Prvi prikazani slučaj transhepatičnog pristupa za hemodijalizu omogućio je bolesniku zadovoljavajuće provođenje postupaka nadomještanja bubrežne funkcije do smrti, uzrokovane poslijeoperacijskim kardiokirurškim komplikacijama, dok je u drugog bolesnika uspješno poslužio kao spasonosna metoda provođenja nadomještanja bubrežne funkcije između disfunkcije prethodnog dijaliznog puta i kondicioniranja bolesnika za trajniju opciju nadomještanja bubrežne funkcije automatiziranom peritonejskom dijalizom.

Zaključak: Dva prikazana slučaja predstavljaju uspješno postavljanje HDK-a transhepatičnim putem kao metodom uspostave dijaliznog pristupa u vitalnoj indikaciji.

Ključne riječi: hemodijaliza, krvožilni pristup, nadomještanje bubrežne funkcije, transhepatični krvožilni pristup, tunelirani kateter za dijalizu

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VARIOUS ROUTES OF AIR SPREAD FOLLOWING IATROGENIC COLORECTAL PERFORATIONS – A SINGLE-CENTER CASE SERIES WITH LITERATURE REVIEW

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Keywords: iatrogenic perforation, retroperitoneum, pneumoperitoneum, pneumothorax, colonoscopy

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Abstract

Over the last decade endoscopic colorectal interventions have been increasingly used to treat polyps and laterally-spreading tumors. Perforations are the most feared complications of both diagnostic and therapeutic endoscopy, and timely recognition and adequate treatment are of paramount importance for successful outcomes. A rare manifestation of iatrogenic retroperitoneal perforation is air propagation through the retroperitoneal space into the mediastinum, pleura, or subcutaneous tissue. In such cases, precise diagnosis and treatment may be challenging. The purpose of this study is to demonstrate a case series of nine patients who underwent colonoscopy and developed radiological signs of retroperitoneal air spreading to distant body compartments. In addition, the pathophysiology, diagnostics and treatment of such clinical scenarios are discussed.

INTRODUCTION

The use of diagnostic and therapeutic colonoscopy is increasing as a result of technological advances which allow more invasive resections of malignant polyps and other focal colorectal mucosal pathologies. Although colonoscopy is generally regarded as a safe method, complications such as bleeding and perforation may happen. Endoscopic resections of mucosal or submucosal lesions have inevitably led to an increased rate of complications, especially rectal wall perforation, which is seen in around 5% of therapeutic colonoscopies (1). Perforations in the colon and upper rectum typically lead to pneumoperitoneum and signs of acute abdomen. However, lower rectal retroperitoneal perforations have a less prominent clinical presentation, as they cause inflammation in the retroperitoneal space, which may be associated with air spreading through different extraperitoneal spaces, including the mediastinal pleura and subcutaneous tissues of various body parts (2). Therefore, the diagnosis of colorectal perforation is sometimes difficult owing to the non-specific clinical presentation and confusing radiological findings. In some cases abdominal X-rays may suggest air in the retroperitoneal space, but this method is much more sensitive for intraperitoneal air (pneumoperitoneum). A more sensitive diagnostic method is computed tomography (CT) with intravenous contrast that may show air bubbles and purulent collections in the area around the suspected perforation, or air bubbles in distant areas such as the mediastinum and subcutaneous tissue of the head and neck (3).

In this study, we demonstrate a single-institution case series of patients with iatrogenic colorectal perforation who developed some of these unusual radiological and clinical scenarios. In addition, we discuss the diagnostics, treatment and possible mechanisms of air dissection through different anatomical planes.

METHODS

We performed a retrospective single-center analysis at the Department of Surgery of the University Hospital Center Zagreb, for the period between January and August 2023, using the Hospital Information System. Data were collected for all patients who had diagnostic or interventional endoscopy and suspected hollow organ perforation with radiological signs of pneumoretroperitoneum. Patients who had other causes (traumatic or surgical) of perforation were excluded, as well as patients who had pneumoperitoneum without the presence of air in the retroperitoneal space. Each case was described with highlights on the presentation, radiological findings and treatment modality. A summary of all cases was presented in figures and tables. The article was approved by the Ethical Committee of the University Hospital Center Zagreb.

RESULTS

Case 1

A 26-year-old female with a history of Crohn's disease, perianal fistulizing disease, and a right hemicolectomy with primary anastomosis underwent regular colonoscopy with manual anal dilatation due to fibrosis of the anal canal opening. The colonoscopy showed a moderately active granulomatous inflammation of the colon. At the end of the procedure, a suspicious rectal perforation was noted and the patient complained of intensive anal pain. A CT scan showed extensive pneumoperitoneum and pneumoretroperitoneum more prominent on the right side of the hemiabdomen, along with an area of free fluid around the sigmoid colon. The rectosigmoid wall was thickened. Urgent surgery was indicated, and revealed a thickened sigmoid and rectal wall, but no signs of abscess or intraperitoneal perforation. Bipolar sigmoidostomy was done for stool derivation, and a pelvic drain was placed. The patient recovered uneventfully and was discharged on postoperative day 9. Stoma reversal surgery was performed 21 months later.

Case 2

An 83-year-old male with a history of right hemicolectomy underwent regular colonoscopy with polypectomy in the descending colon. Immediate postprocedural recovery was uneventful and the patient was discharged on the same day. Five days later he presented to the emergency room (ER) with abdominal pain, bloating and signs of subcutaneous emphysema. An abdominal CT scan revealed pneumoperitoneum, pneumoretroperitoneum, subcutaneous emphysema, and pneumothorax (Figure 1). Colon perforation was suspected and the patient was transferred for emergency surgery. A descending colon perforation and abscess were found. Left hemicolectomy and unipolar colostomy were performed. The patient was discharged on postoperative day 11 and no postoperative complications were noted.

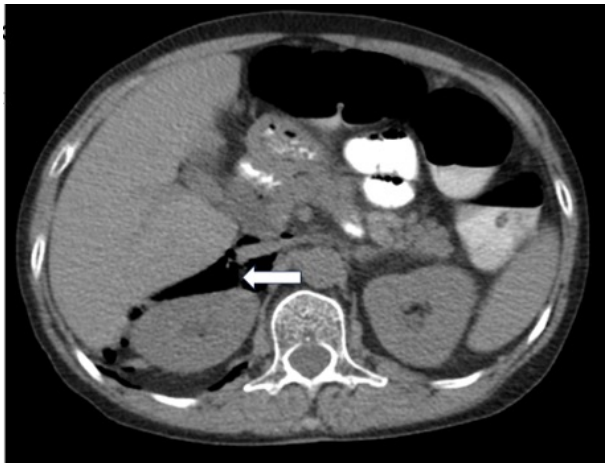

Figure 1. *Computed tomography scan of patient 2 showing pneumoretroperitoneum around right perirenal space (white arrow)*

Case 3

A 49-year-old male patient with a history of adrenal carcinoma with lung metastases and tubulovillous adenoma of the rectum underwent colonoscopy with an attempt of endoscopic mucosal resection. The adenoma was partially resected (25 %) and the patient developed mild abdominal pain two hours after the procedure. A CT scan confirmed a small pneumoretroperitoneum. The patient did not develop severe abdominal pain, tenderness, or swelling of the abdomen. Conservative treatment with antibiotics and restriction of food intake showed good results; the patient recovered well and was discharged from hospital six days after the procedure.

Case 4

A 63-year-old female patient with a history of chronic obstructive pulmonary disease and positive fecal occult blood test had a screening colonoscopy. Endoscopic mucosal resection of a lateral spreading tumor in the ascending colon was done. Abdominal X-ray was performed routinely two hours after the colonoscopy, revealing pneumoperitoneum and pneumoretroperitoneum.

The patient was transferred to the operating room. Intraoperatively, a perforation and localized peritonitis at the level of the mid-ascending colon was found. Right hemicolectomy was performed with formation of an ileostomy. The patient was discharged on postoperative day 6. Stoma reversal surgery was performed five months later.

Case 5

A 67-year-old male patient was evaluated due to persisting anemia, weight loss, and elevated tumor markers. Colonoscopy showed a tumor located 85 cm from the anocutaneous line. A biopsy was taken and the patient was discharged home. Five days later he was readmitted to the hospital due to abdominal pain. An urgent abdominal CT scan confirmed a tumor of the transverse colon and revealed pneumoperitoneum, subcutaneous emphysema, and pneumomediastinum (Figure 2). The patient was transferred to the operating room and a tumor of the transverse colon with gastric infiltration, cecal perforation, and diffuse peritonitis were found. Partial gastrectomy and right hemicolectomy were performed with formation of an ileostomy and mucous fistula. The patient recovered uneventfully and was discharged on postoperative day 10. Stoma reversal surgery was performed 13 months later.

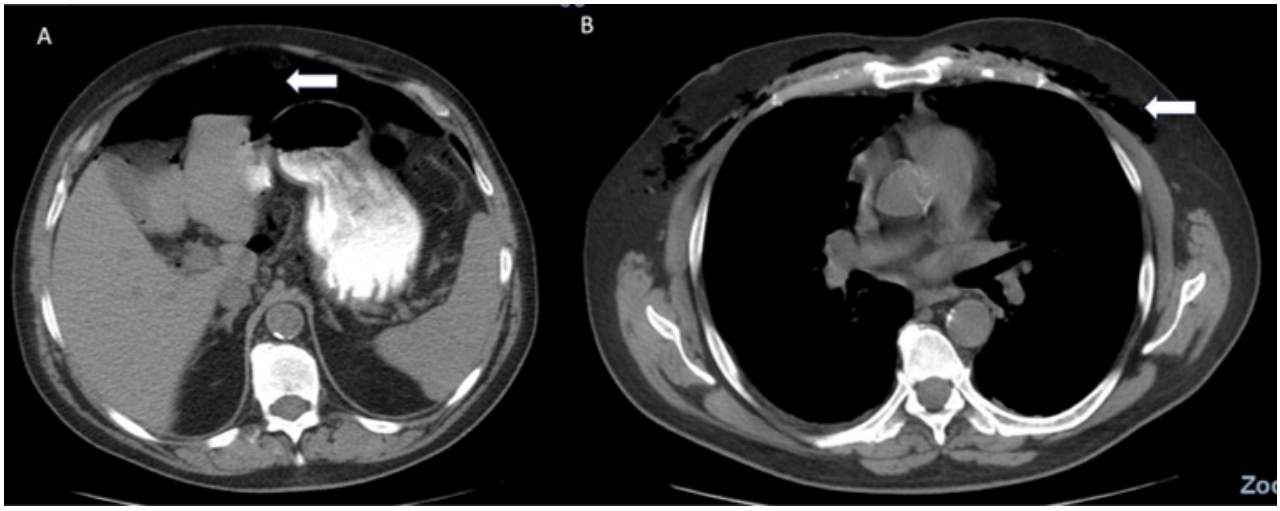

Figure 2. *Computed tomography scan in patient 5 showing a) pneumoperitoneum; b) subcutaneous emphysema (white arrows)*

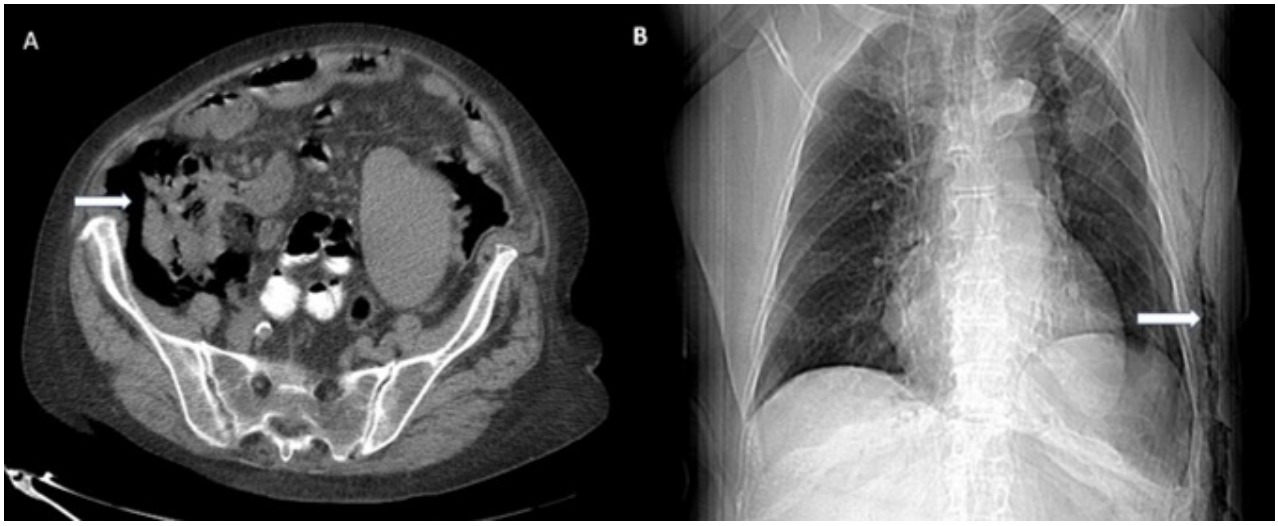

Figure 3. *Computed tomography scan in patient 6 showing a) extensive pneumoretroperitoneum on the right side; b) subcutaneous emphysema on the left thoracic side (white arrows)*

Case 6

A 72-year-old female patient with a history of angina pectoris had colonoscopic polypectomy in the area of the hepatic flexure. She was readmitted to the ER later in the same day due to fever and abdominal pain. Abdominal and thoracic CT revealed pneumoperitoneum, pneumoretroperitoneum, pneumothorax, and pneumomediastinum (Figure 3). The patient was transferred to the operating room, and surgery revealed a perforation defect of the hepatic flexure with diffuse peritonitis. Right hemicolectomy was performed with formation of an ileostomy and mucous fistula. The patient recovered well and was discharged on postoperative day 11. Stoma reversal surgery was performed four months later.

Case 7

A 72-year-old male patient with positive fecal occult blood test had multiple regular screening colonoscopies. He underwent endoscopic removal of a rectal polyp 2 cm from the anocutaneous line and was discharged home the day after the procedure. Four days later, he was readmitted to hospital due to abdominal pain and fever. A CT scan was performed confirming extensive pneumoretroperitoneum (Figure 4). The patient was transferred to the operating room and surgery revealed a perforation defect with abscess on the dorsal rectal wall. Abscess drainage and bipolar sigmoid colostomy were performed. The patient recovered well and was discharged on postoperative day 15. Three months later he was readmitted to hospital due to a rectal fistula and abscess formation. Abscess drainage and a Hartmann procedure were done. Stoma reversal surgery was performed four months later.

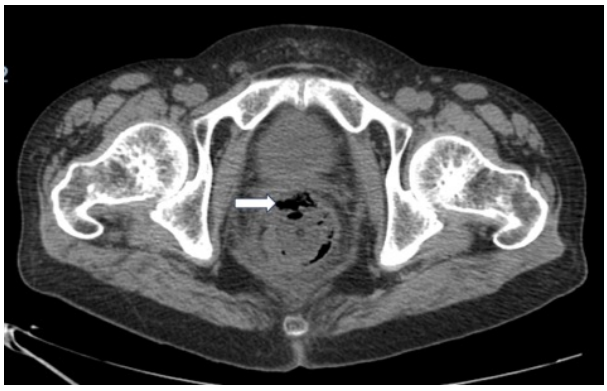

Figure 4. *Air bubbles in the pararectal space (white arrow)*

Case 8

A 58-year-old female patient with a history of hemorrhoidal disease underwent regular colonoscopy. At the end of the procedure an iatrogenic perforation 15 cm from the anocutaneous line was immediately recognized and clipped. A CT scan was preformed and it confirmed extensive pneumoperitoneum and pneumoretroperitoneum with bilateral pneumothorax and pneumomediastinum (Figure 5), and the patient was transferred to the operating room. Urgent surgery was performed, revealing a sigmoid perforation. A Hartmann procedure was performed. The patient recovered uneventfully and was discharged on postoperative day 5. Stoma reversal surgery was performed nine months later.

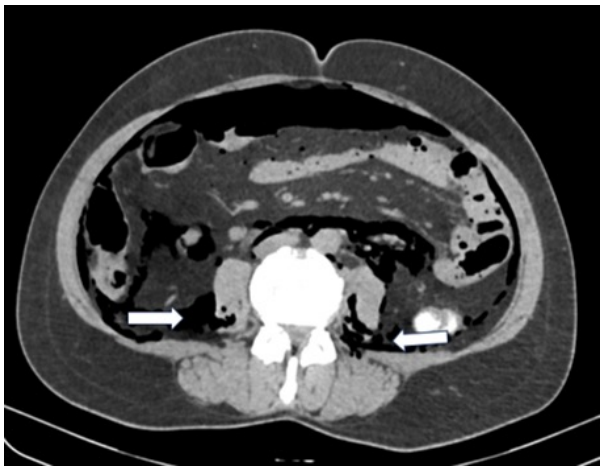

Figure 5. *Computed tomography scan in patient 8 showing extensive pneumoretroperitoneum (white arrows)*

Case 9

An 81-year-old female patient underwent diagnostic colonoscopy and was discharged on the same day. Two days later, she presented to the ER with abdominal pain, diarrhea, and fever. The patient had been on corticosteroid therapy due to chronic myelomonocytic leukemia that was discovered two years previously. Abdominal and chest X-rays revealed pneumoperitoneum and pneumoretroperitoneum, followed by a CT scan which confirmed extensive pneumoperitoneum and pneumoretroperitoneum including signs of chronic cholecystitis. The patient was transferred to the operating room and underwent urgent surgery which showed a perforation of the ascending colon. Right colectomy with bipolar ileostomy, cholecystectomy, and appendectomy were performed. The patient had a prolonged hospital stay due to wound infection, and 27 days after the surgery

she developed acute renal failure followed by cardiac arrest 42 days after the initial surgery.

DISCUSSION

Our study presents a collection of nine cases of pneumoretroperitoneum associated with colorectal perforation. Given the rarity of this complication, our results are very valuable for clinicians who are involved in the treatment of these patients, especially for gastroenterologists, surgeons, and radiologists. In the literature case reports on this topic were predominant; only two reviews were available, but those described only pneumothorax or subcutaneous emphysema after colorectal endoscopy (5, 6). Other causes of pneumoretroperitoneum such as hemorrhoidectomy or diverticulosis were also described, but these were not associated with endoscopic interventions (7). The variability of signs and symptoms as well as the period from intervention to disease presentation contribute to the great challenges in diagnostics and treatment presented by this clinical scenario. The frequently subtle but progressive disease course may lead to serious septic complications. Therefore, timely recognition of colorectal perforation and adequate treatment are of paramount importance for a favorable prognosis. It is also important to emphasize that CO_2 insufflation during laparoscopic procedures is purposely used to create a pneumoperitoneum with the aim to allow space for surgical manipulation inside the abdominal cavity. However, such procedures may also result in pneumoretroperitoneum or subcutaneous emphysema (in case of an accidental

Demographic and clinical data of the nine presented cases are shown in Tables 1 and 2.

Table 1. *Demographic, clinical and treatment characteristics of reported cases with iatrogenic colorectal perforation (N = 9)*

	Age	Sex	Colonoscopy indication	Endoscopic intervention	Time to presentation	Symptoms	Radiological findings
Case 1	26	F	Anal stenosis and Crohn's disease	Colonoscopy with manual anal dilatation	Immediate recognition	Perianal and anal pain	CT scan: PP, PR, localized fluid around sigmoid colon
Case 2	83	M	Regular follow-up	EMR of rectal and transversal polyp	5 days	Abdominal pain, nasal speech, swallowing difficulties, clogged ear	Chest and abdominal X-rays: PP, PR, SE, PM
Case 3	49	M	Polypectomy in rectum	ESR of rectal polyp	2 hours	Abdominal pain	CT scan: PR
Case 4	63	F	Lateral spreading tumor	EMR	24 hours	Acute abdomen	Chest and abdominal X-rays: PP, PR
Case 5	67	M	Anemia and weight loss	Tumor biopsy	5 days	Neck swelling	CT scan: PP, PR, PM, SE
Case 6	72	F	Diagnostic colonoscopy	Polypectomy at hepatic flexure with clipping of defect	1 day	Acute abdomen	CT scan: PR, PP, PT, PM, SE
Case 7	72	M	Lateral spreading tumor	ESR rectum	4 days	Fever and abdominal pain	CT scan: PR
Case 8	58	F	Diagnostic colonoscopy	Clipping of the defect	Immediate recognition	Rectal bleeding	CT scan: PP, PR, PP, PM
Case 9	82	F	Diagnostic colonoscopy	-	2 days	Acute abdomen	Chest and abdominal X-rays: PP, PR

F – female; M – male; PR – pneumoretroperitoneum; PP – pneuperitoneum; PM – pneumomediastinum; PT – pneumothorax; SE – subcutaneous emphysema; EMR – endoscopic mucosal resection; ESR – endoscopic submucosal resection

Table 2. *Management and outcomes of reported cases with iatrogenic colorectal perforation (N = 9)*

	Management	Intraoperative findings	Type of surgery	Outcome	Hospital stay (days)	Inflammatory markers at presentation
Case 1	Surgical	Thickened sigmoid and rectal wall	Sigmoidostomy	Discharged, no complications	9	L 4 CRP 50
Case 2	Surgical	Descending colon perforation and abscess	Left hemicolectomy and unipolar ileostomy	Discharged, no complications	11	L 16 CRP 218
Case 3	Conservative	-		Discharged, no complications	6	L 11 CRP 275
Case 4	Surgery	Ascending colon perforation and localized peritonitis	Right hemicolectomy and unipolar ileostomy	Discharged, recovered from postoperative pneumonia	6	L 10 CRP 200
Case 5	Surgery	Tumor of transverse colon with gastric infiltration, cecal perforation and diffuse peritonitis	Right hemicolectomy and unipolar ileostomy, partial gastrectomy	Discharged, minor wound infection	8	L 11, CRP 220
Case 6	Surgery	Perforation defect of hepatic flexure with peritonitis	Left hemicolectomy with ileostomy	Discharged, no complications	11	L 46 CRP 250
Case 7	Surgery	Perforation defect on dorsal rectal wall with abscess	Bipolar sigmoidostomy	Discharged, percutaneously drained pelvic abscess	15	L22 CRP 310
Case 8	Surgery	Sigmoid perforation	Hartmann procedure	Discharged, no complications	5	L 11 CRP 107
Case 9	Surgery	Perforation of ascending colon	Right hemicolectomy and unipolar ileostomy	Death, cardiac arrest	42	L14 CRP 197

L – leukocyte count; CRP – C-reactive protein

puncture of the subcutaneous or retroperitoneal space during needle insufflation). Moreover, laparoscopy may even cause pneumothorax, which happens when gas escapes into the pleural cavity through diaphragmatic defects or during pleural damage. This complication is predominantly seen in upper gastrointestinal laparoscopic procedures such as the Nissen fundoplication or proximal gastrectomy. In these cases, pneumothorax has been described as a complication in up to 2 % of patients, while in thoracoscopic procedures the rate is much higher. Pneumoperitoneum is usually present and radiologically detectable even up to five days after laparoscopy, while subcutaneous emphysema may persist even longer (up to 3 – 4 weeks) (8). Therefore, it may be challenging to distinguish these benign postoperative findings from serious complications such as hollow organ perforation or gas-forming infections. To avoid unnecessary surgical exploration, clinicians should meticulously evaluate each patient's clinical condition.

Colorectal perforation is most commonly seen after therapeutic interventions, particularly endoscopic submucosal and endoscopic mucosal resection, but it may also occur as a result of barotrauma or thermal

injury, or during simple diagnostic colonoscopy if the camera punctures the colonic wall (2, 4, 9). There are several risk factors for iatrogenic colorectal perforations, the most important being increased age, low body mass index, low plasma albumin level, and underlying colon pathology (8). Technological and technical advances in colorectal endoscopy have resulted in an increased number of more invasive focal lesion excision. On the one hand, this enables many patients to avoid more aggressive surgical resection, but on the other, it inevitably leads to an increased risk of colorectal perforation as a result of deeper mucosal or submucosal dissections. Thus, a high level of critical thinking and endoscopic experience is required when evaluating the indications for polypectomy, especially in large, lateral spreading, or malignant polyps.

Most commonly the perforation is seen in the sigmoid colon, due to its curved anatomy and the fact that it is a common site of colonic pathologies such as diverticulosis or polyps. Following the perforation, the insufflated air may escape through the defect and reach different abdominal and extra-abdominal spaces, depending on the site and type of perforation. Thus, if the perforation occurs in the transverse or sigmoid colon, which are completely intraperitoneal, the air will in most cases accumulate intraperitoneally and cause pneumoperitoneum with typical radiological signs. As the ascending and descending colon are located partially retroperitoneally, perforations may cause both pneumoperitoneum and pneumoretroperitoneum. Lastly, perforations in the rectum below the peritoneal reflections inevitably lead to accumulation of air retroperitoneally, while pneumoperitoneum may occur secondary to air propagation or progression of the perforation size. Once in the retroperitoneum, the ectopic gas may pass into other body compartments through distinct anatomical and fascial planes (2, 9-15).

The peritoneum is a two-layer serous membrane which encases and covers the abdominopelvic wall and viscera (2, 7, 16). The colon consists of four regions: the retroperitoneal ascending and descending part partially covered by the peritoneum, and the intraperitoneal transverse and sigmoid portions completely covered by the peritoneum and suspended by a double layer of peritoneum (mesocolon). In rectal perforations, as well as in cases of posterior colonic wall perforation, the gas migrates into the retroperitoneal space directly. Moreover, it is possible that the gas migrates into the retroperitoneal space through the intact colonic wall and further through the mesocolon (9).

In four out of our nine patients, signs of gas in the thoracic cavity were developed – four of them had pneumomediastinum, three developed signs of subcutaneous emphysema, and two developed pneumothorax. During embryonic development, the chest and abdomen originate from a single celomic cavity lined by a serous membrane. Later in development, that serous membrane evolves into the peritoneal membrane and pleura, both of which present the border between the cavities (abdominal and thoracic) and the retroperitoneal and subpleural (mediastinal) space. Isolation of the thoracic and abdominal cavities develops around the 7th week of gestation. The esophageal diaphragmatic hiatus (Th10 level) admits the esophagus and vagal trunks to transverse between the thorax and abdomen, and can serve as a potential pathway of spread of free air between the mediastinum and retroperitoneum (2, 18, 19).

The diaphragmatic hiatus of the aorta (Th12 level) is another possible pathway of spread of free air between these two subserosal spaces, as well as the inferior vena cava, whose wall is firmly attached to the margin of the diaphragmatic foramen (Th8 level), thus allowing air to pass next to it. Furthermore, the foramina of Morgagni are two defects in the retrosternal region through which internal thoracic vessels pass; in the presence of pneumoperitoneum, a tear in their peritoneal lining can occur, allowing the passage of gas cranially towards the mediastinum. The lumbocostal triangle is a weak spot in the diaphragm which may act as a possible transphrenic pathway for gas migration (20).

Beside these diaphragmatic hiatuses and defects that present a communication between the subperitoneal and subpleural spaces, certain procedures like cardiopulmonary resuscitation or chest drain insertions (pneumothorax decompression) also present a greater risk for the development of pneumomediastinum in case of colonic perforation.

Two of our patients developed pneumothorax. After the passage of gas from the retroperitoneum into the mediastinum via the diaphragmatic hiatuses or unrecognized diaphragmatic defects, a rupture in the mediastinal pleura can occur which causes decompression of air in the pleural space and pneumothorax.

It has to be taken into consideration that every urgent surgery carries a higher risk of pneumothorax that can develop due to barotrauma during intubation and ventilation (4, 5, 22). Three of our patients also developed subcutaneous emphysema that manifested with

palpable crepitus in the neck, chest, and abdominal wall. Abdominal wall subcutaneous emphysema can occur if gas travels along the mesentery towards the abdominal wall (23). As there are no barriers between the subcutaneous tissues of the body, there is no barrier to gas migration from abdominal subcutaneous tissues cranially towards the subcutaneous tissue of the chest and neck (24, 25).

Regarding the treatment, a total of four of our patients had right hemicolectomy performed due to perforations in the cecum, hepatic flexure, ascending colon, and transverse colon. Right hemicolectomy with exteriorization of the ileal and colonic bowel ends was the most frequent urgent operation in our patients. One patient had left hemicolectomy performed due to the perforation site in the descending colon, and two patients had a Hartmann procedure due to the sigmoid and rectal site of perforation. One patient had bipolar sigmoidostomy performed although there was no evident site of perforation observed at operation. In only one patient conservative treatment was possible. He developed pneumoperitoneum and pneumoretroperitoneum shortly after partial endoscopic mucosal resection of a tubulovillous adenoma of the rectum, but no clinical signs of acute abdomen were present.

Therefore, treatment mainly depends on the site of perforation and the clinical signs. In the absence of septic complications and clinical deterioration, a conservative approach may be considered if there is no clear sign of perforation. However, in such cases hospitalization and careful monitoring are required. Recently, laparoscopy has evolved as both a diagnostic and therapeutic procedure in many abdominal surgical emergencies. Consequently, it may also have an important role in the treatment of iatrogenic colorectal perforations, including retroperitoneal perforations. During laparoscopy, the whole abdominal cavity can be explored, and free fluid such as blood, pus, or enteral content may be easily detected. In addition, the laparoscopic technique may be used for abdominal lavage and drain placement, as well as laparoscopic treatment of acute diverticulitis, especially in cases of small perforations with minimal pericolonic inflammation. Taking all this into consideration, every effort should be invested to avoid unnecessary radical open surgical resection or colostomy. However, in cases of progressive septic complications or diffuse peritonitis, a timely surgical intervention is mandatory.

In our series, one patient (an 81-year-old female) had a prolonged hospital stay due to wound infection, and 27 days post operation she developed acute renal failure, followed by cardiac arrest 42 days after initial operation. All other patients that underwent urgent surgery had stoma reversal surgery performed in a period of 4 to 13 months after the initial operation.

CONCLUSION

Iatrogenic colorectal perforation presents a serious complication, and timely recognition and adequate treatment are of paramount importance for favorable outcomes. Clinicians should consider the atypical clinical and radiological presentation of such perforations, including detection of gas in distant abdominal compartments such as the pleural space or subcutaneous tissue. Retroperitoneal perforations are particularly challenging as they may cause slow but progressive septic complications. In such cases, prompt diagnostic and clinical evaluation is required in order to select the most appropriate treatment.

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SAŽETAK

RAZLIČITI PUTEVI ŠIRENJA ZRAKOM NAKON JATROGENIH KOLOREKTALNIH PERFORACIJA – NIZ SLUČAJEVA U JEDNOM SREDIŠTU, S PREGLEDOM LITERATURE

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Tijekom posljednjeg desetljeća kolorektalne endoskopske intervencije sve se više koriste za liječenje polipa i lateralno-širećih tumora. Perforacija je najozbiljnija komplikacija dijagnostičke ili terapijske endoskopije te su pravovremeno prepoznavanje i primjereno liječenje najvažniji za prognozu. Rijetko očitovanje retroperitonejske jatrogene perforacije kolona jest širenje zraka kroz retroperitonejski prostor u medijastinum, pleuru ili potkožno tkivo te u tim slučajevima precizna dijagnoza i liječenje mogu predstavljati velik izazov. Svrha ovog istraživanja jest pokazati niz od devet bolesnika koji su bili podvrgnuti kolonoskopiji i razvili radiološke znakove širenja zraka u retroperitoneum i na udaljene dijelove tijela. Članak opisuje i patofiziologiju, dijagnostiku i liječenje tih kliničkih scenarija.

Ključne riječi: jatrogena perforacija; retroperitoneum; pneumoperitoneum; pneumotoraks; kolonoskopija

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THE POSSIBLE ROLE OF PHARMACOGENETICS WHEN RESUMING ANTICOAGULATION FOLLOWING INTRACRANIAL HEMORRHAGE

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Abstract: Intracranial hemorrhage (ICH) is the most feared complication of anticoagulation, therefore resuming anticoagulation following ICH is challenging. We present the case of a 76-year-old man with progression of left leg deep venous thrombosis (DVT). His previous anticoagulant DVT treatment was complicated by ICH and the anticoagulant was stopped. Without anticoagulant therapy, DVT symptoms worsened. Careful anticoagulant reintroduction was initiated. After two months of subcutaneous enoxaparin application, the patient desired a direct oral anticoagulant (DOAC). Several considerations are important prior to DOACs introduction: age, renal and hepatic function, drug-drug interactions, and bleeding risk. To avoid possible genetically determined DOAC pharmacokinetics alteration and drug-drug interactions, a pharmacogenetic analysis was performed. Following the pharmacogenetic findings, reduced dabigatran doses were introduced. Optimal plasma dabigatran concentrations were confirmed, and the further clinical course was uneventful. An individual approach with pharmacogenetic testing can provide additional information in selecting the appropriate medication in an optimal dosage.

Keywords: cytochrome P450, dabigatran, DOAC, P-glycoprotein, pharmacogenetic, thrombosis

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INTRODUCTION

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality worldwide. The estimation of VTE incidence is 1/1 000 persons annually with PE occurring in up to one third of the cases (1). Direct oral anticoagulants (DOACs) are recommended as the first-choice anticoagulant therapy for acute VTE treatment (2). Current guidelines highlight concomitant drug and comorbidity pharmacokinetic (PK) effects with DOACs (3). All DOACs are transmembrane substrates of the permeability glycoprotein (P-gp), an efflux transporter, which mediates drug export into the cells of the small intestine, blood-brain barrier, hepatocytes, and proximal tubule of the kidney. Consequently, intestinal absorption as well as biliary and urinary excretion can be altered by P-gp inhibition or induction (4-6). Pharmacogenomics of DOACs is a relatively new field that may enable optimal individual choice of the proper medication at the proper dose (4-6). Polymorphisms of genes encoding P-gp and the cytochrome P450 enzyme (CYP) might explain the interindividual variability of DOAC plasma concentrations and assist in predicting treatment failure or toxicity. Other than CYP450, human carboxylesterase gene polymorphisms (CES1) may also influence dabigatran and edoxaban pharmacokinetics (6).

Table 1. *Patient's pharmacogenetic profile*

Gene – allele	Genotype	Phenotype	Method
*CYP2C9 *2, *3*	*1/***2**	Intermediate metabolism	A
*CYP2C19 *2, *17*	*1/***17**	Rapid metabolism	A
*CYP3A4 *22*	*1/***22**	Intermediate metabolism	B
MDR1 (ABCB1) 1236C>T *MDR1 (ABCB1) 3435C>T*	C/**T** C/**T**	Intermediate transport activity	A
ABCG2 421C>A	C/C	Normal transport activity	A
UGT2B7 -161C>T	C/C	Normal metabolism	A

Variant alleles are bolded.
A – Real time PCR TaqMan® SNP Genotyping (Thermo Fisher Scientific, Foster City, CA, USA); B – Real time PCR TaqMan® DME Genotyping (Thermo Fisher Scientific, Foster City, CA, USA); PCR – polymerase chain reaction; SNP – single nucleotide polymorphism; DME – drug metabolizing enzyme

Table 2. *Patient's pharmacogenetic profile and drug roles in metabolic pathways*

Patient's genotype	Patient's phenotype	Drugs - Substrates	Drugs - Inducers
CYP2C9	**IM**	diazepam, phenobarbital	phenobarbital
CYP2C19	**RM**	diazepam, metoprolol, phenobarbital	phenobarbital
CYP3A4	**IM**	apixaban, diazepam, rivaroxaban	phenobarbital
UGT2B7	NM	dabigatran, diazepam	phenobarbital
MDR1 (ABCB1)	**ITA**	apixaban, dabigatran, diazepam, metoprolol, phenobarbital rivaroxaban	phenobarbital
ABCG2 (BCRP)	NTA	apixaban, rivaroxaban	

Risk findings are bolded. DOACs are underlined.
Abbreviations: IM – intermediate metabolism, RM – rapid metabolism, NM – normal metabolism, NTA – normal transport activity, ITA – intermediate transport activity; DOAC – direct oral anticoagulant

CASE REPORT

A 76-year-old man was referred to our Department for a second opinion due to DVT progression. Four months earlier, the patient underwent surgical removal of a meningioma. One month after the surgery he developed left leg proximal DVT. Subcutaneous (SC) dalteparin (7500 international units twice daily) was initiated, but the in-hospital course was complicated by intracranial hemorrhage (ICH). The anticoagulant was stopped, and an inferior vena cava (IVC) filter was implanted to prevent PE. The patient was discharged with the following daily therapy: acetylsalicylic acid (ASA) 100 mg, metoprolol 50 mg, phenobarbital 200 mg, ramipril 1.25 mg, and diazepam 5 mg. Anticoagulation was not resumed and IVC filter extraction was not considered. Within the next two months, the patient recovered neurologically, but pain and swelling of the left leg worsened due to thrombus progression (confirmed by ultrasound).

Table 3. *Coagulation parameters and dabigatran concentrations*

Coagulation tests	Basal results before dabigatran introduction	One week after dabigatran introduction (dose 110 mg BID)		One year after dabigatran introduction (dose 110 mg BID)	
		C trough	C peak	C trough	C trough
PT (%)	95	94	59	82	58
aPTT (s)	28.6	33.3	46.4	35.6	50.6
TT (s)	17.9	137.4	> 150	142.9	> 150
Fibrinogen (g/L)	2.7	3.1	2.8	3.9	4.3
DPC* (ng/mL)		66.2	175.5	65.3	190.1
Expected DPC (dose 150 mg BID) in patients treated with PE/VTE (ng/mL)		60 (39-95)	175 (117-275)	60 (39-95)	175 (117-275)

Abbreviations: BID – lat. bis in die, twice daily; aPTT – Activated partial thromboplastin time; C – concentration; DPC – dabigatran plasma concentrations; PE – pulmonary embolism; PT – prothrombin time; TT – thrombin time; VTE – venous thromboembolism
Coagulation assays were performed in fresh plasma samples within 4 hours of blood collection. PT using Innovin, aPTT using Actin FS, fibrinogen using a modified Clauss method with Multifibren U reagent, and TT using BC Thrombin Reagent on BCS XP analyzer (Siemens Healthcare Diagnostics, Marburg, Germany), whereas D-dimer was measured by the VIDAS D-Dimer Exclusion II assay on the mini VIDAS Immunoassay system (bioMérieux, Marcy l'Etoile, France).
*DPC was measured using in-house diluted thrombin time (dTT) with BC Thrombin as reagent applicated on the BCS XP analyzer (Siemens Healthcare Diagnostics, Marburg, Germany) and calibrated using STA-Dabigatran calibrators (Diagnostica Stago, Asnières sur Seine Cedex, France). Peak and trough samples at steady state were collected for DPC measurement.[7] C trough – plasma samples collected before the next dabigatran dose (within 10 – 16 h after last dabigatran dose); C peak – plasma samples collected 3 h after dabigatran administration.

Upon admission to our Department, the patient presented with severe, painful edema of the left leg, while the remaining physical status was within normal parameters, including liver and renal function. Several concerns arose regarding further management and were discussed by a multidisciplinary team. Anticoagulation resumption could stop thrombosis progression and leg symptoms; however, the patient had a high bleeding risk. Additionally, IVC filters are effective in PE protection, but may also provoke IVC thrombosis as well as other complications. As no further absolute contraindication for anticoagulation existed, mid-level enoxaparin dosage (0.4 mL subcutaneously twice daily) was initiated and IVC filter extraction ensued. ASA was stopped prior to enoxaparin introduction. Three months after admission, the patient requested to be treated with a DOAC. To avoid possible genetically determined DOAC pharmacokinetics alteration and drug-drug interactions (DDIs) with concomitant therapy, a pharmacogenetic analysis was performed (Table 1). Pharmacogenetic results indicated, among other findings, that the patient was a CYP3A4 intermediate metabolizer.

When we compared the metabolic pathways for all concomitant medicines with DOACs to the patient's pharmacogenetic profile (Table 2), three of them, in addition to DOACs, were P-gp substrates. Such a high load of P-gp can cause slower efflux transport function and possible prolonged bioavailability of P-gp drug substrates, leading to their higher concentrations.

It should be emphasized that phenobarbital is both a P-gp substrate and an inductor which, in this array, might have a positive influence on efflux function. As rivaroxaban, apixaban, and edoxaban are metabolized via hepatic CYP, primarily CYP3A, dabigatran was chosen for therapy as it has, among other available DOACs, the most favorable pharmacogenetic profile with the least number of risk alleles.

Considering the pharmacogenetic profile and possible DDI, slightly reduced doses of dabigatran 110 mg twice daily were introduced, along with monitoring of coagulation parameters and dabigatran plasma concentration (DPC). Peak and trough plasma samples at steady state

were collected for determination of the drug concentration, and optimal DPC was confirmed (Table 3).

In a three-month follow-up visit, duplex-ultrasound confirmed leg edema regression and significant recanalization of deep veins with normal findings of D-dimer concentration (0.12 mg/L fibrin equivalent units, FEU) as well as other coagulation parameters, including DPC, without bleeding complications. At the next three-month follow-up visit the patient complained of intermittent palpitations, and 24-hour electrocardiogram confirmed paroxysmal atrial fibrillation indicating the need for lifelong anticoagulation (3). Dabigatran was continued, and the further clinical course was uneventful. One year after dabigatran initiation, duplex-ultrasound confirmed deep vein recanalization with normal findings of D-dimer concentration (0.18 mg/L FEU) as well as other coagulation parameters, including DPC (Table 3), without bleeding complications.

DISCUSSION

Our patient required detailed considerations regarding the administration of anticoagulant therapy due to a combination of interfering factors (recurrent DVT, previous ICH during anticoagulation, older age, and concomitant medication). ICH is one of the most devastating potential complications of anticoagulation, therefore anticoagulation reintroduction following ICH requires careful balancing between drug efficacy and safety. Even though DOACs are often referred to as a uniform drug class, there is increasing evidence from indirect comparisons and observational studies that each DOAC has its own specific risk profile (8, 9). Furthermore, physicians should be aware of potential DDIs with DOACs. Drugs and other P-gp and/or CYP3A4 inductors may decrease DOAC plasma concentrations leading to an increased risk for thromboembolic events, while P-gp and/or CYP3A4 inhibitors may increase DOAC concentrations leading to an increased bleeding tendency. Pharmacokinetic DDIs that may occur in association with DOACs are largely mediated by the P-gp efflux transporter protein alone (all DOACs) or in combination with CYP enzymes (except for dabigatran) (6, 8, 10, 11). Since current guidelines do not recommend one DOAC over another, we performed a preemptive pharmacogenetics analysis in order to determine which product would induce a better clinical response while avoiding adverse events (12). The pharmacogenetic profile should include genes for CYP3A4, CYP3A5, CYP2J2, and CYP1A2 enzymes, as well as transporters P-gp, ABCG2, and SLCO1B1, that is, all major enzymes and transporters involved in DOAC metabolism to enable a more optimal individual choice among DOACs (6).

Although DOACs pharmacogenetic studies have not yet yielded unambiguous results and have not been translated into some form of recommendations, we believe that the approach described may help clinicians. We intend to confirm this claim in an ongoing clinical study.

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SAŽETAK

PONOVNO UVOĐENJE ANTIKOAGULANTE TERAPIJE NAKON INTRAKRANIJSKOG KRVARENJA – MOGUĆA ULOGA FARMAKOGENETIKE

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Intrakranijsko krvarenje (ICH, od eng. intracranial hemorrhage) jedna je od najopasnijih komplikacija antikoagulantne terapije. Potreba za nastavkom antikoagulantne terapije nakon ICH-a je izazovno pitanje u praksi. U radu smo prikazali slučaj 76-godišnjeg bolesnika s progresijom duboke venske tromboze lijeve noge. Njegovo prethodno liječenje antikoagulatnom terapijom zbog duboke venske tromboze kompliciralo se intrakranijskim krvarenjem i antikoagulantna terapija je prekinuta. Bez antikoagulantne terapije simptomi duboke venske tromboze su se pogoršavali. Započeto je pažljivo ponovno uvođenje antikoagulantnog lijeka. Nakon dva mjeseca potkožne primjene enoksaparina bolesnik je želio nastaviti liječenje direktnim oralnim antikoagulantom (DOAK). Prije uvođenja DOAK-a važno je razmotriti nekoliko čimbenika: dob, bubrežnu i jetrenu funkciju, interakcije lijekova te rizik krvarenja. Kako bi se izbjegle moguće genetički određene promjene farmakokinetike DOAK-a i interakcije lijek-lijek, napravljena je farmakogenetička analiza. Sukladno farmakogenetičkom nalazu uveden je dabigatran u smanjenoj dozi. Potvrđene su optimalne koncentracije dabigatrana u plazmi, a daljnji klinički tijek bio je bez komplikacija. Individualan pristup s farmakogenetičkim ispitivanjem može pružiti dodatne informacije u odabiru odgovarajućeg lijeka u optimalnoj dozi.

Ključne riječi: citokrom P450, dabigatran, DOAK, P-glikoprotein, farmakogenetika, tromboza

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TRUDNICA S GLANZMANNOVOM TROMBASTENIJOM

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SAŽETAK

UVOD: Glanzmannova trombastenija je rijedak nasljedni poremećaj trombocita koji obilježava genski uvjetovan poremećaj u glikoproteinskom IIb/IIIa kompleksu uz posljedični poremećaj agregacije trombocita. Za potvrđivanje dijagnoze važan je izostanak agregacije trombocita na sve agoniste osim ristocetina te određivanje količine GIIb/IIIa na membrani trombocita. Fenotip je varijabilan, a najčešće se očituje krvarenjima kože i sluznica. Liječenje epizoda krvarenja sastoji se od primjene antifibrinolitika, transfuzija koncentrata trombocita te rekombinantnog FVIIa.

CILJ: Prikazati rijedak slučaj trudnice s Glanzmannovom trombastenijom i dokazanim antitrombocitnim protutijelima.

PRIKAZ SLUČAJA: Bolesnici je s 13 godina u sklopu obrade gingivalnog krvarenja postavljena dijagnoza Glanzmannove trombastenije na temelju nalaza agregacije trombocita, nakon čega nije imala značajnijih krvarenja i nije se javljala hematologu. U dobi od 28 godina premještena je iz vanjske ustanove u Zavod za hematologiju Kliničkog bolničkog centra (KBC) Zagreb u 37. tjednu do tada uredne trudnoće radi promatranja i liječenja epistakse. U vanjskoj ustanovi učinjena je tamponada nosa te je primila transfuziju koncentrata trombocita. U KBC-u Zagreb učinjena je obrada kojom je utvrđen uredan broj i veličina trombocita te izostanak agregacije trombocita sa svim agonistima osim ristocetinom, produljeni testovi funkcije trombocita, a imunofenotipski se na površini trombocita dokazao smanjen izražaj GPIIb/IIIa (ali > 20 %), što govori u prilog Glanzmannove trombastenije tip III. Naknadno su u serumu bolesnice dokazana i antitrombocita autoprotutijela na GPIIb/IIIa i Ia/IIa kompleks uz genotipizacijom prisutne sve specifične trombocitne antigene. Ovakav nalaz mogao je ukazati i na pseudo-Glanzmannovu trombasteniju. S obzirom na prisutna autoprotutijela i rizik neonatalne trombocitopenije, bolesnica je liječena korikosteroidima i intravenskim imunoglobulinima. Tijekom hospitalizacije dolazi do pojave trudova s 38+1 tjedana gestacije te se pristupi vaginalnom porođaju, koji je protekao uredno. Postpartalno je primila profilaktički rFVIIa u dozi od 90 µg/kg intravenski svaka 3 sata do ukupno 4 doze, uz uterotonik (oksitocin 5 međunarodnih jedinica) te traneksamičnu kiselinu 3 x 1 g tijekom 10 dana, bez potrebe za primanjem transfuzije trombocita. Uz terapiju nije bilo znakova pojačanog krvarenja niti neonatalne trombocitopenije. U kontroli se prati negativizacija antitrombocitnih protutijela, dok poremećaj agregacija trombocita perzistira.

ZAKLJUČAK: Iako je došlo do značajnog napretka u razumijevanju funkcije trombocita, nasljedni poremećaji trombocita još uvijek su u velikoj mjeri nepoznanica, a dijagnostika ne mora dovesti do jednoznačnog zaključka. Važan je multidisciplinaran pristup te pravodobno prepoznavanje i optimiziranje liječenja, što ima dodatno značenje u trudnoći zbog dodatnih rizika za majku i plod.

Ključne riječi: trudnoća, Glanzmannova trombastenija, pseudo-Glanzmannova trombastenija, anti-GPIIb/IIIa protutijela

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UVOD

Glanzmannova trombastenija je rijedak nasljedni poremećaj trombocita koji obilježava poremećaj u glikoproteinskom IIb/IIIa kompleksu na membrani trombocita uz posljedičnu narušenu agregaciju trombocita. GP IIb/IIIa kompleks (αIIbβ3) je adhezijski receptor koji pripada integrinskoj superobitelji. Njegova je glavna funkcija vezanje fibrinogena, vWF-a (von Willebrandov faktor), fibronektina i vitronektina te je nužan za agregaciju trombocita. Bolest se nasljeđuje autosomno recesivno, s incidencijom 1:1 000 000 uz više od 70-ak mutacija zabilježenih u genima ITGA2B ili ITGB3 (1, 2). Ovisno o količini i funkciji glikoproteinskog kompleksa, dijeli se na tri tipa: kvantitativni tip I (< 5 % GPIIb/IIIa) i tip II (10 do 20 % GPIIb/IIIa) te kvalitativni tip III s poremećenom funkcijom kompleksa (1, 2). Fenotip je varijabilan, a najčešće se očituje krvarenjima kože i sluznica, dominantno epistaksom i gingivalnim krvarenjem, već u ranoj životnoj dobi (3, 4). Za dijagnostiku je važan izostanak agregacije trombocita sa svim agonistima trombocita osim s ristocetinom, a dijagnoza se može potvrditi i uz pomoć protočne citometrije određivanjem količine GIIb/IIIa na membrani trombocita (3). Broj i veličina trombocita su normalni. Liječenje epizoda krvarenja sastoji se od primjene antifibrinolitika, transfuzija koncentrata trombocita te rekombinantnog FVIIa (1, 3, 4).

Cilj je ovog rada prikazati rijedak slučaj trudnice s Glanzmannovom trombastenijom i dokazanim antitrombocitnim protutijelima.

PRIKAZ SLUČAJA

Bolesnici je u dobi od 13 godina u sklopu obrade gingivalnog krvarenja i povremenih spontanih hematoma dijagnosticirana Glanzmannova trombastenija na temelju nalaza agregacije trombocita. Obiteljska anamneza na poremećaje krvarenja bila je negativna. Tijekom adolescencije i poslije nije imala značajnijih krvarenja osim povremenog gingivalnog krvarenja tijekom pranja zubi i nije se javljala hematologu.

U dobi od 28 godina premještena je iz vanjske ustanove u Zavod za hematologiju Kliničkog bolničkog centra

Tablica 1. *Pacijentičin nalaz testova funkcije trombocita uz izostanak agregacije trombocita sa svim agonistima osim s ristocetinom (ADP - adenozin difosfat, adrenalin, arahidonska kiselina, kolagen)*

Test	Vrijednost	Jedinica	Referentni Interval
PV	1,2		> 0,7
APTV	25,8	s	20 - 30
Fibrinogen	5,2	g/l	1,8 – 4,1
PFA Adrenalin/Kolagen	> 244	s	80 - 160
PFA ADP/kolagen	> 284	s	60 - 120
Agregacija trombocita s ADP-om	0	%	> 61
Agregacija trombocita s adrenalinom	3	%	> 58
Agregcija trombocita s arahidonskom kiselinom	6	%	> 61
Agregadja trombocita s kolagenom	0	%	> 64
Agregacija trombocita s ristocetinom	79	%	> 58
VWF - aktivnost	200,4	%	49,5 - 187

PV - protrombinsko vrijeme, APTV - aktivirano parcijalno tromboplastinsko vrijeme, PFA - analizator funkcije trombocita (engl. *platelet function analyzer or platelet function assay*), ADP - adenozin difosfat, VWF – Von Willebrandov faktor

Tablica 2. *Pacijentična imunofenotipizacija trombocita periferne krvi - izražaj glikoproteinskog kompleksa GP IIb/IIIa (CD41/CD61) na površini trombocita*

Trombocitni biljeg	Rezultat	Jedinica	Referentna vrijednost
CD41	63	%	> 90
CD42b	98	%	> 90
CD61	40	%	> 90

CD - klaster diferencijacije (engl. *cluster of differentiation*)

(KBC) Zagreb u 37. tjednu do tada uredne trudnoće radi promatranja i liječenja epistakse. Iz anamneze i medicinske dokumentacije doznaje se kako je prethodno imala dvije neuspješne trudnoće (obje završile spontanim pobačajem u 8. tjednu). U aktualnoj trudnoći nije bilo epizoda vaginalnog ili drugog krvarenja, a tijek trudnoće bio je do tada potpuno uredan i nadziran od strane primarnog ginekologa. Prije premještaja u vanjskoj je ustanovi učinjena tamponada nosa te je primila prvu transfuziju koncentrata trombocita (pool trombocita, ABO podudarni), što je uobičajena terapija kod krvarenja u bolesnika s poremećajem primarne hemostaze. Neposredno prije nastupa krvarenja preboljela je blažu infekciju gornjeg dišnog sustava. Učinjena virusološka obrada na najčešće uzročnike bila je negativna. Ginekološkim pregledom nije nađeno znakova krvarenja niti znakova zastoja u razvoju ploda.

U KBC-u Zagreb učinjena je dodatna laboratorijska obrada koja je uključivala i specifične testove hemostaze. U laboratorijskim nalazima zabilježen je hemoglobin od 118 g/l, uz uredne vrijednosti parametara u ferogramu te uredne vrijednosti i veličinu trombocita. Testovima primarne hemostaze uočen je izostanak agregacije trombocita sa svim agonistima osim s ristocetinom (Tablica 1.), produljeni testovi funkcije trombocita (PFA – engl. *platelet function assay or platelet function analyser*), dok se imunofenotipski na površini trombocita dokaže sniženi izražaj GPIIb/IIIa (ali > 20 %), što govori u prilog kvalitativnog poremećaja, odnosno Glanzmannove trombastenije tip III (Tablica 2.). Testovi sekundarne hemostaze bili su uredni.

Naknadno su u serumu bolesnice metodom na mikrosferama dokazana i polispecifična IgG antitrombocitna autoprotutijela na GPIIb/IIIa i Ia/IIa kompleks (LIFECODES Pak Lx Assay, Immucor, Waukesha, SAD). Antitrombocitna aloprotutijela nisu dokazana u serumu.

S obzirom na navedeno, u konzultaciji s transfuziolozima učinjena je genotipizacija specifičnih trombocitnih antigena te je utvrđena prisutnost gena HPA (engl. *human platelet antigens*) za pojedine specifične antigene HPA koji se nalaze na GPIIb/IIIa kompleksu (ID HPAXT, Grifols, Barcelona, Španjolska). Ovakav nalaz može govoriti u prilog i pseudo-Glanzmannove trombastenije, odnosno stečenog poremećaja uzrokovanog autoprotutijelima koja se vežu za GP IIb/IIIa kompleks i inhibiraju njegovu funkciju. Učinjena je dodatna imunološka obrada radi isključenja podležeće sustavne autoimunosne bolesti koja je uključivala sljedeće testove: ANA (antinuklearna antitijela), ANCA (anti-neutrofilna citoplazmatska antitijela), ENA (ekstraktibilni nuklearni antigeni), C3, C4 sastavnice komplementa i ukupni komplement, što je sve bilo negativno. Nije nađeno znakova druge hematološke bolesti.

S obzirom na prisutna autoprotutijela i rizik neonatalne trombocitopenije, bolesnica je liječena intravenskim imunoglobulinima (IVIG) 30 g/dan tijekom tri dana uz metilprednizolon 1 mg/kg. Tijekom hospitalizacije s 38+1 tjedana gestacije dolazi do pojave trudova te je premještena u Odjel rađaonice Klinike za ženske bolesti i porode KBC-a Zagreb. S obzirom na povoljan opstetrički nalaz i dobre trudove, kao i činjenicu da se kod porođaja carskim rezom očekuje u pravilu obilnije krvarenje, u ovom je slučaju odlučeno porođaj voditi vaginalnim putem. Porođaj je bio potpuno urednog tijeka te je nakon pet sati njegove aktivne faze bolesnica uredno vaginalno rodila živo doneseno žensko novorođenče (tjelesne mase 2850 g, duljine 46 cm) urednih ocjena vitalnosti po Apgarovoj ljestvici. Postpartalno je bolesnica profilaktički primila rFVIIa u dozi od 90 µg/kg intravenski svaka tri sata do ukupno četiri doze uz uterotonik (oksitocin 5 međunarodnih jedinica) i traneksamičnu kiselinu 3 x 1 g tijekom 10 dana, bez krvarećih komplikacija i bez potrebe za transfuzijom koncentrata trombocita.

Uz terapiju nije bilo znakova pojačanog krvarenja niti neonatalne trombocitopenije. Četiri mjeseca nakon poroda u bolesnice se prati negativizacija antitrombocitnih protutijela uz i dalje prisutan patološki nalaz testova funkcije trombocita, što govori u prilog nasljednom funkcionalnom poremećaju trombocita.

RASPRAVA

Trudnoća i porođaj u bolesnica s Glanzmannovom trombastenijom predstavljaju rizično razdoblje za krvarenje te zahtijevaju multidisciplinarni pristup i unaprijed osmišljen plan liječenja i porođaja (1, 5, 6). Čak i unatoč profilaksi, prevalancije krvarenja kod porođaja je velika i iznosi oko 40 - 50 % (1). Upravo iz tih razloga potrebno je već antenatalno procijeniti rizik krvarenja i u majke i u ploda, dominantno na temelju prethodne opstetričke anamneze koja uključuje podatke o neonatalnoj trombocitopeniji i intrakranijskom krvarenju te anti-GPIIb/IIa imunizacijskom statusu majke. Prva linija liječenja teškog krvarenja je transfuzija trombocita, ali oko 15 - 30 % bolesnika postaje refraktorno na transfuziju, a značajan dio razvija protutijela protiv GP IIb/IIIa ili HLA (od engl. *human leukocyte antigen*, ljudski leukocitni antigeni). U bolesnica s Glanzmannovom trombastenijom tip I, obiteljskom anamnezom imunizacije te bialelnim nul mutacijama u genima ITGA2B ili ITGB3 postoji povećan rizik razvoja anti-GP IIb/IIIa protutijela. [1] Protutijela se mogu razviti kao odgovor na transfuziju trombocita ili nakon izlaganja fetalnim trombocitima tijekom trudnoće. Glavni fetalni rizik predstavlja prolazak majčinih protutijela kroz placentu uzrokujući fetalnu/neonatalnu trombocitopeniju i povećavajući rizik intrakranijskog krvarenja (2, 7). Upravo iz toga razloga u slučaju visokog titra protutijela preporučuje se antenatalna primjena IVIG-a i kortikosteroida počevši od 20. do 22. tjedna trudnoće, a u slučaju prethodno dokumentirane neonatalne trombocitopenije i prije, već od 12. do 16. tjedna (1).

U naše bolesnice verificirana su protutijela protiv GP IIb/IIIa kompleksa. Sam titar protutijela nije bilo moguće kvantificirati u našem laboratoriju, no s obzirom na činjenicu da su detektirana, iako se radilo već o kasnoj fazi trudnoće, odlučili smo se za primjenu IVIG-a i kortikosteroida radi smanjivanja rizika krvarenja u novorođenčeta te eventualnog utjecaja na inhibicijska protutijela ako se radi o autoimunoj trombocitopatiji. Stečene trombocitopatije su rijetke, mogu biti inducirane lijekovima ili autoimunosne etiologije, a u podlozi se najčešće nalazi neka druga autoimunosna ili limfoproliferativna bolest, iako su opisani i idiopatski slučajevi (8, 9). U naše bolesnice obradom nije verificirana druga sustavna autoimunosna ili zloćudna bolest, postojao je samo anamnestički podatak o prethodno preboljeloj virusnoj infekciji. Na temelju nalaza imunofenotipizacije, gdje je prisutan izražaj glikoproteinskog kompleksa u dovoljnom broju uz dokazana autoprotutijela, inicijalno nije bilo moguće odrediti radi li se o Glanzmannovoj trombasteniji tip III ili pseudo-Glanzmannovoj trombasteniji. Za konačnu potvrdu/isključenje dijagnoze trebalo bi napraviti genetičko testiranje, koje za sada u našim uvjetima nije moguće.

U bolesnica s utvrđenim protutijelima (anti-HLA ili anti- GP IIb/IIIa) preporučuje se uz rutinsku profilaktičku postpartalnu primjenu uterotonika (oksitocina) i traneksamične kiseline 1g intravenski nakon podvezivanja pupčane vrpce primijeniti i rekombinantni FVIIa u dozi od 90 μg/kg unutar prvih 5 minuta nakon porođaja te potom svaka 2 do 3 sata do postizanja hemostaze, dok se transfuzije trombocita primjenjuju samo u slučaju obilnog krvarenja. Dodatne doze mogu se primijeniti u slučaju velikog rizika ili postpartalnog krvarenja. Što se metoda porođaja tiče (vaginalni ili carski rez) treba razmotriti obje opcije uzimajući u obzir rizik od neonatalne trombocitopenije, povijest krvarenja majke i opstetričke uvjete. Epiduralna analgezija je apsolutno kontraindicirana zbog povećanog rizika nastanka epiduralnog ili spinalnog hematoma. Sekundarno postpartalno krvarenje može se pojaviti čak i nakon 6 do 8 tjedana, uz medijan vremena 10 dana nakon porođaja (1, 5, 6).

S obzirom na povoljan opstetrički nalaz i dobre trudove, kao i činjenicu da se kod porođaja carskim rezom očekuje u pravilu obilnije krvarenje, u ovom slučaju odlučeno je porođaj voditi vaginalnim putem jer se ovaj način smatrao poštednijim za majku. Što se tiče rizika krvarenja u neonatusa, vjerovali smo da će provedeno liječenje imunoglobulinom i kortikosteroidima utjecati na njegovo smanjenje, premda titar protutijela nije bilo moguće kvantificirati u našem laboratoriju.

Pacijentica je odmah nakon vaginalnog poroda primila profilaktički rekombinantni FVIIa uz uterotonik i traneksamičnu kiselinu, koju je nastavila primati do 10 dana nakon poroda u bolničkim uvjetima. Uz naveden pristup nije bilo znakova pojačane hemoragijske dijateze.

U kontroli bolesnice nakon porođaja prati se negativizacija autoprotutijela dok poremećena funkcija trom-

bocita perzistira. Testiranjem novorođenčeta odmah nakon poroda zabilježene su uredne vrijednosti trombocita bez kliničkih i radioloških znakova intrakranijskog krvarenja, dok testovi agregacije trombocita nisu još učinjeni.

ZAKLJUČAK

Iako je došlo do značajnog napretka u razumijevanju funkcije trombocita, nasljedni poremećaji trombocita još uvijek su u velikoj mjeri nepoznanica, a dijagnostika ne mora dovesti do jednoznačnog zaključka. Važan je multidisciplinaran pristup te pravodobno prepoznavanje i optimiziranje liječenja, što ima dodatno značenje u trudnoći zbog dodatnih rizika za majku i plod.

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SUMMARY

PREGNANT WOMAN WITH GLANZMANN THROMBASTHENIA – A CASE REPORT

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INTRODUCTION: Glanzmann thrombasthenia is a rare hereditary platelet disorder characterized by a genetically determined disorder in the glycoprotein IIb/IIIa complex with a consequent disorder of platelet aggregation. To confirm the diagnosis, the absence of platelet aggregation to all agonists except ristocetin and the determination of the amount of GIIb/IIIa on the platelet membrane are important. The phenotype is variable, and is most often manifested by bleeding of the skin and mucous membranes. Treatment of bleeding episodes comprises the use of antifibrinolytics, platelet transfusions, and recombinant FVIIa.
OBJECTIVE: To present a rare case of a pregnant woman with Glanzmann thrombasthenia and proven antiplatelet antibodies.
CASE REPORT: At the age of 13, the patient was diagnosed with Glanzmann thrombasthenia based on the findings of platelet aggregation as part of the work-up for gingival bleeding, after which she had no significant bleeding and did not see a hematologist. At the age of 28, in the 37th week of a previously normal pregnancy, the patient was transferred from an external institution to the Department of Hematology of the University Hospital Center (UHC) Zagreb for observation and treatment of epistaxis. Nasal tamponade was performed in the external institution and she received a platelet concentrate transfusion. In UHC Zagreb, the work-up revealed normal values and morphology of platelets and the absence of platelet aggregation with all agonists except ristocetin. Extended tests of platelet function demonstrated immunophenotypically reduced expression of GPIIb/IIIa (but > 20 %) on the surface of the platelets, which indicated Glanzmann thrombasthenia type III. Subsequently, antiplatelet autoantibodies to the GPIIb/IIIa and Ia/IIa complex were demonstrated in the patient's serum, along with all specific platelet antigens present by genotyping. This finding could also indicate pseudo-Glanzmann thrombasthenia. Considering the presence of autoantibodies and the risk of neonatal thrombocytopenia, the patient was treated with corticosteroids and intravenous immunoglobulins. During the hospitalization, she went into labor at 38+1 weeks of gestation, and proceeded to a vaginal birth, which went smoothly. Postpartum, she received prophylactic rFVIIa in a dose of 90 μg/kg intravenously every 3 hours, up to a total of 4 doses with uterotonic (oxytocin 5 international units) and tranexamic acid 3 x 1 g during 10 days, without the need to receive a platelet transfusion. Upon treatment, there were no signs of increased bleeding or neonatal thrombocytopenia. During follow-up negativization of antiplatelet antibodies occurred, while the aggregation disorder persisted.
CONCLUSION: Although there has been significant progress in the understanding of platelet function, hereditary platelet disorders are still largely unknown, and diagnostics do not necessarily lead to an unequivocal conclusion. A multidisciplinary approach as well as timely recognition and optimization of treatment are important, especially in pregnancy, due to additional risks for both mother and fetus.

Keywords: pregnancy, Glanzmann thrombasthenia, pseudo-Glanzmann thrombasthenia, anti-GPIIb/IIIa antibodies

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