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Letter from the Editor-in-Chief
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Dear colleagues,

It is my great pleasure to present the latest issue of Medical Research. As the journal grows, we're committed to making it a relevant scientific platform nationally and across the region.

In recent years, Medical Research has made important progress in improving the quality, visibility, and diversity of published research. This issue reflects our ongoing commitment to supporting multidisciplinary collaboration and fostering knowledge exchange among researchers and clinicians from diverse fields and countries.

We are particularly proud to contribute to the development of regional scientific capacity by providing a space for high-quality research that addresses locally relevant challenges while meeting international standards.

I would like to sincerely thank all authors, reviewers, and members of the editorial board for their continued trust and contribution to the journal's growth.

We hope that this issue will inspire further research, collaboration, and innovation in the field of medical sciences.

Sincerely,

Prof. Dragana Protic, MD, PhD

Editor-in-Chief

ORIGINAL ARTICLE

Hyperthermic intrathoracic chemotherapy (HITHOC) - a tertiary oncological center experience

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Summary

Introduction: This study aimed to present our experience with HITHOC in the field of multimodality treatment of heterogeneous, potentially resectable, chemotherapy-sensitive pleural malignancies—primary and metastatic—limited to the unilateral thoracic inlet.

Methods: The research included all patients who underwent a HITHOC procedure with CRS at the Institute for Oncology and Radiology of Serbia from January 2018 to December 2024. The indications for procedure were: resectable chemo-sensitive primary or residual/recurrent thoracic malignancies confined to one side of the thorax, and various metastatic diseases restricted to the unilateral thoracic inlet with achieved local disease control. HITHOC was performed with cisplatin (100 mg/m2 in 1000 ml of 5 % glucose, gradually heated to 42 °C) perfusion lasting 90 minutes.

Results: Eleven patients were included in the study, with a mean age of 48.27 ± 18.37 years. The most common tumor pathology was thymoma, followed by malignant pleural tumors. Other tumor pathologies included ovarian cancer, Ewing's sarcoma, alveolar rhabdomyosarcoma, and lung cancer. Average follow-up was 41,73 (median: 35; range: 2-72) months. The overall survival rate was 64%.

Conclusion: HITHOC procedure can be regarded as a safe, feasible, and effective approach for well-selected patients. It could be beneficial not only for its current indications, but also for chemosensitive pleural malignancies, both primary and metastatic, limited to the unilateral thoracic inlet.

Keywords: HITHOC, hyperthermic intrathoracic chemotherapy, pleural malignancies, indications, survival

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INTRODUCTION

Hyperthermic intrathoracic chemotherapy (HITHOC) involves the application of elevated temperature and a high dose of a cytotoxic drug to tumor cells. HITHOC is a synergistic interaction that improves local disease control, prolongs survival, and advances the quality of life. Introducing a cytotoxic drug into the thoracic cavity provides direct exposure of tumor cells to the drug, has better pharmacokinetic characteristics, and avoids the side effects of a systemically administered drug. In hyperthermia, the penetration of cytostatic medicines is increased, thereby increasing cytotoxic effects on tumor cells (1).

Hyperthermic perfusion of cytotoxic drugs directly into the cavity-peritoneum was first used in 1980 in a canine model for the treatment of metastatic effusion from cancer in the abdomen (2). The first report on HITHOC for treating malignant pleural seeding or pleural effusion was published in 1995 by Matsuzaki et al (3). HITHOC is only used if there is no tumor outside the thoracic cavity, and it may be used alone or as adjuvant therapy to cytoreductive surgery (CRS). Surgical removal of all visible tumor lesions in the thorax (CRS) is an important factor in the effectiveness of the HITHOC, because cytotoxic drug penetration is limited to 3-4 mm into residual microscopic deposits (4).

The primary tumors responsible for malignant pleural effusion that have shown improvement with HITHOC include malignant mesothelioma (MPM), thymic malignancies, and lung cancer (5), despite techniques and approaches for the treatment of pleural malignancies still being unclear and having not been standardized to date. Also, in the literature, some studies suggest additional indications for HITHOC.

This study aimed to present our 6 years' experience with HITHOC as a multimodal treatment for resectable, chemosensitive, unilateral, primary, or metastatic pleural malignancies.

MATERIAL AND METHODS

In this case series, we included all patients (n = 11) diagnosed with primary or secondary pleural malignancies who underwent HITHOC procedure combined with CRS at the Institute for Oncology and Radiology of Serbia, during the period from January 2018 to December 2024. The following data were collected and analyzed: demographics; pathohistological findings; initial oncological treatments; HITHOC procedure—indications and technique; postoperative period; and lethal outcomes.

This study extends our previously published work by Stojiljković et al. (6); additional patients have been treated at our oncology center using the same therapeutic approach under identical clinical indications. The extended follow-up period provides more powerful insights into the patterns of intrathoracic and distant disease recurrence and mortality, as well as into practice guidelines for optimal standardization of HITHOC in pleural malignancies.

This scientific research study was approved by the Ethics Committee of the Institute for Oncology and Radiology of Serbia with the number 01-1/2025/2028 (date, July 4, 2025).

In brief, the indications for HITHOC with CRS were: resectable chemo-sensitive primary or metastatic (with achieved local disease control) thoracic malignancies confined to one side of the thorax. Patients with contralateral thoracic tumor implants or extra-thoracic metastases, as well as patients with compromised cardiopulmonary function or suffering from renal insufficiency, were excluded. Before surgery, all patients signed an informed consent. CRS was performed as an open chest surgery under general anesthesia. Intraoperative monitoring of central body temperature was performed with an esophageal probe and regulated using cooling solutions injected through the central venous catheter or warming/cooling blankets. Postoperatively, all patients were monitored at the Intensive Care Unit.

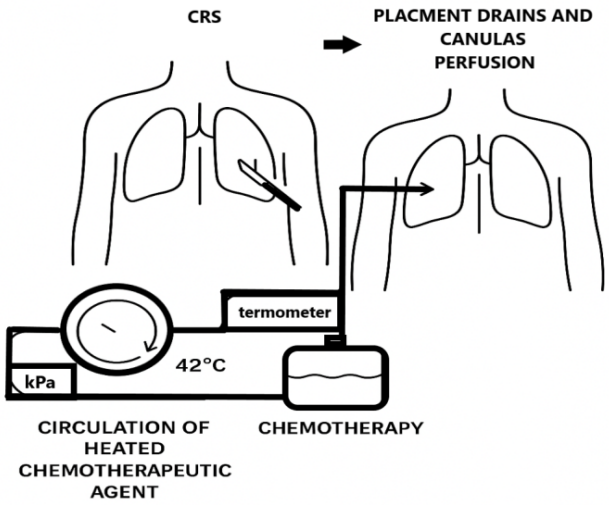

Figure 1. CRS+HITHOC procedure

CRS+HITHOC procedure is presented in **Figure 1**.

RanD® Performer perfusion system is used with cisplatin as a cytotoxic agent. The standard administered dose of cisplatin is 100 mg/m2, adjusted for creatinine clearance. A single medical oncologist calculates the drug concentration needed for each patient, taking into account the patient's comorbidities, previous systemic treatments (with particular attention to cumulative dosage), and body weight and height. Primarily, patients with pleural carcinoma localized to one hemithorax undergo cytoreductive surgical therapy. The goal of the cytoreductive surgical approach is to remove all macroscopically visible tumor lesions localized on one side of the pleural cavity.

After achieving adequate resection, the patient is connected to the RanD® Performer perfusion system by plac-

ing four drains (28 F chest tubes), two inflow and two outflow, with additional fifth superficial chest tube for fluid level control. Each tube is connected to the RanD Performer device. The next step consists of priming solution (1000 ml of 5 % glucose, 38°C), which is once inserted into the pleural space, and gradually heated until the target temperature of 42°C is achieved. In those conditions, cisplatin is added, and the intracavitary circulation of the cytostatic is extended to 90 minutes. The final step is to wash out the dissolved cisplatin using a catheter with reversed inflow and outflow. Suctioning of the remaining substance is achieved using two chest drains in anterior and posterior positions, with suction set at 15-25 cm H2O, before closing the chest in a standard manner.

For the description of relevant parameters, depending on their nature, descriptive statistical measures were used: Frequencies, percentages, mean value (average), median, standard deviation (SD), and range (span). Overall survival was presented using the Kaplan-Meier product-limit method, and the description included a median survival analysis.

RESULTS

Demographic characteristics, pathohistological diagnosis, and initial oncological treatments in patients

The study included 11 patients who underwent a HITHOC procedure with CRS. The mean age of patients was 48.27 ± 18.37 (median: 55, range: 16 – 68) years, and the female-to-male ratio was 5:6. The most common tumor pathology was thymoma, histopathological subtype B (4 patients), followed by malignant pleural tumors (mesothelioma and malignant solitary fibrous tumor of the pleura-3 patients). Other tumor pathologies included one patient each for ovarian cancer, Ewing's sarcoma, alveolar rhabdomyosarcoma, and lung cancer. Oncological treatments before HITHOC with CRS for cystadenocarcinoma serosum ovarii (G2, NG2, with peritoneal carcinomatosis) included CRT with hyperthermic intraperitoneal chemotherapy followed by adjuvant chemotherapy (paclitaxel+carboplatin) (1 patient, female, 48 years old) or bilateral adnexectomy (1 patient, female, 62 years old); for malignant pleural tumor included tumor excision (2 patients, males, 55 and 63 years old) + systemic chemotherapy (1 patient, male, 68 years old), for thymoma (B2, type, Ki67 70-90%) included thymomectomy with atypical lung resection (1 patient, male, 62 years old), thymomectomy with systemic chemotherapy (paclitaxel, adriamycin and cisplatin), adjuvant irradiation and second-line chemotherapy (ifosfamide, oncovin, adriamycin) due to intrathoracic relaps 165 months after last treatment (1 patient, male, 45 years old) or thymomectomy and adjuvant irradiation (1 patient, female, 59 years old); for Ewing Sarcoma of the sacral bone, conventional subtype (1 patient, female, 19 years old) radiotherapy and chemotherapy (first-line to fourth line) and lung surgery (1 patient, female, 19 years old); specific oncological treatments for Li-Fraumeni syndrome (unilateral breast high-grade phyllodes tumor, rosette-forming glioneuronal tumor of the 4th ventricle, adrenocortical carcinoma and pheochromocytoma) (1 patient, female, 32 years old), and for alveolar rhabdomyosarcoma (chest wall tumor mass, localized in the 7-8th intercostal space, with suspicious pleural nodules) initial chemotherapy (1 patient, male, 16 years old).

HITHOC with CRS

The extent of CRS depended on the size, number, and localization of tumor masses within one side of the chest. In 11 patients, all macroscopically visible tumor tissue was removed from the thoracic cavity, and upon receiving the definitive pathohistological results, R0 resection was confirmed. The duration of the heated cytotoxic agent (cisplatin) circulation within the thoracic cavity was 90 minutes. All HITHOC procedures with CRS were uncomplicated, both intraoperatively and postoperatively.

Postoperative follow-up and oncological results, survival time following HITHOC with CRS

Following hospital discharge, all patients underwent evaluation by multidisciplinary teams, and 6 of 11 subsequently received further oncological therapy (chemotherapy, irradiation) according to disease-specific protocols. Out of a total of 11 patients, a lethal outcome was noted in four, among whom were patients with metastatic disease (ovarian cancer and Ewing sarcoma), as well as patients with primary intrathoracic tumors (malignant mesothelioma and solitary malignant pleural tumor), initially graded as stage IV. The overall survival rate was 64%.

Table 1 presents the median overall survival time (MOS) for patients who underwent the HITHOC procedure as part of multimodal treatment, depending on pathology and disease stage. The mean follow-up time after the HITHOC procedure was 41.73 months (median: 35; range: 2-72). The median survival after HITHOC was 72 months **(Figure 2)**.

All patients in our study with thymoma are still alive, with a mean follow-up of 43.6 months (median 33, range 23–71) in stage IVa. Given that the majority of our patients remain alive, ongoing monitoring is maintained. Based on the data from deceased patients, it can be concluded that patients treated with the HITHOC procedure, as part of multimodal therapy, showed a longer survival time than expected.

Table 1. The expected survival time based on disease stage and follow-up

Tumor type	Disease stage	MOS witout HITHOC (months)	Follow-up MAX (months)
MSFTP	no TNM	94.4	51+
Thymoma	I	166	48+
Lung adenocarcinoma	IIIa	27-34	2+
Alveolar rhabdomyosarcoma	IV	NA	54+
Malignant mesothelioma	IV	16	35
Ewing Sarcoma	IVa	16.8	32
Thymoma	IVa	98	71+
Ovarian carcinoma	IVb	31	72

Legend: MOS-median overall survival of patients treated with other forms of treatment without the HITHOC procedure, data taken from other publications; MSFTP-malignant solitary fibrous tumor of pleura; TNM-tumor, node, metastasis stage; NA-not applicable; Folow up MAX- the maximum follow-up duration of our patients treated with HITHOC; + - the patients remain alive and are maintained on a schedule of regular follow-up evaluations

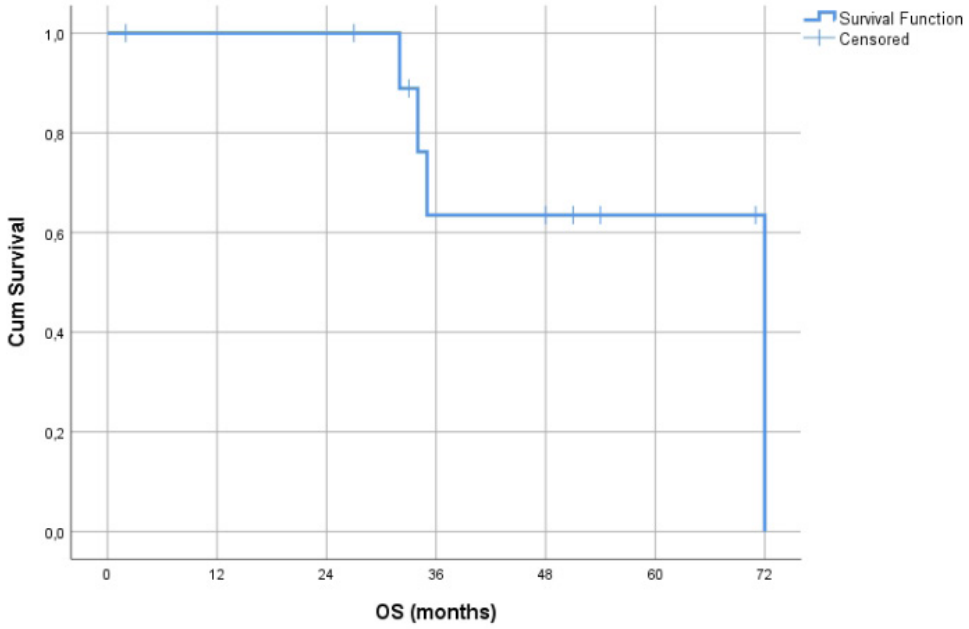

Figure 2. Overall survival (OS) after HITHOC

DISCUSSION

The HITHOC procedure has been utilized in thoracic surgery for over two decades. Nevertheless, its clinical implementation remains non-standardized with respect to crucial variables, such as cytotoxic drug dosage, perfusate volume, temperature, and perfusion duration. Despite this lack of uniformity, efforts to harmonize these parameters continue (7). In a review encompassing 27 studies, 8 identified cisplatin as the most frequently administered chemotherapeutic agent, followed by doxorubicin and mitomycin C. Reported perfusion temperatures ranged from 38 to 43 °C (8). Also, in some literature data, combinations of two cytotoxic agents are used for HITHOC. (9). Although a universal recommendation on the ideal cisplatin dose is lacking, most authors report using 80 - 250 mg/m^2 (10). In this study, we used a cisplatin dose of 100 mg/m2. At our institution, since the adoption of HITHOC, cisplatin has been the agent of choice in accordance with the national Health Insurance Fund guidelines. For priming, we use 1,000 mL of a 5% glucose solution. After introduction into the pleural cavity, the solution is progressively heated to a target temperature of 42 °C. Once the desired temperature is reached, cisplatin is added, and the perfusion is maintained for 90 minutes, although shorter durations are mentioned in some publications (11). This protocol has demonstrated no HITHOC-associated adverse effects while maintaining effective local disease control. The evidence, including data from this study, confirms that CRS combined with HITHOC is a safe, feasible, and effective treatment option for carefully selected patients (12-15). The majority of reports emphasize HITHOC therapeutic benefits in managing malignant pleural mesothelioma and pleural spread of thymoma, whether in stage IV, in "de novo" cases, or in recurrences (16). These conditions represent nearly half of the patients treated at our center. Furthermore, the literature suggests a growing interest in

expanding the indications for this approach, as supported by multiple studies (17-20).

In our study, four patients were diagnosed with thymoma. One of them was classified as stage I, while the remaining three had stage IVa disease, all of whom exhibited histopathological subtype B and a high proliferative index (Ki-67 exceeding 70%). Complete surgical resection remains the most important prognostic factor in thymoma, and surgery should always be considered when achieving complete resection is feasible. Some data suggest that for patients with stage I thymoma, the expected median overall survival reaches up to 166 months. When tumors are resectable in stage IV disease, the median survival drops to approximately 98 months (21). According to Raffael et al., the HITHOC procedure yielded promising results in stage IVa thymoma patients, with 90% survival at 3 years and 70% at 5 years following surgery. (22)

Further supporting these findings, a 2015 study on patients with recurrent pleural thymoma treated with HITHOC reported a mean follow-up time of 64.6 months (median: 78 months; range: 13–107 months). At that point, 85% of patients (11 individuals) were still alive, and 10 of them showed no evidence of disease (23).

As outlined in our results, all patients with thymoma in our cohort remain alive to date. Among those in stage IVa, the average follow-up duration was 43.6 months.

Malignant mesothelioma is typically associated with a poor prognosis, with median overall survival ranging from 9 to 12 months following diagnosis (24). For patients in advanced stages of malignant pleural mesothelioma, chemotherapy remains the cornerstone of treatment—either administered alone or in combination with radiotherapy and/or surgical intervention when the disease is deemed resectable.

In the case of biphasic malignant mesothelioma, as confirmed pathohistologically in our patient, recent publications (2022) report a median survival of approximately 16 months. Even among those who underwent pleurectomy/decortication followed by adjuvant chemotherapy or radiotherapy, recurrence of the disease was frequent and often quickly followed by a fatal outcome.

A 2017 quantitative meta-analysis of 5 studies found a statistically significant improvement in survival among malignant mesothelioma patients who underwent surgical treatment with the HITHOC procedure compared with those who did not (25).

Our patient with malignant mesothelioma underwent surgical resection combined with HITHOC, followed by adjuvant radiation therapy. Although the patient experienced disease recurrence during follow-up, survival was prolonged, and the patient passed away 35 months after the initial treatment.

One of the patients in our study, diagnosed with malignant solitary fibrous tumor of the pleura (MSFTP), was considered for reoperation due to an R1 resection following the initial surgery. Afterward, the patient received adjuvant chemotherapy—initially one cycle consisting of Adriamycin and Ifosfamide, followed by Carboplatin and Etoposide. However, an allergic reaction occurred, prompting a switch to second-line treatment with the VP16-CBDCA protocol. Despite these interventions, the patient experienced a lethal outcome 34 months after the initial follow-up began.

Another patient in our cohort, also diagnosed with MSFTP and treated using a comprehensive multimodal oncologic strategy, remains alive and under follow-up, now at 51 months.

According to the literature, patients with MSFTP had an estimated average survival of 94.4 months (30.6-124.9 months), and survival rates were 84% at 1 year, 67% at 3 years, and 55% at 5 years (26).

-In 2018, our oncology center performed its first HITHOC procedure on a 48-year-old female patient diagnosed with metastatic ovarian carcinoma (19). The initial treatment included CRS combined with hyperthermic intraperitoneal chemotherapy (HIPEC), followed by adjuvant chemotherapy. Due to peritoneal relapse, the patient underwent reoperation, which successfully controlled the local disease. However, 22 months later, pleural metastases appeared, localized to the unilateral thoracic inlet, making the patient eligible for CRS combined with HITHOC. While the typical overall survival for patients with this diagnosis is approximately 31 months, our patient survived six years following the HITHOC procedure. This was achieved despite multiple relapses and ongoing targeted oncological treatments, marking a significant advancement in therapeutic outcomes.

More recently, a case involving a 58-year-old patient with ovarian cancer accompanied by peritoneal and pleural carcinomatosis (27) has been reported. This case demonstrated the successful use of an integrated approach combining CRS and HIPEC, followed by CRS with HITHOC. During a 20-month follow-up period, the patient showed notable improvement in disease-free survival, with reduced recurrence rates and an overall survival exceeding expectations for standard treatment options. The application of HITHOC in managing this condition proved effective in controlling disease progression and alleviating symptoms related to advanced ovarian cancer.

-Sacral Ewing's sarcoma presents a considerable diagnostic challenge, largely due to its distinctive anatomical location. When considering the application of the HITHOC procedure in patients with Ewing's sarcoma, large-scale studies demonstrating its efficacy are scarce. This scarcity is understandable, given that this pathology represents less than 5% of all soft tissue sarcomas, according to NCBI data.

During our literature search, we identified a report describing the successful use of HITHOC in a 16-year-old adolescent treated at the Apollo Proton Cancer Centre in Asia (2022). Our patient, diagnosed with sacral bone

Ewing's sarcoma, began multimodal oncological therapy at age 13. By age 17, the disease had progressed to a metastatic stage and was managed according to standard protocols for this condition.

Since the metastatic disease was limited to one side of the thorax, with local control achieved but ongoing progression of intrathoracic involvement during the fourth line of chemotherapy, the decision was made at age 19 to perform CRS combined with HITHOC. Subsequent treatment included a fifth line of chemotherapy. Unfortunately, the patient experienced a lethal outcome 32 months following HITHOC treatment. However, it is important to note that the median overall survival for patients with this pathology is approximately 16.8 months. Remarkably, our patient, who received multimodal treatment including CRS and HITHOC, survived close to nine years from the initial diagnosis (28).

RMS is the most frequent soft tissue sarcoma among children and adolescents, accounting for approximately 3–4% of all pediatric cancers (29). The introduction of multi-agent chemotherapy has significantly improved the prognosis for children diagnosed with RMS. According to a multicenter study published in 2012, patients with alveolar RMS tend to have a poorer prognosis compared to those with embryonal RMS, with a 5-year overall survival rate of 21.9±6.1% (30).

A literature review reveals a lack of data on the application of the HITHOC procedure for this specific pathology. In our study, we treated one patient diagnosed with RMS. The disease was staged as IV using the modified TNM classification, due to the presence of pleural implants and the primary tumor originating from the chest wall (31).

Following initial chemotherapy, the patient achieved complete radiological regression. Given the chemo-sensitive nature of the primary tumor, which was confined to the unilateral thoracic inlet, the decision was made to perform radical parietal pleurectomy followed by HITHOC. Since that treatment, the patient has remained free of disease relapse and continues to be monitored, currently at 54 months of follow-up.

Stage III non-small cell lung cancer (NSCLC) represents a highly heterogeneous group of patients, distinguished by variations in disease extent and localization, with adenocarcinoma comprising approximately 50% of cases. Median survival tends to be higher in surgically treated patients than in those receiving other therapies, with survival rates ranging from 27 to 34 months in operable cases (32). Regarding the role of the HITHOC procedure in lung cancer management, studies indicate that HITHOC may improve survival for patients with malignant pleural effusion classified as M1a (stage IV) NSCLC (33,34).

The final patient in our study initially underwent oncological treatment for a borderline seromucinous ovarian tumor, which included bilateral adnexectomy. Thirty-six months later, a biopsy of a lung lesion performed at an outside facility confirmed metastatic disease originating from the ovarian tumor. Subsequent treatment consisted of chemotherapy, followed by CRS combined with the HITHOC procedure at our center. Definitive histopathological analysis identified the lesion as mucinous adenocarcinoma of the lung (T4N0M0). Two months post-surgery, the patient remains under regular follow-up.

Given that our two patients with pleural metastases originating from primary tumors outside the thoracic cavity (ovarian cancer and Ewing sarcoma) had undergone extensive oncological treatments over several years, as well as a patient with alveolar rhabdomyosarcoma—a pathology not previously reported for HITHOC treatment—showed favorable local disease control following CRS plus HITHOC, we believe that HITHOC's application may extend beyond established indications. This approach holds promise for select cases involving heterogeneous, chemo-sensitive, and potentially resectable primary or metastatic pleural malignancies confined to the unilateral thoracic inlet, without compromising any future systemic therapies.

CONCLUSION

The median overall survival time for patients who received the HITHOC procedure as part of multimodal treatment is longer than for those who did not, depending on pathology and disease stage. Patients with stage IV tymoma have the highest survival rate. As the sole center in Southeastern Europe offering the HITHOC procedure, our experience with 11 patients, though limited in scale, provides meaningful insights. However, comprehensive, multicenter studies are necessary to establish definitive evidence regarding its oncological efficacy.

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Author contributions: D.S. made the design of the work, acquired the data, analyzed and interpreted the data, prepared the draft and revised the version of manuscript, final approval of the sent version for publishing; S.M. acquired the data, analyzed and interpreted the data, prepared the draft and revised the version of manuscript, final approval of the sent version for publishing; A.C. made the design of the work, acquired the data, analyzed and interpreted the data, prepared the draft and revised the version of manuscript, final approval of the sent version for publishing; V.C. acquired the data, analyzed and interpreted the data, prepared the draft of manuscript, final approval of the sent version for publishing; A. A. analyzed and interpreted the data, prepared the draft and revised the version of manuscript, final approval of the sent version for publishing; T. S. analyzed and interpreted the data, revised the version of manuscript, final approval of

the sent version for publishing; I. S. analyzed and interpreted the data, revised the version of manuscript, final approval of the sent version for publishing.

Ethical approval: This scientific research study was approved by the Ethics Committee of the Institute for Oncology and Radiology of Serbia with the number 01-1/2025/2028; date approved by the Ethics Committee: July 4 2025.

Informed consent: Written informed consent was obtained from the patients for the publication of this paper.

REFERENCES

1. Marksman M. Intraperitoneal chemotherapy. Semin Oncol. 1991;18:248–254.
2. Spratt JS, Adcock RA, Muskovin M, Sherrill W, McKeown J. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res 1980;40:256-260.
3. Y Matsuzaki, K Shibata, M Yoshioka, M Inoue, R Sekiya, T Onitsuka, et al. Intrapleural perfusion hyperthermo-chemotherapy for malignant pleural dissemination and effusion. Ann Thorac Surg. 1995;59(1):127–131. doi: 10.1016/0003-4975(94)00614-D
4. Cregan IL, Dharmarajan AM, Fox SA. Mechanisms of cisplatin-induced cell death in malignant mesothelioma cells: role of inhibitor of apoptosis proteins (IAPs) and caspases. Int J Oncol. 2013;42:444–452. doi: 10.3892/ijo.2012.1715
5. Ried M, Lehle K, Neu R, Diez C, Bednarski P, Sziklavari Z, et all. Assessment of cisplatin concentration and depth of penetration in human lung tissue after hyperthermic exposure. Eur J Cardiothorac Surg. 2015;47(3):563–566. doi:10.1093/ejcts/ezu217.
6. Stojiljkovic D, Santrac N, Mircic D, Ristic D, Stojiljkovic T, Cvetkovic A. Cytoreductive surgery and hyperthermic intrathoracic chemotherapy (HITHOC) in treatment of primary and metastatic pleural malignancies – is extension of indications possible? JBUON. 2021; 26(6): 2658-2663. ISSN: 1107-062525
7. Danuzzo F, Sibilia MC, Vaquer S, Cara A, Cassina EM, Libretti L, et all. The role of hyperthermic intrathoracic chemotherapy (HITHOC) in thoracic tumors. Cancers. 2024;16(14):2513. doi:10.3390/cancers16142513.
8. Zhou H, Wu W, Tang X, Zhou J, Shen Y. Effect of hyperthermic intrathoracic chemotherapy (HITHOC) on the malignant pleural effusion: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(1):e5532. doi: 10.1097/MD.0000000000005532
9. Ambrogi MC, Bertoglio P, Aprile V, Chella A, Korasidis S, Fontanini G et al. Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: A 10-year experience. J Thorac Cardiovasc Surg. 2018;155(4):1857–1866.e2. doi:10.1016/j.jtcvs.2017.10.070.
10. van Ruth S, Baas P, Haas RL et al. Cytoreductive sur-gery combined with intraoperative hyperthermic in-trathoracic chemotherapy for stage I malignant pleural mesothelioma. Ann Surg Oncol 2003;10:176-82. doi: 10.1245/aso.2003.03.022
11. Tilleman TR, Richards WG, Zellos L, , Bruce E Johnson, Michael T Jaklitsch, Jordan Mueller, et al. Extrapleural pneumonectomy followed by intracavitary intraoperative hyperthermic cisplatin with pharmacologic cytoprotection for treatment of malignant pleural mesothelioma: a phase II prospective study. J Thorac Cardiovasc Surg. 2009;138(2):405–411. doi: 10.1016/j.jtcvs.2009.02.046
12. Yi E, Kim D, Cho S, Kim K, Jheon S. Clinical outcomes of cytoreductive surgery combined with intrapleural perfusion of hyperthermic chemotherapy in advanced lung adenocarcinoma with pleural dissemination. J Thorac Dis. 2016;8(7):1550–1560. doi: 10.21037/jtd.2016.06.04
13. Ambrogi MC, Bertoglio P, Aprile V, Chella, A., Korasidis, S., Fontanini, G.et al. Diaphragm and lung-preserving surgery with hyperthermic chemotherapy for malignant pleural mesothelioma: A 10-year experience. J Thorac Cardiovasc Surg. 2018;155(4):1857–1866. e2. doi: 10.1016/j.jtcvs.2017.10.070
14. Aprile V, Bacchin D, Korasidis S, Nesti A, Marrama E, Ricciardi R et al. Surgical treatment of pleural recurrence of thymoma: is hyperthermic intrathoracic chemotherapy worthwhile? Interact CardioVasc Thorac Surg 2020;30(5):765–772.) doi: 10.1093/icvts/ivaa019
15. Till Markowiak, Nadine Kerner, Reiner Neu, Tobias Potzger, Christian Großer, Florian Zeman, et al. Adequate nephroprotection reduces renal complications after hyperthermic intrathoracic chemotherapy. J Surg Oncol 2019;120:1220-6. doi.org/10.1002/jso.25726
16. William G Richards, Lambros Zellos, Raphael Bueno, Michael T Jaklitsch, Pasi A Jänne, Lucian R Chirieac, et al. Phase I to II study of pleurectomy/decortication and intraoperative intracavitary hyperthermic cisplatin lavage for mesothelioma. J Clin Oncol. 2006;24(10):1561–1567. doi: 10.1200/JCO.2005.04.6813
17. Aprile V, Bacchin D, Korasidis S, Ricciardi R, Petrini I, Ambrogi MC et al. Hyperthermic Intrathoracic Chemotherapy (HITHOC) for thymoma: a narrative review on indications and results. Ann Transl Med. 2021;9(11):957. doi:10.21037/atm-20-6704.
18. Zhou H, Wu W, Tang X, Zhou J, Shen Y. Effect of hyperthermic intrathoracic chemotherapy (HITHOC) on the malignant pleural effusion: A systematic review and meta-analysis. Medicine (Baltimore). 2017 Jan;96(1):e5532. doi:10.1097/MD.0000000000005532.
19. Stojiljkovic D, Nikolic S, Cvetkovic A, Jokic V, Spurnic I, Jokic S, et al. Hyperthermic intrathoracic chemotherapy (HITHOC) in ovarian carcinoma - a propos of a case. J B.U.ON. 2018;23(7):153–155. doi: 10.1016/j.ejso.2019.11.434
20. Hirozo Sakaguchi, H Ishida, H Nitanda, N Yamazaki, K Kaneko, Kunihiko Kobayashi, Pharmacokinetic evaluation of intrapleural perfusion with hyperthermic chemotherapy using cisplatin in patients with malignant pleural effusion. Lung Cancer. 2017;104:70–74. doi:10.1016/j.lungcan.2016.12.015
21. Smith A, Cavalli C, Harling L, Harrison-Phipps K, Routledge T, Pilling J et al. Impact of the TNM staging system for thymoma. Mediastinum. 2021;5. doi:10.21037/med-21-24.
22. Refaely Y, Simansky DA, Paley M, Gottfried M, Yellin A. Resection and perfusion thermochemotherapy: a new approach for the treatment of thymic malignancies with pleural spread. Ann Thorac Surg 2001;72:366-370. doi: 10.1016/s0003-4975(01)02786-2
23. Ambrogi MC, Korasidis S, Lucchi M, Fanucchi O, Giarratana S, Melfi F et al. Pleural recurrence of thymoma: surgical resection followed by hyperthermic intrathoracic perfusion chemotherapy. Eur J Cardiothorac Surg. 2016;49(1):321–326. doi:10.1093/ejcts/ezv039.
24. Curran, D., Sahmoud, T., Therasse, P., van Meerbeeck, J., Postmus, PE., & Giaccone, G. (1998). Prognostic factors in patients with pleural mesothelioma: the European Organization for Research and Treatment of Cancer experience. J clin. oncol. 1998;16(1):145-152. doi:10.1200/JCO.1998.16.1.145
25. Zhao Z, Zhao S, Ren M, Liu Z, Li Z, Yang L. Effect of hyperthermic intrathoracic chemotherapy on the malignant pleural mesothelioma: a systematic review and meta-analysis. Oncotarget. 2017;8:100640–100647. doi: 10.18632/oncotarget.22062
26. Nicholas DeVito, Evita Henderson, Gang Han, Damon Reed, Marilyn M Bui, Robert Lavey, et al. Clinical characteristics and outcomes for solitary fibrous tumor (SFT): A single center experience. PLoS One. 2015;10(10):e0140362. doi:10.1371/journal.pone.0140362.
27. Moldovan, B., Saon, CT, Adam, II, Pisica, RM, Silaghi, VT, Untaru, V,et all. Successful Implementation of HITOC and HIPEC in the Management of Advanced Ovarian Carcinoma with Pleural and Peritoneal Carcinomatosis. Diagnostics (Basel,), 14(5), 455. doi:10.3390/diagnostics14050455
28. Durer, S., Gasalberti, D. P., & Shaikh, H. (2024). Ewing Sarcoma. In StatPearls. Treasure Island (FL): StatPearls Publishing;2025.
29. McEvoy MT, Siegel DA, Dai S, Okcu MF, Zobeck M, Rajkumar V, et al. Pediatric rhabdomyosarcoma incidence and survival in the Unit-

ed States: An assessment of 5656 cases, 2001–2017. Cancer Med. 2024. doi:10.1002/cam4.5211.

30. Van Gaal JC, Van Der Graaf WT, Rikhof B, Van Hoesel QG, Teerenstra S, Albert J H Suurmeijer et al. The impact of age on outcome of embryonal and alveolar rhabdomyosarcoma patients. A multicenter study. Anticancer Res. 2012;32(10):4485–4497.
31. Crane JN, Xue W, Qumseya A, Gao Z, Arndt CAS, Sarah S Donaldson et al. Clinical group and modified TNM stage for rhabdomyosarcoma: A review from the Children's Oncology Group. Pediatr Blood Cancer. 2022;69(6):e29644. doi:10.1002/pbc.29644.
32. Casal-Mouriño, A., Ruano-Ravina A., Lorenzo-González M., Rodríguez-Martínez Á, Giraldo-Osorio A., Varela-Lema L., et al (2021). Epidemiology of stage III lung cancer: frequency, diagnostic characteristics, and survival. Transl lung cancer res., 2021; 10(1), 506–518. doi: 10.21037/tlcr.2020.03.40.
33. Yablonskii P, Nefedov A, Arseniev A, Andrey Kozak, Makhmud Mortad, Alexey Patsyuk. Non-small cell lung cancer, pleural effusion and carcinomatosis: always a criterion of inoperability? AME Med J. doi: 2020;5:10.
34. Migliore M, Nardini M. Does cytoreduction surgery and hyperthermic intrathoracic chemotherapy prolong survival in patients with N0-N1 non-small cell lung cancer and malignant pleural effusion? Eur Respir Rev. 2019;28:190018. doi:10.21037/atm-20-6514.

HIPERTERMIČKA INTRATORAKALNA HEMIOTERAPIJA (HITHOC) - ISKUSTVO TERCIJARNOG ONKOLOŠKOG CENTRA

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Sažetak

Uvod: Ova studija ima za cilj da predstavi naše iskustvo sa hipertermičkom intratorakalnom hemioterapijom (HITHOC) - procedurom u oblasti multimodalnog lečenja heterogenih, potencijalno resektabilnih, hemiosenzitivnih pleuralnih maligniteta, primarnih i sekundarnih, ograničenih na jednu polovinu grudne duplje.

Metode: Istraživanjem su obuhvaćeni svi pacijenti lečeni hipertermičkom intratorakalnom hemioterapijom (HITHOC) uz citoreduktivni hirurški tretman (CRH) u Institutu za onkologiju i radiologiju Srbije, u periodu od januara 2018. do decembra 2024. godine. Indikacije su bile: resektabilni hemiosenzitivni primarni ili rezidualni/rekurentni torakalni maligniteti ograničeni na jednu polovinu grudne duplje, kao i različite metastatske bolesti sa istim ograničenjem kod kojih je postignuta lokalna kontrola bolesti. Kod svih pacijenata HITHOC je izvođen perfuzijom cisplatinom tokom 90 minuta (100 mg/m^2 cisplatin u 1000 ml 5%-glukoze, postepeno zagrevana do 42 °C).

Rezultati: Studijom je prikazano 11 pacijenata, prosečnog uzrasta 48,27 ± 18,37 godina. Najčešća patologija tumora je timom, praćena pleuralnim primarnim malignitetima. Ostalu patologiju činili su karcinom jajnika, Ewing-ov sarkom, alveolarni rabdomiosarkom i karcinom pluća. Prosečno vreme praćenja pacijenata nakon procedure je 41,73 (medijana 35; opseg: 2-72) meseci. Ukupna stopa preživljavanja je 64%.

Zaključak: HITHOC procedura se može smatrati bezbednom i efikasnom metodom lečenja kod dobro odabranih pacijenata. Pokazuje korist ne samo za trenutne indikacije, već potencijalno i za druge hemiosenzitivne, ograničene pleuralne malignitete, kako primarne tako i metastatske.

Ključne reči: HITHOC, hipertermička intratorakalna hemioterapija, maligniteti pleure, indikacije, preživljavanje

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ORIGINAL ARTICLE

Scaphocephaly: a retrospective series examining treatment strategies and long-term follow-up

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Summary

Introduction: Scaphocephaly, the most common form of craniosynostosis, is caused by the premature fusion of the sagittal suture, resulting in an elongated skull shape and constrained cranial growth.

Material and methods: This retrospective study included all consecutive patients with sagittal synostosis who were operated at the Clinic of Neurosurgery, UCCS, in the 20-year period. Detailed patient data were obtained from medical records and neuroradiological diagnostics. The follow-up period for these patients ranged from 6 to 20 years. The acquired data were thoroughly statistically analyzed.

Results: There were 93 children with a clear male preponderance. In the majority of children, there were no perinatal complications, and the majority of mothers didn't have any chronic illnesses. Three types of surgical treatment were used, with an almost equal distribution. The mean blood loss during surgery varied across the three operative techniques, with the lowest blood loss observed using the TSEO technique. Successful treatment was observed in only 57.1% patients who underwent strip-suturectomy, 96.6% patients treated with the π procedure, and all patients treated with the TSEO technique. Statistical analysis revealed a significantly higher success rate of the TSEO and π procedure compared to strip-suturectomy. Cranial index remained dolichocephalic in 6/28 children treated with strip-suturectomy alone, while in all cases treated with TSEO and π procedure, cranial index normalized. The majority of operated children had no complications.

Conclusion: Successful treatment of scaphocephaly requires a case-specific approach that extends beyond the surgical procedure itself. This series emphasizes the need for individualized treatment plans and a multidisciplinary approach throughout the surgical process.

Keywords: craniosynostosis surgery, pediatric neurosurgery, sagittal synostosis

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INTRODUCTION

Craniosynostosis is a condition defined by the premature fusion of one or more cranial sutures, resulting in an atypical cranial appearance and constrained cranial growth (1). Scaphocephaly (sagittal synostosis) is the most common form of isolated (unisuture) craniosynostosis with a distinct prevalence in the male population (3.5-4:1) (2, 3). It occurs in 0.2-1% of newborns and is, in most cases, easily recognized immediately at birth by a typical, narrowed, and elongated skull shape (4). Scaphocephaly holds considerable significance owing to its potential impact on a child's aesthetic appearance, neurological development, and psychosocial health. Early diagnosis and treatment are crucial to prevent not only cosmetic issues, but also increased intracranial pressure, impaired vision, developmental delays, and permanent neurological deficits. (5-8) The involvement of a multidisciplinary team, which includes neurosurgeons, plastic surgeons, pediatricians, nurses, physical therapists, and social workers, is vital throughout the treatment process.

MATERIAL AND METHODS

This retrospective study includes all consecutive patients with sagittal synostosis who were operated at the Clinic of Neurosurgery, University Clinical Center of Serbia, over the period of 20 years, from January 1999 to December 2018. Detailed patient data were obtained from medical records and accompanying neuroradiological diagnostics.

The clinical data included prenatal medical history, family history, pregnancy history, associated congenital anomalies, age, and weight of the child at the time of surgery. Craniometric reference values included occipito-frontal circumference (OFC) and preoperative and postoperative cranial index (CI). Surgical intervention data included the type of surgical technique used, perioperative blood loss, presence of complications, and reoperations.

The outcomes were assessed through direct anthropometric measurements (head growth rate and cranial index), neuroradiological findings, and the Sloan classification systems to evaluate surgical results.

The surgery was indicated in cases when clear premature sagittal synostosis was diagnosed after clinical and neuroradiological examination – closed sagittal suture and its characteristic ridging, accompanied by characteristic head shape and the signs of increased intracranial pressure - "thumb printing" and subarachnoid collections over the frontal lobes.

Spiral computed tomography was performed from the skull base to the vertex using a Siemens SOMATOM Definition AS 128-slice Computed Tomography System (Siemens AG, Munich, Germany). All patients were scanned in a supine position in the axial plane. For the majority of children, neither general anesthesia nor sedation was used during imaging. The technical scanning parameters included a fast scan mode, wider collimation, rapid rotation time (0.5 seconds), and exposure parameters of 80-100 kV and 60-150 mA. The image was reconstructed with 1 mm-thick slices, and a 3D model was generated using Radiant DICOM Viewer (Medixant).

The follow-up period for these patients ranged from 6 to 20 years.

All statistical analyses were performed using IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient demographics, surgical details, and outcomes. The Kruskal-Wallis test was used to compare perioperative blood loss across the three surgical techniques, due to a violation of normality in one group (assessed using the Shapiro-Wilk test). Post hoc pairwise comparisons were conducted using the Mann-Whitney U test, with Bonferroni correction for multiple comparisons. Differences in ordinal outcomes, such as the Sloan classification, were analyzed using the Kruskal-Wallis test with post hoc Bonferroni adjustment. Comparisons of categorical data between groups were performed using the Chi-square test or Fisher's exact test, as appropriate. All patients included in the study had complete follow-up and relevant outcome data; there was no loss to follow-up. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. All statistical analyses were performed on anonymized patient data, ensuring that individual identities could not be disclosed or compromised.

This study has been conducted in full accordance with national and international ethical guidelines and standards relevant to this type of study.

RESULTS

There were 93 children with sagittal craniosynostosis surgically treated at the Clinic of Neurosurgery, UCCS, in the period from January 1999 to December 2018. There was a clear male preponderance, since there were 71.0% (66) boys and 29.0% (27) girls. The median age at the time of the surgery was 6 months, with the youngest child being only 2 months old and the oldest 3.5 years old. The minimal weight of an operated child was 4450 g, with high variability, since the oldest child was 3.5 years old and weighing 18 kg.

In the perinatal period, 8.6% of children experienced asphyxia during delivery, and 1.1% had intracranial hemorrhage. In the remaining 90.3% there were no perinatal complications. The majority of children (98.9%) were born to pregnancies conceived naturally. Over 90% of the mothers were non-smokers, did not consume caffeine, and did not suffer from chronic illnesses. The majority of pregnancies were full-term, 82.8%, while only 16.1% were premature, and only 1.1% were post-term. There were no associated anomalies in 94.6% of children. How-

Table 1. Compared variables between the groups according to the type of surgical treatment

PROCEDURE	STRIP-CRANIECTOMY	π PROCEDURE	TSEO
Blood loss	197.5 ml (IQR 171)	240.0 ml (IQR 105)	127.5 ml (IQR 90)
Sloan Classification – Good outcome (1,2)	16 (57.1%)	32 (97.0%)	32 (100%)
Postoperative OFC lower than normal (N)	6	0	0
CI < 75 (N)	6	0	0
Complications	3	2	2
Restenosis	3	1	0
N	28	33	32

ever, there was only one case of cleft palate and one case of congenital blindness. The youngest father was 20 and the oldest 41, with the mean age of 30.5 years. The youngest mother was 18 and the oldest was 39, with the mean age of 26.7 years.

Three types of surgical treatment were used. In 30.1% of cases, only a simple strip-suturectomy was performed, although the majority of these were cases done before 2010. A little more than a third (35.5%) were treated using the standard π procedure, and the remaining 34.4% were treated with the surgical technique created and modified in our institution in 2013 (Table 1) (9). The median blood loss during surgery varied across the three operative techniques. Patients who underwent strip-suturectomy had a median blood loss of 197.5 ml (IQR 171), compared to 240.0 ml (IQR 105) for the π procedure and 127.5 ml (IQR 90) for TSEO **(Table 1)**.

Blood loss was compared among the three surgical technique groups using the Kruskal-Wallis test, due to a violation of normality in one group. Kruskal-Wallis test revealed a significant difference in intraoperative blood loss among the three surgical techniques ($p < 0.001$). Subsequent pairwise comparisons were conducted using the Mann-Whitney U test with Bonferroni correction for multiple comparisons (adjusted significance threshold $p < 0.017$) and showed that the blood loss was statistically significantly higher only in the π-procedure group compared to the TSEO group ($p < 0.001$). Although the median blood loss appeared lower in the TSEO group compared to the strip-suturectomy group, this difference did not reach statistical significance in the pairwise analysis ($p = 0.065$), as shown in **Table 2**.

The success of surgical treatment for sagittal synostosis was evaluated using the Sloan classification and by comparing the cranial index (CI) before and after surgery. According to the Sloan classification, classes 1 and 2 are considered successful treatment, and this was achieved in 86.0% of cases. When analyzed according to the surgical technique used, successful treatment was observed in only 57.1% patients who underwent strip-suturectomy, 97.0% patients treated with the π procedure, and all patients treated with the TSEO technique (Table 1). Statistical analysis revealed a significant difference between groups (Kruskal-Wallis test, $p<0.001$). Pairwise comparisons using the Mann-Whitney U test, with Bonferroni correction applied (significance threshold $p < 0.017$), demonstrated statistically significant differences between all surgical techniques. Specifically, the outcome scores differed significantly between strip-suturectomy and π procedure ($p < 0.001$), strip-suturectomy and TSEO ($p < 0.001$), as well as between the π procedure and TSEO ($p = 0.006$). These findings indicate that each surgical technique was associated with significantly different treatment outcomes.

The rate of successful treatment (Sloan 1 or 2) was significantly higher in the TSEO (32/32, 100%) and π procedure (32/33, 97.0%) groups compared to the strip-suturectomy group ($p < 0.001$). Post hoc pairwise Fisher's exact tests with Bonferroni correction confirmed that both the TSEO and π procedure groups had significantly higher success rates than strip-suturectomy ($p < 0.001$ for both comparisons). In contrast, the difference between TSEO and the π procedure was not statistically significant ($p = 0.508$) as shown in **Table 3**.

The proportion of patients with an abnormal postoperative cranial index (CI < 75) differed significantly between surgical techniques. Among children treated using strip-suturectomy, 6/28 children had a persistently abnormal CI, whereas all patients in the TSEO and π procedure groups achieved normalization of the cranial index **(Table 1)**. This difference was statistically significant ($p <0.001$). The occipito-frontal circumference (OFC) in these 6 cases also remained below the appropriate value for age and gender **(Table 1)**. Preoperative and immediate postoperative shape of the skull in a patient with sagittal synostosis using the TSEO technique in our series is presented in **Figure 1**.

Table 2. Comparison of blood loss among surgical techniques

Comparison	Median Blood Loss (ml)	p-value (Kruskal-Wallis)	Pairwise p-values (Mann-Whitney, Bonferroni adj.)
Strip-suturectomy	197.5		strip-suturectomy vs π procedure: 0.090
π procedure	240.0	<0.001	strip-suturectomy vs TSEO: 0.065
TSEO	127.5		π procedure vs TSEO: <0.001

Table 3. Comparison of good outcome (Sloan 1 and 2)

Comparison	Good Outcome	p-value (Chi-square/Fisher's exact)	Pairwise p-values (Fisher's exact test)
Strip-suturectomy	16/28 (57.1%)		strip-suturectomy vs π procedure: <0.001
π procedure	32/33 (97.0%)	<0.001	strip-suturectomy vs TSEO: <0.001
TSEO	32/32 (100%)		π procedure vs TSEO: 0.508

The majority of operated children had no complications (92.5%); however, there were 4 cases of wound infection, two respiratory infections, and one case of liquorrhea. Three children operated using strip-suturectomy and one using the π procedure were reoperated because of restenosis. All cases of wound infection were mild and resolved after antibiotic treatment.

DISCUSSION

Preoperative considerations for scaphocephaly include accurate diagnosis to differentiate between synostotic and nonsynostotic cases, as the treatment varies (10, 11). An absolute contraindication for neurosurgical intervention is microcephaly, in which the skull sutures close secondarily, due to the absence of normal brain development and expansion (12). The patient's age, severity of the deformity, and associated risks such as elevated intracranial pressure must be assessed. Surgical options range from limited-access cranial vault remodeling for younger patients with less severe deformities to total cranial vault remodeling for older patients (12). Understanding the potential for blood loss and the length of hospital stay is crucial for planning and optimizing patient outcomes. In our series, particularly with the specifically developed TSEO technique, blood loss was lower than in both strip-suturectomy and π procedure. However, statistical significance was observed only in comparison with the π procedure.

Most studies suggest that the best time to perform surgery is between 3 and 6 months of age. This period is considered ideal due to the flexibility of the skull at this age, which minimizes the risks of complications such as reossification or restenosis after surgery (12-14). In our series, this period is highly variable, varying from 2 months to 3.5 years; however, no significant difference was found, since the majority of cases achieved excellent surgical outcomes.

There are various surgical choices and views on the ideal treatment, but clear guidelines are still not available, and there is insufficient research to endorse a specific surgical method (12). While early intervention is generally recommended, the choice of surgical technique and timing should be tailored to the individual patient's condition and the surgeon's expertise (12-14).

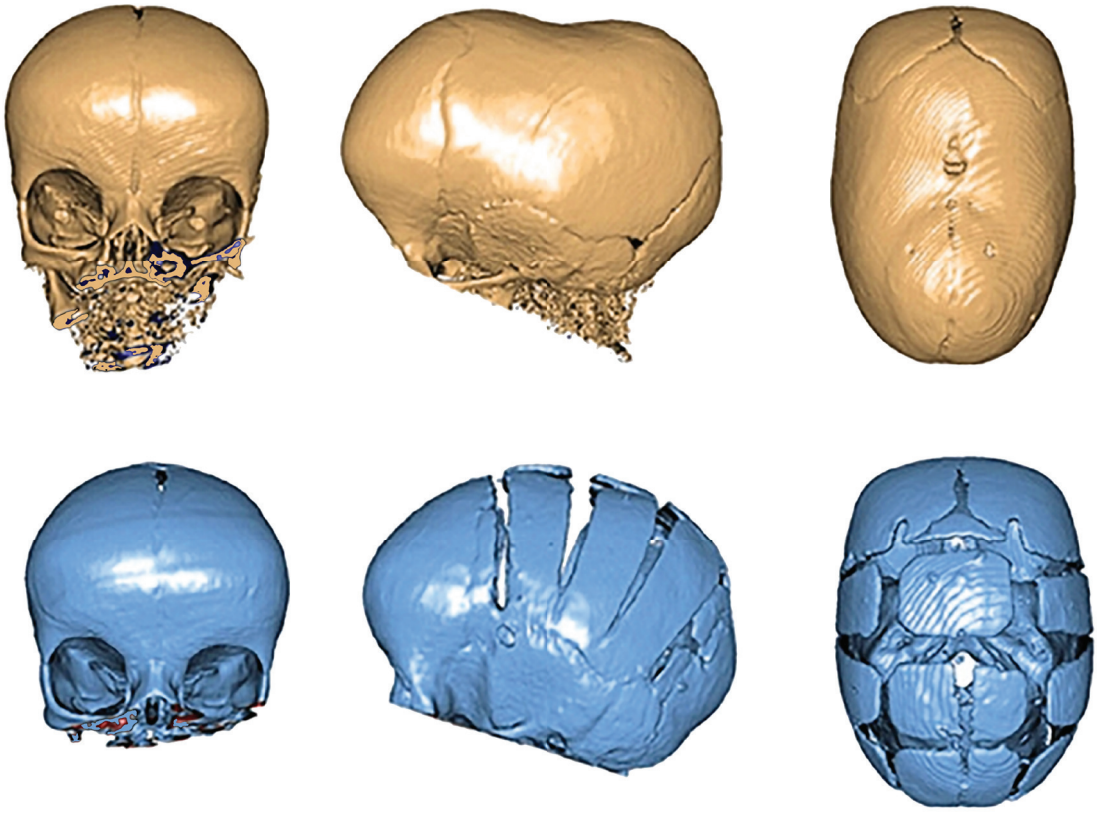

Figure 1. Preoperative (top row) and immediate postoperative (bottom row) shape of the skull in a patient with sagittal synostosis using the TSEO technique in our series

There are many available surgical options. The initial treatment, in the early years of craniosynostosis surgeries, consisted of a simple sagittal suturectomy; however, as is also shown in our series, the aesthetic outcome and the achieved cranial decompression were poor.

Then, the π procedure was developed, which involves creating a specific bone incision pattern that resembles the letter "π" on the skull (15). A subgaleal flap is raised to visualize the skull from the front fontanel area and the coronal sutures to the lambdoid sutures. A 4-cm strip of bone is carefully taken out from the bregma to the lambda along the superior sagittal sinus. The temporal/parietal bone flaps are cut or greenstick-fractured at their bases while still connected to a piece of temporal muscle, allowing for widening of the temporal/parietal area. The anterior–posterior length is reduced immediately; the midline bone flap is shortened to fit this new distance from bregma to lambda. Then, this midline bone flap is divided into two parts that are placed back and fixed with transosseous sutures to cover the sagittal sinus.

In our institution, we modified this technique to reduce blood loss, enhance the esthetic results, and achieve better decompression. Therefore, the TSEO technique was introduced to protect the superior sagittal sinus during cranial vault reconstruction and to extend the distance between osteotomes, thus reducing the rate of restenosis. It also involves remodeling of the frontal bone or occipital bone, depending on whether there is frontal bossing or occipital prominence (9).

In the last 5 years, throughout many craniosynostosis centers, the endoscopic-assisted craniosynostosis surgery (EACS) has been frequently used with helmet therapy. This procedure is claimed to be less invasive and leads to reduced blood loss and shorter hospital stays than open cranial vault reconstruction (16, 17). Infants are typically operated on at an early age, ideally before 3 months, to take advantage of rapid brain growth and skull plasticity. A small skin incision measuring approximately 2.5-3 cm is made behind the hairline, subsequently followed by a strip craniectomy along the fused sagittal suture. It provides comparable craniometric outcomes at 48 months after the surgery (16, 17).

Common complications of craniosynostosis surgery include CSF leaks, infection risk, blood loss, and temperature dysregulation (18-20). In our series, we have found a very low rate of complications (7.5%) and a very low volume of blood loss during surgery in the last 10 years, especially with the TSEO technique.

The intermediate postoperative phase, spanning from 1-6 months post-surgery, requires monthly clinical evaluations to assess skull growth patterns and monitor for potential relapse. Long-term follow-up continues until skeletal maturity, with annual assessments of head shape, growth parameters, cognitive development, visual function, and social adaptation. Psychological support for both family and patient, integration with pediatric therapy services when needed, educational support planning, and ongoing monitoring of aesthetic outcomes all contribute to comprehensive care (21). Healthcare providers must offer detailed explanations of the surgical process and expected outcomes, provide guidance on head positioning and handling, ensure families can recognize potential complications, and connect them with appropriate support groups and resources. Family support and education represent crucial elements of successful treatment.

A key limitation of this retrospective study is the potential for unmeasured confounding factors, such as variations in patient age, baseline severity, or comorbidities, which may have influenced surgical outcomes. Although multivariate regression analysis was considered, the sample size within each surgical group limited the feasibility of adjusting for multiple covariates. Future studies with larger cohorts may benefit from multivariate approaches to better account for potential confounders.

CONCLUSION

Successful treatment of scaphocephaly requires a case-specific, tailored approach that extends well beyond the surgical procedure itself. In our study, both the π procedure and TSEO were associated with better surgical outcomes compared to strip-suturectomy, particularly in terms of aesthetic results and normalization of the cranial index. Careful attention to both presurgical planning and postsurgical care, combined with comprehensive family support and long-term follow-up, provides the best foundation for optimal outcomes. As medical techniques continue to evolve and our understanding of craniosynostosis improves, treatment protocols will likely continue to be refined, potentially leading to even better outcomes for patients affected by this condition. Ongoing research and clinical experience will continue to improve surgical approaches, aiming for enhanced safety and efficacy in managing this condition.

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Ethical approval: This study has been conducted in full accordance with national and international ethical guidelines and standards relevant to this type of study.

Informed consent: Informed consent was obtained from all subjects involved in the study.

REFERENCES

1. Di Rocco C. Craniosynostosis in old Greece: political power and physical deformity. Childs Nerv Syst. 2005;21(10):859. DOI 10.1007/s00381-005-1250-1
2. Gracia A, Arsuaga JL, Martinez I, Lorenzo C, Carretero JM, Bermudez de Castro JM, et al. Craniosynostosis in the Middle Pleistocene human Cranium 14 from the Sima de los Huesos, Atapuerca, Spain. Proc Natl Acad Sci U S A. 2009;106(16):6573-8. DOI 10.1073/pnas.0900965106
3. Gracia A, Martinez-Lage JF, Arsuaga JL, Martinez I, Lorenzo C, Perez-Espejo MA. The earliest evidence of true lambdoid craniosynostosis: the case of "Benjamina", a Homo heidelbergensis child. Childs Nerv Syst. 2010;26(6):723-7. DOI 10.1007/s00381-010-1133-y
4. Cunningham ML, Seto ML, Ratisoontorn C, Heike CL, Hing AV. Syndromic craniosynostosis: from history to hydrogen bonds. Orthod Craniofac Res. 2007;10(2):67-81. DOI 10.1111/j.1601-6343.2007.00389.x
5. Bir SC, Ambekar S, Notarianni C, Nanda A. Odilon Marc Lannelongue (1840-1911) and strip craniectomy for craniosynostosis. Neurosurg Focus. 2014;36(4):E16. DOI 10.3171/2014.2.FOCUS13559
6. Feinsod M, Davis NL. Unlocking the brain: attempts to improve mental function of microcephalic retarded children by "craniotomy". Neurosurgery. 2003;53(3):723-30; discussion 30. DOI 10.1227/01.neu.0000079627.28240.63
7. Posnick JC. Paediatric craniofacial surgery: historical perspectives, recent advancements and refinements. Br J Oral Maxillofac Surg. 1995;33(6):343-61. DOI 10.1016/0266-4356(95)90136-1
8. Williams JK, Ellenbogen RG, Gruss JS. State of the art in craniofacial surgery: nonsyndromic craniosynostosis. Cleft Palate Craniofac J. 1999;36(6):471-85. DOI 10.1597/1545-1569_1999_036_0471_sotaic_2.3.co_2
9. Micovic M, Zivkovic B, Bascarevic V, Mijalcic R, Rasulic L. Triple square extended osteotomies for treatment of scaphocephaly (Renier's "H" technique modification). Neurosurg Rev. 2016;39(1):115-22; discussion 22. DOI 10.1007/s10143-015-0661-z
10. Ghizoni E, Denadai R, Raposo-Amaral CA, Joaquim AF, Tedeschi H, Raposo-Amaral CE. Diagnosis of infant synostotic and nonsynostotic cranial deformities: a review for pediatricians. Rev Paul Pediatr. 2016;34(4):495-502. DOI 10.1016/j.rpped.2016.01.004
11. Kreppel M, Kauke M, Safi AF, Grandoch A, Pocek-Behn N, Nickenig HJ, et al. Clinical evaluation of non-syndromic scaphocephaly surgically corrected with the procedure of total vertex craniectomy. J Craniomaxillofac Surg. 2018;46(9):1465-9. DOI 10.1016/j.jcms.2018.05.057
12. Faasse M, Mathijssen IMJ, Craniosynostosis ECWGo. Guideline on Treatment and Management of Craniosynostosis: Patient and Family Version. J Craniofac Surg. 2023;34(1):418-33. DOI 10.1097/SCS.0000000000009143
13. Bruce WJ, Chang V, Joyce CJ, Cobb AN, Maduekwe UI, Patel PA. Age at Time of Craniosynostosis Repair Predicts Increased Complication Rate. Cleft Palate Craniofac J. 2018;55(5):649-54. DOI 10.1177/1055665617725215
14. Pagnoni M, Fadda MT, Spalice A, Amodeo G, Ursitti F, Mitro V, et al. Surgical timing of craniosynostosis: what to do and when. J Craniomaxillofac Surg. 2014;42(5):513-9. DOI 10.1016/j.jcms.2013.07.018
15. Lauritzen C, Tarnow P. Craniofacial surgery over 30 years in Goteborg. Scand J Surg. 2003;92(4):274-80. DOI 10.1177/145749690309200407
16. Honeycutt JH. Endoscopic-assisted craniosynostosis surgery. Semin Plast Surg. 2014;28(3):144-9. DOI 10.1055/s-0034-1384810
17. Jimenez DF, Barone CM. Multiple-suture nonsyndromic craniosynostosis: early and effective management using endoscopic techniques. J Neurosurg Pediatr. 2010;5(3):223-31. DOI 10.3171/2009.10.PEDS09216
18. Esparza J, Hinojosa J. Complications in the surgical treatment of craniosynostosis and craniofacial syndromes: apropos of 306 transcranial procedures. Childs Nerv Syst. 2008;24(12):1421-30. DOI 10.1007/s00381-008-0691-8
19. Han RH, Nguyen DC, Bruck BS, Skolnick GB, Yarbrough CK, Naidoo SD, et al. Characterization of complications associated with open and endoscopic craniosynostosis surgery at a single institution. J Neurosurg Pediatr. 2016;17(3):361-70. DOI 10.3171/2015.7.PEDS15187
20. Whitaker LA, Bartlett SP, Schut L, Bruce D. Craniosynostosis: an analysis of the timing, treatment, and complications in 164 consecutive patients. Plast Reconstr Surg. 1987;80(2):195-212. PMID: 3602170
21. Magge SN, Westerveld M, Pruzinsky T, Persing JA. Long-term neuropsychological effects of sagittal craniosynostosis on child development. J Craniofac Surg. 2002;13(1):99-104. DOI 10.1097/00001665-200201000-00023

SKAFOCEFALIJA: RETROSPEKTIVNA ANALIZA TERAPIJSKIH PRISTUPA I DUGOROČNOG PRAĆENJA

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Sažetak

Uvod: Skafocefalija, najčešći oblik kraniosinostoze, uzrokovana je prevremenim srastanjem sagitalne suture, što dovodi do elongiranog oblika lobanje i ograničenja njenog rasta.

Metod: Ova retrospektivna studija obuhvatila je sve uzastopne pacijente sa sagitalnom sinostozom koji su operisani u Klinici za neurohirurgiju, UCCS, u periodu od 20 godina. Detaljni podaci o pacijentima prikupljeni su iz medicinske dokumentacije i neuroradiološke dijagnostike. Period praćenja pacijenata kretao se od 6 do 20 godina. Prikupljeni podaci su detaljno statistički analizirani.

Rezultati: Operisano je 93 dece sa jasnom prevalencom muškog pola. Kod većine dece nije bilo perinatalnih komplikacija, a kod većine majki nije bilo hroničnih bolesti. Korišćene su tri vrste hirurškog lečenja, gotovo ravnomerno raspoređene. Prosečan gubitak krvi tokom operacije varirao je između tri hirurške tehnike, sa najmanjim gubitkom krvi kod TSEO tehnike. Uspešno lečenje zabeleženo je kod samo 57,1% pacijenata koji su podvrgnuti strip-suturektomiji, kod 96,6% pacijenata tretiranih π procedurom i kod svih pacijenata tretiranih TSEO tehnikom. Statistička analiza je pokazala značajno viši stepen uspeha TSEO i π procedure u poređenju sa strip-suturektomijom. Kranijalni indeks ostao je u opsegu dolihocefalije kod 6/28 dece tretirane isključivo strip-suturektomijom, dok je kod svih slučajeva tretiranih TSEO i π procedurom kranijalni indeks normalizovan. Većina operisane dece nije imala komplikacije.

Zaključak: Uspešno lečenje skafocefalije zahteva specifičan pristup za svakog pacijenta koji prevazilazi samo poznavanje hirurške procedure. Ova serija pacijenata ističe potrebu za individualizovanim planom lečenja i multidisciplinarnim pristupom celokupnog hirurškog procesa.

Ključne reči: hirurgija kraniosinostoze, pedijatrijska neurohirurgija, sagitalna sinostoza

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ORIGINAL ARTICLE

Effects of NMDA receptor antagonists on acute postoperative pain

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Summary

Introduction: Pain represents a multifactorial process with detrimental effects on the entire organism. This randomized, open-label pilot study investigated the effect of preemptive administration of ketamine and magnesium-sulfate on the intensity of postoperative pain after laparoscopic colon tumor resection.

Methods: Sixty patients were randomized into the ketamine-magnesium (KM) and the control (C) groups. After the introduction to anesthesia, patients in the KM group received an i.v. bolus dose of 0.5 mg/kg ketamine, followed by a continuous infusion of 0.6 mg/kg/h lasting until the end of surgery. After a bolus dose of ketamine, they also received magnesium-sulfate 20 mg/kg in an intravenous infusion (5-10 minutes). Group C received only 0.9% NaCl infusion. After the patients were awakened (0h), the pain intensity was compared (0-46h) between the two groups.

Results: The Mann-Whitney test implied significantly ($p<0.05$) lower visual analog scale (VAS) scores, in KM group at 0, 1, 2, 10, 22 and 30 hours after the surgery, and no statistical significance ($p>0.05$) for VAS scores after 6, 14, 18, 38 and 46 hours, compared to C group. Ketamine and magnesium-sulfate significantly ($p<0.05$) reduced the postoperative consumption of analgesics, increased the sedation level at 0h postoperatively, and increased the overall patient satisfaction with the treatment.

Conclusion: Preemptive administration of ketamine and magnesium-sulfate combination has a beneficial effect on postoperative pain after laparoscopic colon tumor resection.

Keywords: NMDA-antagonists, ketamine, magnesium-sulfate, acute pain

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INTRODUCTION

Pain represents a multifactorial process with detrimental effects on the entire organism. Inadequately controlled postoperative pain affects the overall outcome of patient treatment and is associated with increased morbidity, diminished quality of life, and impaired functional recovery. In the current era of surgical advancement, characterized by the use of minimally invasive procedures and a trend toward prompt discharge after surgery, it is necessary to adapt analgesic strategies to align with the rapid recovery of patients following surgical intervention (1). According to the recommendations for acute pain therapy by the American Society of Anesthesiologists (ASA), acute pain is defined as pain present in surgical patients after the procedure, a consequence of trauma caused by the procedure itself, or due to complications related to the procedure (2).

Patients undergoing major surgical procedures experience significant clinical symptoms in the form of pain both at rest and during activity. Pain at rest is usually moderate, having an average visual analog scale (VAS) score of 3 to 4 out of 10 during the first 2 to 3 days after surgery, disappearing within the first week after the surgery. In contrast, pain during activity may reach scores of 7 to 8 and can last for weeks (3).

The mechanism by which harmful peripheral stimuli are transmitted to the central nervous system is called nociception (4). It consists of transduction, peripheral and central transmission, and synaptic transmission with modulation processes. At the synaptic level, the primary mediator involved in pain transmission is glutamate. Fast synaptic excitatory transmission occurs *via* glutamate released from the central terminals of nociceptors, which acts on ligand-gated ion channels on the postsynaptic membrane of central neurons (5,6). Ionotropic glutamate receptors are cation channels that allow the entry of positively charged ions, Na^+ and Ca^{2+}, into the postsynaptic cell, eliciting an excitatory postsynaptic potential, depolarization of the postsynaptic membrane, and increased excitability of the postsynaptic neuron (7). The glutamatergic excitatory postsynaptic potential induced by low-frequency action potentials in primary afferent neurons is generated mainly by the activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate glutamate receptors. NMDA (N-methyl-D-aspartate) receptors, also localized on excitatory primary afferent synapses, contribute little to the postsynaptic response to low-frequency presynaptic action potentials. Such a situation is due to the presence of tonic inhibition of ion flow through the NMDA receptor ion channel, resulting from a voltage-dependent blockade by extracellular magnesium ions (Mg^2) at the resting membrane potential, and because the activity of NMDA receptors is inherently down-regulated by a shift of the kinase/phosphatase regulatory system toward dephosphorylation (8,9). NMDA receptor antagonists, such as ketamine and magnesium, reduce the central mechanism of pain impulse transmission, thereby decreasing acute pain and preventing the development of chronic pain (10,11). Previous studies have investigated the effects of ketamine and magnesium alone, or in combination with other analgesics, particularly opioids. There are limited clinical data on their combined preventive use in laparoscopic colorectal procedures (10,11).

This study aims to examine the effect of the preemptive administration of a ketamine-magnesium combination on postoperative pain intensity reduction after laparoscopic surgery for colon tumors.

MATERIAL AND METHODS

Recruitment of participants and randomization

This pilot, randomized, open-label study was conducted on 60 patients undergoing elective laparoscopic surgery for colon tumors at the Department of Anesthesia, Resuscitation and Intensive Care, University Medical Center "Zvezdara" in Belgrade, from December 1, 2022, to December 1, 2023. The study was approved by the Ethics Committee of the "Zvezdara" University Medical Center on January 13, 2022. under the number IRB00009457, and conducted in compliance with the Declaration of Helsinki. Inclusion criteria were patients with ASA I and ASA II status, aged over 18 years, of both genders, with a diagnosis of colon tumor. Exclusion criteria were patients with ASA III and ASA IV status, younger than 18 years, those with ischemic heart disease, psychiatric and neurological disorders, and renal and hepatic insufficiency. Following routine preoperative preparation and fulfillment of the inclusion criteria, the study was explained to the patients, and the VAS was presented, along with instructions on how to use it as an instrument in the study. Patients were divided into two groups by simple randomization: the ketamine-magnesium group (KM) and the control group (C).

Drugs administration

Both groups received premedication consisting of 0.07 mg/kg midazolam intramuscularly (i.m.), 0.01 mg/kg atropine i.m., and 40 mg pantoprazole intravenously 30 minutes before surgery. Induction of anesthesia was performed with propofol and remifentanil using a target-controlled infusion (TCI) pump. The pharmacokinetic Schnider model was used for remifentanil at 6 ng/ml plasma concentration and for propofol at 6 μg/ml in brain tissue until loss of consciousness, along with rocuronium at an induction dose of 0.7 mg/kg for intubation.

After induction of anesthesia, patients in the KM group first received an intravenous bolus dose of 0.5 mg/

kg ketamine, followed by a continuous infusion at 0.6 mg/kg/h (10 mcg/kg/min) until near the end of the surgery (removal of ports). After the bolus dose of ketamine, they also received 20 mg/kg of magnesium-sulfate via intravenous infusion over 5–10 minutes. The control group received an infusion of 0.9% NaCl instead of a ketamine or magnesium solution. Thirty minutes before the end of the surgery, all patients received 4 mg of ondansetron intravenously and 100 mg of tramadol diluted in 100 ml of 0.9% NaCl.

Measurements of pain, analgesics consumption, Ramsay Sedation Score (RSS) parameters, and patient satisfaction

All patients were awakened in the operating room, and pain was assessed by reading the VAS. Measurements were taken after 0, 1, 2, 6, 10, 14, 18, 22, 30, 38, and 46 hours. The "zero hour" was defined as the time of patient admission to the Intensive Care Unit (ICU).

A VAS score above four was set as the threshold for administering the analgesic ketorolac 30 mg in 100 ml 0.9% NaCl (maximum dose 90 mg/24 h); if the VAS remained above four after one hour, tramadol 100 mg in 100 ml 0.9% NaCl (maximum dose 400 mg/24 h) was administered. The total consumption of tramadol and ketorolac was measured 48 hours after the completion of the surgery. Additionally, the RSS parameters and patient satisfaction were recorded.

Statistical analysis

Depending on the nature of the data, parametric (independent sample t-test) and nonparametric (Friedman's test, Mann-Whitney U, Kruskal–Wallis) tests were used to analyze the results. Also, the assessment of the difference between the two treatments was examined using a mixed-effect linear regression model. The assessment of the normality of the distribution of numerical variables was performed using the Shapiro-Wilk test. The analysis of research data was performed using the statistical data processing program SPSS (Statistical Package for Social Sciences) version 27. A statistical significance level of 0.05 or less was considered significant.

RESULTS

Characteristics of patients

The study included 60 patients evenly divided into two groups (KM and C), with 30 patients in each. The distribution of patients by examined parameters is presented in **Table 1**. In both the KM and C groups, the variables age, body height, body weight, Body Mass Index (BMI), and procedure duration have satisfied the normality of the distribution. An independent t-test showed that there were no statistically significant differences between the groups for any of the examined variables.

Table 1. Distribution of patients by examined parameters

Variable	Group	N	Mean	SD	p
Age (years)	KM	30	69.00	8.81	0.670
	C	30	67.80	8.86	
Height (cm)	KM	30	172.00	8.94	0.601
	C	30	173.55	9.62	
Weight (kg)	KM	30	77.95	21.44	0.573
	C	30	81.25	14.65	
BMI (kg/m^2)	KM	30	25.99	5.02	0.512
	C	30	26.93	3.88	
Procedure duration (min)	KM	30	196.95	51.77	0.528
	C	30	207.5	52.88	

KM - ketamine-magnesium group; C- control group; BMI - Body Mass Index

In the KM group, the ratio of men to women was 16:14 (53.3%:46.7%), while in the C group, it was 18:12 (60%:40%). The mean value of the ASA score in the KM group was 1.95, while in the C group, it was 1.65. In both the KM and C groups, the variable ASA status does not satisfy the normality of the distribution. The nonparametric Mann-Whitney U test reveals statistical significance (p=0.019) in the ASA score between the two groups.

Propofol and remifentanil consumption

Propofol and remifentanil were normally distributed, so the comparison by group was tested with an independent t-test **(Table 2)**. The t-test for independent samples with homogeneous variances (p=0.296), where the condition of homogeneity of variances is satisfied, implied that Ho should be rejected with a 5% error risk and that there is significantly (p=0.001) higher propofol consumption in the C than in the KM group. The t-test for independent samples with homogeneous variances (p=0.156), where the condition of homogeneity of variances is satisfied, showed that there is significantly (p<0.001) higher remifentanil consumption in the C than in the KM group.

Table 2. Propofol and remifentanil consumption

Drug	Group	N	Mean	SD	p*
Propofol (mg)	KM	30	1054.80	405.85	0.001
	C	30	1610.00	540.15	
Remifentanil (µcg)	KM	30	1113.15	344.59	0.001
	C	30	1598.00	409.42	

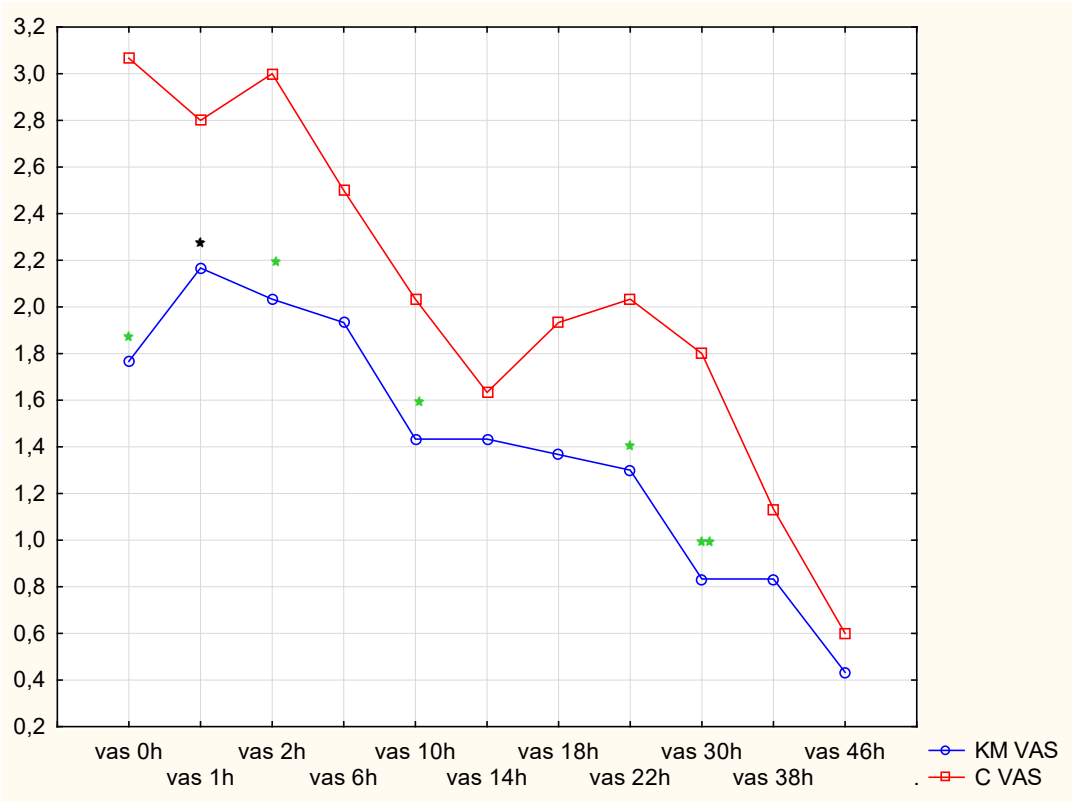
*t-test for independent samples

Postoperative VAS scores

VAS score measurements were taken after 0, 1, 2, 6, 10, 14, 18, 22, 30, 38, and 46 hours. Figure 1 illustrates the time interval dependence of VAS scores for the KM and C groups, respectively.

The Friedman test for repeated measurements for all the examined patients indicates a difference in pain

Figure 1. Mean of visual analog scale scores at different time intervals in ketamine-magnesium and control groups. *p<0.05, ** p<0.01



VAS - visual analog scale; KM - ketamin-magnesium; C – control

intensity in the examined groups over time. In other words, during the 11 time periods, patients' pain intensity significantly changed in both the KM (p<0.001) and C (p<0.001) groups. Also, the mixed-effect linear regression model showed that there were statistically significant differences (p<0.001) between the KM and C groups in terms of VAS scores. The C group displayed the highest mean VAS score of about 3 during the first 2 hours and then showed a fall to 2.03 at the 10-hour period. However, the KM group displayed a mean VAS score of about 2 during the first 6 hours, followed by a VAS of 1.43 at 10 10-hour period. During the rest of the time, VAS scores decreased slowly, and they are consistently lower in the KM group than in the C group.

Considering that the VAS scores do not satisfy the normality of the distribution, the nonparametric Mann-Whitney U test showed the existence of a statistically significant difference for the VAS scores between groups by time: VAS 0h (p<0.034), VAS 1h (p<0.029), VAS 2h (p<0.043), VAS 10h (p<0.019), VAS 22h (p<0.017) and VAS 30h (p<0.001), while there was no statistically significant difference in VAS 6h (p<0.340), VAS 14h (p<0.185), VAS 18h (p<0.147), VAS 38h (p<0.198) and VAS 46h (p<0.865). **Table 3** presents descriptive statistics of VAS scores of KM and C groups and the comparison of VAS scores between KM and C groups in the examined time intervals.

According to VAS scores, significantly higher pain intensity was found in the C group compared to the KM group at time intervals 0h, 1h, 2h, 10h, 22h, and 30h. No statistically significant difference in pain between groups was shown at 6h, 14h, 18h, 38h, and 46h time intervals **(Table 3)**.

Consumption of analgesics

The variables tramadol and ketoprofen consumption do not conform to a normal distribution. The Mann-Whitney U test in both groups implies that Ho should be rejected with a 5% error risk and that there is a significantly higher consumption of tramadol and ketoprofen in the C group compared to the KM group (p<0.001) **(Table 4)**.

Postoperative RSS scores

RSS measured at 0h, 1h and 4h postoperatively was used to determine the level of sedation. Friedman's repeated measures test shows that there are statistically significant differences within groups, in the KM group (p=0.001), while in the C group, there are no statistically significant differences (p=0.513). *Post hoc* tests in the KM group revealed statistically significant differences between RSS 0h and RSS 1h (p=0.001) and between RSS 0h and RSS 4h (p=0.001). In contrast, the C group showed no differences. The normality of the distribution was not satisfied in the variable RSS. Testing between groups, the Mann-Whitney U test showed that there were statistically significant differences between RSS 0h (p=0.001), and that there were no differences between RSS 1h (p=0.157) and RSS 4h (p=1.000) **(Table 5)**.

Table 3. Visual analog scale scores of the ketamine-magnesium and control groups and their comparison in the examined time intervals

Time interval	Group	N	Mean	Median	Min	Max	p
VAS 0h	KM	30	1.77	2	0	6	0.034
	C	30	3.07	3	0	6	
VAS 1h	KM	30	2.17	2	0	6	0.029
	C	30	2.80	3	0	6	
VAS 2h	KM	30	2.03	2	1	7	0.043
	C	30	3.00	3	1	7	
VAS 6h	KM	30	1.93	2	0	4	0.340
	C	30	2.50	2	1	4	
VAS 10h	KM	30	1.43	2	0	4	0.019
	C	30	2.03	2.5	1	3	
VAS 14h	KM	30	1.43	2	0	4	0.185
	C	30	1.63	1.5	0	2	
VAS 18h	KM	30	1.37	2	0	4	0.147
	C	30	1.93	2	1	2	
VAS 22h	KM	30	1.30	1	0	3	0.017
	C	30	2.03	2	1	3	
VAS 30h	KM	30	0.83	1	0	2	0.001
	C	30	1.80	2	0	2	
VAS 38h	KM	30	0.83	1	0	2	0.198
	C	30	1.13	2	0	2	
VAS 46	KM	30	0.43	1	0	2	0.865
	C	30	0.69	1	0	2	

VAS - visual analog scale; KM - ketamin-magnesium; C – control

Table 4. Tramadol and ketoprofen consumption

Drug	Group	N	Median	Min	Max	p*
Tramadol (mg)	KM	30	200.00	200.00	300.00	0.001
	C	30	400.00	200.00	400.00	
Ketoprofen (µcg)	KM	30	60.00	30.00	90.00	0.001
	C	30	90.00	60.00	90.00	

*Mann-Whitney U test

Table 5. Postoperative Ramsay Sedation Scores

	Group	N	Median	Min	Max	p*
RSS 0h	KM	30	3.00	2.00	4.00	0.001
	C	30	2.00	1.00	3.00	
RSS 1h	KM	30	2.00	2.00	3.00	0.157
	C	30	2.00	2.00	2.00	
RSS 4h	KM	30	2.00	2.00	2.00	1.000
	C	30	2.00	2.00	2.00	

*Mann-Whitney U test
RSS - Ramsay Sedation Scores; KM - ketamine-magnesium; C - control

Patient satisfaction with analgesia

In the KM group, 90% of patients were very satisfied with analgesia; the other 10% were satisfied. In the C group, 50% of patients were very satisfied with analgesia, 40% were satisfied, and 10% were dissatisfied. The Kruskal–Wallis test shows a statistically significant difference in the quality of analgesia between the two examined groups (p=0.003) **(Table 6)**. It is concluded that the KM group has a higher level of analgesia quality than the C group.

Table 6. Patient satisfaction with analgesia

Group		Very satisfied	Satisfied	Dissatisfied	p*
KM	N	27	3	0	0.003
	%	90	10	0	
C	N	15	12	3	
	%	50	40	10	

*The Kruskal–Wallis test

DISCUSSION

Patients undergoing laparoscopic surgical interventions for intestinal tumors were examined in the conducted study. The study included a total of 60 patients, evenly divided into two groups. Both groups were homogeneous regarding age, body height, weight, BMI, and procedure duration, meaning that the patients in the studied groups were similar in characteristics, rendering the groups comparable concerning the other examined parameters.

The laparoscopic approach in colorectal surgery is widely accepted because it is associated with lower pain intensity and reduced analgesic consumption, lower morbidity, including a lower incidence of wound infections, faster recovery, and a shorter hospital stay, all without compromising the surgical outcome. However, the laparoscopic surgical technique carries a higher risk of high-intensity pain compared to open surgery because it involves three main surgical principles that increase the risk of pain occurrence (12,13). These are the penetration of surgical instruments into the abdominal cavity, the creation of pneumoperitoneum, and the actual manipulation of surgical instruments.

Tissue trauma at the incision site is the principal source of pain following laparoscopy (14). Patients may develop nociceptive pain, inflammatory pain in response to tissue trauma, as well as neuropathic pain. Pain intensity is highest during the first 4-12 postoperative hours. Laparoscopic surgery is also associated with the risk of developing chronic pain. A large number of patients describe persistent postoperative pain as a constant, deep, dull pain in the abdomen or as persistent shoulder pain (15).

Standardized enhanced recovery programs combined with laparoscopic surgery have revolutionized clinical outcomes in elective colorectal surgery. Optimal pain control is central to the success of enhanced recovery programs (16). Pain management in colorectal surgery requires multimodal analgesia, utilizing complementary mechanisms to improve pain control while reducing exposure to high-risk medications.

One method of implementing multimodal analgesia in laparoscopic colorectal surgery is the use of ultra-short-acting opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and NMDA receptor antagonists, along with the administration of weak opioids to reduce the need for potent opioids (1,17,18).

Ketamine acts through the noncompetitive antagonism of NMDA receptors. It binds to the phencyclidine site in the NMDA receptor ion channel when the channel is open. When glutamate dissociates from its binding site, ketamine remains trapped in the now-closed channel, causing a prolonged tonic blockade (19). Ketamine exerts its antinociceptive effect by antagonizing NMDA receptors at the level of the spinal cord and brain.

The use of magnesium as an adjuvant in perioperative analgesia is relatively new. Its application is based on magnesium's properties as an NMDA receptor antagonist and its inhibitory effect on calcium channels, which leads to secondary neuronal changes. This mechanism may prevent central sensitization associated with nociception and reduce the increased activity of wide dynamic range neurons in the dorsal horn after prolonged stimulation (1,20).

A large percentage of patients undergoing laparoscopic bariatric surgery develop postoperative apnea due to the use of high amounts of opioids, as well as due to concomitant sleep apnea. To ensure a safer postoperative course and reduce both opioid doses and their harmful effects, ultra-short-acting opioids such as remifentanil are increasingly being used (21). In the examined patient groups, the consumption of propofol and remifentanil was analyzed. It was found that the consumption of both drugs was significantly higher in the control group than in the KM group. Considering that both groups were dosed according to the TCI model and that the depth of anesthesia and pain level were monitored by entropy and the SPI index, it can be concluded that the addition of ketamine and magnesium-sulfate reduces consumption of propofol and remifentanil.

NMDA receptor antagonists (ketamine and magnesium-sulfate) have an analgesic effect, reducing central sensitization and preventing the development of chronic postoperative pain. When administered in sub-dissociative doses, ketamine contributes to better pain control and a reduced need for opioids, particularly in patients with high opioid tolerance. In addition to its analgesic and opioid-sparing effects, ketamine administration has led to a reduction in the incidence of nausea and vomiting, a lower occurrence of hyperalgesia, and reduced residual pain in the first six postoperative months (22).

Numerous studies have investigated the use of magnesium in various types of pain and at different doses. One meta-analysis demonstrated that perioperative intravenous magnesium administration can improve postoperative pain (23). Additionally, in patients undergoing septorhinoplasty surgery or laparoscopic cholecystectomy, magnesium reduced the use of opioid analgesics and postoperative pain (24,25). Although the maximal analgesic benefit of magnesium is often achieved in major upper abdominal, thoracic, and orthopedic surgery, magnesium can also be used with good results in colorectal surgery (16).

Upon leaving the operating room and arriving in the ICU, all patients had their pain levels assessed using the VAS scale. The pain intensity was higher in patients in the C group and over a longer time interval (in the first 10 h) postoperatively compared to the KM group, in which the pain intensity was lower. In other time intervals, up to 30 hours postoperatively, the pain intensity in patients in the KM group showed a faster decline compared to the C group. In later time intervals, the pain intensity did not differ. In general, a lower level of pain was observed in the KM group than in the control group, which means that preemptive ketamine-magnesium treatment significantly reduced pain intensity in patients with laparoscopic colon tumor surgery. In the present study, this effect lasted up to 30h postoperatively.

For postoperative analgesia, tramadol and ketoprofen were administered based on the pain level as interpreted *via* the VAS scale. The consumption of tramadol and ketoprofen was measured in the examined groups, with greater consumption observed in the control group compared to the group that received ketamine and magnesium-sulfate.

In the present study, the RSS scores evaluation demonstrates that ketamin-magnesium treatment significantly increases the level of sedation only in the immediate postoperative period (RSS 0h), without affecting RSS later postoperatively. This is consistent with the well-known sedative effects of both NMDA antagonists (8). However, other studies have shown that subanesthetic doses of ketamine in the perioperative period do not cause an increased level of sedation and may even reduce it, likely due to decreased opioid consumption (26).

At the end of the study, all patients were evaluated for their overall satisfaction with the treatment and the quality of analgesia. Higher levels of satisfaction and quality of analgesia were noted in the KM group than in the C group.

A limited number of studies in animals and humans examined the additive and synergistic effects of the simultaneous use of ketamine and magnesium-sulfate on postoperative analgesia. In various animal models of pain, ketamine and magnesium may display additive, antagonistic, and synergistic interactions. Ketamine and magnesium-sulfate block NMDA receptors *via* different mechanisms, achieving these effects. In most studies, the ketamine and magnesium combination is more effective in various pain conditions than ketamine alone (27-29).

It is assumed that the contradictory results in the literature are primarily due to the use of different doses of ketamine and magnesium-sulfate and the various types of pain studied. A randomized, double-blind, placebo-controlled study did not demonstrate a reduction in pain or the use of other analgesics after laparoscopic sleeve gastrectomy when given a small intravenous dose of ketamine and/or magnesium-sulfate before surgery (30). In contrast, a prospective, randomized, double-blind study following scoliosis surgery observed reduced postoperative morphine consumption in patients who received both ketamine and magnesium concurrently compared to those who received ketamine alone. Although the VAS scores did not show a statistically significant difference between the two groups, patient satisfaction and sleep quality were higher within the group that received ketamine and magnesium (31). However, what is common to all studies is that, by blocking NMDA receptor activity, ketamine and magnesium reduce the central transmission of pain impulses, thereby decreasing acute pain and preventing the development of chronic pain. Therefore, they can be used as analgesics within a multimodal pain management approach (10,11).

CONCLUSION

Analgesic techniques should aim to achieve optimal pain control and facilitate important recovery milestones, such as early oral intake of fluids and food and early mobilization. In the context of rapid patient recovery, anesthesia techniques that reduce opioid usage should be increasingly implemented to minimize the dose-dependent adverse effects of these drugs and to prevent delays in recovery. The present prospective randomized pilot clinical study demonstrated that preemptive administration of ketamine and magnesium significantly reduced postoperative VAS score, *i.e.*, pain intensity level, and the postoperative consumption of analgesics, increased RSS score, *i.e.*, sedation level, and the overall satisfaction with the treatment and the quality of analgesia after laparoscopic colon tumor surgery. NMDA antagonists should be incorporated as part of multimodal analgesia for major surgical procedures, abdominal surgery, and in patients at high risk for developing chronic postoperative pain.

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Ethical approval: This study was conducted in accordance with Declaration of Helsinki and was approved by the Ethics Committee of "Zvezdara" University Medical Center, approval number IRB00009457/2022. Written informed consent was obtained from all participants prior to inclusion in the study.

REFERENCES

1. Ljunggvist O, de Boer HD, Balfour A, Fawcett W, Lobo DN, Nelson G, et al. Opportunities and challenges for the next phase of enchanced recovery after surgery. A review, JAMA Surg 2021; 156(8): 775-784. DOI: 10.1001/jamasurg.2021.0586, PMID: 3388146
2. An updated report by the American Society of Anesthesiologists Task force on acute pain management. Anesthesiology 2012; 116: 248-273. DOI: 10.1097/ALN.0b013e31823c1030, PMID: 22227789.
3. Mariano ER, Dickerson DM, Szokol JW, Harned M, Mueller JT, Philip BK, et al. A multisociety organizational consensus process to define guiding principles for acute perioperative pain management. Reg Anesth Pain Med 2022; 47(2): 118-127. DOI: 10.1136/rapm-2021-103083, PMID: 34552003
4. Tassou A, Richebe P, Rivat C. Mechanisms of chronic postsurgical pain. Reg Anesth Pain Med 2025; 50(2): 77-85. DOI: 10.1136/rapm-2024-105964. PMID: 39909543
5. Vučković S, Prostran M. Pharmacology of pain: nociceptors and the posterior horns of the spinal cord. In: Stevanović P, Nešić D, Lađević N. Pain Medicine: Faculty of Medicine, University of Belgrade, Belgrade, Serbia; 2019. pp. 147-164.
6. Cheung CK, Adeola JO, Beutler SS, Urman RD. Postoperative pain management in enhanced recovery pathways. J Pain Res 2022; 15: 123-135. DOI: 10.2147/JPR.S231774, PMID: 35058714
7. Moisset X, Bouhassira D, Attal N. French guidelines for neuropathic pain: An update and commentary. Rev Neurol 2021; 177(7): 834-837. DOI: 10.1016/j.neurol.2021.07.004, PMID: 34332778
8. Ferraro MC, Cashin AG, O'Connell NE, Visser EJ, Shaheed CA, Wewege MA, et al. Ketamine and other NMDA receptor antagonists for chronic pain. Cochrane Database Syst Rev. 2023; 2:CD015373. DOI: 10.1002/14651858.CD015373, PMCID: PMC9950034
9. Puşcaşu C, Chiriță C, Negreș S, Blebea NM. Exploring the therapeutic potential of N-Methyl-D-Aspartate receptor antagonists in neuropathic pain management. Int J Mol Sci 2024; 25(20): 11111; DOI: 10.3390/ijms252011111, PMID: 39456894

10. Israel JE, St Pierre S, Ellis E, Hanukaai JS, Noor N, Varrassi G, et al. Ketamine for the treatment of chronic pain: A comprehensive review. Health Psychol Res 2021; 9(1): 25535. DOI: 10.52965/001c.25535, PMID: 34746491
11. Urits I, Jung JW, Amgalan A, Fortier L, Anya A, Wesp B, et al. Utilization of magnesium for the treatment of chronic pain. Anesth Pain Med 2021; 11(1): e112348. DOI: 10.5812/aapm.112348, PMID: 34221945
12. Lirk P, Badaoui J, Stuempflen M, Hedayat M, Freys SM, Joshi GP. PROcedure-SPECific postoperative pain management guideline for laparoscopic colorectal surgery: A systematic review with recommendations for postoperative. Eur J Anaesthesiol 2024; 41(3): 161-173. DOI: 10.1097/EJA.0000000000001945, PMID: 38298101
13. Smail A, Slimane NN, Benhocine Y, Taieb. The impact of laparoscopic surgery on postoperative pain: A prospective study. WJARR 2024; 22(01): 1727-1732. DOI: 10.30574/wjarr.2024.22.1.1273
14. Wang J, Cheng L, Liu J, Zhang B, Wang W, Zhu W, et al. Laparoscopy vs. Laparotomy for the management of abdominal trauma: A systematic review and meta-analysis. Front Surg 2022; 9:817134. DOI: 10.3389/fsurg.2022.817134, PMID: 35350141
15. Li K, Li X. Time characteristics of shoulder pain after laparoscopic surgery. JSLS 2021; 25(2): e2021.00027. DOI: 10.4293/JSLS.2021.00027, PMID: 34248341
16. Ivascu R, Dutu M, Stanca A, Negutu M, Morlova D, Dutu C, et al. Pain in colorectal surgery: How does it occur and what tools do we have for treatment? J Clin Med 2023; 12: 6771. DOI: 10.3390/jcm12216771, PMID: 37959235.
17. Sun Z, Liu C, Huang L, Bo L, Li X, Lv C, et al. The efficacy of preemptive multimodal analgesia in elderly patients undergoing laparoscopic colorectal surgery: a randomized controlled trial. Sci Rep 2024; 14:25438. DOI: 10.1038/s41598-024-75720-7, PMID: 39455612
18. O'Neill A, Lirk P. Multimodal analgesia. Anesthesiol Clin 2022; 40(3): 455-468. DOI: 10.1016/j.anclin.2022.04.002, PMID: 36049874
19. Schwenk ES, Pradhan B, Nalamasu R, Stolle L, Wainer IW, Cirullo M, et al. Ketamine in the past, present, and future: mechanisms, metabolites, and toxicity. Curr Pain Headache Rep 2021; 25(9): 57. DOI: 10.1007/s11916-021-00977-w, PMID: 34269883
20. Morel V, Pickering ME, Goubayon J, Djobo M, Macian N, Pickering G. Magnesium for pain treatment in 2021? State of the art. Nutrients 2021; 13(5): 1397. DOI: 10.3390/nu13051397, PMID: 33919346
21. Kasputytė G, Gecevičienė P, Karbonskienė A, Macas A, Maleckas A. Comparison of postoperative recovery after manual and target-controlled infusion of remifentanil in bariatric surgery. Medicina 2021; 57(10): 1114. DOI: 10.3390/medicina57101114, PMID: 34684151
22. Viderman D, Mukazhan D, Kapessova K, Tungushpayev M, Badenes R. The impact of ketamine on outcomes in acute pain management: An Umbrella review. J Clin Med 2024; 13(24): 7699. DOI: 10.3390/jcm13247699, PMID: 39768621
23. Mahmoodpoor A, Latifi K, Ghojazadeh M, Nikbakht ME, Hosseini MS, Sarfaraz T, et al. Effect of magnesium sulfate on postoperative pain: A systematic review and meta-analysis. J Res Clin Med 2024; 12: 32. DOI: 10.34172/jrcm.34629
24. Kilica K, Sakat MS, Sahin A, Ahiskalioglu EO, Altunok H. Efficacy of intravenous magnesium sulfate infusion on postoperative pain and quality of recovery for septorhinoplasty: a randomized controlled study. Acta Otolaryngol 2023; 143(11-12): 979-983. DOI: 10.1080/00016489.2023.2289584, PMID: 38108626
25. Yaseen T, Rizvi SAM, Mahmood K, Malik UE, Aziz M, Khan A. Analgesic effects of magnesium sulphate in patients undergoing laparoscopic cholecystectomy. Pak rmed Forces Med J 2024; 74(SUPPL-2): S204-S207. DOI: 10.51253/pafmj.v74iSUPPL- 2.10322
26. Fattahi-Saravi Z, Jouybar R, Haghighat R, Asmarian N. Comparison of the effect of ketamine, ketamine-midazolam and ketamine-propofol on post-tonsillectomy agitation in children. Malays J Med Sci 2021; 28(5): 72-81. DOI: 10.21315/mjms2021.28.5.7, PMID: 35115889
27. Vujović KS, Vučković S, Vasović D, Medić B, Knežević N, Prostran M. Additive and antagonistic antinociceptive interactions between magnesium sulfate and ketamine in the rat formalin test. Acta Neurobiol Exp (Warsz) 2017; 77: 137-146. DOI: 10.21307/ane-2017-046, PMID: 28691718.
28. Savić Vujović KR, Vučković S, Srebro D, Medić B, Stojanović R, Vučetić C, et al. A synergistic interaction between magnesium sulphate and ketamine on the inhibition of acute nociception in rats. Eur Rev Med Pharmacol Sci 2015; 19: 2503-2509. DOI: 10.1016/j.physbeh.2014.01.006, PMID: 26214789.
29. Vučković SM, Savić Vujović KR, Srebro DP, Medić BM, Stojanović RM, Vučetić CS, et al. The antinociceptive efficacy of morphine-ketamine-magnesium combination is influenced by the order of medication administration. Eur Rev Med Pharmacol Sci 2015; 19: 3286-3294. DOI: 10.2478/acve-2018-0009, PMID: 26400536.
30. Adhikary SD, Thiruvenkatarajan V, McFadden A, Liu WM, Mets B, Rogers A. Analgesic efficacy of ketamine and magnesium after laparoscopic sleeve gastrectomy: A randomized, double-blind, placebo-controlled trial. J Clin Anesth 2021;68:110097. DOI: 10.1016/j.jclinane.2020.110097, PMID: 33120301
31. Jabbour HJ, Naccache NM, Jawish RJ, Zeid HAA, Jabbour KB, Rabbaa-Khabbaz LG, et al. Ketamine and magnesium association reduces morphine consumption after scoliosis surgery: prospective randomised double-blind study. Acta Anaesthesiol Scand 2014; 58: 572-579. DOI: 10.1111/aas.12304, PMID: 24635528.

DEJSTVA ANTAGONISTA NMDA RECEPTORA NA AKUTNI POSTOPERATIVNI BOL

Maja Stojanović[1,2], Predrag Stevanović[2,3], Sonja Vučković[2,4], Katarina Savić Vujović[2,4]

Sažetak

Uvod: Bol predstavlja multifaktorijalni proces sa štetnim efektima na ceo organizam. Randomizovana, otvorena pilot studija istražuje efekat preventivne kombinovane primene ketamina i magnezijum-sulfata na intenzitet postoperativnog bola nakon laparoskopske resekcije tumora debelog creva.

Metod rada: Šezdeset pacijenata je randomizirano u ketamin-magnezijumsku (KM) i kontrolnu (C) grupu. Nakon uvoda u anesteziju, pacijentima KM grupe primenjena je i.v. bolus doza od 0,5 mg/kg ketamina, nakon čega sledi kontinuirana infuzija od 0,6 mg/kg/h koja traje do kraja operacije. Nakon bolus doze ketamina, takođe su dobijali magnezijum-sulfat 20 mg/kg u intravenskoj infuziji (5-10 minuta). Grupa C primila je samo infuziju 0,9% NaCl. Nakon buđenja (0h), intenzitet bola je poređen (0-46h) između dve grupe.

Rezultati: Mann-Whitney test je pokazao značajno ($p<0,05$) niže rezultate vizuelno analogne skale (VAS) u KM grupi 0, 1, 2, 10, 22 i 30 sati nakon operacije, i bez statističke značajnosti ($p>0,05$) za VAS rezultate nakon 6, 14, 18, 38 i 46 sati, u odnosu na C grupu. Ketamin i magnezijum-sulfat su značajno ($p<0,05$) smanjili postoperativnu potrošnju analgetika, povećali nivo sedacije u 0h postoperativno i povećali ukupno zadovoljstvo pacijenata tretmanom.

Zaključak: Preventivna primena kombinacije ketamina i magnezijum-sulfata ima povoljno dejstvo na postoperativni bol posle laparoskopske resekcije tumora debelog creva.

Ključne reči: NMDA-antagonisti, ketamin, magnezijum-sulfat, akutni bol

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ORIGINAL ARTICLE

Prognostic significance of indexed stroke volume in asymptomatic patients with moderate or severe aortic stenosis and preserved left ventricular ejection fraction

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Summary

Introduction: When to intervene in asymptomatic patients with moderate or severe aortic stenosis (AS) and preserved left ventricular ejection fraction (LVEF) has not yet been determined. In patients with AS, low flow through the aortic valve is defined as indexed stroke volume (SVi) ≤35 ml/m^2. Our work aimed to determine the relationship between SVi and all-cause mortality in asymptomatic patients with moderate or severe AS, concordantly high mean gradient across the aortic valve (P_{mean}), and preserved LVEF.

Methods: The study included 121 asymptomatic patients (69 men, mean age 66±11) with moderate-to-severe AS (aortic valve area ≤1.5 cm^2), concordantly high P_{mean} (≥30 mmHg), and preserved LVEF (≥50%). The median follow-up was 38 months (IQR 35-42 months).

Results: Ten patients (8%) died during the follow-up. All-cause mortality was significantly higher in the group of AS-patients with SVi ≤35 ml/m^2 compared to those with SVi >35 ml/m^2 (15% vs. 4%, p<0.045). The cumulative incidence of all-cause mortality was significantly higher in the group of AS-patients with SVi ≤35 ml/m^2 compared to those with SVi >35 ml/m^2 (log-rank p=0.035). The group of AS-patients with SVi ≤35 ml/m^2 had a 3.8-fold higher risk of all-cause mortality during long-term follow-up compared with those with SVi >35 ml/m^2 (HR: 3.845; 95% CI: 1.004-14.871; p=0.041).

Conclusion: Left ventricular SVi may be a significant predictor of all-cause mortality during long-term follow-up in asymptomatic patients with moderate or severe AS, concordantly elevated $P_{mean,}$ and preserved LVEF. Larger studies are needed to confirm these findings.

Keywords: aortic stenosis, asymptomatic stroke volume, stroke volume index, Doppler echocardiography, outcome

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INTRODUCTION

Aortic stenosis (AS) is the most frequent valvular disease requiring intervention in high- and mid-income countries (1). AS leads to impaired flow through the aortic valve, resulting in an increased pressure gradient and, in turn, increased left ventricular (LV) afterload. These processes lead to concentric LV hypertrophy to maintain stroke volume (SV), but prolonged pressure overload eventually results in systolic dysfunction and, consequently, reduced SV (2).

Severe AS is defined when the aortic valve area (AVA) is ≤1.0 cm^2, the maximum flow velocity (V_{max}) is ≥4.0 m/s, and the mean pressure gradient (P_{mean}) is ≥40 mmHg (3). However, approximately 50% of patients with severe AS have low SV despite preserved left ventricular ejection fraction (LVEF) (4). A reduction in blood flow across the aortic valve is determined by an LV stroke volume index (SVi) ≤35 ml/m^2 (5).

Patients with severe AS and low SVi with preserved LVEF (≥50%) can be classified into one of the two groups: patients with low flow (SVi ≤35 ml/m^2) and low mean gradient across the aortic valve (P_{mean} <40 mmHg) (either with decreased or with normal LVEF) and patients with low flow and concordantly high P_{mean} across the aortic valve (≥ 40 mmHg) (6-7). Patients with low-flow and low-gradient AS with preserved LVEF have increased mortality during 5-year follow-up (8-9). In contrast, the prognostic significance of low flow in patients with high-gradient AS and preserved LVEF has been much less studied.

In any case, if a patient with AS is symptomatic, the management is obvious, and aortic valve replacement is mandatory. However, the treatment approach to asymptomatic AS patients is still debatable. Timely risk stratification of these patients is crucial to achieving optimal outcomes. Thus, additional parameters, including echocardiography-derived parameters, could facilitate patient-tailored decisions.

Our study aimed to determine whether low SVi was associated with all-cause mortality in asymptomatic patients with moderate or severe AS (AVA ≤1.5 cm^2), concordantly high P_{mean} across the aortic valve (≥ 30mmHg), and preserved LVEF (≥50%).

METHODS

Patient population

Between 2009 and 2018, 121 asymptomatic patients with moderate (AVA ≤1.5 cm^2) or severe AS (AVA ≤1.0 cm^2) and preserved LVEF (≥50%) were prospectively enrolled in the study **(Table 1)**. Key exclusion criteria were: patients ≤18 years old; the presence of mild AS (AVA >1.5 cm^2); the presence of subvalvular or supravalvular AS; the presence of significant mitral regurgitation; the presence of more than moderate mitral regurgitation or more than mild mitral stenosis; severe chronic kidney disease with estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2; and shortened life expectancy (<3 years). A detailed list of inclusion and exclusion criteria is given in Table 1. The study was conducted in the clinical echocardiography laboratory at the Cardiology Department, University Clinical Center of Serbia, Belgrade, Serbia, in accordance with national legal requirements, institutional policies, and the revised Declaration of Helsinki. All patients gave written informed consent to participate in the study, which was approved by the Ethical Committee of the University of Belgrade - Faculty of Medicine (number: 440IVI-13, June 19th 2009).

Echocardiography

Commercially available ultrasound systems were used to perform a comprehensive Doppler echocardiographic study in all patients. Transthoracic echocardiographic

Table 1. Full inclusion and exclusion criteria for patient participation in the study.

Inclusion criteria	Exclusion criteria
1. Presence of moderate or severe aortic stenosis (AVA ≤1.5 cm^2); 2. Left ventricular ejection fraction ≥50%; 3. The patient can sign informed consent.	1. Patients aged ≤18 years old; 2. Mild aortic stenosis (AVA >1.5 cm^2); 3. Subvalvular or supravalvular aortic stenosis; 4. Mitral regurgitation and/or aortic regurgitation ≥2+; 5. Moderate or severe mitral stenosis (mean gradient >5 mmHg); 6. Patients with a significantly dilated ascending aorta (>45 mm); 7. Presence of a prosthetic aortic valve and/or mitral valve; 8. Patients with a shortened life expectancy (<3 years); 9. Coronary artery disease is defined as the presence of at least one coronary stenosis >50% diameter stenosis assessed by visual estimation. 10. Any previous myocardial infarction; 11. Any previous percutaneous coronary intervention; 12. Previous aorto-coronary by-pass grafting surgery (CABG); 13. Left ventricular hypertrophy; 14. Cardiomyopathies (dilated, hypertrophic, restrictive); 15. Chronic kidney disease (<30 ml/min/1.73 m^2).

examination was performed on the General Electric Vivid 4 and Vivid 9 cardiac ultrasound systems (BTO6, 1.5-3.6 MHz; GE Healthcare Technologies, Waukesha, WI, USA). Patients were examined in all standard echocardiographic positions. The left ventricle's internal dimensions, the posterior wall thickness (PWT), and the interventricular septal thickness (IVST) were measured in end-diastole apically in relation to the tips of the mitral valve leaflets in the two-dimensional long-axis parasternal view (10). Using the corrected formula of the American Society of Echocardiography and body surface area indexing, the LV mass of each individual was calculated (11). The Simpson biplane model was used to determine LV end-diastolic and end-systolic volumes, as well as LVEF (12). Online software was used to calculate maximum velocity, velocity-time integral, systolic ejection time, maximum pressure, and pressure differences from continuous-wave Doppler recordings at the apex and the right intercostal space. The simplified Bernoulli equation was used to calculate gradients across the aortic valve (13). The AVA was determined using the continuity equation. A parasternal long-axis view at mid-systole was used to measure the subaortic diameter at the level of the aortic leaflets. Apical five-chamber pulsed Doppler recordings were obtained with the sample volume shifted axially from the aortic annulus, typically 0.5 to 1.0 cm below the valve, to measure maximum velocity and velocity-time integrals. Stroke volume was calculated as VTI LVOT × CSA LVOT, the main systolic transvalvular volume flow ratio as SV/SEP (14) (left ventricular outflow tract [LVOT], cross sectional area [CSA]; velocity time integral [VTI]; systolic ejection period [SEP], measured as the time between the opening and closing of the aortic valve echoes in the aortic Doppler recording. Indexed stroke volume was calculated in ml as Stroke volume / Body surface area in m^2, where: Stroke volume = Cardiac Output in ml / Heart rate in beats per minute (bpm) (14).

A single operator did all echocardiographic measurements.

Follow-up

Clinical data during follow-up were obtained from all patients either through direct examination or a telephone interview. The primary endpoint was all-cause mortality. Documentation provided by patients and/or hospital data was used to confirm the primary endpoint. The patients were followed up for an average of 38 months (interquartile range [IQR] 35-42 months).

Statistical analysis

Continuous variables were tested for normality using the Kolmogorov-Smirnov test and were reported as mean ± SD, while categorical variables were reported as counts and percentages. Patients were divided into two groups based on the previously defined SVi threshold of 35 ml/m^2 (5). For statistical analysis, Pearson's chi-square test for independence or Fisher's exact test was used, depending on group size, along with the Student's t-test for independent samples. Survival rates and 95% confidence intervals (95% CI) were estimated using Kaplan-Meier analysis and the log-rank test. Univariate Cox proportional hazards regression was used to examine the association between individual variables and all-cause mortality. A multivariate Cox proportional hazards regression analysis was not conducted due to a small number of events of interest and an unfavorable ratio between outcomes and predictors. Statistical significance was set at $p<0.05$. All data were entered into a database and processed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corporation, Armonk, New York).

RESULTS

Demographic, clinical, and echocardiographic characteristics of the study population, according to SVi, are presented in **Table 2**. The mean age was 66 ± 11 years (range: 23-83 years), and 69 patients (57%) were male. Ninety-two patients (76%) had severe AS (AVA: 0.75 ± 0.15 cm2, V_{max}: 4.34 ± 0.46 m/s, peak gradient (P_{max}): 76.22 ± 16.07 mmHg, P_{mean}: 44.93 ± 10.64 mmHg), whereas 29 (24%) of them had moderate AS (AVA: 1.16 ± 0.12 cm2, V_{max}: 3.79 ± 0.37 m/s, P_{max}: 58.11 ± 11.19 mmHg, P_{mean}: 32.65 ± 8.27 mmHg). A total of 47 patients (39%) had SVi ≤35 ml/m^2, of which 41 (87%) had severe AS and 6 (13%) had moderate AS.

As shown in **Table 2**, the study groups based on SVi > and ≤35 ml/m^2 showed no differences in terms of age, gender, body mass index, frequency of hypertension, diabetes, smoking, hyperlipidemia, or family history. Among echocardiographic parameters, LVEF, LV end-systolic diameter, LV mass, LV mass index, relative wall thickness, as well as V_{max}, P_{max}, and P_{mean}, were similar between the two patient groups (Table 2). In contrast, AVA, AVA index, LV end-diastolic diameter, cardiac output, and cardiac index were significantly lower in the group of AS-patients with SVi ≤35 ml/m^2 compared with those with SVi >35 ml/m^2 (Table 2). Also, the LV diastolic function parameter E/e` was higher in the group of AS-patients with SVi ≤35 ml/m^2 compared with those with SVi >35 ml/m^2, at the level of borderline significance **(Table 2)**.

Impact of stroke volume index on outcome

During a median (IQR) follow-up of 38 months (35-42 months), 10 patients (8%) died, with a significant difference in all-cause mortality between the two groups **(Table 3)**. All-cause mortality was significantly higher in the group of patients with SVi ≤ 35 ml/m^2 when compared to the group of patients with SVi >35 ml/m^2 (15% vs. 4%, $p<0.045$) **(Table 3)**.

Table 2. Demographic, clinical, and echocardiographic characteristics of the whole study group and according to the stroke volume index (SVi) cut-off of 35 mL/m².

Variable	All (n=121)	SVi >35 ml/m² (n=74)	SVi ≤35 ml/m² (n=47)	p-value
Age, years, (mean ± SD)	66 ± 11	66 ± 12	67 ± 9	0.381
Gender, males, n (%)	69 (57)	44 (59)	25 (53)	0.497
BMI, kg/m², (mean ± SD)	27.4 ± 4.0	27.5 ± 4.1	27.4 ± 4.1	0.953
Hypertension, n (%)	86 (71)	54 (73)	32 (68)	0.563
Diabetes, n (%)	25 (21)	13 (18)	12 (26)	0.292
Smoking, n (%)	16 (13)	7 (9)	9 (19)	0.125
Hyperlipidemia, n (%)	54 (45)	32 (43)	22 (47)	0.701
Family history, n (%)	12 (10)	6 (8)	6 (13)	0.534
LVEF, %, (mean ± SD)	72 ± 7	72 ± 7	72 ± 7	0.825
LV EDD, cm, (mean ± SD)	5.09 ± 0.50	5.17 ± 0.49	4.96 ± 0.49	0.021
LV ESD, cm, (mean ± SD)	3.18 ± 0.51	3.22 ± 0.50	3.15 ± 0.52	0.470
LV mass, g, (mean ± SD)	275.28 ± 74.89	283.67 ± 81.04	255.29 ± 57.63	0.130
LV mass index, g/m², (mean ± SD)	139.71 ± 30.97	144.39 ± 34.58	129.98 ± 20.05	0.063
Relative wall thickness, (mean ± SD)	0.50 ± 0.08	0.49 ± 0.07	0.52 ± 0.09	0.132
Left atrium, cm, (mean ± SD)	4.18 ± 0.57	4.16 ± 0.52	4.21 ± 0.64	0.588
Cardiac output, L/min, (mean ± SD)	4.92 ± 1.88	5.50 ± 1.85	4.06 ± 1.63	<0.001
Cardiac index, L/min/m², (mean ± SD)	2.66 ± 0.976	3.00 ± 0.89	2.12 ± 0.85	<0.001
AVA, cm², (mean ± SD)	0.84 ± 0.23	0.91 ± 0.23	0.74 ± 0.19	<0.001
AVA index, cm/m², (mean ± SD)	0.45 ± 0.11	0.48 ± 0.11	0.38 ± 0.09	<0.001
Vmax, m/s, (mean ± SD)	4.21 ± 0.50	4.25 ± 0.49	4.14 ± 0.49	0.234
Peak PG, mmHg, (mean ± SD)	72.09 ± 16.88	73.41 ± 17.19	69.61 ± 15.99	0.225
Mean PG, mmHg, (mean ± SD)	42.12 ± 11.37	43.07 ± 17.81	40.51 ± 9.77	0.219
E/E`, (mean ± SD)	12.73 ± 5.16	12.17 ± 4.71	14.04 ± 5.63	0.052
Pnet, (mean ± SD)	32.20 ± 10.67	32.97 ± 11.52	31.61 ± 8.92	0.507

Data are expressed as mean ± SD or as number (%). AVA = aortic valve area; AVR = aortic valve resistance; BMI = body-mass index; LV = left ventricle; LVEF = left ventricle ejection fraction; EDD = end-diastolic diameter; ESD = end-systolic diameter; ELI = energy loss index; PG = pressure gradient; Pnet = net pressure; Vmax = maximal aortic jet blood velocity; E/E' – indicator of left ventricular diastolic function.

According to the Kaplan–Meier analysis **(Figure 1)**, the cumulative incidence of all-cause mortality at mid- to long-term follow-up was significantly higher among patients with SVi ≤35 ml/m² than among those with SVi >35 ml/m² (log-rank p=0.035). The univariate Cox regression analyses **(Table 4)** demonstrated that higher SVi was associated with a lower hazard for all-cause mortality (HR: 0.872; 95% CI: 0.810-0.939; p<0.001). Accordingly, the all-cause mortality risk at long-term follow-up in AS patients decreases by 15% (1/0.872=1.15) for an additional measurement unit in SVi. Similarly, the group of AS-patients with SVi ≤35 ml/m² was associated with a 3.8 higher risk of all-cause mortality during long-term follow-up compared to the group of AS-patients with SVi >35 ml/m² (HR: 3.845; 95%CI: 1.004-14.871; p=0.041). Other variables significantly associated with all-cause mortality were AVA (HR: 0.014; 95% CI: 0.001-0.426; p=0.014) and AVA index (HR: 0.001; 95% CI: 0.001-0.022; p=0.003).

DISCUSSION

The most important finding of our study is that a reduced left ventricular SVi below 35 ml/m² may predict all-cause mortality during long-term follow-up in asymptomatic patients with moderate or severe AS, concordantly high P_{mean} across the aortic valve, and preserved LVEF. The predictive importance of low-flow in asymptomatic patients with severe AS was also documented by Marechaux et al. (8) and Rusinaru et al. (15), but our study is the first to extend this finding to SVi ≤35 ml/m² rather than ≤30

Table 3. All-cause mortality at median follow-up of 38 months (interquartile range 35-42 months) in the whole study group and according to stroke volume index (SVi) cut-off of 35 ml/m².

	All (n=121)	SVi >35 ml/m² (n=74)	SVi ≤35 ml/m² (n=47)	p-value
All-cause mortality, n (%)	10 (8)	3 (4)	7 (15)	0.045

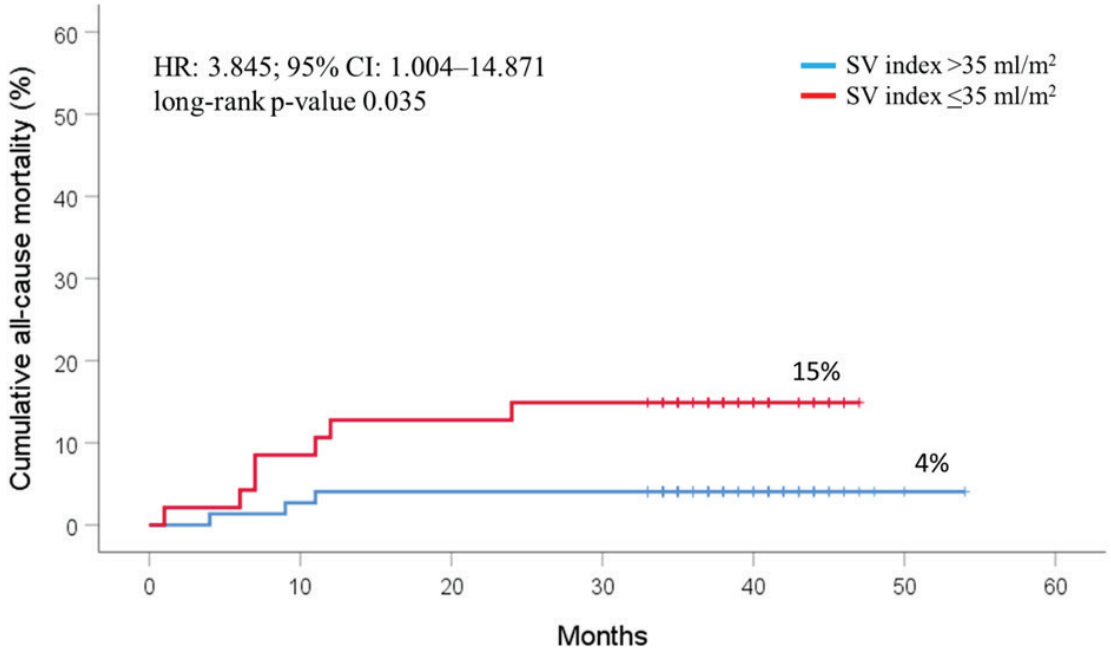

Figure 1. The Kaplan–Meier survival curve of all-cause mortality according to stroke volume (SV) index > and ≤35 ml/m². Median follow-up was 38 months (interquartile range: 35–42 months). CI – confidence interval; HR – hazard ratio.

Table 4. Univariate Cox regression analyses for all variables in predicting long-term all-cause mortality rate in patients with moderate-to-severe aortic stenosis with preserved ejection fraction and nonobstructed coronary arteries.

Univariate Cox regression analysis			
Variable	**HR**	**95% CI**	**p-value**
Age, years	1.039	0.965 – 1.119	0.306
Gender, males	1.053	0.297 – 3.731	0.937
BMI, kg/m²	1.085	0.921 – 1.278	0.332
Hypertension	1.603	0.340 – 7.549	0.551
Diabetes	2.469	0.697 – 8.751	0.161
Smoking	1.729	0.367 – 8.144	0.488
Hyperlipidemia	1.865	0.482 – 7.213	0.366
Family history	23.502	(–) - (-)	0.500
LVEF, %	0.955	0.873 – 1.045	0.316
LV EDD, cm	1.857	0.544 – 6.340	0.323
LV ESD, cm	2.739	0.836 – 8.972	0.096
LV mass, g	0.999	0.986 – 1.011	0.821
LV mass index, g/m²	0.993	0.960 – 1.027	0.679
Relative wall thickness	0.001	0.001 – 55.162	0.175
Left atrium, cm	2.053	0.708 – 5.947	0.185
Cardiac output, L/min	0.795	0.563 – 1.123	0.193
Cardiac index, L/min/m²	0.553	0.266 – 1.152	0.113
AVA, cm²	0.014	0.001 – 0.426	0.014
AVA index, cm/m²	0.001	0.001 – 0.022	0.003
Vmax, m/s	1.305	0.376 – 4.530	0.675
Peak PG, mmHg	1.008	0.972 – 1.045	0.675
Mean PG, mmHg	1.005	0.952 – 1.061	0.858
E/E`	1.047	0.940 – 1.167	0.402
Pnet	1.017	0.962 – 1.076	0.550
SV index, ml/m² (continuous variable)	0.872	0.810 – 0.939	<0.001
SV index, ml/m² (categorical variable)	3.845	1.004 – 14.871	0.041

Dependent variable: all-cause mortality at long-term follow-up.
CI – confidence interval; HR – hazard ratio; SV – stroke volume. Other abbreviations are in **Table 2**.

ml/m². However, our cohort is small and has few events, and thus should be viewed as hypothesis-generating.

In patients with severe AS, a state of low LV stroke volume, defined as SVi ≤35 ml/m², can be associated either with a concordantly high P_{mean} or lower-than-expected P_{mean} over the aortic valve. These patients with severe AS and low SVi can be further divided into:

a) patients with reduced LVEF (<50%; so-called "classical low-flow low-gradient AS"); and
b) patients with preserved LVEF - (≥50%; so-called "paradoxical low-flow low-gradient AS") (3,5-8).

The poorer prognosis of patients with "classical low-flow low-gradient AS" is not surprising, given the generally increased risk of adverse events in patients with low LVEF. However, it has also been shown that patients with so-called "paradoxical low-flow low-gradient AS" who, by definition, have normal LVEF and low SVi, have a less favorable prognosis than patients with concordantly high mean-gradient AS (3). On the other hand, data on the prognostic significance of low SVi in AS patients with concordantly high P_{mean} over the aortic valve are limited. Our results similarly show that SVi has prognostic importance in patients with AS and concordantly high P_{mean} across the aortic valve, with the threshold for low SVI set at 35 ml/m², a value previously proposed for patients with low-flow low-gradient AS (3-7). Our cohort, similar to patients with "paradoxical low-flow low-gradient" AS, is characterized by increased LV afterload, high systolic wall stress, and compensatory LV hypertrophy. Both parameters lead to impaired flow across the aortic valve and consequent multi-organ hypoperfusion. This also translates to myocardial hypoperfusion and potential scarring of the myocardium. The process of hypoperfusion often precedes AS-related symptoms, while consequential myocardial damage may be irreversible even in the case of a successful aortic valve replacement (AVR) procedure (16). Furthermore, almost all echocardiographic parameters used to determine AS severity are flow-dependent; thus, it is important to recognize the low-flow state and avoid underestimating AS severity, which might, as stated above, delay the AVR, a life-saving and myocardial-saving procedure.

Until recently, the prognosis for asymptomatic patients with moderate and/or severe AS and preserved LVEF was considered relatively favorable, meaning that no intervention was indicated for these patients (17). However, it has been shown that the natural history of asymptomatic patients with moderate or severe AS is not benign (18-19). Moreover, in recent years, several randomized studies have shown that early intervention in these patients leads to better long-term outcomes than monitoring and medical management of comorbidities until symptoms develop or other guidelines-directed indications for intervention arise (20-22). It is not known whether the benefits of early surgical or transcatheter aortic valve replacement observed in the aforementioned randomized studies can be extrapolated to asymptomatic patients with low-flow AS, as this subgroup was not explicitly addressed in these studies. Until the indication for early aortic valve replacement in truly asymptomatic patients with moderate-to-severe AS and normal LVEF is confirmed, additional parameters could help guide decisions regarding potential intervention. These parameters include assessment of extracardiac damage, detection of myocardial fibrosis using cardiac magnetic resonance, and echocardiographic analysis of LV parameters, including LV SVi (23).

Study limitations

Our study has limitations given the relatively small number of patients and the few events of interest. Therefore, larger, prospective studies are required to further confirm the prognostic significance of LV SVi in the analyzed patient population with hemodynamically significant aortic stenosis. We were also unable to stratify mortality by cardiovascular or non-cardiovascular causes, which would further aid in understanding the prognostic significance of SVi.

We did not assess intraobserver variability. However, as we included both patients with moderate and severe AS, we believe that the possibility of including patients without hemodynamically significant AS was minimal. Similarly, given that V_{max} is the echocardiographic variable least susceptible to measurement error, we do not believe that intraoperator variability significantly affects the accuracy of AS severity assessment or flow across the aortic valve.

CONCLUSION

The left ventricular SVi could be a significant predictor of all-cause mortality during long-term follow-up in asymptomatic patients with moderate or severe AS, concordantly high Pmean, and preserved LVEF. Further research with a larger number of patients is needed to confirm SVi as a risk-stratification and decision-making tool for these patients.

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Conflict of Interest: The authors disclose no conflict of interest relevant to this research

Author contributions:

MB, IN, SA, and VG contributed to the conception and design of the work, the interpretation of data, the critical revision of the manuscript, and the overall supervision of the project. They also provided technical support with echocardiographic indexing and visualization. IS performed statistical analysis. NM and ST contributed to data analysis and interpretation, and drafted the manuscript. SJ, AĐ, NB, and SD were responsible for acquiring and processing echocardiographic and clinical data. MO,

MR, IB, and KŽ contributed to patient selection, data quality control, and clinical interpretation. DŠ, TS, LP, AB, and AS assisted in database management and literature review.

All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethical approval: Ethical Committee of the University of Belgrade - Faculty of Medicine (number: 440IVI-13, June 19th 2009).

Informed consent: All patients gave written informed consent to participate in the study.

References:

1. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al: Guidelines on the management of valvular heart disease. Eur Heart J 2012;33:2451–496. doi:10.1093/eurheartj/ehs109.
2. Rana M. Aortic Valve Stenosis: Diagnostic Approaches and Recommendations of the 2021 ESC/EACTS Guidelines for the Management of Valvular Heart Disease -A Review of the Literature. Cardiol Cardiovasc Med. 2022 Jun; 6(3):315-24. doi:10.1186/1476-7120-4-27.
3. Snir AD, Ng MK, Strange G, Playford D, Stewart S, Celermajer DS. Prevalence and outcomes of low-gradient severe aortic stenosis—from the national echo database of Australia. J Am Heart Assoc. 2021; 10(22):e021126. doi: 10.1161/JAHA.121.021126.
4. Delgado V, Bax JJ. Left ventricular stroke volume in severe aortic stenosis and preserved left ventricular ejection fraction: prognostic relevance. Eur Heart J 2018; 39(21):2000–2. doi:10.11909/j.issn.1671-5411.2016.06.001.
5. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation. 2007;115:2856–64. doi: 10.1161/CIRCULATIONAHA.106.668681.
6. Clavel MA, Pibarot P, Dumesnil JG. Paradoxical low flow aortic valve stenosis: incidence, evaluation, and clinical significance. Curr Cardiol Rep. 2014;16:431. doi: 10.1007/s11886-013-0431-x.
7. Hahn R, Pibarot P. Low-flow, low-gradient severe aortic stenosis: diagnosis, treatment and prognosis. Eurointervention 2016; 12 (6):627-36. doi: 10.4244/EIJV9SSA8.
8. Maréchaux S, Rusinaru D, Altes A, Pasquet A, Vanoverschelde JL, Tribouilloy C. Prognostic Value of Low Flow in Patients With High Transvalvular Gradient Severe Aortic Stenosis and Preserved Left Ventricular Ejection Fraction: A Multicenter Study. Circulation: Cardiovascular Imaging. 2019;12(10):e009299. doi:10.1161/CIRCIMAGING.119.009299.
9. Sen J, Huynh Q, Stub D, Neil C, Marwick TH. Prognosis of Severe Low-Flow, Low-Gradient Aortic Stenosis by Stroke Volume Index and Transvalvular Flow Rate. J Am Coll Cardiol Img 2021;(5) 915–927. doi: 10.1016/j.jcmg.2020.12.029.
10. Sahn DJ, DeMaria A, Kisslo J, Weyman A. The committee on M-Mode Standardization of the American Society of Echocardiography: Recommendations regarding quantification in M-mode echocardiography: Results of a survey of echocardiographic measurements. Circulation 1978; 58:1072-83. doi:10.1161/01.cir.58.6.1072.
11. Hammond IW, Devereux RB, Alderman MH, Lutas EM, Spitzer MC, Crowley JS, et al. The prevalence and correlates of echocardiographic left ventricular hypertrophy among patients with uncomplicated hypertension. J Am Coll Cardiol 1986; 7:639-50. doi: 10.1016/s0735-1097(86)80476-4.
12. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. American Society of Echocardiography Committee on Standards. Recommendations for quantification of the left ventricle by two-dimensional echocardiography. J Am Soc Echocardiogr 1989; 2:358-67. doi: 10.1016/s0894-7317(89)80014-8.
13. Otto CM, Pearlman AS, Gardner CL, Enomoto MD, Togo T, Tsuboi H, et al. Experimantal validation of Doppler echocardiographic measurement of volume flow through the stenotic aortic valve. Circulation 1988; 78(2):435-41. doi:10.1161/01.cir.78.2.435.
14. Otto CM, Pearlman AS, Comess KA, Reamer RP, Janko CL, Huntsman LL. Determination of the stenotic aortic valve area in adults using Doppler echocardiography. J Am Coll Cardiol 1986; 7(3):509-17. doi: 10.1016/s0735-1097(86)80460-0.
15. Rusinaru D, Bohbot Y, Anne Ringle, Maréchaux S, Diouf M, Tribouilloy C. Impact of low stroke volume on mortality in patients with severe aortic stenosis and preserved left ventricular ejection fraction Eur Heart J. 2018;39(21):1992-9. doi:10.1093/eurheartj/ehy123.
16. Thornton GD, Bennett JB, Nitsche C, et al. Myocardial Hypoperfusion in Severe Aortic Stenosis Is Reversed Early After Aortic Valve Replacement. J Am Coll Cardiol Img 2024; 7 (8):1006–1008. doi.org/10.1016/j.jcmg.2024.03.008.
17. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Stephan Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022;43: 561-632. doi: 10.1093/eurheartj/ehac051.
18. Strange G, Stewart S, Celemajer D, Prior D, Scalia GM, Marwick T, et al. Poor Long-Term Survival in Patients With Moderate Aortic Stenosis. J Am Coll Cardiol 2019; 15:1851-1863. doi: 10.1016/j.jacc.2019.08.004.
19. Kvaslerud AB, Santic K, Hussain AI, Auensen A, Fiane A, Skulstad H, et al. Outcomes in asymptomatic, severe aortic stenosis. PloS One 2021; 4: e0249610. doi: 10.1371/journal.pone.0249610. eCollection 2021.
20. Banovic M, Putnik S, Penicka M, Doros G, Deja MA, Kockova R, et al. Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis: The AVATAR Trial. Circulation 2022;145(9):648-58. doi:10.1161/CIRCULATIONAHA.121.057639.
21. Banovic M, Putnik S, Da Costa B. Aortic valve replacement vs. conservative treatment in asymptomatic severe aortic stenosis: long-term follow-up of the AVATAR trial. Eur Heart J 2024; 45(42):4526-4535. doi: 10.1093/eurheartj/ehae585.
22. Généreux P, Schwartz A, Oldemeyer B, Pibarot P, Cohen DJ, Blanke P, et al. Transcatheter Aortic-Valve Replacement for Asymptomatic Severe Aortic Stenosis. N Eng J med 2025; 392:217-227. doi: 10.1056/NEJMoa2405880.
23. Banovic M, Iung B, Wojakowski W, Mieghem NV, Bartunek J. Aymptomatic Severe and Moderate Aortic Stenosis: Time for Appraisal of Treatmant Indication. Struct Heart 2023;7(5):100201. doi: 10.1016/j.shj.2023.100201.

PROGNOSTIČKI ZNAČAJ INDEKSIRANOG UDARNOG VOLUMENA KOD ASIMPTOMATSKIH PACIJENATA SA UMERENOM DO TESNOM AORTNOM STENOZOM I OČUVANOM EJEKCIONOM FRAKCIJOM LEVE KOMORE

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Sažetak

Uvod: Kad intervenisati kod asimptomatskih pacijenata sa umerenom/tesnom aortnom stenozom (AS) i očuvanom ejekcionom frakcijom leve komore (EFLK) još nije utvrđeno. Kod pacijenata sa AS nizak protok preko aortne valvule se definiše kao indeksiran udarni volumen (UVi) ≤35 ml/m^2. Cilj našeg rada je bio da utvrdimo odnos između UVi i ukupnog mortaliteta kod asimptomatskih pacijenata sa umerenom ili tesnom AS, odgovarajuće visokim srednjim gradijentom preko aortne valvule ($P_{srednje}$) i očuvanom EFLK.

Metode: U studiju je uključen 121 asimptomatski pacijent (69 muškaraca, prosečne starosti 66±11 godina) sa umerenom ili tesnom AS (površina aortnog ušća ≤1,5 cm^2), odgovarajuće visokim $P_{srednje}$ (≥30 mmHg) i očuvanom EFLK (≥50%). Medijana perioda praćenja pacijenata je iznosila 38 meseci (IQR 35-42 meseca).

Rezultati: Tokom perioda praćenja umrlo je deset pacijenata (8%). Ukupna smrtnost je bila značajno veća u grupi AS-pacijenata sa UVi ≤35 ml/m^2 u odnosu na grupu AS-pacijenata sa UVi >35 ml/m^2 (15% vs. 4%, p<0,045). Kumulativna incidenca ukupnog mortaliteta je bila značajno veća u grupi AS-pacijenata sa UVi ≤35 ml/m^2 u odnosu na grupu AS-pacijenata sa UVi >35 ml/m^2 (log-rank p=0,035). Grupa AS-pacijenata sa UVi ≤35 ml/m^2 je bila udružena sa 3,8 puta većim rizikom od ukupnog mortaliteta u dugoročnom periodu praćenja u odnosu na grupu AS-pacijenata sa UVi >35 ml/m^2 (HR: 3,845; 95%CI: 1,004-14,871; p=0,041).

Zaključak: Na osnovu naših rezultata, UVi bi mogao biti značajan prediktor mortaliteta kod asimptomatskih pacijenata sa umerenom ili tesnom AS, visokim $P_{srednje}$ i očuvanom EFLK. Studije sa većim brojem ispitanika i događaja su neophodne kako bi potvrdile ove rezultate.

Ključne reči: aortna stenoza, asimptomatski udarni volumen, indeksiran udarni volumen, Doppler ehokardiografija, ishod

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REVIEW ARTICLE

Neurodevelopmental disorders in children with 22q11.2 deletion syndrome and recommendations for pediatric follow-up

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Summary

Neurodevelopmental disorders are the most prevalent chronic diagnoses in pediatric primary care, with rising incidence and significant impact on cognitive, motor, social, and communication functioning. 22q11.2 deletion syndrome (22q11.2 DS)—the most common human microdeletion syndrome—presents with a broad spectrum of somatic and neurodevelopmental abnormalities. Nearly all individuals with 22q11.2 DS show neurodevelopmental difficulties, including delays in motor and speech milestones, cognitive impairments, and behavioral challenges. The disorder affects approximately 1 in 2,500 newborns and is also associated with congenital heart defects, palatal anomalies, hypocalcemia, and immunodeficiency. Neurodevelopmental manifestations typically begin in infancy with delayed motor and speech development and progress into school age with difficulties in learning, attention, and peer interaction. Intellectual disabilities are common, with a distribution skewed toward lower IQ scores. Children often exhibit a verbal-performance IQ discrepancy and may experience further cognitive decline in adolescence or adulthood. Over 40% of affected individuals meet criteria for autism spectrum disorder, attention-deficit/hyperactivity disorder, or both. They also have increased risks for psychiatric conditions such as anxiety, depression, and schizophrenia. Pediatricians, as primary care providers, play a critical role in early identification and long-term monitoring. Recommendations include routine developmental assessments, early interventions (e.g., speech and occupational therapy), and regular IQ and adaptive functioning evaluations, especially during educational transitions. Early diagnosis and individualized, multidisciplinary approaches are essential to improve developmental outcomes and quality of life in children with 22q11.2 DS.

Keywords: 22q11.2 deletion syndrome, DiGeorge syndrome, neurodevelopmental disorders

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INTRODUCTION

Neurodevelopmental disorders arise during childhood, are usually multifactorial, and create chronic, often lifelong cognitive, motor, social, speech, communication, and other problems. This definition excludes disorders such as anxiety or depression in children and adolescents, which have a more episodic occurrence. In addition, ICD-11 classification excludes psychoses (e.g., schizophrenia) and bipolar affective disorder (1). Developmental problems are the most common chronic diagnosis made in primary pediatric health care. Their prevalence is not only high, but also increasing and reaches 17.08%, with the most significant contribution of attention-deficit/hyperactivity disorder (9.5%), autism spectrum disorder (2.5%) and intellectual disability (0.9%-1.2%, $P < .05$). Only the prevalence (4.1%) of disorders classified as other developmental delay seems to be slightly decreasing (2). Research studies also show that developmental disorders are more common among boys, children with birth weight ≥2500 g, those of lower socioeconomic status, and those who live in urban areas, with less educated mothers or with a mentally ill family member (2,3).

A term 22q11.2 deletion syndrome (22q11.2 DS) is a collective name for a range of phenotypes previously described as DiGeorge syndrome, Shprintzen or Velocardiofacial syndrome, or Conotruncal anomaly face syndrome. It is caused by a deletion of the 22q11.2 region of about 2.5-3 Mb in size, which is the most common (approximately 1:2500 newborns) microdeletion occurring in the human genome. 22q11.2 DS is characterized by a wide range of neurodevelopmental and somatic disbalances, growth disturbances, anomalies of the heart, palate, and urinary tract, hypoparathyroidism with hypocalcemia, and thymic hypoplasia with T-cell immunodeficiency as presented in **Table 1** (4-8). Neurodevelopmental symptomatology can be observed in almost all children with 22q11.2 DS by careful clinical examination and/or formal testing (4).

METHODS

For this narrative review, a comprehensive literature search was conducted using the PubMed database. The search included studies published at any time up to March 2025, without restrictions on publication date. The following keywords were used individually and in combination to identify relevant references: 22q11.2 deletion syndrome, neurodevelopmental disorders, and follow-up. The selection of articles focused on studies addressing the neurodevelopmental outcomes and follow-up of individuals with 22q11.2 deletion syndrome, including both clinical and research-based findings. Additional references were identified through manual screening of citations within the selected articles to ensure a broad and representative overview of the available literature. Only English-language publications were considered.

DIAGNOSIS OF 22q11.2 DS

The first step in the diagnosis of 22q11.2 DS is to raise the clinical suspicion of this syndrome, or, in less clear phenotypic presentations, of a genetic dysmorphic disorder in general (9,10). After that, during pre-test counseling, we discuss with patients and/or parents the potential benefits and limitations of genetic testing and choose the most appropriate test. Test results will be discussed during post-test counseling.

The detection of microdeletion 22q11.2 in the genome of affected children and adults has become much easier and more precise with the introduction of modern genomic testing (11). As presented in **Table 1**, the gold standard is molecular karyotyping (chromosomal microarray) on a sample of the patient's extracted DNA. This analysis enables the detection of microdeletion, but also precise characterization by determining its size and exact localization in the genome. Moreover, this approach allows, with very high confidence, searching throughout the genome and exclusion of associated chromosomal rearrangements (4).

Next-generation sequencing (NGS) is a cutting-edge diagnostic approach in genetics that has changed the face of clinical genetics over the last decade. Initially designed for the detection of intragenic variants (e.g., point mutations), this method has now been perfected to detect also chromosomal variants (aberrations) with a high precision that is only slightly lower than the precision of molecular karyotyping. Thus, in patients with an unclear phenotype, which is so common in the clinical geneticist's practice, this single method can provide a comprehensive genome search, including the detection of both intragenic and chromosomal variants (11,12).

More traditional diagnostic approaches (e.g., fluorescence in situ hybridization or multiplex ligation-dependent probe amplification (MLPA)) are usually used when the patient's phenotype is clear. Therefore, genomic search is not necessary (9). Additionally, MLPA, as a fast and not overly expensive method, can be used for a wide range of testing in a less selected group of patients (13).

SPECTRUM OF NEURODEVELOPMENTAL DISORDERS IN 22q11.2 DS

Individuals with 22q11.2 DS are at increased risk for neurodevelopmental disorders, specifically for a range of cognitive, behavioral, and emotional difficulties. This can result in various problems in the sphere of learning, interpersonal relationships, and social functioning (14). In this article, we will briefly review the most common

Table 1. Basic principles of management of patients with 22q11.2 deletion syndrome

Management category	Key Points
When to suspect 22q11.2 deletion syndrome	• congenital heart defects (especially conotruncal anomalies) • hypocalcemia/hypoparathyroidism • immune deficiency (recurrent infections) • facial dysmorphism, palatal anomalies • developmental delay (speech, motor, social) • behavioral issues (ADHD, ASD, anxiety)
Recommended diagnostic genetic tests	• First-line: CMA; consider MLPA or FISH if phenotype is typical • second-line: NGS if CMA is negative, for broader (intragenic) variant detection
Basic principles of treatment (other than developmental support)	• specialist-directed treatments: management of cardiac, palate, renal, autoimmune, endocrine, and psychiatric conditions is guided by respective specialists • immune system support: aggressive infection management, possible use of prophylactic antibiotics or immunoglobulins; consider irradiated blood products/postponement of live vaccines until immune function normalizes • growth, nutritional, and gastrointestinal care: consider growth hormone, calcium supplementation, treatment for reflux or dysmotility disturbances • sensory support: hearing aids for hearing loss; treatment for ocular anomalies.
Prenatal testing recommendations	• testing of parents before pregnancy for an accurate assessment of recurrence risk • CMA is the most commonly used method, which also analyzes other chromosomal regions

ADHD – attention deficit hyperactivity disorder; ASD – autism spectrum disorder; CMA – chromosomal microarray; FISH – fluorescence in situ hybridization; MLPA – multiplex ligation-dependent probe amplification; NGS – next generation sequencing

neurodevelopmental concerns encountered in children and adolescents with 22q11.2 DS.

In infancy and toddlerhood, the main concerns are related to taking care of heart defects, feeding problems, acquiring milestones of gross motor skills, first words, and basic social skills in children with 22q11.2 DS. In general, the mean age at walking is 18 months, associated with a delay in the acquisition of speech (many are non-verbal until the age of 2-3 years, often with an acceleration in expressive speech after that) (15). A recent study confirmed that children with 22q11.2 microdeletion have impaired articulation skills and expressive language abilities. However, it did not report weaker receptive language skills and immediate verbal memory compared to healthy controls. Authors propose that children with 22q11.2DS should be considered as a risk category for the development of speech–sound pathology and expressive language abilities, and should be examined and included in a program of early speech–language stimulation immediately after diagnosis (16).

As the start of school approaches, intellectual disability, difficulties in learning and attention, as well as functional relationships with peers, come into focus. For early recognition, it is helpful to know that children and adults diagnosed with intellectual disabilities are mainly recruited from the population of the youngest with a diagnosis of global developmental delay, and this is the case not only for 22q11.2 DS but also for other syndromes with developmental challenges. Children and youth with 22q11.2 have a normal distribution of intellectual achievement shifted by about 30 points to the left compared to the general population, and with peak incidence at IQ 70-75. The incidence further declines on both sides, with about 40-45% of those having mild to moderate intellectual disabilities (17,18). It is worth mentioning that a relatively significant proportion of people with 22q11.2 DS face a relatively mild but gradual intellectual decline after elementary school age and later during adulthood (19,20). Also, it should be noted that the total IQ score does not accurately represent the functionality of an affected individual, given the significantly higher verbal IQ score compared to the performance IQ score. Thus, these two dimensions should be considered separately (15).

In the study of Niklasson et al, 100 consecutively referred individuals with 22q11.2 DS were investigated for autism spectrum disorders (ASDs), attention deficit/hyperactivity disorder (ADHD), and intellectual disability (ID) using in-depth neuropsychiatric assessments and questionnaire screens. ASDs, ADHD, and ID were diagnosed in 23, 30, and 51 individuals, respectively, with some patients having more than one of these diagnoses. Females had a higher IQ than males. The results show that more than 40% of individuals with 22q11.2 DS meet criteria for either ASD, ADHD, or both (18). It also seems that individuals with 22q11.2 microdeletion, as well as with some other CNVs, who don't meet full autism diagnostic criteria, have elevated levels of autistic traits (21).

The risk of a child developing some of the neuropsychiatric disorders later during adolescence and life is increased, and is also among the major concerns of parents. Early predictors might involve attention deficit, hyperactivity, poorer impulse control, shyness, withdrawal, and autistic features with or without intellectual or language impairment. Current data show that individuals with 22q11.2 DS are at increased risk for anxiety, depression, and psychosis, with schizophrenia being diagnosed in approximately 25% of patients (22).

RECOMMENDATIONS FOR SCREENING OF NEURODEVELOPMENTAL DISORDERS IN 22q11.2 DS FOR PEDIATRICIANS

The task of the health and other related systems is to recognize the initial phase of neurodevelopmental delay on time and, through informing, supporting, and specific programs, enable patients and parents to mitigate the consequences for the functionality and the quality of life as a whole. It is helpful to know that intellectual and overall cognitive achievements do not only depend on genetic factors, i.e., microdeletion and modifier genes, but also on parental, family, and broader social factors of resilience and vulnerability. This, together with the increased risk for behavioral and psychiatric problems, suggests the need for early psychological/psychiatric monitoring and interventions in individuals with 22q11.2 DS (17).

Pediatricians are professionals who are the first to meet children and follow them, in many countries, until the end of secondary school or up to 18 years of age. Further in this section, we present some of the recommendations for developmental assessment and follow-up of children with 22q11.2 DS that can be useful to pediatricians at different levels of health care, especially primary care:

- Formal developmental testing is recommended for children of all ages at the time of diagnosis.
- In case of early diagnosis of 22q11.2 DS, formal testing is recommended as early as the first year of life, even without clinically apparent developmental delays. Almost all infants/children with the syndrome show at least some degree of neurodevelopmental delay.
- For infants and toddlers, early consideration and implementation of developmental interventions is necessary and usually includes physio/occupational/speech therapy and sensory integration.
- The assessment of speech and communication should include not only expressive speech, but also receptive speech (i.e., comprehension); otherwise, it can lead to overestimation of a child's capacities.
- For school-age children, periodic formal assessments of IQ and adaptive functioning are recommended, especially during transition periods (preschool-primary and elementary-secondary school).
- The type of schooling depends on overall cognitive capacities, educational profile, and various individual and environmental factors. Schooling with adapted educational programs, as well as more intensive interventions (supports) in the educational process, is considered (15,23).

CONCLUSION

Neurodevelopmental disorders are present in the vast majority of pediatric patients with 22q11.2 DS. As children grow older, the prevalence of specific neurodevelopmental entities changes, along with possible cognitive decline and the occurrence of neuropsychiatric disorders in some affected individuals.

Repeated formal neurodevelopmental assessments from early childhood to adolescence are recommended to provide better support, optimize interventions, and generally promote better health and quality of life. Although most of the recommendations listed above are applicable to everyone with 22q11.2 DS, management of developmental issues can be tailored to the characteristics of the individuals and the capacities of the community. Hence, some patients may require an even more comprehensive approach to the recognition and monitoring of neurodevelopmental risks/disorders.

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References

1. Latas M, Ivković M, Janjić V. Psihopatologija u okvirima MKB-11. Beograd: CEDUP; 2022.
2. Zablotsky B, Black LI, Maenner MJ, Schieve LA, Danielson ML, Bitsko RH, et al. Prevalence and Trends of Developmental Disabilities among Children in the United States: 2009-2017. Pediatrics. 2019 Oct;144(4):e20190811. doi: 10.1542/peds.2019-0811. PMID: 31558576; PMCID: PMC7076808
3. Yang Y, Zhao S, Zhang M, Xiang M, Zhao J, Chen S, et al. Prevalence of neurodevelopmental disorders among US children and adolescents in 2019 and 2020. Front Psychol. 13:997648. doi: 10.3389/fpsyg.2022.997648
4. Firth HV, Hurst JA. Oxford desk reference: clinical genetics and genomics. 2nd ed. Oxford: Oxford University Press; 2017.
5. Rakonjac M, Cuturilo G, Stevanovic M, Jelicic L, Subotic M, Jovanovic I, et al. Differences in speech and language abilities between children with 22q11.2 deletion syndrome and children with phenotypic features of 22q11.2 deletion syndrome but without microdeletion. Res Dev Disabil. 2016 Aug;55:322-9. doi: 10.1016/j.ridd.2016.05.006. Epub 2016 May 25. PMID: 27235769.
6. Cuturilo G, Drakulic D, Krstic A, Gradinac M, Ilisic T, Parezanovic V, et al. The role of modern imaging techniques in the diagnosis of malposition of the branch pulmonary arteries and possible association with microdeletion 22q11.2. Cardiol Young. 2013 Apr;23(2):181-8. doi: 10.1017/S1047951112000571. Epub 2012 Apr 26. PMID: 22717372.
7. Cuturilo G, Drakulic D, Stevanovic M, Jovanovic I, Djukic M, Miletic-Grkovic S, et al. A rare association of interrupted aortic arch type

C and microdeletion 22q11.2. Eur J Pediatr. 2008 Oct;167(10):1195-8. doi: 10.1007/s00431-007-0632-7. Epub 2007 Nov 27. PMID: 18040716.

8. Cuturilo G, Drakulic D, Jovanovic I, Ilic S, Kalanj J, Vulicevic I, et al. The Impact of 22q11.2 Microdeletion on Cardiac Surgery Postoperative Outcome. Pediatr Cardiol. 2017 Dec;38(8):1680-1685. doi: 10.1007/s00246-017-1713-7. Epub 2017 Sep 22. PMID: 28940032.
9. Cuturilo G, Drakulic D, Jovanovic I, Krstic A, Djukic M, Skoric D, et al. Improving the Diagnosis of Children with 22q11.2 Deletion Syndrome: A Single-center Experience from Serbia. Indian Pediatr. 2016 Sep 8;53(9):786-789. doi: 10.1007/s13312-016-0931-z. PMID: 27771646.
10. Cuturilo G, Menten B, Krstic A, Drakulic D, Jovanovic I, Parezanovic V, et al. 4q34.1-q35.2 deletion in a boy with phenotype resembling 22q11.2 deletion syndrome. Eur J Pediatr. 2011 Nov;170(11):1465-70. doi: 10.1007/s00431-011-1533-3. Epub 2011 Jul 22. PMID: 21833498.
11. Bergant G, Maver A, Lovrecic L, Čuturilo G, Hodzic A, Peterlin B. Comprehensive use of extended exome analysis improves diagnostic yield in rare disease: a retrospective survey in 1,059 cases. Genet Med. 2018 Mar;20(3):303-312. doi: 10.1038/gim.2017.142. Epub 2017 Sep 14. PMID: 28914264.
12. Stojanovic JR, Miletic A, Peterlin B, Maver A, Mijovic M, Borlja N, et al. Diagnostic and Clinical Utility of Clinical Exome Sequencing in Children With Moderate and Severe Global Developmental Delay / Intellectual Disability. J Child Neurol. 2020 Feb;35(2):116-131. doi: 10.1177/0883073819879835. Epub 2019 Oct 17. PMID: 31623504.
13. Miletic A, Stojanovic JR, Parezanovic V, Rsovac S, Drakulic D, Soldatovic I, et al. Genetic evaluation of newborns with critical congenital heart defects admitted to the intensive care unit. Eur J Pediatr. 2021 Oct;180(10):3219-3227. doi: 10.1007/s00431-021-04097-w. Epub 2021 May 7. PMID: 33963417.
14. Swillen A, Moss E, Duijff S. Neurodevelopmental outcome in 22q11.2 deletion syndrome and management. Am J Med Genet A. 2018 Oct;176(10):2160-2166. doi: 10.1002/ajmg.a.38709. Epub 2018 Apr 25. PMID: 29696780; PMCID: PMC6202262.
15. McDonald-McGinn DM, Hain HS, Emanuel BS, et al. 22q11.2 Deletion Syndrome. 1999 Sep 23 [updated 2024 May 9]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1523/
16. Rakonjac M, Cuturilo G, Kovacevic-Grujicic N, Simeunovic I, Kostic J, Stevanovic M, et al. Speech Sounds Production, Narrative Skills, and Verbal Memory of Children with 22q11.2 Microdeletion. Children (Basel). 2024 Apr 19;11(4):489. doi: 10.3390/children11040489. PMID: 38671706; PMCID: PMC11049265.
17. Swillen A, McDonald-McGinn D. Developmental trajectories in 22q11.2 deletion. Am J Med Genet C Semin Med Genet. 2015 Jun;169(2):172-81. doi: 10.1002/ajmg.c.31435. Epub 2015 May 18. PMID: 25989227; PMCID: PMC5061035.
18. Niklasson L, Rasmussen P, Oskarsdóttir S, Gillberg C. Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. Res Dev Disabil. 2009 Jul-Aug;30(4):763-73. doi: 10.1016/j.ridd.2008.10.007. Epub 2008 Dec 13. PMID: 19070990.
19. Gothelf D, Frisch A, Michaelovsky E, Weizman A, Shprintzen R. Velo-cardio-facial syndrome. J Ment Health Res Intellect Disabil. 2009; 2:149.doi: 10.1080/19315860902756136.
20. Green T, Gothelf D, Glaser B, Debbane M, Frisch A, Kotler M, et al. Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11. 2 Deletion) Syndrome. J Am Acad Child Psy. 2009; 48:1060–1068.
21. Chawner SJRA, Doherty JL, Anney RJL, Antshel KM, Bearden CE, Bernier R, et al. A genetics-first approach to dissecting the heterogeneity of autism: phenotypic comparison of autism risk copy number variants. Am J Psychiatry. 2021 Jan 1;178(1):77–86. doi: 10.1176/appi.ajp.2020.20010015. PMID: 33384013; PMCID: PMC8022239.
22. Bassett AS, McDonald-McGinn DM, Devriendt K, Digilio MC, Goldenberg P, Habel A, et al. Practical guidelines for managing patients with 22q11.2 deletion syndrome. J Pediatr. 2011;159(2):332–9.e1.
23. Óskarsdóttir S, Boot E, Crowley TB, Loo JCY, Arganbright JM, Armando M, et al. Updated clinical practice recommendations for managing children with 22q11.2 deletion syndrome. Genet Med. 2023 Mar;25(3):100338. doi: 10.1016/j.gim.2022.11.006. PMID: 36729053.

NEURORAZVOJNI POREMEĆAJI KOD DECE SA 22q11.2 DELECIJSKIM SINDROMOM I PREPORUKE ZA PEDIJATRIJSKO PRAĆENJE

Goran Čuturilo[1,2], Zorana Pavlović[1,3], Danijela Drakulić[4]

Sažetak

Neurorazvojni poremećaji predstavljaju najčešće hronične dijagnoze u primarnoj pedijatrijskoj zaštiti, sa sve većom učestalošću i značajnim uticajem na kognitivno, motoričko i socijalno funkcionisanje. Sindrom delecije 22q11.2 (22q11.2 DS) — najčešći mikrodelecijski sindrom kod ljudi — karakteriše širok spektar somatskih i neurorazvojnih abnormalnosti. Gotovo svi pojedinci sa 22q11.2 DS pokazuju neurorazvojne poteškoće, uključujući kašnjenje u razvoju motorike i govora, kognitivna oštećenja i probleme u komunikaciji i ponašanju. Ovaj poremećaj pogađa otprilike jedno od 2.500 novorođenčadi i povezan je i sa urođenim srčanim manama, anomalijama nepca, hipokalcemijom i imunodeficijencijom. Neurorazvojne manifestacije najčešće počinju u ranom detinjstvu kašnjenjem u razvoju motorike i govora, a nastavljaju se u školskom uzrastu kroz poteškoće u učenju, pažnji i socijalnim interakcijama. Intelektualne teškoće su česte, sa distribucijom učestalosti pomerenom ka nižim vrednostima koeficijenta inteligencije. Deca često pokazuju razliku između verbalnog i neverbalnog skora i mogu imati dodatni kognitivni pad tokom adolescencije ili odraslog doba. Više od 40% pacijenata ispunjava kriterijume za poremećaj iz spektra autizma, poremećaj pažnje/hiperaktivnosti, ili oba. Takođe imaju povećan rizik od psihijatrijskih stanja kao što su anksioznost, depresija i šizofrenija. Pedijatri, kao lekari primarne zdravstvene zaštite, imaju ključnu ulogu u ranom prepoznavanju i dugoročnom praćenju. Preporuke za praćenje uključuju rutinske razvojne procene, rane razvojne intervencije (npr. govornu i radnu terapiju) i redovno procenjivanje koeficijenta inteligencije i adaptivnog funkcionisanja, naročito tokom prelaznih obrazovnih perioda. Rana dijagnoza i individualizovani, multidisciplinarni pristupi su od suštinskog značaja za unapređenje razvojnih ishoda i kvaliteta života dece i odraslih sa 22q11.2 DS.

Ključne reči: sindrom delecije 22q11.2, DiGeorge sindrom, neurorazvojni poremećaji

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REVIEW ARTICLE

Epidemiology of ischemic heart disease

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Summary

Ischemic heart disease (IHD), or coronary artery disease, ranks as the primary global cause of mortality and disability.

This narrative review summarizes the epidemiology of IHD, focusing on global distribution, risk factors, and prevention.

A literature search was conducted using PubMed, Scopus, and Google Scholar databases to identify relevant studies from the past decade.

In 2019, IHD affected 197.2 million individuals, resulting in 9.1 million deaths, and 182.0 million disability-adjusted life years (DALYs) worldwide. While age-standardized mortality rates, DALYs, and prevalence have declined, the number of reported cases continues to rise. The highest prevalence was reported in Central and Eastern Europe and Central Asia, while the lowest was in South Asia. Modifiable and non-modifiable risk factors influence IHD. The main causal risk factors, such as hypertension, dyslipidemia, diabetes, smoking, and age, are independently associated with IHD development.

Environmental factors (air pollution, noise exposure, and climate change) further increase the risk of IHD. The emerging concept of the exposome emphasizes that the cumulative and combined influence of environmental risk factors plays a crucial role in the development of IHD.

IHD can be prevented from developing through primordial (targeting social determinants like urbanization, poverty, illiteracy, living conditions) and primary prevention (management of risk factors through lifestyle interventions, pharmacotherapies).

IHD is a growing global health and economic challenge, disproportionately affecting low-income regions, as a result of population aging, limited access to healthcare, and the presence of numerous risk factors that require appropriate prevention and treatment.

Keywords: ischemic heart disease, risk factors, prevention

INTRODUCTION

Ischemic heart disease (IHD), also referred to as coronary artery disease, ranks as the primary cause of death worldwide and a major contributor to disability (1). IHD had been the leading cause of death worldwide for at least 30 years before the COVID-19 pandemic. In 2019, IHD affected 197.2 million individuals globally, resulting in 9.1 million deaths, and 182.0 million disability-adjusted life years (DALYs). Age-standardized rates of IHD for DALYs, deaths, and prevalent cases declined during the past two decades globally, indicating that the rise in IHD cases is attributable to population growth and aging. However, it is estimated that the age-standardized mortality rate is increasing in many regions (1). The epidemiology of IHD is of relevance not only to public health experts but also to clinicians because IHD places a substantial medical and economic burden on society (2). The financial impact of IHD arises from hospitalizations, medical procedures, clinic and emergency visits, and prescribed medications (3). However, IHD is preventable if the risk factors are effectively controlled. Preventing IHD underscores the interconnected influence of political, economic, and social aspects, alongside health policies, financial structures, risk factor management at both population and individual levels, secondary prevention efforts, and medical education.

This narrative review aims to present the distribution and health burden of IHD, along with its associated risk factors and prevention strategies.

METHODS

A literature search of published studies reporting epidemiological data of IHD was conducted. PubMed, Scopus and Google Scholar databases were searched during January and February 2025 to identify relevant studies published within the last ten years. The keywords used included: ischaemic/ischemic heart disease, coronary heart disease, epidemiology, risk factors, and prevention. The extracted studies were grouped and analyzed with a specific focus on regional and global trends and disease burden, non-modifiable and modifiable risk factors, and prevention strategies. Articles unrelated to the three designated areas of interest were excluded from consideration.

GEOGRAPHICAL DISTRIBUTION OF IHD

Prevalence

It is estimated that 315 million people worldwide were living with IHD in 2022 (4). The age-standardized prevalence was 3,605 per 100,000 population, reflecting a measurable 18% decrease since 1990 (4). The highest age-standardized prevalence was reported in Central Europe, Eastern Europe, and Central Asia, while the lowest was reported in South Asia. Although the age-standardized prevalence rates decreased globally, the number of prevalent cases is rising due to population growth and an aging society (1). Differences in disease prevalence across regions may be attributed to multiple factors, including varying stages of the epidemiological transition, the presence of war, infectious diseases, or genetic predisposition to IHD risk factors (6, 7).

Incidence

In 2019, approximately 5.8 million new cases of IHD were reported across the 57 European Society of Cardiology (ESC) member countries, making IHD the most common form of incident cardiovascular disease (CVD) (8). The median age-standardized IHD incidence estimates were more than twice as high in middle-income countries as in high-income countries (8). During the period from 1990 to 2019, incidence rates significantly declined in all high-income countries, while the declines in middle-income countries were lower or, in some countries, incidence increased. Worldwide, the incidence of IHD decreased by 3.6% from 2010 to 2019, with a more pronounced decline among males compared to females (9).

Mortality

An estimated nine million people died due to IHD in 2019, representing more than 15% of global deaths (10). Around 1 in 7 deaths are caused by IHD worldwide. Although the age-standardized IHD mortality rates have been decreasing globally since 1990, in many areas across South, East, and Southeast Asia, including China, an upward trend has been observed (1). The highest decline was observed in developed Western nations (7). Reduction in major cardiovascular risk factors accounts for 45% to 75% of the decrease in IHD mortality, while advancements in emergency care and secondary prevention contributed to 25% to 55% of the reduction (11). However, over the past 5 years, the decline in mortality of IHD has slowed, plateaued, or even reversed in some high-income countries like the United States and the United Kingdom (1).

IHD among CVD

IHD is the primary contributor of CVD mortality in all regions and both genders, except in females in Sub-Saharan Africa and in both males and females in South Asia, where stroke remains the predominant cause of CVD-related mortality (12). In the United States, IHD is attributable to 40.3% of all CVD deaths (12). In ESC member countries, IHD accounted for 33% of all CVD deaths among females and 40% among males (13). Data from the national Serbian Registry for acute coronary syndrome

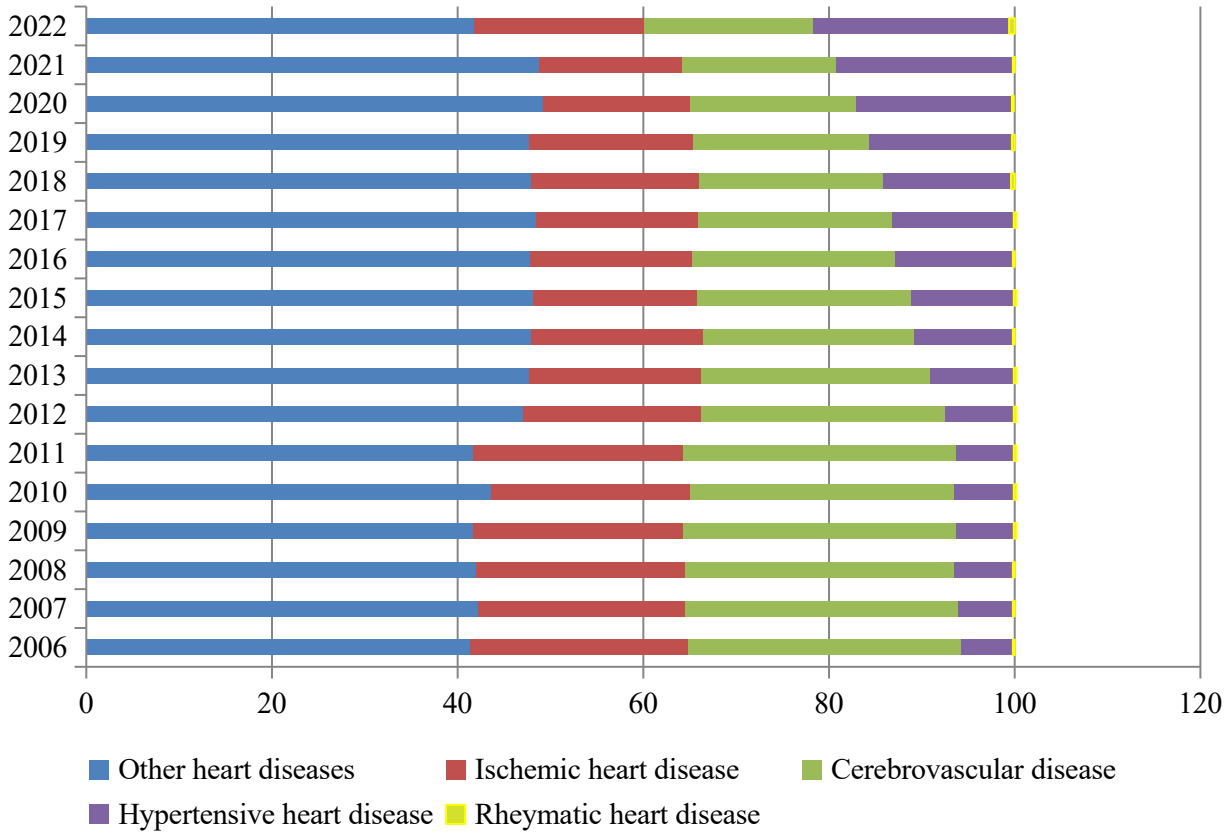

Figure 1. Proportion of ischemic heart disease deaths among all cardiovascular disease mortality in the Republic of Serbia during the period from 2006 to 2022

from 2006 to 2022 showed that other heart diseases are the leading cause of CVD death (14), accounting for 47.1% (range 41.4%-64.5%) of all CVD mortality on average, while cerebrovascular diseases and IHD were responsible for 24.3% and 19.4% of deaths, respectively **(Figure 1)**.

Observed differences in IHD proportion among CVD between Serbia and the rest of Europe may suggest potential reporting inaccuracies and deficiencies in the overall quality of data collection (15). It can also point to systemic issues in the coding of death certificates, including the use of ill-defined codes for CVDs. In 2020 and 2021, the proportion of other heart diseases among all CVDs increased, while the shares of IHD and cerebrovascular diseases declined, likely as a consequence of reduced hospital admissions and cardiovascular interventions during the COVID-19 pandemic, which may have further complicated accurate diagnosis and coding **(Figure 1)**.

Burden of IHD

In 1990 and 2010, IHD was the second leading cause of DALYs, considering all age groups and genders together, while in 2021 it was the third leading cause after COVID-19 and neonatal disorders (16). However, IHD is the leading cause of DALYs among adults (7). Age-standardized DALY rates declined during the period 1990-2019 worldwide (1). Areas with the highest DALY rates are Eastern Europe, Central Asia, Oceania, and the Middle East/North Africa regions (1). At the national level, Uzbekistan, Ukraine, Tajikistan, and several Oceanian islands exhibit the highest DALY rates, whereas Japan, the Republic of Korea, and France record the lowest rates (1). These patterns can be explained by high exposure to risk factors and limited availability of preventive healthcare services.

In 2050, IHD is expected to remain the leading cause of cardiovascular deaths, with approximately 20 million fatalities worldwide, particularly in areas with a lower sociodemographic index (SDI), and high systolic blood pressure will be the most significant cardiovascular risk factor contributing to these deaths (17).

RISK FACTORS FOR IHD

Risk factors for IHD are classified into modifiable and non-modifiable risk factors.

Modifiable risk factors

Modifiable risk factors include physical inactivity, tobacco use, diet, hyperlipidemia, hypertension, diabetes mellitus, psychosocial stress, and being overweight. Non-modifiable risk factors are those that cannot be changed through lifestyle adjustments or medical treatments.

These include age, sex, ethnicity, genetic predisposition, and the patient's family history (17). Research from 2019 shows that while age, sex, and race are responsible for up to 80% of IHD occurrence, interventions targeting modifiable risk factors have still significantly reduced its prevalence (18).

To better reflect the complexity of IHD etiology, risk factors can also be grouped into: sociodemographic characteristics, lifestyle, environmental, and clinical risk factors (8).

Since the launch of the Framingham study in the mid-20th century, numerous risk factors have been identified (19). The INTERHEART case-control study, published in 2004 and conducted in 52 countries, including 15152 cases and 14820 controls, revealed that nine modifiable risk factors contributed to the majority of myocardial infarction (MI) risk across all populations worldwide (20).

In the Serbian population, risk factors for MI included favorable socioeconomic conditions, alcohol consumption, exposure to one or more stressful life events, hypertension, reduced levels of high-density lipoprotein cholesterol (HDL), and family history of MI. At the same time, prior participation in leisure sports activities was associated with a reduced risk (21).

In 2019, the top three risk factors contributing to the burden of IHD worldwide include elevated systolic blood pressure (54.6%), high low-density lipoprotein (LDL) cholesterol levels (46.6%), and tobacco use (23.9%) (5). In 2021, ambient particulate matter pollution emerged as one of the top three contributors to IHD-related deaths and DALYs (22).

Although genetic predisposition and lifestyle choices remain important, growing evidence suggests they do not fully account for the multifactorial nature of IHD and cardiovascular risk. Heart health is shaped by a complex web of external influences from the air we breathe to the communities we inhabit (24).

In recent years, the concept of the exposome has emerged as a comprehensive framework that integrates all environmental and internal exposures an individual experiences throughout life (24). This approach helps researchers understand how cumulative exposures interact and evolve, emphasizing the importance of timing, duration, and intensity in shaping cardiovascular outcomes (25). By considering the full spectrum of exposures from conception onward, it provides a more comprehensive view of cardiovascular risk and supports more effective, equitable prevention strategies (24, 25).

Non-modifiable risk factors

Advancing age significantly increases the risk of developing IHD partly due to prolonged exposure to various risk factors over time (26). The onset of IHD typically begins around the age of 30, but clinical symptoms often do not appear until the age of 50 (7). As individuals grow older, structural and functional alterations in the cardiovascular system, such as endothelial dysfunction and increased arterial stiffness, contribute to a higher incidence of IHD (26).

Men generally develop IHD at an earlier age compared to women, likely due to the protective effects of estrogen in premenopausal women. However, postmenopausal women experience a rapid increase in risk, often presenting with atypical symptoms and worse clinical outcomes (27). A positive family history is an independent risk factor for IHD, highlighting the significant role of genetic predisposition in its development. Genome-wide association studies have identified multiple genetic loci associated with an elevated risk of IHD, especially variants in genes related to lipid metabolism, inflammation, and vascular function (28). Individuals with a first-degree relative who had IHD before age 55 in men or 65 in women face a considerably elevated risk of the disease progressing (28).

Hypertension

Hypertension is a well-established and significant risk factor for IHD, contributing to the development and progression of atherosclerosis, MI, and heart failure. High blood pressure increases the mechanical stress on arterial walls, leading to endothelial dysfunction, vascular inflammation, and accelerated atherogenesis (29). Chronic hypertension promotes left ventricular hypertrophy and arterial stiffness, both of which elevate myocardial oxygen demand while reducing coronary perfusion, thereby heightening the risk of ischemic events (304). In addition, hypertension is often linked to other cardiovascular risk factors, which further exacerbate the risk of IHD (30. Clinical trials have shown that effective blood pressure control significantly decreases the incidence of MI and cardiovascular mortality (30). Between 1990 and 2019, Europe and the Americas saw a 41% increase in the number of hypertensive adults, while Southeast Asia and the Western Pacific experienced a dramatic 144% rise (31). Despite its prevalence, hypertension remains underdiagnosed and undertreated: only 54% of affected adults are diagnosed, 42% receive treatment, and merely 21% achieve adequate blood pressure control (31).

In the Serbian population, the standardized prevalence of elevated blood pressure and hypertension was 40.6% and 34.5%, with 57.8% of individuals with hypertension receiving medical treatment (32).

Dyslipidemia

Dyslipidemia is a key contributor to both the onset and progression of IHD. It encompasses several lipid abnormalities, including high LDL cholesterol levels, decreased HDL cholesterol, and increased triglycerides. LDL cholesterol ("bad" cholesterol) particles are a major

contributor to atherosclerotic plaque formation by delivering cholesterol to the arterial walls, where it can be oxidized and trigger inflammatory responses. Statins, which lower LDL cholesterol, have been proven to reduce the incidence of MI and improve cardiovascular outcomes (33). HDL cholesterol, known as "good" cholesterol, plays a crucial role in clearing excess cholesterol from the bloodstream and preventing plaque buildup in the arteries (33). Elevated triglycerides are often seen in individuals with obesity, insulin resistance, and metabolic syndrome, and they are strongly associated with the progression of atherosclerosis and endothelial dysfunction (34). Dyslipidemia is often not a single abnormality but a combination of lipid issues. Individuals with high LDL cholesterol and low HDL cholesterol levels are at an even higher risk of IHD than those with isolated lipid abnormalities (35). There is considerable regional variability in cholesterol levels and trends. Historically, non-optimal cholesterol was most prevalent in high-income countries such as those in northwestern Europe, North America, and Australasia (12). However, recent data show that the highest cholesterol-related risk is now concentrated in middle-income countries in East and Southeast Asia, as well as parts of Central Latin America (12).

Diabetes

Diabetes is a significant and independent risk factor for IHD. Adults with diabetes are about twice as likely to develop IHD, mainly due to metabolic and inflammatory processes that trigger atherosclerosis through oxidative stress, inflammation, and lipid imbalances (36). Diabetes and IHD share several common risk factors, including hypertension, dyslipidemia, obesity, and a sedentary lifestyle (364). Managing blood glucose levels and addressing associated risk factors can significantly reduce the likelihood of adverse cardiovascular events in individuals with diabetes. The global diabetes burden has surged over the past three decades, with cases rising from 200 million in 1990 to 830 million in 2022 (37). The highest age-standardized rates were recorded in North Africa and the Middle East. Alarmingly, over half of those affected did not receive medication (38). Type 2 diabetes accounts for the vast majority of cases (96.0%) in 2021 and 95.4% of diabetes-related DALYs, particularly among older adults. In the Republic of Serbia, an estimated 700,000 adults (12.2%) have diabetes, with a comparative prevalence of 9.1% (39).

Clinical conditions

Certain clinical conditions contribute to the development and progression of IHD, either directly or indirectly, by influencing vascular health, metabolic status, or increasing the burden on the cardiovascular system. These conditions include chronic kidney disease (CKD), atrial fibrillation (AF), heart failure (HF), and cancer. CKD affects over 10% of the global population and is more common among older adults, women, racial minorities, and those with diabetes or hypertension (41). The burden is especially high in low- and middle-income countries. (41). AF affects up to 1 in 3–5 people over age 45. Between 2010 and 2019, global prevalence increased from 33.5 million to 59 million (42). HF incidence is stabilizing or declining in industrialized countries, but prevalence is rising due to population aging, better survival from IHD, and life-prolonging therapies (43). The highest HF prevalence is seen in Central Europe, North Africa, and the Middle East, with lower rates in Eastern Europe and Southeast Asia (43). Cancer increases IHD risk through the pro-inflammatory effects of cancer and treatments like chemotherapy, which can induce cardiotoxicity and worsen endothelial dysfunction, further promoting atherosclerosis (44). Cancer patients often have comorbidities such as obesity and hypertension, which further elevate cardiovascular risk (44). Approximately one in five men or women develops cancer in a lifetime.

Tobacco

Cigarette smoking is one of the most important factors for IHD. Research also shows that even alternative forms of tobacco use, such as low-tar cigarettes and smokeless tobacco, are linked to a heightened risk of cardiovascular events in comparison with non-smokers (45, 46).

Additionally, secondhand smoke (environmental tobacco smoke) poses a significant health risk. Even at significantly lower levels of exposure (1/100th of direct smoking), individuals exposed to secondhand smoke face about a 30% higher risk of developing IHD compared to non-smokers. This risk is still substantial, given that active smokers experience around an 80% increase in their risk for IHD (47). Even brief exposure to secondhand smoke is harmful to cardiovascular health and contributes to increased rates of heart disease (48). Cigarette smoking is associated with IHD due to the detrimental effects of nicotine, carbon monoxide, and other toxic substances present in tobacco smoke. These substances contribute to the development of atherosclerosis by promoting endothelial dysfunction, increasing oxidative stress, and stimulating inflammation, all of which accelerate the process of plaque formation in the arteries (45).

Furthermore, smoking is linked to higher levels of blood pressure, dyslipidemia, and blood clotting factors (47). Global smoking prevalence dropped from 22.7% in 2007 to 17% in 2021, yet there are still over one billion smokers worldwide due to population growth (49). In Serbia, tobacco use causes the premature death of approximately 15,000 people annually. The prevalence of tobacco product use among individuals aged 15 and older was 31.9% in 2019 (50).

Alcohol

Alcohol consumption has a dose-dependent effect on IHD. Moderate drinking may offer protective benefits by exerting antioxidant and anti-inflammatory effects, increasing HDL cholesterol, reducing LDL cholesterol, and lowering the risk of thrombosis (51). However, excessive alcohol consumption significantly elevates the risk of IHD through mechanisms like hypertension, dyslipidemia, oxidative stress, and myocardial injury (51). This leads to a distinctive two-phase, "J-shaped" risk pattern. Chronic heavy drinking can lead to arrhythmias and cardiomyopathy, although the clinical signs typically appear after more than a decade of alcohol abuse. (52). Drinking patterns, rather than the total quantity consumed, play a crucial role in determining IHD risk. Irregular binge drinking is linked to a higher cardiovascular risk compared to individuals who distribute their alcohol intake evenly across the week through moderate daily consumption (52). According to ESC guidelines, the recommended maximum for alcohol consumption is around 100g of pure alcohol per week (53). Global alcohol per capita consumption fluctuated between 2010 and 2019, with an overall decline of less than 5% (54). The highest levels of alcohol consumption were recorded in European countries, whereas the lowest were found in predominantly Muslim countries across Northern Africa, the Middle East, and parts of Asia (55). In Serbia, 50.7% of the population does not consume alcohol (39.3% have never tried it, and 11.4% did not consume it in the past 12 months) (50).

Diet

Diet plays a significant role in both the onset and progression of IHD, and eating habits provide clearer insights than isolating individual nutrients or food items (56). Evaluating general dietary patterns is now considered a leading method for understanding the role of nutrition in IHD (57). In high and upper-middle SDI countries, the primary dietary risk factors for IHD include excessive intake of red and processed meats, high sodium intake, and insufficient intake of legumes (57). High consumption of red and processed meats is associated with elevated levels of saturated fats and cholesterol. Excessive sodium intake, typical in many Western diets, is closely linked to hypertension (57).

In contrast, low and lower-middle-income SDI countries face different dietary challenges. The key dietary risks in these regions are inadequate intake of fiber, fruits, nuts, seeds, polyunsaturated fatty acids (PUFAs), and omega-3 fatty acids from seafood, as well as vegetables and whole grains. Specifically, omega-3 fatty acids, found in seafood, are known to have anti-inflammatory properties and improve lipid profiles, thus reducing IHD risk (57). Insufficient intake of fruits and vegetables, which are rich in antioxidants and fiber, also contributes to an increased risk of developing IHD. The Mediterranean diet, characterized by a high consumption of minimally processed plant-based foods and monounsaturated fats from olive oil, along with a lower consumption of saturated fats, meat, and dairy, is considered an excellent nutritional approach for supporting heart health (56). Consumption of full-fat dairy products, eggs, and processed meat increased the risk of MI, while consumption of fish and poultry more than twice a week, along with a daily intake of fresh vegetables, has been shown to significantly reduce the risk of MI in the Serbian population (58). Both the American Heart Association (AHA) and the European Society of Cardiology(ESC) emphasize plant-based diets for IHD prevention, recommending more fruits, vegetables, nuts, whole grains, and fish, while limiting salt, sugary drinks, processed meat, and alcohol (59). In Serbia in 2019, 50.2% of the population consumed vegetables and 39.4% consumed fruit daily (50). Fish was consumed one to three times a week by 33.3% of the population, and 6.0% reported never eating fish. Additionally, every eleventh person stated they add salt to food before tasting it (50).

Body mass index and physical activity

Body mass index (BMI) and physical inactivity are both significant determinants of IHD risk. The global burden of IHD linked to high BMI and low physical activity (PA) has risen in absolute numbers from 1990 to 2021, despite a decline in age-standardized DALYs and mortality rates, indicating that the prevalence of obesity and PA continues to increase (60). Obesity contributes to IHD through various genetic, physiological, and biochemical pathways. It is linked to both traditional risk factors like type 2 diabetes, hypertension, and dyslipidemia, as well as novel factors such as insulin resistance, inflammation, and clotting abnormalities (61). Central obesity, a core feature of metabolic syndrome, is a major contributor to cardiovascular risk and is now acknowledged as an independent risk factor for IHD (61). In 2022, 43% of adults were overweight, including 1 in 8 people globally who were living with obesity (62). This marks a significant rise from 1990, when only 25% of adults were overweight (74). Regional prevalence varies from 31% in Southeast Asia and Africa to 67% in the Americas. In Serbia in 2019, 40.5% of the population aged 15 and older had a normal nutritional status, while more than half were overweight (50).

PA decreases the risk of IHD by improving key risk factors such as blood pressure, blood lipids, insulin sensitivity, and obesity. Additionally, exercise enhances vascular health, reduces inflammation, improves endothelial function, and decreases arterial stiffness, all of which contribute to cardiovascular protection (63). It also alleviates stress and depression. PA is strongly linked to the burden of IHD, with low PA contributing significantly to higher deaths and DALYs, particularly in females and re-

gions with lower SDIs. Increasing PA is crucial for reducing IHD-related mortality and morbidity (60). In 2022, 31% of adults worldwide were physically inactive, a 5% increase since 2010 (64). Women are less active than men, and inactivity rises after age 60. In Serbia (2019), 75.2% of people walked daily for at least 10 minutes, while only 8.8% engaged in fitness or sports at least three times a week, with men more than women (50).

Environmental factors

Drawing upon the exposome concept, recent research has highlighted air pollution, noise pollution, and climate change as major contributors to IHD.

Air pollution consists of diverse particles and gases introduced into the environment as a result of human activities. It encompasses both outdoor (ambient) pollution and indoor (household) pollution (65). The association between air pollution and IHD can be attributed to various mechanisms, including the induction of oxidative stress, inflammation, disruptions in autonomic and neuroendocrine systems, heightened vasoconstriction and blood clotting, and the infiltration of particulate matter into the bloodstream (66). Brief exposure to particulate air pollution elevates the risk of acute cardiovascular events by approximately 1% to 3% within days. In contrast, extended exposure significantly amplifies this risk, around 10%, partly due to the onset of cardiometabolic disorders such as hypertension and diabetes (65). Countries across East, South, and Southeast Asia experience the heaviest cardiovascular burdens from air pollution (66). Ambient air pollution has become the leading environmental cause of disease and premature death worldwide, surpassing even traditional risk factors such as tobacco smoking (24).

Noise exposure negatively impacts cardiovascular health by activating the stress axis and releasing hormones like cortisol and adrenaline, which contribute to hypertension, atherosclerosis, and other heart conditions. It also disrupts sleep, increases sympathetic activity, and promotes inflammation, endothelial dysfunction, gene regulation abnormalities, metabolic imbalances, and psychological stress, all of which worsen cardiovascular health (67). Over 100 million people worldwide are exposed to noise levels above 60 decibels, with traffic noise being the main source in urban areas, affecting over 85% of residents (67).

Synergistic effects of PM2.5 and traffic noise, particularly during nighttime, exacerbate risks for atherosclerosis and IHD. Additionally, climate change, driven by fossil fuel use and global warming, contributes to increased cardiovascular risks through higher temperatures, natural disasters releasing PM2.5, and its interplay with other environmental hazards, creating a compounding effect on health (68).

Psychosocial stress

Emerging evidence from epidemiological and clinical studies indicates that psychosocial factors independently influence the risk of IHD, even after adjusting for classic cardiovascular risk factors (69). Persistent psychosocial stressors, including work-related pressure, family life challenges, insufficient social support, negative emotions like depression and hostility, caregiving responsibilities, and low socioeconomic status (SES), have been identified as significant contributors to the risk of IHD. Stress can influence IHD both directly, through neuroendocrine and platelet activation, and indirectly, by increasing the likelihood of unhealthy behaviors. Work-related stress and financial difficulties have been identified as leading psychosocial factors strongly linked to an increased risk of IHD in the Serbian population (69). A global survey of 300,000 participants from 131 countries found that 35.1% experience stress, which is strongly linked to income instability, health problems, and food insecurity (70). Psychosocial factors have been shown to influence both mortality and survival after IHD, and patients who live alone have higher long-term all-cause mortality following MI (71, 72).

IHD incidence and mortality rates are lowest in high-development areas, where they have also declined the most (73). In upper-middle-income regions, IHD incidence remained relatively stable until 2000, after which a notable decline occurred, likely due to the implementation of comprehensive public health policies (73). Individuals from lower SES groups often exhibit higher prevalence of risk factors, although some studies indicate an independent association. Beyond traditional risk factors, other contributors to increased IHD risk in lower SES populations include limited health literacy, barriers to healthcare access, inadequate treatment, poorer physical and mental health, and adverse environmental conditions in disadvantaged neighborhoods (13).

ESTIMATION OF RISK FOR IHD

Risk estimation for IHD is essential for early detection and prevention, helping to identify persons at high risk for adverse cardiovascular events. Several tools and models have been developed to predict the likelihood of IHD based on various clinical and demographic factors. A widely used tool, the Framingham Risk Score (FRS), assesses the 10-year CVD risk by incorporating key factors such as cholesterol levels, blood pressure, smoking habits, and diabetes status. The European Society of Cardiology developed Systematic Coronary Risk Evaluation SCORE2 and SCOREop. The SCORE2 model is an improved version of the original SCORE tool, designed to predict the 10-year risk of fatal and non-fatal cardiovascular events, including IHD. It is primarily used among

adults between 40 and 69 years of age and incorporates traditional risk factors such as age, sex, blood pressure, cholesterol levels, smoking status, and diabetes. SCORE2 provides regional risk estimates specific to different European countries, accounting for variations in cardiovascular disease prevalence (74). SCOREop is a specialized version of the SCORE model tailored for individuals aged 70 and older (75). Both SCORE2 and SCOREop help clinicians make informed decisions about preventive interventions specifically tailored to the individual's age and regional cardiovascular risk profile.

So far, no widely used clinical risk score includes environmental exposures such as air pollution or noise, even though these factors are increasingly recognized as relevant in the development of IHD. Including this dimension could further emphasize the importance and potential of the exposome approach in improving risk prediction in the future.

PREVENTION OF IHD

IHD is a preventable disorder if the risk factors are effectively controlled (76). It can be prevented through primordial prevention in populations, as well as on an individual level through primary prevention. These strategies involve lifestyle modifications, medical interventions, and public health policies. The primordial strategy addresses societal influences on health, including political, economic, and social conditions such as unregulated urban growth, lack of education, poverty, and workplace and living environment challenges (76). The primary prevention focus is on modification of risk factors through lifestyle interventions and pharmacotherapies. An adequate diet has been shown to reduce IHD risk (77) significantly. Regular physical activity is one of the most effective ways to prevent IHD. The World Health Organization (WHO) advises engaging in a minimum of 150 minutes of moderate-intensity aerobic exercise each week for reducing IHD risk (78). Even modest increases in physical activity lead to significant reductions in cardiovascular events. Quitting smoking significantly reduces the risk of IHD, with the greatest benefits seen in individuals who stopped at a younger age (54).

Statin therapy is a cornerstone for reducing LDL cholesterol and preventing IHD. Statins have been shown to reduce both primary and secondary cardiovascular events (54). Effective management of hypertension with ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers can significantly reduce the risk of IHD (54). Additionally, patients with diabetes or high cholesterol often benefit from medications that improve lipid profiles or insulin sensitivity.

Early detection of risk factors such as hypertension, dyslipidemia, and diabetes is essential for IHD prevention, and routine screening is recommended to identify persons at high risk (54).

Policies targeting smoking reduction, such as smoking bans, tobacco taxes, and public health campaigns, have been effective in reducing IHD incidence (79). Public health campaigns that focus on lifestyle modifications, such as increasing physical activity and improving dietary habits, can significantly reduce IHD risk. Public health policies should also focus on improving access to preventive care, particularly for high-risk populations (79).

Secondary prevention involves treatments designed to avert additional cardiac damage in individuals with a history of IHD.

CONCLUSION

IHD continues to pose a significant challenge to public health, causing a huge medical burden and economic loss. While age-standardized rates of IHD have declined in many high-income countries due to advancements in healthcare and public health initiatives, the overall burden continues to expand, driven by both population growth and aging. The disease disproportionately affects individuals in lower-income regions, where access to preventive care is limited, and risk factors such as hypertension, smoking, and poor diet are more prevalent. Efforts to decrease the global burden of IHD must focus on addressing modifiable risk factors, improving access to healthcare, and implementing comprehensive prevention strategies that take into account the social, economic, and environmental determinants of health.

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REFERENCES

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021. doi: 10.1016/j.jacc.2020.11.010. PMID: 33309175.
2. Wang F, Yu Y, Mubarik S, Zhang Y, Liu X, Cheng Y, et al. Global Burden of Ischemic Heart Disease and Attributable Risk Factors, 1990-2017: A Secondary Analysis Based on the Global Burden of Disease Study 2017. Clin Epidemiol. 2021;13:859-870. doi: 10.2147/CLEP.S317787. PMID: 34584461.

3. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SKBM, AlKatheeri R, et al. Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study. Cureus. 2020;12(7):e9349. doi: 10.7759/cureus.9349. PMID: 32742886.
4. Stark, B, Johnson, C, Roth, G. Global prevalence of coronary artery disease: an update from the global burden of disease study. JACC. 2024 Apr, 83 (13_Supplement) 2320.https://doi.org/10.1016/S0735-1097(24)04310-9.
5. Safiri S, Karamzad N, Singh K, Carson-Chahhoud K, Adams C, Nejadghaderi SA, et al. Burden of ischemic heart disease and its attributable risk factors in 204 countries and territories, 1990-2019. Eur J Prev Cardiol. 2022;29(2):420-431. doi: 10.1093/eurjpc/zwab213. PMID: 34922374.
6. Ralapanawa U, Sivakanesan R. Epidemiology and the Magnitude of Coronary Artery Disease and Acute Coronary Syndrome: A Narrative Review. J Epidemiol Glob Health. 2021;11(2): 169-177. doi: 10.2991/jegh.k.201217.001. PMID: 33605111.
7. Hashim MJ. Epidemiology of Ischemic Heart Disease. In: Ischemic Heart Disease. Ed: Concistrè G. Springer International Publishing: Switzerland 2023. Doi: https://doi.org/10.1007/978-3-031-25879-4.
8. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, et al; Atlas Writing Group, European Society of Cardiology. European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J. 2022;43(8):716-799. doi: 10.1093/eurheartj/ehab892. PMID: 35016208.
9. Nedkoff L, Briffa T, Zemedikun D, Herrington S, Wright FL. Global Trends in Atherosclerotic Cardiovascular Disease. Clin Ther. 2023;45(11):1087-1091. doi: 10.1016/j.clinthera.2023.09.020. PMID: 37914585.
10. Wolf S, Schievano E, Amidei CB, Kucher N, Valerio L, Barco S, et al. Mortality trend of ischemic heart disease (2008-2022): A retrospective analysis of epidemiological data. Int J Cardiol. 2024;406:132042. doi: 10.1016/j.ijcard.2024.132042. PMID: 38614362.
11. Vancheri F, Tate AR, Henein M, Backlund L, Donfrancesco C, Palmieri L, et al. Time trends in ischaemic heart disease incidence and mortality over three decades (1990-2019) in 20 Western European countries: systematic analysis of the Global Burden of Disease Study 2019. Eur J Prev Cardiol. 2022;29(2):396-403. doi: 10.1093/eurjpc/zwab134. PMID: 34487157.
12. World heart report 2023. Confronting the world's number one killer. Geneva: Switzerland;2023. Available from: https://world-heart-federation.org/wp-content/uploads/World-Heart-Report-2023.pdf. Accessed (251 January 2025).
13. Timmis A, Aboyans V, Vardas P, Townsend N, Torbica A, Kavousi M, et al; ESC National Cardiac Societies. European Society of Cardiology: the 2023 Atlas of Cardiovascular Disease Statistics. Eur Heart J 2024; 45(38): 4019-4062. doi: 10.1093/eurheartj/ehae466. PMID: 39189413.
14. Institute of Public Helath of Serbia "Dr Milan Jovanovic Batut". Incidence and mortality of acute coronary syndrome in Serbia 2006-2022. Serbian Acute Coronary Syndrome Registry. Belgrade: IPHS; 2022. Available from: https://batut.org.rs/ Accessed (15 February 2025).
15. Vujcic IS, Sipetic SB, Dubljanin ES, Vlajinac HD. Trends in mortality rates from coronary heart disease in Belgrade (Serbia) during the period 1990-2010: a joinpoint regression analysis. BMC Cardiovasc Disord. 2013; 13: 112. doi: 10.1186/1471-2261-13-112. PMID: 24320937.
16. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2133-2161. doi: 10.1016/S0140-6736(24)00757-8.
17. Shi H, Xia Y, Cheng Y, Liang P, Cheng M, Zhang B, et al. Global Burden of Ischemic Heart Disease from 2022 to 2050: Projections of Incidence, Prevalence, Deaths, and Disability-Adjusted Life Years. Eur Heart J Qual Care Clin Outcomes. 2024:qcae049. doi: 10.1093/ehjqcco/qcae049. PMID: 38918062.
18. Brown JC, Gerhardt TE, Kwon E. Risk Factors for Coronary Artery Disease. StatPearls Publishing, 2025. PMID: 32119297.
19. Teo KK, Rafiq T. Cardiovascular Risk Factors and Prevention: A Perspective From Developing Countries. Can J Cardiol. 2021;37(5):733-743. doi: 10.1016/j.cjca.2021.02.009. PMID: 33610690.
20. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52. doi: 10.1016/S0140-6736(04)17018-9. PMID: 15364185.
21. Ratkov I, Šipetić S, Vlajinac H, Marinković J, Maksimović N, Matanović D, Vasiljević Z. Risks for primary nonfatal myocardial infarction in Serbia. Coll Antropol 2013;37:499-505.
22. Tan J, Xue M, Li H, Liu Y, He Y, Liu J, et al. Global, Regional, and National Burden of Ischemic Heart Disease Attributable to 25 Risk Factors and Their Summary Exposure Value Across 204 Countries With Different Sociodemographic Index Levels, 1990-2021: A Systematic Fixed-Effects Analysis and Comparative Study. Clin Epidemiol. 2025;17:105-129. doi: 10.2147/CLEP.S510347. PMID: 39996156.
23. Wang C, Sun Y, Jiang D, Wang C, Liu S. Risk-Attributable Burden of Ischemic Heart Disease in 137 Low- and Middle-Income Countries From 2000 to 2019. J Am Heart Assoc. 2021;10(19):e021024. doi: 10.1161/JAHA.121.021024.
24. Montone RA, Camilli M, Calvieri C, Magnani G, Bonanni A, Bhatt DL, et al. Exposome in ischaemic heart disease: beyond traditional risk factors. Eur Heart J. 2024;45(6):419-438. doi: 10.1093/eurheartj/ehae001. PMID: 38238478.
25. Al-Kindi S, Nasir K. The Exposome: Introducing a New Lens on Cardiovascular Health. Methodist Debakey Cardiovasc J. 2024;20(5):1-5. doi: 10.14797/mdcvj.1500. PMID: 39525381.
26. Duggan JP, Peters AS, Trachiotis GD, Antevil JL. Epidemiology of Coronary Artery Disease. Surg Clin North Am. 2022;102(3):499-516. doi: 10.1016/j.suc.2022.01.007. PMID: 35671770.
27. Rajendran A, Minhas AS, Kazzi B, Varma B, Choi E, Thakkar A, et al. Sex-specific differences in cardiovascular risk factors and implications for cardiovascular disease prevention in women. Atherosclerosis. 2023;384:117269. doi: 10.1016/j.atherosclerosis.2023.117269. PMID: 37752027.
28. Lenarda F, Balestrucci A, Terzi R, Lopes P, Ciliberti G, Marchetti D, et al. Coronary Artery Disease, Family History, and Screening Perspectives: An Up-to-Date Review. J Clin Med. 2024;13(19):5833. doi: 10.3390/jcm13195833. PMID: 39407893.
29. NCD Risk Factor Collaboration. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398(10304):957-980. doi: 10.1016/S0140-6736(21)01330-1. PMID: 34450083.
30. Masenga SK, Kirabo A. Hypertensive heart disease: risk factors, complications and mechanisms. Front Cardiovasc Med. 2023;10:1205475. doi: 10.3389/fcvm.2023.1205475. PMID: 37342440.
31. Kario K, Okura A, Hoshide S, Mogi M. The WHO Global report 2023 on hypertension warning the emerging hypertension burden in globe and its treatment strategy. Hypertens Res. 2024;47(5):1099-1102. doi: 10.1038/s41440-024-01622-w. PMID: 38443614.
32. Šipetić Grujičić S, Miljuš D, Soldatović I, Nikolić A, Vujčić I. Prehypertension and hypertension prevalence and risk factors among adult population in Republic of Serbia: A cross-sectional study. Vojnosanit Pregl 2020; 77(6): 590–600. doi.org/10.2298/VSP180330114S.
33. Abedi F, Sadeghi M, Omidkhoda N, Kelesidis T, Ramezani J, Samadi S, et al. HDL-cholesterol concentration and its association with coronary artery calcification: a systematic review and meta-analysis. Lipids Health Dis. 2023;22(1):60. doi: 10.1186/s12944-023-01827-x. PMID: 37158895.
34. Esan O, Wierzbicki AS. Triglycerides and cardiovascular disease. Curr Opin Cardiol. 2021;36(4):469-477. doi: 10.1097/HCO.0000000000000862. PMID: 33797418.

35. Wazir M, Olanrewaju OA, Yahya M, Kumari J, Kumar N, Singh J, et al. Lipid Disorders and Cardiovascular Risk: A Comprehensive Analysis of Current Perspectives. Cureus. 2023;15(12):e51395. doi: 10.7759/cureus.51395. PMID: 38292957.
36. Suman S, Biswas A, Kohaf N, Singh C, Johns R, Jakkula P, Hastings N. The Diabetes-Heart Disease Connection: Recent Discoveries and Implications. Curr Probl Cardiol. 2023;48(11):101923. doi: 10.1016/j.cpcardiol.2023.101923. PMID: 37399858.
37. WHO. Diabetes. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes#:~:text=The%20number%20of%20people%20living%20with%20diabetes%20rose,not%20take%20medication%20for%20their%20diabetes%20in%202022. Accessed (20 January 2025).
38. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402(10397):203-234. doi: 10.1016/S0140-6736(23)01301-6. PMID: 37356446.
39. Institute of Public Health of Serbia "Dr Milan Jovanovic Batut". Incidence and mortality of diabetes in Serbia 2022. Serbian Diabetes Registry. Belgrade: IPSH; 2022. Available from: IncidencijaIMortalitetOdDijabetesaUSrbiji2022.pdf. Accessed (10 January 2025).
40. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. Circulation. 2021;143(11):1157-1172. doi: 10.1161/CIRCULATIONAHA.120.050686. PMID: 33720773.
41. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022;12(1):7-11. doi: 10.1016/j.kisu.2021.11.003. PMID: 35529086.
42. Linz D, Gawalko M, Betz K, Hendriks JM, Lip GYH, Vinter N, et al. Atrial fibrillation: epidemiology, screening and digital health. Lancet Reg Health Eur. 2024; 37:100786. doi: 10.1016/j.lanepe.2023.100786. PMID: 38362546.
43. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118(17):3272-3287. doi: 10.1093/cvr/cvac013. PMID: 35150240.
44. Condurache DG, Raisi-Estabragh Z, Ghosh AK, Mamas MA. Ischemic Heart Disease in the Cancer Population: Trends, Outcomes, Epidemiology, and Challenges in Diagnosis and Treatment. Cardiol Clin. 2025;43(1):57-67. doi: 10.1016/j.ccl.2024.08.001. PMID: 39551562.
45. Ishida M, Sakai C, Kobayashi Y, Ishida T. Cigarette Smoking and Atherosclerotic Cardiovascular Disease. J Atheroscler Thromb. 2024;31(3):189-200. doi: 10.5551/jat.RV22015. PMID: 38220184
46. Berg CJ, Haardörfer R, Lanier A, Childs D, Foster B, Getachew B, et al. Tobacco Use Trajectories in Young Adults: Analyses of Predictors Across Systems Levels. Nicotine Tob Res. 2020;22(11):2075-2084. doi: 10.1093/ntr/ntaa048. PMID: 32170324.
47. Mallah MA, Soomro T, Ali M, Noreen S, Khatoon N, Kafle A, et al. Cigarette smoking and air pollution exposure and their effects on cardiovascular diseases. Front Public Health. 2023;11:967047. doi: 10.3389/fpubh.2023.967047. PMID: 38045957.
48. Flor LS, Anderson JA, Ahmad N, Aravkin A, Carr S, Dai X, et al. Health effects associated with exposure to secondhand smoke: a Burden of Proof study. Nat Med. 2024;30(1):149-167. doi: 10.1038/s41591-023-02743-4. PMID: 38195750.
49. World Health Organization. WHO report on the global tobacco epidemic, 2021: addressing new and emerging products. Geneva: World Health Organization; 2021. Available from: https://iris.who.int/handle/10665/343287. Accessed (5 Fabruary 2025).
50. Milic N, Stanisavljevic D, Krstic M, Jovanovic V, Brcanski J, Kilibarda J, et al. The 2019 Serbian national health survey. Belgrade: OMNIA BGD; 2021. Available from: https://publikacije.stat.gov.rs/G2021/pdfE/G20216003.pdf. Accessed (4 February 2025).
51. Minzer S, Losno RA, Casas R. The Effect of Alcohol on Cardiovascular Risk Factors: Is There New Information? Nutrients. 2020;12(4):912. doi: 10.3390/nu12040912. PMID: 32230720.
52. Piano MR. Alcohol's Effects on the Cardiovascular System. Alcohol Res. 2017;38(2):219-241. PMID: 28988575.
53. Chiva-Blanch G, Badimon L. Benefits and Risks of Moderate Alcohol Consumption on Cardiovascular Disease: Current Findings and Controversies. Nutrients. 2019;12(1):108. doi: 10.3390/nu12010108. PMID: 31906033.
54. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42(34):3227-3337. doi: 10.1093/eurheartj/ehab484. PMID: 34458905.
55. WHO. Global status report on alcohol and health and treatment of substance use disorders. Geneva: World Health Organization; 2024. Available from: https://www.who.int/publications/i/item/9789240096745. Accessed (15 February 2025).
56. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean Diet and Cardiovascular Health. Circ Res. 2019;124(5):779-798. doi: 10.1161/CIRCRESAHA.118.313348. PMID: 30817261.
57. Rostami R, Moradinazar M, Moradi S, Samannejad B, Cheshmeh S, Saber A, Pasdar Y. Impact of dietary risk on global ischemic heart disease: findings from 1990-2019. Sci Rep. 2024;14(1):18012. doi: 10.1038/s41598-024-69089-w. PMID: 39097603.
58. I. Vujcic, S. Sipetic-Grujicic, H. Vlajinac, E. Dubljanin. Diet as a risk factor for myocardial infarction in population of Belgrade. Atherosclerosis, Volume 241, Issue 1, e140 - e141.
59. Riccardi G, Giosuè A, Calabrese I, Vaccaro O. Dietary recommendations for prevention of atherosclerosis. Cardiovasc Res. 2022;118(5):1188-1204. doi: 10.1093/cvr/cvab173. PMID: 34229346.
60. Lin W, Jiang X, Chen J, Yuan Y, Li Q, Wu H, Huang F, Zhu P. Global, regional and national burden of ischaemic heart disease attributable to high body mass index and low physical activity from 1990 to 2021. Diabetes Obes Metab. 2025;27(5):2561-2572. doi: 10.1111/dom.16256. PMID: 39963796.
61. Katta N, Loethen T, Lavie CJ, Alpert MA. Obesity and Coronary Heart Disease: Epidemiology, Pathology, and Coronary Artery Imaging. Curr Probl Cardiol. 2021;46(3):100655. doi: 10.1016/j.cpcardiol.2020.100655. PMID: 32843206.
62. WHO. Obesity and overweight. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed (4 February 2025).
63. Tucker WJ, Fegers-Wustrow I, Halle M, Haykowsky MJ, Chung EH, Kovacic JC. Exercise for Primary and Secondary Prevention of Cardiovascular Disease: JACC Focus Seminar 1/4. J Am Coll Cardiol. 2022;80(11):1091-1106. doi: 10.1016/j.jacc.2022.07.004. PMID: 36075680.
64. WHO. Physical activity. 2024. Available from: https://www.who.int/news-room/fact-sheets/detail/physical-activity. Accessed (5 february 2025).
65. Montone RA, Rinaldi R, Bonanni A, Severino A, Pedicino D, Crea F, Liuzzo G. Impact of air pollution on ischemic heart disease: Evidence, mechanisms, clinical perspectives. Atherosclerosis. 2023;366:22-31. doi: 10.1016/j.atherosclerosis.2023.01.013. PMID: 36696748.
66. Mao Q, Zhu X, Zhang X, Kong Y. Effect of air pollution on the global burden of cardiovascular diseases and forecasting future trends of the related metrics: a systematic analysis from the Global Burden of Disease Study 2021. Front Med (Lausanne). 2024;11:1472996. doi: 10.3389/fmed.2024.1472996. PMID: 39464269.
67. Rajagopalan S, Al-Kindi SG, Brook RD. Air Pollution and Cardiovascular Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(17):2054-2070. doi: 10.1016/j.jacc.2018.07.099. PMID: 30336830.
68. Münzel T, Daiber A, Engelmann N, Röösli M, Kuntic M, Banks JL. Noise causes cardiovascular disease: it's time to act. J Expo Sci Environ Epidemiol. 2025;35(1):24-33. doi: 10.1038/s41370-024-00732-4. PMID: 39658622.
69. Vujcic I, Vlajinac H, Dubljanin E, Vasiljevic Z, Matanovic D, Maksimovic J, Sipetic S. Psychosocial Stress and Risk of Myocardial Infarction: A Case-Control Study in Belgrade (Serbia). Acta Cardiol Sin. 2016;32(3):281-9. doi: 10.6515/acs20150424k.

70. Smith MD, Wesselbaum D. Global evidence on the prevalence of and risk factors associated with stress. J Affect Disord. 2025;374:179-183. doi: 10.1016/j.jad.2025.01.053. PMID: 39805499.
71. Vujcic I, Vlajinac H, Dubljanin E, Vasiljevic Z, Matanovic D, Maksimovic J, Sipetic S, Marinkovic J. Long-term prognostic significance of living alone and other risk factors in patients with acute myocardial infarction. Ir J Med Sci. 2015;184(1):153-8. doi: 10.1007/s11845-014-1079-2.
72. Đurković S, Đurić P, Šipetić Grujičić S, Maksimović J, Vujčić I. Long-term survival of patients with acute myocardial infarction. SerbJPH 2023;97:55.
73. Wang Y, Wang X, Wang C, Zhou J. Global, Regional, and National Burden of Cardiovascular Disease, 1990-2021: Results From the 2021 Global Burden of Disease Study. Cureus. 2024;16(11):e74333. doi: 10.7759/cureus.74333.
74. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J. 2021;42(25):2439-2454. doi: 10.1093/eurheartj/ehab309. PMID: 34120177.
75. SCORE2-OP working group and ESC Cardiovascular risk collaboration. SCORE2-OP risk prediction algorithms: estimating incident cardiovascular event risk in older persons in four geographical risk regions. Eur Heart J. 2021;42(25):2455-2467. doi: 10.1093/eurheartj/ehab312. PMID: 34120185.
76. Gupta R, Wood DA. Primary prevention of ischaemic heart disease: populations, individuals, and health professionals. Lancet. 2019;394(10199):685-696. doi: 10.1016/S0140-6736(19)31893-8.
77. Ghodeshwar GK, Dube A, Khobragade D. Impact of Lifestyle Modifications on Cardiovascular Health: A Narrative Review. Cureus. 2023;15(7):e42616. doi: 10.7759/cureus.42616. PMID: 37641769.
78. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54(24):1451-1462. doi: 10.1136/bjsports-2020-102955. PMID: 33239350.
79. Vellakkal S, Khan Z, Alavani H, Fledderjohann J, Stuckler D. Effects of public policies in the prevention of cardiovascular diseases: a systematic review of global literature. Public Health. 2022;207:73-81. doi: 10.1016/j.puhe.2022.03.021. PMID: 35567826.

EPIDEMIOLOŠKE KARAKTERISTIKE ISHEMIJSKIH BOLESTI SRCA

Isidora Vujčić[1], Jadranka Maksimović[1], Sandra Šipetić-Grujičić[1]

Sažetak

Ishemijska ili koronarna bolest srca (IBS) je vodeći uzrok smrti i nesposobnosti na globalnom nivou. Cilj ovog preglednog rada je da pruži uvid u epidemiologiju IBS sa fokusom na distribuciju, faktore rizika i prevenciju.

Pretraga literature je sprovedena korišćenjem PubMed, Scopus i Google Scholar baza podataka kako bi se identifikovale relevantne studije objavljene u poslednjih deset godina.

U 2019. godini od IBS bolovalo je 197.2 miliona ljudi, uzrokovale su 9,1 miliona smrtnih ishoda i 182,0 miliona DALY-ja (engl. disability-adjusted life years). Iako su standardizovane stope mortaliteta, DALY-ja i prevalencije od IBS u svetu opale, broj registrovanih slučajeva i dalje raste. Najviša prevalencija IBS se beleži u Srednjoj i Istočnoj Evropi i Centralnoj Aziji, a najniža u Južnoj Aziji.

Faktori rizika za IBS se mogu podeliti na promenljive i nepromenljive. Glavni nezavisni faktori rizika kao što su pušenje, hipertenzija, dislipidemija, dijabetes, starost uzročno su nezavisno povezani sa nastankom oboljenja. Sredinski faktori (aerozagađenje, buka, klimatske promene) dodatno povećavaju rizik od IBS-a. Novonastali koncept eksposoma ukazuje da je za nastanak IBS važna kumulativna izloženost i zajednički uticaj svih faktora rizika u životnoj sredini.

Nastanak IBS se može sprečiti primordijalnim (mere usmerane prema socijalnim determinantama zdravlja kao što su: urbanizacija, siromaštvo, pismenost, uslovi života i rada) i primarnim merama prevencije (modifikacija faktora rizika promenom načina života, medikamentozna terapija).

IBS predstavljaju sve veći globalni zdravstveni problem, pogotovo u nerazvijenim zemljama, što je posledica starenja populacije, ograničenog pristupa zdravstvenoj zaštiti i prisustva brojnih faktora rizika što zahteva adekvatnu prevenciju i lečenje.

Ključne reči: ishemijska bolest srca, faktori rizika, prevencija

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REVIEW ARTICLE

Surgical significance of anatomical variations of the parathyroid glands

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Summary

A solid understanding of the surgical anatomy of the parathyroid glands is based on a thorough knowledge of their embryonic development. Anatomical variations in the number, morphology, vascularization, and localization of the parathyroid glands present a challenge during surgical exploration of the neck, both in the treatment of hyperparathyroidism (HPT) and in thyroid surgery. In about 2.3% of patients undergoing thyroidectomy, incidental parathyroidectomy occurs. Our review aims to highlight the incidence of anatomical variations in the localization, number, morphology, and vascularization of the parathyroid glands, as well as their significance in the surgical treatment of parathyroid gland functional disorders. A good understanding of embryologic development and neck anatomy is essential for parathyroid surgery. Contemporary imaging diagnostic modalities used in parathyroid surgery do not have the same sensitivity and specificity as in other surgical fields, and they significantly increase treatment costs. The success of surgical treatment largely depends on the surgeon's knowledge and experience.

If parathyroid glands are not found in their usual locations, an extensive bilateral neck exploration must be performed. Meanwhile, parathyroid adenomas located in the mediastinum below the aortic arch require a specialized diagnostic and surgical approach. Measurement of intraoperative PTH (ioPTH) levels increases the success rate of surgical interventions.

Keywords: parathyroid glands, PTH, anatomical variations

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INTRODUCTION

A thorough understanding of parathyroid embryology is essential for mastering their surgical anatomy. Parathyroid glands are of endodermal origin, derived from the third and fourth pharyngeal pouches, sharing a common embryonic origin with the thymus and thyroid gland.

The third pouch gives rise to the thymus and inferior parathyroid glands (parathyroid III), which migrate near the lower pole of the thyroid. In contrast, the superior parathyroid glands (parathyroid IV) arise from the fourth pouch, together with the ultimobranchial body, the precursor of thyroid C cells. During normal development, the thymus descends caudally and medially, dragging the inferior parathyroids, which explains the variable final position of these glands (1,2). Experimental studies in chick embryos demonstrated that removal of the ventral portion of the third pharyngeal arch results in the absence of the inferior parathyroids on the affected side, confirming their embryonic origin from this region (3).

At the molecular level, HOX gene expression, particularly HOXA3, HOXB3, and HOXD3, regulates development of the third to sixth arches; mutations in these genes disrupt thymic, thyroid, and parathyroid formation and migration (4,5).

Understanding this embryological and molecular background is essential for explaining the topographic variability and possible ectopic locations of parathyroid glands, which have significant implications in surgical anatomy and pathology (6,7).

Knowledge of these variations, supported by embryological data, contributes to higher success rates in parathyroidectomy, especially in reoperations and cases of ectopic or supernumerary glands (8,9,10,11,12,13).

Comprehensive assessment through integrated multimodal evaluation, combining quantitative and qualitative imaging and intraoperative findings, enables a more precise correlation between anatomical variations and clinical outcomes (9,10,11,12,13).

Finally, surgical outcomes are significantly influenced by the surgeon's experience and the center's volume. Reports indicate that the success rate of parathyroid surgery is 90% in specialized centers, compared with approximately 76% in general hospitals, while reoperations carry higher complication rates (14,15,16,17,18,19,20).

Our review aims to highlight the incidence of anatomical variations in the localization, number, morphology, and vascularization of the parathyroid glands, as well as their significance in the surgical treatment of parathyroid gland functional disorders.

METHODS

A search of the PubMed database was performed to identify studies on the surgical significance of parathyroid gland anatomical variations, published in English within the last 110 years. This encompassed experimental and clinical trials, as well as review articles. The following keywords were used: anatomical variations, parathyroid glands.

SURGICAL ANATOMY OF THE PARATHYROID GLANDS

Ectopic localization of parathyroid glands

Parathyroid glands can be located anywhere from cranial to the hyoid bone down to the mediastinum. Parathyroid ectopy occurs in approximately 10% of patients with HPT (21, 22).

In the majority of cases, the cause of unsuccessful operative treatment of HPT is an ectopically located parathyroid gland. Therefore, during neck exploration, each identified parathyroid gland should be verified as upper (parathyroid gland IV) or lower (parathyroid gland III) on the respective side. In surgical exploration of the neck for removal of a pathologically altered parathyroid gland, if three normal glands are identified but the fourth is not found in its usual anatomical location, an extensive exploration of all potential ectopic sites in the entire neck and upper mediastinum must be undertaken. Only parathyroid glands located "deep" in the mediastinum (1–2% of cases) cannot be identified with such meticulous exploration; these require additional imaging diagnostics and a specialized operative strategy (10, 13, 15, 23).

Twenty-seven studies ($n=7106$ patients, $n=23,519$ PTG) analyzing the prevalence, location, or morphology of PTG were included. The included studies ranged in date from 1916 to 2016 **(Table 1)**.

The prevalence of parathyroid ectopy ranges from 28% to 42% in anatomical studies, whereas in clinical studies of HPT patients undergoing surgery, it ranges from 6.3% to 16%. In patients reoperated after initially unsuccessful surgery, ectopic glands are found in up to 45% of cases (8).

An extensive anatomical study by Lappas et al. examined 942 cadavers (574 male, average age 61.3 years, average height 169.4 cm; 368 female, average age 67.4 years, average height 160.2 cm) that underwent autopsy between 1988 and 2009. Neck dissection spanned from the floor of the mouth to the sternal manubrium, identifying parathyroid glands in their typical locations. To identify ectopic parathyroid glands, a thoracotomy and exploration of thymic tissue were performed. In total, 3,796 parathyroid glands were identified and confirmed by histopathological analysis. Of these, 324 glands (8.5%) were ectopic. Seven glands (0.2%) were intrathyroidal; 79 (2%) were in variable locations in the neck relative to their usual positions; 152 (4.1%) were in the upper mediastinum, and 86 (2.2%) were in the lower mediastinum. The vast majority of parathyroid glands (91.5%) were in eutopic (standard)

Table 1. Characteristics of included studies

Study ID	Country	Type of study	Pathology	Number of patients	Number of analyzed PTG
Abboud 2008 (24)	Lebanon	Intraoperative	Various thyroid diseases	574	2219
Akerstrom 1984 (25)	Sweden	Cadaveric	Healthy	503	2032
Alveryd 1968 (26)	Sweden	Cadaveric	Healthy	352	1405
Arnalsteen 2003 (27)	France	Intraoperative	MEN1	79	340
Botelho 2004 (28)	Brazil	Cadaveric	Healthy	19	76
Butterworth 1998 (29)	UK	Intraoperative	SHPT	60	241
de Andrade 2014 (30)	Brazil	Intraoperative	SHPT	166	664
Edis 1987 (31)	Australia	Intraoperative	SHPT	20	73
Ghandur 1986 (32)	USA	Cadaveric	Healthy	166	502
Gilmour 1938 (33)	UK	Cadaveric	Healthy	428	1713
Gomes 2007 (33)	Brazil	Intraoperative	SHPT	35	143
Heinbach 1933 (34)	USA	Cadaveric	Healthy	25	86
Hellman 1998 (34)	Sweden	Intraoperative	MEN1	50	206
Hibi 2002 (35)	Japan	Intraoperative	SHPT	822	—
Hojaij 2011 (20)	Brazil	Cadaveric	Healthy	56	220
Kawata 2008 (36)	Japan	Intraoperative	SHPT	44	163
Lappas 2012 (18)	Greece	Cadaveric	Healthy	942	3796
Milas 2003 (37)	USA	Intraoperative	PHPT	828	3250
Nanka 2006* (38)	Czech Republic	Cadaveric	Healthy	101	280
Numano 1998 (39)	Japan	Intraoperative	SHPT	570	2377
Okada 2016 (40)	Japan	Intraoperative	SHPT	131	457
Pacini 1983 (41)	Italy	Intraoperative	PHPT and SHPT	42	163
Périé 2005 (42)	France	Intraoperative	SHPT	20	80
Pool 1916 (42)	USA	Cadaveric	Healthy	25	60
Prazenica 2015 (43)	Czech Republic	Intraoperative	Various thyroid diseases	788	1937
Pyrtek 1964 (44)	USA	Cadaveric	Healthy	100	391
Wang 1976 (45)	USA	Cadaveric	Healthy	160	645

locations. The level of the cricothyroid junction, i.e., the level of the upper pole of the thyroid gland, was the most common location of the superior parathyroid glands. For the inferior parathyroid glands, the most common location was at the level of the lower thyroid pole and along the thyrothymic ligament (the tract from the lower pole of the thyroid to the mediastinal thymus) (18).

A smaller Portuguese anatomical study reported an even higher prevalence of parathyroid ectopy. In 56 cadavers, at least one ectopic parathyroid gland was present in 42.8% of cases. The central ectopic regions were the mediastinum and thymus (19.6%), the subcapsular space of the thyroid (12.5%), and the thyroid parenchyma (5.4%). The morphological features and localization of parathyroid tissue did not correlate with the anthropometric or demographic characteristics of the specimens. In over 90% of cases, a relationship with the inferior laryngeal nerve was noted: the superior parathyroid glands were located medial to the nerve, and the inferior glands lateral to it (20, 33).

In a clinical study of patients with HPT undergoing initial parathyroid surgery, the highest incidence of parathyroid ectopy was observed in intrathymic glands (38%), followed by the tracheoesophageal groove (31%) and intrathyroidal locations (18%) (46).

It has also been observed that patients with primary HPT have higher serum calcium levels when an ectopically located parathyroid adenoma causes the disease. In these patients, the adenomas are significantly larger compared to those in patients with PHPT without parathyroid ectopy. In one study of 145 PHPT patients who underwent surgery, ectopic parathyroid glands were detected in 13 patients (9%). Of the ectopic glands found, 4 (31%) were located in the tracheoesophageal groove, 4 (31%) intrathymically, 2 (15%) intrathyroidally, and 1 each in the aortopulmonary window and the anterior mediastinum (extrathymic) (47, 48, 25). Other studies report similar results (49, 50).

In the clinical setting of secondary hyperparathyroidism (SHPT), all parathyroid glands are hyperplastic, increasing the likelihood of finding all glands during surgery. SHPT is therefore a valuable model for analyzing parathyroid anatomical variations. It has been noted that 45.7% of patients with SHPT have at least one ectopic parathyroid gland (33, 51, 48) **(Table 2)**.

A review of the literature shows that few clinical studies have analyzed patients after prior neck exploration. Shin et al. surveyed patients with persistent or recurrent HPT who had already undergone previous surgery. Among other factors, they analyzed the locations of eutopic and ectopic abnormal parathyroid glands in these patients.

Table 2. Ectopic parathyroid gland locations and frequency (52)

Main region	Localization	Percentage (%)
Cervical	Undescended – High Cervical	5
	Intra-thyroidal	20
	Carotid Sheath	3
Anterosuperior mediastinum	Intrathymic	25
	Thyrothymic ligament or pretracheal	5
Mediastinum	Para-(retro)esophageal	20
	Mediastinal Fat	10
	Aorto-pulmonary window	5
	Pleural-pericardial	2

The results showed that the most common area of ectopic parathyroid glands was intrathymic (23.8% of cases). "Descended" (low-lying) parathyroid glands accounted for 13.1%, while mediastinal parathyroid glands accounted for 11.9%. Additionally, of all ectopic parathyroid glands, 9.52% were located within the thyroid gland, and parathyroid glands in the carotid sheath or in proximity to the esophagus accounted for 8.3% and 7.1%, respectively (53).

UPPER PARATHYROID GLANDS

Superior (upper) parathyroid glands are usually located on the posterior-medial aspect at the junction of the middle and upper thirds of the ipsilateral thyroid lobe, or less commonly at the upper pole of the thyroid. In about 95% of cases, they can be found within a 2 cm radius of the point where the recurrent laryngeal nerve crosses the inferior thyroid artery (6).

The incidence of ectopic superior parathyroid glands is lower than that of inferior parathyroid glands, due to differences in embryological migration (2, 54).

The majority of superior parathyroid glands are located at the level of the cricothyroid junction or behind the upper pole of the thyroid gland (55).

In 2–4% of cases, a usually positioned (pathologically unaltered) superior parathyroid gland may be found more caudally than usual – distal to the trunk of the inferior thyroid artery within the tracheoesophageal groove, or even cranial to the upper pole of the thyroid gland. In fewer than 1% of cases, a superior parathyroid gland can be located in a retropharyngeal or retroesophageal position (55, 25).

Hyperparathyroidism associated with parathyroid ectopy is more often caused by an adenoma of a superior parathyroid gland (22).

Adenoma of the superior parathyroid gland that causes HPT can be ectopically located in up to 40% of patients, even if the gland initially had a normal embryonic position. This phenomenon, known as pseudoectopia, occurs due to the migration of the enlarged parathyroid gland under the influence of its increased mass, gravity, and swallowing movements (15, 23, 18, 20, 49). In such cases, an enlarged superior parathyroid gland can travel along the prevertebral fascia into the posterior mediastinum. Extensive descent of the gland is usually prevented by its vascular pedicle arising from the inferior thyroid artery. A pseudoectopic gland, even when located "deep" in the posterior mediastinum, can still be removed via a transcervical approach. It is important to note that more than 50% of pseudoectopic adenomas are not identified during neck exploration, even after medial retraction of the thyroid lobe. A pseudoectopic adenoma of the superior parathyroid gland, along with the recurrent laryngeal nerve, is covered by pretracheal fascia that stretches between the thyroid medially and the carotid sheath laterally; this relationship must be kept in mind during parathyroidectomy. Because a pathologically enlarged superior parathyroid gland often occupies a position in the lower neck (paraesophageal area) or in the upper part of the posterior mediastinum, these regions must be routinely explored whenever a superior parathyroid gland is not found in its usual location (15, 54, 55, 25, 56).

Ectopic superior parathyroid glands along the upper pole of the thyroid can sometimes be firmly adherent to the thyroid capsule, making them difficult to distinguish from the surrounding tissue. Also, the literature describes cases of ectopic localization of the upper parathyroid glands, 2 cm cranial to the upper pole of the thyroid gland and medial to the carotid sheath at the level of the piriform sinus. It is known that the upper parathyroid glands can be found in the wall of the pharynx, extramucosally, covered by the pharyngeal musculature. In sporadic cases, the superior glands may be localized in the neck lateral to the carotid sheath (57).

LOWER PARATHYROID GLANDS

Inferior (lower) parathyroid glands are located up to 2 cm below the lower pole of the thyroid gland in approximately 80% of cases **(Figure 1)**. Because of their more complex embryonic migration, the inferior parathyroid glands are subject to more frequent anatomical variations (6) .

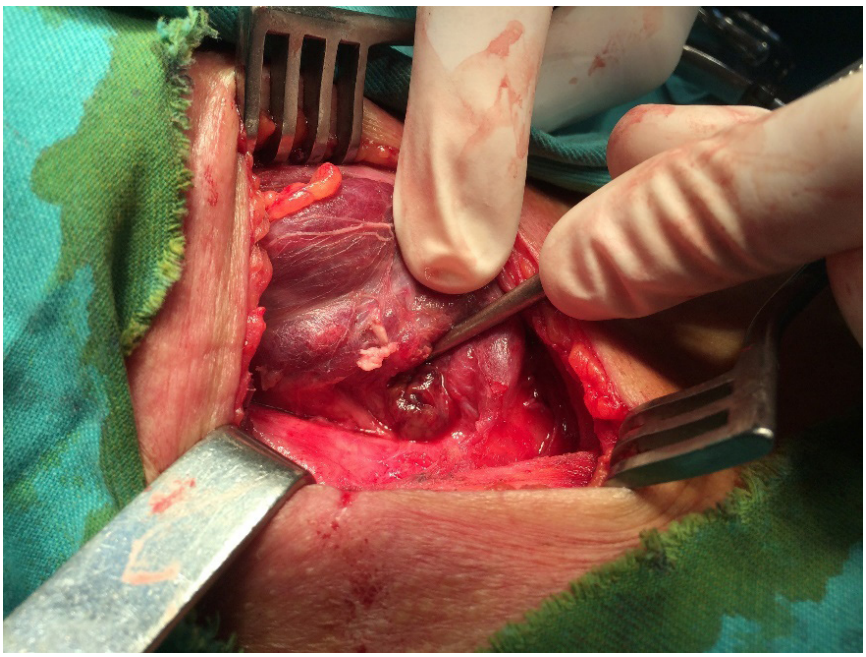

Figure 1. Inferior parathyroid gland, common location (Image shows only the surgical field; no patient-identifying features are visible)

Numerous studies indicate that the most common location of normal inferior parathyroid glands (and their adenomas) is within the thyrothymic ligament or in atrophic thymic tissue in adults. Nearly all intrathymic adenomas located above the aortic arch can be removed via a transcervical approach (15, 46, 47, 25).

In a study of 312 inferior parathyroid glands, the observed anatomical distribution was:

In 42% of cases, the inferior parathyroid glands are located on the anterior or posterolateral aspect of the lower pole of the thyroid. Ectopic inferior parathyroid glands are located within the upper pole of a thymic lobe in 39% of cases. Only about 2% of inferior parathyroid glands are located roughly 3–4 cm below the jugular notch of the sternum, within the mediastinal portion of the thymus (55).

Inferior parathyroid glands can be found within the thyroid capsule in 1–4% of patients with HPT. In intrathyroidal parathyroid glands, they are situated in the lower third of the thyroid lobe in the majority of cases, though occasionally in the middle third. These intrathyroidal parathyroid glands are palpable in only ~50% of cases, but they can be readily detected with intraoperative ultrasound. Suppose an inferior parathyroid gland is not identified in the usual locations, and retention in or near the thymus has been excluded. In that case, the search should be directed to the lower pole of the thyroid gland (15, 45, 25, 58).

Another important potential location for an ectopic inferior parathyroid gland is near the bifurcation of the common carotid artery, i.e., within the carotid sheath. This location results from the gland being retained during its embryonic migration. Such parathyroid ectopy is almost always associated with a small amount of residual thymus tissue (15, 45, 25, 59). Additionally, an inferior parathyroid gland can occasionally be located cranial to the carotid bifurcation, along the course of the internal carotid artery, even as high as behind the submandibular salivary gland (60).

In a detailed analysis of the aforementioned anatomical study of 312 inferior parathyroid glands, Wang concluded that adenomas of ectopic parathyroid glands located high in the neck occur in approximately 2% of cases (33, 39). In a clinical series of previously unoperated patients, the incidence of such high cervical parathyroid adenomas is reported to be under 1% (25).

During surgical neck exploration for HPT, parathyroid ectopy at the carotid bifurcation or within the carotid sheath should be considered. To rule out this possibility, the carotid sheath should be incised from the clavicle up to the level of the internal carotid artery. Only after this extensive exploration proves harmful should one suspect a mediastinal ectopic gland located below the aortic arch, which is the case in merely 1–2% of parathyroid adenomas (25, 60, 61).

MEDIASTINAL PARATHYROID GLANDS

Special attention is warranted for parathyroid glands located in the mediastinum, as these are uncommon **(Figure 2)**. Reports on the embryologic origin of ectopic parathyroid glands in the middle mediastinum are contradictory. Some authors consider these glands to be the superior parathyroid glands, since their embryonic development is closely linked to that of the great vessels of the mediastinum and heart. On the other hand, mediastinal ectopic parathyroid glands are not associated with an absence of the superior parathyroid glands and are often classified as supernumerary glands (62). The true prevalence of ectopic mediastinal parathyroid glands is unknown, but some studies estimate it at 1–2% (63, 64, 65).

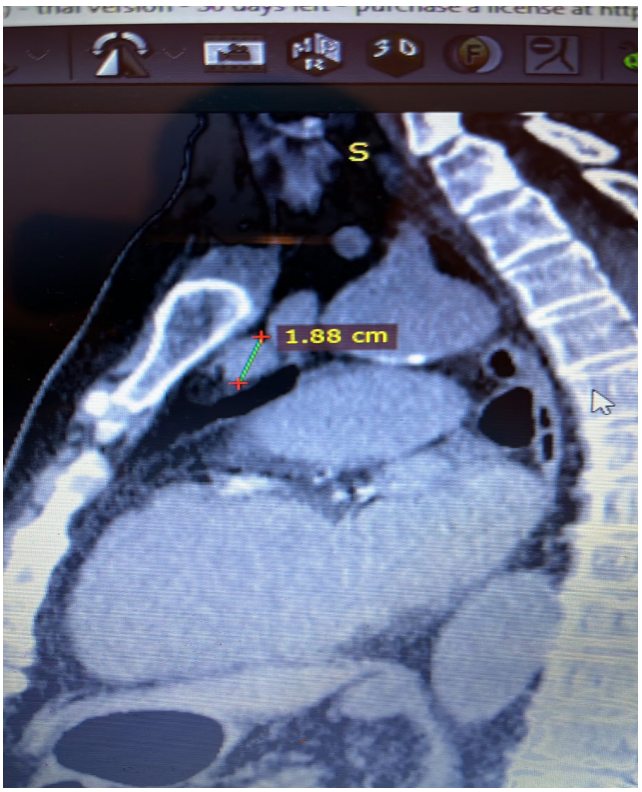

Figure 2. Ectopic parathyroid gland in the anterior mediastinum (MSCT; image shows only the surgical field; no patient-identifying features are visible)

The most common location of this type of parathyroid ectopy is the aortopulmonary window, either behind the pulmonary trunk or in front of the tracheal carina. In the rarest cases, mediastinal parathyroid glands are found within the pericardium. A multicenter study conducted in 8 European medical centers found that 19 parathyroid glands (0.24% of all glands) in 7,869 HPT patients were located in the aortopulmonary window region. In addition to these, another 181 patients (2.3%) were found to have pathologically altered, ectopic mediastinal parathyroid glands. Out of 19 patients with aortopulmonary window parathyroid tumors, three had an initial misdiagnosis of a mediastinal tumor, which was removed in the first surgery. Seventeen patients with ectopic parathyroid glands in the aortopulmonary window underwent bilateral neck exploration as well. The final results showed that 12 of the ectopic mediastinal glands were supernumerary: 4 originated from the superior parathyroid glands and 1 from an inferior parathyroid gland (62).

Patients with mediastinal parathyroid ectopy require a special diagnostic and surgical approach. Technetium (99mTc) sestamibi scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and selective arteriography are particularly valuable in these cases (66, 67).

Possible surgical treatments for intrathoracic ectopic parathyroid adenomas include median sternotomy, thymectomy, arterial embolization via selective angiography of the internal thoracic artery, as well as video-assisted thoracoscopic surgery (VATS) (63, 68).

The surgical approach for these patients can be challenging. Iihara et al. suggest using the aortic arch on a horizontal chest CT as a landmark when deciding on the surgical approach. Parathyroid adenomas located above the aortic arch can be removed via a transcervical approach, whereas adenomas located below the aortic arch should be approached through a transthoracic route (69).

In open surgery, a left thoracotomy provides the best access for the removal of such ectopic parathyroid glands (61). The use of an intraoperative gamma probe to identify parathyroid tissue can be helpful, though in the mediastinum, it is limited by radioactive tracer uptake in the myocardium (69, 70).

Measuring intraoperative parathyroid hormone (ioPTH) levels is extremely useful, as it reduces the rate of unsuccessful surgeries from 21.2% to 3%. Intraoperative frozen-section pathological verification (an ex tempore biopsy) can also be of help (71).

NUMBER AND MORPHOLOGY OF PARATHYROID GLANDS

The number of parathyroid glands varies from 1 to 12. In the vast majority of people (about 94%), there are four parathyroid glands. In anatomical series, a supernumerary (fifth) parathyroid gland occurs in 5–6% of individuals, whereas only three glands are present in about 2% of cases. In clinical parathyroid surgery series, a variable number of glands is reported in roughly 2–5% of cases. Only 1% of individuals have a single parathyroid gland, and 1% have more than 7 glands (18, 33, 23).

If four normal parathyroid glands are identified during surgical neck exploration for HPT, one should suspect the presence of an abnormal supernumerary gland (5, 15, 18, 49). A supernumerary parathyroid gland is most often ectopic and located intrathymically (33, 72).

The shape of the parathyroid glands is variable. Most commonly, they are oval, but they can also be tongue-shaped, discoid, or leaf-shaped (45, 59). They have a compact texture and are surrounded by a fragile capsule, so they must be handled carefully during surgery to avoid rupturing the capsule and causing seeding of parathyroid cells. This phenomenon, known as parathyromatosis, can lead to recurrence of the disease that is difficult to treat with reoperation (6).

Typically, a normal parathyroid gland has a smooth, glistening surface and well-defined edges. It usually lies within a fat pad, which can serve as a guide to the gland's location. The color of parathyroid glands ranges from reddish to yellowish, depending on fat content, vascularity, and the number of oxyphil cells. In cases of chronic illness or malnutrition, or during excessive infusion of crystalloid solutions (when interstitial edema occurs), the parathyroid glands become "pale yellow" in color, resembling the lobules of surrounding fatty tissue, which can make them

harder to identify. Parathyroid glands are soft and elastic in consistency on palpation. On cross-section, they have a granular appearance. Their soft consistency allows them to conform their shape to surrounding structures. The softness of parathyroid glands upon palpation also helps differentiate them from lymph nodes and thyroid lobules (45).

Freed from surrounding fat, parathyroid glands measure about 5 × 3 × 1 mm. Their average weight is 35–40 mg (6, 18, 25) **(Table 3)**.

Table 3. Characteristics of the parathyroid glands (1)

Parameter	Minimum	Maximum	Mean
Length (mm)	5.49	7.57	6.76
Width (mm)	3.08	4.32	3.97
Thickness (mm)	1.12	1.44	1.31
Weight (mg)	30	57	40

Morphologically, there is no size difference between the two upper and the two lower parathyroid glands. There is also no difference in size between genders **(Table 4)**.

Table 4. Number, average size, and weight of the parathyroid glands in relation to their localization and sex (1)

Parameter	Number	Average size (mm^3)	Average weight (mg)
Superior parathyroid glands	1,784	18.02	44
Inferior parathyroid glands	2,012	14.78	38
Right parathyroid glands	1,879	16.79	39
Left parathyroid glands	1,917	16.93	40
Parathyroid glands in males	2,234	17.01	41
Parathyroid glands in females	1,562	16.84	40

A positive correlation is noted between parathyroid gland weight and age: gland weight increases up to age 20–24, plateaus around age 60–64, and then declines in later years **(Figure 3)** (18, 33, 25) .

VASCULARIZATION OF PARATHYROID GLANDS

The arterial supply of the parathyroid glands is terminal in type (6). Most parathyroid glands receive blood from the inferior thyroid artery—on the right in about 86% and on the left in 77% of cases (73). When this artery is absent, the superior thyroid artery typically provides the main supply. In cases of mediastinal ectopy, blood flow may derive from branches of the internal thoracic or bronchial arteries (68).

Anastomotic branches between the superior and inferior thyroid arteries contribute significantly to the vascularization of the superior glands. Nobori et al. reported this pattern in 45% of cases (74). At the same time, Delattre et al. found that 77.1% of superior glands are supplied by the inferior thyroid artery, 15.3% by anastomotic branches, and 90.3% of inferior glands by the inferior thyroid artery (75).

Venous drainage occurs via the thyroid capsular plexus and small intrathyroidal veins, with outflow through the superior, middle, and inferior thyroid veins into the internal jugular vein. Occasionally, a thyroidea ima vein forms a common trunk draining into the brachiocephalic vein (6).

DIFFERENTIATION OF PARATHYROID GLANDS

Professor Jonathan Van Heerden emphasized that during parathyroid surgery, the superior glands are typically found above and the inferior glands below their expected locations (6). Although generally accurate, this rule requires caution, as embryologic development can lead to positional variations. Rarely, superior and inferior glands may fuse into a "kissing" pair, which should be distinguished from a more common bilobate gland—differentiation is possible only through meticulous dissection without capsule disruption (6,45).

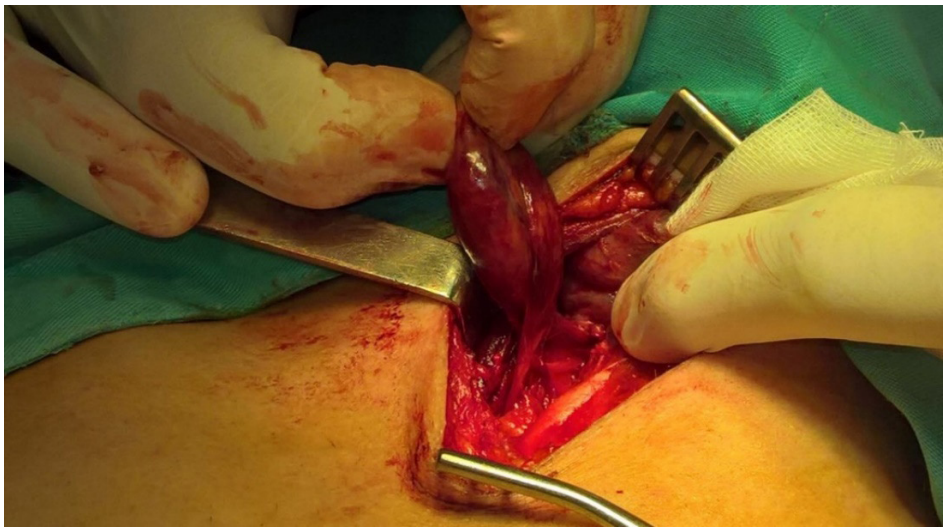

Figure 3. Enlarged lower parathyroid gland (Image shows only the surgical field; no patient-identifying features are visible)

Parathyroid glands exhibit bilateral symmetry in about 80% of cases, with contralateral glands occupying similar positions (6). The presence of rudimentary thymic tissue can help localize an undescended inferior gland, while a superior gland may occasionally lie unusually low; in such cases, its vascular pedicle entering from below aids in identification (45).

TECHNIQUES FOR LOCALIZATION OF PARATHYROID GLANDS

Accurate preoperative localization of parathyroid lesions is crucial for successful surgery. However, no consensus exists on the optimal approach. The integration of advanced diagnostic modalities enables comprehensive evaluation of morphological and functional substrates, representing a key step in understanding parathyroid pathophysiology (77). A multimodal approach that combines imaging with serum biomarkers enhances diagnostic precision and supports effective localization and management of parathyroid disorders (76, 78). Ultrasonography and technetium-99m-sestamibi single-photon emission computed tomography/computed tomography (SPECT/CT) are the most commonly used techniques, although precise localization can be challenging in multiglandular, ectopic, recurrent, or normocalcemic disease (79, 80). To enhance diagnostic accuracy, newer modalities such as positron emission tomography/computed tomography (PET/CT) and parathyroid venous sampling (PVS) have been developed, demonstrating improved sensitivity and precision (85, 99). Combining different imaging approaches provides both anatomical and functional information, and the choice of modality should depend on the patient's clinical context, cost, radiation exposure, and available expertise. Ultrasonography is a first-line method for detecting parathyroid pathology; normal glands (≈4 mm) are typically not visualized, whereas adenomas appear as well-defined, hypoechoic oval lesions (7).

99mTc-sestamibi scintigraphy remains the standard radionuclide technique since its introduction by Coakley et al. (83). When combined with SPECT/CT, it provides complementary anatomical and functional data, improving sensitivity and enabling differentiation from thyroid nodules or lymph nodes (84, 86–90). PET/CT is a high-sensitivity molecular imaging method that uses tracers such as ^{18}F-FDG, ^{11}C-methionine, ^{11}C-choline, and ^{18}F-fluorocholine (85, 91, 92), with ^{18}F-choline preferred for its longer half-life and greater availability.

Four-dimensional computed tomography (4D-CT) integrates multiphase contrast-enhanced data from arterial, venous, and delayed phases, providing excellent spatial resolution, particularly in reoperative cases, though it entails higher radiation exposure (93, 96). PET/MRI combines functional PET data with MRI's superior soft-tissue contrast and reduced radiation exposure, but its use is limited by cost and accessibility (94). Contrast-enhanced ultrasound (CEUS) employs microbubble contrast agents to assess vascularity, offering a radiation-free alternative, though its accuracy is operator-dependent (95). MRI and 4D MRI serve as valuable radiation-free options, especially for identifying ectopic or mediastinal glands; while less sensitive than sestamibi scintigraphy and 4D-CT, 4D MRI shows promise by providing both anatomical and perfusion-related information (97, 98).

PARATHYROID VENOUS SAMPLING IN DIFFICULT CASES

Selective parathyroid venous sampling (PVS) can be a useful technique when localization is inconclusive with the noninvasive tests described above or when the disease recurs after the first operation (16, 99).

Finally, parathyroid venous sampling (PVS) is reserved for complex or recurrent cases when noninvasive imaging is inconclusive, offering valuable functional localization guidance (16, 99) **(Table 5)**.

In addition to the above preoperative diagnostic methods, intraoperative techniques enable more precise and accurate identification of the parathyroid glands.

INTRAOPERATIVE FUNCTIONAL TECHNIQUES

Several intraoperative functional techniques have been developed to improve the accuracy of parathyroid surgery. Intraoperative PTH monitoring (ioPTH) measures the rapid decline in parathyroid hormone levels after gland excision, leveraging its short half-life of 3–5 minutes to confirm successful removal of hyperfunctioning tissue. However, it requires rapid assay setup and increases costs (100). Radioguided surgery employs a handheld gamma probe to detect radiotracer uptake following preoperative sestamibi injection, aiding in the localization of small or ectopic glands but necessitating coordination with nuclear medicine services (101). Indocyanine Green (ICG) fluorescence imaging involves intravenous administration of ICG dye, which becomes visible under infrared light and assists in assessing vascularity and identifying parathyroid glands; however, it requires specialized equipment and remains off-label in parathyroid surgery. Near-infrared autofluorescence imaging (NIRAF) utilizes the natural autofluorescence of parathyroid tissue when exposed to near-infrared light, enabling real-time gland identification without radiation or contrast agents, though it cannot distinguish between normal and hyperfunctioning tissue (102).

Numerous studies have shown that appropriate diagnostic evaluation significantly improves surgical outcomes by reducing operative time, minimizing tissue

Table 5. Advantages and disadvantages of diagnostic methods (91)

Method	Advantages	Disadvantages
Ultrasonography	Inexpensive Lack of radiation exposure Convenient Widely available	Operator-dependent Limited ability to assess ectopic glands
Technetium-99m-sestamibi scan – SPECT/CT	Assessment of ectopic glands Acquisition of both functional and anatomical information	False-positive results Low sensitivity in detecting multiglandular disease
11C-methionine PET	Assessment of ectopic glands	Low availability Short half-life (20 minutes) Low sensitivity in detecting multiglandular disease
Choline PET	High sensitivity Assessment of ectopic glands	High cost Low availability
Four-dimensional computed tomography (4D-CT)	Detailed anatomy Assessment of multiglandular disease and ectopic glands	High radiation dose Difficult interpretation Low availability
Parathyroid venous sampling	Assessment of ectopic glands, recurrent disease, and discordant or unlocalized lesions by various imaging studies	Invasive High cost Requires an experienced radiologist
Near-infrared autofluorescence	Real-time, rapid technique	Not well validated in detecting hyperfunctioning parathyroid tissue

dissection, and increasing the likelihood of successful localization, particularly in cases of multiglandular disease or ectopic adenomas (103). Furthermore, recent research indicates that preoperative assessment of inflammatory markers and patients' nutritional status, based on standard laboratory parameters, can further optimize perioperative management and accelerate recovery. This multidisciplinary approach represents a key factor in achieving better surgical results and improving overall treatment outcomes (104).

CONCLUSION

Good knowledge of embryologic development and neck anatomy is essential for parathyroid surgery.

Parathyroid glands exhibit anatomical variations in localization, number, morphology, and vascularization. Parathyroid ectopy and variation in gland number are the most common causes of persistent or recurrent HPT.

Contemporary imaging diagnostic modalities used in parathyroid surgery do not have the same sensitivity and specificity as in other surgical fields, and they significantly increase treatment costs. The success of surgical treatment largely depends on the surgeon's knowledge and experience.

If parathyroid glands are not found in their usual locations, an extensive bilateral neck exploration must be performed. Meanwhile, parathyroid adenomas located in the mediastinum below the aortic arch require a specialized diagnostic and surgical approach. Measurement of intraoperative PTH (ioPTH) levels increases the success rate of surgical interventions.

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References

1. Sadler TW, Langman J. Langman's medical embryology [Internet]. 12th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012 [cited 2024 Feb 29]. 384 p. Available from: http://catdir.loc.gov/catdir/enhancements/fy1211/2011025451-d.html ISBN: 9781451113426
2. Moore KL, Persaud TVN, Torchia MG. The developing human: clinically oriented embryology [Internet]. 9th ed. Philadelphia, PA: Saunders/Elsevier; 2013 [cited 2024 Feb 29]. 540 p. Available from: http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20090604190 ISBN: 9781437720020
3. Mérida-Velasco JA, Sánchez-Montesinos I, Espín-Ferra J, García-García JD, Roldán-Schilling V. Ectodermal ablation of the third branchial arch in chick embryos and the morphogenesis of the parathyroid III gland. J Craniofac Genet Dev Biol. 1999;19(1):33–40.
4. Carlson BM. Human embryology and developmental biology [Internet]. 5th ed. Philadelphia, Pa.: Elsevier/Saunders; 2014 [cited 2024 Feb 29]. 506 p. (ClinicalKey). Available from: http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20110053127 ISBN: 9781455727940

5. Manley NR, Capecchi MR. Hox group 3 paralogs regulate the development and migration of the thymus, thyroid, and parathyroid glands. Dev Biol. 1998 Mar 1;195(1):1–15. DOI: 10.1006/dbio.1997.8827
6. Živaljević V. Hirurgija paratiroidnih žlezda. Medicinski fakultet Univerziteta u Beogradu; ISBN: 9788672681628
7. Janković J. Hirurgija tiroidne i paratiroidnih žlezda. Zavod za udžbenike i nastavna sredstva Beograd;
8. Ozoğul B, Nuran Akçay M, Kisaoğlu A, Atamanalp SS, Oztürk G, Aydinli B. Incidental parathyroidectomy during thyroid surgery: risk factors, incidence, and outcomes. Turk J Med Sci. 2014;44(1):84–8. DOI: 10.3906/sag-1210-36
9. Nelson BD, Dierberg K, Šćepanović M, Mitrović M, Vuksanović M, Milić L, et al. Integrating quantitative and qualitative methodologies for the assessment of health care systems: emergency medicine in post-conflict Serbia. BMC Health Serv Res. 2005 Feb 17;5:14. DOI: 10.1007/s11547-015-0578-9
10. Toriie S, Sugimoto T, Hokimoto N, Funakoshi T, Ogawa M, Oki T, et al. Evaluation of the minimally invasive parathyroidectomy in patients with primary hyperparathyroidism: A retrospective cohort study. Ann Med Surg (Lond). 2016 May;7:42–7. ISBN: 9788672681628
11. Noussios G, Anagnostis P, Natsis K. Ectopic parathyroid glands and their anatomical, clinical and surgical implications. Exp Clin Endocrinol Diabetes. 2012 Nov;120(10):604–10. DOI: 10.1016/j.hansur.2015.01.005
12. Hoda NE, Phillips P, Ahmed N. Recommendations after non-localizing sestamibi and ultrasound scans in primary hyperparathyroid disease: order more scans or explore surgically? J Miss State Med Assoc. 2013 Feb;54(2):36–41.
13. Michaud L, Balogova S, Burgess A, Ohnona J, Huchet V, Kerrou K, et al. A Pilot Comparison of 18F-fluorocholine PET/CT, Ultrasonography and 123I/99mTc-sestaMIBI Dual-Phase Dual-Isotope Scintigraphy in the Preoperative Localization of Hyperfunctioning Parathyroid Glands in Primary or Secondary Hyperparathyroidism: Influence of Thyroid Anomalies. Medicine (Baltimore). 2015 Oct;94(41):e1701. DOI: 10.1016/j.amjsurg.2008.03.006
14. Udelsman R, Åkerström G, Biagini C, Duh QY, Miccoli P, Niederle B, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. J Clin Endocrinol Metab. 2014 Oct;99(10):3595–606. DOI: 10.1016/j.ijsu.2016.03.003
15. Thompson NW, Eckhauser FE, Harness JK. The anatomy of primary hyperparathyroidism. Surgery. 1982 Nov;92(5):814–21.
16. Kunstman JW, Kirsch JD, Mahajan A, Udelsman R. Clinical review: Parathyroid localization and implications for clinical management. J Clin Endocrinol Metab. 2013 Mar;98(3):902–12. DOI: 10.1016/j.surge.2012.01.004
17. Malmaeus J, Granberg PO, Halvorsen J, Akerström G, Johansson H. Parathyroid surgery in Scandinavia. Acta Chir Scand. 1988;154(7–8):409–13. DOI: 10.1016/j.wneu.2014.06.039
18. Lappas D, Noussios G, Anagnostis P, Adamidou F, Chatzigeorgiou A, Skandalakis P. Location, number and morphology of parathyroid glands: results from a large anatomical series. Anat Sci Int. 2012 Sep;87(3):160–4.
19. Chen H, Wang TS, Yen TWF, Doffek K, Krzywda E, Schaefer S, et al. Operative failures after parathyroidectomy for hyperparathyroidism: the influence of surgical volume. Ann Surg. 2010 Oct;252(4):691–5. DOI: 10.1016/j.jss.2012.03.026
20. Hojaij F, Vanderlei F, Plopper C, Rodrigues CJ, Jácomo A, Cernea C, et al. Parathyroid gland anatomical distribution and relation to anthropometric and demographic parameters: a cadaveric study. Anat Sci Int. 2011 Dec;86(4):204–12. DOI: 10.1007/s00423-012-1028-1
21. Kara M, Tellioglu G, Bugan U, Krand O, Berber I, Seymen P, et al. Evaluation of intraoperative parathormone measurement for predicting successful surgery in patients undergoing subtotal/total parathyroidectomy due to secondary hyperparathyroidism. Laryngoscope. 2010 Aug;120(8):1538–44.
22. Gunasekaran S, Wallace H, Snowden C, Mikl D, England RJA. Parathyroid ectopia: development of a surgical algorithm based on operative findings. J Laryngol Otol. 2015 Nov;129(11):1115–20. DOI: 10.1002/bjs.1800691006
23. Schneider R, Bartsch DK, Schlosser K. Relevance of bilateral cervical thymectomy in patients with renal hyperparathyroidism: analysis of 161 patients undergoing reoperative parathyroidectomy. World J Surg. 2013 Sep;37(9):2155–61. ISBN: 9781437720020
24. Abboud B, Sleilaty G, Braidy C, Ghorra C, Abadjian G, Tohme C, et al. Enlarged parathyroid glands discovered in normocalcemic patients during thyroid surgery. Am J Surg. 2008 Jan;195(1):30–3. DOI: 10.1002/hed.21934
25. Akerström G, Malmaeus J, Bergström R. Surgical anatomy of human parathyroid glands. Surgery. 1984 Jan;95(1):14–21. DOI: 10.1002/lary.22177
26. Alveryd A. Parathyroid glands in thyroid surgery. I. Anatomy of parathyroid glands. II. Postoperative hypoparathyroidism--identification and autotransplantation of parathyroid glands. Acta Chir Scand. 1968;389:1–120. DOI: 10.1002/hed.21415
27. Arnalsteen L, Proye C. [Surgery of hyperparathyroidism and of its potential recurrence in the MEN I setting]. Ann Chir. 2003 Dec;128(10):706–9. DOI: 10.1002/hed.23163
28. Botelho JBL, Cançado ARS, Sousa EA de. Importância anatomocirúrgica das características macroscópicas, localização e suprimento vascular das glândulas paratireóides cervicais. Rev Col Bras Cir. 2004;31:132–8.
29. Butterworth PC, Nicholson ML. Surgical anatomy of the parathyroid glands in secondary hyperparathyroidism. J R Coll Surg Edinb. 1998 Aug;43(4):271–3. DOI: 10.1210/jc.2008-1941
30. Andrade JSC de, Mangussi-Gomes JP, Rocha LA da, Ohe MN, Rosano M, das Neves MC, et al. Localization of ectopic and supernumerary parathyroid glands in patients with secondary and tertiary hyperparathyroidism: surgical description and correlation with preoperative ultrasonography and Tc99m-Sestamibi scintigraphy. Braz J Otorhinolaryngol. 2014;80(1):29–34. DOI: 10.1007/s12020-010-9404-0
31. Edis AJ, Levitt MD. Supernumerary parathyroid glands: implications for the surgical treatment of secondary hyperparathyroidis DOI: 10.1530/EJE-09-0959m. World J Surg. 1987 Jun;11(3):398–401. DOI: 10.1530/EJE-09-0959
32. Ghandur-Mnaymneh L, Cassady J, Hajianpour MA, Paz J, Reiss E. The parathyroid gland in health and disease. Am J Pathol. 1986 Nov;125(2):292–9.
33. Gomes EMS, Nunes RC, Lacativa PGS, Almeida MH de, Franco FM, Leal CTS, et al. Ectopic and extranumerary parathyroid glands location in patients with hyperparathyroidism secondary to end stage renal disease. Acta Cir Bras. 2007;22(2):105–9. DOI: 10.1097/SLA.0000000000003017
34. Hellman P, Skogseid B, Oberg K, Juhlin C, Akerström G, Rastad J. Primary and reoperative parathyroid operations in hyperparathyroidism of multiple endocrine neoplasia type 1. Surgery. 1998 Dec;124(6):993–9. DOI: 10.1001/jamasurg.2016.0842
35. Hibi Y, Tominaga Y, Uchida K, Takagi H, Imai T, Funahashi H, et al. Cases with fewer than four parathyroid glands in patients with renal hyperparathyroidism at initial parathyroidectomy. World J Surg. 2002 Mar;26(3):314–7. ISBN: 9780702053252
36. Kawata R, Kotetsu L, Takamaki A, Yoshimura K, Takenaka H. Ultrasonography for preoperative localization of enlarged parathyroid glands in secondary hyperparathyroidism. Auris Nasus Larynx. 2009 Aug;36(4):461–5. DOI: 10.1002/bjs.1800700121
37. Milas M, Wagner K, Easley KA, Siperstein A, Weber CJ. Double adenomas revisited: nonuniform distribution favors enlarged superior parathyroids (fourth pouch disease). Surgery. 2003 Dec;134(6):995–1003; discussion 1003-1004. DOI: 10.1097/00000658-199908000-00015
38. Nanka O, Sedý J, Vítková I, Libánský P, Adámek S. Surgical anatomy of parathyroid glands with emphasis on parathyroidectomy. Prague Med Rep. 2006;107(2):261–72.
39. Numano M, Tominaga Y, Uchida K, Orihara A, Tanaka Y, Takagi H. Surgical significance of supernumerary parathyroid glands in renal

hyperparathyroidism. World J Surg. 1998 Oct;22(10):1098–102; discussion 1103. DOI: 10.1016/j.surg.2005.02.004

40. Okada M, Tominaga Y, Yamamoto T, Hiramitsu T, Narumi S, Watarai Y. Location Frequency of Missed Parathyroid Glands After Parathyroidectomy in Patients with Persistent or Recurrent Secondary Hyperparathyroidism. World J Surg. 2016 Mar;40(3):595–9.
41. Pacini P, Biondi G, Cicchi P, Borrelli D, Solfanelli E. [The number and topographical location of parathyroid glands in man]. Arch Ital Anat Embriol. 1983;88(2):177–90.
42. Pool EH, Falk HC. CONCERNING THE SURGICAL ANATOMY OF THE THYROID WITH SPECIAL REFERENCE TO THE PARATHYROID GLANDS. Ann Surg. 1916 Jan;63(1):71–7. DOI: 10.1245/s10434-010-1367-0
43. Praženica P, O'Keeffe L, Holý R. Dissection and identification of parathyroid glands during thyroidectomy: association with hypocalcemia. Head Neck. 2015 Mar;37(3):393–9. DOI: 10.1245/s10434-009-0759-2
44. Pyrtek L, Painter RL. AN ANATOMIC STUDY OF THE RELATIONSHIP OF THE PARATHYROID GLANDS TO THE RECURRENT LARYNGEAL NERVE. Surg Gynecol Obstet. 1964 Sep;119:509–12.
45. Wang C. The anatomic basis of parathyroid surgery. Ann Surg. 1976 Mar;183(3):271–5. DOI: 10.1016/j.amjsurg.2007.08.037
46. Roy M, Mazeh H, Chen H, Sippel RS. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. World J Surg. 2013 Jan;37(1):102–6. DOI: 10.1007/s00268-012-1803-2
47. Mendoza V, Ramírez C, Espinoza AE, González GA, Peña JF, Ramírez ME, et al. Characteristics of ectopic parathyroid glands in 145 cases of primary hyperparathyroidism. Endocr Pract. 2010;16(6):977–81. DOI: 10.4158/EP10087.OR
48. Vulpio C, Bossola M, De Gaetano A, Maresca G, Bruno I, Fadda G, et al. Usefulness of the combination of ultrasonography and 99mTc-sestamibi scintigraphy in the preoperative evaluation of uremic secondary hyperparathyroidism. Head Neck. 2010 Sep;32(9):1226–35. DOI: 10.1002/hed.21352
49. Sellitri F, Tamburrini A, Tacconi F, Bollero P, Ortensi A, Mineo TC. Intrathymic ectopic parathyroid adenoma caused primary hyperparathyroidism with vitamin D deficiency several years after bariatric surgery. Thorac Cancer. 2015 Jan;6(1):101–4. DOI: 10.1111/1759-7714.12118
50. Stalberg P, Grodski S, Sidhu S, Sywak M, Delbridge L. Cervical thymectomy for intrathymic parathyroid adenomas during minimally invasive parathyroidectomy. Surgery. 2007 May;141(5):626–9. DOI: 10.1016/j.surg.2007.01.009
51. Pattou FN, Pellissier LC, Noël C, Wambergue F, Huglo DG, Proye CA. Supernumerary parathyroid glands: frequency and surgical significance in treatment of renal hyperparathyroidism. World J Surg. 2000 Nov;24(11):1330–4. DOI: 10.1007/s00268-000-0057-2
52. Rabazzi G, Elia G, Aprile V, Korasidis S, Mastromarino MG, Bacchin D, et al. Surgical Management of Mediastinal Ectopic Parathyroids. J Pers Med. 2025 Jun 30;15(7):276. DOI: 10.3390/jpm15070276
53. Shin JJ, Milas M, Mitchell J, Berber E, Ross L, Siperstein A. Impact of localization studies and clinical scenario in patients with hyperparathyroidism being evaluated for reoperative neck surgery. Arch Surg. 2011 Dec;146(12):1397–403. DOI: 10.1001/archsurg.2011.253
54. Lee JC, Mazeh H, Serpell J, Delbridge LW, Chen H, Sidhu S. Adenomas of cervical maldescended parathyroid glands: pearls and pitfalls. ANZ J Surg. 2015 Dec;85(12):957–61. DOI: 10.1111/ans.13242
55. Wang F, Wang H, Fan J, Zhang Y, Wang H, Zhao Q. Pancreatic Injury Patterns in Patients With Coronavirus Disease 19 Pneumonia. Gastroenterology. 2020 Jul;159(1):367–70. DOI: 10.1053/j.gastro.2020.03.033
56. Wei B, Inabnet W, Lee JA, Sonett JR. Optimizing the minimally invasive approach to mediastinal parathyroid adenomas. Ann Thorac Surg. 2011 Sep;92(3):1012–7. DOI: 10.1016/j.athoracsur.2011.05.012
57. Simeone DM, Sandelin K, Thompson NW. Undescended superior parathyroid gland: a potential cause of failed cervical exploration for hyperparathyroidism. Surgery. 1995 Dec;118(6):949–56. DOI: 10.1016/0003-4975(95)00355-5
58. Nakada T, Akiba T, Inagaki T, Marushima H, Morikawa T, Ohki T. A case of a retroesophageal parathyroid adenoma with an aberrant right subclavian artery: a potential surgical pitfall. Ann Thorac Cardiovasc Surg. 2014;20 Suppl:786–9. DOI: 10.5761/atcs.cr.14-00068
59. Smayra T, Abi Khalil S, Abboud B, Halabi G, Slaba S. [Unusual location of a parathyroid adenoma: the carotid sheath]. J Radiol. 2006 Jan;87(1):59–61. DOI: 10.1016/j.rad.2005.07.004
60. Rioja P, Mateu G, Lorente-Poch L, Sancho JJ, Sitges-Serra A. Undescended parathyroid adenomas as cause of persistent hyperparathyroidism. Gland Surg. 2015 Aug;4(4):295–300. DOI: 10.3978/j.issn.2227-684X.2015.08.04
61. Shields TW. Mediastinal surgery. Philadelphia, Lea & Fabiger; 1991. ISBN: 9780721629677
62. Arnault V, Beaulieu A, Lifante JC, Sitges Serra A, Sebag F, Mathonnet M, et al. Multicenter study of 19 aortopulmonary window parathyroid tumors: the challenge of embryologic origin. World J Surg. 2010 Sep;34(9):2211–6. DOI: 10.1007/s00268-010-0725-1
63. Hu J, Ngiam KY, Parameswaran R. Mediastinal parathyroid adenomas and their surgical implications. Ann R Coll Surg Engl. 2015 May;97(4):259–61. DOI: 10.1308/003588415X14171112245869
64. Conn JM, Goncalves MA, Mansour KA, McGarity WC. The mediastinal parathyroid. Am Surg. 1991 Jan;57(1):62–6. DOI: 10.1177/000313499105700111
65. Downey NJ, McGuigan JA, Dolan SJ, Russell CF. Median sternotomy for parathyroid adenoma. Ir J Med Sci. 1999;168(1):13–6. DOI: 10.1007/s11845-998-0193-5
66. Mariani G, Gulec SA, Rubello D, Boni G, Puccini M, Pelizzo MR, et al. Preoperative localization and radioguided parathyroid surgery. J Nucl Med. 2003 Sep;44(9):1443–58. DOI: 10.1016/j.jnumed.2003.09.058
67. Hindié E, Zanotti-Fregonara P, Tabarin A, Rubello D, Morelec I, Wagner T, et al. The role of radionuclide imaging in the surgical management of primary hyperparathyroidism. J Nucl Med. 2015 May;56(5):737–44. DOI: 10.2967/jnumed.114.146482
68. Ali M, Kumpe DA. Embolization of bronchial artery-supplied ectopic parathyroid adenomas located in the aortopulmonary window. J Vasc Interv Radiol. 2014 Jan;25(1):138–43. DOI: 10.1016/j.jvir.2013.10.018
69. Iihara M, Suzuki R, Kawamata A, Horiuchi K, Okamoto T. Thoracoscopic removal of mediastinal parathyroid lesions: selection of surgical approach and pitfalls of preoperative and intraoperative localization. World J Surg. 2012 Jun;36(6):1327–34. DOI: 10.1007/s00268-012-1577-0
70. Ishikawa T, Onoda N, Ogawa Y, Takashima T, Matsunaga N, Michigami S, et al. Thoracoscopic excision for ectopic mediastinal parathyroid tumor. Biomed Pharmacother. 2002;56 Suppl 1:34s–6s. DOI: 10.1016/S0753-3322(02)00156-0
71. Sagan D, Goździuk K. Surgical treatment of mediastinal parathyroid adenoma: rationale for intraoperative parathyroid hormone monitoring. Ann Thorac Surg. 2010 Jun;89(6):1750–5. DOI: 10.1016/j.athoracsur.2009.12.052
72. Spinelli C, Liserre J, Pucci V, Massart F, Grosso M, Brandi ML. Primary hyperparathyroidism: fifth parathyroid intrathymic adenoma in a young patient. J Pediatr Endocrinol Metab. 2012;25(7–8):781–4. DOI: 10.1515/jpem-2012-0103
73. Alveryd A. Parathyroid glands in thyroid surgery. I. Anatomy of parathyroid glands. II. Postoperative hypoparathyroidism--identification and autotransplantation of parathyroid glands. Acta Chir Scand. 1968;389:1–120. ISBN: 9781437720020
74. Nobori M, Saiki S, Tanaka N, Harihara Y, Shindo S, Fujimoto Y. Blood supply of the parathyroid gland from the superior thyroid artery. Surgery. 1994 Apr;115(4):417–23. DOI: 10.1002/bjs.1800670415
75. Delattre JF, Flament JB, Palot JP, Pluot M. [Variations in the parathyroid glands. Number, situation and arterial vascularization. Anatomical study and surgical application]. J Chir (Paris). 1982 Nov;119(11):633–41. DOI: 10.1016/0021-7697(82)90138-3

76. Milić L, Grigorov I, Krstić S, Ćeranić MS, Jovanović B, Stevanović J, et al. Serum Level of HMGB1 Protein and Inflammatory Markers in Patients with Secondary Peritonitis: Time Course and the Association with Clinical Status. J Med Biochem. 2017 Jan;36(1):44–53. DOI: 10.1515/jomb-2017-0005

77. Ana Starčević, Marija Marjanović-Haljilji, Ljiljana Milić, Branka Filipović. Is there a difference between patients with functional dyspepsia and irritable bowel syndrome in headache manifestation? Српски архив за целокупно лекарство, (Serbian Archives of Medicine). DOI: https://doi.org/10.2298/SARH221006118S

78. Dragica Mitrović, Predrag Erceg, Ljiljana Milić, Vladica Ćuk, Jovan Juloski, Radosav Radulović, Ljubica Konstantinović, Zoran Radojičić, Vesna R. Jovanović, Sanja Dugonjić. Measurement properties of New Mobility Score to evaluate functional recovery in the elderly following total hip arthroplasty. Српски архив за целокупно лекарство, (Serbian Archives of Medicine). DOI: https://doi.org/10.2298/SARH200713005M

79. Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young JEM, Rejnmark L, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos Int. 2017 Jan;28(1):1–19. DOI: 10.1007/s00198-016-3706-2

80. 80. Wilhelm SM, Wang TS, Ruan DT, Lee JA, Asa SL, Duh QY, et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg. 2016 Oct 1;151(10):959–68. DOI: 10.1001/jamasurg.2016.2319

81. Potchen EJ, Adelstein SJ, Dealy JB. RADIOISOTOPE LOCALIZATION OF THE OVERACTIVE HUMAN PARATHYROID. Am J Roentgenol Radium Ther Nucl Med. 1965 Apr;93:955–61. DOI: 10.2214/ajr.93.4.955

82. Fukunaga M, Fujita T, Yonekura Y, Dokoh S, Yamamoto I, Morita R, et al. [Visualization of parathyroid tumor with 201Tl-chloride (author's transl)]. Kaku Igaku. 1979 May;16(3):327–31.

83. Coakley AJ, Kettle AG, Wells CP, O'Doherty MJ, Collins RE. 99Tcm sestamibi--a new agent for parathyroid imaging. Nucl Med Commun. 1989 Nov;10(11):791–4. DOI: 10.1097/00006231-198911000-00017

84. Siraj QH. Radionuclide parathyroid imaging. Cham: Springer; 2020. Chapter 5, Parathyroid Scintigraphy; p. 41-61. ISBN: 9783030583434

85. Siraj QH. Radionuclide parathyroid imaging. Cham: Springer; 2020. Chapter 6, Parathyroid PET; p. 61-5. ISBN: 9783030583434

86. Krausz Y, Bettman L, Guralnik L, Yosilevsky G, Keidar Z, Bar-Shalom R, et al. Technetium-99m-MIBI SPECT/CT in primary hyperparathyroidism. World J Surg. 2006 Jan;30(1):76–83. DOI: 10.1007/s00268-005-0365-0

87. Neumann DR, Obuchowski NA, Difilippo FP. Preoperative 123I/99mTc-sestamibi subtraction SPECT and SPECT/CT in primary hyperparathyroidism. J Nucl Med. 2008 Dec;49(12):2012–7. DOI: 10.2967/jnumed.107.047485

88. Kim YI, Jung YH, Hwang KT, Lee HY. Efficacy of ^{99}mTc-sestamibi SPECT/CT for minimally invasive parathyroidectomy: comparative study with ^{99}mTc-sestamibi scintigraphy, SPECT, US and CT. Ann Nucl Med. 2012 Dec;26(10):804–10. DOI: 10.1007/s12149-012-0617-5

89. Neumann DR, Obuchowski NA, Difilippo FP. Preoperative 123I/99mTc-sestamibi subtraction SPECT and SPECT/CT in primary hyperparathyroidism. J Nucl Med. 2008 Dec;49(12):2012–7. DOI: 10.2967/jnumed.107.047485

90. Akram K, Parker JA, Donohoe K, Kolodny G. Role of single photon emission computed tomography/computed tomography in localization of ectopic parathyroid adenoma: a pictorial case series and review of the current literature. Clin Nucl Med. 2009 Aug;34(8):500–2. DOI: 10.1097/CLN.0b013e3181adbdc4

91. Treglia G, Giovannini E, Di Franco D, Calcagni ML, Rufini V, Picchio M, et al. The role of positron emission tomography using carbon-11 and fluorine-18 choline in tumors other than prostate cancer: a systematic review. Ann Nucl Med. 2012 Jul;26(6):451–61. DOI: 10.1007/s00259-012-2162-6

92. Kluijfhout WP, Pasternak JD, Drake FT, Beninato T, Gosnell JE, Shen WT, et al. Use of PET tracers for parathyroid localization: a systematic review and meta-analysis. Langenbecks Arch Surg. 2016 Nov;401(7):925–35. DOI: 10.1007/s00423-016-1461-4

93. Hunter GJ, Schellingerhout D, Vu TH, Perrier ND, Hamberg LM. Accuracy of four-dimensional CT for the localization of abnormal parathyroid glands in patients with primary hyperparathyroidism. Radiology. 2012 Sep;264(3):789–95. DOI: 10.1148/radiol.12110590

94. Noltes ME, Rotstein L, Eskander A, Kluijfhout WP, Bongers P, Brouwers AH, et al. 18F-fluorocholine PET/MRI versus ultrasound and sestamibi for the localization of parathyroid adenomas. Langenbecks Arch Surg. 2023 Apr 20;408(1):155. DOI: 10.1007/s00423-023-02925-3

95. Liu F, Zang L, Li Y, Guan Z, Liu Y, Yu X, et al. Application value of contrast-enhanced ultrasound in preoperative localization of microwave ablation for primary hyperparathyroidism. J Appl Clin Med Phys. 2022 Dec;23(12):e13802. DOI: 10.1002/acm2.13802

96. Rodgers SE, HG Hamberg LM, et al. Parathyroid imaging with 4-dimensional computed tomography: techniques, patterns, and role in primary hyperparathyroidism management. Radiographics. DOI: 10.1148/rg.334125099

97. Altintop SE, Cerit MN, Cindil E, Sendur HN, Barlas T, Yalcin MM, et al. Dynamic 4 dimensional contrast enhanced MRI for localization in primary hyperparathyroidism. Endocrine. 2025 Jul;89(1):267–75. DOI: 10.1007/s12020-025-03670-2

98. Al-Difaie Z, Scheepers MHMC, Engelen SME, Havekes B, Bouvy ND, Postma AA. Diagnostic Value of Four-Dimensional Dynamic Computed Tomography for Primary Hyperparathyroidism in Patients with Low Baseline Parathyroid Hormone Levels. Diagnostics (Basel). 2023 Aug 8;13(16):2621. DOI: 10.3390/diagnostics13162621

99. Ibraheem K, Toraih EA, Haddad AB, Farag M, Randolph GW, Kandil E. Selective parathyroid venous sampling in primary hyperparathyroidism: A systematic review and meta-analysis. Laryngoscope. 2018 Nov;128(11):2662–7. DOI: 10.1002/lary.27287

100. Staibano P, Au M, Zhang H, Yu S, Liu W, Pasternak JD, et al. Intraoperative Parathyroid Hormone Monitoring Criteria in Primary Hyperparathyroidism: A Network Meta-Analysis of Diagnostic Test Accuracy. JAMA Otolaryngol Head Neck Surg. 2025 Mar 1;151(3):190–200. DOI: 10.1001/jamaoto.2025.0190

101. Casella C, Rossini P, Cappelli C, Nessi C, Nascimbeni R, Portolani N. Radioguided Parathyroidectomy with Portable Mini Gamma-Camera for the Treatment of Primary Hyperparathyroidism. Int J Endocrinol. 2015;2015:134731. DOI: 10.1155/2015/134731

102. Frey S, Bannani S, Caillard C, Le Bras M, Drui D, Ansquer C, et al. Parathyroid near-infrared autofluorescence use for parathyroidectomy in mild primary hyperparathyroidism: Results from a randomized monocentric trial. Surgery. 2025 Jan;177:108878. DOI: 10.1016/j.surg.2024.108878

103. Hindié E, Schwartz P, Avram AM, Imperiale A, Sebag F, Taïeb D. Primary Hyperparathyroidism: Defining the Appropriate Preoperative Imaging Algorithm. J Nucl Med. 2021 Jul;62(Suppl 2):3S-12S. DOI: 10.2967/jnumed.121.262525

104. Cuk V, Karamarkovic A, Juloski J, Arbutina D, Radulovic R, Milic L, et al. Prognostic Value of Combined Hematological/Biochemical Indexes and Tumor Clinicopathologic Features in Colorectal Cancer Patients—A Pilot Single Center Study. Cancers (Basel). 2023 Mar 14;15(6):1761. DOI: 10.3390/cancers15061761

HIRURŠKI ZNAČAJ ANATOMSKIH VARIJACIJA PARATIREOIDNIH ŽLEZDA

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Sažetak

Solidno razumevanje hirurške anatomije paratiroidnih žlezda zasniva se na temeljnom poznavanju njihovog embrionalnog razvoja. Anatomske varijacije u broju, morfologiji, vaskularizaciji i lokalizaciji paratiroidnih žlezda predstavljaju izazov tokom hirurške eksploracije vrata, kako u lečenju hiperparatiroidizma (HPT), tako i u hirurgiji štitne žlezde. Kod oko 2,3% pacijenata koji se podvrgavaju tiroidektomiji, dolazi do incidentne paratiroidektomije. Cilj našeg pregleda je da istaknemo učestalost anatomskih varijacija u lokalizaciji, broju, morfologiji i vaskularizaciji paratiroidnih žlezda, kao i značaj ovih anatomskih varijacija u hirurškom lečenju funkcionalnih poremećaja paratiroidnih žlezda. Dobro poznavanje embriološkog razvoja i anatomije vrata je od suštinskog značaja u hirurgiji paratiroidnih žlezda. Savremene dijagnostičke metode snimanja koje se koriste u hirurgiji paratiroidnih žlezda nemaju tako visoku osetljivost i specifičnost kao u drugim hirurškim oblastima i značajno povećavaju troškove lečenja. Uspeh hirurškog lečenja u velikoj meri zavisi od znanja i iskustva hirurga.

Ako se paratiroidne žlezde ne pronađu na svojim uobičajenim lokacijama, mora se izvršiti opsežna bilateralna eksploracija vrata. U međuvremenu, paratiroidni adenomi koji se nalaze u medijastinumu ispod aortnog luka zahtevaju specijalizovan dijagnostički i hirurški pristup. Merenje intraoperativnog nivoa PTH (ioPTH) povećava stopu uspeha hirurških intervencija.

Ključne reči: paratireoidne žlezde, PTH, anatomske varijacije

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CASE REPORT

Case report of severe cytomegalovirus infection in pregnancy: prevention and treatment options

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Summary

Introduction: Human cytomegalovirus (CMV) is the leading cause of congenital infection worldwide. It can be the cause of serious clinical manifestations, leading to permanent disability in infected children. Unlike most other TORCH infections, both primary and non-primary CMV infection can affect fetus.

Case Report: We present a case of congenital CMV infection that was diagnosed after the onset of severe fetal anomalies in the third trimester. The patient was referred to our hospital in 35. weeks of pregnancy complicated by severe intrauterine growth restriction and fetal brain anomalies seen on the ultrasound and magnetic resonance imaging (MRI): simplified gyration and a highly suspected band heterotopia (differential diagnosis: lissencephaly), dilated temporal and occipital horns of lateral ventricles with intraventricular septations, vermian hypoplasia, zones of t2 hyperintense lesions. Serology testing revealed positive results for CMV-specific IgM antibodies and a positive result for CMV-specific IgG antibodies with high avidity (91,7%). After performing the amniocentesis (PCR), we got positive result for CMV. The patient was informed about the poor prognosis of the congenital CMV infection with those findings on the fetal brain. She opted for the termination of pregnancy.

Conclusion: Given that this is the most common congenital infection, it is necessary to continually raise awareness among pregnant women about primary prevention methods. In the meantime, efforts should focus on research aimed at timely detection and treatment, to prevent severe forms of congenital infection.

Keywords: congenital infection, cytomegalovirus, screening, antiviral therapy

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INTRODUCTION

Human cytomegalovirus (CMV) is the most common cause of congenital infection worldwide. The majority of infected children are asymptomatic, but some may develop serious clinical manifestations such as: neurodevelopmental delays, vision impairment, intellectual disability, and other systemic findings (1). The most common long-term health problem is non-genetic sensorineural hearing loss (SNHL) (1). Although the seriousness of this congenital infection has been recognized for a long time, little progress has been made in preventing it.

One reason is that maternal infection is most often asymptomatic. In addition, unlike other TORCH infections, both primary and non-primary infections can harm the fetus (2). Since infection can occur at any time before or during pregnancy, universal screening has not been introduced anywhere. As a result, timely diagnosis is often missed. Without early diagnosis of maternal infection, it is difficult to discuss the effectiveness of agents for the prevention of congenital infection.

The aim of this report is to present a case of cytomegalovirus infection diagnosed in 35 weeks of pregnancy.

CASE REPORT

A 27-year-old woman, gravida 2 para 1, was referred to our hospital with a pregnancy complicated by severe intrauterine growth restriction and fetal brain anomalies seen on the ultrasound and magnetic resonance imaging (MRI). She was 35 weeks pregnant. That was her second pregnancy. The first pregnancy was uneventful. She reported the history of chronic hypertension and was taking antihypertensive therapy.

The transabdominal ultrasound confirmed symmetrical intrauterine growth restriction. The estimated fetal weight was 1660g (less than 1%). The amniotic fluid index was within normal ranges. Doppler assessment of the placental and fetal circulation showed normal values. Ultrasound revealed the presence of mild ventriculomegaly, with dilated occipital and temporal horns of the lateral ventricles with normal frontal horns. Other fetal anatomy was normal **(Figure 1)**.

MRI examination of the fetal brain indicated smaller diameters of the cerebral hemispheres for the gestational age, with simplified gyration and a highly suspected band heterotopia (differential diagnosis: lissencephaly). Ventriculomegaly was described as mild, with dilated

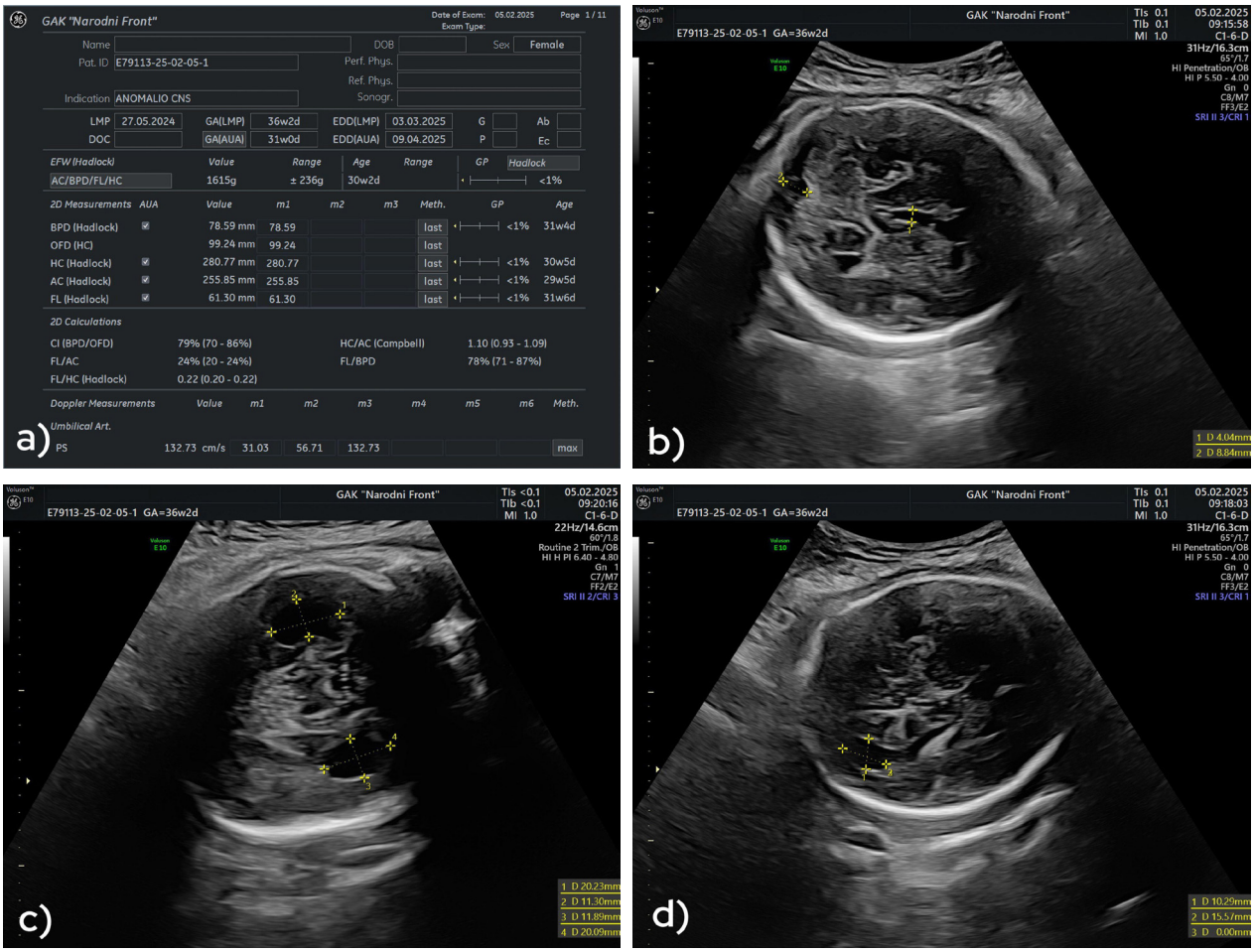

Figure 1. Sonographic features: a) intrauterine growth restriction; b) mild ventriculomegaly; c) dilated temporal horns of lateral ventricles; d) intraventricular septations in occipital horns of lateral ventricles.

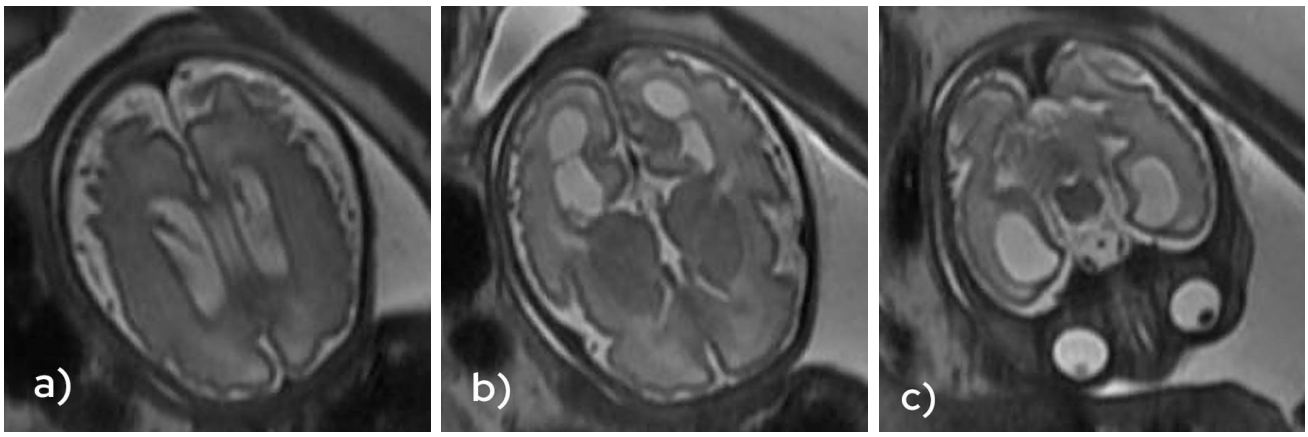

Figure 2. MRI of fetal brain: a) simplified gyral pattern with mild ventriculomegaly, b) dilated occipital horns of lateral ventricles with intraventricular septations, c) dilated temporal horns of lateral ventricles with white matter rarefaction

temporal horns of lateral ventricles, diameters 12mm on the left side and 11mm on the right side with white matter rarefaction, especially on the left side. Occipital horns were dilatated with intraventricular septations. Vermian hypoplasia was described. There were zones of t2 hyperintense lesions, predominantly in temporal lobes. Those changes were described as suspicious for sequelae of an infectious or metabolic disorder **(Figure 2)**.

The tests for blood count, blood group and biochemistry showed results within the reference range. Screening for preeclampsia showed low risk (sFlt-1/PlGF rat 28,88%).

The results of TORCH test were: no detected Toxoplasmosis specific IgM or IgG antibodies; no detected Rubella specific IgM antibodies, positive result for Rubella specific IgG antibodies; positive result for CMV specific IgM antibodies and positive result for CMV specific IgG antibodies with high avidity (91,7%) **(Table 1)**.

Table 1. Serology for cytomegalovirus (CMV) infection

	Result	Ref values	Unit of measurement
CMV IgM	1.12	Non-reactive <0.85 Reactive >1.00	Index
CMV IgG	1102.4	Non-reactive <6.0 Reactive >6.0	U/ml
CMV Av	91.7	Low avidity <50.0 Grey zone 50.0-59.9 High avidity >60.0	%

Given the ultrasound-diagnosed severe intrauterine growth restriction, the presence of CNS anomalies, as well as suspicious CMV serology, it was decided to perform a diagnostic amniocentesis. The result of diagnostic quantitative fluorescent-polymerase chain reaction (QF-PCR) was normal (rsa(X,13,18,21)x2). The microarray test showed a normal molecular karyotype (arr(X,1-22) x2). Polymerase chain reaction (PCR) for CMV diagnosis infection was positive (92750 copies/mL).

The diagnosis was congenital cytomegalovirus infection with a severely symptomatic fetus. The patient was informed at the Fetal Anomalies Committee about the poor prognosis of the congenital CMV infection, especially with those findings on the fetal brain. She opted for the termination of pregnancy.

The fetus and placenta were sent to an autopsy. An autopsy confirmed ventriculomegaly and histological analysis revealed small foci of mineralization in the periventricular white matter, suggesting damage to the brain parenchyma, most likely of infectious origin.

DISCUSSION

Congenital CMV infection affects 0.48% of all live-born infants in high-income countries and 1.42% in low- and middle-income countries and is responsible for significant morbidity, especially in infants who are symptomatic in the neonatal period (3). The rate of transmission to the fetus during primary CMV infections is 30%–40% and 1-2% during non-primary infection (1,3). The risk of sequelae is the greatest following maternal primary infection in the periconception period and first trimester (3,4).

Infected fetuses may be classified into one of three prognostic categories: asymptomatic, mild or moderately symptomatic and severely symptomatic. An asymptomatic fetus has no visible anomalies, has a risk of hearing loss, but generally has a good prognosis. A mild or moderately symptomatic fetus has anomalies like hyperechogenic bowel, mild ventriculomegaly, or isolated calcifications. The prognosis is uncertain and needs an ultrasound or MRI follow-up to define the prognosis. A severely symptomatic fetus has severe brain anomalies: microcephaly, ventriculomegaly, white matter anomalies and cavitations, intracerebral hemorrhage, and delayed cortical development. The prognosis is poor (3).

Maternal serology is used for the diagnosis of primary maternal infection: the appearance of CMV-specific IgG in a woman who was previously seronegative or by the detection of CMV IgM antibody with low IgG avidity. Diagnosis of non-primary CMV infection is not possible using serology (3).

In spite of the high morbidity that may follow the CMV infection, routine screening is not recommended

(5). Some guidelines recommend offering pre-pregnancy or early pregnancy screening for women who are at high risk of infection. Those are the women who have young children at home or who work in childcare, since children under three years old have prolonged viral shedding in their saliva and urine (2). One of the reasons for not screening is that we can't predict the risk of fetal infection, and when we prove fetal infection, we can't always predict the magnitude of fetal/neonatal impairment. Second, half of congenital CMV infections occur following non-primary infection, which means that routine screening would miss half of the cases (3,6). The next reason is that we still don't have approved therapy that can prevent congenital infection (2). Besides that, there is always a question of cost-effectiveness (7).

For the last few years, many clinical trials have been conducted to find a therapy for the secondary prevention of CMV congenital infection or at least serious postnatal sequelae. The older studies did not confirm the efficacy of the use of hyperimmune globulin in the prevention of congenital infection (8,9,10). New studies on the impact of high-dose valacyclovir on the outcomes of cytomegalovirus infection in pregnancy have promising results (11,12). The initiation of therapy soon after the diagnosis of maternal primary infection in the first trimester can lower the risk of vertical transmission (11). More evidence from larger randomised trials is needed to introduce this agent into clinical practice. If the efficacy of valacyclovir is proven, it will be necessary to revise the positions related to screening. Namely, most women have asymptomatic CMV infection, which means that the majority will not benefit from antiviral therapy.

Most current guidelines, including ours, agree not to screen for CMV infection, but there are some discordances on the terms of follow-up. Some recently updated guidelines recommend considering antiviral therapy at the time of maternal infection diagnosis. Following the diagnosis, serial ultrasound examinations should be performed, and fetal brain MRI should be considered in the third trimester. Amniocentesis (PCR) should be conducted at least 6–8 weeks after the diagnosis of maternal infection and no earlier than the 17th week of gestation, although most recommendations suggest performing it after the 21st week of gestation (13). While a negative amniocentesis result can't definitively rule out the presence of a congenital infection, it is indicative of almost no risk for serious neonatal injury (14,15).

The prognostic criteria are the other main focus of research. CMV viral load at second-trimester amniocentesis has low prognostic value, especially in the absence of visible anomalies (16,17). Other indicators, such as fetal thrombocytopenia or viral load, offer superior prognostic value, though they require invasive procedures that are not routinely advised (18). Despite certain limitations, ultrasound and MRI remain the most widely used tools for prognostic assessment (19,20,21). Cytomegalovirus (CMV) exhibits a pronounced neurotropic effect, with the potential to affect various brain cell types, particularly during the early stages of fetal development (19,22). The resulting cerebral anomalies are most often irreversible, which underscores their clinical significance. The involvement of the reticuloendothelial system, manifested as anemia, thrombocytopenia and hepatosplenomegaly, is of lesser significance, as these changes are often reversible (22). CMV has also been shown to affect cytotrophoblast differentiation and migration, leading to placental insufficiency and, in turn, fetal growth restriction (22). All of these effects should be taken into consideration during the follow-up period.

In our case, the patient was admitted to our hospital in the third trimester of pregnancy with a severely symptomatic fetus. Based on the serologic findings and the time of diagnosis, we could not determine whether it was a primary or non-primary infection. Since there are no national recommendations for routine TORCH screening, the diagnosis was established following ultrasound abnormalities. Even if we knew about maternal acute infection, we could only closely monitor the pregnancy, since we do not have national recommendations on the prevention of the vertical transmission. Described central nervous system anomalies are the sign of poor prognosis, so the patient was counselled regarding the option of termination of pregnancy.

CONCLUSION

All pregnant women should be given information about CMV infection and its impact on the fetus and neonatus. They should be informed about the primary prevention measures. Research related to preventive therapy should be supported. National screening recommendations should be subject to ongoing evaluation as new evidence emerges, to ensure timely diagnosis and appropriate treatment.

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Informed consent: Written informed consent was obtained from the patient for the publication of her anonymized information in this article.

REFERENCES

1. Leber AL. Maternal and congenital human cytomegalovirus infection: laboratory testing for detection and diagnosis. J Clin Microbiol. 2024 Apr 10;62(4):e0031323. doi: 10.1128/jcm.00313-23. Epub 2024 Feb 23. Erratum in: J Clin Microbiol. 2024 Sep 11;62(9):e0116424. doi: 10.1128/jcm.01164-24. PMID: 38391188; PMCID: PMC11005381.
2. Xie M, Tripathi T, Holmes NE, Hui L. Serological screening for cytomegalovirus during pregnancy: A systematic review of clinical practice guidelines and consensus statements. Prenat Diagn. 2023 Jun;43(7):959-967. doi: 10.1002/pd.6397. Epub 2023 Jun 17. PMID: 37309996.
3. Khalil A, Heath PT, Jones CE, Soe A, Ville YG; Royal College of Obstetricians and Gynaecologists. Congenital Cytomegalovirus Infection: Update on Screening, Diagnosis and Treatment: Scientific Impact Paper No. 56. BJOG. 2025 Jan;132(2):e42-e52. doi: 10.1111/1471-0528.17966. Epub 2024 Oct 21. PMID: 39434207.
4. D'Alberti E, Rizzo G, Khalil A, Mappa I, Pietrolucci ME, Capannolo G. et al. Counseling in fetal medicine: Congenital cytomegalovirus infection. Eur J Obstet Gynecol Reprod Biol. 2024 Apr;295:8-17. doi: 10.1016/j.ejogrb.2024.01.037. Epub 2024 Feb 1. PMID: 38310675.
5. Billette de Villemeur A, Hoen B, Billaud E, Deruelle P, Goueslard K, Halley des Fontaines V. et al. Current evidence gaps to support systematic cytomegalovirus screening in pregnancy. EClinicalMedicine. 2024 Nov 22;78:102941. doi: 10.1016/j.eclinm.2024.102941. PMID: 39640941; PMCID: PMC11617987.
6. Chan ES, Suchet I, Somerset D, de Koning L, Chadha R, Soliman N. et al. Maternal Cytomegalovirus (CMV) Serology: The Diagnostic Limitations of CMV IgM and IgG Avidity in Detecting Congenital CMV Infection. Pediatr Dev Pathol. 2024 Nov-Dec;27(6):530-544. doi: 10.1177/10935266241253477. Epub 2024 Sep 13. PMID: 39270128; PMCID: PMC11568646.
7. Seror V, Leruez-Ville M, Özek A, Ville Y. Leaning towards Cytomegalovirus serological screening in pregnancy to prevent congenital infection: a cost-effectiveness perspective. BJOG. 2022 Jan;129(2):301-312. doi: 10.1111/1471-0528.16966. Epub 2021 Nov 9. PMID: 34651405.
8. Hughes BL, Clifton RG, Rouse DJ, Saade GR, Dinsmoor MJ, Reddy UM. Et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. A Trial of Hyperimmune Globulin to Prevent Congenital Cytomegalovirus Infection. N Engl J Med. 2021 Jul 29;385(5):436-444. doi: 10.1056/NEJMoa1913569. PMID: 34320288; PMCID: PMC8363945.
9. Hughes BL, Clifton RG, Rouse DJ, Saade GR, Dinsmoor MJ, Reddy UM. Et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network. Randomized Trial of Hyperimmune Globulin for Congenital CMV Infection - 2-Year Outcomes. N Engl J Med. 2023 Nov 9;389(19):1822-1824. doi: 10.1056/NEJMc2308286. PMID: 37937785; PMCID: PMC10683876.
10. Fitzpatrick A, Cooper C, Vasilunas N, Ritchie B. Describing the Impact of Maternal Hyperimmune Globulin and Valacyclovir on the Outcomes of Cytomegalovirus Infection in Pregnancy: A Systematic Review. Clin Infect Dis. 2022 Oct 12;75(8):1467-1480. doi: 10.1093/cid/ciac297. PMID: 35438780.
11. Shahar-Nissan K, Pardo J, Peled O, Krause I, Bilavsky E, Wiznitzer A. et al. Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial. Lancet. 2020 Sep 12;396(10253):779-785. doi: 10.1016/S0140-6736(20)31868-7. Erratum in: Lancet. 2020 Oct 10;396(10257):1070. doi: 10.1016/S0140-6736(20)32075-4. PMID: 32919517.
12. D'Antonio F, Marinceu D, Prasad S, Khalil A. Effectiveness and safety of prenatal valacyclovir for congenital cytomegalovirus infection: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2023 Apr;61(4):436-444. doi: 10.1002/uog.26136. PMID: 36484439.
13. Sorrenti S, Elbarbary N, D'Antonio F, Mascio DD, Khalil A. Diagnosis and management of congenital Cytomegalovirus: Critical Appraisal of Clinical Practice Guidelines. Eur J Obstet Gynecol Reprod Biol. 2025 Mar;306:172-180. doi: 10.1016/j.ejogrb.2025.01.020. Epub 2025 Jan 17. PMID: 39848071.
14. Bilavsky E, Pardo J, Attias J, Levy I, Magny JF, Ville Y et al. Clinical Implications for Children Born With Congenital Cytomegalovirus Infection Following a Negative Amniocentesis. Clin Infect Dis. 2016 Jul 1;63(1):33-8. doi: 10.1093/cid/ciw237. Epub 2016 Apr 24. PMID: 27114380.
15. Chatzakis C, Sotiriadis A, Dinas K, Ville Y. Neonatal and long-term outcomes of infants with congenital cytomegalovirus infection and negative amniocentesis: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2023 Feb;61(2):158-167. doi: 10.1002/uog.26128. PMID: 36412976; PMCID: PMC10107880.
16. Mappa I, D'Antonio F, Khalil A, De Vito M, Alameddine S, Capannolo G. et al; ENSO group. Prognostic Value of Amniotic Fluid Viral Load to Predict Adverse Outcome in Pregnancies Complicated by Congenital Cytomegalovirus Infection: A Multicenter Study. Fetal Diagn Ther. 2023;50(1):1-7. doi: 10.1159/000528936. Epub 2023 Jan 9. PMID: 36623501.
17. Gilad N, Agrawal S, Philippopoulos E, Murphy KE, Shinar S. Is a Higher Amniotic Fluid Viral Load Associated with a Greater Risk of Fetal Injury in Congenital Cytomegalovirus Infection-A Systematic Review and Meta-Analysis. J Clin Med. 2024 Apr 7;13(7):2136. doi: 10.3390/jcm13072136. PMID: 38610901; PMCID: PMC11012373.
18. Pomar L, Contier A, Stojanov M, Guenot C, Sichitiu J, Truttmann AC. Et al. Contribution of fetal blood sampling to determining the prognosis of congenital cytomegalovirus infections: a case-cohort study in Switzerland. Am J Obstet Gynecol. 2024 Dec;231(6):643.e1-643.e12. doi: 10.1016/j.ajog.2024.03.032. Epub 2024 Mar 26. PMID: 38527603.
19. Diogo MC, Glatter S, Binder J, Kiss H, Prayer D. The MRI spectrum of congenital cytomegalovirus infection. Prenat Diagn. 2020 Jan;40(1):110-124. doi: 10.1002/pd.5591. Epub 2020 Jan 6. PMID: 31802515; PMCID: PMC7027449.
20. Di Mascio D, Rizzo G, Khalil A, D'Antonio F; ENSO Working Group. Role of fetal magnetic resonance imaging in fetuses with congenital cytomegalovirus infection: multicenter study. Ultrasound Obstet Gynecol. 2023 Jan;61(1):67-73. doi: 10.1002/uog.26054. PMID: 36056700.
21. Tanimura K, Uchida A, Uenaka M, Imafuku H, Tairaku S, Hashimura H. et al. Fetal Ultrasound and Magnetic Resonance Imaging Abnormalities in Congenital Cytomegalovirus Infection Associated with and without Fetal Growth Restriction. Diagnostics (Basel). 2023 Jan 13;13(2):306. doi: 10.3390/diagnostics13020306. PMID: 36673117; PMCID: PMC9857471.
22. Cheeran MC, Lokensgard JR, Schleiss MR. Neuropathogenesis of congenital cytomegalovirus infection: disease mechanisms and prospects for intervention. Clin Microbiol Rev. 2009 Jan;22(1):99-126, Table of Contents. doi: 10.1128/CMR.00023-08. PMID: 19136436; PMCID: PMC2620634.

PRIKAZ SLUČAJA TEŠKE KONGENITALNE INFEKCIJE CITOMEGALOVIRUSOM: PREVENCIJA I MOGUĆNOSTI LEČENJA

Jelica Uljarević[1], Marko Stanković[1], Suzana Drobnjak[1], Gordana Tošović[2], Nataša Karadžov Orlić[1,3]

Sažetak

Uvod: Humani citomegalovirus (CMV) je vodeći uzrok kongenitalnih infekcija širom sveta. Može dovesti do ozbiljnih kliničkih manifestacija koje vode trajnom invaliditetu inficirane dece. Za razliku od drugih izazivača kongenitalnih infekcija, fetalna CMV infekcija može biti posledica primarne infekcije u trudnoći, ali i reinfekcije.

Prikaz slucaja: Predstavljamo slučaj kongenitalne CMV infekcije koja je ustanovljena u trećem trimestru trudnoće, nakon pojave ozbiljnih fetalnih anomalija. Pacijentkinja je upućena na našu kliniku u 35. nedelji trudnoće komplikovane teškim zastojem u rastu ploda i anomalijama centralnog nervnog sistema, koje su viđene ultrazvučnim pregledom i magnetnom rezonancom: smanjena kortikalna girifikacija i visoko suspektna "*band* heterotopija" (diferencijalna dijagnoza: lizencefalija), dilatacija temporalnih i okcipitalnih rogova bočnih komora sa intraventrikularnim septama, hipoplazija vermisa, zone T2 hiperintenziteta. Serološkim testiranjem je ustanovljeno je postojanje pozitivnih IgM i pozitivnih IgG antitela za CMV sa visokim aviditetom (91,7%). Dijagnostičkom amniocentezom (PCR analiza) dobijen je pozitivan rezultat za CMV. Pacijentkinja je informisana o lošoj prognozi kongenitalne CMV infekcije, naročito u prisustvu opisanih anomalija centralnog nervnog sistema, nakon čega je zatražila prekid trudnoće.

Zaključak: S obzirom da se radi o najčešćoj kongenitalnoj infekciji, potrebno je raditi na informisanju trudnica o načinima primarne prevencije. Paralelno fokus istraživanja treba da bude na pronalaženju metoda pravovremene detekcije i lečenja infekcije, u cilju prevencije teških formi bolesti.

Ključne reči: kongenitalna infekcija, citomegalovirus, skrining, antivirusna terapija

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