MEDICAL UNIVERSITY
"PROF. DR. PARASKEV STOYANOV" - VARNA
FACULTY OF MEDICINE
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TRANSABDOMINAL LAPAROSCOPIC TREATMENT OF ADRENAL TUMORS IN ADULDS AND CHILDREN

AUTHOR'S DISSERTATION SUMMARY

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The public defense of the dissertation will take place on 02.09.2025 at .... at the University Hospital "St. Marina" before a scientific jury composed of:

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The defense materials are available in the Scientific Department and are published on the website of Medical University of Varna.

Note: The numbers of tables and figures in the abstract do not correspond to those in the dissertation.

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LIST OF ABREVIATIONS

ACC – adrenocortical carcinoma
ACE inhibitors – angiotensin-converting enzyme inhibitors
ACTH – adrenocorticotropic hormone
AG – adrenal gland
AI – artificial intelligence
ARB – angiotensin receptor blockers
AR – augmented reality
ASA – American Society of Anesthesiologists
AVS – adrenal venous sampling
BGA – blood gas analysis
BMD – bone mineral density
CAH – congenital adrenal hyperplasia
CAD – coronary artery disease
CBC – complete blood count
COMT – catechol-O-methyl transferase
COPD – chronic obstructive pulmonary disease
CRH – corticotropin-releasing hormone
CSA – cortex-sparing adrenalectomy
CNS – central nervous system
CT – computed tomography
CVC – central venous catheter
CVP – central venous pressure
DBP – diastolic blood pressure
DHEA / DHEA-S – dehydroepiandrosterone and its sulfate form
DICU – Department of Anesthesiology and Intensive Care
DST – dexamethasone suppression test
ECG – electrocardiography
ENSAT – European Network for the Study of Adrenal Tumors
ES/PNET – Ewing sarcoma / primitive neuroectodermal tumor
FNA – fine-needle aspiration biopsy
GRE – glucocorticoid response elements
GR – glucocorticoid receptors
HPA – hypothalamic-pituitary-adrenal
HR – heart rate

ICG – indocyanine green
ISA – inferior adrenal artery
IVC – inferior vena cava
MAO – monoamine oxidase
MEN2 – multiple endocrine neoplasia type 2
MRI – magnetic resonance imaging
MSA – middle adrenal artery
NF1 – neurofibromatosis type 1
PASS – pheochromocytoma of the adrenal gland scaled score
PET-CT – positron emission tomography-computed tomography
POMC – pro-opiomelanocortin
RA – robotic adrenalectomy
SBP – systolic blood pressure
SBRT – stereotactic body radiotherapy
SP-PRA – single-port posterior retroperitoneoscopic adrenalectomy
SSA – superior adrenal artery
StAR – steroidogenic acute regulatory protein
UFC – urine free cortisol
VHL – von Hippel–Lindau disease
WHO – World Health Organization

I. INTRODUCTION

The adrenal gland was anatomically described as early as 1563 by Eustachius, but its significance for human physiology began to be understood only in the 19th century thanks to the studies of Thomas Addison (1855) and Brown-Séquard (1856) (1). The history of its surgical treatment began in 1890, when Thornton reported the first successfully performed adrenalectomy. In the following decades, surgical approaches and techniques underwent numerous modifications, but the true breakthrough came in 1992 when Gagner and colleagues published the first three cases of laparoscopic adrenalectomy. This innovative approach marked the beginning of a new era in adrenal surgery and established itself as the preferred method for treating most functional and non-functional tumors. Already in the early 1990s, expert publications recommended open surgery only for invasive adrenal carcinomas and malignant forms of pheochromocytoma (2).

Our team focused on studying the operative outcomes of applying the minimally invasive transabdominal approach for laparoscopic adrenalectomy.

Adrenal tumors are often incidental findings during imaging performed for other reasons. A large proportion of them are of no clinical significance and require only follow-up. In other patients, due to the endocrine function of the adrenal gland, primary presentation may be related to complications from hormonal overproduction. Therefore, the diagnosis, discussion, and treatment of patients with adrenal tumors must be multidisciplinary.

Transabdominal laparoscopic adrenalectomy has been established as the leading method for surgical treatment of adrenal tumors in both adults and children. This reflects the overall trend towards minimally invasive surgery across various medical fields. Since its first description in 1992, the laparoscopic technique—especially via the transabdominal approach—has demonstrated several advantages over traditional open surgery: reduced blood loss, shorter hospital stay, faster recovery, and better cosmetic outcomes (3,4). These benefits have been observed in both adults and children, making laparoscopic adrenalectomy the preferred method for most benign adrenal tumors (3,5,6).

The transabdominal approach is particularly preferred as it provides a wider operative field and clearer anatomical visualization, facilitating removal of more complex or larger tumors and offering better visualization of vascular structures (7,8). This is especially important when additional intra-abdominal interventions are required or in obese patients, as the transabdominal approach is less affected by perirenal fat compared to the retroperitoneal approach (7).

In adults, laparoscopic adrenalectomy is already considered the gold standard for benign tumors and for certain malignant lesions when there is no evidence of local invasion or lymph node involvement (3,9,10). The accumulated surgical experience and technological advancements have expanded the indications for laparoscopic removal to include larger tumors – some centers successfully resect adrenal masses exceeding 10 cm (7,8,10).

In children, despite the relative rarity of adrenal tumors and their specific biological behavior in this age group, minimally invasive adrenalectomy is also gaining wider application (5,6,11). The most common adrenal pathology in childhood is neuroblastoma, which often poses surgical challenges due to its tendency to invade vascular structures.

Although classical “open” surgery remains the method of choice for large, invasive, or malignant tumors, laparoscopic transabdominal adrenalectomy is increasingly used for smaller and localized lesions. Data show that when performed by experienced surgeons, this approach has comparable safety and efficacy to open surgery (5,6,11).

Contemporary multicenter studies emphasize the high success rates of laparoscopic interventions, low postoperative morbidity, and short hospital stays in children. This supports the laparoscopic approach as the preferred method for most benign and some malignant adrenal tumors in the pediatric population (5,6).

Despite its numerous advantages, the laparoscopic approach is not without limitations. Tumor size, suspicion of malignancy, and presence of local invasion remain key factors in choosing the appropriate surgical technique (7,9,10). For adrenocortical carcinoma and other aggressive malignant tumors, open surgery is still recommended to achieve complete resection and avoid tumor cell dissemination (9,10).

It should be emphasized that conversion to open surgery should not be regarded as a failure but as a necessary measure to ensure patient safety in more complex cases (4,10).

II. AIM AND OBJECTIVES

1. Aim

The aim of this dissertation is to analyze the outcomes of transabdominal laparoscopic adrenalectomy in adults and children.

2. Objevtive

1. To analyze the clinical characteristics of the patients.
2. To analyze the anatomical features.
3. To evaluate the early postoperative outcomes.
4. To evaluate the late postoperative outcomes.
5. To investigate the impact of endocrine disorders on intraoperative outcomes.
6. To investigate the impact of endocrine disorders on postoperative complications.

Between 2008 and 2024, 82 patients with adrenal neoplasms operated via transabdominal laparoscopic adrenalectomy were identified.

III. MATERIALS AND METHODS

1. Materials and design of the study

The present dissertation addresses a retrospective, observational, single-center study. It was conducted by the surgical team of the First Department of Surgery at St. Marina University Hospital, Varna, with the doctoral candidate as principal investigator. The study was carried out within the facilities of St. Marina University Hospital, Varna, and encompasses laparoscopic adrenalectomies performed between January 1, 2008, and December 31, 2024. The study was approved by the Research Ethics Committee (REC) of the Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, Decision No. 12/27.03.2025. The object of the study comprises patients with adrenal gland tumors who underwent laparoscopic adrenalectomy. The subject of the study includes intraoperative and postoperative parameters.

1.1. Inclusion Criteria

The following inclusion criteria were defined for patient selection in the study:

- Patients hospitalized at St. Marina University Hospital who signed the general hospital informed consent form for surgical treatment of adrenal diseases.
- Patients who underwent elective laparoscopic adrenalectomy in the period between 2008 and 2024.

1.2. Exclusion Criteria

The following exclusion criteria were defined for the study:

- Patients who underwent adrenal tumor surgery via conventional open approach.
- Patients who underwent adrenalectomy as part of another multivisceral surgical procedure.

1.3. Patient Selection Process in the Study

As shown in Figure 1, the algorithm for patient selection in the study is presented. Following written authorization from the Executive Director of St. Marina University Hospital, the Statistics Department of the hospital provided us with a list of all surgical interventions performed under Clinical Pathway No. 189 for the period 2008–2016 and Clinical Pathway No. 203 for the period 2017–2024 with ICD codes – D35.0 (Benign neoplasm of adrenal gland), D48.3 (Neoplasm of uncertain behavior of retroperitoneum), C74 (Malignant neoplasm of adrenal gland), and C79.7 (Secondary malignant neoplasm of adrenal gland), coded in the hospital system as laparoscopic adrenalectomy, for the study period (n=94). We obtained the complete medical records of these patients from the hospital archive. Upon document review, cases that did not meet the inclusion criteria were excluded from further analysis (n=12). The final study included 82 laparoscopic adrenalectomy procedures (n=82). Within the specified period, six patients underwent staged bilateral adrenalectomy (left and right) – three for pheochromocytoma and three for hypercortisolism – with each procedure included as a separate case in the study.

The patients included in the study were grouped into four categories from a clinical and functional perspective according to their preoperative status:

- Group 1: Pheochromocytoma – patients with complete clinical and laboratory evidence of a tumor originating from the adrenal medulla associated with catecholamine hypersecretion (n=22).
- Group 2: Hyperaldosteronism – patients with clinical and laboratory evidence of an adenoma originating from the adrenal cortex associated with aldosterone hypersecretion (n=13).
- Group 3: Hypercortisolism – patients with clinical and laboratory evidence of an adenoma originating from the adrenal cortex associated with cortisol hypersecretion (n=21).

– Group 4: Others – patients with imaging and clinical evidence of an adrenal tumor indicated for adrenalectomy, without clinical or laboratory evidence of adrenal hormone hypersecretion, including malignant neoplasms (n=26).

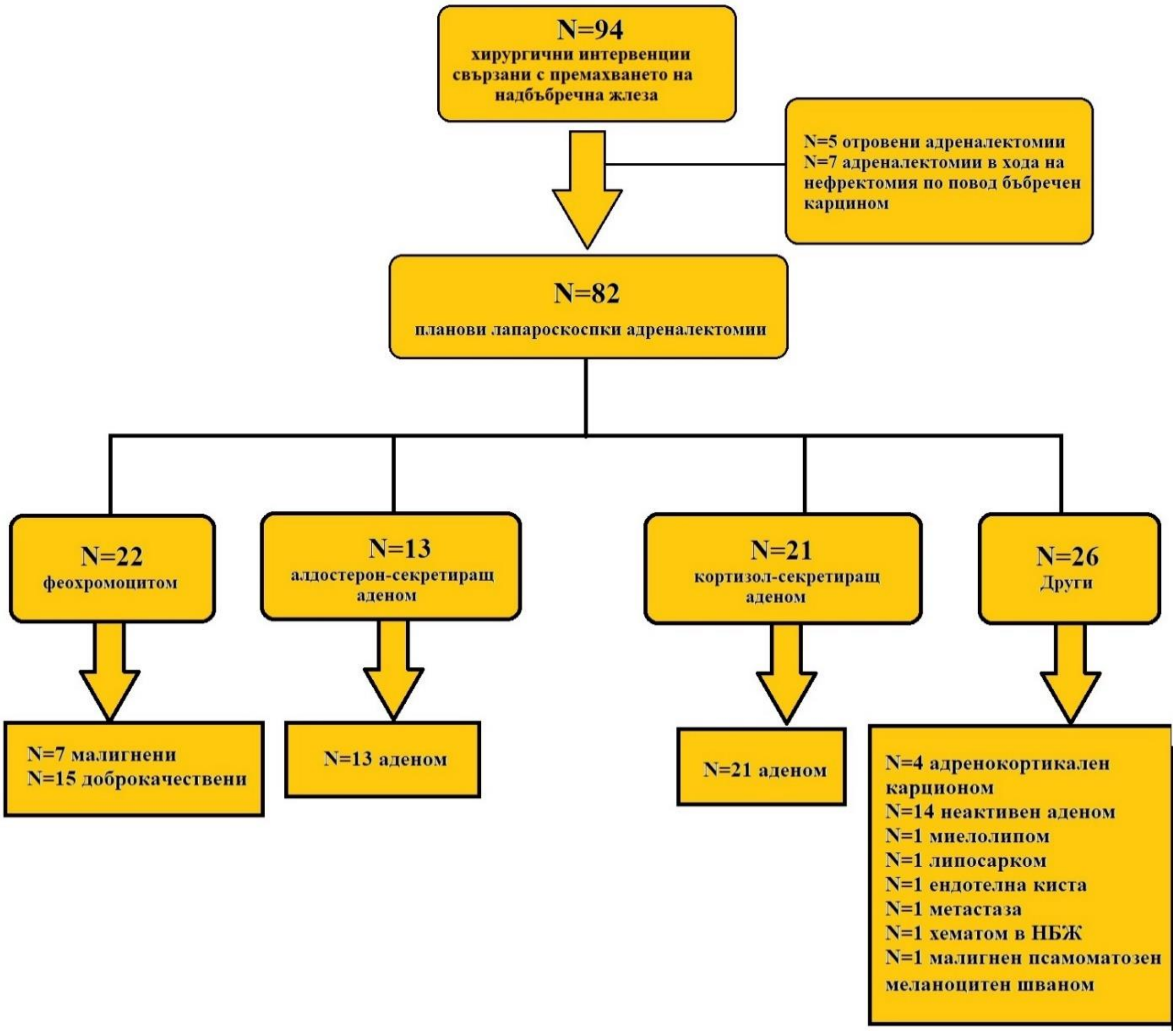


Figure 1 Diagram of patients'selection process in the study

2. Methods

2.1. Documental methods

For the selected patient cohort, data were collected on the following: demographic characteristics (sex and age); clinical characteristics (BMI, comorbidities, ASA classification, antihypertensive therapy, tumor size, side of the affected adrenal gland, preoperative alpha-blockade, adrenal hormone levels);

intraoperative hemodynamic parameters (SBP, DBP, and HR), techniques and medications used for their control in the subgroup with pheochromocytoma, histological variants, intraoperative blood loss, operative time, time to mobilization, need for postoperative analgesia, intraoperative complications, and need for conversion. All study data were obtained through processing and analysis of information from documentary sources – complete medical records of each patient; discharge summaries related to the disease; anesthesiology and intensive care charts; operative reports; laboratory, imaging, and histological results; and clinical logs. During data processing, all legal regulations concerning personal data protection were strictly observed.

2.2. Clinical methods

For all patients, a detailed medical history was obtained and documented, including past and chronic diseases and related medications. Anthropometric data – age, height, weight – were recorded, and BMI was calculated for each patient. Standard physical and clinical examinations were performed multiple times pre- and postoperatively, with all findings duly recorded in the medical records. All patients underwent a standard 12-lead ECG. Preoperative preparation included a clinical assessment by an anesthesiologist based on the patient's functional status, with evaluation according to the American Society of Anesthesiologists (ASA) Physical Status Classification System. When necessary, patients were additionally consulted by various specialists such as cardiologists, endocrinologists, and others.

2.3. Radiological methods

Imaging methods used for diagnosis and follow-up most commonly included computed tomography (CT) of the abdomen and pelvis, and, when necessary, CT scans of other regions (see Figure 2). The examinations were performed using a Siemens SOMATOM Force scanner with an adrenal protocol at a tube voltage of 120 kVp. The protocol consisted of three phases: a native (non-contrast) phase; a venous phase acquired between 60 and 75 seconds after intravenous contrast administration; and a delayed phase acquired 15 minutes post-contrast. A dual-source configuration with 2x576 detectors and a slice thickness of 1 mm was used. The contrast agents administered included iohexol (Omnipaque, GE Healthcare) at concentrations of 300 and 350 mg I/mL and iodixanol (Visipaque, GE Healthcare) at concentrations of 270 and 320 mg I/mL. The volume of contrast administered ranged from 75 to 150 mL depending on patient body weight, with an injection rate between 2.5 and 3 mL/s according to clinical indication – adenoma versus suspected malignancy (383–385). Additional imaging modalities included magnetic resonance imaging (MRI) (see Figure 3); positron emission tomography-computed tomography (18-FDG or 64Cu-DOTATATE PET-CT); abdominal ultrasound and ultrasound of other regions as clinically indicated. In selected cases, adrenal venous sampling was performed under fluoroscopic guidance based on clinical judgment. For some patients who were not surgical candidates but presented with significant clinical symptoms, selective catheterization and embolization of adrenal arteries were performed.

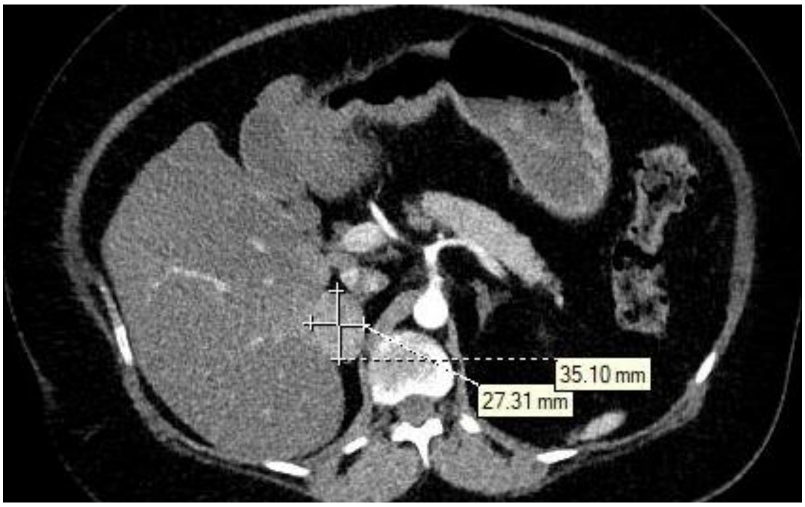


Figure 2 CT of abdomone with adrenal glan contrast protocol, there is seen adrenal gland adenoma with size of 35x27mm.

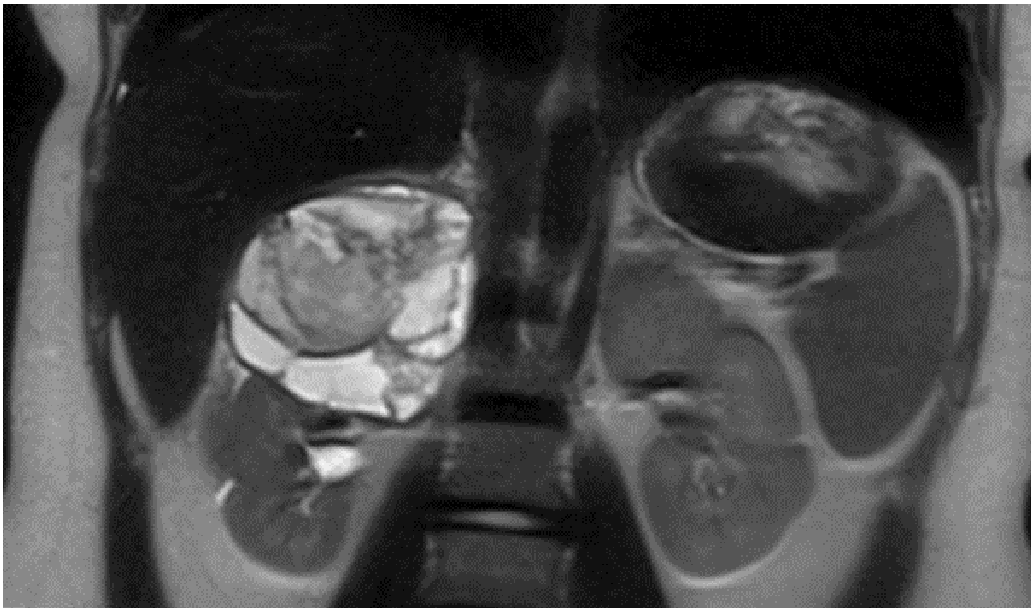


Figure 3 MRI view of tumor formation with cystic appereance in right adrenal gland

2.4. Laboratory methods

Preoperative hormonal analysis was performed according to an established protocol at the Department of Endocrinology of St. Marina University Hospital – Varna. Following surgical intervention, patients continued their follow-up at the Department of Endocrinology.

The following laboratory parameters were assessed pre- and postoperatively: standard blood tests (CBC, biochemical panels, coagulation status, BGA), urinalysis, and specific tests for tumor hormonal activity.

The assessment of hormonal activity followed the diagnostic algorithm of the Bulgarian Society of Endocrinology, which includes multiple biochemical and hormonal indicators.

In cases of suspected pheochromocytoma, the algorithm begins with measurement of urinary free metanephrines or plasma fractionated metanephrines. A threefold increase in metanephrines above the upper reference limit is a strong indicator of pheochromocytoma. For patients with a twofold increase, diagnosis may be accepted after proper interpretation of clinical presentation, laboratory results, and imaging findings (51).

The next step in diagnostic evaluation is assessment of the aldosterone-to-renin ratio under appropriate pre-analytical conditions. Aldosterone is measured in pmol/L and renin as direct concentration in uIU/mL. A positive aldosterone/renin ratio (>80) indicates a probable diagnosis of Conn's syndrome (150).

Cushing's syndrome is diagnosed upon detection of abnormalities in the normal circadian rhythm of cortisol (serum cortisol at 08:00 and 23:00), 24-hour urinary free cortisol, 1 mg overnight dexamethasone suppression test (rapid test), and 48-hour low-dose dexamethasone suppression test with 2 mg/day dexamethasone. For both rapid and low-dose dexamethasone tests, a threshold morning serum cortisol value of 50 nmol/L is accepted (130).

Measurement of serum ACTH levels is used to differentiate ACTH-dependent from ACTH-independent forms of Cushing's syndrome.

All analyses were performed in licensed clinical laboratories at St. Marina University Hospital – Varna, using calibrated and quality-assured equipment, and are documented in the medical records along with the reference ranges specific to each method.

2.5. Therapeutic methods

2.5.1. Anesthesia Techniques

The patients included in this dissertation underwent elective surgical interventions. During preoperative preparation, the type, size, and anatomical relationships of the tumors were thoroughly assessed.

2.5.1.1. Preoperative period

Patients underwent consultations with the anesthesiology team, ASA classification was determined, and pharmacological correction was initiated in patients with significant comorbidities when deviations from normal values were identified. In cases of confirmed pheochromocytoma, and at the discretion of the team for suspected cases, following multidisciplinary discussion with endocrinologists, surgeons, and anesthesiologists, patients underwent a preoperative course of alpha-adrenergic blockade using prazosin administered twice daily with gradually increasing doses from 0.5 mg up to a maximum of 16 mg/24h (average 4–6 mg/24h). Immediately preoperatively, the adequacy of alpha-blockade was assessed based on the presence of normotension, normal ECG complexes, regular heart rhythm, mild orthostatism, and nasal congestion. On the day of surgery, or the preceding day, all patients had a central venous catheter placed in the internal jugular vein (left or right, depending on individual anatomical considerations). Catheterization was performed under local infiltration anesthesia with 1% lidocaine using the Seldinger technique under ultrasound guidance, following all aseptic and antiseptic protocols (see Figure 4). At the same

Figure 2 Set for central vein catheter placement

time, based on individual assessment, an epidural catheter was placed at the Th10–Th11 level for postoperative analgesia.

All patients adhered to the established preoperative fasting protocol: no oral intake of solid foods for 6 hours, non-clear liquids for 4 hours, and clear liquids for 2 hours before surgery. For patients receiving alpha-blockers, the last dose was administered at 06:00 on the morning of surgery.

All laparoscopic adrenalectomies were performed under general endotracheal anesthesia with muscle relaxation, with or without epidural analgesia.

In patients with known or suspected pheochromocytomas, an arterial cannula for continuous invasive blood pressure monitoring was routinely placed. An Allen test was performed to assess arterial blood flow to the hand, after which ultrasound-guided catheterization of the radial artery was performed using the Seldinger technique, following standard aseptic and antiseptic protocols (see Figure 5).

Figure 3 Placement of arterial cannula for invasive arterial pressure monitoring

2.5.1.2. Intraoperative period

Maintenance of general anesthesia was carried out using standard practices with a combination of inhalational and intravenous anesthetics, opioid analgesics, and mechanical ventilation. Continuous monitoring included ECG, measurement of SBP/DBP via brachial cuff and arterial cannula, heart rate, pulse oximetry, and respiratory parameters. Urine output was measured after placement of a urinary catheter from induction of anesthesia until transfer to the ICU.

In patients undergoing laparoscopic adrenalectomy for pheochromocytoma, intraoperative hemodynamic control techniques included multiple approaches:

- Adjusting the depth of anesthesia as a method for blood pressure control, monitored via MAC/BIS values on the anesthesia machines.
- Monitoring and calculating the volume of infused crystalloid and colloid solutions according to urine output.
- In cases of tachycardia and hypertension, after ensuring adequate intraoperative analgesia, vasodilators such as glyceryl trinitrate 1 mg/mL or sodium nitroprusside 1 mg/mL were administered via continuous infusion in selected cases (following specific administration protocols, including use of dark syringes).
- In cases of combined intraoperative hypertension and tachycardia, intravenous bolus doses of metoprolol were used; lidocaine 1 mg/kg bolus or amiodarone continuous infusion were administered for hemodynamically significant arrhythmias.
- In cases of hypotension, sympathomimetic agents such as ephedrine in incremental bolus doses, continuous infusion of dopamine 4000 mcg/mL, and/or norepinephrine 80 mcg/mL were administered.
- Manipulation of pheochromocytomas prior to ligation of the adrenal vein can lead to massive catecholamine release into the bloodstream;

management strategies included cessation of surgical manipulation until normalization of extreme hemodynamic changes and performing atraumatic tumor handling.

2.5.2. Surgical technique

All laparoscopic adrenalectomies were performed by the same surgical team, in the same department, using the same operative technique and dissection plan.

A lateral transperitoneal approach was used. Patients were positioned in the lateral jackknife position on the operating table according to the localization of the pathology (see Figure 6). The arms were abducted to 90°, with the upper arm placed above the patient's head on a pre-mounted armrest. Patients were supported with a vacuum beanbag, which, once vacuumed, allowed safe repositioning of the operating table during the procedure. The laparoscopic equipment is shown in (Figure 7).

Figure 6 Patient position on the operative table

Figure 7 Laparoscopic troley

After thorough antiseptic preparation of the operative field, carbon dioxide was insufflated via a Veress needle inserted at the Hasson point in the corresponding subcostal region to create a pneumoperitoneum with a pressure of 12–14 mmHg. In patients with a history of previous abdominal surgeries, the operation was initiated in the supine position. A supraumbilical Hasson entry was created to avoid inadvertent injury to adhesed structures attached to the abdominal wall. After intraoperative assessment, the patient was rotated to the appropriate lateral decubitus position.

Four working ports were placed 5 cm subcostally in the following sequence: along the midclavicular line, and along the anterior, middle, and posterior axillary lines (see Figure 8). Close placement of the ports should be avoided as it hampers the surgeon’s maneuverability. The optimal distance between ports is approximately 8 cm. The laparoscope was inserted through the port along the anterior axillary line. For right-sided lesions, a Nathanson retractor was used to elevate the right lobe of the liver, allowing better visualization of the adrenal gland (see Figure 9).

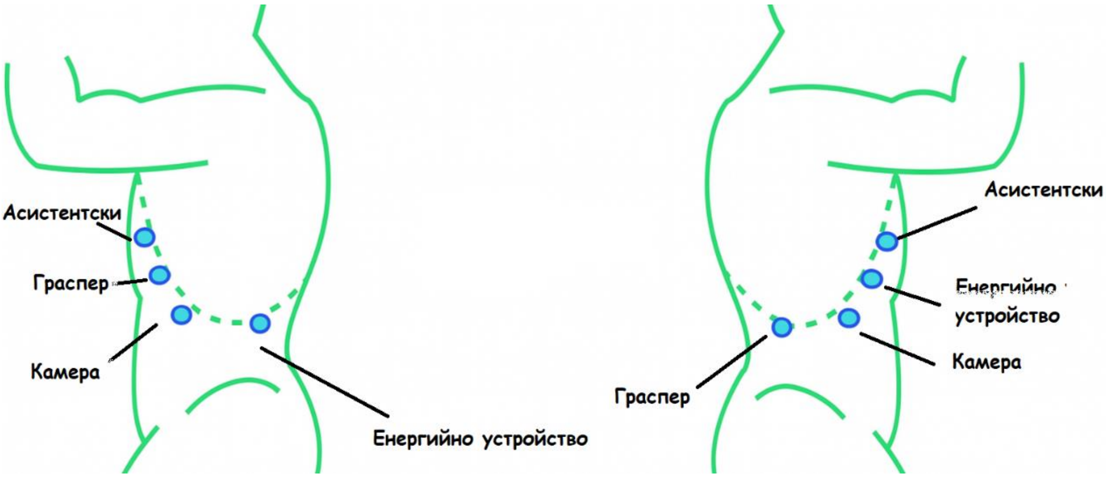


Figure 4 Port positions in left and right laparoscopic adrenalectomy

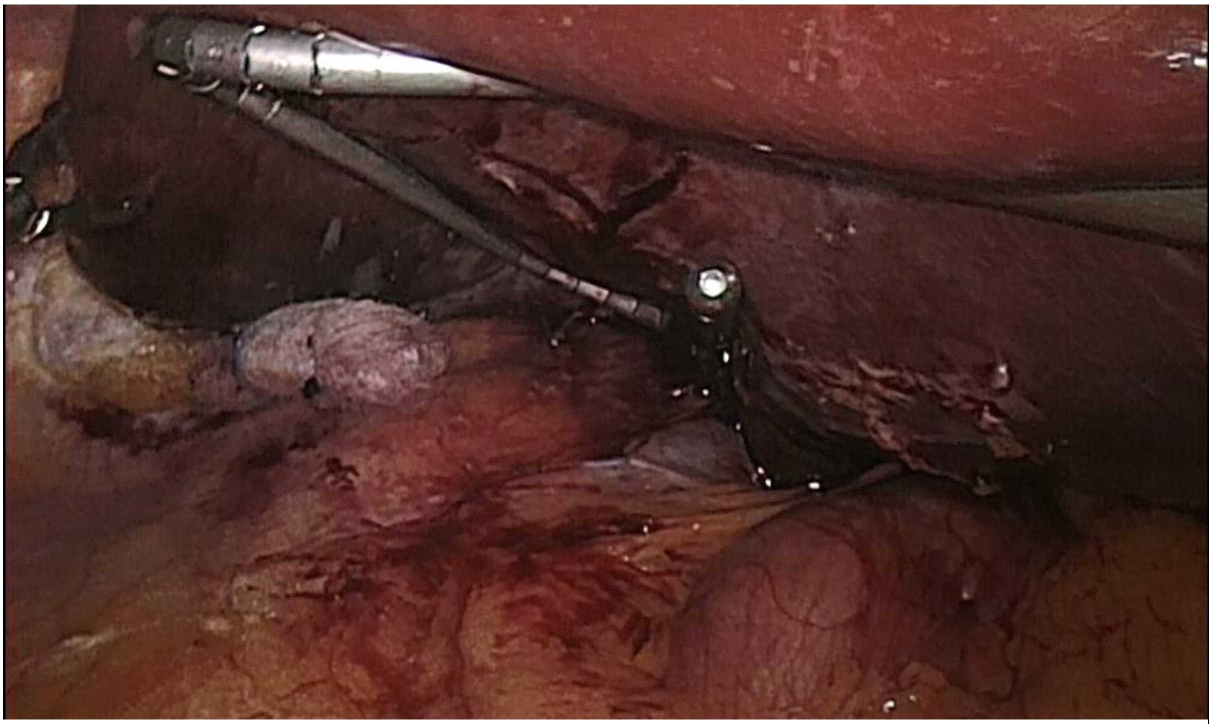


Figure 5 Plecement of Nathanson liver retractor for right-sided adrenalectomy

Dissection was performed using an Ethicon© Harmonic Ace ultrasonic scalpel, Medtronic© LigaSure, and a monopolar cautery device (see Figure 10). For vessel ligation exceeding 3 mm in diameter, metal or polymer clips were applied. In cases of pheochromocytoma, preliminary ligation of the vessels prior to gland dissection was preferred to prevent catecholamine release into the circulation (see Figure 11).

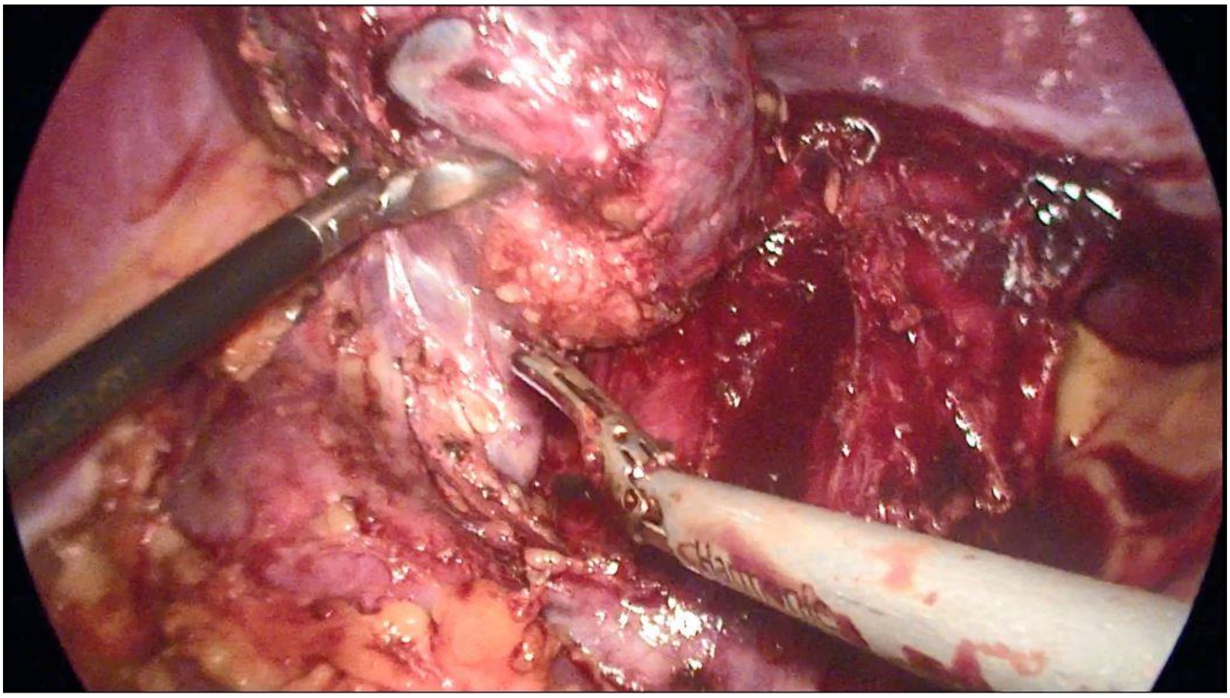


Figure 7 Tumor dissection from right renal vein and vena cava inferios with the aid of Harmonic ACE ultrasound dissector

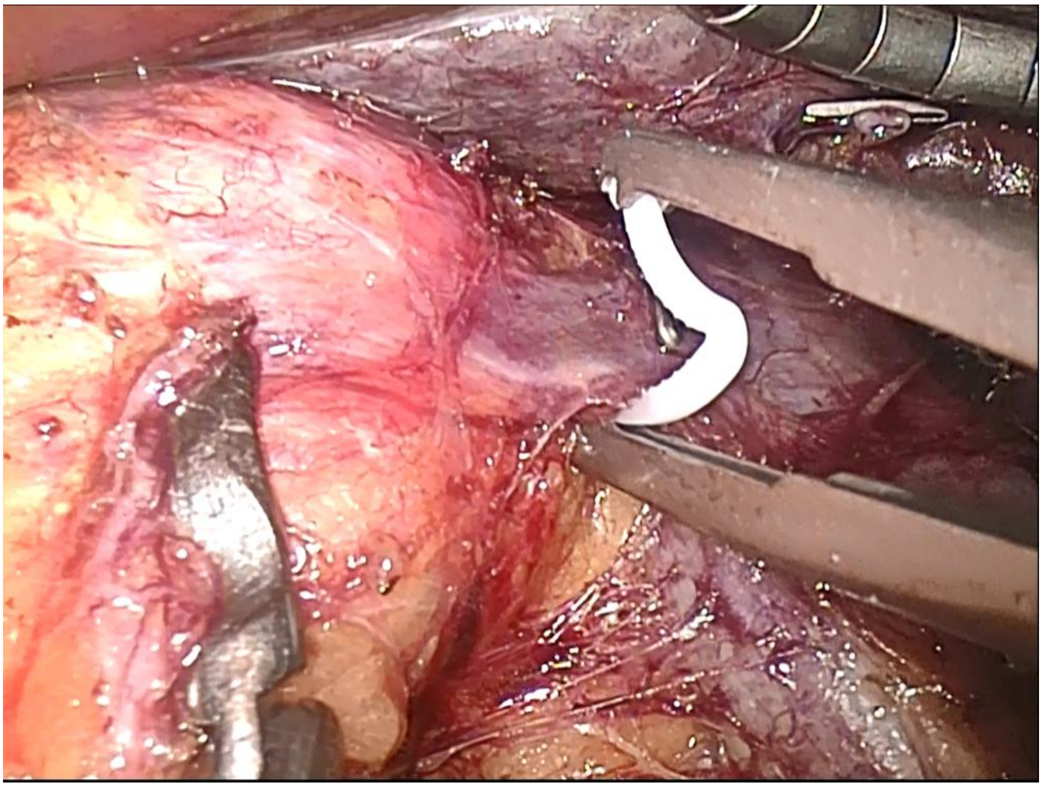


Figure 6 Selective ligation of right adrenal vein with polimer clip as first stage of adrenal gland dissection

The specimen was extracted from the abdominal cavity using an Endo-bag retrieval system (see Figure 12). A single contact drain was placed in the adrenal bed (see Figure 1Figure 9). All trocar sites were closed in layers.

Figure 8 Speciment placement in special endo-bag system for extraction

Figure 9 Placement of drainage tube in adrenal gland fossa

2.5.2.1. Postoperative period

All patients, following laparoscopic adrenalectomy and emergence from anesthesia, were transferred to the Intensive Care Unit (ICU) for intensive monitoring and treatment for a minimum period of 24 hours. During this time, continuous monitoring of vital signs was performed, and all deviations were documented in the ICU charts and progress notes within the medical records. Postoperative blood tests were conducted, including complete blood count (CBC), biochemical panels, blood gas analysis (BGA), and other tests as deemed necessary.

2.5.3. Pathological methods

All resected specimens underwent histological evaluation and pathological analysis following standard fixation in neutral formalin solution and staining with hematoxylin and eosin (H&E) (see Figures 14 and 15). In certain cases, at the discretion of the pathology laboratory, immunohistochemical studies were performed to further clarify the diagnosis. There was no discrepancy between the preoperatively established clinical and laboratory diagnosis and the postoperative histological results for the patients included in this study.

Figure 10 Macroscopic appereance of speciment from tumor formation affecting righ adrenal gland

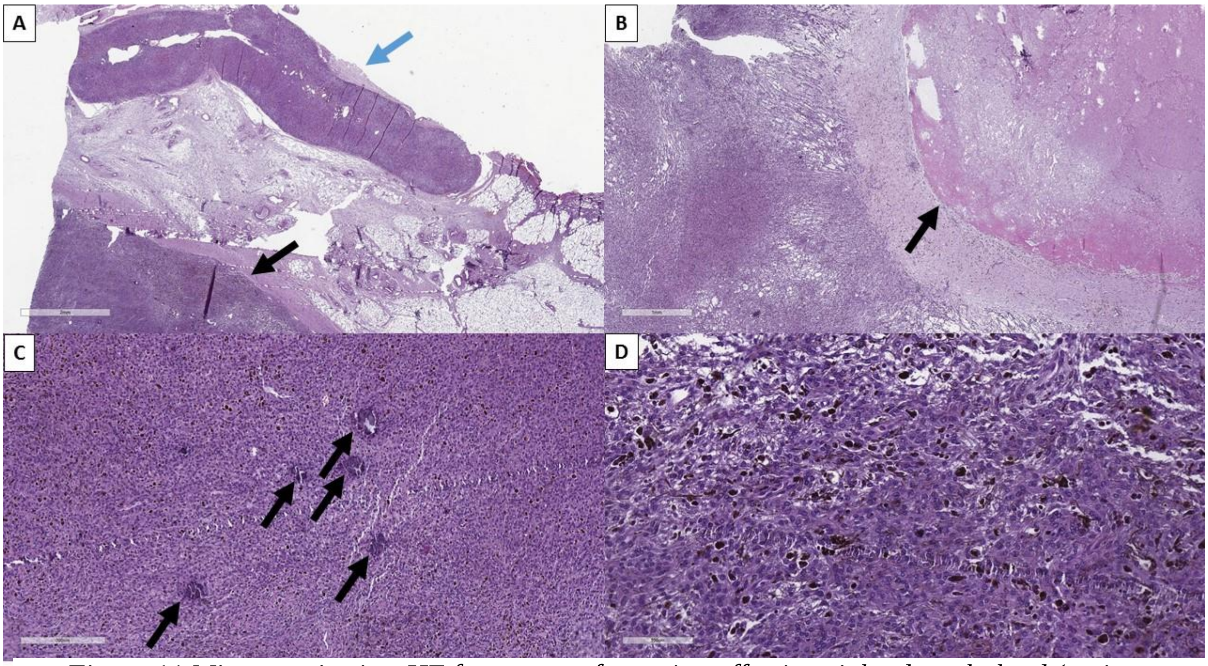


Figure 11 Microscopiv view HE from tumor formation affecting righ adrenal gland (seeing – Psammomatous melanotic schwanomma)

2.5.4. Statistical methods

Statistical analysis of the data was performed using IBM SPSS software, version 27.01. Continuous variables were presented as mean ± standard deviation (SD) and analyzed using variance analysis. Normality was assessed prior to applying parametric tests using the Shapiro-Wilk test. Alternative analysis was applied for qualitative variables. Comparisons of parametric data among the four groups were conducted using One/Two-way ANOVA. For nominal and categorical variables, comparisons were performed using the Kruskal-Wallis test. Categorical variables were compared between two groups using the Chi-square test, Fisher's exact test, t-test, and Mann-Whitney U test. Correlation analyses were employed to identify relationships between variables. For post-hoc analysis, Tukey's HSD was used. Logistic regression was used for predictor analysis. Statistical significance was accepted at $p \leq 0.05$. Microsoft Office Excel 2021 was used for graphical representation of the results.

V. Results and discussion

1. Demographic and clinical characteristics

The study included 82 elective laparoscopic adrenalectomies performed at St. Marina University Hospital, Varna, between January 1, 2008, and December 31, 2024. Patients were divided into four groups according to the hormonal activity of the tumor. Group 1 included patients with clinical and laboratory evidence of pheochromocytoma (n=22, 27%); Group 2 – with hyperaldosteronism (n=13, 16%); Group 3 – with hypercortisolism (n=21, 25%); and Group 4 – other patients without evidence of hormonal activity (n=26, 32%). The grouped distribution is presented in (Figure 16).

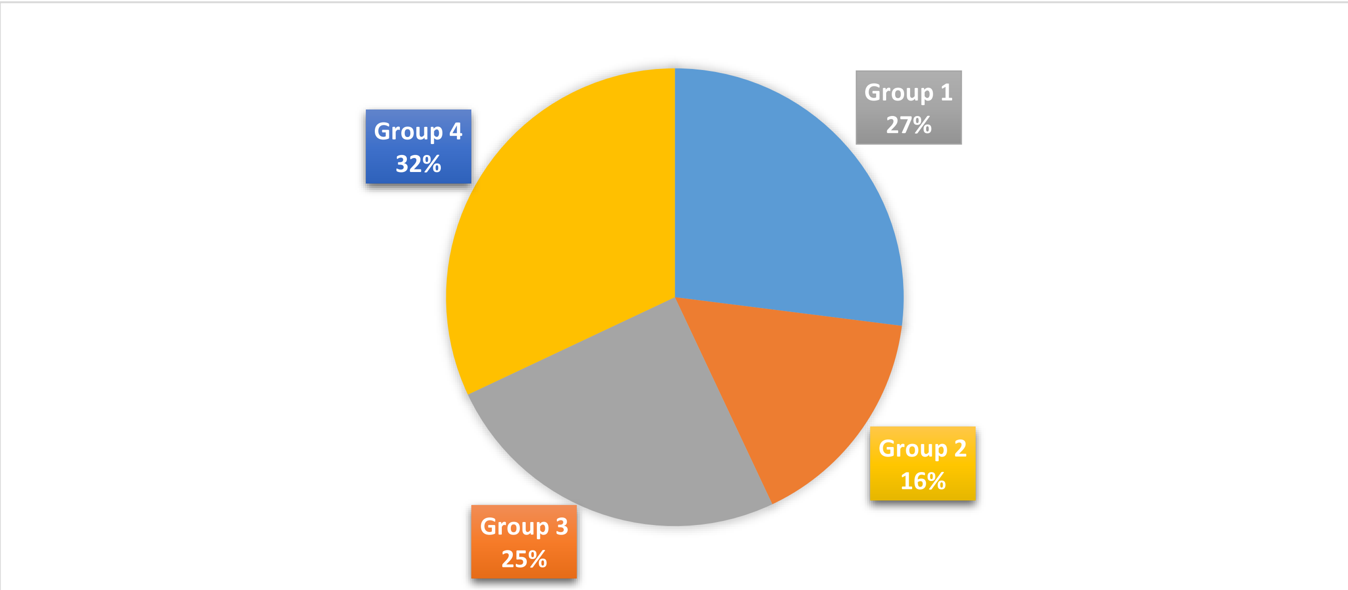


Figure 12 Graphic illustration of different group formation

Due to the retrospective nature of the study, Table 1 shows the annual distribution of surgical interventions by group, which is graphically presented in Figure 17.

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Overall	3	8	4	5	1	3	3	8	6	8	2	9	4	3	6	3	2
Group 1	2	5	2	0	0	0	2	1	1	3	0	3	2	0	1	0	0
Group 2	0	1	0	0	0	1	0	0	2	2	1	1	1	1	2	0	1
Group 3	0	0	1	3	1	0	2	2	2	1	1	3	0	1	1	2	0
Group 4	1	2	1	2	0	2	4	3	1	2	0	2	1	1	2	1	1

Table 1 Operative interventions shown in groups and overall by years

It is clearly illustrated that the total number of cases shows a variable trend over the years, with a relatively stable frequency of surgical interventions. No positive trend in the frequency of individual groups can be identified. During the study period, an average of 4.76 (SD=2.76) adrenal gland resections per year were performed at our center. The highest number of adrenalectomies was performed in 2019 (n=9, 11.11%). The lowest number of surgeries per year was one (1.23%),

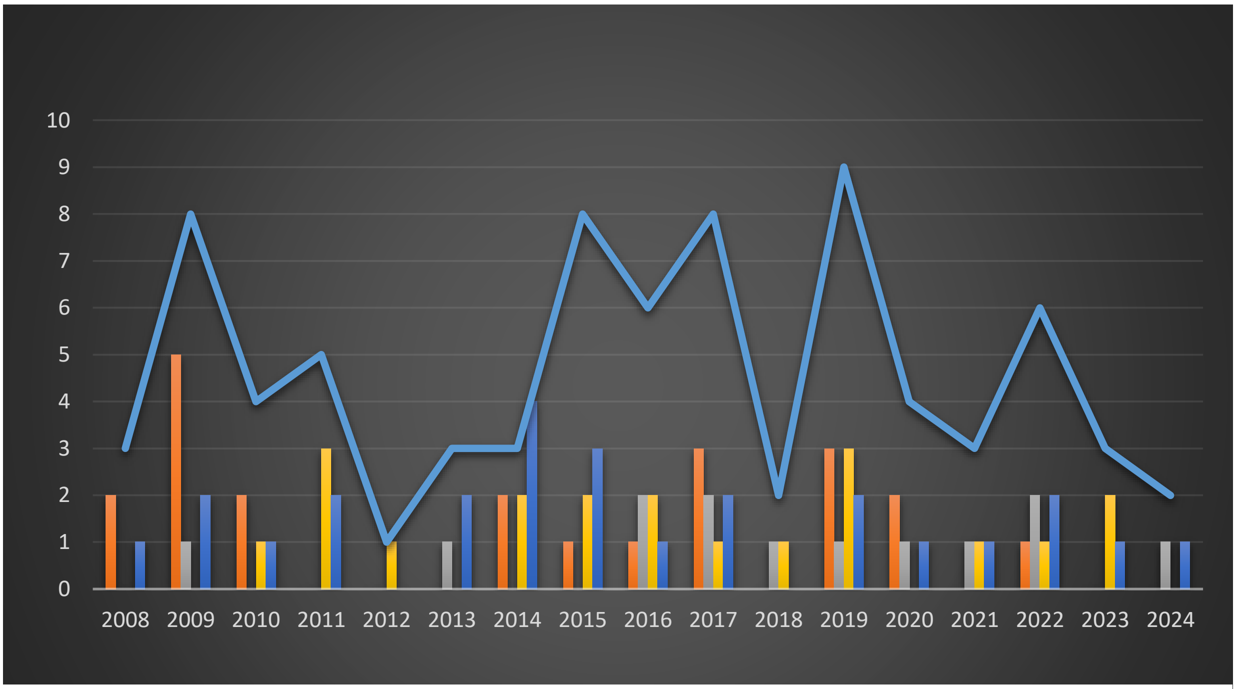


Figure 13 Graphical representation of the annual distribution by groups

which occurred in 2012. There are no single-center studies by Bulgarian authors in the literature to allow comparison of the surgical workload in our institution with other centers performing transabdominal laparoscopic adrenalectomy in Bulgaria.

Of the total number of patients included in the study, 46 (56.79%) were female and 35 (43.21%) were male. The sex distribution within the individual groups is presented in Table 2 and graphically in Figure 18.

Gender	Group 1		Group 2		Group 3		Group 4		Overall	
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Female	13	59.09	10	76.92	16	76.19	13	50	52	63.41
Male	9	40.91	3	23.08	5	23,81	13	50	30	36.59
Overall	22	100	13	100	21	100	26	100	82	100

Table 2 Distribution by gender in different groups

In the studied population, a predominance of the female sex was observed – both in the overall sample (n=45, 59.2%) and in most of the individual subgroups (n=13, 59.09%; n=10, 76.92%; and n=16, 76.19%, respectively). Only in Group 4 was the distribution between males and females equal (n=12, 50%). Although a higher prevalence of adrenal tumors was observed among women, this difference did not reach statistical significance and is considered to be due to random factors ($\chi^2(3)=4.69$, $p=0.196$, $p>0.005$).

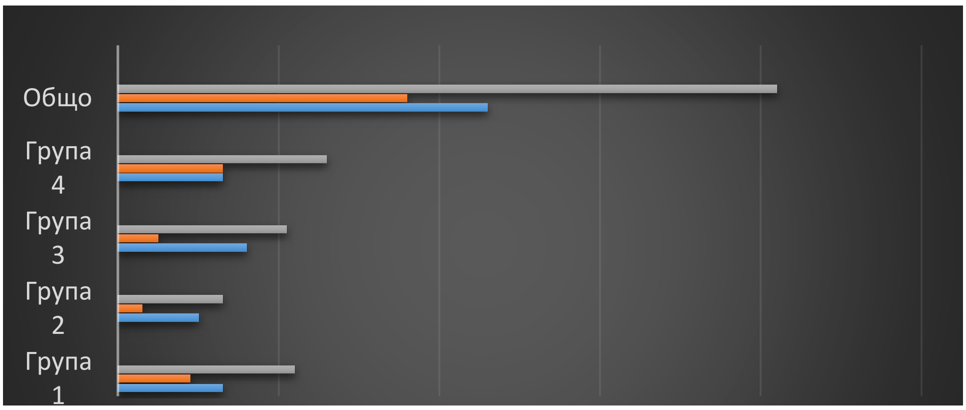


Figure 14 Distribution by gender in different groups

Age distribution is another parameter that requires separate evaluation. Table 3 presents the age characteristics of the population examined in our study by group. A graphical representation of the data can be seen in Figure 19.

Age [years]	Group 1	Group 2	Group 3	Group 4	Overall
N	22	13	21	26	82
Mean	50.83	57.08	49.53	54.71	52.10
SD	15.58	10.17	14.06	13.94	14.32
Range	56	38	59	59	67
Min	20	40	11	11	11
Max	76	78	70	70	78

Table 3 Distribution by age in different groups

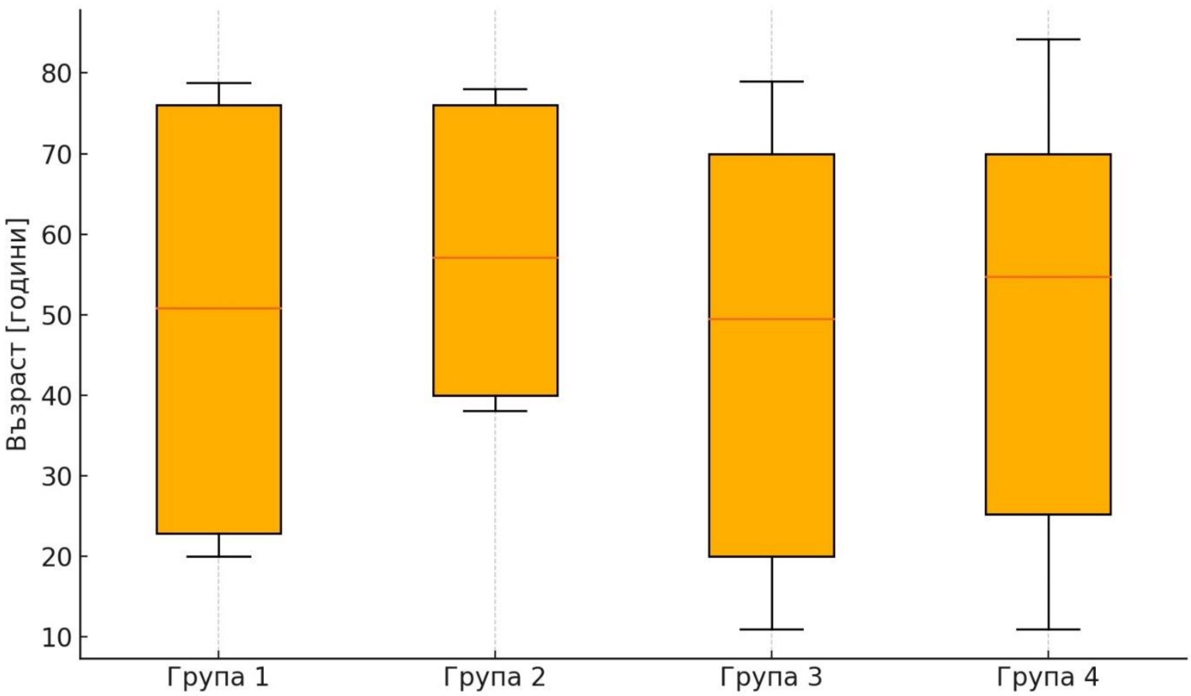


Figure 15 Distribution by age in different groups

Analysis of the age distribution showed that the mean age of all patients was 52.1 years with a standard deviation of 14.23. Groups 3 and 4 included the youngest participants, with mean ages of 49.53 and 54.71 years, respectively, while the greatest within-group variation (SD = 15.58) was observed in Group 1. The youngest recorded patients were 11 years old and were also included in these two groups. The oldest participant, aged 78 years, was part of Group 2. The least variation in age was observed in Group 2, where the standard deviation was 10.17. There was no statistically significant difference in age between the groups ($F=1.50$, $p=0.221$). Despite the heterogeneity of Group 4 (which includes multiple histological variants but no hormonal activity), it also did not show a statistically significant difference in age.

In our study, it was observed that hormonally active adrenal tumors are diagnosed at approximately the same age as non-functional lesions.

The adrenal gland is a paired organ, and depending on the localization of the tumor formation, surgical intervention may be required on either the left or right side. The distribution of lateralization and surgical intervention is presented in Table 4.

Side of operation	**Group 1**		**Group 2**		**Group 3**		**Group 4**		**Overall**	
	n	%	n	%	n	%	n	%	n	%
Right	14	63,6	7	53,8	8	38,1	11	42,3	40	48,8
Left	8	36,4	6	46,2	13	61,9	15	57,7	42	51,2
Overall	22	100	13	100	21	100	26	100	82	100

Table 4 Distribution by side of operation

In the analyzed patient group, a slight predominance of left-sided adrenalectomies was observed – 51.2% (n=42) of cases, compared to 48.8% (n=40) right-sided interventions. However, the 2.4% difference did not reach statistical significance ($\chi^2=3.47$, $p=0.324$). A deviation from the overall trend of left-sided localization was noted only in the subgroups with pheochromocytoma (Group 1), where right-sided localization was found in 63.6% of patients (n=14), and in Group 2, where it was observed in 53.8% (n=17). In both cases, analysis did not demonstrate statistically significant differences ($\chi^2=0.464$, $p=0.830$ and $\chi^2=0.634$, $p=0.514$, respectively). In patients with hypercortisolism (Group 3), the opposite pattern was observed – tumors were more frequently located in the left adrenal gland (61.9%, n=15) compared to the right (38.1%, n=11), although this difference was also not statistically significant ($\chi^2=1.19$, $p=0.275$). In Group 4, similar results were seen, with a predominance of left-sided localization – 57.7% (n=11) versus right-sided localization – 42.3% (n=11), again without statistical significance (χ^2=0.62, p=0.433). The data are graphically presented in Figure 20.

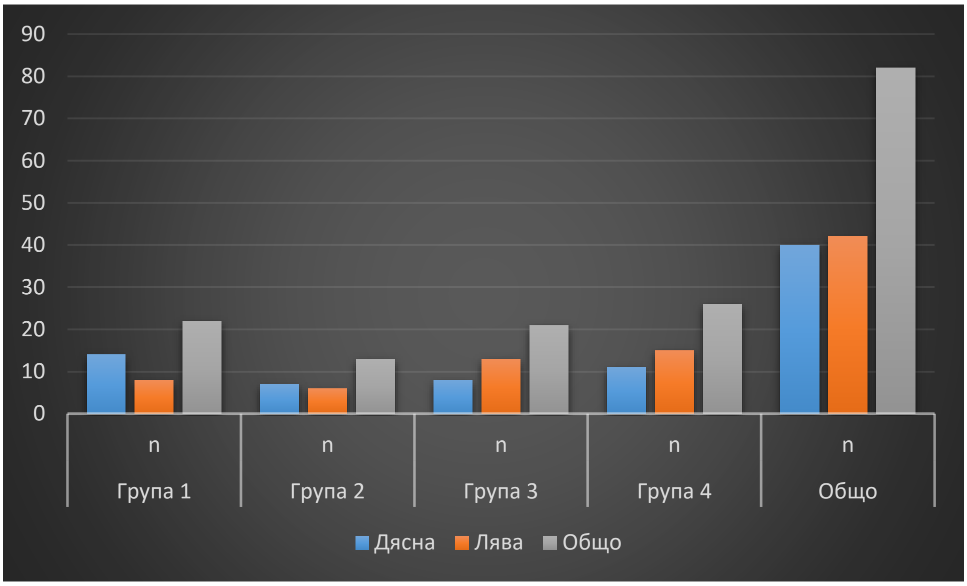


Figure 20 Distribution by side of operation

From the medical documentation during diagnostic evaluation, we collected data on the patients' BMI, summarized in Table 5 and graphically presented in Figure 21.

BMI [kg/m^2]	Group 1	Group 2	Group 3	Group 4	Overall
N	22	13	21	26	82
Mean	29.86	30.57	31.74	31.28	30.96
SD	5.65	20.9	19.0	19.8	6.46
Range	20.0	8.15	6.21	6.58	20.9
Min	21.2	21.1	23.0	22.2	21.1
Max	41.1	41.9	42.1	42.0	42.1

Table 5 Distribution by BMI in groups

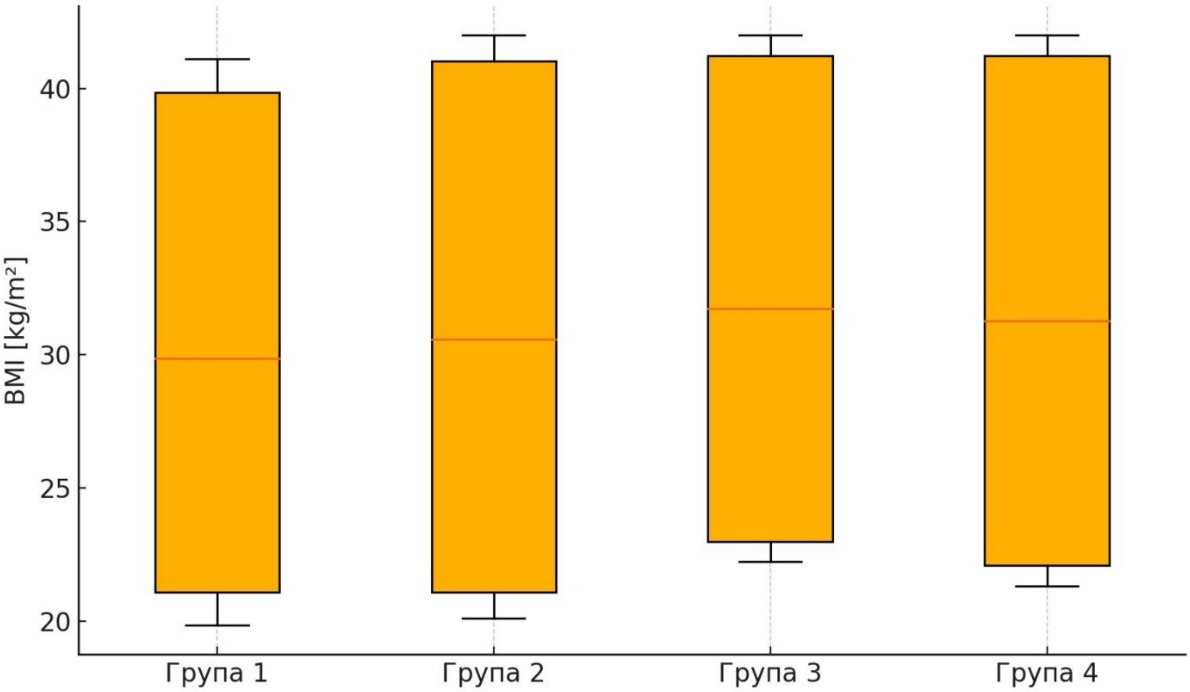


Figure 16 Distribution by BMI in groups

The mean BMI in the studied population was 30.96±6.46 kg/m². The highest BMI (42.1 kg/m²) was recorded in Group 3, while the lowest BMI (21.1 kg/m²) was found in Group 2. Classical hypercortisolism is associated with centripetal fat accumulation and impaired carbohydrate metabolism, with the highest mean BMI observed in Group 3 patients – 31.74±19.0 kg/m². The analysis did not identify a statistically significant difference in BMI between the groups (F(3)=0.53, p=0.666).

Although the mean age of the patients was relatively low (52.10±14.32 years), a characteristic feature of the sample was the presence of significant comorbidities. The distribution of the most common comorbid conditions is presented in Table 6.

Diseases	Group 1		Group 2		Group 3		Group 4		Overall	
	N	%	N	%	N	%	N	%	N	%
Coronary artery disease	5	22,7	7	53,85	8	38,09	6	23,1	26	32,1
Myocardial infarction	3	13,64	2	15,38	5	23,81	3	11,53	13	16,05
Arrythimia	4	18,18	4	30,77	5	23,81	3	14,29	16	18,39
Hypertension	19	86,36	13	100,0	21	100,0	21	80,77	74	91,36
Cardiomyopathy	13	59,09	2	15,38	3	14,29	1	3,85	19	23,46
Diabetes mellitus	6	27,27	4	30,77	9	42,86	12	46,15	31	38,27
Obesity	4	18,18	5	38,41	18	85,71	16	61,54	43	53,09
COPD/Asthma	3	13,64	2	15,38	1	4,76	8	30,77	14	17,28
Chronic kidney disease	1	4,44	3	23,08	3	14,29	5	19,23	12	14,81
Liver dysfuncion	1	4,54	2	15,38	1	4,76	5	19,23	9	11,1
Cerebrovascular disease	4	18,18	2	15,38	4	19,05	8	30,77	18	22,2
Other malignant tumor	4	18,18	2	15,38	1	4,76	6	28,57	13	16,05

Table 6 Distribution of patients by their concomitant diseases

Only two of all patients included in this study (2.47%) reported no other comorbidities apart from the primary indication for adrenalectomy – an 11-year-old child and a 34-year-old man, both from Group 4. The most common comorbidity was arterial hypertension, recorded in 74 patients (91.36%), and it predominated in all subgroups: in Group 1 – 86.36% of patients (n=19); in Groups 2 and 3 – in all patients (100%, n=13 and n=21, respectively); and in Group 4 – 80.77% (n=26). This trend corresponds to the well-established pathophysiological effects of excessive adrenal hormone secretion observed in the respective subgroups. The second most common comorbidity in the overall cohort was obesity – 53.09% (n=43), followed by diabetes mellitus – 38.27% (n=31), coronary artery disease – 32.1% (n=26), and cardiomyopathy – 23.46% (n=19). The percentage distribution of the analyzed chronic diseases across subgroups and the overall population is graphically presented in Figure 22.

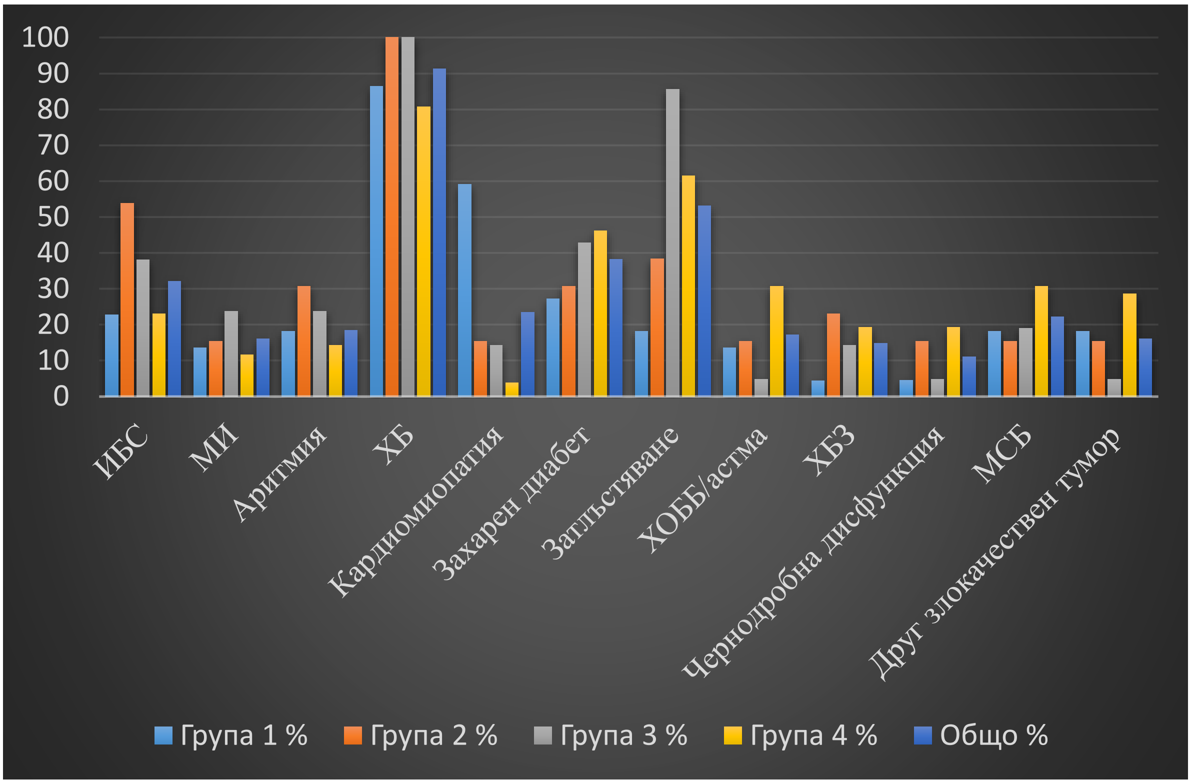


Figure 17 Percentage distributions of concomitant diseases in different patient groups

Notably, there was a significantly higher prevalence of diagnosed cardiomyopathy in Group 1, 59.09% (n=13, p=0.0096), which was statistically significant compared to the overall cohort (23.46%, n=19) and each of the other groups individually (Group 2 – 15.38%, n=2; Group 3 – 14.29%, n=3; Group 4 – 3.85%, n=1).

Obesity was statistically significant between groups, with the highest prevalence in Group 3 (85.71%, n=18; p=0.0134). The results of our analysis correspond with the known fact that hypercortisolism predisposes to centripetal obesity and high BMI values. Borderline statistical significance was found regarding COPD/asthma, with the highest percentage in Group 4 (30.77%) and the lowest in Group 3 (4.76%), p=0.0599. The statistical significance of differences in comorbidities between groups is presented in Table 7.

	Kruskal-Wallis H	*df*	*p-value*
Ischemic hearth disease	2,080	3	0.3616
Myocardial infactions	2,023	3	0.7432
Arrythmia	3,133	3	0.6602
Hypertension	4,297	3	0.3703
Cardiomyopathy	24,947	3	**0,0096**
Diabetes mellitus	1,845	3	0.5197
Obesity	21,354	3	**0,0134**
COPD/Astma	8,039	3	0,0599
Chronic kidney disease	2,436	3	0.3627
Liver disfunction	4,115	3	0.3704
Cerebrovascular disaese/ Stroke	2,082	3	0.7437
Other malignant tumors	3,845	3	0.7348

Table 7 Statistical significance of differences in comorbidities between the groups

The assessment of patients' overall functional status prior to surgery and the level of control over their chronic comorbidities was performed during the pre-anesthetic consultation using the ASA score and classification. This scale, used for planned surgical interventions, ranges from ASA I to ASA IV. The distribution of patients in this study according to their respective functional categories is illustrated in Table 8 and visualized in Figure 23.

ASA	**Group 1**		**Group 2**		**Group 3**		**Group 4**		**Overall**	
	N	%	N	%	N	%	N	%	N	%
ASA I	0	0	0	0	0	0	2	9,52	2	2,47
ASA II	5	22,72	3	23.08	4	4,76	6	23,08	18	18,52
ASA III	15	68,18	10	76,92	14	66,66	12	46,15	51	62.2
ASA IV	2	9,09	0	0	3	14,29	6	23.08	11	13.41

Table 8 Distribution by ASA in different groups

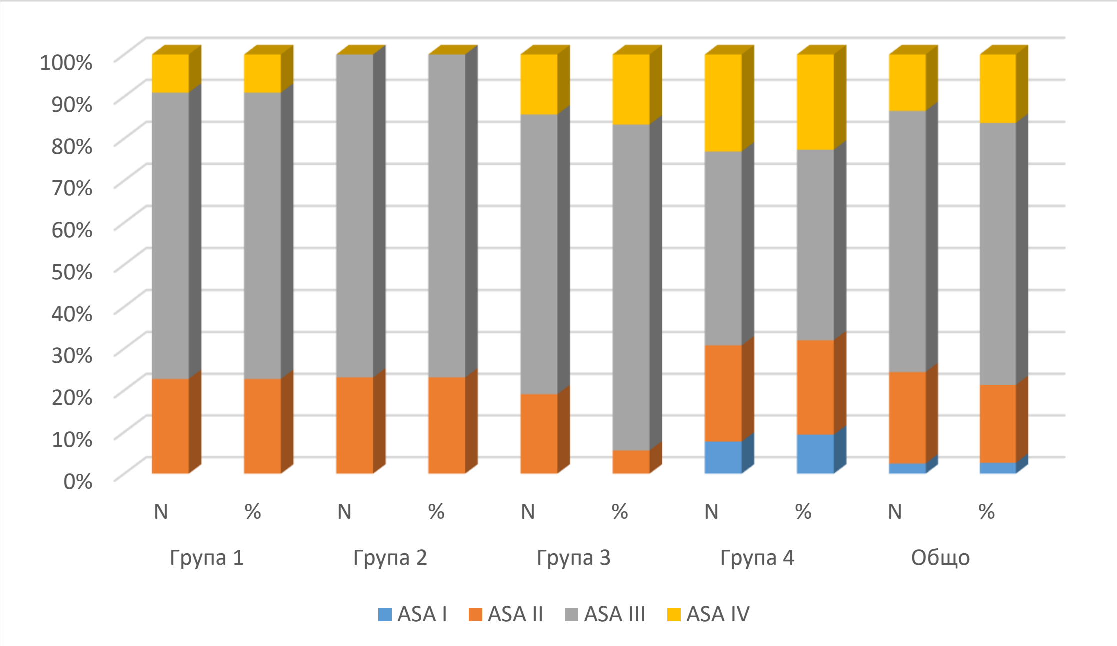


Figure 18 Distribution by ASA in different groups

Analysis of the presented data showed that the majority of patients – 62.2% (n=51) – were categorized as ASA III, indicating the presence of at least one severe systemic disease. This distribution was similar across the individual groups. Two patients (2.47%) were classified in the lowest category – ASA I. Patients with severe, potentially life-threatening systemic diseases classified as ASA IV constituted 13.41% (n=11) of the sample, with the highest proportion observed in Groups 3 and 4 – 14.29% (n=3) and 23.08% (n=6), respectively. No statistically significant difference between the groups in terms of ASA classification distribution was found (Kruskal-Wallis test H = 0.662; p=0.882).

Preoperative antihypertensive therapy was analyzed separately due to its essential importance in controlling intraoperative hemodynamic parameters, which directly influences the surgical technique in patients with hormonally active tumors. Patients were grouped according to the number of medications they regularly took to control blood pressure (see Table 9). The percentage distribution is shown in Figure 24.

Antihypertensive therapy	Group 1		Group 2		Group 3		Group 4		Overall	
	n	%	n	%	n	%	n	%	n	%
None	1	4,5	-	-	1	4,8	6	23,1	8	9,8
One medication	3	13,6	1	7,7	3	14,3	9	4,2	16	19,5
Two medications	17	77,3	3	23,1	5	23,8	7	33,3	32	39
Three or more medications	1	4,5	9	69,2	12	57,1	4	13,9	26	31,7

Table 9 Distribution of antihypertensive therapy by group

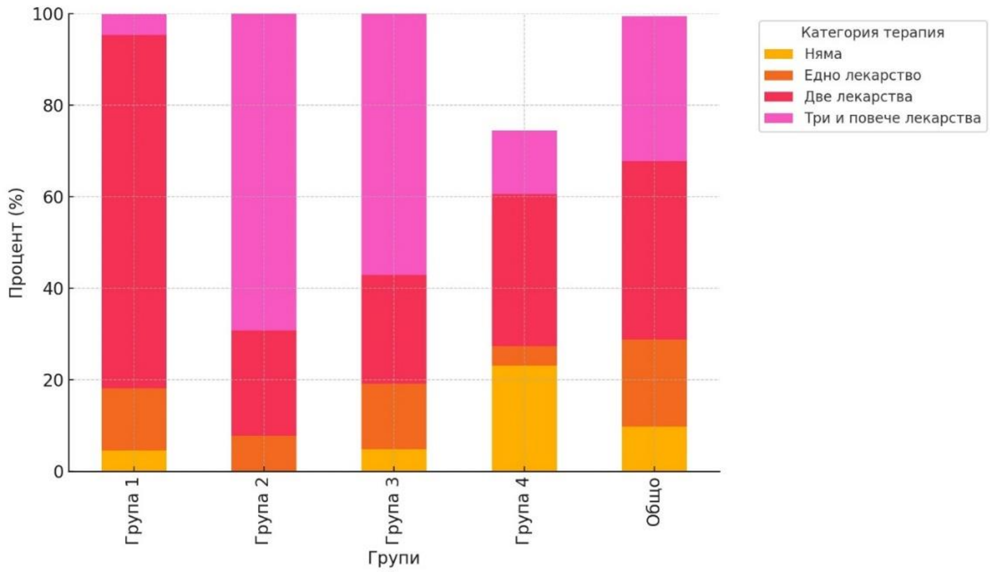


Figure 19 Distribution of antihypertensive therapy by group

It was observed that in 5 patients (9.8% of all patients), antihypertensive therapy was not required. A more detailed analysis revealed that in the pheochromocytoma group, only one patient required a triple medication regimen. On the other hand, in Group 2, there were no patients without antihypertensive treatment, and only one of them was on monotherapy. The statistical significance of the differences in antihypertensive therapy between the groups is presented in Table 10.

Groups	*Mann-Whitney U Test*	*p value*
Groups 1 - 2	8.0	1,000
Groups 1 - 3	5,0	0,467
Groups 1 - 4	7,0	0,884
Groups 2 - 3	7,0	0,885
Groups 2 - 4	7,5	1,000
Groups 3 - 4	10,0	0,685

Table 10 Statistical analysis of antihypertension therapy by groups

Based on the data, it was observed that the highest proportion of patients treated with three or more antihypertensive medications was found in Groups 2 and 3, while in Group 1 there was only one such case. Among patients with hyperaldosteronism, 69.2% (n=9), and among those with hypercortisolism, 57.1% (n=12), were on triple or quadruple therapy.

In the present study, a higher frequency of combined antihypertensive therapy with two or more medications was observed compared to data from other authors. This discrepancy is likely due to the fact that the cited studies focus solely on cases of pheochromocytoma, whereas our sample includes patients with a broader spectrum of endocrine hypertensive conditions. Another possible explanation lies in the differences between cardiology treatment algorithms across centers, as well as the lack of information regarding concomitant essential hypertension in some of the analyzed cases.

In patients with pheochromocytoma, standard preoperative practice includes the addition of an alpha-blocker to the antihypertensive regimen to achieve adequate blood pressure control before surgery. This corresponds to the observed 100% pharmacological preparation (n=22) in Group 1 in our cohort. Details regarding the administration of alpha-blockers in the patients included in this study are presented in Table 11 and visualized in Figure 25.

Alpha blockade	**Group 1**		**Group 2**		**Group 3**		**Group 4**		**Overall**	
	n	%	n	%	n	%	n	%	n	%
Present	22	100	11	76,9	11	52,4	11	42,3	56	68,3
None	0	0	2	23,1	10	47,6	15	57,7	26	31,7

Table 11 Distribution by groups of used preoperative alpha blockede

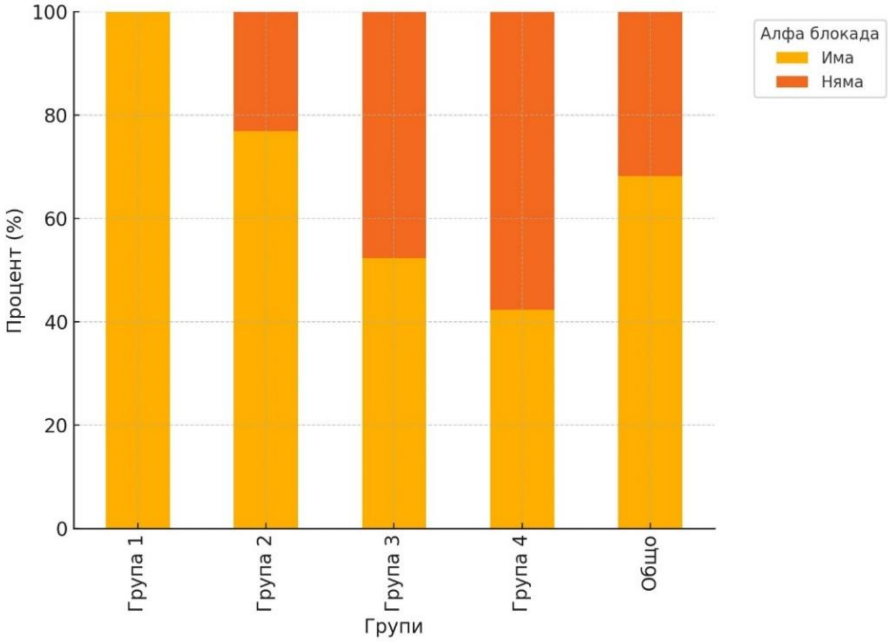


Figure 20 Distribution by groups of used preoperative alpha blockede

At our institution, preoperative therapy with alpha-blockers was administered to 68.3% (n=56) of patients undergoing laparoscopic adrenalectomy. Specifically, in Group 2, such pharmacological preparation was carried out in 76.9% (n=11) of patients, and in Group 3 – in 52.4% (n=11). Notably, even in Group 4, where there were no clinical or laboratory indications of hormonal activity, 42.3% (n=11) received an alpha-blocker prior to surgery. Statistical analysis using the Kruskal-Wallis H test did not reveal a significant difference between Groups 2, 3, and 4 ($H(2) = 0.854$; $p = 0.765$).

After thorough analysis of tumor size based on preoperative imaging studies and postoperative measurements of the resected specimens, the data were summarized in Table 12 and illustrated in Figure 26.

Tumor size [mm]	Group 1	Group 2	Group 3	Group 4	Overall
N	22	13	21	26	82
Mean	55.17	26.23	38.95	67.15	50.57
SD	28.83	10.93	14.08	61.11	41.01
Range	125	38	63	253	253
Min	25	12	23	7	7
Max	150	50	86	260	260

Table 12 Distribution of tumor size

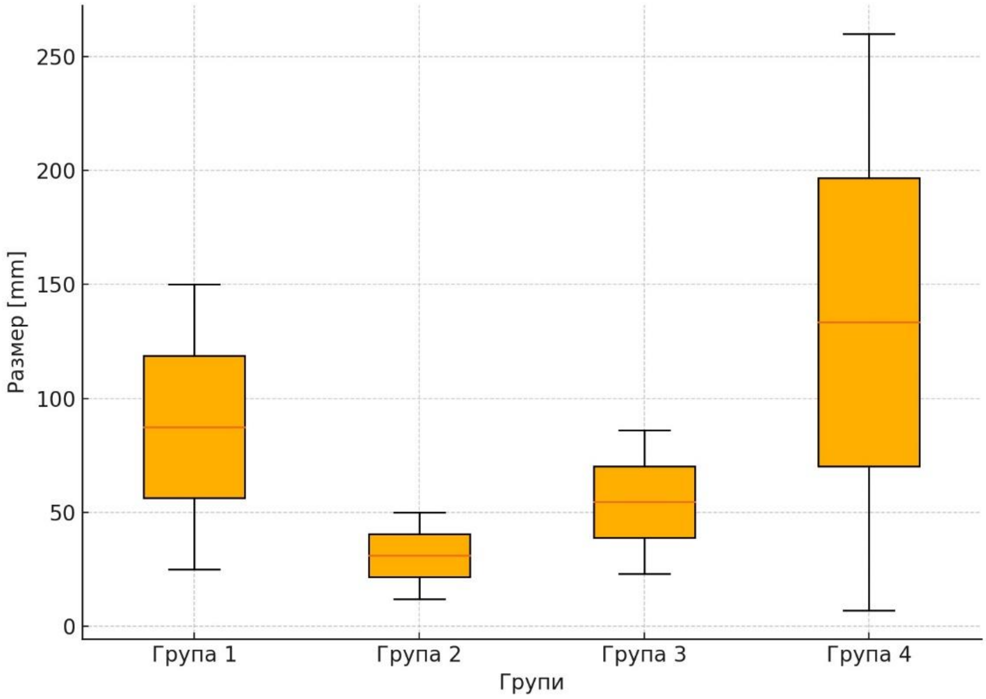


Figure 21 Distribution of tumor size

In the studied population, the mean tumor size was 50.57±41.01 mm. The smallest neoplasms were observed in Group 2 (26.23±10.93 mm), while the largest were in Group 4 (67.15±61.11 mm). Graphical representation of the data shows variations in tumor size among the different groups. Statistical analysis revealed significant differences due to the disparity between the mean size in Group 2 compared to Groups 4 and 1 (t=4.458; t= -4.941; p<0.001). Approximately 29.63% of cases (n=24) involved tumors with a size ≥50 mm, and in 8.64% (n=7) the size exceeded 80 mm.

The hormonal secretion profiles of the identified tumors are presented in Table 13. Group 1 included patients with increased production of catecholamines – epinephrine and norepinephrine. Due to the short half-life of these substances, diagnosis usually relies on the determination of their metabolites in plasma or urine. In Group 2, elevated metanephrine levels were observed in three patients, as well as in two patients each from Groups 3 and 4, although no diagnosis of pheochromocytoma was confirmed by histological analysis or clinical presentation. Such falsely elevated values may result from the use of certain medications (e.g., tricyclic antidepressants, non-selective alpha-blockers, MAO inhibitors, sympathomimetics) as well as pre-analytical factors such as inappropriate body positioning or lack of information regarding current medications (Zaharieva, 2012) (398).

Group 2 was characterized by hypersecretion of aldosterone. Among the remaining participants, only one patient from Group 1 demonstrated abnormalities, which were likely due to prior use of spironolactone. It is known that age, sex, and certain medications (e.g., beta-blockers, ACE inhibitors, ARBs, diuretics, or hormone replacement therapy) can also influence laboratory results (Zaharieva, 2012) (398).

In Group 3 patients, the tumors showed increased secretion of glucocorticoids, specifically cortisol. For the purposes of analysis, both morning serum cortisol levels and 24-hour urinary cortisol results were included.

Hormonal activity	Group 1	Group 2	Group 3	Group 4	Overall	Norm
Metanephrine Pl [ng/l]						***< 80***
Mean	1063,26	58,44	63,25	52,76	308,93	
SD	1308,84	22,49	73,72	29,17	777,74	
Min	45	21	21	22	21	
Max	4787	95	334	154	4787	
Normetanephrine Pl [ng/l]						***< 180***
Mean	1826	94,15	105,32	82,93	526,07	
SD	1929,05	36,79	53,62	36,28	1210,47	
Min	89	38,5	31	34	31	
Max	7627	175,0	218	152	7627	
Cortisol Pl [nmol/l]						***118-618***
Mean	398,97	312,17	781,89	421,09	473,33	
SD	120,92	113,80	222,26	143,25	228,75	
Min	240,5	140	348,53	187,6	140	
Max	680,54	476,36	1100,7	698	1100,70	
Cortisol Urine [nmol/24h]						***55-286***
Mean	383,18	276,75	824,31	307,79	435,64	
SD	351,48	166,08	661,71	169,69	427,74	
Min	129,4	144,80	102	77	77	
Max	1728	751,00	2999	841	2999	
Aldosteron Pl [pmol/ml]						***30-650***
Mean	188,00*	694,35	236,78	283,97	381,74	
SD	415,51	159,6	226,61	411,09		
Min	99,7	310	47	35	35	
Max	2770	1980	629	837	2770	
Renin Pl [uIU/ml]						***2,8–39,9***
Mean	17,30*	0,85	13,63	28,9	25,62	
SD	0,59	9,35	30,18	60,72		
Min	1,1	0,01	1,6	1,1	0.01	
Max	500	2,2	35	138,9	500	
Aldosteron/Renin Ratio						***≤ 80***
Mean	17,00*	8454,53	25,01	18,24	1798,01	
SD	16303,32	17,55	18,53	8070,53		
Min	0,26	242,38	2,24	1,02	0,26	
Max	118,00	45990,00	61,90	61,00	45990	

Table 13 Distribution of hormonal activity by groups

In two patients from Group 1 and three patients from Group 4, elevated plasma cortisol levels were recorded. However, interpretation of these data is challenging, as cortisol is a key hormone in the body's stress response, and its levels can fluctuate under the influence of numerous factors. In these patients, there was no additional evidence from other diagnostic tests to support the presence of hypercortisolism. Furthermore, due to the limited diagnostic value of isolated morning cortisol measurements, endogenous cortisol hypersecretion cannot be confidently confirmed.

Additionally, nine patients from Group 1, five from Group 2, and twelve from Group 4 had 24-hour urinary free cortisol levels exceeding the reference ranges of the respective laboratory. However, these values were not significantly elevated, and the results were based on a single measurement, without confirmation from other positive screening tests (e.g., assessment of the circadian rhythm of cortisol, dexamethasone suppression test, etc.). Possible pre-analytical errors, such as improper urine collection, which could affect test results, should also not be overlooked.

Despite the subdivision of tumors based on hormonal activity, they can also be considered in the context of their biological potential. It should be noted that for patients in Group 1, the clinical, hormonal, and histopathological diagnoses correlated – pheochromocytoma. The distinction arises after the histopathological analysis and immunohistochemistry (IHC) with PASS scoring for their malignant potential. Among the histologically diagnosed pheochromocytomas (n=22), variants with malignant potential were identified in 36.4% (n=8). Benign pheochromocytomas were diagnosed in 14 patients (63.6%). For patients in Groups 2 and 3, imaging and histopathological diagnoses corresponded – adrenal adenoma, with the difference arising from clinically proven hormone overproduction – aldosterone (n=13) for Group 2 and cortisol (n=21) for Group 3. The greatest histological pleomorphism was observed in Group 4, which included adrenal formations without hormonal activity. For easier interpretation of the data, Table 14 presents the histological variants of the examined tumor formations in Group 4. The data are graphically illustrated in Figure 27.

Histological type	Group 4			
	Benign		**Malignant**	
	N	**%**	**N**	**%**
Adrenocortical carcinoma	-	-	4	13,4
Hormonal incactive adenoma	14	53,8	-	-
Myelolypoma	2	7,7	-	-
Lyposarcoma	-	-	1	3,8
Mestastasis of non-small cell lung carcinoma	-	-	1	3,8
Malignant psammomatous melanotic schwanomma	-	-	1	3,8
Haematoma in adrenal gland	1	3,8	-	-
Endothelium cyst	2	7,7	-	-
Overall	19	73,1	7	26,9

Table 14 Distribution of histological type of tumors in Group 4

Figure 22 Distribution of histological type of tumors in Group 4

Statistical analysis did not reveal a significant association between the biological potential of the tumor and its hormonal activity (χ^2=1.15, df=1, p=0.284), indicating no direct relationship between malignancy and hormone synthesis.

2. Intraoperative indicators

2.1. Operative time

The operative time for the intervention was defined as the duration from the first incision to the closure of the last port site. The data are summarized and presented in Table 15 and Figure 28.

Operative time [min]	Group 1	Group 2	Group 3	Group 4	Overall
N	22	13	21	26	82
Mean	142.30	152.54	167.58	165.92	157.46
SD	47.30	62.75	51.17	49.21	51.67
Range	163	160	164	165	179
Min	77	80	90	75	75
Max	240	240	254	240	254

Table 15 Distribution of operative time in groups

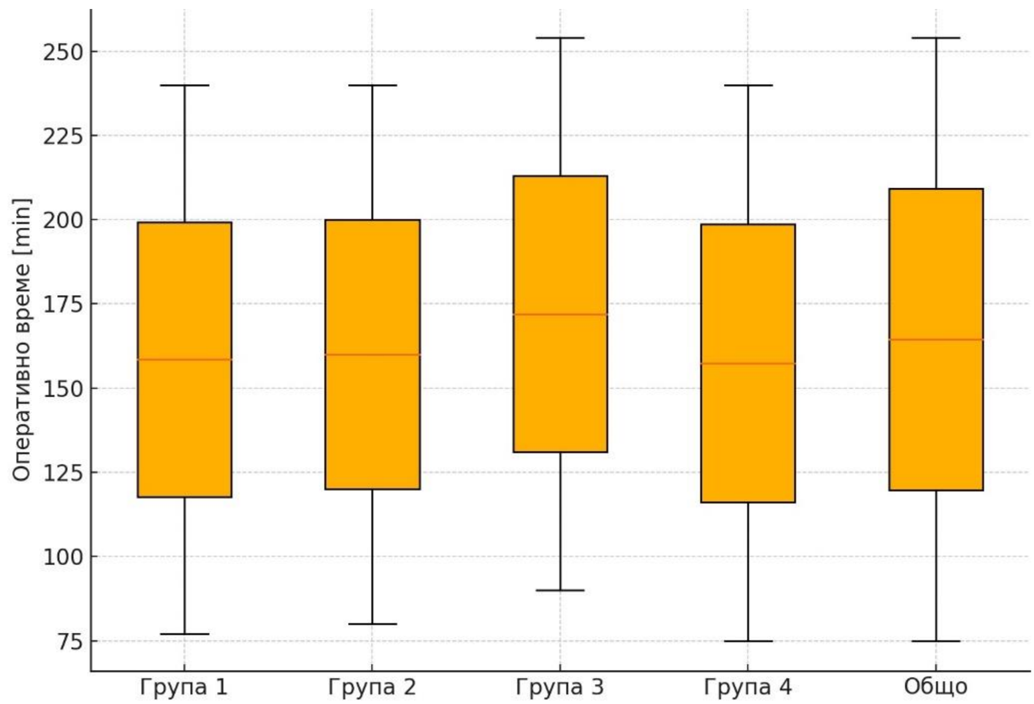


Figure 23 Distribution of operative time in groups

During the analyzed period, the mean operative time for laparoscopic adrenalectomies performed at our institution was 157.46±51.67 minutes. The shortest interventions lasted 75 minutes, while the longest reached up to 254 minutes. It was noted that operative times were longest in patients with cortisol-secreting tumors – an average of 167.58±51.17 minutes. The difference in duration was not statistically significant compared to Group 1 (T-HSD= -0.122, p=0.903) and Group 2 (T-HSD= -0.727, p=0.475). The longer duration in patients with cortisol-secreting tumors is likely due to the higher mean BMI values in this group, as well as intraoperative difficulties associated with obesity. No statistically significant difference in operative time was found between the other groups ($p > 0.05$). Operative time depends on numerous factors, which complicates direct comparison between studies. In the present study, the primary criterion for patient grouping was the hormonal activity of the tumors, with the corresponding hormone secretion values summarized in Table 14.

2.2. Inraoperative heamodynamics

Intraoperative hemodynamic control is a pivotal aspect of ensuring the safety of any surgical intervention. Of particular interest is the hemodynamic profile during surgery in patients with adrenal gland disorders, as some of these conditions influence blood pressure and heart rate both directly and indirectly. From an anesthesiological perspective, important considerations include episodes of hypotension – their severity and duration – as well as episodes of extreme hypertension. These indicators can indirectly reflect tissue perfusion and the risks of cardiovascular complications. A critical aspect in the management of adrenal tumors is intraoperative hypertension, especially in cases of pheochromocytoma, as any surgical manipulation of the tumor can directly affect blood pressure and thereby induce systemic disturbances. As part of the anesthetic protocols, we analyzed intraoperative hypertensive crises and their relationship to the underlying disease prompting laparoscopic adrenalectomy.

During the analysis of intraoperative hypertension, a personalized assessment approach was applied, based on an increase in systolic arterial pressure (SAP) by 30% or more compared to baseline, in order to avoid false-positive results. The results of this method are visualized in Figure 29. It is evident that in all patients from Group 1, an episode of significantly elevated SAP was recorded. In Group 2, such episodes were registered in 36% of cases (n=5), in Group 3 – in 58% (n=12), and in Group 4 – in 14% (n=4). Statistical analysis revealed that the frequency of significant hypertension was markedly higher in Group 1 compared to the other groups (Kruskal-Wallis $H(3)=161.45$, $p < 0.001$).

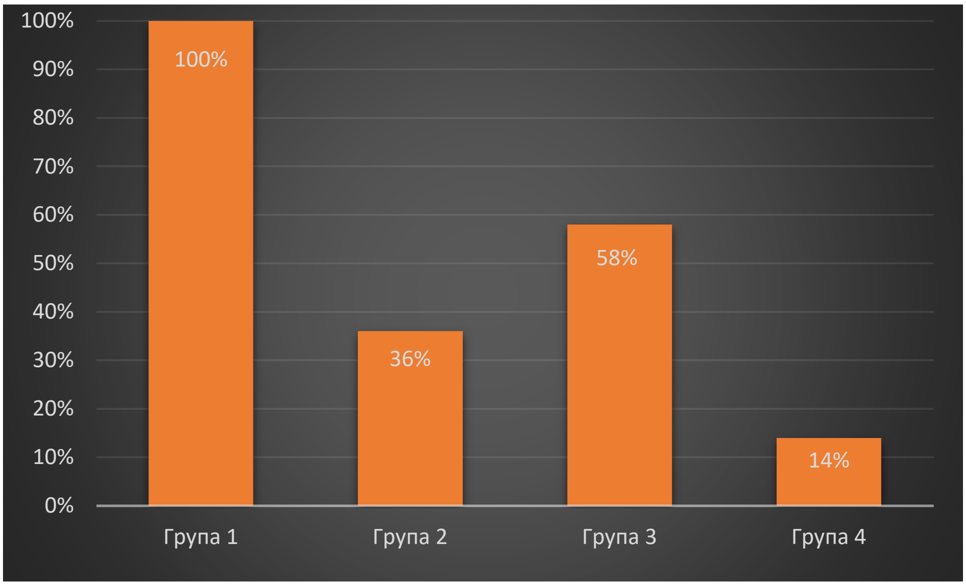


Figure 24 Registered episodes of hypertension by type of hormonal activity

The recorded severe episodes of hypertension necessitated temporary cessation of the surgery until hemodynamic stabilization was achieved, which directly influenced intraoperative parameters such as operative time and complication rates. Data from our study showed that all patients with pheochromocytoma exhibited some degree of intraoperative hemodynamic instability. Combined with other patients who demonstrated significant fluctuations, we found that 52.4% exhibited a form of sustained alteration in blood pressure.

2.3. Blood loss

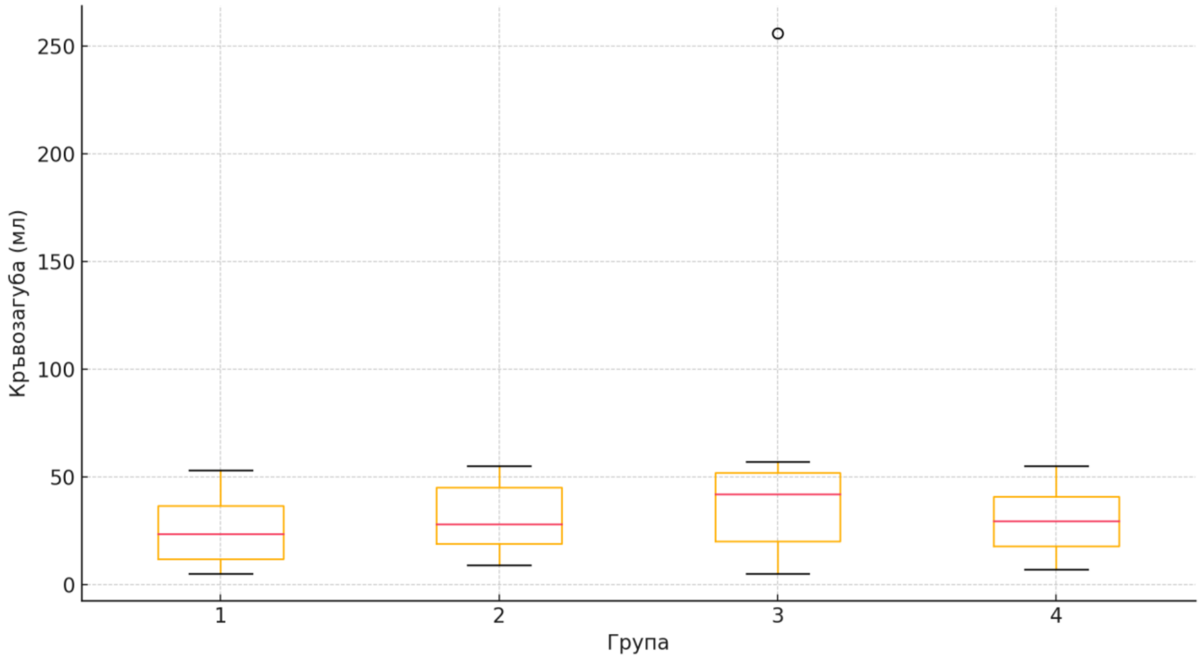
Blood loss during laparoscopic adrenalectomy is an important indicator of the safety and effectiveness of the surgical intervention. The adrenal glands are highly vascularized organs, and their proximity to major blood vessels poses a risk of significant intraoperative hemorrhage. The volume of blood loss depends on various factors – including tumor size, anatomical variations, and the chosen surgical approach. Minimizing blood loss is crucial for reducing postoperative complications and accelerating recovery.

During the analyzed period, the mean blood loss was 139.95±91.09 milliliters. The smallest recorded blood loss was 20 milliliters, while the highest amounted to 650 milliliters. It was noted that intraoperative blood loss was greatest in patients with cortisol-secreting tumors – 150.59±116.43 ml. The analyzed data are summarized in Table 16 and graphically illustrated in Figure 30.

Blood loss [ml]	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Overall**
N	22	13	21	26	82
Mean	72.52	72,52	91.47	77.12	81,38
SD	34.58	34,58	70.55	33.43	45,35
Range	112	112	329	21	329
Min	21	21	21	135	21
Max	133	133	350	114	350

Table 16 Intraoperative blood loss distributed by groups

Blood loss did not show statistically significant differences between the four groups according to the Kruskal-Wallis test (H=2.30, p=0.512). This suggests that group assignment based on hormonal activity does not have a substantial influence on intraoperative blood loss in the studied population.



Фигура 25 Statistical analysis of intraoperative blood loss distributed by groups

2.4. Vascular anomalies

The adrenal glands are characterized by extremely rich and variable blood supply, which results from their complex embryological origin. Vascular anomalies in this region represent significant anatomical and clinical interest, as variations in the number, origin, and branching of arteries and veins can directly influence the surgical approach during adrenalectomy, as well as the risk of intraoperative complications (402). The absence of a standardized vascular anatomy necessitates individualized preoperative assessment and heightened caution during imaging diagnostics and surgical planning. Knowledge of these variations is crucial for the safe and effective treatment of diseases affecting the adrenal glands.

Vascular anomalies	Group 1	Group 2	Group 3	Group 4	Overall
Yes	2	-	1	-	3
No	20	13	20	26	79

Table 17 Distribution of vascular anomalies

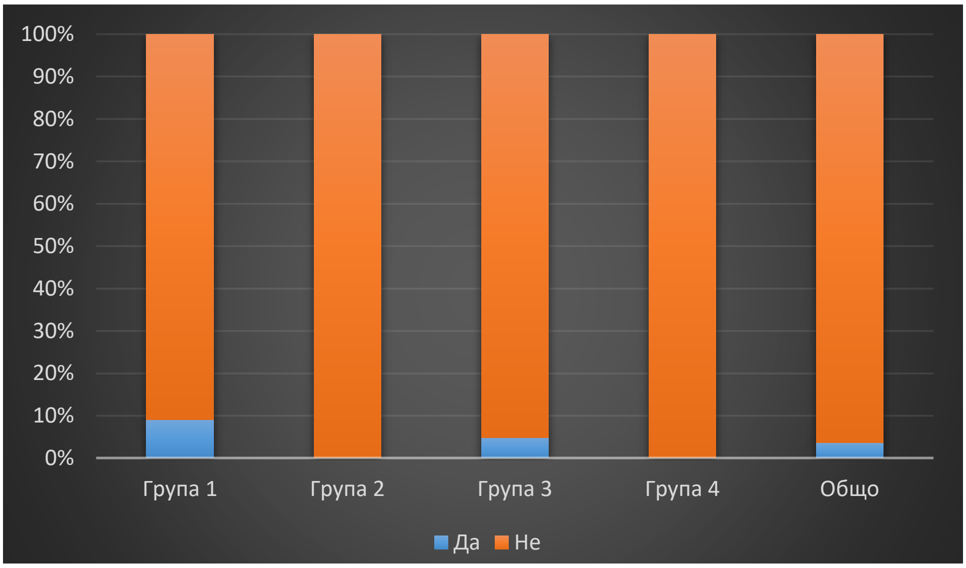


Figure 26 Graphic illustration of vascular anomalies distributed by groups

Vascular variations in the studied cohort were identified in three patients (n=3, 3.66%), with two of them in Group 1 and one in Group 3. The results are presented in Table 17 and visualized in Figure 31. Correlation analysis between the presence of vascular anomalies and intraoperative blood loss showed no statistically significant association ([r]= -0.116, p=0.299). The reported vascular anomaly involving the drainage of the adrenal vein into the inferior vena cava in one patient from Group 3 with Cushing's syndrome and right-sided localization may be attributed to an error during preoperative preparation or surgical technique.

2.5. Coversions

Conversions during adrenalectomy represent the transition from a laparoscopic to an open approach, typically necessitated by the occurrence of complications or difficulties in maintaining an adequate operative field. Despite advances in minimally invasive surgery, certain anatomical features, vascular variations, or technical challenges can limit the safety of the laparoscopic approach. Therefore, preoperative risk assessment and an individualized approach for each case are key to successful surgical management.

Conversion was required in six patients (n=6, 7.32%) due to the large size of the tumor, which prevented further continuation of the intervention by laparoscopic means. Classified according to the Clavien-Dindo system, these patients had complications of grade IIIb, requiring additional surgical intervention beyond the original operative plan.

2.6. Complications

Complications during adrenalectomy can occur regardless of the surgical approach used and are related both to the anatomical localization of the adrenal glands and to the functional profile of the tumor. They range from intraoperative hemorrhage and vascular injuries to postoperative infections, hormonal imbalances, or the need for additional invasive procedures and prolonged hospital care. Timely recognition and appropriate management of these complications are essential for successful patient recovery.

The complications that occurred were classified according to the standardized Clavien-Dindo system, with the data presented in tabular and graphical form (Tables 18–19 and Figure 32).

Grade	Deffinitions	Cases
I	• Any deviation from the normal postoperative course not requiring pharmacological treatment or surgical, endoscopic, and radiological interventions • Requirement for pharmacological therapy such as antiemetics, antipyretics, analgesics, diuretics, and electrolyte solutions, as well as physiotherapy • Wound suppuration managed at the bedside	4
II	• Requirement for pharmacological treatment with drugs other than those allowed for Grade I complications • Blood transfusion and total parenteral nutrition	4
III	Requiring surgical, endoscopic, or interventional procedure	-
IIIa	Intervention without general anesthesia	-
IIIb	Intervention under general anesthesia	1
IV	Life-threatening complication (including central nervous system complications – cerebral hemorrhage, ischemic stroke, subarachnoid hemorrhage, excluding transient ischemic attacks) requiring intensive care and resuscitation	-
IVa	Single organ dysfunction (including dialysis)	1
IVb	Multiorgan failure	-
V	Patients death	-

Table 18 Complications distributed by Clavien-Dindo complication scale

Complications were observed in ten patients (n=10, 12.2%). According to the Clavien-Dindo classification, Grade I complications were identified in four patients (n=4, 4.88%), two of whom had wound suppuration managed conservatively with irrigation and antibiotic therapy, and two cases of postoperative fever lasting up to the third postoperative day, resolved conservatively. Intraoperative hypertensive crises with blood pressure values up to 300/120 mmHg occurred in three patients (n=3), and postoperative pneumonia was recorded in one patient (n=1); these were classified as C-D Grade II complications (n=4, 4.88%).

Intraoperative bleeding classified as C-D Grade IIIb was observed in one patient, requiring hemostatic intervention. One patient, discharged on the third postoperative day, was readmitted on the fourth postoperative day with clinical signs of massive pulmonary thromboembolism in the intensive care unit. During treatment, the patient developed an ischemic stroke and, following intensive care, was discharged on the thirty-ninth postoperative day – classified as C-D Grade IV (n=1, 1.2%). No postoperative mortality was recorded.

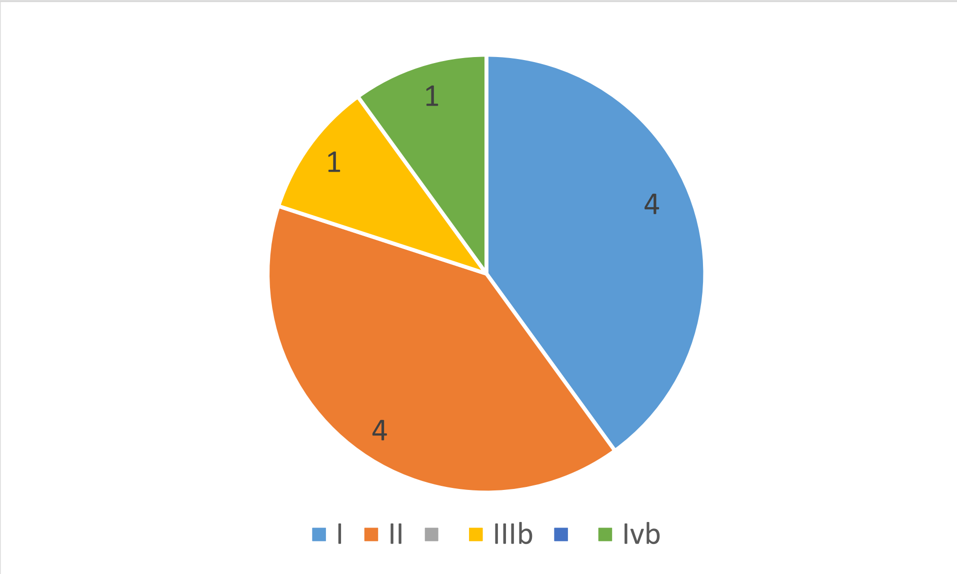


Figure 27 Complications classified by Clavien-Dindo

Clavien-Dindo complications	Group 1	Group 2	Group 3	Group 4	Overall
I	1	-	1	2	4
II	3	-	1	-	4
IIIa	-	-	-	-	-
IIIb	-	-	1	-	1
IVa	-	-	-	-	-
IVb	-	-	1	-	1
V	-	-	-	-	-

Table 19 Complications distributed by hormonal activity of the tumor

It is noteworthy that when complications are distributed by groups according to the hormonal activity of the tumor, Groups 1 and 3 each account for four cases (n=4), but the most severe complications (C-D Grades III–IV) are exclusively associated with cortisol-secreting tumors in Group 3. No complications were observed in Group 2, associated with aldosterone secretion. The data are presented in Table 26. Statistical analysis showed no significant difference in the frequency and severity of complications between the groups (Chi-square test $\chi^2=7.5$; $p=0.277$; Fisher's Exact Test $p=0.429$).

3. Postoperative indicators

The advantages of laparoscopic adrenalectomy include reduced surgical trauma, faster recovery, and decreased need for postoperative analgesia. However, limitations imposed by the healthcare system, specifically treatment protocols under clinical pathways requiring a minimum hospital stay for patients undergoing adrenal surgery regardless of whether performed conventionally or laparoscopically were noted. This circumstance in itself eliminates the possibility of statistical analysis of hospital stay duration. Therefore, we introduced several parameters to objectively assess the impact of minimally invasive interventions. To achieve greater objectivity, we evaluated the time required postoperatively for patients to achieve independent mobilization and their need for postoperative analgesia. These two parameters were defined as the number of days requiring rehabilitation and assistance for mobilization, and the number of days analgesics were needed, respectively.

3.1. Time to ambulation

Analysis of the time to mobilization showed that patients began to ambulate on average at 1.29±0.77 days postoperatively. The earliest independent mobilization was observed on postoperative day 1, while the longest period of immobilization was recorded as 7 days in a patient from Group 1. The data from the analysis are presented in Table 20 and Figure 33.

Time to ambulation [days]	Group 1	Group 2	Group 3	Group 4	Overall
N	22	13	21	26	82
Mean	3,62	1	1,24	1,21	1,29
SD	1,63	0	0,71	0,59	0,77
Range	5	0	3	3	3
Min	2	1	1	1	1
Max	7	1	4	4	7

Table 20 Analysis of time needed to full ambulation

Statistical analysis demonstrated a significant difference between the groups regarding time to mobilization (Kruskal-Wallis H (3) = 47.14, p-value < 0.001). The data from the direct comparisons between the groups are presented in Table 21

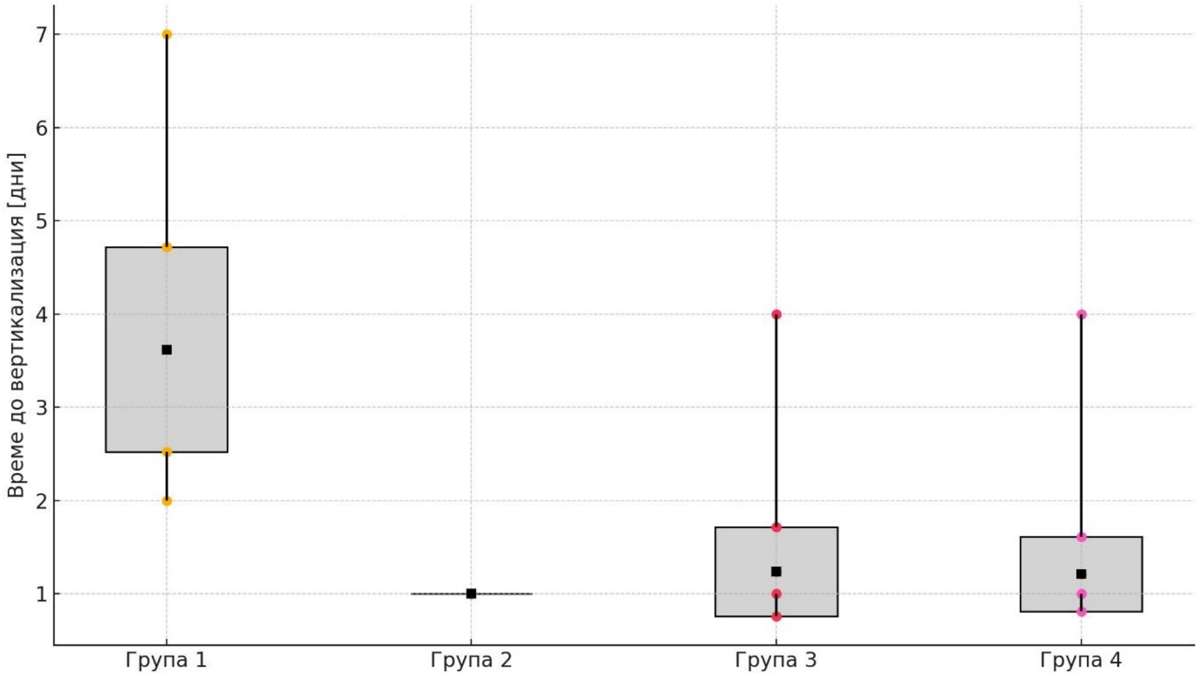


Figure 28 Analysis of time needed to full ambulation

	p-value	U-statistics	Statistical significance
Group 1 vs Group 2	4.479	286.0	True
Group 1 vs Group 3	6.879	429.5	True
Group 1 vs Group 4	3.407	542.0	True
Group 2 vs Group 3	0.013	84.5	False
Group 2 vs Group 4	0.044	123.5	False
Group 3 vs Group 4	0.438	10	False

Table 21 Intergroup analysis of time needed to full ambulation

The conducted analysis revealed that Group 1 exhibited a longer time to mobilization, which may be attributed to a more severe clinical condition, a more invasive surgical approach, or other specific characteristics of this population. The remaining three groups demonstrated rapid recovery with minimal variation.

3.2. Postoperative analgesia requirement

One of the main advantages of laparoscopic surgical methods is associated with the requirement for smaller skin incisions and reduced surgical trauma to the myofascial layers compared to open surgery, which in turn leads to diminished pain both during the intervention and in the postoperative period. The use of epidural analgesia in minimally invasive procedures is generally limited, as the potential risks inherent to the technique often outweigh its possible benefits. However, adrenalectomy represents an exception to this trend.

The epidural administration of anesthetic and opioid medications can decrease catecholamine secretion by blocking the sympathetic nervous system at the spinal level. This results in attenuation or even complete elimination of the physiological stress response to surgical intervention (389). Typically, this reaction is characterized by activation of the hypothalamic-pituitary-adrenal axis and release of hormones such as ACTH, cortisol, adrenaline, noradrenaline, and vasopressin, as well as stimulation of the renin-angiotensin-aldosterone system. In the presence of adrenal neoplasms – particularly functionally active ones – this reaction may be exaggerated, leading to dangerously elevated arterial blood pressure, increased heart rate, and serious cardiovascular complications, especially in patients with significant comorbid systemic diseases.

Data regarding the use of epidural analgesia within our study are presented in (Table 22) and visualized in (Figure 34).

	N	%	Wald $\chi 2$	p value
Group 1	9	40,9	0.727	0.394
Group 2	1	7,7	9.31	**0.0023**
Group 3	4	19	0.10	0.752
Group 4	4	15,4	0.022	0.883
Overall	18	21,9	6.92	0.075

Table 22 Statistical significance in usage of epidural analgesia

The analysis did not identify statistically significant differences in the frequency of epidural analgesia use among the four studied groups (Kruskal-Wallis H(3)=6.83, p=0.077). However, due to the observed trend towards significance, a separate analysis was performed for each group. Further evaluation revealed that in Group 2 (p=0.0023), the number of patients in whom neuraxial analgesia was not used was significantly higher compared to those who received it. In the remaining groups, the distribution between patients with and without an epidural catheter did not demonstrate statistically significant differences (Kruskal-Wallis H(2)=16.00, p=0.453), suggesting relative parity in the choice of analgesic approach within these subgroups.

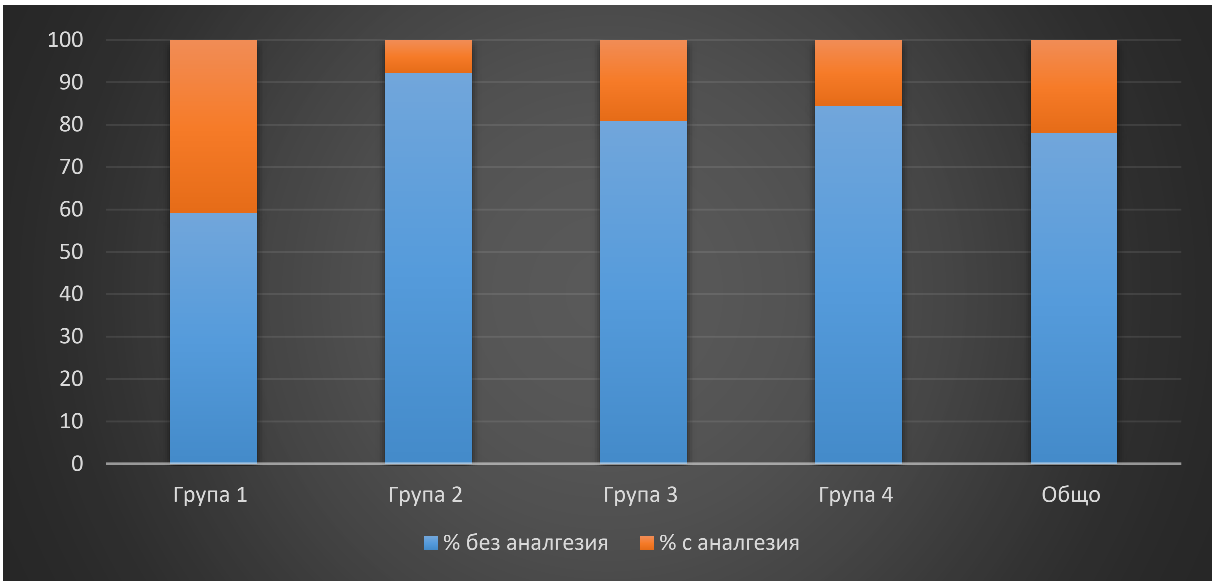


Figure 29 Application of neuroaxial techniques in groups

The database was analysed regarding the need for postoperative epidural and pharmacological analgesia, with data presented by groups in (Table 22) and graphically in (Figure 35). Statistical analysis revealed that differences between groups in postoperative analgesia requirements were statistically significant (Kruskal-Wallis H(3)=81.00, p-value<0.001). Pairwise comparisons between groups using the Mann-Whitney U test (with p-value adjustment via Benjamini-Hochberg correction) demonstrated the following: Group 1 had a significantly higher need for postoperative analgesia compared to Group 2 ($p < 0.001$), Group 3 ($p < 0.001$), and Group 4 ($p < 0.001$). Group 2 differed significantly from Group 3 (adjusted p=0.020), but not from Group 4 ($p \approx 0.053$, near the significance threshold). No statistically significant difference was found between Group 3 and Group 4 (p=0.438). These results confirm that Group 1 required a substantially longer period of postoperative analgesia, while the remaining groups demonstrated relatively similar outcomes.

Postoperative analgesia requirement [days]	Group 1	Group 2	Group 3	Group 4	Overall
N	22	13	21	26	82
Mean	3,62	2	2,44	2,48	2,78
SD	1,63	0	1,50	1,29	1,46
Range	5	0	8	8	8
Min	2	2	2	2	2
Max	7	2	10	10	10

Table 22 Length of postoperative analgesia

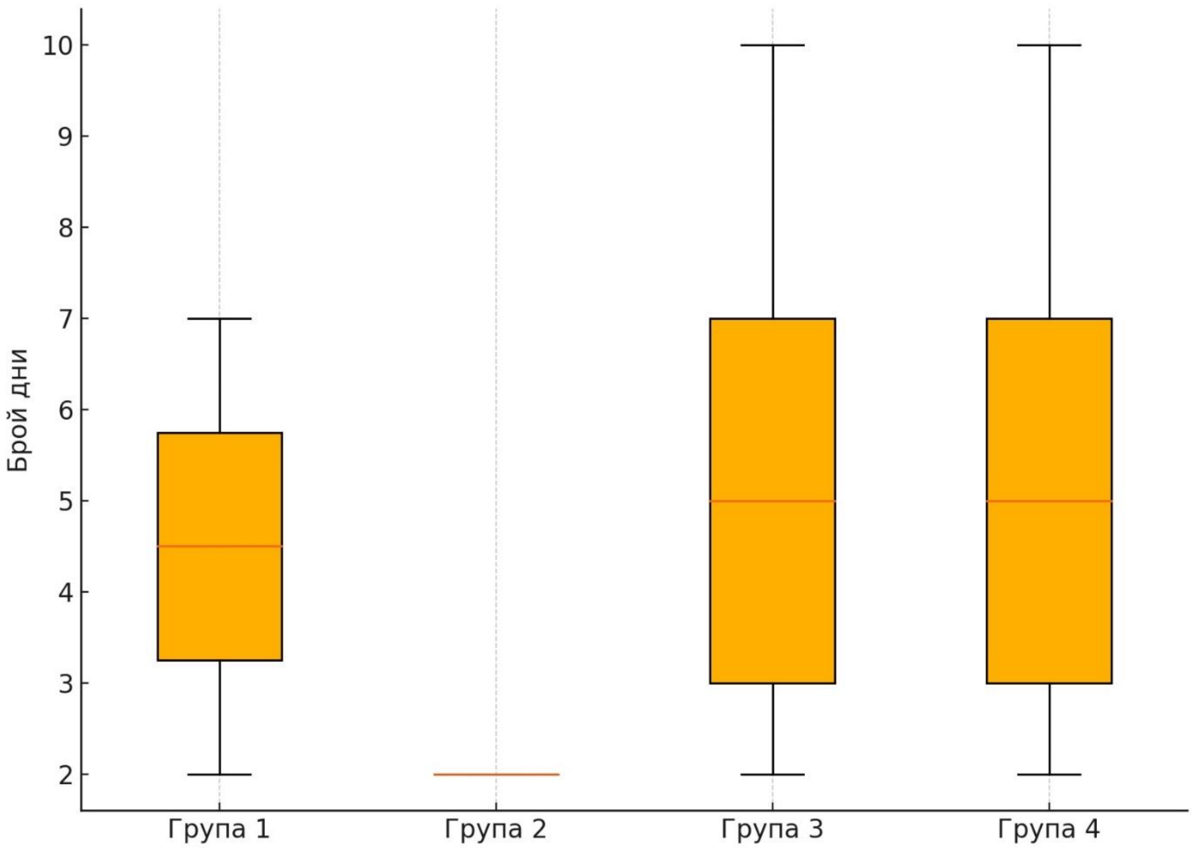


Figure 30 Length of postoperative analgesia

3.3. Hospital stay

For the analysed period, the mean hospital stay amounted to 8.1±4.42 days. The shortest stay was 4 days, while the longest was recorded in a patient with

Clavien-Dindo grade IVa complications, lasting 37 days. It was noted that the longest hospitalisation was observed in patients with pheochromocytomas – 8.52±3.27 days. Conversely, the shortest hospital stay was found in Group 2, associated with aldosterone-producing tumours, with an average duration of 6.92±1.12 days. The analysed data are summarised in (Table 23) and graphically presented in (Figure 36).

Hospital stay [days]	Group 1	Group 2	Group 3	Group 4	Overall
N	22	13	21	26	82
Mean	8,52	6,92	8,24	8,23	8,1
SD	3,27	1,12	7,29	3,17	4,42
Range	16	4	33	15	33
Min	5	5	4	4	4
Max	21	9	37	19	37

Table 23 Distribution of hospital stay by groups

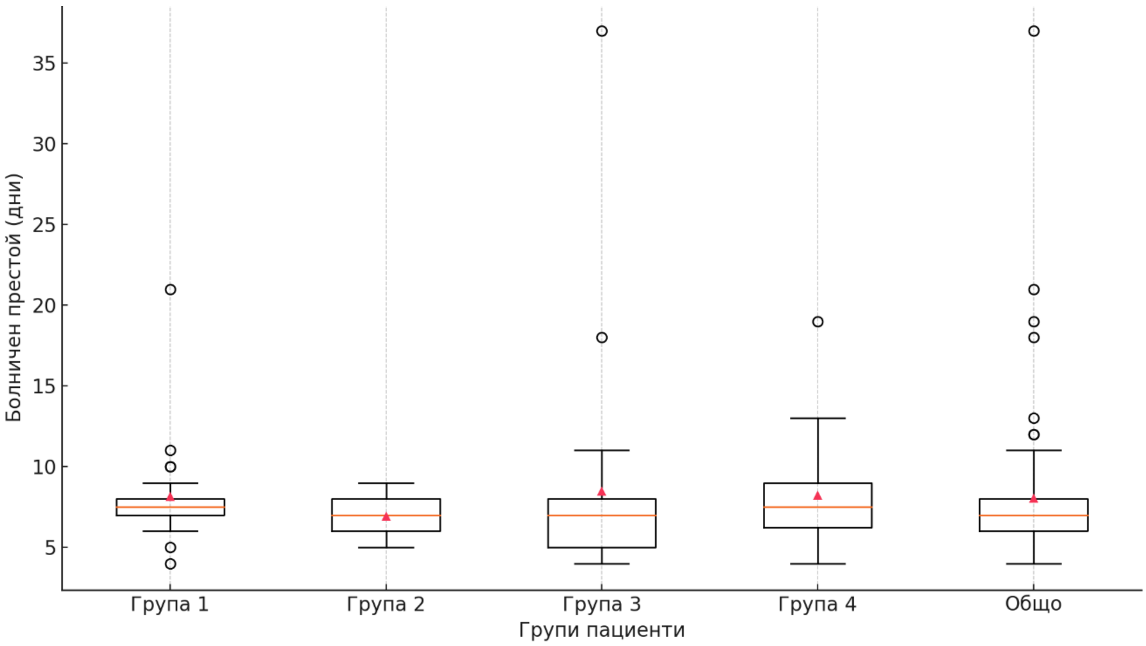


Figure 36 Graphic illustration of stastistical analysis of hospital stay between groups

The statistical analysis conducted using the Kruskal-Wallis test (H = 3.62, p = 0.306) showed no statistically significant difference in hospital stay among the four patient groups. This indicates that the duration of hospitalization is not substantially influenced by the hormonal activity of the tumor or by the group to which the patient belongs.

It is important to note that due to the healthcare financing system for different nosological entities in Bulgaria, the minimum required hospital stay for patients undergoing adrenal gland surgery is five days. Patients discharged on the fourth postoperative day were exceptions, as their treatment was self-funded, which does not require adherence to the minimum hospitalization criteria. Because of this, we analyzed two additional key indicators – time to mobilization and the need for postoperative analgesia, presented in detail in Section V, items 3.1 and 3.2, which more accurately reflect the benefits of minimally invasive surgery. After a critical analysis of the obtained results, it is evident that patients in this cohort undergoing laparoscopic adrenalectomy could be discharged as early as the 2nd or 3rd postoperative day, but due to the restrictions mentioned above, discharge occurs on average on the 8.1st day.

In our study, no statistically significant difference in hospital stay was found between the different patient groups ($p=0.306$). These results are consistent with data from the global literature, where hospital stays following laparoscopic adrenalectomy usually range between 2 and 7 days, depending on comorbidities and tumor hormonal activity (9,421).

4. Comperative analysis

We compared intraoperative parameters with respect to tumor localization and complication rates. Statistical analyses performed (χ^2 test and Fisher's exact test) assessing the association between tumor localization (left/right) and the presence of postoperative complications revealed no statistically significant relationship in any of the scenarios examined ($p > 0.05$). This indicates that tumor laterality does not have a substantial impact on complication rates in the studied population. The results were confirmed by both the χ^2 test and Fisher's exact test, further supporting their reliability. The data are presented in (Table 24).

	Chi-square test	Fisher's exact test
Group 1	$\chi^2 = 0.003$; p = 0.958	Odds ratio = 0.5; p = 0.602
Group 2	No complications registered	No complications registered
Group 3	$\chi^2 = 0.000$ p = 1.000	Odds ratio = 1.83 p = 0.618
Group 4	$\chi^2 = 0.000$ p = 1.000	Odds ratio = 1.4 p = 1.000
Overall	$\chi^2 = 0.000$ p = 1.000	Odds ratio = 1.06 p = 1.000

Table 24 Statistical comperative analysis between tumor localization and complication rates

In Group 1, an OR of 0.5 was observed, suggesting a reduced but statistically non-significant likelihood of complications (p = 0.602). In Groups 3 and 4, OR values >1 were noted (1.83 and 1.4, respectively), indicating a trend towards higher risk, though without statistical significance (p > 0.6). The absence of complications in Group 2 highlights the potentially low surgical risk in this subgroup.

A comparative analysis was performed to examine the association between complication rates and the recorded BMI of patients in order to determine whether obesity is a statistically significant risk factor for complications within the studied cohort. A t-test was conducted, revealing no significant difference between the two independent groups with normal distribution (t = 0.94, p = 0.368). Additionally, a Mann-Whitney U test was performed, confirming the absence of statistical significance (U = 413.5, p = 0.405). The results are presented in Figure 37 and Table 25. Furthermore, a Two-Way ANOVA was carried out, with the tabulated data shown in Table 26.

	t-test (p)	Mann-Whitney U (p)
Group 1	0.406	0.417
Group 2	No complications registered	No complications registered
Group 3	0.786	0.682
Group 4	0.194	0.163

Table 25 Comperative analysis between patients BMI and complication rates

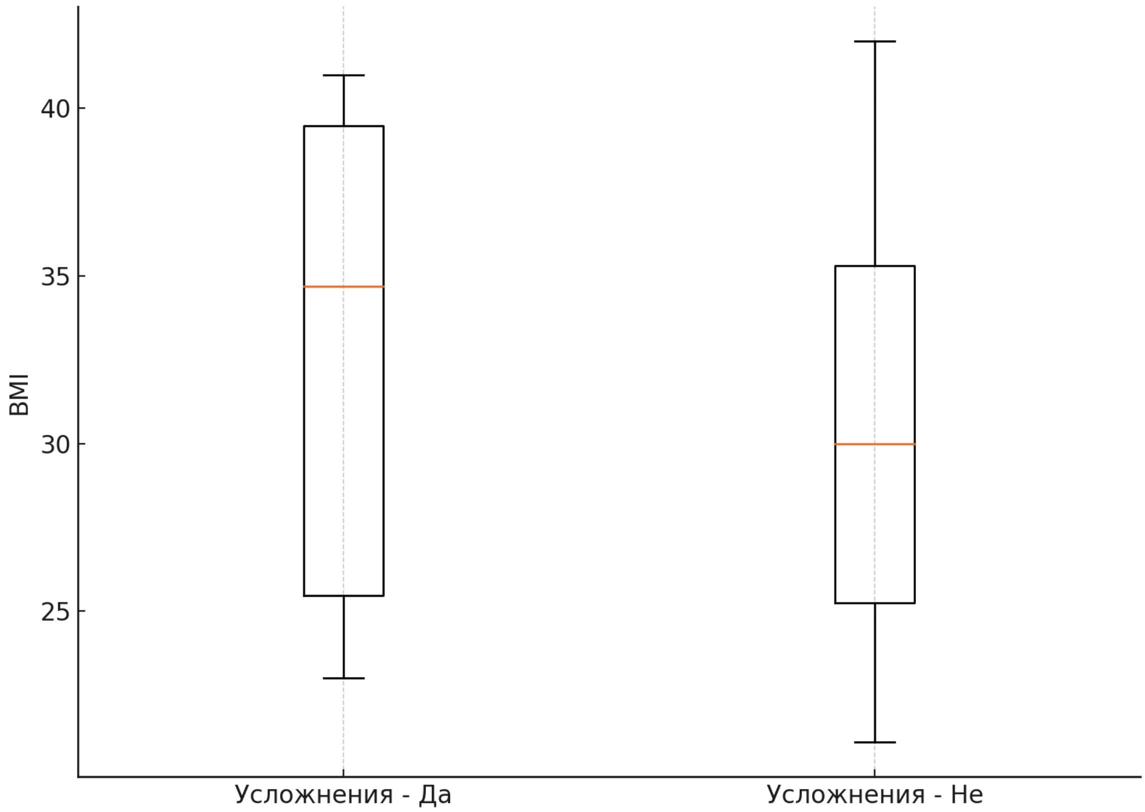


Figure 37 Comperative analysis between patients BMI and complication rates

	sum_sq	df	F	PR(>F)
Groups	114.5274	3.0	1.3166	0.274
Complications	71.6303	1.0	0.7365	0.3936
Groups vs Complications	99.4402	2.0	0.5706	0.5673
Residue	2384.2794	82.0	-	-

Table 26 Two-Way ANOVA analysis of complications based on BMI

Independent t-tests and Mann-Whitney U tests performed within groups 1, 3, and 4 showed no statistically significant differences in BMI between patients with and without complications ($p > 0.05$ for both tests). The Two-Way ANOVA analysis similarly revealed no statistically significant differences in BMI between groups, no effect of BMI on complication rates, and no significant interaction between the two factors. This indicates that neither group affiliation nor patient BMI exerts a substantial influence on the occurrence of complications ($p > 0.05$), both at the population level and within each specific group.

Literature data demonstrate a significant increase in operative time with rising patient BMI. Therefore, we conducted a correlation analysis between these parameters within our cohort. Pearson's linear correlation analysis revealed a strong positive correlation ($r = 0.82$, $p < 0.001$), as did Spearman's rank correlation ($rho = 0.81$, $p < 0.001$). These results indicate that higher BMI is associated with longer operative times, with the findings being statistically significant for both tests ($p < 0.001$). The data from this analysis are presented in (Figure 38).

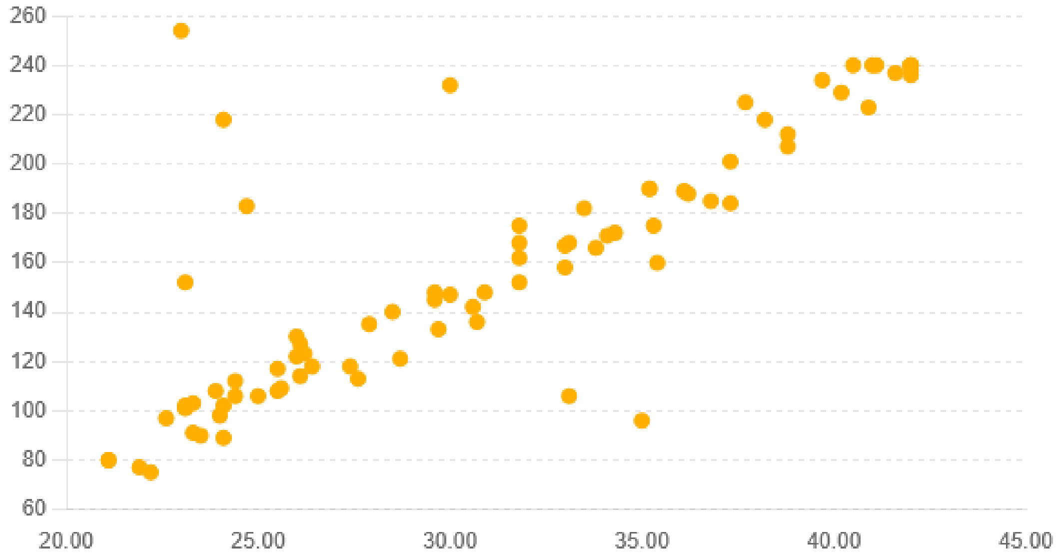


Figure 38 Corelation analysis between BMI and operative time

A comparative and correlational analysis was performed to evaluate the association between tumor hormonal activity and complication rates within the overall cohort. The analyses demonstrated no statistically significant association or correlation between hormonal activity and complication frequency (Chi-square - $\chi^2 = 0.45$, $p = 0.501$; Fisher's exact test - $OR = 0.51$, $p = 0.318$; Spearman correlation - rho = -0.11; p = 0.313). According to Spearman's test, there was a weak negative but non-significant correlation.

The correlation analysis between patient age and hospital stay (Pearson - r = -0.02, p = 0.848; Spearman - rho = -0.10, p = 0.357) indicated no statistically significant correlation between age and length of hospitalization (p > 0.05). The direction of the association was weakly negative but non-significant. Graphical representation of these results is shown in (Figure 39).

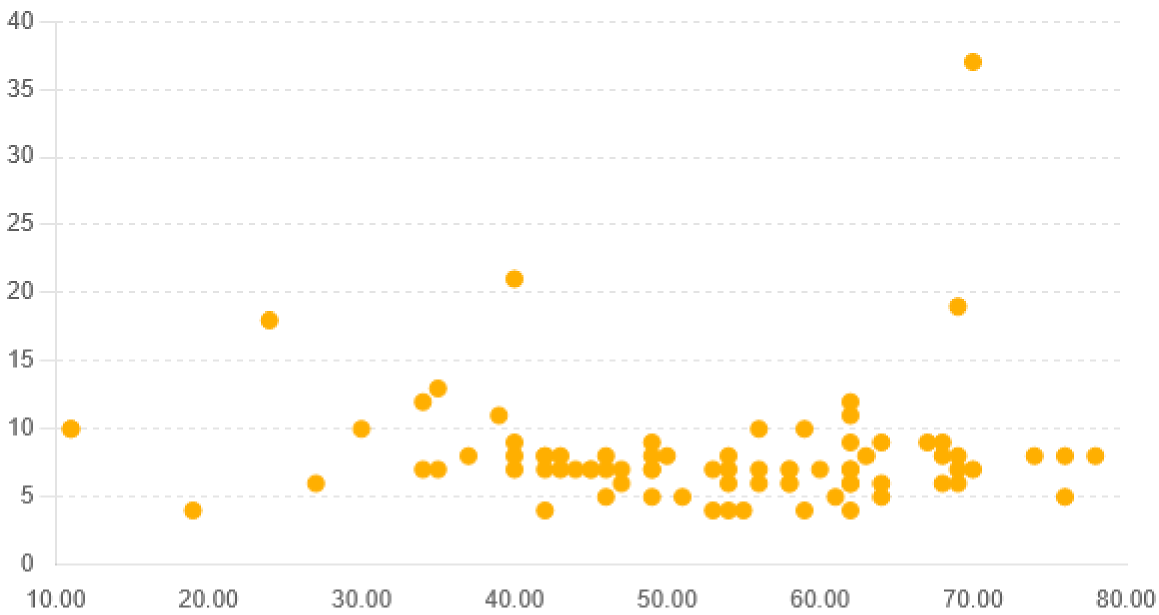


Figure 39 Correlation analysis between patient age and hospital stay

Our data are consistent with the findings of Akpınar et al., as we did not observe a significant correlation between age and hospital stay in our cohort. Consequently, we conducted additional analyses to determine whether age influences postoperative outcomes such as time to mobilization and analgesic requirements. Correlation analysis demonstrated no significant relationship between patient age and either time to mobilization or the need for analgesia. However, an additional analysis revealed a strong positive correlation between time to mobilization and analgesic requirement (rho = 0.672, p < 0.001). These data are presented in (Table 27) and graphically illustrated in (Figure 40).

	rho	p-value
Age & Time to ambulation	-0.127	0.260
Age & Postoperative analgesia requirement	-0.155	0.168
Time to ambulation & Postoperative analgesia requirement	0.672	<0.001

Table 27 Data from correlation analysis between different postoperative indicators

Visualization using a Spearman heatmap revealed the rank-based dependencies among the three examined parameters: age, time to mobilization, and analgesic requirement. A moderately strong positive correlation was identified between time to mobilization and the number of days requiring analgesia (rho = 0.672, $p < 0.001$). This suggests that patients who mobilize more slowly after surgery tend to require analgesia for a longer period, reflecting a slower recovery process and a more pronounced postoperative pain syndrome. No statistically significant correlations were found between age and the other two parameters (rho = -0.127 and rho = -0.155, $p > 0.05$). Analysis using Pearson correlation did not identify any statistically significant linear relationships between the three examined variables (all $p > 0.05$).

These findings indicate that the relationships are not strictly linear, but rather monotonic, or may be influenced by other factors such as the type of surgical intervention, individual pain thresholds, and comorbidities.

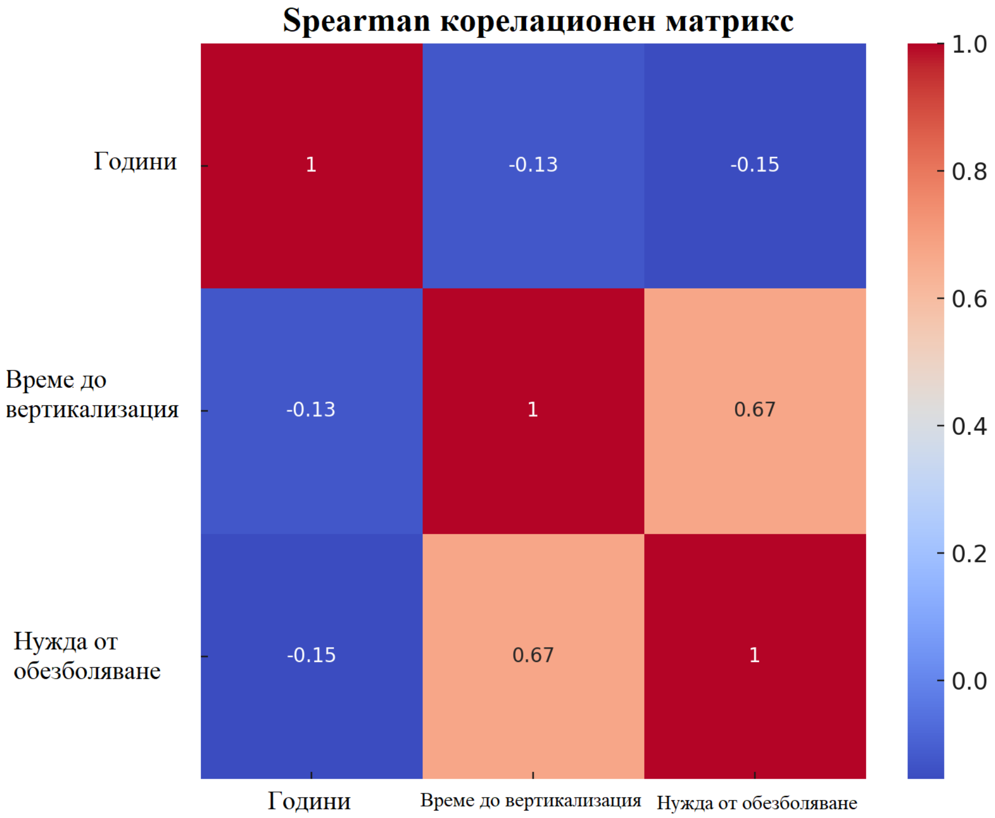


Figure 40 Graphic of correlation matrix between age – time ot ambulation – analgesia requirement

The results of this study highlight that a longer time to first mobilization is significantly associated with a prolonged need for analgesia, which correlates with literature data demonstrating the role of early mobilization in reducing pain and shortening hospital stay (Kehlet et al., 2008; Tang et al., 2015) (423,424). The absence of a significant relationship between age and the analyzed parameters indicates that chronological age per se is not a limiting factor, with functional status and overall physiological reserve playing a more important role (425,426).

Comparative analysis between patient age, histological variant, and hospital stay yielded the results presented in Table 28 and visualized in Figure 41. ANOVA analysis showed p = 0.875 for age and p = 0.990 for histological variant. Neither age nor histological type had a significant impact on hospital stay within this cohort. Kruskal-Wallis test (H = 10.90, p = 0.366) also did not identify statistically significant differences in hospital stay distribution among the various histological groups. Tukey HSD confirmed the ANOVA results.

	sum_sq	df	F	PR(>F)
Histological type	53.314906	10.0	0.243760	0.990400
Age	0.542081	1.0	0.024784	0.875365
Residue	1509.159764	69.0	-	-

Table 28 Comperative analysis between age of patients, histotology type and hospital stay

The lack of statistical significance in our cohort is likely due to the small sample size in certain subgroups, limiting the power of the analysis. Nevertheless, the results confirm that laparoscopic adrenalectomy is a safe and feasible procedure for a wide range of patients, regardless of age or tumor histology.

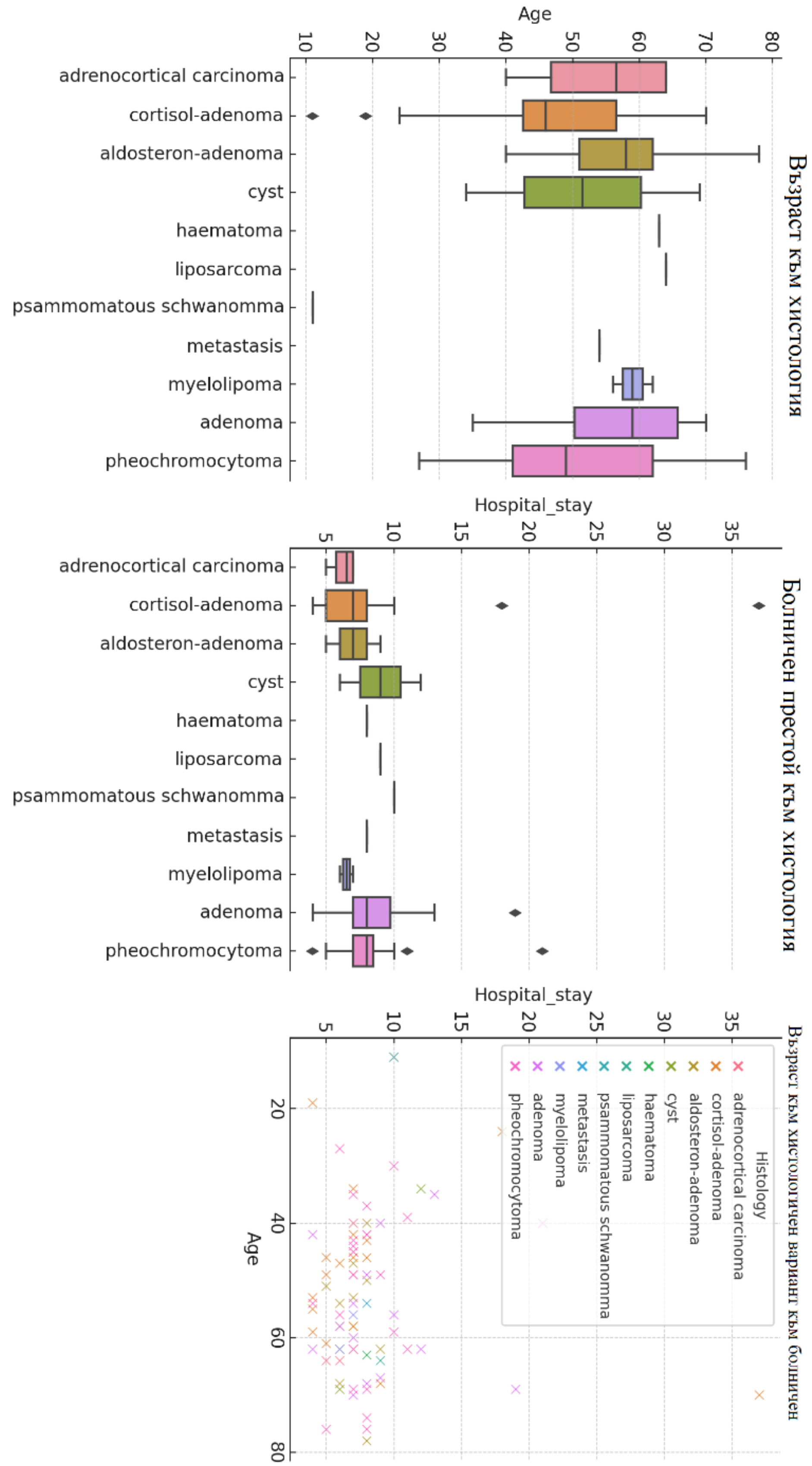


Figure 41 Comperative analysis between age of patients, histotology type and hospital stay

A predictor analysis using logistic regression was conducted to identify which factors influence the occurrence of complications (Table 29). The model did not identify any statistically significant predictors of complications. BMI showed an uncertain trend towards increased risk, but p>0.05. Neither tumor laterality nor age were significant. The pseudo R-squared value was 0.020, indicating low explanatory power of the model.

Predictor	OR (Odds Ratio)	95% CI	p-value
Age	1.008	0.961 – 1.058	0.731
BMI	1.057	0.954 – 1.172	0.290
Localisation (right vs left)	0.960	0.253 – 3.649	0.953
Intercept (Const)	0.016	0.000 – 1.345	0.067

Table 29 Logistic regression analysis between independent patient indicators

The forest plot in the present analysis illustrates that BMI showed an OR=1.06 (95% CI: 0.95–1.17), suggesting a slight increase in complication risk with higher BMI, although this result was not statistically significant (p=0.29). Age demonstrated an OR=1.01 (95% CI: 0.96–1.06) without a significant association (p=0.73). Tumor laterality (right vs. left) was also not a significant predictor (OR=0.96, p=0.95). The red vertical line at OR=1 indicates no effect, and all confidence intervals crossed 1, confirming the lack of statistical significance (Figure 42)

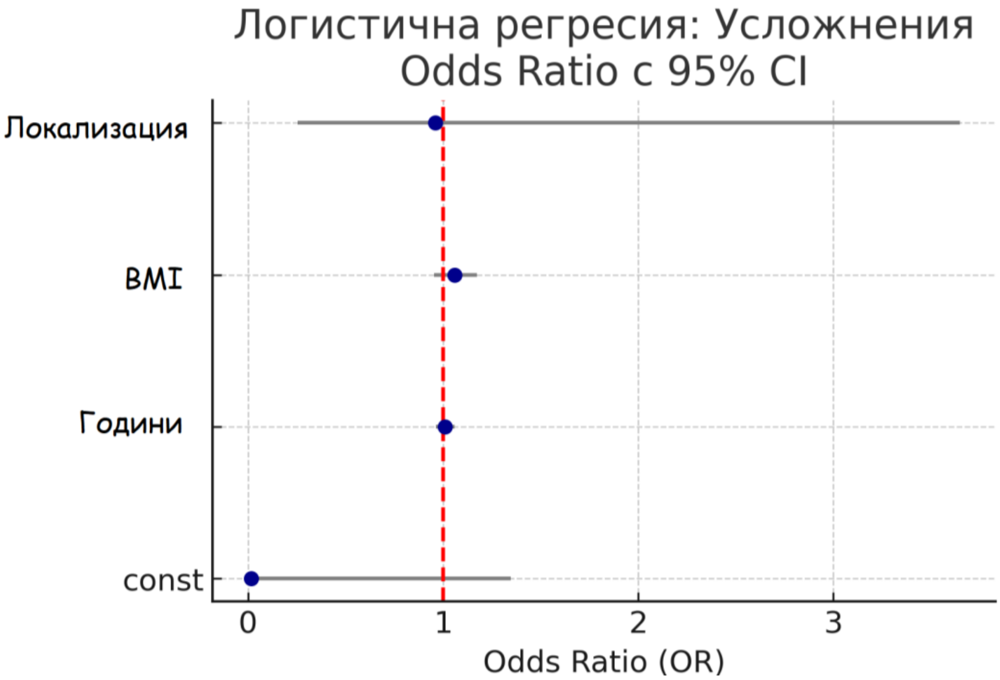


Figure 42 Forest plot analysis between independent patient indicators

The ROC curve assesses the discriminatory ability of the model to differentiate patients with complications from those without. An AUC of 0.61 indicates a low predictive value (Figure 43). Therefore, the current model demonstrates limited clinical applicability for predicting postoperative complications.

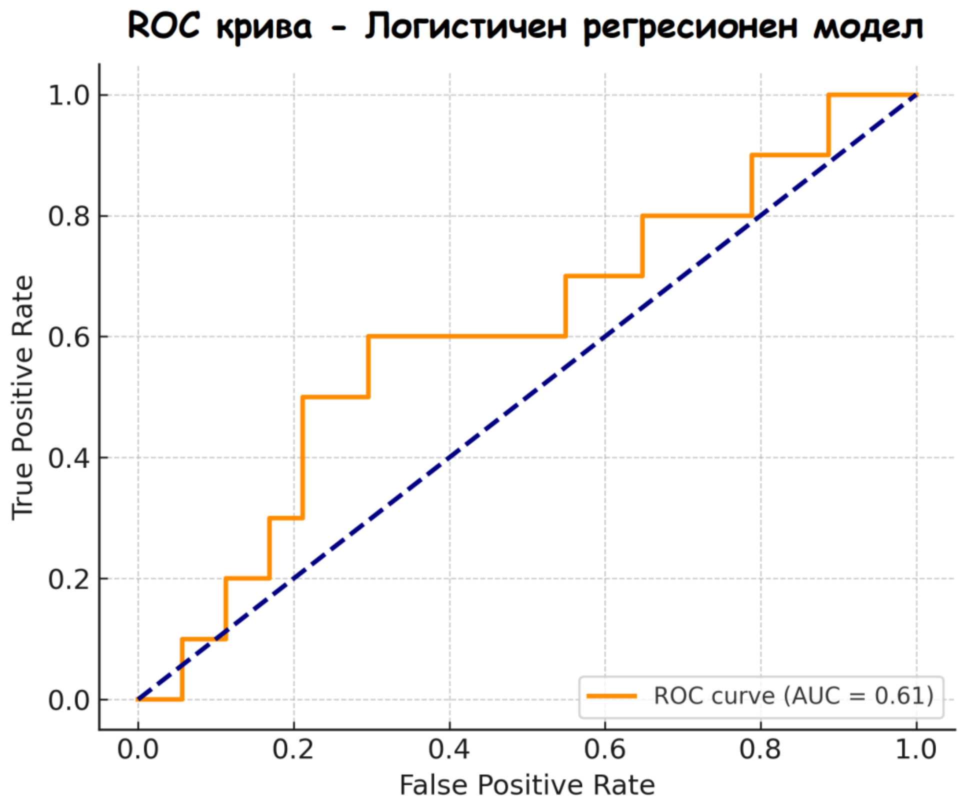


Figure 43 ROC-curve based on logistic regression analysis

The results of logistic regression analysis indicate that age, BMI, and tumor localization are not statistically significant predictors of postoperative complications following laparoscopic adrenalectomy in the present cohort. Although a slight trend towards an increased risk was observed among patients with higher BMI (OR=1.06), this did not reach statistical significance. The ROC curve further confirms the model's low discriminatory capacity (AUC=0.61).

5. Postoperative hormonal profile

Analysis of the patients' hormonal status preoperatively, as presented above in (Table 13), and at the first postoperative follow-up (Table 30), one month after surgical treatment, demonstrated a significant reduction in catecholamine metabolites (metanephrine and normetanephrine) in Group 1 (a decrease of over 80%). This correlates with the surgical removal of the pheochromocytoma and serves as an indicator of the procedure's effectiveness. Plasma and urinary cortisol levels also showed a marked reduction following adrenalectomy, particularly in Group 3, where a decrease of nearly 50% was recorded, consistent with resection of cortisol-producing adenomas. Regarding aldosterone and renin, divergent dynamics were observed among the groups, with Group 2 showing a significant decrease in the aldosterone/renin ratio (a reduction of 99%), aligning with the correction of hyperaldosteronism in Conn's syndrome.

Postoperative hormonal profile	**Group 1**		**Group 2**		**Group 3**		**Group 4**		**Norm**
	Value	%-decrease	Value	%-decrease	Value	%-decrease	Value	%-decrease	
Metanephrine Pl [ng/l]									*< 80*
Mean	180	83,07	45,32	22,8	55	13,04	50	5,23	
Normetanephrine Pl [ng/l]									***< 180***
Mean	300,1	83,52	80,1	15,1	90	14,55	85	-2,5	
Cortisol Pl [nmol/l]									***118-618***
Mean	350,18	12,17	290	7,1	399,8	49,04	360,1	14,41	
Cortisol Urine [nmol/24h]									***55-286***
Mean	289,8	24,38	200,5	27,71	241,1	69,98	228,3	26,27	
Aldosteron Pl [pmol/ml]									***30-650***
Mean	170,2	9,51	310	55,35	200	15,34	250,1	11,86	
Renin Pl [uIU/ml]									***2,8–39,9***
Mean	18	-4,05	8	-841,2	15	-10,1	25	13,49	
Aldosteron/Renin Ratio									***≤ 80***
Mean	55,00	-223,53	39	99,54	30	-19,9	22	-20,61	

Table 30 Distribution by hormonal analysis at the first postoperative follow-up

These results confirm that transabdominal laparoscopic adrenalectomy is effective in normalising hormonal hypersecretion, which is the primary therapeutic goal for endocrinologically active tumours.

6. Limitations of the study

When interpreting and applying the results and conclusions of the present study, certain potential limitations should be considered.

This is a retrospective observational study, which inherently imposes several methodological and analytical constraints affecting the extent of interpretation and generalisability of the findings. The retrospective nature carries a risk of incomplete or inaccurate data, as it relies on existing medical documentation. Omissions in recording clinical parameters, operative complications, or laboratory results are possible. All surgeries and follow-up assessments were performed within a single medical centre by a single surgical team, which may limit the generalisability of these results to other hospitals and surgical teams with different levels of expertise and resources.

The total number of patients included was 82, which, when subdivided into groups based on age, histological type, hormonal activity, and other parameters, reduces the statistical power for between-group comparisons. Furthermore, the study lacks a control group of patients treated with open surgery or alternative surgical approaches, limiting the ability to draw direct comparative conclusions regarding the efficacy and safety of the lateral transabdominal laparoscopic approach.

The patient cohort includes both children and adults with diverse types of adrenal tumours (benign, malignant, functioning, non-functioning), complicating the isolation of the surgical approach's effect on specific subtypes. The analysis does not include data on long-term outcomes such as disease recurrence, late complications, or postoperative quality of life.

Despite these limitations, the study provides valuable insights into the practical applicability, safety, and surgical characteristics of the transabdominal laparoscopic approach for adrenal tumour treatment in a broad clinical context.

7. Conclusion

This retrospective single-centre study aimed to analyse intra-, peri-, and postoperative characteristics in patients with adrenal tumours and various endocrine disorders who underwent laparoscopic adrenalectomy via a lateral transabdominal approach. The study encompassed 82 planned laparoscopic adrenalectomies performed over a sixteen-year period. Patients were classified into four main groups according to the endocrine activity of the neoplasm: pheochromocytoma (22 patients), primary hyperaldosteronism (13 patients), hypercortisolism (21 patients), and non-functioning tumours (26 patients). The reported prevalence of the different tumour types varies across the literature depending on diagnostic criteria, the nature of the included population (conservatively or surgically treated), sample size, and study period. Despite these differences, there is a clear trend towards an increasing rate of detection and surgical management of adrenal tumours in recent years.

The results provide valuable insights into patient profiles and key intraoperative characteristics associated with this surgical approach. Data analysis showed that the mean age was 52.10 years (±14.32), with a predominance of female patients (56.8%). The left adrenal gland was most frequently affected (51.8%). The mean BMI was 31.28 kg/m² (±19.08), indicating a high prevalence of overweight and obesity in the study population. The mean tumour size was 50.57 mm (±41.01), and mean operative time was 157.46 minutes (±51.67), consistent with established durations for laparoscopic adrenalectomy reported in the literature. Most patients were categorised as high operative risk, with ASA III recorded in 62.8% of cases.

This retrospective analysis provides an overview of patients undergoing laparoscopic transabdominal adrenalectomy, focusing on preoperative status, intraoperative parameters, and postoperative recovery. Notably, 39% of patients were on two antihypertensive medications, while 28% required combination therapy with three or more drugs, highlighting the high prevalence of concomitant arterial hypertension. The most common comorbidities were hypertension, obesity, diabetes mellitus, and ischaemic heart disease – conditions necessitating thorough preoperative assessment and a multidisciplinary approach.

Regarding surgical safety, complications were observed in 10 out of 82 operated patients (12.2%), with severe complications (Clavien-Dindo grade III and IV) recorded in only two cases. The mean intraoperative blood loss was 139.95 ml (±91.09), confirming the minimally invasive nature of the laparoscopic technique. Patients achieved mobilisation on average by postoperative day 1.29 (±0.77), and the need for postoperative analgesia was limited to an average of 2.78 days (±1.46), indicating rapid and tolerable recovery.

From a histological perspective, benign neoplasms accounted for 73.1% of all cases, aligning with literature data and emphasising the importance of precise preoperative imaging and hormonal diagnostics.

These findings confirm the effectiveness and applicability of the laparoscopic transabdominal approach for adrenal tumour treatment across a broad patient group, including those with high anaesthetic risk, obesity, and large lesions. The data underscore the need for an individualised approach in preoperative evaluation and surgical planning to optimise safety and outcomes.

IV. Discussion

Adrenal tumors are increasingly detected due to the widespread use of multimodal cross-sectional imaging. Clinically overt hormonal syndromes such as Cushing's syndrome, pheochromocytoma, or primary aldosteronism are identified in approximately 1–15% of all adrenal tumors, although most large population-based studies report lower rates—around 4.5% (130,157,160). In a population study including 1,287 patients, significant hormonal activity was observed in 4.5% of cases (130). In another large cohort of patients with adrenal incidentalomas (AI), 15% demonstrated symptoms or clinical signs suggestive of hormonally active lesions (171). A review of 2,005 patients with adrenal incidentalomas reported the following frequencies: subclinical cortisol hypersecretion – 10.4%; overt Cushing's syndrome – 5.1%; pheochromocytoma – 3.9%; and primary aldosteronism – 3.9% (62). In a separate study from a tertiary referral center, Cushing's syndrome was reported in 11.5%, primary hyperaldosteronism in 8.7%, and pheochromocytoma in 3.4% of patients with adrenal tumors (1). Our findings are consistent with those of Zhu et al., where 64% of adrenalectomized patients had functionally active tumors, and 25% of them were pheochromocytomas (171). Similarly, we found that among hormonally active tumors (n = 56, 69%), the largest proportion were pheochromocytomas (n = 22, 27%) (6). The distribution of adrenal tumor subtypes described in the literature varies considerably depending on multiple factors, including the diagnostic approach (whether incidental or targeted), treatment modality (surgical or conservative), the size of the studied population, and the time frame of the research (Vassiliades et al., 2020; Chuan-yu et al., 2014; Ebbehoj et al., 2020) (68,71,389).

Similar observations regarding gender distribution were noted in our study and have been reported by other authors, where a predominance of female patients is observed, though no significant association with intraoperative findings has been established (Dogrul et al., 2012; Chen et al., 2018; Gaujoux et al., 2016; Livingstone et al., 2015; Thompson et al., 2019) (3,350,389,390).

The mean age values obtained in our analysis are consistent with findings reported by other researchers (Chen et al., 2018; Liao et al., 2011; Pan et al., 2015) (211,388,391). The comparison of age between groups did not reveal statistically significant differences ($F = 1.50$, $p = 0.221$). Despite the heterogeneity of Group 4—which included multiple histological variants without hormonal activity—there were no statistically significant differences in age distribution. Our study demonstrates that hormonally active adrenal tumors are diagnosed at approximately the same age as nonfunctioning lesions.

According to a study by Gaujoux et al. (2016), the distribution of right versus left adrenal tumor localization was 43.6% and 56.4%, respectively, favoring the left adrenal gland (390). The authors did not find an association between tumor laterality and the incidence of intraoperative complications, despite the known anatomical differences between the right and left adrenal glands. These findings are supported by our own observations, which revealed no significant correlation between side and intraoperative technical difficulty.

In a meta-analysis by Danwang et al., obese patients with a BMI >30 kg/m^2 were found to be in a significantly higher anesthetic risk category (ASA III–IV) compared to non-obese patients (71.1% vs. 48.6%). Obesity was also significantly associated with longer operative time (72.5 min vs. 60 min) and increased intraoperative blood loss (40 mL vs. 20 mL). However, there were no significant differences in conversion rates to open surgery, postoperative morbidity, or length of hospital stay (366).

The high burden of comorbidities observed in our patient cohort contributed to more complex perioperative and postoperative courses. Although excess corticosteroids have been associated with cardiotoxic effects (Frustaci et al., 2019; Pingle et al., 2020), the majority of cardiomyopathy cases in our series were reported in patients with pheochromocytoma (George et al., 2021) (392–394). Elevated catecholamine levels can induce various forms of myocardial injury, including dilated, hypertrophic, and stress-induced cardiomyopathy (Kassim et al., 2008) (395). The presence of such cardiac comorbidities must be carefully evaluated during pre-anesthetic assessment, as they can lead to severe intraoperative complications such as acute pulmonary edema, total heart failure, and characteristic ST-segment changes on the electrocardiogram (Kumar et al., 2021) (396).

In contrast to our findings regarding the ASA classification of preoperative functional status, the study by Chen et al. (2018) reported that 67.4% of patients were categorized as ASA I or II, while only 32.6% were classified as ASA III or IV (391). Similar trends are observed in the data presented by Pan et al. (2011), where all patients fell into ASA categories I or II (388). A likely explanation for these discrepancies is the difference in the general health status of populations across countries where these studies were conducted.

In their study, Brunaud et al. (2014) reported that 36% of patients were not receiving any pharmacologic therapy at the time of diagnosis, 30% were treated with a single agent, 20% required two medications, and 14% were on combination therapy with three or more drugs (397). It is important to note that their analysis included only patients with pheochromocytoma. Similarly, the study by Gaujoux et al. (2016), also focused on catecholamine-secreting tumors, presented the following distribution: 33.5% of patients required no treatment, 30.9% were on monotherapy, 25.5% on dual therapy, and 10.1% required three or more antihypertensive agents (390).

Although the inclusion of alpha-blockers in the preoperative management of pheochromocytoma is recommended by various international and European guidelines (Lenders et al., 2014; Brunaud et al., 2014), high-quality randomized trials confirming the efficacy and safety of this practice remain lacking (Castinetti et al., 2022) (48,159,397). The need for such therapy remains controversial, especially in certain tumor subtypes—such as dopamine-secreting tumors, normotensive patients with elevated catecholamines, and so-called "silent" pheochromocytomas that lack clinical symptoms or biochemical abnormalities but are confirmed histologically by the presence of chromaffin cells. According to retrospective data (Lafont et al., 2015; Shao et al., 2011; Kumar et al., 2012), these cases are also associated with intraoperative blood pressure fluctuations (396,398,399). This likely explains the clinical rationale for administering alpha-blockers even in patients without laboratory-confirmed pheochromocytoma but with difficult-to-control arterial hypertension—a tendency we also observe in our clinical practice. No published data have been identified reporting the use of alpha-blockers in adrenal neoplasms other than pheochromocytomas. The potential risk of a catecholamine crisis during adrenal manipulation, even in tumors originating from the adrenal cortex, remains hypothetical at this stage. Nonetheless, in our center, alpha-blockade is routinely implemented as a precautionary measure in all patients with adrenal tumors and severe, treatment-resistant hypertension.

Compared to data from other authors, our sample demonstrates larger tumor sizes. For instance, Chuan-Yu et al. reported a mean tumor size of 42 mm, Brunaud reported 45 mm, and Thompson reported 50 mm (350,389,397). Some publications associate larger tumor volumes with a higher incidence of intraoperative complications (Bozkurt et al., 2015; Sung et al., 2022; Fouche et al., 2013), as well as an increased risk of postoperative complications (Bergamini et al., 2011; Chen et al., 2018) (219,328,330,336,391). In pheochromocytomas, larger tumors are linked to higher plasma catecholamine concentrations and the potential for massive release of these substances during surgical manipulation of the lesion (Lei et al., 2023), further complicating intraoperative handling and increasing the risk of complications (16). The tumor size in the non-functioning group, often diagnosed at a later stage due to the absence of hormonal symptoms, tends to be greater. Literature data confirm a significant association between larger tumor size and an increased frequency of complications in such cases (219).

When assessing the hormonal status of patients, it is known that age, sex, and certain medications (e.g., beta-blockers, ACE inhibitors, angiotensin II receptor blockers, diuretics, or hormone replacement therapy) can affect laboratory findings (Zaharieva, 2012) (398). Falsely elevated values may result from the intake of specific medications (e.g., tricyclic antidepressants, non-selective alpha-blockers, MAO inhibitors, sympathomimetics) or pre-analytical factors such as inappropriate body positioning during sampling or failure to account for ongoing medications (Zaharieva, 2012) (398).

In the present study, the mean operative time for laparoscopic adrenalectomy was 157.46 ± 51.67 minutes, which aligns with data published in the international literature. According to Pearlstein et al. (2020), the average duration for laparoscopic procedures in cases of pheochromocytoma was significantly longer—355 minutes (IQR: 301–406)—a finding attributed to the hormonal activity and more complex intraoperative hemodynamics associated with these tumors (399). A study by Brunaud et al. (2014) reported a mean operative time of 150 minutes, with no significant difference observed between laparoscopic and robot-assisted adrenalectomy (395). Other authors, such as Knewitz et al. (2024), reported average durations of approximately 137 minutes for laparoscopic access (414). These discrepancies between studies may be explained by factors such as tumor type and size, patient body mass index, tumor laterality, surgical approach, and the surgical team’s level of experience. The data from our study confirm that transabdominal laparoscopic adrenalectomy demonstrates operative times consistent with internationally published standards, supporting its safety and efficacy as a surgical technique.

Takeda et al. reported hemodynamic instability in 37% of their cohort, with 14.7% of patients exhibiting systolic blood pressure levels ≥ 200 mmHg. In their multivariate analysis, diabetes mellitus was identified as the only independent predictor of intraoperative hemodynamic instability (348,349). Our findings indicate that all patients with pheochromocytoma experienced a degree of intraoperative hemodynamic instability. When considering the total cohort of patients with significant blood pressure fluctuations, this represents 52.4% of the cases, demonstrating persistent alterations in arterial pressure.

In their series of over 300 laparoscopic adrenalectomies, Dworak et al. (2019) reported uncontrollable bleeding in two patients—one due to injury to the inferior vena cava and the other due to extensive retroperitoneal hemorrhage (400). Similar results regarding intraoperative blood loss and conversion rates due to uncontrolled bleeding were also reported by Tarallo et al. (2020), Catellani et al. (2012), and Arezzo et al., aligning with the data presented in our study (209,368,401).

Sun et al. conducted a single-center study involving 302 patients, in which venous anatomical variations were identified in 20.5% of the adrenalectomies. Compared to patients with normal venous anatomy, those with anatomical deviations demonstrated larger tumor volume, increased diameter of the adrenal veins, and a higher prevalence of medullary tumors, which collectively increased the risk of intraoperative bleeding and postoperative complications (387). Additional variations in venous drainage were also reported by MacGillivray and colleagues, whose findings are consistent with those observed in our study (402). High-resolution contrast-enhanced preoperative CT imaging is an essential component of surgical planning, as it allows for the detection of anatomical anomalies and helps avoid potentially life-threatening complications and morbidity.

In a cohort study including 244 subjects, Schweitzer et al. reported a conversion rate from laparoscopic to open surgery of 7.7%. The main reasons for conversion included adhesions (n=8), bleeding (n=6), and technical difficulties during dissection (n=5) (345). These data are consistent with our findings, where the conversion rate was 8.54%. In all but one case, the conversion was necessitated by dissection difficulties due to tumor size.

Multiple published studies have shown an association between the rate of conversions and the year of the study, supporting the hypothesis of a learning curve effect (228,285,300,403,404). As surgical teams gain experience and minimally invasive techniques evolve, the need for open surgical conversion continues to decline. Although differences in mean intraoperative blood loss were observed between subgroups, this variability did not result in clinically significant consequences, as the frequency of transfusions remained similar (247,405). Furthermore, no significant difference was found in the rate of intra- or postoperative complications between laparoscopic and alternative surgical approaches. While isolated cases of mortality have been reported following laparoscopic adrenalectomy, the overall mortality rate does not differ significantly between surgical techniques. This highlights the relative safety of the laparoscopic approach, particularly when performed by experienced teams and in carefully selected patients (158,225,406,407).

The time to verticalization after laparoscopic adrenalectomy is an important indicator reflecting postoperative recovery and the invasiveness of the surgical intervention. In our study, the mean time to independent mobilization was 1.29 ± 0.77 days, which is consistent with data published by Chen et al. (2018), who observed early mobilization within 1–2 days postoperatively in most patients in their cohort (388). Similar findings were reported by Thompson et al. (2019), who described a median time to mobilization of approximately 24 hours, emphasizing the advantages of minimally invasive techniques in reducing postoperative immobilization (386). Brunaud et al. (2014) also highlighted that laparoscopic adrenalectomy significantly shortens recovery time compared to open approaches, allowing earlier return to daily activities (395). Early mobilization is key to reducing the risk of thromboembolic complications and respiratory problems, aligning with the concept of enhanced recovery after surgery (Pearlstein et al., 2020) (399). Overall, our findings support the literature that laparoscopic adrenalectomy is associated with rapid postoperative mobilization, reflecting its minimally invasive nature and favorable recovery profile.

According to the literature, the average duration of postoperative analgesia corresponds with our findings—up to 2.78 ± 1.46 days—supporting the advantages of laparoscopic adrenalectomy in terms of reduced postoperative pain and faster recovery (381,388,408). Dancea et al. (2000) reported that minimally invasive adrenalectomy approaches lead to a significantly reduced need for analgesics compared to open surgery, with an average duration of analgesia below 3 days (413). Pearlstein et al. (2020) reported similar results, with a mean need for analgesia of 2.5 days after laparoscopic resection of pheochromocytoma (399). In a meta-analysis by Gaujoux et al. (2012), laparoscopic access was found to reduce both hospital stay duration and postoperative opioid requirements compared to open adrenalectomy (386). The low pain scores observed in our patients can be attributed to minimal surgical trauma, limited damage to myofascial structures, and earlier mobilization—findings that are consistent with the published data on the benefits of laparoscopic approaches in adrenal surgery.

It is important to note that due to the structure of healthcare funding in Bulgaria, the minimum required hospital stay for patients undergoing adrenal surgery is five days. Patients discharged on the fourth postoperative day were exceptions due to self-financing of treatment, which does not require adherence to the minimum hospital stay criterion. For this reason, we analyzed two additional key indicators—time to verticalization and duration of analgesia—presented in detail in Section V, paragraphs 3.1 and 3.2, which more accurately reflect the impact of minimally invasive surgery. Based on critical analysis of our results, patients undergoing laparoscopic adrenalectomy in the studied cohort could be safely discharged on postoperative day 2 or 3; however, due to the aforementioned constraints, actual discharge occurred on average on day 8.1.

In our study, no statistically significant difference was found in the length of hospital stay among the different patient groups ($p = 0.306$). These results are consistent with global literature, where postoperative hospitalization after laparoscopic adrenalectomy typically ranges from 2 to 7 days, depending on comorbidities and the hormonal activity of the tumor (9,421). For example, Tsuru et al. (2005), in a cohort of 126 patients, reported a mean hospital stay of 4.2 days after laparoscopic adrenalectomy, with no significant difference between patients with aldosteronomas, cortisol-producing adenomas, and pheochromocytomas (9). Similar findings were presented by Akpinar et al. (2024) in a meta-analysis, where the average hospital stay was reported between 3 and 5 days for laparoscopic approaches, regardless of histological subtype (421). However, some authors, such as Economopoulos et al. (2017), have noted that pheochromocytomas may be associated with a prolonged hospital stay due to the need for preoperative preparation and hemodynamic stabilization (407). Our study indicates that when a standardized preoperative protocol and laparoscopic technique are applied, group affiliation does not significantly influence hospitalization duration. This supports the benefits of minimally invasive techniques in reducing recovery time, in line with international findings (9,407,421).

The current data also confirm that tumor laterality (left or right) has no significant impact on the incidence of postoperative complications following laparoscopic adrenalectomy. This observation is supported by studies such as Henry et al. (2000), who conducted a retrospective analysis of 169 laparoscopic adrenalectomies (149 left-sided, 10 bilateral) and found an overall complication rate of 7.5% with no significant difference based on tumor side (409). Similarly, Rieder et al. (2009) analyzed 109 left and 54 right adrenalectomies and found no statistically significant difference in complications, although there was a tendency for less blood loss during right-sided procedures (410). Wang et al. (2021), in a systematic review including 780 patients, reported that the risk of complications did not differ between right and left laparoscopic adrenalectomies; however, right-sided procedures were associated with greater blood loss and higher conversion rates to open surgery (7). Gunseren et al. (2019), in a retrospective study of 272 cases, also found increased intraoperative blood loss in right-sided procedures, while no statistically significant differences in other complications were observed (411).

In a study by Dancea et al. (2012) including 80 patients divided into BMI >30 and <30 kg/m², nine complications were recorded among the 49 overweight patients, whereas no complications occurred in patients with normal BMI ($P < 0.011$), indicating a significantly increased risk in obese patients (412). However, more recent studies show differing results. Knewitz et al. (2024) analyzed 278 patients grouped by BMI ≥35 kg/m² and found no significant differences in intra- or postoperative complications between groups undergoing minimally invasive adrenalectomy (413). Pędziwiatr et al. (2017) included 520 patients stratified by BMI (normal, overweight, obese, morbidly obese), with complication rates of 12.8%, 8.8%, 8.2%, and 11.5%, respectively ($P = 0.5295$), again showing no significant difference (414). Hu et al. (2015) analyzed 353 patients undergoing retroperitoneal adrenalectomy and observed longer operative times in obese patients, but similar outcomes in terms of complications, blood loss, and hospital stay between groups (415). These literature data are consistent with our findings, indicating that complication rates are not significantly influenced by BMI.

Literature data are consistent with the observed positive correlation between operative time and obesity. Dancea et al. (2000) reported, based on regression analysis, a weak but significant correlation coefficient between BMI and operative time (standardized $\beta = 0.163$, $p < 0.05$) (412). Zhao et al. (2024) conducted a multivariate analysis confirming BMI as an independent predictor of prolonged operative duration ($OR \approx 1.61$, $p \approx 0.045$) (416). The correlation between BMI and operative time is further supported by Pearlstein et al. (2020) and Knewitz et al. (2024) (413,417).

Gao et al. (2024), in a large study involving 3,775 patients with adrenal tumors (88.5% treated laparoscopically), found that hormonally active tumors, such as those causing Cushing's syndrome, were associated with a higher risk of complications following laparoscopic adrenalectomy (418). Similarly, Izawa et al. (2024) identified endocrine-active tumors—especially pheochromocytomas—as risk factors for specific postoperative complications, such as postoperative fever (419). However, Utsumi et al. (2023), in a subgroup analysis of patients with pheochromocytoma, found significantly larger tumor size and blood loss, but without a corresponding increase in overall complication rates (420). Our findings align with this variability, suggesting that while endocrine-active tumors may increase the risk of certain complications, they do not consistently elevate the overall postoperative complication rate across centers, confirming the heterogeneity in reported outcomes.

In a cohort study by Akpınar et al. (2024) involving 86 patients (median age 54 years, range 20–78), with a median hospital stay of 2 days, regression analysis found that age was not a statistically significant predictor of prolonged hospitalization (≥3 days; $p = 0.323$) (421). Despite this, the authors noted that in other studies—such as those by Chen et al. and Kuriansky et al.—patients over the age of 65 were often associated with longer hospital stays and a higher incidence of complications (391,422).

Correlation analysis of postoperative variables in our study—time to mobilization vs. need for analgesia vs. patient age—demonstrated that delayed ambulation was significantly associated with prolonged analgesia requirements. This finding supports previous data showing the role of early mobilization in reducing pain and shortening hospital stay (Kehlet et al., 2008; Tang et al., 2015) (423,424). The lack of significant correlation between age and these parameters further suggests that chronological age alone is not a limiting factor; rather, the patient's functional status and physiological reserve are more predictive of postoperative outcomes (425,426).

The correlation between patient age, histological subtype, and hospital stay in our study is in line with literature indicating that postoperative hospitalization after laparoscopic adrenalectomy is more dependent on surgical and periprocedural factors—such as operative time, blood loss, and complications—than on age or histological tumor type (118,409). Porpiglia et al. (427), in a study of 126 laparoscopic adrenalectomies, identified postoperative complications as the primary predictor of extended hospital stay, with patient age showing no statistically significant effect. Similarly, Chen et al. (391), in a retrospective analysis, did not find an association between histological variant and duration of hospitalization.

Our logistic regression results showed that age, BMI, and tumor laterality were not statistically significant predictors of complications following laparoscopic adrenalectomy in this cohort. Although a slight trend toward increased risk was observed in patients with higher BMI (OR = 1.06), the result did not reach statistical significance. The ROC curve confirmed the model's low discriminatory ability (AUC = 0.61). These findings align with publications reporting that BMI alone does not significantly predict complication rates, although it is associated with longer operative time and increased blood loss

(412,413). Porpiglia et al. noted that although laparoscopic adrenalectomy in obese patients presents greater technical challenges, complication rates do not significantly increase (427). However, some authors have identified BMI as an independent risk factor in more complex laparoscopic procedures (286). Most recent studies do not consider age a significant predictor (391).

Postoperative hormonal profiles in our patients confirmed the effectiveness of transabdominal laparoscopic adrenalectomy in normalizing endocrine hypersecretion—a primary therapeutic goal in hormonally active tumors. The greatest reduction in plasma metanephrines was observed in patients with pheochromocytoma, consistent with findings by Wang et al. (2010) (299). In aldosterone-producing adenomas, both aldosterone levels and the aldosterone/renin ratio significantly decreased, indicating biochemical remission. Similar results were reported by Picado et al. (2021), who observed complete biochemical remission in over 90% of patients with primary hyperaldosteronism following laparoscopic adrenalectomy, and in meta-analyses by Hawn et al. (2002) regarding Cushing's syndrome, where mean cortisol reduction exceeded 85% (292,428).

V. Findings

1. The examined patient cohort demonstrated heterogeneity in terms of clinical presentation related to excessive hormonal synthesis. As an additional factor, patients presented with significant comorbidity, with the majority exhibiting arterial hypertension prior to surgical treatment. This condition necessitates clarification of the underlying etiology, requiring an active diagnostic approach and careful preoperative assessment.

2. Anatomical variations in the vascular supply and localisation of the adrenal glands exert substantial influence on the execution of the surgical technique. Arterial and venous anomalies are more frequently observed in right-sided lesions, demanding greater precision during dissection. The transabdominal approach provides excellent visualisation, enabling identification and control of anatomical structures regardless of individual variations.

3. Early postoperative results demonstrate rapid recovery with a low complication rate. The mean time to mobilisation and the need for analgesia are short, while intraoperative blood loss remains within acceptable limits. This confirms the benefits of the laparoscopic technique in terms of minimal invasiveness and accelerated recovery.

4. Late outcomes indicate stable clinical improvement and a low recurrence rate in patients with benign lesions. Endocrine-active tumours achieve sustained hormonal remission. No significant late complications related to the laparoscopic approach or the functional residual capacity of the contralateral gland were observed.

5. The presence of hormonally active tumours, particularly pheochromocytomas and corticosteroid-producing neoplasms, correlates with a higher rate of intraoperative haemodynamic instability. Despite mandatory preoperative pharmacological preparation, haemodynamic control during surgery plays an additional key role in significantly reducing the risk of intraoperative complications.

6. Patients with hormonally active tumours are at increased risk of postoperative hormonal imbalances, including hypoadrenalism and hypertensive crises. Nevertheless, with adequate endocrinological monitoring and timely initiation of replacement therapy, the incidence and severity of postoperative complications remain low and manageable.

VI. Contributions

Scientific-Theoretical and Scientific-Practical Contributions of the Dissertation:

1. A detailed literature review has been conducted on laparoscopic methods for the treatment of adrenal tumours.
2. A contemporary and statistically reliable study has been performed on the application of the transabdominal laparoscopic approach as a treatment method for adrenal tumours.
3. For the first time in Bulgaria, an analysis has been carried out on the outcomes of transabdominal laparoscopic adrenalectomy in both adults and children.
4. For the first time, a comparison has been made of the results from transabdominal laparoscopic adrenalectomy across different pathological and functional processes affecting the adrenal glands.
5. A comparative analysis has been performed between transabdominal laparoscopic adrenalectomy outcomes in Bulgaria and those reported in Europe and worldwide.
6. The diagnostic and therapeutic algorithm developed at University Hospital "St. Marina" – Varna has been analysed, aiming to serve as a structured guide for both preoperative assessment and postoperative follow-up of patients.

VII. Scientific Publications Related to the Dissertation

1. **Mihaylov S.** Minimally invasive treatment methods for adrenal tumors. Scripta Scientifica Medica. 2024;Online First. ISSN 0582-3250 (Print), ISSN 1314-6408 (Online).
2. **Mihaylov S.** Fever of unknown origin in a patient with myasthenia gravis following laparoscopic adrenalectomy—a case report. Scripta Scientifica Medica. 2025;Online First. ISSN 0582-3250 (Print), ISSN 1314-6408 (Online).
3. Zlatarov A, Drenakova P, **Mihaylov S**, Zgurova N, Petkova L, Ivanov KD. Malignant psammomatous melanotic schwannoma mimicking adrenal cyst: case report. Ann Pediatr Surg. 2022;18(1):51. doi: 10.1186/s43159-022-00189-w. Epub 2022 Jul 7. PMID: 35818469; PMCID: PMC9261228.
4. Aleksandar Zlatarov, **S. Mihaylov**, P. Stamov, Minimally Invasive Treatment Methods for Adrenal Tumors. Poster Session, 11th Conference of ESES in Izmir 22-24.05.2025, Izmir, Tukey

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